IPVC 2020 ABSTRACTS

Interdisciplinary
WORKSHOP 1: VIRUS

HOW IT WORKS? HPV LIFE CYCLE, ENTRY & CARCINOGENESIS

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The high-risk papillomaviruses have a number of molecular characteristics, which are not shared by the low-risk types, but which contribute to their unique tissue tropisms and cancer associations. Most high-risk HPV infections are however controlled by the immune system, with neoplasia and cancer progression being associated with chronic deregulated viral gene expression. This occurs at particular epithelial sites, with the oropharynx and the transformation zones of the anus and cervix being the most significant. These sites have an unusual epithelial architecture, which facilitates virus entry and lesion formation, and which also allows deregulated expression of the viral E6 and E7 genes. In individuals who are incapable of raising an effective antiviral immune response, cancer progression follows a well-defined path, with genetic errors accumulating in the infected cell over a period of years or decades. Recent advances in our understanding of the cervical transformation zone, reserve cell function, and the biology of HPV infection and clearance at these sites, is now helping us to understand the relative value of cervical screening approaches, and the limitations of our current strategies for disease treatment.

Interdisciplinary
WORKSHOP 1: VIRUS

HPV CARCINOGENESIS

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High-risk human papillomaviruses (HPVs) are potent carcinogens that drive tumor initiation as well as progression. HPV associated cancers often express only two viral genes, E6 and E7. Continued E6 and E7 expression is necessary for tumor maintenance. The HPV E6 and E7 proteins play key roles in reprogramming infected host cells to support viral persistence and progeny production. Host cells combat this “unfriendly takeover” by viral infection by eliciting a variety of cellular defense responses that the HPV E6 and E7 genes have evolved to subvert. The oncogenic activities of the high-risk HPV E6 and E7 genes result from these activities that are necessary for the viral life cycle.

Interdisciplinary
WORKSHOP 1: VIRUS

IMMUNE RESPONSES TO HPV

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The viral antigens present in HPV-associated oropharyngeal squamous cell cancer (OPSCC) cervical cancer (CxCa) may trigger potent immunity. Therefore, we studied the relationship between the presence of intratumoral HPV-specific T-cell responses, the immune contexture in tumor microenvironment and clinical outcome. For this purpose an in-depth analysis of tumor-infiltrating immune cells in prospective OPSCC and CxCa patient cohorts was performed and key findings were validated using the publicly available cancer genomic atlas database. We show that despite the same etiology of these tumors, the composition and functionality of their lymphocytic infiltrate substantially differ. CxCa displayed a 3-fold lower CD4:CD8 ratio and contained less CD4+CD161+ effector memory T-cells than OPSCC. These differences were reflected in the detection rate of intratumoral HPV-specific CD4+ T-cells, being 64% of the OPSCC and 35% of CxCa, and in their impact on OPSCC and CxCa survival. The presence of a strong intratumoral HPV16-specific type 1 CD4+ T cell response was associated to better overall survival, higher numbers of intratumoral DCs and of CD161+ effector T cells, which produced the highest cytokine levels among tumor-specific T-cells, but also with the infiltration of activated Tbet+ Foxp3+ Tregs with full capacity to impede such type 1 effector T cell responses. A more in-depth analysis of the intratumoral DCs revealed that they comprised a fairly unknown population of cytokine producing CD1c+CD11c+CD163+ cDC2 which specifically stimulated the IFNγ-production of cognate antigen-stimulated patient-derived HPV16-specific CD4+ T cells. High numbers of CD163+ cDC2 correlated both with a strong T-cell infiltrate and with improved survival. Welters et al. Clin Cancer Res 2018, Santegoets et al. Clin Cancer 2019, Santegoets et al. J. Immunother. Cancer 2019

Interdisciplinary
WORKSHOP 2: BURDEN OF DISEASE

NATURAL HISTORY OF HPV AMONG FEMALES: IMPLICATIONS FOR CONTROL

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Although epidemiologic studies have given us insight into the natural history, many pieces remain missing including transmission dynamics and the final steps required for the transition from CIN 3 to invasive cancer. Current studies show young women appear the most vulnerable to acquiring HPV and that the majroity of casual HPV (those that lead to cancer) occur by age 25 years. But not all countries show a peak in young women and 90% of those infections in young women “regress”. It has also become clear that “detection” does not necessarily equate with “infection” and may reflect partner contamination. Innate immune responses to HPV are likely critical to clearance of initial infections and adaptive immune response for clearance after persistence. The higher rate of transmission from females to males than vice versa suggest women are more likely to develop strong T-cell memory. The longer the persistence, the more likely the infection will not clear, and precancerous CIN 3 becomes almost inevitable. Recent data suggest that the vaginal microbiome plays a critical role in the natural history and that Lactobaccillus-dominant microbiomes assist in viral control. The final stages of cancer development are likely multi-faceted as in many cancers but include HPV’s ability to cause cell cycle dysregulation and/or viral integration with loss of tumor suppressor gene function or increased expression of oncogenes. The low positive predictive value of an HPV positive test underscores the complexity of the natural history of HPV and the importance of targeting pre-sexually active youth for vaccination.

Interdisciplinary
WORKSHOP 4: VACCINATION

HOW GOOD ARE THE HPV VACCINES IN THE IMMUNOSUPRESSED AND HOW BEST TO VACCINATE

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Immunosuppression is a known risk factor for the development of HPV-associated pre-cancers and cancers including cervical, vaginal, vulvar and anal cancers. This vulnerability includes genetic, viral and iatrogenic immunosuppression. Persons living with HIV appear particularly vulnerable with rates of anal cancer in HIV infected men who have sex with men reaching rates of 80 per 100,000. Other groups shown to be vulnerable include those individuals with autoimmune disease specifically systemic lupus erythematosus. Other groups including rheumatoid arthritis and inflammatory bowel disease appear vulnerable if on immunosuppressive agents. Data on HPV vaccination are mixed. Most studies show that sero-positivity and antibody titers after HPV vaccination are lower in those immunosuppressed. Little to no data is available on efficacy. One trial performed in adolescent and adult persons living with HIV was prematurely stopped because of futility in preventing anal pre-cancers. One study in perinatally HIV infected adolescents and young adults who were HPV vaccinated found high rates of abnormal cytology—over 40%. HPV types associated with the abnormal cytology is unknown and trials are underway. Because of these data, current recommendations are to give all three doses to immunosuppressed individuals even if <15 years of age and to continue close surveillance for cervical and anal cancer. Recommendations for vaccination and current screening strategies will be reviewed.

Interdisciplinary
WORKSHOP 4: VACCINATION

VACCINE PRICING AND POLICY IMPLICATIONS

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The vaccine dose price is one of the main determinants of vaccination program costs. Centralized procurement can lead to price reductions, partly through economies of scale, enabling countries to sustainably introduce new vaccines. Low and middle income countries have been able to procure vaccines by international group purchasing through external procurement agents such as the UNICEF's Supply Division and PAHO. In most high-income countries, procurement usually takes place at a national or even regional level. Although less powerful than international group purchasing, national tendering has also led to a large reduction in vaccine dose prices as compared to pharmacy list prices. In this presentation, I will give an overview of the development of tender-based HPV vaccine prices globally as well as in member states of the European Union over the last decade. I will illustrate the effect of tender-based pricing on the outcomes of health economic evaluations where I will focus in particular on the scope for sex-neutral vaccination in relation to vaccine uptake. Finally, I will look at vaccine pricing from a supply instead of a demand perspective and I will elaborate on the relation between vaccine price and shortage. The supply perspective is especially relevant in light of the recent shortage as noted by the WHO SAGE working group.

Basic Science
WORKSHOP 1: HPV VIRAL ENTRY, REPLICATION AND TRAFFICKING

ROLE OF L2 IN TRAFFICKING

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During cell entry, papillomavirus DNA traffic to the nucleus where viral DNA replication occurs. Although the major capsid protein L1 plays the major role in binding of the virion to the cell surface, the minor capsid protein L2 plays an essential role in this trafficking process. HPV proteins and DNA travel to the nucleus inside membrane bound compartments that comprise the retrograde transport pathway. This strategy presumably protects HPV from cytoplasmic innate immune sensors during entry. The cellular protein complex known as retromer is required for the incoming HPV virion to enter the retrograde pathway. We have found that the L2 protein contains a cell-penetrating peptide sequence that transfers the C-terminus of L2 through the endosomal membrane into the cytoplasm where it binds directly to retromer to initiate retrograde trafficking. In the absence of retromer binding, the virus becomes trapped in the endosome. Small peptides derived from L2 can bind retromer and titrate it away from entering virus, blocking infection in cell culture and in a mouse model. This finding validates intracellular trafficking as a new antiviral target. In addition, we have isolated a series of small artificial proteins that inhibit HPV entry at various steps. Detailed analysis of one of these inhibitory proteins shows that it inhibits HPV entry by inhibiting cycling of the small GTPase, Rab7, which is required for retromer action during HPV entry. These experiments elucidate mechanistic features of HPV entry and suggest that chemicals that block Rab7 cycling may have antiviral activity.

Basic Science
WORKSHOP 2: HPV GENERA AND ASSOCIATED DISEASES

LOW RISK ALPHA TYPES AND ASSOCIATED DISEASES; USING RESPIRATORY PAPILLOMATOSIS AS A MODEL TO UNDERSTAND THE BIOLOGY OF MUCOSAL HPVS

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Recurrent respiratory papillomatosis (RRP), caused by HPVs type 6/11, is characterized by benign lesions that are treated by surgery. The papillomas express early viral proteins in coordinated fashion, and express the late proteins and produce virus in a subset of cells. Papilloma cells can be cultured *in vitro* for several passages, permitting study of the molecular biology of the alpha HPVs in their normal host cells without the confounding variables of cancers that harbor many cellular mutations. While RRP is rare (prevalence: approximately 3/100,000), the papillomas recur following surgery. Recurrence is highly variable between patients, ranging from a few instances at long intervals (months) before permanent remission, to every 3-4 weeks for many years. Thus, RRP is ideal for studying variation in host immune response to HPV. Using this system, we have discovered that recurrence is due to persistence of latent HPV infection. The transcriptional pattern of the infected cells bears a marked similarity to tumor cells, with alterations in expression of genes controlling growth and differentiation. Infection also alters expression of many immune response genes, which interact with variations in the host immune response genes to generate a local T_H2/Treg microenvironment that prevents control of the active infection. Finally, we have discovered that some of the cellular differences that promote viral expression are intrinsic to the airway of the patient, rather than caused by the virus. Thus, subtle cellular differences in susceptibility to infection or viral persistence may play a key role in the biology of the alpha HPVs.

Basic Science
WORKSHOP 3: NEW TECHNOLOGIES

CHROMATIN REORGANIZATION IN 3D: INSIGHTS FROM HI-C TECHNOLOGY

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Within the nucleus, the three-dimensional chromatin organization contributes to chromosome compartmentalization and the formation of gene regulatory interactions, ensuring appropriate genome function. Recent technological innovations have provided exciting new insights into genome architecture. In particular, the development of chromosome conformation capture, commonly referred as '3C technology', has enabled the study of chromosome organization in a genome-wide manner. Information acquired by 3C technologies has advanced the understanding of chromosome folding to unprecedented levels and allows the identification of DNA loops connecting *cis* -regulatory elements to promoters that can range up to 100 kb in size. I will focus in a further exciting development: the ability to use sequence-specific capture approaches to enrich for regions of interest within 3C or Hi-C interaction libraries, a step that overcomes some of the resolution limitations of interaction libraries owing to their high complexity. Capture Hi-C can be been used in distinct cellular and physiological contexts to interrogate the interactome of promoters and thereby assign regulatory elements such as enhancers, silencers and boundary elements to their target promoters. These studies are beginning to reveal the general principles of how chromosome folding and DNA loops impact on gene regulation and genome function. Importantly, the comparison of the 3D chromatin organization between two states enables the identification of key differences in their regulatory networks.

Clinical Science
WORKSHOP 2: SCREENING AND MANAGEMENT IN NON-CERVICAL DISEASE

DIAGNOSING AND MANAGEMENT OF HPV-ASSOCIATED VULVAR DISEASE

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Low-risk (LR) and high-risk (HR) HPV are found in benign, precancerous and cancerous lesions of the vulva. **Genital warts (GW)** LR-HPV HPV 6/11 are found in 95% of HPV+ GW. GW are mostly asymptomatic. Itchiness, bleeding and color change can be reported. Asymmetrical papillomatosis is seen. Internal inspections should be warranted. For new lesions, no test is recommended unless atypical features are observed. Many different home/in-clinic treatments of external GW can be done. It is impossible to recommend one treatment over others because of a lack of uniformity for treatment success criteria. HR HPV can be found in mostly in flat warts or in GW in conjunction with LR HPV. Giant condylomata acuminata of the vulva or Buschke-Lowenstein tumor is rare but can progress to cancer mainly in immunocompromised hosts. **Low-grade disease of the vulva (LGSIL/LSIL or VIN 1)** LSIL is associated with LR and/or HR-HPV. Some time it is very difficult to differentiate from GW. Treatments are frequently the same as for GW. **High-grade disease of the vulva (HGSIL/HSIL or VIN 2-3)** HSIL is mostly associated with HR-HPV. Confirmation by biopsy is warranted to exclude cancer. External and internal evaluation of the anogenital tracts is recommended. Treatments are mostly by immune stimulation and/or ablative surgery. **Prophylactic vaccine** 4v or 9v vaccine is recommended for the prevention of recurrence at the same or another site for unvaccinated patients. Prophylactic vaccines have no therapeutic value. **Cancer of the vulva** HPV+ cancers of the vulva are mainly caused by HR-HPV. LR-HPV can be detected in such cancers but are rarely the cause. Evaluation of the whole anogenital tract is warranted in such cases. **Conclusion** HPV causes different types of vulvar lesions. Biopsy is recommended in cases of persistent GW, LSIL, HSIL, and cancers. HPV prophylactic vaccines are already having an impact on GW incidence.

Clinical Science
WORKSHOP 3: COMMUNICATION SKILLS

SEXUAL AND NON-SEXUAL TRANSMISSION DYNAMICS OF HPV

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Questions about HPV transmission often arise when people are learning about HPV. Learning objectives for this presentation are to gain knowledge that may help to address patients' common questions about sexual acts that pose risk for transmission and ways to prevent transmission. Main messages include: the need to destigmatize, as most sexually active people will have an HPV infection at some point in their lives; that HPV is most easily transmitted via vaginal or anal intercourse; that there is no practical method to find out when one first acquired HPV (or from whom); that condoms offer some protection, albeit incomplete; and that HPV vaccination can be considered well into adulthood.

Public Health
WORKSHOP 1: HPV VACCINE

AN OVERVIEW OF VACCINATION STATUS GLOBALLY

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The promise and power of HPV vaccines to radically alter the epidemiology of HPV-related infections and disease is now eminently apparent. Numerous studies have empirically documented the significant decline in HPV prevalence, genital warts, and cervical precancers in countries with markedly successful vaccination programs. As of the end of 2019, 103 WHO member states and 21 independent territories have added HPV vaccine to their vaccination schedule, primarily targeting a single age or single grade cohort of young adolescent girls. In the early years of introduction, many high-income countries conducted catch-up campaigns up to age 18 years to accelerate impact and also provide HPV vaccine to adolescent boys. While early adoption of HPV vaccine progressed in countries that could afford the high price, poorer countries are now rapidly scaling-up HPV vaccines through support from Gavi, the Vaccine Alliance with 12 low- and lower-middle income countries introducing in 2018 and 2019. This session will give an overview of HPV vaccine introductions globally, focusing on the program structures, factors for success, common challenges, and reported estimates of coverage from a variety of countries. The potential for new scientific developments to improve current programs or catalyze other countries to introduce HPV vaccines will also be presented.

Plenary Session
LIVE - IPVC PLENARY SESSION 3

DNA METHYLATION AND WOMEN'S CANCERS

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While prevention of most female specific cancers (ovarian, breast, endometrial) has not progressed substantially in recent years, significant progress has been made with cervical cancer due to accessibility of the cell of origin (cervical smear) and availability of a test for the causal agent (human papilloma virus); together these enable identification of high risk individuals and interventions to prevent infection or halt progression to invasive cancer. Our consortium has developed an exciting opportunity to utilise clinically abundant cervical cells in tandem with a multi-omics enabled (genome, epigenome, metagenome) analysis pipeline to understand an individual's risk of developing a female specific (gynaecological and breast) cancer and to direct a personalised screening and prevention strategy. Cervical cells –currently collected within cervical cancer screening – provide an ideal window into other female specific cancers because they are (i) an excellent non-invasive source of high quality DNA, (ii) provide a readout for environmental exposure, (iii) are part of the Müllerian tract and (iv) are hormone sensitive, recording (via the epigenome) various hormonal conditions over a lifetime that trigger cancer development. Within the FORECEE (Female cancer prediction using cervical omics to individualise screening and prevention) and the BRCA-ERC programmes, we have tested the above hypotheses. Our work has been funded by H2020 FORECEE (634570), ERC (742432) and The Eve Appeal (https://eveappeal.org.uk/).

Plenary Session
IPVC PLENARY SESSION 4

RESOURCE-APPROPRIATE IMMUNOTHERAPEUTIC APPROACHES TO THE ELIMINATION OF CERVICAL CANCER

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Cervical cancer is the leading cause of cancer death among women in sub-Saharan Africa (SSA). The global elimination of cervical cancer is theoretically feasible, as the tools to prevent cervical cancer exist. However, significant limitations to the current technologies prevent widespread effective use of these tools. For primary prevention of cervical cancer, a highly effective vaccine is available. In SSA less than 2% of females between the ages of 10-20 have completed the vaccine series. Furthermore, many SSA countries utilize the bivalent HPV vaccine national vaccination programs, potentially limiting vaccine effectiveness. Adjuvants are immune-stimulating molecules that have been shown to improve the breadth, durability and magnitude of immune responses for many modern vaccines. Data will be shown on the efficacy of novel toll-like receptor agonist adjuvants in enhancing immune responses to HPV vaccination. Secondary prevention of cervical cancer in SSA currently focuses on resource-appropriate approaches to identifying and ablating high-grade cervical dysplasia. The efficacy of these approaches in low-resource settings is reduced by limited availability, persistence or recurrence after therapy, and sequelae from the procedures. We have developed a self-amplifying / self-adjuvanted RNA replicon that delivers HPV E6 and E7 oncoproteins to the cytoplasm via a nanostructured lipid carrier. This novel platform induces potent mucosal cytotoxic CD8 T-cell responses, in addition to robust neutralizing antibodies. Technology to manufacture both the vaccine adjuvant and the immunotherapeutic vaccine have already been transferred to South Africa and can be affordably scaled. Phase 1 studies to evaluate the efficacy of this platform that will be enrolling in the near future. Finally, both the use of intratumoral adjuvants and therapeutic RNA vaccines could play an adjunctive or palliative role in the treatment of cervical cancer in low-resource settings. Strategies to deploy these technologies for this indication will be reviewed.

Dedicated Symposium
HEAD AND NECK WORKSHOP

HPV-ASSOCIATED HEAD AND NECK CANCER AND IMMUNOTHERAPY

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Human papillomavirus (HPV) is the causative agent in a growing proportion of incident cases of head and neck squamous cell carcinoma (HNSCC). HPV infected cells express immunogenic, foreign viral antigens. However, in a subset of patients, the virus is able to evade the host immune system resulting in persistent viral infection and subsequent malignant transformation. Two phase III clinical trials have demonstrated clinical benefit of anti-PD-1 blockade in HNSCC patients; yet, HPV status has not been found to be a biomarker of response to immunotherapy. We review key mechanisms of immune evasion utilized by HPV as well as discuss novel strategies that are actively being explored to enhance HPV-specific anti-tumor host immune responses in head and neck cancer patients.

Dedicated Symposium
HEAD AND NECK WORKSHOP

UPDATE ON THE ROLE OF TORS IN HPV+ HEAD AND NECK CANCER PATIENTS

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Importance: Current objectives for treating low-stage HPV-associated oropharyngeal cancer(OPSCC) is maximal efficacy with minimal toxicity. Patients presenting with p16-positive squamous cell cancer(SCCa) in level II node(s) in the neck may have cancer of unknown primary(CUP). In these circumstances, radiation is often delivered to the presumptive primary sites, causing possible increased mucosal toxitiy. **Objective:** To determine if the addition of diagnostic lingual tonsillectomy would decrease mucosal irradiation in p16-positive CUP. **Methods:** We established an institutional standard for patients presenting with p16-positive SCCa lymph nodes where no primary was identified after the following diagnostic work-up: physical exam, endoscopy, contrast-enhanced CT, PET/CT, evaluation under anesthesia, elective tonsillectomy, and directed biopsies of the tongue base. If primary site remained indeterminate, diagnostic lingual tonsillectomy ± ipsilateral neck dissection was performed. From October 2016 to August 2019, 25 patients with p16-positive level 2a nodal disease underwent TORS lingual tonsillectomy and ipsilateral neck dissection level Ib-IV for OPSCC CUP at a tertiary-care academic comprehensive cancer center. Adjuvant radiation to primary site was omitted if margins were >2 mm or if primary was unidentified. Adjuvant chemotherapy was incorporated for extranodal extension(ENE). **Results:** Twenty-five consecutive patients with pathologic stage T0-T1, N1-N2 (8th Ed. AJCC, HPV-associated) OPSCC, with an average age of 61.5 years were treated. All patients presented as carcinoma of unknown primary. Tumor location was identified in 17/25 (68%) within the tongue base. Thirteen of 17(84%) identified tumors were entirely excised during TORS diagnostic lingual tonsillectomy. Twenty-four patients received adjuvant radiation therapy, of which 18 spared intentional RT to the oropharynx (18/24 = 75%). Mean follow-up time is 16 months (3-36). No patient has experienced local, regional, or distant recurrence. **Conclusions: Addition of lingual tonsillectomy for p16-positive CUP site resulted in sparing intentional oropharyngeal mucosal irradiation to 75% of patients with unknown primary** without compromising local control. Long-term follow-up is needed. The significant benefit may be in establishing a clinical protocol sparing RT to the primary for CUP.

Dedicated Symposium
HEAD AND NECK WORKSHOP

EUROPEAN RRP REGISTRY PROJECT

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Recurrent respiratory papillomatosis is a rare disease: sharing patients' data is mandatory for studying large cohorts and therefore obtain reliable epidemiological and clinical information. A French national registry of RPP cases is under construction and expected to be online before the summer. Besides clinical aspect, financial, ethic and legal aspects are indeed about to be settled. Structure and running of the database will be detailed. First, only pediatric patients will be included and adults secondarily. The fully functional database will then be proposed to the European Rare Disease head and neck network in order to be extended to all willing and applicant countries.

Dedicated Symposium
GLOBAL SUPPLY, DEMAND, AND PRICING FOR HPV VACCINES AND HPV TESTING

HPV VACCINE. GLOBAL MARKET DYNAMICS

T. Cernuschi
World Health Organization WHO, Vaccine Pricing, Supply, Procurement, Geneva, Switzerland

Dr. Cernuschi will present in a session on HPV Vaccine Market Dynamics covering aspects related to current global vaccine demand (through UNICEF, the PAHO Revolving fund and self-procurement as well as both public and private markets) and its potential evolution under different scenarios. The presentation will also cover current knowledge on the HPV supply landscape (current and pipeline vaccines) and supply/demand balance and affordability issues.

BASIC SCIENCE ORAL SESSION ABSTRACTS

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

FURIN PROMOTES HPV CAPSID "DECORATION" WITH HEPARAN SULFATE (HS) PROTEOGLYCANS PRIOR TO VIRION UPTAKE AND HS-DEPENDENT INFECTION

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Introduction: Previous studies concluded that oncogenic HPVs can infect cells via an HSPG independent route after L2 is cleaved by furin. HPV pseudovirions (PsVs) exposed to furin in cell lysates or in "furin-conditioned medium" (FCM) from CHOΔfurin cells overexpressing furin were able to infect HSPG-deficient cells. Yet, furin inhibition does not prevent HPV entry into keratinocytes. As furin activates matrix metalloproteinases, which trigger HSPG shedding, we hypothesized that FCM provides soluble HS/HSPG molecules to HPV virions to promote infectious uptake.
Methods: FCM from CHOΔfurin cells was investigated for effects on HPV PsVs and raft tissue-derived virions. "Furin pre-cleaved mutant" (FPC-L2) PsVs were engineered to contain L2 proteins lacking the first 12 N-terminal amino acids. HS antagonists, heparinase III and protamine sulfate, were used to assess the role of HS in infection. Confocal microscopy was used to localize HPV capsids, HS molecules and endosomal markers.
Results: Treating HPV PsVs and tissue-derived virions with FCM leads to robust infection of HSPG-deficient cells, consistent with previous reports. FCM contains ≈4-fold more HS compared to normal cells. FCM-mediated infection correlates with increased HPV binding to cells. Both cell/ECM binding and infectivity are reversed when cells or FCM-treated HPV particles are incubated with HS antagonists. This suggests that FCM provides soluble HS to virions and HPV infection remains HS-dependent. Preliminary data indicate that HS/HSPG molecules remain with HPV virions during endocytosis, implying they may be required for infectious uptake. Curiously, FPC-L2 PsVs are unable to bind cells/ECM and noninfectious; however, binding and infection are rescued upon FCM treatment. This suggests that FCM supports virus infection by providing soluble HS, regardless of L2 cleavage.
Conclusions: Our data are inconsistent with the idea that furin promotes HSPG-independent infection. We propose a new model wherein furin promotes HS/HSPG decoration of HPV virions, which is essential for HPV infectious uptake.

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

HPV16 GENETIC VARIANTS AFFECT E7 PROTEIN LEVELS AND TRANSCRIPTION FACTOR BINDING TO A NOVEL ELEMENT IN THE UPSTREAM REGULATORY REGION

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Introduction: Introduction: HPV16 causes most cervical cancer worldwide. We previously identified protective amino acid-altering viral variants in the E7 gene and polymorphisms in the Upstream Regulatory Region (URR) in HPV16+, cancer-free women.
Methods: Methods: Mutant E7 proteins were expressed in HeLa and 293-T cell lines, electrophoretic mobility shift assay (EMSA) were used to detect protein binding, specific antibodies to detect proteins bound to DNA, and Western blots to determine protein expression levels.
Results: Results: Mutant E7 proteins D14E, N29H, E33K, E80K, D81N, and P92L all show lower levels of steady-state protein in the nucleus of HeLa and 293-T cells, and lower activity in scratch and colony-formation assays. Using HPV16 genome sequence data, we determined that the 7359T and 7387C nucleotide variants were nearly always on the same protective viral haplotype and were predicted to bind RUNX family, OCT-1, and CEBP/A transcription factors. An oligonucleotide probe containing these two sites showed that multiple protein complexes differentially bind to this region in the cervical (CaSki, C33A, HeLa) and non-cervical cell lines (293T, MCF7). A probe with both mutant sites showed reduced protein complex binding. Competition with specific antibodies showed that RUNX3 is part of this protein complex in HeLa and C33A, and RUNX2 in CaSki cells; Western blot analyses confirmed differential protein expression of RUNX2 and RUNX3 in these cell lines. We also documented competition by OCT-1 and CEBP-specific antibodies.
Conclusions: Conclusions: Most protective mutations of the E7 protein are expressed at low levels potentially attenuating activity. The function of the 5' region of the URR has not been clearly defined, although some data supports the binding of this region to the nuclear matrix. We demonstrate active protein binding to this region that is associated with specific nucleotide variants and reduced cervical cancer risk. The mechanism of action of this region on oncogene expression or replication is under investigation.

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

ECOLOGICAL OPPORTUNITY DRIVES RADIATION AND DIVERSIFICATION OF PAPILLOMAVIRUSES

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Introduction: Papillomaviruses (PVs) are part and parcel of the skin microbiota in all mammals. PVs have a wide host range, infecting mammals, birds, turtles and snakes, and ancestral PVs already infected the ancestral bony vertebrates. The recent discovery of PVs in different fish species allows for a more complete reconstruction of the evolutionary history of the viral family. In this study we combine fossil record estimates and molecular dating to analyse evolutionary events that occurred during PV evolution, as well as to estimate speciation and evolutionary rates.
Methods: We have used four different data sets to explore and correct for potential biases that particular taxa combinations may introduce in phylogenetic inference.
Results: When considering the evolution of speciation rates, we show that these are not constant through time, suggesting the occurrence of distinct evolutionary events such as adaptive radiations. We identified four periods along the evolutionary timeline of PVs: (i) a slow increase of PV lineages, parallel to the basal diversification of amniotes; (ii) an initial radiation PVs infecting fish, birds, turtles and ancestral mammals; (iii) a secondary radiation of PVs, parallel to the radiation of placental mammals; and (iv) a final virus-host co-divergence, parallel to PV diversification within their hosts. We show strikingly different trends in evolutionary rates by PV genus, revealing clade-specific events during the evolution of a highly diverse primate PV lineage: the clinically relevant AlphaPVs. Calibrating with younger nodes tended to render higher substitution rates compared to older nodes,This behavior reflects changes in the available host niches and show and a power-law rate decay model performs well to correct for this phenomenon within PVs.
Conclusions: Our results provide new insights into the evolutionary history of PVs, where ecological opportunity seems to be the main driving force for the different radiation and key-innovation events observed, such as the emergence of oncogenicity.

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

HPV-INDUCED CHEMOKINE DYSREGULATION CREATES THE IMMUNOSUPPRESSIVE TUMOR MICROENVIRONMENT AND PROMOTES HPV-ASSOCIATED CANCER PROGRESSION

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Introduction: By analyzing the transcriptomes of cervical (CxCa) and head/neck cancer (HNC) patient tissues, we previously revealed that expression of CXCL14, constitutively expressed in basal epithelial cells, is downregulated. In contrast, the expression of proinflammatory chemokines CXCL1, CXCL2, and CXCL8, which bind to the common receptor CXCR2, are significantly upregulated throughout cancer progression.
Methods: To determine the roles of these chemokines in HPV-driven cancer development, CXCL14 expression was restored by lentiviral ORF transduction, and CXCL1 and CXCL2 genes were deleted using a CRISPR-Cas9 knockout system in HPV-positive murine HNC cells. Using these stably engineered HNC cells, we investigated tumor growth, immune cell infiltration, and metastasis in immunocompetent syngeneic mice. We also analyzed correlations between chemokine expression and patient survival rates using the data obtained from The Cancer Genome Atlas.
Results: Restored expression of CXCL14 in HPV-positive HNC cells leads to tumor-free survival in the majority of mice implanted with the engineered HNC cells. Mechanistically, CXCL14 expression increases MHC-I antigen presentation on the cancer cell surface by facilitating MHC-I trafficking through the Golgi and suppresses tumor growth through antigen-specific $CD8^+$ T cell activity. In contrast, expression of CXCL1, CXCL2, and CXCL8 is significantly upregulated in both HPV-positive and -negative HNCs. While high CXCL14 expression is linked to longer patient survival, high CXCL1, CXCL2, and CXCL8 expression correlates to poor patient survival. Interestingly, the CRISPR knockout of CXCL1 and CXCL2 delays in vivo tumor growth, decreases myeloid-derived suppressor cell (MDSC) infiltration in the tumor, and reduces lung metastasis.
Conclusions: These results suggest that the dysregulation of chemokine expression in HPV-infected cells plays an important role in regulating tumor growth, antitumor immune responses, and metastasis of HPV-driven cancer. Our findings provide promising strategies to develop novel immunotherapies for HPV-positive cancer patients which can likely be extended to other non-viral cancers with immunosuppressive phenotypes.

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

ADAPTATIVE HOMEOSTASIS OF SQUAMOCOLUMNAR EPITHELIAL JUNCTION NICHE: THE HOT SPOTS OF INFECTION AND CANCER

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Introduction: The transition zones (TZ) between squamous and columnar epithelium constitutes critical zones of enhanced disposition to infections and carcinogenesis, which often preceded by metaplasia, where one epithelial type replaces the neighboring one. However, it remains unknown how the cellular heterogeneity and spatial organization of the stratified and columnar epithelial niches are maintained, how they merge at the TZ and maintain the boundary between the two epithelia, and how the TZ niche is altered during metaplasia.
Methods: To identify the cellular subsets of the cervix and decipher regulatory relationships between individual cells in the context of their niche, we used single-cell RNA-sequencing. Further, we employed in vivo lineage tracing, tissue mimetic epithelial 3D organoid models, single-molecule RNA in situ hybridization and a vitamin A deficient mouse model of squamous metaplasia to provide mechanistic insights into homeostasis of TZ, alterations involved in squamous metaplasia development and what cells give rise to cervical ADC and SCC.
Results: Here we show that in the cervix, WNT signaling stimulated by the underlying stroma drives the columnar lineage while imposing quiescence of squamous lineage-specific stem cells that exist in the same milieu. During squamous metaplasia development, the endocervical stroma undergoes extensive remodeling, in particular, a subpopulation of stromal cells showing upregulation of WNT inhibitor Dkk2. Further, Notch signaling is required for squamous cell stratification. Moreover, transcriptome analysis implied that ADC and SCC originate from two distinct lineages rather than a common precursor.
Conclusions: Our study provides a major conceptual advance in the understanding of the mechanisms that maintain cervical epithelial junctions and during metaplasia in our body. It suggests that homeostasis at the TZ results from divergent signals from the stromal compartment that drive the differential proliferation of the respective cell lineages at the squamocolumnar junction.

ORAL SESSION 1: VIRUS AND HOST INTERACTIONS

A SUBGROUP OF HPV-POSITIVE OROPHARYNGEAL SQUAMOUS CELL CARCINOMA WITH UNFAVORABLE PROGNOSIS SHOWS OXIDATIVE STRESS SIGNATURES AND A MESENCHYMAL-LIKE PHENOTYPE

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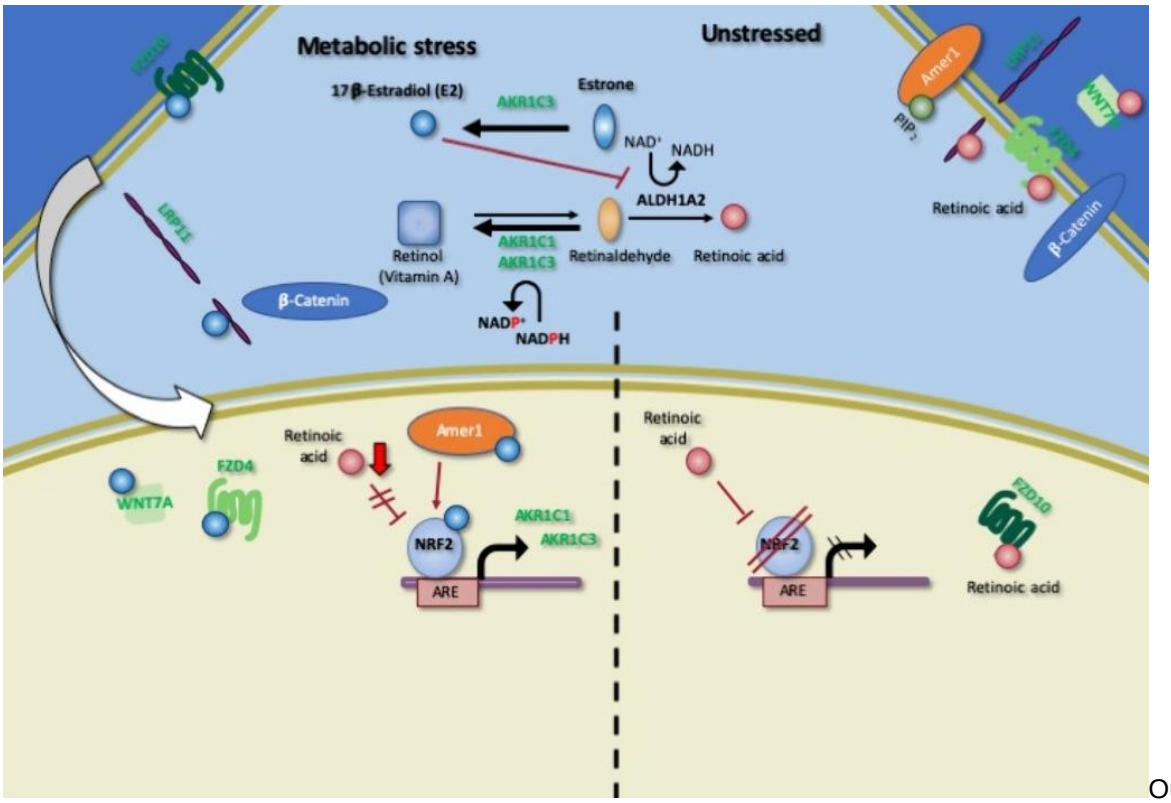
Introduction: Oropharyngeal squamous cell carcinoma (OPSCC) patients frequently develop metastases and inoperable local and regional recurrences. We previously have reported that a subgroup of OPSCC with integrated HPV 16 and upregulated HPV16-E6*I expression shows oxidative stress signatures such as upregulated NRF2, AKR1C1 and AKR1C3 expression going along with unfavourable prognosis (Huebbers et al., Int J Cancer 2019). The aim of this study was to further investigate these oxidative stress signatures and their possible relation to a mesenchymal like (EMT) phenotype.
Methods: 51 OPSCC samples including 28 HPV-positive cases with both FFPE and fresh frozen tissue were available. Based on bioinformatic analysis of previously published data, expression of key components of the EMT, PI3K, retinoic acid and oxidative stress pathways including NRF2, AKR1C1/3, ALDH1A2, Frizzled 10, β-Catenin, E-Cadherin, Vimentin, Amer1, PI3K, miR-9 and miR-16-2 were assessed by immunohistochemistry, RT-qPCR and/or in situ hybridization. The impact of viral oncogenes on EMT-relevant components was addressed in primary human keratinocytes overexpressing HPV16-E6 and/or -E7.
Results: Expression analysis revealed that subgroups of OPSCC predominantly related to HPV-infection and overexpression of HPV16-E6*I exhibit an increased oxidative stress response (NRF2, AKR1C1/3) as well as activating EMT pathway signatures (Frizzled 10, Amer1, β-Catenin, E-Cadherin, Vimentin, miR-9 and miR-16-2), frequent metastasis, aberrant PI3K expression and downregulated retinoic acid synthesis (ALDH1A2). Moreover, in vitro experiments showed that HPV16-E6 expression results in induction of miR-9, miR-16-2 and β-Catenin expression.
Conclusions:



Our data show, that OPSCC presenting with upregulation of HPV16-E6*I and oxidative stress response signatures have a higher tendency to undergo EMT. Frizzled 10 expression known to be regulated by retinoic acid was highly correlated to ALDH1A2 expression and inversely correlated to EMT, PI3K and oxidative stress. Our data implicate that subgroups of tumours might benefit from adjuvant treatment with retinoids, which should be further studied.

ORAL SESSION 2: TRANSFORMATION AND CARCINOGENESIS

HIGH-RISK HPV E7 PROTEINS DEGRADE PTPN14 TO LIMIT KERATINOCYTE DIFFERENTIATION

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Introduction: Human papillomaviruses uncouple proliferation from differentiation in order to enable virus replication in epithelial cells, and the HPV E7 oncoprotein is a major driver of this uncoupling. HPV E7 promote proliferation by binding to and inactivating retinoblastoma family proteins and other cell cycle inhibitors. Until recently, mechanisms by which high-risk HPV E7 inhibit differentiation had not been defined. We discovered that high-risk HPV E7 recruit the ubiquitin ligase UBR4 to target the candidate tumor suppressor and non-receptor protein tyrosine phosphatase PTPN14 for proteasome-mediated degradation. Our recent studies have aimed to define the consequences of PTPN14 degradation in human epithelial cells. Specific goals are to determine whether PTPN14 inactivation is required for HPV replication and whether PTPN14 inactivation contributes to HPV-mediated oncogenic transformation.
Methods: We have used HPV16 E7 variants that cannot degrade PTPN14 and CRISPR/Cas9 gene editing in primary human keratinocytes to assess the consequences of PTPN14 inactivation in keratinocyte growth and differentiation assays.
Results: We find that the loss of PTPN14 impairs keratinocyte differentiation and conversely, that PTPN14 overexpression promotes differentiation. Gene expression changes that result from PTPN14 loss are recapitulated in HPV16 E6/E7-expressing keratinocytes and in HPV-positive, but not HPV-negative, head and neck squamous cell carcinomas.
Conclusions: Our data support the idea that PTPN14 degradation contributes to the effects of high-risk HPV E7 on the growth and immortalization of primary human keratinocytes. We are testing the model that high-risk HPV E7 must both inactivate RB1 and degrade PTPN14 to enable oncogenic transformation. Additionally, we propose that high-risk HPV E7-mediated PTPN14 degradation could provide the first mechanism by which E7 actively inhibit differentiation. We are investigating the details of such a mechanism and anticipate that the ability to restore epithelial differentiation could have therapeutic potential in HPV-positive cancer and other cancers.

ORAL SESSION 2: TRANSFORMATION AND CARCINOGENESIS

COMPARATIVE RNA SEQUENCING REVEALS THAT HPV16 E6 ABROGATES THE EFFECT OF E6*I ON ROS METABOLISM

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Introduction: High-risk Human Papillomavirus infections are responsible for anogenital and oropharyngeal cancers. Alternative splicing is an important mechanism controlling HPV16 gene expression. Modulation in the splice pattern leads to polycistronic HPV16 early transcripts encoding a full length E6 oncoprotein or truncated E6 proteins, named E6*. Spliced E6*I transcripts are the most abundant mRNAs produced in HPV-related cancers and cellular models. To date, the biological function of the E6*I isoform remains controversial.
Methods: In this study, we created stable models expressing either both HPV16 E6 and E6*I isoforms, or only E6*I in U-2 OS cells. Then, we used whole transcriptome sequencing to identify deregulated cellular genes and pathways. Finally, we validated our results in several W12 clones, a cellular model naturally infected by HPV16.
Results: RNA-seq analyses revealed that genes implicated is ROS metabolism, among others, were deregulated in E6*I cells. Concomitantly, E6*I-expressing cells displayed high levels of ROS. However, co-expression of E6 with E6*I didn't deregulated these genes and had no effect on ROS production. In W12 clones expressing different E6/E6*I levels, we showed that newly identified targets CCL2, RAC2 and PDGFB are increased by E6*I but decreased by E6 expression.
Conclusions: Taken together, these data support the idea that E6*I acts independently of E6 to increase ROS production. The new target genes identified cold represent a new pathway by which ectopic E6*I is able to deregulate ROS metabolism. Finally we demonstrate that E6 has the ability to abrogate the effects of E6*I. This asks the question of how E6*I can be considered separately of E6 in the natural history of HPV16 infection.

ORAL SESSION 2: TRANSFORMATION AND CARCINOGENESIS

CIRCULAR RNA CIRCCDKN2B-AS1 PROMOTES AEROBIC GLYCOLYSIS VIA HK2 MRNA AND IMP3 PROTEIN IN HPV16 POSITIVE CERVICAL CANCER CELLS

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Introduction: The effectiveness of recurrent chenmotherapeutic drugs is limited for advanced cervical cancer. The aim of the study is to identify the function and mechanism of circRNA (circCDKN2B-AS1) in reprogramming glycolysis metabolism in cervical cancer cells and to find novel therapeutic target for advanced cervical cancer.
Methods: HPV16 positive cervical cancer samples, HPV negative normal cervical tissue samples were used to verify the expression level of circCDKN2B-AS1. RNase R digestion experiment, rt-PCR using divergent primers, and RNA FISH were used to identify the closed loop of circCDKN2B-AS1.Specific siRNAs targeting the junction of circ CDKN2B-AS1 and constructs were used to regulate circCDKN2B-AS1 expression. CCK8 assay, transwell assay, and FCM were undertaken to detect cellular proliferation, migration, and apoptosis, respectively. Seahorse XF 96 analyzer was used to measure the glycolysis metabolism level. RNA-Seq, RNA pulldown, RIP, and western blot were used to screen and identify the target gene of circCDKN2B-AS1.
Results: The expression level of CircCDKN2B-AS1 is higher in HPV16 positive cervical cancer samples than HPV negative normal cervical tissue samples.CircCDKN2B-AS1 konckdown repressed cellular proliferation, migration and invasion, and aerobic glycolysis metabolism level, contrarily CircCDKN2B-AS1 overexpression promoted above phenotypes, in siha and caski cells.CircCDKN2B-AS1 regulated HK2 mRNA expression and interacted with IMP3 protein. Blocking the interaction between circCDKN2B-AS1 and IMP3 protein by transfection of inhibitory peptide inhibited glycoPER in cervical cancer cells.
Conclusions: CircCDKN2B-AS1 stabilizes HK2 mRNA and sponges IMP3 protein, consequently promotes aerobic glycolysis in cervical cancer cells. Our findings may provide a new approach for cervical cancer therapeutics.

ORAL SESSION 2: TRANSFORMATION AND CARCINOGENESIS

CERVICAL CANCER-INSTRUCTED STROMAL FIBROBLASTS ENHANCE IL-23 EXPRESSION IN DENDRITIC CELLS VIA AN IL-6/C/EBPB/IL-1B PATHWAY TO SUPPORT TH17 EXPANSION

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Introduction: Persistent infection with high-risk human papillomavirus (HPV) is a prerequisite for the development of cervical cancer. Progression to malignancy is linked to an inflammatory microenvironment. We previously demonstrated that cervical cancer cells contribute to T-helper-17 (Th17) cell recruitment, a cell type with pro-tumorigenic properties. In this study we analysed the molecular mechanisms how cervical cancer cells promote the expression of the Th17-promoting cytokine Interleukin(IL)-23 in the cervical cancer micromilieu.
Methods: Cytokine expression was analyzed by qRT-PCR, ELISA and *in situ* analysis, signaling pathway analysis with siRNA knock-down and neutralization experiments, Th17 expansion with flow cytometry, CD83/IL23$^+$ and Th17 cells *in situ* with immunofluorescence.
Results: Our study demonstrated that CD83$^+$ mature dendritic cells (mDC) co-expressed IL-23 in the stroma of cervical squamous cell carcinomas *in situ*. This correlated with stromal Th17 cells, with advanced tumor stages, with lymph node metastasis and with recurrent cervical cancers. We showed that co-cultures of cervical cancer-instructed mDC and cervical fibroblasts led to potent Th17 expansion *in vitro* but failed to induce Th1 differentiation. Correspondingly, cervical cancer-instructed cervical fibroblasts increased IL-23 production in cervical cancer-instructed mDC which mediated subsequent Th17 expansion. In contrast, production of the Th1-polarizing cytokine IL-12 in cervical cancer-instructed mDC was strongly reduced. This differential IL-23 and IL-12 regulation was the consequence of an increased expression of the IL-23 subunits IL-23p19 and IL-12p40 but decreased expression of the IL-12 specific subunit IL-12p35 in cervical cancer-instructed mDC. As the underlying mechanism we identified cervical cancer cell-derived IL-6 as the key regulatory factor. IL-6 directly suppressed IL-12p35 in mDC. However, it indirectly induced IL-23 expression in fibroblasts-primed mDC via CAAT/enhancer-binding protein b (C/EBPβ)-dependent IL-1β induction.
Conclusions: We unraveled a novel molecular mechanism how cervical cancer cells shape their local micromilieu to support Th17 expansion, which may contribute to cervical cancer progression and severity of the disease.

ORAL SESSION 3: ADAPTATIVE AND NON-ADAPTATIVE IMMUNOLOGY

IMPAIRED MONOCYTE AND LANGERHANS CELL INNATE IMMUNITY IN PATIENTS WITH RECURRENT RESPIRATORY PAPILLOMATOSIS (RRP)

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Introduction: The micromilieu within premalignant respiratory papillomas supports persistent HPV6/11 infection and disease recurrence in recurrent respiratory papillomatosis (RRP). These patients show polarized (T_H2-/Treg) adaptive immunity in papillomas and blood, enriched immature Langerhans cell (iLC) numbers, and overexpressed COX2/PGE_2 in the upper airway. To better understand the adaptive and innate dysregulation in RRP, we studied blood-derived monocytes, iLCs, and tissue-derived iLCs from RRP patients and controls.
Methods: Monocyte subpopulations were isolated, differentiated into iLCs, activated, and then assessed by flow cytometry. Monocytes were induced to differentiate into iLCs with/without added PGE_2, and then activated by IL-36γ, PGE_2, PGE_2+IL36γ, or LPS. iLC CD83 expression was identified by flow cytometry. Monocyte-derived iLCs, papilloma, foreskin, and abdomen skin iLCs, were also analyzed by qPCR for select chemokine/cytokine mRNA expression after isolation, 24 hrs later in culture, and again after poly(I:C) or TNFα stimulation.
Results: The three monocyte sub-populations differed between patients and controls, and patients' monocytes generated fewer iLCs. Classical monocytes generated most, but not all iLCs. PGE_2 levels were higher in RRP plasma, and added PGE_2 reduced control, but not patients' monocyte-iLC differentiation. PGE_2 had no effect on iLC maturation identified by CD83 expression. Papilloma-derived iLCs expressed low CCL-1, and high CCL-20 mRNA and were unresponsive to poly(I:C) or TNFα. Tissue-specific cytokine/chemokine responses between iLCS from papillomas, foreskin and abdominal skin differed. Only papilloma iLCs expressed IL-36γ after isolation, and they up-regulated CCL1 mRNA 24 hrs later without further stimulation.
Conclusions: Monocyte/iLC innate immunity is impaired in RRP, in part due to increased PGE_2 exposure. The immunosuppressive papilloma micromilieu likely alters iLC responses that skew, HPV6/11-specific T_H2/Treg adaptive immunity in RRP.

ORAL SESSION 3: ADAPTATIVE AND NON-ADAPTATIVE IMMUNOLOGY

CHANGES OF L1 CAPSID PROTEIN EXPRESSION OF MASTOMYS NATALENSIS PAPILLOMAVIRUS AS A NOVEL MECHANISM TO CIRCUMVENT ADAPTIVE IMMUNITY

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Introduction: PVs have developed multiple immune evasion strategies. Many mucosal high-risk and cutaneous HPVs and animal PVs encode alternative start codons in the L1 gene potentially rendering longer isoforms of the major capsid protein. Although only the shortest L1 isoform can self-assemble to VLPs, function, synthesis and immunological responses against the longer isoforms *in vivo* are unknown so far. The immunocompetent African rodent *Mastomys coucha* is naturally and persistently infected with the *Mastomys natalensis* papillomavirus (MnPV) and represents a promising model system to investigate a natural PV infection thereby mimicking many aspects of cutaneous HPV infections in humans.
Methods: The seroreactivity of 60 MnPV-infected *Mastomys* against viral capsid proteins and their isoforms was monitored over 20 months using various ELISAs and Pseudovirion-based neutralization assays (>680 sera). L1 isoforms were produced in different expression systems to study their expression and efficacy of self-assembly to VLPs and PsVs. L1 isoforms were further visualized in skin lesions via IHC.
Results: Like many HPVs, also MnPV encodes several L1 start codons. In contrast to the $L1_{SHORT}$ isoform, $L1_{LONG}$ is unable to form VLPs or PsVs. Nevertheless, although $L1_{LONG}$ antibodies do not neutralize viral particles, seroconversion against $L1_{LONG}$ considerably precedes seroresponses against $L1_{SHORT}$. The immunogenic epitope in $L1_{LONG}$ may further prevent L1 self-assembly. Consistently, despite the observation that capsids assemble only in terminally differentiated skin layers, $L1_{LONG}$ was detected already in basal layers of skin lesions.
Conclusions: The synthesis of $L1_{LONG}$ prior to capsid formation distracts the host immune system to generate neutralizing antibodies in early infection. This novel mechanism contributes to the immune escape strategy of PVs that allows viral accumulation to establish clinical symptoms in terms of epithelial lesions.

ORAL SESSION 3: ADAPTATIVE AND NON-ADAPTATIVE IMMUNOLOGY

INSIGHTS INTO THE ROLE OF INNATE IMMUNITY IN CERVICOVAGINAL PAPILLOMAVIRUS INFECTION FROM STUDIES USING GENE DEFICIENT MICE

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Introduction: To gain insight into innate immunity to papillomaviruses we infected genetically deficient mice with MmuPV1, targeting adaptor molecules of innate immune signaling pathways, including MyD88 for Toll-like and IL-1 receptors, STING for cytosolic DNA sensors, MAVS for RIG-I receptors, RIP2 for NOD receptors, and STAT1 for interferon receptors, as well as mice deficient in inflammasome protein, caspase-1, and chemokine receptors (CCR6, CXCR2 and CXCR3).
Methods: Mice were challenged vaginally with MmuPV1 wart extract and sacrificed 3-5 months post challenge. The lower genital tract was dissected, and tissue solubilized in Trizol for RNA analysis or formalin for RNAScope and histopathology by H&E and Ki67 staining. TaqMan RT-PCR was performed for 757/3139 spliced transcripts, using a forward primer downstream of late promoter P533. RNAscope was performed with probes in E6 and E7 ORFs, which are mostly upstream of promoter P533.
Results: Viral spliced 757/3139 transcripts (mean copies/ug RNA) were detected in STING-/- (80; P=0.06), caspase-1 (29; P=0.014), STAT1-/- (median, 7547; P=0.024), Myd88-/- (1347; P=0.035), and CCR6-/- (117; P=0.019), while MAVS-/, RIP2-/-, CXCR2-/-, and CXCR3-/- mice were negative. RNAScope was positive in STAT1-/-, MyD88-/- and CCR6-/- mice, but not STING-/- and caspase-1-/- mice. The strongest signal was observed in CCR6-/- mice. H&E stains showed normal epithelium in STING-/- and caspase-1-/- mice, and mild morphological abnormalities in STAT-/- and Myd88-/- mice, characterized by atypical parabasal cells with increased nuclear/cytoplasm ratio. CCR6-/- mice showed morphological changes resembling HSIL/CIN2, characterized by atypical parabasal cells in middle and upper thirds of epithelium, increased nuclear/cytoplasm ratio, dyskeratosis, and occasional mitoses. Ki67 proliferation index was increased in CCR6-/- mice.
Conclusions: We propose a working model of innate immune control of cervicovaginal papillomavirus infection in which type I interferons restrict late viral gene expression principally through a MyD88-dependent pathway, and CCR6+ immune cells mediate clearance of dysplastic epithelial cells expressing E6 and E7.

ORAL SESSION 3: ADAPTATIVE AND NON-ADAPTATIVE IMMUNOLOGY

CLONING AND CHARACTERIZATION OF HPV SPECIFIC HUMAN MONOCLONAL ANTIBODIES FOLLOWING VACCINATION

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Introduction: Comparison of HPV neutralizing antibody gene sequences elicited by HPV vaccination with predicted germline sequences enables us to better understand the mechanisms leading to potent neutralization.
Methods: Antibody secreting and memory B cells were isolated from vaccinated individuals, one week or one month after HPV vaccine injections. Paired heavy and light chain antibody variable regions were sequenced, and a subset were cloned into expression vectors adding appropriate IgG1, kappa or lambda constant regions. Paired heavy and light chains were co-expressed and resulting antibodies purified and tested in binding and neutralization assays. Antibody variable region gene sequences were compared with predicted germline sequences (IGMT). Site-directed mutagenesis was performed prior to testing in functional assays to assess the importance of somatic mutations.
Results: Seventy one antibody sequences were analyzed. Seven antibodies were identified that used the same heavy (V_H 1-70) and light chain variable genes (V_L λ2-40). A region of the light chain that often contacts antigen (CDRL2) showed evidence for convergent evolution. The importance of this region for antigen recognition was confirmed for five of seven antibodies, by substituting amino acids encoded by the predicted germline sequence into this region and performing binding and neutralization assays. However, for two antibodies, similar substitutions had little effect. A set of nine antibodies used the same diversity gene segment resulting in a conserved amino acid sequence (WSGYR) in a region of the heavy chain variable region known to contact antigen (CDRH3). These antibodies required the WGSYR sequence for neutralization as substitution with alanines ablated activity.
Conclusions: Antibodies having the WGSYR sequence in their CDRH3 and antibodies with paired V_H 1-70 with V_Lλ2-40 variable genes were found in the four subjects studied so far suggesting that these types of antibodies are commonly induced by HPV vaccination and by implication that these antibodies recognize public epitopes.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

LONG-TERM HPV-SPECIFIC IMMUNE RESPONSE AFTER ONE VERSUS TWO AND THREE DOSES OF BIVALENT HPV VACCINATION IN DUTCH GIRLS

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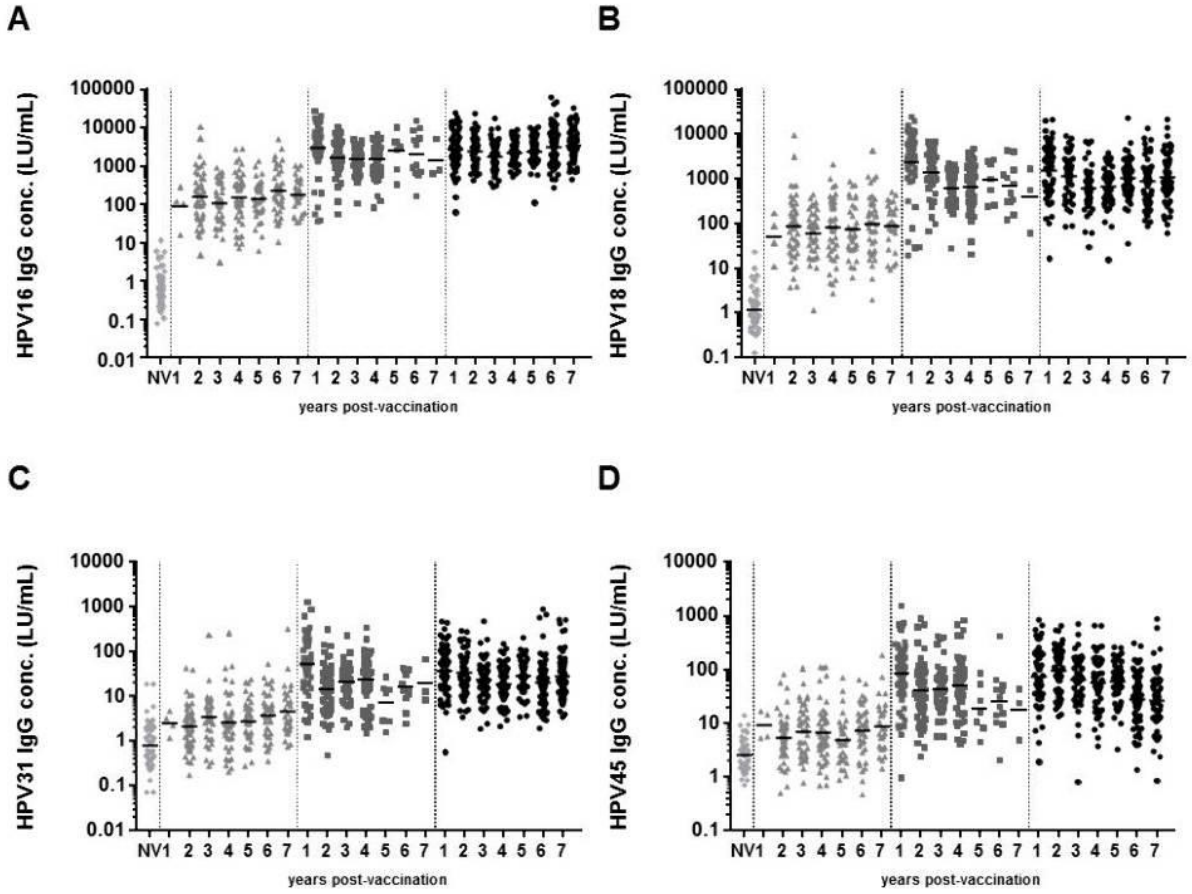
Introduction: In view of further reduction of HPV vaccination schedules, gaining more insight into humoral and cellular immune responses after a single HPV vaccine is of great interest. Therefore, these responses were evaluated after different doses of the 2vHPV-vaccine in girls.
Methods: Blood was cross-sectional collected and PBMCs isolated from girls vaccinated at 12-16 years of age according to a one-, two- or three-dose schedule. HPV-type-specific IgG and IgA-antibody levels, IgG-isotypes and avidity indexes were measured by a virus-like-particle-based multiplex-immuno-assay for two vaccine and five non-vaccine HPV types. HPV-type-specific memory B-cell numbers- and T-cell cytokine responses were determined in a subpopulation by ELISPOT and Legendplex.

Results: HPV-type-specific antibody concentrations were significantly lower in one- than in two- and three-dose vaccinated girls but remained stable over seven years. The lower antibody response coincided with reduced HPV-type-specific B- and T-cell responses. There were no differences in both the IgG subtypes and the avidity of the HPV16-specific antibodies between the groups.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HPV16 IgG conc. (LU/mL)
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years post-vaccination
B
HPV18 IgG conc. (LU/mL)
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NV1 2 3 4 5 6 7 1 2 3 4 5 6 7 1 2 3 4 5 6 7
years post-vaccination
C
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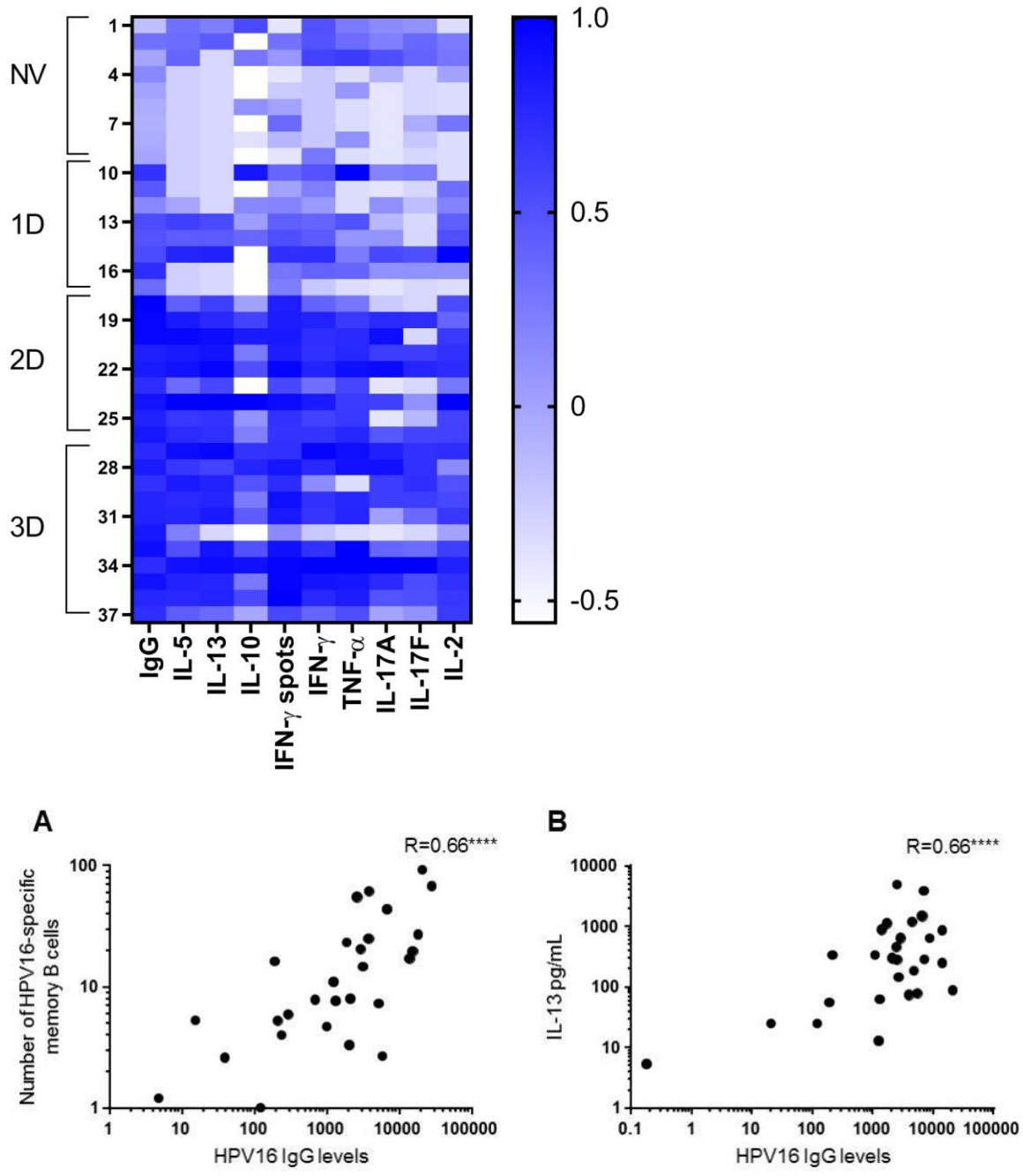

Conclusions: One-dose of the 2vHPV vaccine is immunogenic, but results in less B- and T-cell memory and considerable lower antibody responses when compared with more doses. The lower antibody response coincided with a significantly lower production of T cell produced cytokines. Therefore, at least part of the one-dose vaccinated girls might be at higher risk for waning immunity to HPV on the long-term.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

TOWARDS A CGMP-GRADE CHIMERIC PAPILLOMAVIRUS VACCINE: PROTECTION OVER ONE YEAR OF HPV16 RG-1 VLP COMPARED TO A GARDASIL-9 VACCINATION IN PRE-CLINICAL PAPILLOMAVIRUS ANIMAL MODELS

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Introduction: We previously initiated the process development of a monovalent HPV16-RG1VLP vaccine for first-in-human studies. HPV16-RG1VLP is a chimeric papillomavirus VLP that displays 360 copies of the highly conserved epitope RG1 (amino acid 17-36 of minor capsid protein HPV16 L2) in the D-E loop of HPV16L1 VLP. Here we describe a 1 year challenge study in rabbits comparing the durability of cross-protection induced by engineering-run HPV16-RG1VLPs formulated with alhydrogel® compared against Gardasil-9® in an established papillomavirus disease model.
Methods: Using cottontail rabbit papillomavirus quasivirions derived from eight high-risk oncogenic HPVs, *in vivo* protection was assessed by cutaneous challenge at 2 weeks, 6 months and 12 months post vaccination following three intra-muscular administrations of 80 ug of HPV16-RG1, or human doses of Gardasil-9®. Immunogenicity via ELISA to HPV16 L1-VLP and 9 different HPV RG1-homologues were also evaluated at 2 weeks, 6 months, 10 months and 12 months post-vaccination.
Results: Following 2 weeks post-vaccination with monovalent HPV16-RG1VLP, robust levels of cross-neutralizing RG1-specific antibodies and equivalent protection as per Gardasil-9 were demonstrated against papillomavirus infections. At 6 months and 12 months post-vaccination. Vaccination with HPV16-RG1VLP was still able to confer equivalent protection as Gardasil-9, and in some instances provided superior protection against non-vaccine HPV types. ELISA data demonstrated titers to both HPV16 L1 VLP and RG-1 peptide declined at 6months and stabilized by 1 year. Finally, HPV16 L1 VLP titers elicited by HPV16-RG1VLP and Gardasil-9 were comparable throughout the year demonstrating incorporation of RG1 epitope into HPV16 L1-VLP backbone does not compromise L1-specific immunity.
Conclusions: HPV16-RG1VLP holds promise as a single antigen preventative vaccine that could potentially provide broader protection against all high-risk HPV types (i.e. including several not covered by the currently licensed HPV vaccines) while being simpler to produce than highly multivalent L1 VLP formulations needed to achieve similarly broad immunity

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

SENSITIVITY OF HUMAN PAPILLOMAVIRUS (HPV) LINEAGE AND SUBLINEAGE VARIANT PSEUDOVIRUSES TO NEUTRALIZATION BY NONAVALENT VACCINE ANTIBODIES

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Introduction: Natural variants of Human papillomavirus (HPV) have been classified into lineages and sublineages based upon whole genome sequence. Variants exhibit both geographical bias in their distribution and differential disease risk and efforts are underway to understand the evolution of HPV variants from their prehistoric origins. The impact of HPV variant diversity on protein function and the potential consequences for vaccine immunity are unclear.
Methods: We investigated the susceptibility of 37 representative pseudovirus variants of HPV16, HPV18, HPV31, HPV33, HPV45, HPV52 and HPV58 to neutralization by nonavalent vaccine (Gardasil®9) sera. Serum samples from vaccinees were collected *ca*. 6 months after the last dose of vaccine and the median age of the donors at sample collection was 14. Donors and where applicable legal guardians provided consent.
Results: Many (18/30; 60%) variants demonstrated significant differences in neutralization sensitivity from their consensus A/A1 variant, but most of these were of a low magnitude. HPV52 D and HPV58 C variants exhibited >4-fold reduced sensitivities compared to their consensus A/A1 variant and should be considered distinct serotypes with respect to nonavalent vaccine-induced immunity.
Conclusions: For most genotypes, these data suggest that nonavalent vaccine antibodies recognize global variants similarly. However, these empirical observations provide support for HPV52 lineage D and HPV58 lineage C capsid proteins being antigenically distinct within their respective genotypes, but the possible implications for global health remain to be seen.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

TARGETING DNA DAMAGE RESPONSE AS A STRATEGY TO TREAT HPV INFECTIONS

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Introduction: Introduction: Mucosotropic human papillomaviruses (HPVs) cause prevalent anogenital infections, some of which can progress to cancers. It is imperative to identify new and efficacious drug candidates, as there are no effective therapeutics to treat infections. We have recapitulated a robust productive program of HPV-18 in organotypic raft cultures of primary human keratinocytes. To facilitate viral DNA amplification in suprabasal, differentiated cells, the viral E7 oncoprotein reactivates S phase and activates ATM and ATR, regulators of DNA damage response (DDR) pathways. Their activation results in a prolonged G2 phase during which viral DNA amplifies.
Methods: Using our productive HPV-18 raft culture model system we tested efficacy of a number of small molecule inhibitors of DDR regulators. Effects of inhibitors were assessed by in-situ and biochemical assays. Effective inhibitor was also tested in raft cultures of cervical cancer cell lines.
Results: We showed that the inhibitors impaired S-phase reentry and progression as well as HPV DNA amplification. Among the four ATR/Chk1 and ATM/Chk2 inhibitors, the Chk1 inhibitor MK8776 was the most effective, achieving a reduction of 90-99% in viral DNA amplification. Prolonged exposure to Chk1 inhibitor also induced apoptosis, preferentially in HPV infected cells. The sensitivity to the inhibitor was imparted by the E7 protein alone. We found that the Chk1 inhibitor caused extensive cell death of these cancer cell lines grown as monolayer or raft cultures. Moreover, it sensitized the cancer cells to a low concentration of cisplatin, a standard chemotherapeutic agent to treat cervical cancer.
Conclusions: Based on these observations, Chk1 inhibitor MK8776 emerges as one of the potential effective agents to treat the spectrum of HPV infections. The synthetic lethality of MK8776 and cisplatin in cervical cancer cell lines in 3D cultures merits careful testing in preclinical and clinical studies.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

ATOMIC LAYER DEPOSITION TECHNOLOGY FOR PREPARING SINGLE-SHOT, THERMOSTABLE HUMAN PAPILLOMAVIRUS VACCINES.

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Introduction: Cold-chain requirements affect worldwide distribution of currently licensed HPV vaccines. In addition, these HPV vaccines require multiple doses that impose logistical and financial burdens, as well as compliance barriers. To address such limitations, we applied two new technologies in order to develop thermostable, single-shot, prime-boost microparticle HPV vaccines based on HPV16 L1 capsomere antigens.
Methods: The first technology thermostabilized microparticle formulations by spray-drying HPV16 L1 capsomeres from solutions of disaccharides and high-T_g polysaccharides. The resulting glassy-state powders retained full immunogenicity in mice, even after 3 months storage at 70°C. The second technology used atomic layer deposition (ALD) in repeating, self–limiting reactions to deposit nanometer-thick layers of alumina (Al_2O_3) on the surfaces of the vaccine microparticles. Each cycle of the sequential reactions added a 2.3 Å-thick, conformal, single-molecule layer of alumina on the microparticle surface. With multiple cycles, layers that were 100-500 nm thick could be applied. These nanoscopic layers serve multiple functions, such as protecting the embedded antigens from water vapor damage during vaccine storage and serving as adjuvants similar to alum. Importantly, when the alumina-coated antigen particles are injected *in vivo*, the coating delays the release of internal antigen, providing a booster dose of antigen with a time-to-release that depends on the thickness of the applied ALD coating.
Results: Thermostabilized powders containing HPV16 L1 capsomeres were prepared by spray drying, coated with up to 1000 molecular layers of alumina, and injected into mice. Antibody responses were measured weekly by ELISA for 30 weeks, and neutralizing antibodies measured by pseudovirus neutralization assays at selected time-points. Single doses of the ALD–coated vaccine formulations produced neutralizing responses and antibody titers that were equivalent or superior to conventional prime-boost doses of liquid formulations.
Conclusions: Single-dose, thermostable antigen preparations may overcome current limitations in HPV vaccine delivery.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

THERAPEUTICAL REMOVAL OF PRE-EXISTING PAPILLOMAVIRUS INFECTION IN RHESUS MACAQUES BY VACCINATION WITH ADENOVIRAL VECTOR

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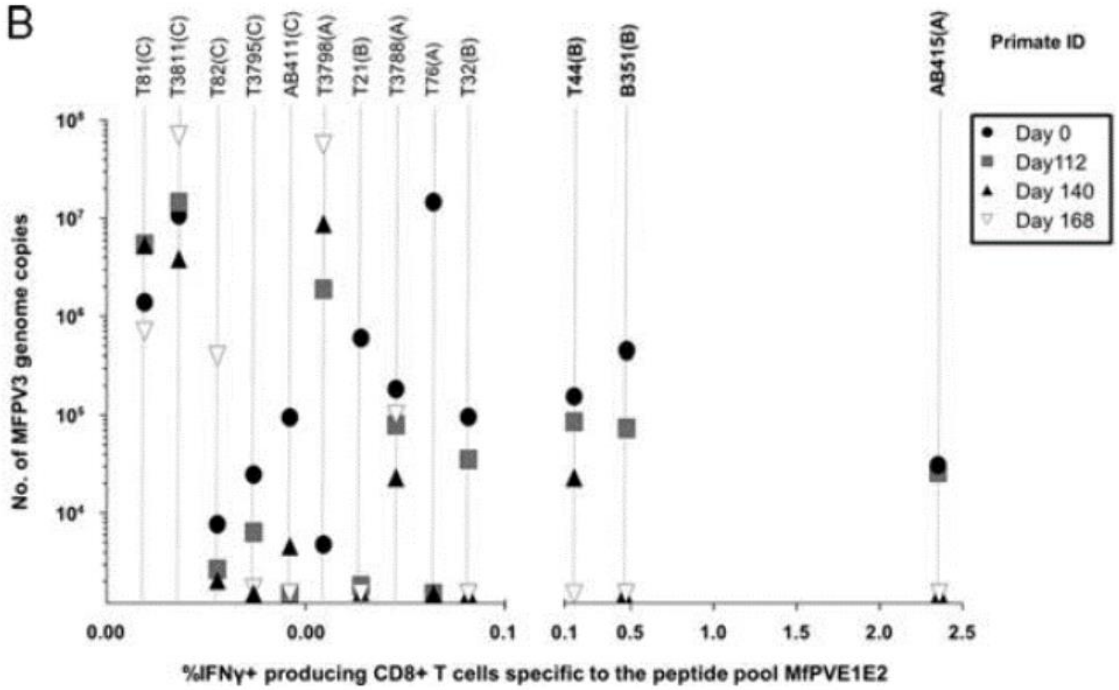
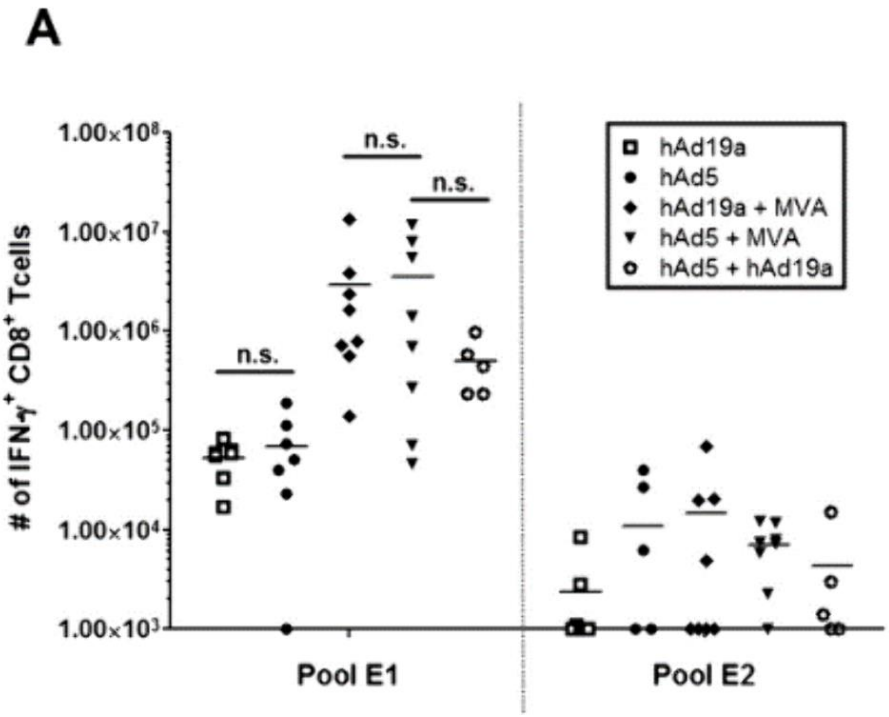
[1]University of Copenhagen, Centre For Medical Parasitology, Isim, København, Denmark, [2]University of Copenhagen, Isim, København, Denmark, [3]NIH, Nia, Bethesda, United States of America

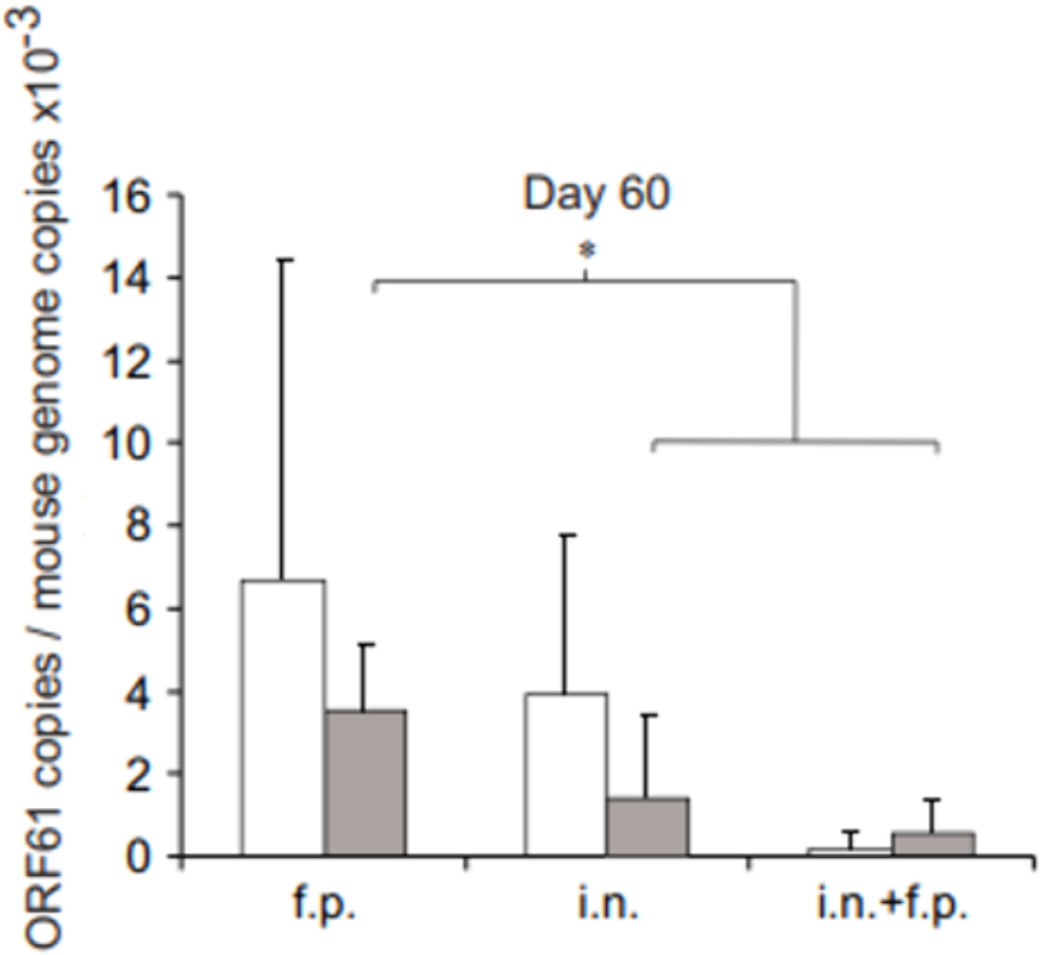
Introduction: The currently licensed vaccines against HPV have shown to protect against new infection, but there is no known therapy for already existing infection. We have previously shown that an adenoviral vectored vaccine encoding ancestral sequences of E1 and E2 in sequence with the CD8 T cell adjuvant Invariant Chain can induce a CD8 T cell mediated immune response in rhesus macaque monkeys infected with macaca fascicularis papilloma virus. We saw that all animals who responded to the vaccine achieved clearance of the pre-existing papilloma virus infection. However, 3 out of 7 non-vaccinated control animals also achieved spontaneous clearance of the viral infection. We have therefore set out to investigate if this therapeutic tendency was truly due to a protective vaccine-induced immune response.



Methods: A new vaccine focusing solely on one MfPV3, the most prevalent type in female Indonesian Cynomolgus macaques, has been designed. The antigen has been encoded into a replication deficient Adenovirus vector serotype 19 in sequence with Invariant Chain. This vector has the advantage of much lower incidence of pre-existing immunity in the human population compared to Ad5. For a viral infection residing primarily in cells in mucosal tissue, it is important to consider the route of immunization. Therefore, the optimal route of immunization is assessed in a murine prophylactic model.
Results: The adenoviral vector serotype 19 has shown to induce CD8 responses on par with Ad5.



It has been shown in mice that the combination of systemic and mucosal immunization was superior to each route individually, at inducing a long term protective CD8 response against a mucosal challenge with a murine virus causing chronic infections.



Conclusions: We believe, that these preliminary results, in combination with our access to a novel Adenoviral vector and to the MfPV3 primate model, will make it possible to assess an optimized therapeutical vaccine against papillomavirus infection.

ORAL SESSION 4: VACCINES AND NEW TREATMENT APPROACHES

FIRST EXAMPLE OF CURING CANCER USING CRISPR/CAS GENE EDITING. TREATING HPV CANCERS IN PRECLINICAL ANIMAL MODELS.

N. Mcmillan, L. Jubair, A. Idris, Y. Tayyar
Griffith University, Menzies Health Institute Queensland, Southport, Australia

Introduction: We have examined the use of CRISPR/Cas to develop a new treatment for HPV-driven cancers. CRISPR/Cas allows for the targeting and subsequent deletion or interruption of a specific gene in the host. This has resulted in a whole new field of gene editing therapies. Building on our previous RNAi work we have applied our in vivo expertise and delivery nanoparticle systems to examine the use of C/Cas i*n vivo* both in preclinical animal models looking at both direct tumour killing and subsequent immune responses.
Methods: Using novel nanoparticles (Wu et al J Control Release, 2011. **155**(3): p. 418-26.) we introduced DNA expressing Cas and guide RNAs to target the HPV E7 oncogene. Cell viability was monitored by colony formation and viability assays. Mice were injected with tumour cells and once formed, treated with IV injections of nanoparticles containing CRISPR/Cas. Tumour formation was monitored. In synergic models, immune cell death was monitored
Results: We show that CRISPR/Cas9 delivered systemically in vivo using PEGylated liposomes results in tumor elimination and complete survival in treated animals. We compared treatment and editing-efficiency of two Cas9 variants, WT Cas9 and the highly specific FokI- dCas9, and showed that the latter was not effective. We also explored high-fidelity repair (HDR) but found repair was inefficient, occurring in 6-8% of cells, while NHEJ was highly efficient, occurred in ~80% of the cells. Finally, we explored the post gene-editing events in tumours and showed that cell death is induced by apoptosis but this did not induce immune cell death. Treatment caused no significant toxicity in the spleen or liver. Overall, our work demonstrates that in vivo CRISPR/Cas editing treatment of pre-existing tumours is able to eliminate HPV tumours in vivo.
Conclusions: Overall targeting of the E7 gene via CRISPR/Cas is highly effective in treating HPV-driven cancers.

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES

BETA- AND GAMMA-HPV INFECTIONS IN ASSOCIATION WITH INCIDENT CUTANEOUS SQUAMOUS CELL CARCINOMA: A PROPSECTIVE COHORT STUDY

D. Rollison[1,2], N. Fenske[3], B. Cherpelis[3], J. Messina[4], Y. Zhao[2], R. Amorrortu[2], M. Schell[5], V. Sondak[4], A. Giuliano[1,2], T. Waterboer[6], M. Pawlita[6], T. Gheit[7], M. Tommasino[7]
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Introduction: Cutaneous human papillomavirus (cuHPV) infections have been associated with squamous cell carcinomas (SCC) in previous epidemiological studies, often retrospective in nature and including limited numbers of infection biomarkers. We conducted a prospective cohort study, the VIRUSCAN Study, to examine SCC risk associated with baseline cuHPV infection measured using multiple biomarkers.
Methods: 1,179 skin cancer screening patients were enrolled in 2014-2017 and followed for SCC through 2018. CuHPV infection was measured by serology (17 beta, 7 gamma types) at baseline and by viral DNA detection (46 beta, 52 gamma types) in skin swabs (SSW) and eyebrow hairs (EBH) at baseline and in incident tumors. Associations between baseline cuHPV infection and incident SCC were modeled using Cox proportional hazards, adjusted for age, sex and recent ultraviolet radiation exposure.
Results: Prevalence of any beta-HPV/gamma-HPV infection in SSW and EBH was 96%/77% and 66%/31%, respectively; no associations were observed with incident SCC overall. SSW positivity for any of 19 beta species-1 HPV types was associated with SCC (HR=1.89, 95% CI=1.14-3.16); this association strengthened when comparing infection in both SSW and EBH to neither site (HR=2.15, 95% CI=1.20-3.87). SCC was not associated with baseline seropositivity. Of 149 individuals who developed incident SCC, 25 (18%) had at least one beta-HPV-positive tumor. While type concordance between tumor and baseline samples was high among those who developed HPV-positive tumors (16 of 25), the absolute percentage of HPV-positive participants at baseline who developed HPV-positive SCC was low, ranging from 1% for HPV 23 and 28 to 11% for HPV 14.
Conclusions: Beta-HPV infection present in both SSW and EBH was significantly predictive of SCC risk, regardless of the subsequent tumor's HPV status. Therefore, SSW and EBH beta-HPV positivity may be useful biomarkers for identifying high risk individuals who could benefit from increased screening and/or novel SCC prevention strategies.

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES

DIVERGENCE OF HPV16 SUBLINEAGES REFLECTS LOCI UNDERGOING INTER-HOST POSITIVE SELECTION, POTENTIALLY IMMUNOLOGIC SELECTION

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Introduction: HPV16's unique carcinogenicity remains poorly understood. We and others have demonstrated histology-specific cervical cancer risk differences among HPV16 sublineages (e.g., A4, D2, D3). Here, we expanded this analysis to examine the evolution of HPV16 through an analysis of viral nucleotide diversity.
Methods: We used HPV16 whole-genome sequencing data from 3,215 women in the NCI-KPNC PaP cohort. To measure the strength of natural selection in the HPV16 genome, we calculated the ratio of non-synonymous to synonymous substitutions (d_N/d_S) for each gene as well as an unsupervised sliding window approach to identify regions exhibiting strong evidence of selection. $d_N/d_S < 1$ is indicative of purifying selection, $d_N/d_S > 1$, of positive (Darwinian) selection, and $d_N/d_S = 1$ of neutral evolution.
Results: Overall, as expected, the HPV16 genome displays evidence of purifying selection (d_N/d_S = 0.267; P<0.001). However, among sublineages, we discovered 26 regions with d_N/d_S values ranging from 1.28 – 33.52, indicative of extremely strong positive selection. A subset of these regions overlapped lineage-defining residues, so we analyzed individual sublineages separately. Remarkably, 13 of these 26 regions were discovered independently in the A1 sublineage alone, with d_N/d_S values up to 59.44. Nine of these 13 regions match known HPV CTL epitopes obtained from databases that include peptides presented by HLA.
Conclusions: We conclude that positive selection likely played a key role in the historical divergence of HPV16 sublineages, probably as a mechanism of immune evasion. Our data imply that positive selection is still targeting the same loci that historically define lineages and sublineages and that they overlap CTL epitopes. Though HPV16 sublineages differ greatly with respect to risk, carcinogenicity is likely an unfortunate consequence. Host immune genotype (e.g., HLA) may play a key role in disease outcome and should be included in future studies of HPV and cervical cancer.

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES

VIRAL GENOME VARIATION IN VULVAR HPV16- ASSOCIATED HIGH GRADE PRECANCER LESIONS AND INVASIVE CANCERS

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Introduction: Human Papillomavirus (HPV) is associated with a high percentage of Vulvar Intraneoplasia (VIN) and Squamous Cell Carcinomas (VSCCs). Although, HP16 is by far the most frequently detected genotype in VIN lesions there is a need of new molecular markers able to identify VIN with high risk of progression to VSCC and distinguish them from those with low risk. We have evaluated the HPV16 genome variation in 191 VIN and 106 VSCC to analyse the (sub)lineage and single-nucleotide variant (SNV) distribution and identify their association with the risk of invasive progression.
Methods: HPV16 genome sequences were determined by next generation sequencing (NGS) in 297 FFPE vulvar samples included in the Institut Català d' Oncologia (ICO) international collection. (sub)lineages were classified based on the maximum-likelihood tree topology. We evaluated associations of each SNV and the combined effects by viral gene region comparing VIN and VSCCs lesions.
Results: Results: The most common lineage identified was A followed by D, C and B. We identified significant differences associated with the geographical area studied ($p<0.001$), being D the most frequent in Latin America and Africa. Risk of VSCC was higher in women A4, C or D variants than in women with A1,2,3 variants. We also observed that women diagnosed with VSCC were older than women diagnosed with VIN (median 48.10 vs 60.21, $p<0.001$). We identified 21 SNVs significantly associated with invasive progression 15 of them with a FDR<0.05. The minor allele of all the identified SNVs were associated with an increased risk of VSCC and frequently identified in D and C variants
Conclusions: NGS analysis will determine if HPV16 genome variability is an important factor associated with the risk of progression of vulvar HPV associated lesions

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES

ATOMIC RESOLUTION CRYOEM STRUCTURE OF MOUSE PAPILLOMAVIRUS

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Introduction: Human papillomavirus (HPV) is a significant health burden and leading cause of virus-induced cancers. HPV is epitheliotropic and its replication is tightly associated with the terminal differentiation of basal cells into keratinocytes. The restricted tropism makes production and purification of high titer virus preparations for research problematic. Alternative HPV production methods have been developed within the HPV research community for molecular biology and structural studies. Virus-like particles (VLPs) can be comprised of only the major structural protein (L1) or of the major and minor capsid proteins (L1/L2) and are not infectious since they are devoid of a native viral genome. Structural studies of these VLPs have been limited in resolution due to the heterogeneity, fragility, and stability of the capsids. Mouse papillomavirus (MmuPV1) provides opportunities to study a native papillomavirus in the context of a common laboratory animal.
Methods: This study used cryoEM to solve the structure of MmuPV1 using a local symmetry refinement method to break the virus into smaller, symmetry related sub-volumes. The existing HPV16 crystal structure with substitutions to match the amino acid sequence of MmuPV1 was used to initiate the building of the structure.
Results: We achieved 3.4 Å resolution in the final map.
Conclusions: The resulting virus structure is a promising step forward in the study of papillomavirus and will provide a framework for continuing biochemical, genetic and biophysical research for papillomaviruses.

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES
HPV DISTRIBUTION IN DIFFERENT ANATOMICAL SITES

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[1]International Agency for Research on Cancer (IARC), Infections And Cancer Biology Group, Lyon, France, [2]International Agency for Research on Cancer, Epigenetics Group, Lyon, France, [3]San Gallicano Dermatologic Institute IRCCS, Sti/hiv Unit, Rome, Italy, [4]Moffitt Cancer Center, Department Of Cancer Epidemiology, Tampa, United States of America

Introduction: More than 200 different human papillomavirus (HPV) types have been listed by the International HPV Reference Center, and this number continues to expand. HPV types are organized into five major genera – alpha, beta, gamma, mu, and nu – and are classified as cutaneous or mucosal according to their tropisms. The genus gamma includes the majority of the known HPVs, followed by the genera alpha and beta. With the advent of new molecular tools, it became apparent that a large number of HPV types exist and are ubiquitously distributed in many anatomical sites. Specifically, independent studies revealed that beta and gamma HPV types are detected in mucosal and cutaneous epithelia, highlighting their possible dual tropism. However, the preferential site of infection for the majority of the HPV types is still not yet fully elucidated.
Methods: To gain new insights of the distribution of the different HPV types in many anatomical sites and their possible associations with human diseases, we have (i) established a Luminex®-based platform for detecting more than 120 HPV types from the alpha, beta, and gamma genera, and (ii) developed next-generation sequencing-based strategies.
Results: Our epidemiological data and independent studies showed that many of these cutaneous HPV types are present in the mucosal epithelium (e.g. anal canal, oral cavity, etc.), suggesting a dual tropism. Of the five beta species, beta-1 and beta-2 are abundantly present in the skin, whereas beta-3 appears to be more present in the mucosa of upper-respiratory tract and in anal mucosa. Findings on the distribution of large number of known and novel beta and gamma HPV types in broad spectrum of epithelia will be presented.
Conclusions: These findings warrant further studies to better understand the role of beta and gamma species in diseases of the mucosal epithelia.

ORAL SESSION 5: OTHER ANATOMICAL SITES AND DISEASES

TRANSLATIONAL STUDIES OF PEDIATRIC RESPIRATORY PAPILLOMATOSIS

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Introduction: Recurrent respiratory papillomatosis (RRP), characterized by papillomas of the aerodigestive tract, is usually caused by low risk types 6 and 11 of the human papilloma virus (HPV). Although this is the most common benign neoplasm of the larynx in children, disease risk and progression are poorly understood. The clinical course of RRP poses a severe burden including mortality. Despite the use of a variety of adjuvant therapies, no single agent has been effective at eliminating pediatric RRP. Most importantly, we cannot currently predict which patients will respond to any particular drug or treatment.
Methods: Clinical progress in the pediatric RRP field has been hindered by the absence of authentic model systems. We have partnered with a team of clinician/scientists who care for one of the largest cohort of children and young adults with RRP in the USA and have recruited 20 patients to date. Using fresh tumor and matched normal tissue, we have established a pipeline of internally controlled, patient-specific RRP keratinocytes and 3D organotypic epithelial rafts for studies of the differentiated environment.
Results: Exposure of RRP keratinocytes to the liquid-air interface resulted in the generation of stratified epithelium. Rafts from two donors, RRP1 and RRP5, harbored distinct morphologic and biologic features including hyperplasia, compared to their respective controls. To genomically profile one donor RRP5 with uniquely aggressive disease, we carried out whole genome sequencing of RRP5 cells. Preliminary computational analyses revealed HPV11 sequences, with viral integration into the WNT7A gene, and a structural variant within FANCB intronic sequences. Parallel, transcriptomic studies revealed a shared RRP-expression signature with significant ontologies in cellular adhesion and EMT. Relevant pathways are currently functionally interrogated.
Conclusions: Paired RRP/normal keratinocyte populations and rafts represent a personalized model for the application of “omics” technologies to identify RRP-specific molecular mechanisms, biomarkers and drug targets.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

CYCLOSPORIN A IMMUNOSUPPRESSION PROMOTES SKIN CARCINOGENESIS IN MUS MUSCULUS PAPILLOMAVIRUS 1 (MMUPV1) INFECTED MICE

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Introduction: Numerous (sero-)epidemiological studies implicated cutaneous human papillomavirus infection in the development of non-melanoma skin cancer (NMSC) in immunosuppressed organ transplant recipients (OTR). Herein, we established a MmuPV1-induced model for skin cancer in immunosuppressed mice.
Methods: Immunocompetent FVB/N mice, infected with MmuPV1 on tail and back skin, received cyclosporine A (CsA)-based immunosuppression with or without concomitant UVB-irradiation. Virus copy numbers, the presence of MmuPV1 E1^E4 and E6/E7 oncogene mRNA and L1/L2 capsid proteins in tumors were determined by real-time PCR, RNA-in-situ hybridization and immunohistochemistry. Tumor dignity and composition were evaluated by (immuno)histological analyses. UVB-induced and systemic immunological effects were assessed by immunohistochemical staining of skin tumors and draining lymph nodes, respectively. Tumor cells from a MmuPV1-induced squamous cell carcinoma (SCC) were administered to athymic nude mice.
Results: MmuPV1 skin infection caused outgrowth of premalignant and malignant SCCs after 25-30 weeks in 67%/100% (tail/back) of CsA-treated and in 89%/47% (tail/back) of CsA-treated/UVB-irradiated mice, whereas immunocompetent MmuPV1-infected mice did not develop malignancies. Elevated viral (onco)gene expression and transcriptional activity corroborated the causative viral involvement in tumorigenesis. Surprisingly, concomitant UVB-irradiation led to smaller tumor sizes on back skin in the immunosuppressed MmuPV1-infected animals. CsA immunosuppression increased Bak expression in the virus-induced tumors, regardless of UVB. In the MmuPV1-infected tumors p53-positive cells were more numerous after CsA-treatment and highest after CsA/UVB-treatment. In CsA-treated animals, irrespective of MmuPV1, draining lymph nodes were enlarged, but lacked proliferation in secondary follicles. *In vivo* passage of tumor cells resulted in outgrowth of malignant skin lesions, which showed epithelial-to-mesenchymal transition and vascularization, but lack of viral DNA.
Conclusions: MmuPV1 infection caused skin SCCs in CsA-immunosuppressed mice. This papillomavirus-induced skin cancer model may allow future investigations regarding viral involvement, pathogenesis and life cycle aiming at understanding and controlling the high incidence of NMSC in OTR.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

SEXUAL TRANSMISSION OF MURINE PAPILLOMAVIRUS (MMUPV1) IN MUS MUSCULUS

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Introduction: Human papillomavirus (HPV) is the most commonly sexually transmitted infection in the United States. The use of animal models to study papillomavirus infection and sexual transmission has historically been difficult due to their strict species-specific tropism. The recent discovery of a murine papillomavirus (MmuPV1) provides the opportunity to study papillomavirus infections in a tractable, *in vivo*laboratory model. MmuPV1 can infect and cause disease in the cutaneous epithelium, as well as the mucosal epithelia found in the oral cavity and anogenital tract. We recently established a murine model of MmuPV1 infection and neoplastic disease in the female reproductive tracts of immunocompetent FVB/N (wild-type) mice. We sought to adapt this model to test whether MmuPV1 is sexually transmissible in wild-type mice.
Methods: Female mice were experimentally infected with MmuPV1 and served as virus “donors”. Monogamous breeding pairs consisting of an infected female ‘donor’ and a male breeder were established for at least 3 weeks. The male breeder was removed and placed into a cage with an uninfected female ‘recipient’ mouse for at least 3 weeks. Recipient females were screened for MmuPV1 by cervicovaginal lavage and PCR for the MmuPV1 E2 gene at various time points after breeding.
Results: We found that 32% (n=7/22) of female recipient mice contracted MmuPV1 via sexual transmission. Of the MmuPV1-positive recipient females, 57% (n=4/7) established prolonged infections. We also detected MmuPV1 infection in the penile epithelium in 15% (n=4/22) of male breeders. Sexual transmission in male and female mice occurred in the absence of genetic or environmental manipulation. MmuPV1 infections were verified in tissues using *in situ* hybridization.
Conclusions: This study reveals that MmuPV1 is a sexually transmitted virus in immunocompetent mice, thus providing a platform for fundamental studies in papillomavirus natural infection, persistence, and sexual transmission.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

3D HUMAN CERVICAL ORGANOIDS TO MODEL COINFECTIONS: THE TRIPARTITE INTERFACE OF A HOST, HPV E6E7 AND CHLAMYDIA

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Introduction: The most prevalent ecto and endo-cervical transition zone pathologies are caused by HPV, however, co-infections with Chlamydia is emerging as an essential cofactor in driving HPV-induced carcinogenesis. Our previous studies have illuminated how Chlamydia disrupt cell-autonomous functions, affecting cellular and genomic integrity in ways that are pro carcinogenic. However, the impact of co-infections could be much more complex, considering the tripartite communication between the epithelial host, HPV and Chlamydia.
Methods: We developed a 2D and 3D cultures that supports the long-term expansion of primary human cervical cells from healthy donors. These HPV negative cervical cell models together with complementary approaches like global transcriptomics, repair assays and target inhibition, we investigate and validated the alterations induced by HPVE6E7, Chlamydia and co-infection on the host cell.
Results: We found that both HPVE6E7 and Chlamydia enhanced the host cell proliferation, however, the presence of HPVE6E7 fostered aberrant chlamydial-development. Our transcriptomic analysis revealed that Chlamydia and HPVE6E7 modulate host-signaling in profound ways that are either similarly up or down-regulated. However, certain genes are inversely-regulated by Chlamydia and HPVE6E7, including the genes that are predominantly associated with DNA damage response pathways (DDR). Interestingly, while HPVE6E7 induced up-regulation of mismatch repair (MMR) and base excision repair (BER), Chlamydia suppressed these HPVE6E7-induced DDR. Additionally, by using plasmid-based in vitro MMR and BER repair assays, we confirmed that Chlamydia infected cells have reduced ability to repair mismatches and oxidative base lesions irrespective of HPV status. Proteasomal-degradation and p53-MDM2 pathway were found to be the major mechanisms that delineate the inverse regulation of MMR and BER by HPVE6E7 and Chlamydia.
Conclusions: Together, we modeled the HPVE6E7 and Chlamydia co-infection using near-physiological 3D primary human culture system. We provide first comprehensive insights into the interplay of HPVE6E7 and Chlamydia coinfection on host signaling. Further gained deeper mechanistic insights into mutational processes fostered during coinfection scenario.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

DEVELOPMENT OF SPONTANEOUS HPV-16 E6/E7-EXPRESSING CERVICOVAGINAL PRECLINICAL MODEL THAT FOLLOWS CLINICAL TUMOR PROGRESSION VIA INTEGRATION OF HPV ONCOGENES

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Introduction: A suitable preclinical HPV tumor model should possess the following characteristics: (1) forms spontaneous, localized, HPV-16 E6/E7-expressing tumor, (2) displays carcinoma morphology, (3) possesses locally immunosuppressive tumor microenvironment, resembling that of HPV16(+) tumors in patients, (4) tumor formation follows clinical progression starting from precancerous to cancerous state, (5) tumor-bearing mice can respond appropriately to immunotherapeutic strategies and generate antitumor immunity, and (6) tumorigenesis can be easily monitored.
Methods: To this end, we recently developed a method to induce the spontaneous formation of HPV-16 E6/E7-expressing tumors in the cervicovaginal tracts of C57BL/6 mice by transiently depleting systemic T cells and submucosally injecting plasmids encoding HPV16 E6/E7, luciferase, constitutively active AKT, c-Myc, and Sleeping Beauty transposase into the cervicovaginal area of mice, followed by electroporation. Tumor formation was closely monitoried by bioluminescence imaging and gene expressions were characterized by immunohistochemical staining and RNA *in situ* hybridization.
Results: Formation of luciferase-expressing tumor in the cervicovaginal tract of injected mice occurred in 80-100% of animals by week 5 after electroporation (**Figure 1**). Remarkably, histologic progression from precancerous lesions (squamous intraepitheliual lesions) to invasive squamous cell carcinoma resembled cancer progression of HPV-associated malignancies in human patients (**Figure 2**). Furthermore, the expression of transfected oncogenes and HPV E6/E7 oncogenes was demonstrated in the tumor (**Figure 3**).

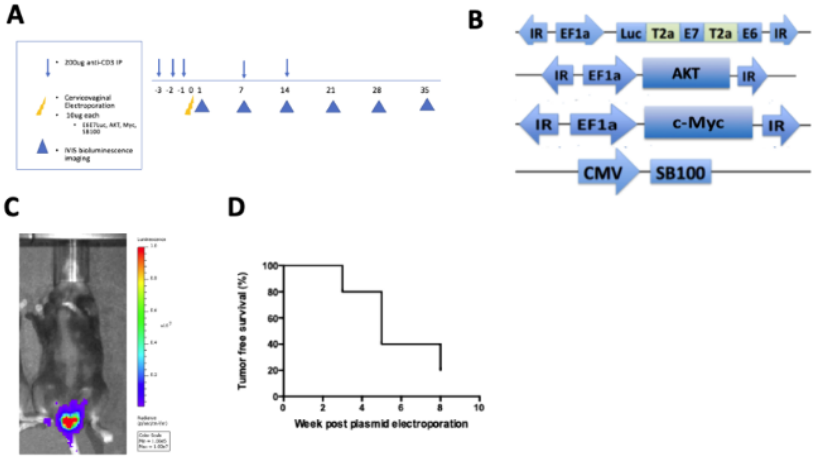

Figure 1. Generation of spontaneous HPV+ cervicovaginal carcinoma model in C57Bl/6 mice (A) Schematic of experimental design (B) Schematic of plasmids used to induce cervicovaginal tumors by oncogene transfection (C) Representative image of cervicovaginal tumor as measured by IVIS Spectrum imaging. Bioluminescence was recorded by IVIS Spectrum after intraperitoneal injection of luciferase solution (D) Survival shown by percentage. Mice were sacrificed when tumor diameter >15mm

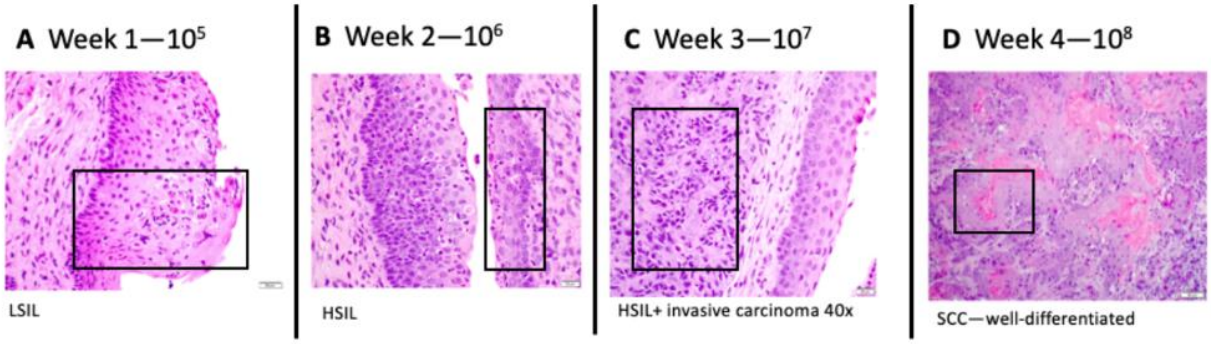

Figure 2. Progression of lesion from LSIL→HSIL→SCC in spontaneous HPV+ cervicovaginal carcinoma model. At each timepoint corresponding with the indicated luminescence value, 3 mice were sacrificed and their reproductive tract was harvested for sectioning (A) Representative images of vaginal tissue with ~10^5 luminescence signal at 1 week post-electroporation exhibiting low grade squamous intraepithelial lesion (LSIL)[see box]. (B) Representative images of vaginal tissue with ~10^6 luminescence signal at 2 weeks post-electroporation exhibiting high grade squamous intraepithelial lesion (HSIL). (C) Representative images of vaginal tissue with ~10^7 luminescence signal at 3 weeks post-electroporation exhibiting HSIL and invasive carcinoma [see box]. (D) Representative images of tumor tissue with ~10^8 luminescence signal at 4 weeks post-electroporation. Tumor presents as well-differentiated SCC with presence of keratin pearls [see box]

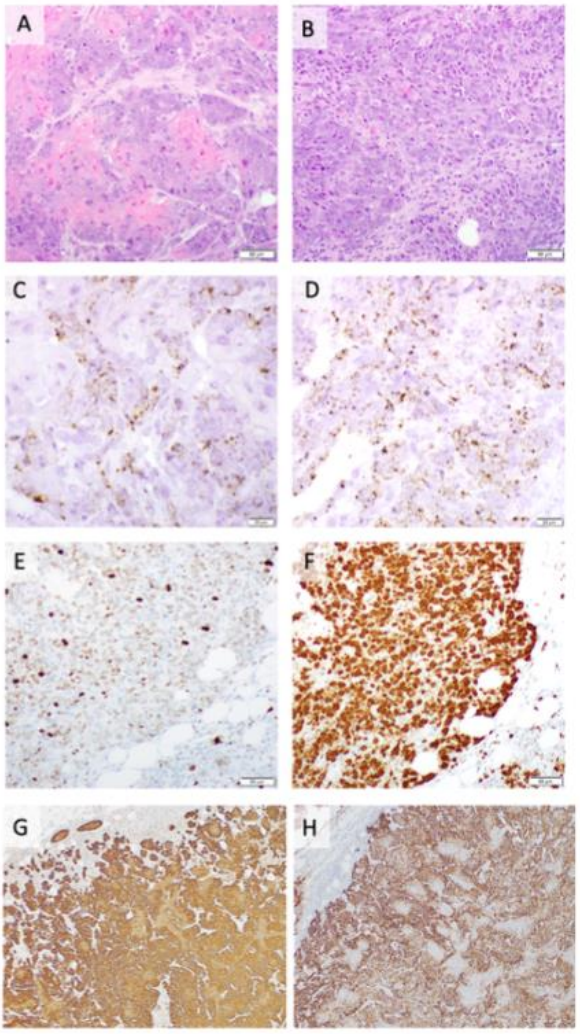

Figure 3. Characterization of spontaneous HPV+ SCC. (A) Representative H&E of well-differentiated HPV+ SCC (B)) Representative H&E of poorly-differentiated HPV+ SCC (C) RNAscope detecting HPV16E6 RNA in spontaneous HPV+ SCC in part A (D) RNAscope detecting HPV16E6 RNA in spontaneous HPV+ SCC in part B (E) Representative image of IHC detecting ki-67 proliferation marker (F) Representative image of IHC detecting c-myc (G) Representative image of IHC detecting CK14 epithelial cell marker (H) Representative image of IHC detecting AKT

Conclusions: This new preclinical tumor model has potential utility for the preclinical evaluation of treatments for precancerous lesions, and offers several advantages as preclinical model for HPV-associated malignancies for the evaluation of novel cancer treatments and immunotherapies compared to transplantable tumor models and transgenic mouse models such as the ability to extend to the creation of tumor model generated by different high risk types of HPV, the lack of central immune tolerance for HPV E6/E7 oncogenic proteins and the application to mice with different MHC class genetic background.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

EXPRESSION OF E8^E2 IS REQUIRED FOR WART FORMATION BY MOUSE PAPILLOMAVIRUS 1 IN VIVO

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Introduction: HPV E8^E2 knock-out (k.o.) genomes have revealed that E8^E2 is a potent inhibitor of viral genome replication and transcription in undifferentiated cells. Unexpectedly, HPV16 E8^E2k.o. genomes also showed increased amplification and expression of viral late E4 and L1 proteins upon differentiation suggesting that E8^E2 limits productive replication. We therefore analyzed E8^E2´s function in the context of Mus musculus PV1 (MMuPV1) to investigate its relevance in in vivo.
Methods: Transcription reporter assays, qPCR, MMuPV1 genome inoculation of nude mice.
Results: MMuPV1 E8^E2 (mE8^E2) represses transcription from a reporter plasmid as efficiently as HPV31 E8^E2. Deletion of E8 or co-transfection of a dominant-negative NCOR fragment interferes with mE8^E2´s repression activity suggesting that mE8^E2 also recruits cellular NCoR/SMRT corepressor complexes to inhibit transcription. Wild type (w.t.) and E8^E2 k.o. MMuPV1 genomes were transfected into primary mouse tail keratinocytes and viral transcription was analyzed 3, 6 and 9d later. Compared to w.t., E8^E2 k.o. genomes displayed a 9.5-fold increase on d3 and a 15-fold increase on d6 and d9 of spliced E1^E4 transcripts. Spliced late viral URR^E4 and E4^L1 transcripts were also increased from E8^E2 k.o. genomes. This indicates that mE8^E2 limits viral transcription in a comparable manner to HPV. Tails of athymic nude female mice were inoculated with w.t. and E8^E2 k.o. MMuPV1 genomes. The mice that received w.t. genome developed warts (9/10) within 22 weeks, but the E8^E2 genome failed to produce any visible warts (0/10). Viral transcripts were detected by qPCR analysis in w.t. but not E8^E2 k.o. inoculated sites.
Conclusions: The inhibitory function of E8^E2 is conserved between HPV and MMuPV1. Surprisingly, our data indicate that E8^E2 expression is required for wart formation even in mice with a compromised immune system. This suggests that E8^E2 provides a critical biological function beyond a postulated role in limiting viral expression to avoid immunological detection.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

STRUCTURE-FUNCTION ANALYSES OF CANDIDATE SMALL MOLECULE RPN13 INHIBITORS FOR TREATMENT OF HPV-RELATED CANCERS

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Introduction: The HPV viral oncoproteins coopt proteasome function to rapidly degrade several key cell cycle control proteins and promote cancer cell growth and viability. RPN13 is a subunit within the constitutive proteasome's 19S regulatory particle which mediates recognition of the polyubiquitinated substrates and their deubiquitination prior to degradation.
Methods: We synthesized a series of candidate inhibitors based upon our prototypic bis-benzylidine piperidone-based inhibitor RA190 that targets cysteine 88 of RPN13 and tested their impact on proteasome function and tumor cell growth.
Results: We showed the benefit of the central nitrogen-bearing piperidone ring moiety compared to a cyclohexanone, the importance of the span of the aromatic wings from the central enone-piperidone ring, the contribution of both wings to drug activity, and that substituents with stronger electron withdrawing groups were more cytotoxic. Potency was further enhanced by coupling of a second warhead to the central nitrogen-bearing piperidone as RA375 exhibited ten-fold greater activity against cancer lines than RA190, reflecting its nitroring substituents and the addition of a chloroacetamide warhead. Treatment with RA375 caused a rapid and profound accumulation of high molecular weight polyubiquitinated proteins and reduced intracellular glutathione levels, which produce endoplasmic reticulum and oxidative stress, and trigger apoptosis. RA375 was highly active against cell lines of multiple myeloma and diverse solid cancers, while sparing normal cells. For cervical and head and neck cancer cell lines, those associated with HPV were significantly more sensitive to RA375 by 5-fold on average. RA375 inhibited proteasome function in leg muscle for >72h after a single *i.p.* dose, and twice weekly treatment reduced tumor burden and extended survival of nude mice carrying a human cancer xenograft.
Conclusions: RA375 warrants further exploration for treatment of HPV-driven cancers.

ORAL SESSION 6: ANIMAL AND IN VITRO MODELS

HPV16 INDUCES SQUAMOUS CELL CARCINOMA IN THE TONGUE BASE IN TRANSGENIC MICE: ASSOCIATION WITH A SQUAMOCOLUMNAR JUNCTION IN THE CIRCUMVALLATE PAPILLA.

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Introduction: Head and neck squamous cell carcinomas associated with human papillomavirus (HPV) infection are specifically located in the tonsils and the tongue base, but the reasons for this specificity remain unknown.
Methods: We studied the distribution of lesions in the oral cavity and the pharynx of HPV16-transgenic mice where the expression of all the HPV16 early genes is targeted to keratinizing squamous epithelia by the cytokeratin 14 (CK14) gene promoter.
Results: At 30 weeks-old, 100% of the animals spontaneously developed low- and high-grade intraepithelial dysplastic lesions at multiple oral sites. Invasive cancers were observed in 20% of animals and were remarkably restricted to the tongue base, in association with the circumvallate papilla. The lesions maintained expression of CK14 and the HPV16 *E6* and *E7* oncogenes and displayed typical features of HPV-induced carcinogenesis, including deregulated cell proliferation and $p16^{INK4A}$ up-regulation. Morphologically, these malignant lesions were poorly differentiated and destroyed the underlying tongue musculature. We hypothesized that the tongue base area might contain a transformation zone similar to those observed in the cervix and anus, explaining why HPV-positive cancers specifically target that area. Immunohistochemistry for two transformation zone markers, CK7 and p63, revealed a squamocolumnar junction located in the terminal duct of von Ebner's gland as it meets the oral mucosa, composed of $CK7^+$ luminal cells and $p63^+$ basal cells. Dysplastic and invasive lesions retained diffuse p63 expression but only scattered positivity for CK7.
Conclusions: These results suggest that site-specific HPV pathogenesis in the tongue base may be explained by the presence of a transformation zone located in the circumvallate papilla. This model recapitulates HPV-induced carcinogenesis and reproduces key morphological and molecular features of HPV-positive Head and neck squamous cell carcinomas, providing a unique *in vivo* tool for basic and translational research.

ORAL SESSION 7: HOST GENOMICS AND VIRAL GENE REGULATION

CHROMOSOMAL INTEGRATION AND APOBEC PROFILES DIFFER BETWEEN HPV16 AND HPV18 POSITIVE CERVICAL SAMPLES

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Introduction: Deep sequencing allows for in-depth characterization of HPV events in carcinogenesis, such as the generation of minor nucleotide variants and chromosomal integration events. Recent studies have revealed genomic variability indicating intra-host viral evolution and adaptation acquired through various mutagenic processes, one of which is APOBEC. We aimed to compare the extent and nature of genomic events in HPV16 and HPV18 positive clinical samples with different morphology.
Methods: HPV16 (n=157) and HPV18 (n=75) positive cervical samples were included, categorized into the four categories normal/ASCUS/LSIL with no lesions within four years follow up (n=71), CIN2 (n=60), CIN3/AIS (n=96) and ICC (n=5). Samples were sequenced using the whole genome HPV deep sequencing protocol TaME-seq, assessing both nucleotide variants, viral genomic deletions and chromosomal integration.
Results: Samples with a mean coverage more than 300x reads (n=131) were included for analyses. Sequence analyses revealed a higher overall HPV integration rate in HPV18 positive samples compared to HPV16, characterized in 30/51 (59%) of HPV18 positive samples and in 10/80 (13%) of HPV16 positive samples. In addition, the number of integration breakpoints per sample was generally higher for HPV18 compared to HPV16 positive samples, ranging from 1 to 21 integrations per sample. Considering CIN3/AIS/ICC samples showing integration events, 8 of 10 HPV16-human breakpoints (80%; n=4) and 37 of 60 HPV18-human breakpoints (62%; n=14) were located in or in close proximity to cancer-related genes. Similar rates of minor nucleotide variants in HPV16 and HPV18 sequences were observed, with distinct APOBEC signatures for HPV16.
Conclusions: We show different integration and APOBEC profiles in HPV16 and HPV18 positive cervical samples of different diagnostic categories. These are important findings to understand differences in the biology and pathogenicity of HPV types, which require further attention. Viral breakpoints, genomic deletions and chromosomal locations of integration sites will be presented.

ORAL SESSION 7: HOST GENOMICS AND VIRAL GENE REGULATION

HUMAN PAPILLOMAVIRUS SUBVERSION OF HOST RNA SPLICING MACHINERY IN EARLY EPITHELIAL INFECTION.

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Introduction: The HPV genome is small and polycistronic, with highly efficient use of the few genes it expresses. HPV relies on host splicing factors to generate viral transcripts whose products subvert host machinery to drive choreographed splicing events leading to viral maintenance. It is challenging to measure early events as clinical conditions manifest long after viral genome integration and disruption of both host and virus is established and extreme. The powerful W12 cell line model of early HPV infection represents a large series of isogenic clones with highly variable HPV oncogene activity and phenotype on a homogenous host genetic background. We use deep RNAseq to measure the specific effects of viral oncoproteins on host alternative splicing factors and consequent control of the both viral and host gene and isoform expression.
Methods: 1. Deep RNA-sequencing of isogenic series of W12 cell lines with HPV oncoprotein expression. 2. siRNA knockdown of HPV16_E7 and microarray analysis of consequent host gene expression. 3. Integrated computational modeling of host splicing factor binding to HPV, host/virus isoform expression and differential splicing.
Results: 1. HPV coordinates a complex network of host splicing factor levels to modulate the expression of oncoprotein isoforms 2. Those splicing factors in turn significantly impact host gene expression and isoform usage. 3. Differential splicing changes affect host phenotype and lead to changes in host transcription which directly affect the cellular processes leading to cancer. 4. We show the causal direction of virus/host splicing changes and build a quantitative model of virus-host splicing interactions which predict viral isoform levels accurately based on host splicing factor levels.
Conclusions: These findings point to a new and potentially important mechanism by which HPV drives host epithelial cells into a pre-cancerous and then invasive state and highlight exciting opportunities for early detection and potentially interventions to prevent HPV mediated cancers.

ORAL SESSION 7: HOST GENOMICS AND VIRAL GENE REGULATION

FUNCTIONAL ARCHITECTURE OF HPV REPLICATION FOCI

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Introduction: The life cycle of HPV depends on the differentiation status of keratinocytes; the virus modulates and takes advantage of various host cellular pathways to regulate its infectious cycle. At late stages of infection, viral genomes are amplified in nuclear replication foci in differentiated keratinocytes to produce progeny virions. A multitude of cellular factors are recruited to HPV replication foci to replicate and process viral DNA; each of these factors has a very distinctive location within replication foci.
Methods: To investigate the different processes occurring throughout the foci, we have characterized the localization of many host factors using confocal microscopy and 3D image reconstruction. We have employed high resolution STED microscopy, DNA and RNA FISH, and pulse labeling with nucleotide analogs to pinpoint the exact location of DNA synthesis. We have also developed HPV-containing keratinocyte cell lines that express fluorescent host proteins related to viral replication for visualization by live cell microscopy.
Results: Taken together, these data enabled us to build a model of how different processes, such as viral transcription and replication, are spatially separated in the HPV viral factories.
Conclusions: Perhaps not surprisingly, papillomaviruses have evolved ingenious strategies to navigate, manipulate and hijack the architecture of the host nucleus.

ORAL SESSION 7: HOST GENOMICS AND VIRAL GENE REGULATION

CERVICAL CARCINOMAS FROM UGANDA HAVE HPV CLADE-SPECIFIC EPIGENOME AND TRANSCRIPTOME LANDSCAPES

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Introduction: HPV-infected cervical carcinoma is the leading cause of cancer-related mortality for sub-Saharan African women, but comprehensive molecular profiling has not been performed in this population. We aimed to stratify HIV-affected (HIV+) and HIV-unaffected (HIV-) primary cervical carcinoma patients from Uganda using their genomic, transcriptomic, and epigenomic landscapes as part of the HIV+ Tumor Molecular Characterization Project.
Methods: In our study, 118 cervical cancer samples, 72 of which were from HIV+ patients, were subjected to whole genome sequencing and RNA-sequencing. To study the epigenome, 115 of the samples were profiled using the Illumina Human 850K Methylation EPIC Array, and 52 of the samples were analyzed using ChIP-sequencing of the 6-core histone modifications (H3K4me1/3, H3K27ac, H3K36me3, H3K9me3, H3K27me3).
Results: Cervical cancers from HIV+ and HIV- patients showed few molecular differences, although our cohort had unusual overrepresentation of HPV18 and HPV45, both of which are reported to be more prevalent in HIV+ populations. We did however detect pronounced HPV clade-driven differences in DNA methylation and promoter- and enhancer-associated histone mark profiles (H3K4me3, H3K27ac, and H3K4me1). We report that these differential epigenetic profiles contribute to differential gene expression of distinct cellular processes.

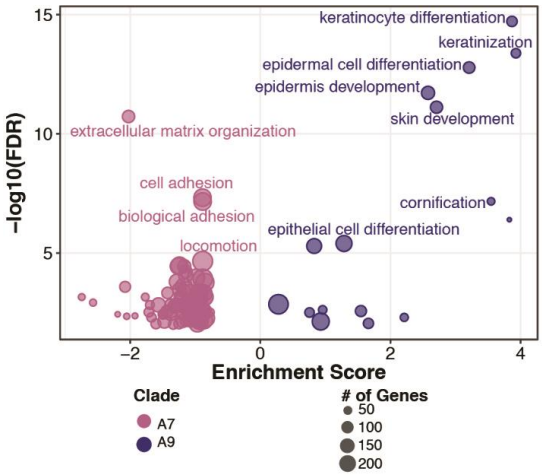

Figure 1: Functional enrichment of differential molecular processes enriched in HPV clades A9 and A7.

We also identified dramatic enrichment of active histone modifications at HPV integration events that were associated with increased expression of nearby genes and endogenous retroviruses (ERVs). Increased local dysregulation of histone modifications significantly correlated with the number of HPV integrations closely juxtaposed within genomic regions. High expression of ERVs due to HPV integration was significantly correlated with increased T cell content within the tumour inferred by CIBERSORT.

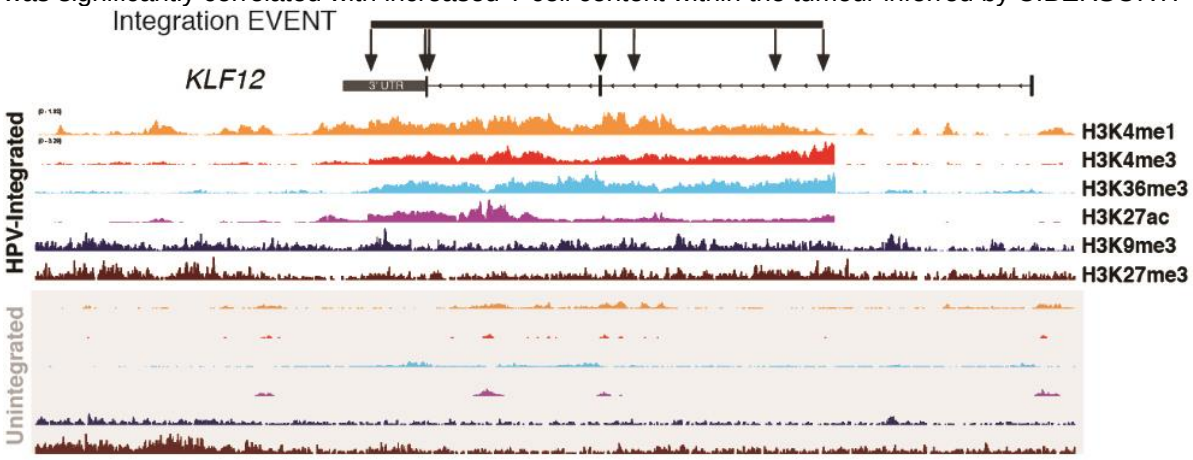

Figure 2: An example of active histone mark enrichment at an HPV integration event within the gene body of *KLF12*. The sample containing the integration event is compared to a reference sample without HPV integration within the region. Arrow heads denote HPV integration sites.

Conclusions: Our study investigated the important relationship between HIV and HPV co-infection in the genomic landscapes of cervical cancers and revealed for the first time epigenomic and transcriptomic differences within cervical cancers infected by different HPV clades that could have functional consequences to the disease presentation.

ORAL SESSION 7: HOST GENOMICS AND VIRAL GENE REGULATION

HPV18 UTILIZES TWO ALTERNATIVE BRANCH SITES FOR E6*I SPLICING TO PRODUCE E7 PROTEIN

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Introduction: Human papillomavirus 18 (HPV18) E6 and E7 oncogenes are transcribed as a single bicistronic E6E7 pre-mRNA. The E6 ORF region in the bicistronic E6E7 pre-mRNA contains an intron (E6 intron). Splicing of this intron disrupts the E6 ORF integrity and produces a spliced E6*I RNA for efficient E7 translation. Here we aim to map the branch point sequence (BPS) required for the E6 intron splicing.
Methods: The E6 intron BPS was computational predicted at *Human Splicing Finder* software. The selected candidates were validated by in vitro or in vivo splicing reaction followed by lariat RT-PCR. Plasmids containing single or double mutations at nt 384 and nt 388 were used to check the E6*I splicing efficiency by in vitro splicing reaction and lariat RT-PCR. Additional plasmids containing the branch site mutations and a flag sequence were constructed to detect E6 and E7 protein levels at HEK293T and U2OS cell lines.
Results: The E6 intron has two overlapped BPS upstream of its 3' splice site (3'ss), to produce the *E6*I RNA*, with an identical heptamer AACUAAC. One heptamer has a branch site adenosine (underlined) at nt 384 and the other at nt 388. E6*I splicing efficiency correlates to the expression level of E6 and E7 proteins depends on the selection of which branch site. In general, E6*I splicing prefers the 3'ss-proximal branch site at nt 388 over the distal branch site at nt 384. Inactivation of the nt 388 branch site was found to activate a cryptic acceptor site at nt 636 for aberrant RNA splicing and consequently reduction at E7 protein level.
Conclusions: HPV18 modulates its production ratio of E6 and E7 proteins by alternative selection of the two mapped branch sites for the E6*I splicing, which could be beneficial in its productive or oncogenic infection according to the host cell environment.

CLINICAL SCIENCE ORAL SESSION ABSTRACTS

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

THE PERFORMANCE OF HPV 16 DNA METHYLATION AND E6 ONCOPROTEIN IN PREDICTING THE RISK OF CERVICAL PRECANCERS: A 10-YEAR PROSPECTIVE COHORT STUDY

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Introduction: Human papillomavirus (HPV) DNA methylation and E6 oncoprotein testing are proposed as a promising triage tool for HPV positive women. However, the longitudinal data on how well they predicted the risk of progression up to a decade and identified precancers compared to other triage options was desirable.
Methods: All HPV 16 positive baseline specimens in a cohort of 1742 screening population with 10-year follow-up were detected for quantification of viral methylation levels using pyrosequencing. Associations between HPV 16 DNA methylation levels and E6 oncoprotein levels and the risk of incident cervical intraepithelial neoplasia grade 3 or worse (CIN3+) were assessed using Kaplan-Meier methods for cumulative incidence rate (CIR) and Cox proportional hazard models for hazard ratios (HR). Area under the curve (AUC) was used to evaluate the clinical performance of viral methylation and HPV E6 oncoprotein compared to cytology, HPV viral load and visual inspection with acetic acid (VIA).
Results: Elevated HPV16 methylation levels were significantly associated with the incremental 10-year CIR of CIN3+. A clear risk stratification was observed when they are used as methylation panel combining any two (panel-A, HR= 6.88, 95%CI =1.81 - 26.21) and three (methylation panel-B, HR=9.28, 95% CI: 2.69 - 32.02) of these six CpG sites. Two methylation panels had AUCs of 0.75, HPV E6 oncoprotein had 0.70, comparable with cytology (LSIL) of 0.80 and , superior to cytology (ASCUS) of 0.68, viral load of 0.66 and VIA of 0.56. The highest sensitivity of and specificity for the combination of methylation panels and HPV E6 oncoprotein reached 72.73% (95% CI: 43.44 - 90.25%) and 94.44% (95% CI: 81.86 - 98.46%) ,respectively.
Conclusions: HPV DNA methylation and E6 onprotein were promising for triage of HPV positive women and may provide objective and more timely identification of women at high risk of high-grade cervical lesions at baseline screening.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

LONGITUDINAL PATTERNS OF HPV18 AND HPV45 METHYLATION AND ASSOCIATIONS WITH CERVICAL PRECANCER AND CANCER RISK

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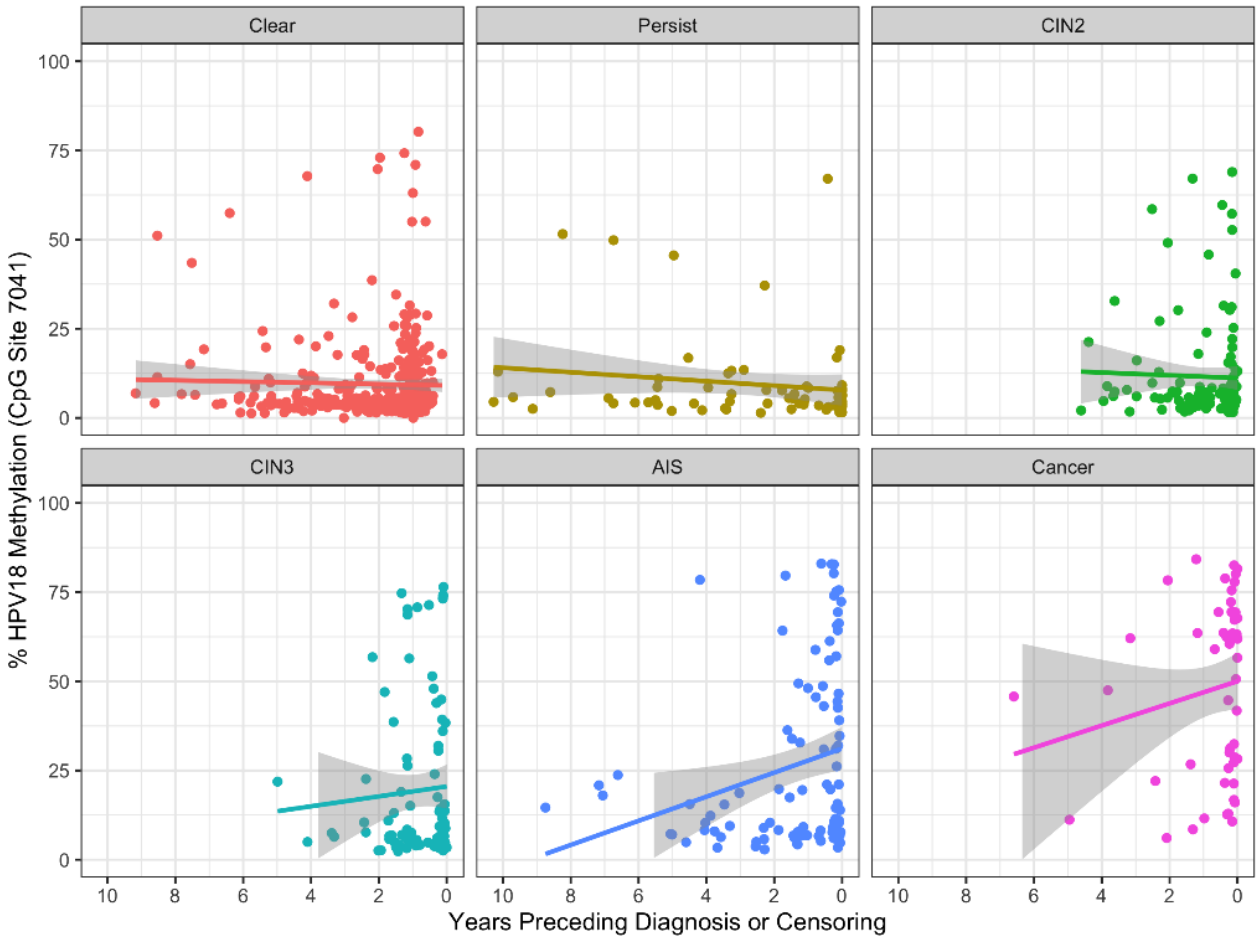
Introduction: Human papillomavirus (HPV) DNA methylation is a promising biomarker for HPV triage. Few observational studies have evaluated longitudinal patterns of HPV methylation with respect to cervical precancer and cancer. Here, we evaluated the methylation status of HPV18 and HPV45 in longitudinal samples.
Methods: This retrospective cohort study includes HPV18- and HPV45-positive samples from 923 women who underwent routine screening at Kaiser Permanente Northern California, 2006-2016. Samples were selected from the time of diagnosis or censoring, integrating all available preceding visits. Outcomes included cervical cancer, adenocarcinoma in situ (AIS), cervical intraepithelial neoplasia grades 2 (CIN2) and 3 (CIN3), and <CIN2. HPV L1 and L2 bisulfite-converted sequences (14 CpGs per type) were quantified using next-generation sequencing. We evaluated percent methylation levels using descriptive statistics and Kruskal-Wallis tests. Analyses using linear mixed models to estimate longitudinal changes in methylation levels and heterogeneity across groups are underway.
Results: A total of 590 HPV18-positive (811 visits) and 333 HPV45-positive women (471 visits) were included. Within a year of diagnosis or censoring, mean viral methylation across all HPV18 sites was 22.5% in <CIN2, 24.6% in CIN2, 33.7% in CIN3, 45.0% in AIS, and 60.3% in cancers (p=0.0001) and 15.9%, 18.1%, 23.0%, 44.0%, and 51.7%, respectively for HPV45 (p=0.0001). Methylation levels tended to increase leading up to the diagnosis of AIS and cancer for both HPV18 and HPV45 and were highest at the time of diagnosis for most CpG sites (e.g., HPV18, CpG_7041, Figure). Methylation remained stable over time in women with all other outcomes, most notably CIN3 and CIN2, which had increased methylation at the time of diagnosis only.



Conclusions: Women with CIN2+ had higher methylation levels within a year of diagnosis compared to those with <CIN2. Among women diagnosed with AIS or cancer**,** there was a trend of increasingly methylation levels of HPV18 and HPV45 leading up to diagnosis.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

PREDICT AND PRIORITIZE: DETECTION OF CIN3 LESIONS UP TO 5 YEARS BEFORE THEIR DEVELOPMENT USING A METHYLATION CLASSIFIER

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Introduction: Methylation markers have shown great potential for diagnosis of CIN2/3 lesions. This study aimed to continue further and assess the performance of a DNA methylation classifier, S5, at predicting progression of histologically normal but high-risk HPV positive samples to high-grade cervical lesions using baseline samples taken up to 5 years before diagnosis. A second aim was to confirm the usefulness of S5 to detect prevalent CIN2/3 lesions for triage of high-risk HPV women.
Methods: We used archived liquid-based cytology material from the prospective randomised ARTISTIC trial. The S5 classifier comprising target regions of host gene *EPB41L3* and viral regions of HPV16, 18, 31 and 33 was assayed by pyrosequencing on 1187 samples (327 CIN2/3 samples and 860 controls).
Results: S5 could discriminate between the baseline sample of progressers to CIN2/3 and HPV-positive women who did not progress using samples that were, on average, taken 5 years before the high-grade disease was diagnosed. S5 performed better than HPV typing with HPV16, HPV16/18, HPV16/18/31 or HPV16/18/31/33 at detecting CIN2/3 or CIN3 only. The AUC of S5 for detecting CIN3 at screening round 1 was 0.85 (95%CI 0.80-0.90) and 0.74 (95%CI 0.67-0.80) for HPV16/18 genotyping. At the 0.8 cut-off for S5, sensitivities were 84% (95%CI 77-90%) for detecting CIN2/3 and 92% (95%CI 88-97%) for detecting CIN3, specificities were 56% for both CIN2/3 and CIN3 respectively. Using HPV16/18 typing to detect prevalent CIN2/3 and CIN3 gave a sensitivity of 56% (95%CI 48-65%) and 67% (95%CI 56-77) respectively and a specificity of 65% for both outcomes.
Conclusions: S5 classifier could be an accurate triage test for hrHPV women in cervical cancer-screening programmes. Its implementation can be cost-effective and avoid unnecessary referral to colposcopy of women clearing HPV infection. S5 could also be used to identify women at risk of developing CIN3 lesions within 5 years with close follow-up.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

EFFECTIVE METHYLATION TRIAGE OF HPV-POSITIVE WOMEN WITH ABNORMAL CYTOLOGY IN A MIDDLE-INCOME COUNTRY

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Introduction: Introduction. The S5 methylation test has not been validated in Low-Middle-Income Countries (LMIC). We compared S5 to HPV16/18 genotyping and conventional Pap smear for triage hrHPV+ in women with ASC-US cytology from Colombia.
Methods: Methods. All hrHPV+ cases with an expert confirmed biopsy diagnosis of CIN2+ (n=183) and an equal number of age-matched hrHPV+ controls with <CIN2 were selected from 2,661 women followed-up for 2 years in a randomized pragmatic trial. Baseline specimens were tested blinded to cytology, histology and initial HPV test results. S5 cut-offs of 0.8, 1.4 and 3.1 were used to define methylation positives.
Results: Results. S5 had AUCs of 0.70 (95% CI 0.65–0.75) and 0.67 (95% CI 0.60–0.74) for CIN2+ and CIN3+. The accuracy of S5 for CIN2+ and CIN3+ of points representing the S5 scores at a cut-off of 3.1 was better than the accuracy at 0.8 or 1.4 cut-offs. The sensitivity for CIN2+ of S5 at 3.1 (55.19%, 95% CI 47.99–62.40) was higher than the sensitivity of HPV16/18 (48.09%, 95% CI 40.85–55.33, p = 0.0164) or cytology (31.21%, 95% CI 24.50–37.93, p = <0.0001). The specificity (75.96%, 95% CI 69.76–82.15) was higher to HPV 16/18 (67.21%, 95% CI 60.41–74.01, p=0.0062) and similar to cytology (75.57%. 95% CI 69.734–81.79). The sensitivity of S5 for CIN3+ at 3.1 cut-off (64.58%, 95% CI 51.05–78.11) was also higher to HPV16/18 (50%, 95% CI 35.86–64.14, p=0.0233) or cytology (36.96%, 95% CI 23.30–50.61) and specificity (64.15%, 95% CI 58.88–69.42) was similar to HPV 16/18 (61.01%, 95% CI 55.65–66.37) and lower than cytology (73.60%. 95% CI 68.75–78.44).
Conclusions: Conclusions. High sensitivity is crucial in LMIC and S5 at a cut-off 3.1 exceeded the sensitivity of HPV16/18 genotyping and cytology and had comparable specificity to cytology plus HPV16/18 genotyping but substantially fewer false positives.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

NON-INVASIVE METHYLATION TEST TO DETECT CERVICAL PRE-CANCER IN SELF-COLLECTED VAGINAL AND URINE SPECIMENS.

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Introduction: The implementation of HPV testing as a primary screen will soon become the norm worldwide. Because HPV testing is a very sensitive method, but not specific enough, the choice of an appropriate triage strategy for hrHPV positive women will be one of the future key issues facing the cervical screening community. Clinician taken samples are the gold standard but **s**elf-sampling including urine may be a useful alternative. We have developed a triage classifier for the detection of CIN2+, based on DNA methylation of HPV16, HPV18, HPV31 and HPV33 and the human gene *EPB41L3*. We will test S5 classifier on two non-invasive specimens: a self-collected vaginal sample and urine. We aim to assess whether S5 can identify women who are CIN2+ using self-collected samples and comparing several collection devices.
Methods: Women attending the colposcopy clinic at The Royal London Hospital as a consequence of abnormal screening cytology and/or a positive HPV result were recruited as part of the 'Self-sampling for vaginal HPV. 503 women provided a urine sample using the Colli-Pee™ device. In total 600 women provided self-collected vaginal samples using either Flocked swab and Diagene or HerSwab and Qvintip. DNA was extracted, Bisulfite converted, followed by pyrosequencing assays for the 6 S5 markers. Average methylation was calculated to generate the S5 score.
Results: S5 showed a good and statistically significant separation between <CIN2 and CIN2+ samples for both urine and vagina self-samples (p=<0.0001). The area under the ROC curve was 0.7254 (p=<0.0001) for urine samples and 0.7388 (p=<0.0001) for vaginal self-samples. At the pre-defined cut-off of 0.8, the sensitivity for urine samples was 66% and specificity 72% and vaginal self-samples was 71% and specificity 68%.
Conclusions: We demonstrated that S5 can be successfully amplified in urine and vaginal self-collected samples and that the classifier is able to correctly identify CIN2+ women.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

HPV16 VIRAL LOAD AND DNA METHYLATION OF THE HPV16 L1 AND EPB41L3 GENES AMONG HPV-16 POSITIVE WOMEN LIVING WITH HIV

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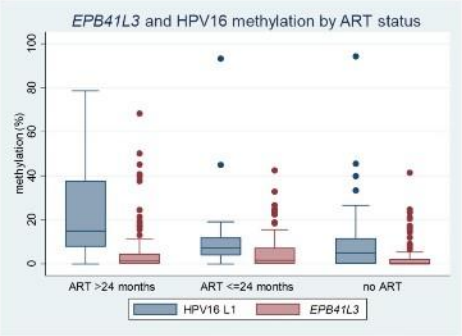
Introduction: To evaluate associations of HPV16-E6 viral load (VL) and DNA methylation of human gene *EPB41L3* and HPV16-L1 gene with prevalent CIN2+ and HPV16 persistence among women living with HIV-1 (WLHIV) in Burkina Faso and South Africa.
Methods: Case-control study of WLHIV aged 25-50 with histology-determined CIN2+ (n=152) and ≤CIN1 (n=210) with HPV16-infection determined using INNO-LiPA. *EPB41L3 (*CpG regions:438,427,425) and HPV16-L1 (CpG:6367,6389) methylation measured by pyrosequencing of bisulfite-converted DNA; HPV16 -VL quantitation of E6 gene DNA by real-time PCR from exfoliated cervical specimens among HPV16-positive women at baseline and 16 months later (endline).
Results: Among 362 women, 110 (31%) were HPV16-positive (44 CIN2+; 66 ≤CIN1 at baseline); 62 (61%) cleared infection and 40 (39%) had persistent HPV16 at endline. Compared to women with ≤CIN1, levels of *EPB41L3* methylation and HPV16 VL were elevated in women with CIN2+ at baseline (*EPB41L3*: Mann-Whitney p=0.004; HPV16 VL: p=0.002) but not for HVP16-L1 methylation (p=0.216). Among 64 women without CIN2+, there was no difference in levels of the three markers among women who had persistent HPV16 compared to women who cleared infection 16-months later. HPV16-L1 methylation was significantly elevated among women taking prolonged (>2 years) ART, and short (≤2 years) ART compared to ART-naïve women (Cuzick p-trend<0.001; **Figure**). A similar trend was observed for *EPB41L3* methylation (p-trend=o.005) but not for HPV16 VL (p-trend=o.893).

Figure. Median methylation (%) of HPV16 L1 and *EPB41L3* according to ART status



Conclusions: Among women with HPV16 at baseline, *EPB41L3* methylation and HPV16 VL were significantly higher among women with CIN2+ at baseline. HPV16-L1 methylation was positively associated with ART use and duration.

ORAL SESSION 1: METHYLATION POTENTIAL USE FOR CLINICAL PRACTICE

METHYLATION ESTIMATES THE RISK OF PRECANCER IN HPV-INFECTED WOMEN WITH DISCREPANT RESULTS BETWEEN CYTOLOGY AND HPV16/18 GENOTYPING

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Introduction: Surveillance of women with high-risk human papillomavirus (hrHPV) is necessary in cancer screening programs. We evaluated performance of S5 (targeting DNA methylation in HPV16,18,31,33 and human gene EPB41L3) to classify cervical intraepithelial neoplasia grade 2 or higher (CIN2+) in a sample of hrHPV-infected women in FRIDA Study, a large screening trial in Mexico.
Methods: A nested case-control sample with women referred to colposcopy by atypical squamous cells of undetermined significance or higher (ASCUS+) in cytology and/or positive for HPV16/18 was tested by S5. Seventy-nine cases of CIN2+ were age-matched to 237 controls of <CIN2. DNA from exfoliated cervical cells was bisulfite converted, PCR amplified for S5 targets and methylation was quantified at specific cytosines by pyrosequencing.
Results: The S5 classifier separated women with CIN2+ from <CIN2 with a significant area under the curve (AUC) of 0.75 (95%CI 0.69-0.82), while AUC for CIN3+ was 0.81 (95%CI 0.74-0.89). To optimize sensitivity and specificity for Mexico, an alternative S5 cutoff of 3.7 was implemented considering the overall higher methylation seen in our already triaged women. All 3 invasive cancers were detected by methylation or HPV16/18 but none by cytology. Sensitivity of S5 for CIN2+ was 62% (95%CI 50.4–72.7%), specificity was 73% (95%CI 66.9–78.5%), and adjusted PPV was 15.1% (95%CI 12.0-18.3%). In contrast, the crude sensitivity of HPV16/18 detection and cytology were 63.3% (95%CI 51.7-73.9%) and 57.0% (95%CI 45.3-68.1%) respectively; specificity was 29.1% (95%CI 23.4-35.3%) and 62.4% (95%CI 55.9-68.6%), while adjusted PPV was 6.4% (95% CI 4.9-8.1%) and 10.5% (95%CI 8.0-13.1%). Methylation could reduce colposcopy referrals up to 50% with virtually no loss of sensitivity for CIN2+.
Conclusions: S5 testing on hrHPV-positive women significantly increased diagnostic information compared to triage by HPV16/18 plus cytology and appears to have clinical utility as an additional test to substantially lessen burdens on colposcopy.

ORAL SESSION 2: CERVICAL/ANAL SCREENING AND MANAGEMENT

PERFORMANCE OF A NEW ONCOPROTEIN E6/E7 TEST TO DETECT CIN3+ WITHIN THE ESTAMPA STUDY

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Introduction: HPV testing is highly sensitive but its low specificity demands the use of triage to avoid unnecessary colposcopy. The easy-to-perform and less costly OncoE6 Cervical Test targeting E6 oncoproteins for HPV16 and HPV18 have shown promising results as triage of HPV positive women. The test has limited sensitivity as it does not detect lesions related to other high-risk HPV infections. We evaluated the performance of a new prototype, targeting E6/E7 oncoproteins for eight HPV types: 16, 18, 31, 33, 35, 45, 52, 58, to detect CIN3+ within the ESTAMPA study (NCT01881659).
Methods: Women aged 30-64 are screened with HPV and cytology and those positive are referred to colposcopy with biopsy and treatment as appropriate. The new oncoprotein E6/E7 test was done in dry swabs collected at screening from a sub-cohort of 872 women, including HPV negatives and women with lesions of different grades including cervical cancer. The sensitivity and specificity of the test for CIN3+ and cancer detection were estimated overall and by age.
Results: The overall sensitivity for CIN3+ detection was 60% (95%CI: 54-66) and 66% (95%CI: 60-72) when restricted to lesions associated to the targeted HPV types. The overall sensitivity was reached after including E6/E7 oncoproteins for six of the eight targeted types: 16, 18, 52, 45, 31 and 33. At the cancer threshold, the overall sensitivity of 73% (95%CI: 63-81) was reached after including E6/E7 oncoproteins for only four target types: 16, 45, 18 and 52. The sensitivity for CIN3+ detection increased with age (30-44y: 55%, 95%CI: 47-62; 45-64y: 69%, 95%CI: 59-78). Specificity for each target type was high, varying from 95% to 98%, but the overall specificity of the test was moderate (81%, 95%CI: 77-84).
Conclusions: The new oncoE6/E7 test showed promising results, however, further refinement of the prototype is undergoing ahead of full clinical validation.

ORAL SESSION 2: CERVICAL/ANAL SCREENING AND MANAGEMENT

VALIDATION OF A QUANTIGENE-HPV CERVICAL DISEASE-SCREENING TEST USING RT-QPCR

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Introduction: Cervical cancer is caused by persistent HPV infection and characterized by a pre-malignant phase ranging from CIN I to CIN III. The screening in Germany is based on cytology and HPV-testing. While cytology has a low sensitivity (50%) and a high specificity (>90%), molecular HPV-testing has a very high sensitivity (>95%) but a low specificity (<40%). Thus, additional tests like colposcopy, biopsy, p16/Ki67 immunohistochemistry, and testing of other biomarkers have to be performed. There is the need of a triage method with high specificity, sensitivity, and positive predictive value.
Methods: We designed a multiplexed mRNA quantifying assay that combines detection of HPV genotype-specific oncogene expression with cellular biomarkers routinely used for diagnosis and cancer stem cells and tumor markers. The Luminex bead-based QuantiGene 2.0 technology platform (Thermo Fisher Scientific) is used to detect mRNA expression of all markers simultaneously from a crude lysate of a cervical smear sample. In order to validate the data we performed RT-qPCR analysis for the subset of biomarkers: HPV16-E7, HPV18-E7, STMN1, BIRC5, MCM2, Ki67, ALDH1A1, CDKN2A, TERT, UBC, and ACTB.
Results: 46 markers were validated in a clinical retrospective (300 samples) and a prospective trial (1400 consecutively collected samples) and were proven to distinguish the different clinical dysplasia stages: normal, low grade (CIN I, CIN II), high-grade (CIN III), and invasive cancer, with high accuracy (e.g. 90% for CIN III). For the validation of the QuantiGene data for the subset of biomarkers, we set up a SYBR-Green dye-based RT-qPCR assay with efficiencies of the primer pairs in the desirable window of 90-110%. Comparing the RT-qPCR data with the QuantiGene data, correlation coefficients between -0.33 and -0.9 (r_s) were observed.
Conclusions: mRNA quantification by QuantiGene Plex is reliable and reproducible by RT-qPCR and both assays could be alternative methods for mRNA expression profiling for dysplasia diagnosis.

ORAL SESSION 2: CERVICAL/ANAL SCREENING AND MANAGEMENT

DISTINCT ANAL CANAL MICROBIOME IS CORRELATED WITH HSIL IN HIV-POSITIVE MEN WHO HAVE SEX WITH MEN

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Introduction: High-risk HPV (hr-HPV) infection is necessary but insufficient for development of the cancer precursor lesion, high-grade squamous intraepithelial lesion (HSIL). This study aimed to determine whether alterations of the microbiome are associated with anal HSIL in individuals with anal hr-HPV infection.
Methods: High resolution anoscopy (HRA) was performed on HIV-positive men who have sex with men (MSM). Sterile swabs moistened with sterile water were used to sample the anal canal at the start of the visit. Participants were additionally provided with microbiome sampling kits and asked to mail-in stool samples from home. 16S sequencing was used to compare the microbiome characteristics between anal and stool samples and between anal samples of hr-HPV positive participants with HRA-guided, biopsy-proven anal HSIL and participants with no squamous intraepithelial lesion (SIL). Beta diversity and fold change estimates of abundance were assessed.
Results: Anal canal and stool samples were obtained from 103 HIV-positive MSM. Mean age and CD4 count were 58 and 644/mm^3 respectively. 64 HIV-positive MSM were hr-HPV positive. Of these, 30 had anal HSIL, 22 had low-grade squamous intraepithelial lesion and 12 had no SIL. Beta diversity showed distinct clustering of stool and anal samples in terms of location ($p=0.001$) and dispersion ($p<0.001$), reflecting a discrete anal microbiome (image). Differential abundance analysis identified 31 species significantly different between anal and stool samples. The anal canal was enriched with *Prevotella, Finegoldia and Peptoniphilus* compared with stool (table 1). Comparison of the anal canal microbiome between hr-HPV HIV-positive individuals with HSIL and no SIL revealed 42 significantly different species, including enrichment with *Fusobacterium* and *Bacteroides* in participants with HSIL (table 2).

Image: Cluster Analysis of Anal and Stool Samples Using Bray-Curtis Dissimilarity Index

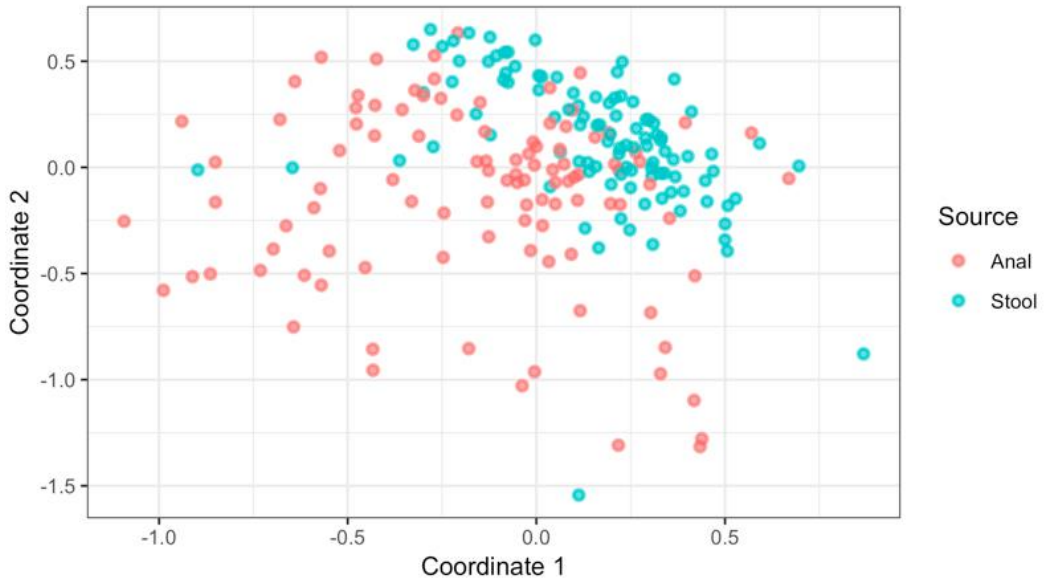

Table 1: Differential Abundance of Anal and Stool Samples

Species	Average count in stool samples	Fold change in anal samples	Adjusted p-value
Finegoldia magna	1230.84	41.63	<0.01
Streptococcus pneumoniae	520.45	11.13	<0.01
Prevotella bivia	631.8	84.81	<0.01
Blautia obeum	156.6	0.45	<0.01
Peptoniphilus urinimassiliensis	66.13	86.47	<0.01
Escherichia coli	494.11	6.69	<0.01
Peptostreptococcus anaerobius	294.65	37.87	<0.01
Anaerococcus vaginalis	118.09	68.91	<0.01
Faecalibacterium prausnitzii	2848.39	0.52	<0.01
Holdemanella biformis	171.65	0.7	<0.01
Blautia schinkii	187.95	0.49	<0.01
Prevotella disiens	405.05	82.32	<0.01
Slackia isoflavoniconvertens	44.27	0.61	<0.01
Blautia massiliensis	287.75	0.53	<0.01
Senegalimassilia anaerobia	78.65	0.71	<0.01
Prevotella corporis	222.54	112.75	<0.01
Lachnospira pectinoschiza	121	0.52	<0.01
Prevotella buccalis	107.8	192.45	<0.01
Prevotella copri	7212.08	0.43	<0.01
Negativibacillus massiliensis	31.47	0.88	<0.01
Dialister propionicifaciens	121.09	91.05	<0.01
Streptococcus anginosus	121.43	28.02	<0.01
Corynebacterium singulare	107.32	59.92	<0.01
Staphylococcus aureus	67.68	16.72	0.01
Collinsella aerofaciens	872.02	0.58	0.01
Roseburia faecis	821.44	0.6	0.02
Fusobacterium equinum	756.91	27.27	0.02
Peptoniphilus lacrimalis	48.5	140.34	0.03
Anaerostipes hadrus	220.98	0.66	0.04
Casaltella massiliensis	42	82.94	0.04
Prevotella timonensis	109.3	77.59	0.05

Table 2: Differential Abundance of HSIL and no SIL in Hr-HPV Cohort

Species	Average count in no SIL	Fold change in HSIL	Adjusted p-value
Bacteroides uniformis	131.89	1.55	<0.01
Corynebacterium singulare	68.12	2.18	<0.01
Peptoniphilus lacrimalis	44.21	3.46	<0.01
Streptococcus agalactiae	841.98	1.53	<0.01
Lactobacillus ruminis	56.5	0.49	<0.01
Acidaminococcus timonensis	134.31	0.55	<0.01
Prevotellamassilia timonensis	1186.24	1.07	<0.01
Megasphaera massiliensis	150.81	1.04	<0.01
Peptostreptococcus stomatis	16.11	1.72	<0.01
Anaerococcus vaginalis	159.22	1.47	<0.01
Peptostreptococcus anaerobius	116.96	1.4	<0.01
Sutterella wadsworthensis	329.67	0.82	<0.01
Coprobacillus cateniformis	45.44	1.24	<0.01
Dialister propionicifaciens	82.97	1.35	<0.01
Fusobacterium nucleatum	140.53	1.53	<0.01
Porphyromonas bennonis	34.35	1.35	<0.01
Tyzzerella nexilis	133.18	1.2	<0.01
Alistipes shahii	33.87	1.37	<0.01
Phascolarctobacterium faecium	97.02	0.77	<0.01
Acidaminococcus intestini	22.44	1.03	<0.01
Prevotella bivia	266.72	1.35	<0.01
Porphyromonas asaccharolytica	23.1	1.4	<0.01
Atopobium vaginae	31.64	1.49	<0.01
Bacteroides caccae	99.1	1.17	<0.01
Eubacterium coprostanoligenes	43.64	0.6	<0.01
Bacteroides fragilis	489.04	1.25	<0.01
Mycoplasma hominis	30.28	1.18	<0.01
Prevotella timonensis	62.07	1.05	<0.01
Ruthenibacterium lactatiformans	62.81	1.65	0.01
Fusobacterium equinum	682.93	1.33	0.01
Bacteroides vulgatus	1857.79	1.11	0.01
Neglecta timonensis	3.09	1.02	0.01
Jonquetella anthropi	12.42	1.18	0.01
Desulfovibrio piger	150.7	1.1	0.01
Butyrivibrio crossotus	14.9	0.66	0.01
Finegoldia magna	689.45	1.22	0.02
Enterobacter cloacae	17.91	1.42	0.02
Hungatella hathewayi	16.18	1.4	0.03
Brevibacterium paucivorans	10.88	1.43	0.03
Fusobacterium ulcerans	9.68	0.67	0.04
Alistipes finegoldii	33.56	1.12	0.05

Conclusions: In this cohort, the microbiome of the anal canal is distinct from the remainder of the gastrointestinal tract. Differences in its bacterial community are associated with development of anal

canal HSIL in hr-HPV patients.

ORAL SESSION 2: CERVICAL/ANAL SCREENING AND MANAGEMENT

VALIDATION OF HOST CELL DNA METHYLATION MARKERS FOR CANCER RISK STRATIFICATION OF HIGH-GRADE ANAL INTRAEPITHELIAL NEOPLASIA IN HIV-POSITIVE MEN

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Introduction: High-grade anal intraepithelial neoplasia (HGAIN; AIN2/3) are highly prevalent in HIV+ men, but only a minority will progress towards cancer. Currently, risk of progression cannot be established, and therefore all HGAIN are treated, resulting in overtreatment. In this study we validated previously identified host cell DNA methylation markers for the detection of HGAIN and anal cancer in an independent dataset, and assessed their association with progression to cancer.
Methods: A large cross-sectional series of 345 anal cancer, AIN3, AIN2, AIN1 and control tissue specimens of HIV+ men was tested for DNA methylation of six genes using quantitative methylation-specific-PCR. We determined accuracy for detection of AIN3 and cancer (AIN3+) by simple and multiple logistic regression, followed by leave-one-out-cross-validation. In a longitudinal series of cases with biopsies of both anal cancer and preceding HGAIN at the same localization, we compared methylation levels to the cross-sectional series.
Results: Methylation of all genes increased with increasing severity of disease (p<0.05). HGAIN revealed a heterogeneous methylation pattern, with a subset resembling cancer. The gene *ZNF582* showed highest accuracy (AUC=0.88) for AIN3+ detection, which was slightly improved by addition of *ASCL1* and *SST* (AUC=0.89). In the longitudinal series, HGAIN preceding cancer displayed high methylation levels, similar to cancers.
Conclusions: We validated methylation markers for the detection of anal cancer and HGAIN; high methylation levels in HGAIN were associated with progression to cancer. Therefore, these markers provide a promising tool to identify HGAIN in need of treatment, preventing overtreatment of HGAIN with a low cancer risk.

ORAL SESSION 3: CLINICAL ASPECTS OF CERVICAL PREVENTION AND TREATMENT

CLEARANCE OF HSIL AND MODULATION OF IMMUNE RESPONSES TO HPV ONCOGENES WITH LOW DOSE POMALIDOMIDE: A PHASE II STUDY IN INDIVIDUALS WITH PERSISTENT ANAL HSIL

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Introduction: Anal high-grade intraepithelial lesions (HSIL), present a target for early intervention and cancer prevention. Spontaneous HSIL clearance is associated with systemic CD4 T-cell response to the HPV oncogene E6. Pomalidomide may enhance immune responses to HPV and be therapeutic in HSIL.
Methods: This phase II single centre study (NCT3113942) recruited participants with persistent (>12 months) biopsy-proven anal HSIL. Therapy was oral pomalidomide, 2mg for 21 of 28 days for up to 6 months. Primary outcome was response at end therapy (CR defined as histological clearance; PR as ≥50% reduction in area); secondary included response after 6 further months observation. Immune activation markers (CD38, HLA DR) were assessed with flow cytometry and antigen-specific CD4+ T-cell responses to HPV E6 and E7 with OX40 immunoassay.
Results: 26 participants were enrolled, 24 were evaluable for response. All male; median age 54 (range 41-74). All AIN3 HSIL, median duration HSIL 37 months (15-86), median octants 2 (0.5-5); HPV16 in 55%; multiple high risk HPV types in 50%. Overall response (CR+PR) was 52% (CI: 31-73) at end therapy, increasing to 63% (95% CI 40-81) after 6 further months observation. Adverse events (AEs) were mild and self-limited, including cytopenias, constipation, and rash. Over 137 cycles (c), attributable grade 3/4 events were grade 3 neutropenia (4 c) and grade 3 angina (1 c). Systemic CD4 T-cell responses to HPV E6 but not E7 increased significantly during therapy, peaking day 14 of therapy: baseline 0.06%, (IQR 0.01 – 0.12%), median increase day 14 0.13% (IQR: 0.02 – 0.26%), p=0.001. Activation of CD4 and CD8 cells increased significantly during therapy. Parameters returned to baseline after therapy.
Conclusions: Low dose pomalidomide was tolerated and induced durable continuing clearance of anal HSIL of multiple genotypes in even in chronic extensive disease. Induced HPV-specific CD4+ responses and immune activation support an immunological mechanism of action.

ORAL SESSION 3: CLINICAL ASPECTS OF CERVICAL PREVENTION AND TREATMENT

COMPARISON OF TITERS IN THE GARDASIL IMMUNOGENICITY WITH NEEDLE-FREE INJECTION TRIAL AND THE COSTA RICA HPV VACCINE TRIAL SUGGEST CLINICAL PROTECTION BY NEEDLE-FREE INJECTION

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Introduction: Needle-free injection (NF) in the intra-dermal (ID) space uses one-fifth the vaccine volume, reduces pain and can decrease costs. A pilot trial of 150 women aged 18-26 in Thailand (GINI) compared the immunogenicity of of NF-ID and NF-intra-muscular (NF-IM) injections to standard needle-syringe IM (NS-IM) using three doses of the quadrivalent-HPV (qHPV) vaccine. All groups had high rates of seroconversion, but HPV16 titers were inferior to MS-IM in the NF-ID group. As the GINI trial did not assess clinical efficacy, we conducted an immunobridging study to compare GINI-immunogenicity to bivalent HPV (bHPV)-vaccine-induced antibodies in similarly-aged participants in the Costa Rica HPV Vaccine Trial (CVT), where clinical efficacy was demonstrated.
Methods: Women in GINI aged 18-26 were randomized into three arms (n=50 per group): NS-IM; NF-IM; NF-ID, and followed 24-months. For immunobridging assessment, available month-24 GINI sera were re-tested alongside month-24 sera from 60 CVT women (30 1-dose and 30 standard-dose [3-dose or 2-dose at 0/6 months), aged 18-25. Sera from both studies were tested by ELISA and SEAP (NCI-HPV Immunology Laboratory).
Results: By ELISA, nearly all women seroconverted regardless of vaccination group (Table). Three doses of NF-IM injection of qHPV elicited significantly higher geometric mean titer (GMT) values for HPV16 and 18 compared to 1-dose of bHPV (GMT ratio HPV16: 2.06 [95%CI 1.22 to 3.48] and HPV18: 1.65 [1.03 to 2.65]). Three-doses NF-ID injection of qHPV elicited GMTs no different from 1-dose of bHPV: ratio of GMTs for HPV16 1.21 (0.70 to 2.08) and HPV18 0.94 (0.62 to 1.44). All groups receiving qHPV, regardless of administration route, had inferior GMTs to women who received standard dosing of bHPV. Results were similar using SEAP.

Table. Comparisons of HPV16 (top) and HPV18 (bottom) antibodies at 24-months post-dose 1, measured by ELISA, across vaccinated groups

GINI							CVT						GMT Ratio (95%CI)
HPV16	N	GMT	SD	Range	IQR	%+		N	GMT	SD	Range	IQR	%+	HPV16
Needle-syringe IM (NS-IM)	40	59.1	66.4	2.2 - 654	32.9 - 114	100	1 dose	30	21.3	21.7	3.2 - 286	9.2 - 41.8	100	2.77 (1.65 to 4.66)
							2 (0/6) or 3 dose	30	232	181	37 - 1589	127 - 363	100	0.25 (0.16 to 0.40)
Needle-free IM (NF-IM)	37	44.0	48.5	4.5 - 652	22.4 - 75.7	100	1 dose	30	21.3	21.7	3.2 - 286	9.2 - 41.8	100	2.06 (1.22 to 3.48)
							2 (0/6) or 3 dose	30	232	181	37 - 1589	127 - 363	100	0.19 (0.12 to 0.31)
Needle-free ID (NF-ID)	45	25.8	31.9	0.8 - 330	12.8 - 41.8	97.8	1 dose	30	21.3	21.7	3.2 - 286	9.2 - 41.8	100	1.21 (0.70 to 2.08)
							2 (0/6) or 3 dose	30	232	181.3	37 - 1589	127 - 363	100	0.11 (0.07 to 0.18)
HPV18	N	GMT	SD	Range	IQR	%+		N	GMT	SD	Range	IQR	%+	HPV18
Needle-syringe IM (NS-IM)	40	20.2	20.7	2.8 - 248	10.4 - 41.7	100	1 dose	30	10.1	10.4	2.1 - 137	4.8 - 13.8	100	2.00 (1.22 to 3.29)
							2 (0/6) or 3 dose	30	85.0	81.3	12.1 - 1887	48.5 - 148	100	0.24 (0.15 to 0.38)
Needle-free IM (NF-IM)	37	16.6	14.9	2.9 - 111	10.0 - 29.5	100	1 dose	30	10.1	10.4	2.1 - 137	4.8 - 13.8	100	1.65 (1.03 to 2.65)
							2 (0/6) or 3 dose	30	85.0	81.3	12.1 - 1887	48.5 - 148	100	0.20 (0.12 to 0.31)
Needle-free ID (NF-ID)	45	9.5	7.4	1.6 - 46.8	5.1 - 16.5	100	1 dose	30	10.1	10.4	2.1 - 137	4.8 - 13.8	100	0.94 (0.62 to 1.44)
							2 (0/6) or 3 dose	30	85.0	81.3	12.1 - 1887	48.5 - 148	100	0.11 (0.07 to 0.17)

IM Intramuscular, ID Intradermal, GMT Geometric Mean Titer, SD Standard deviation, IQR Intraquartile range, %+ percent seropositive

Conclusions: Lower titers obtained by NF-ID administration were no different than single-dose titers obtained after bHPV, previously shown to provide clinical protection against HPV infection. NF approaches merit further study and development.

ORAL SESSION 3: CLINICAL ASPECTS OF CERVICAL PREVENTION AND TREATMENT

IMMUNOGENICITY AND SAFETY OF A NINE-VALENT HUMAN PAPILLOMAVIRUS VACCINE IN WOMEN AGED 27–45 YEARS VERSUS 16–26 YEARS: AN OPEN-LABEL PHASE 3 TRIAL

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Introduction: The efficacy of the nine-valent human papillomavirus (9vHPV; HPV 6/11/16/18/31/33/45/52/58) vaccine has been demonstrated in women aged 16–26 years. Our study compared 9vHPV vaccine immunogenicity and safety in women aged 27–45 years with women aged 16–26 years.
Methods: Participants received the 9vHPV vaccine on Day 1, Month 2 and Month 6. Blood was collected for immunogenicity testing on Day 1 and Month 7. A distinct per-protocol immunogenicity population was assessed for each HPV type. Anti-HPV 6/11/16/18/31/33/45/52/58 geometric mean titers (GMTs) and seropositivity rates at Month 7 were summarized. The primary objective was to demonstrate non-inferiority of anti-HPV 16/18/31/33/45/52/58 GMTs in women aged 27–45 years versus 16–26 years, which required ruling out a >2-fold decrease in immunogenicity between these age groups. The safety evaluation included injection-site and systemic adverse events (AEs) for 15 days post-vaccination and serious AEs (SAEs) during the entire study.
Results: 1,212 women enrolled (570 aged 16–26 years; 642 aged 27–45 years); 1,210 received ≥1 dose of 9vHPV vaccine. Month 7 anti-HPV 16/18/31/33/45/52/58 responses in women aged 27–45 years were non-inferior to women aged 16–26 years, and GMT ratios for these HPV types ranged from 0.66–0.73; the 95% CI lower bounds ranged from 0.60–0.67, demonstrating non-inferiority. Seroconversion for each of the 9 HPV types was >99% in both groups. A similar proportion of women aged 16–26 years and 27–45 years experienced injection-site AEs (85.5% versus 87.9%, respectively) and vaccine-related systemic AEs (24.1% versus 25.1%, respectively). No participants died during the study and there were no vaccine-related SAEs.
Conclusions: The 9vHPV vaccine was highly immunogenic in women aged 16–45 years, resulting in non-inferior anti-HPV GMTs in women aged 27–45 years compared with 16–26 years; the 9vHPV vaccine was generally well tolerated.

ORAL SESSION 3: CLINICAL ASPECTS OF CERVICAL PREVENTION AND TREATMENT

VAGINAL SELF-SAMPLING EQUIVALENT TO ASSISTED SAMPLING IN HPV PREVALENCE AND DETECED CIN2+ FOR SAMPLES APPLIED TO THE FTA CARD AND ANALYZED WITH THE HPVIR TEST

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Introduction: In Sweden 65% of all cervical cancer cases occur in women not attending the organized screening program. By providing the option of self-sampling, the population coverage can be increased and non-attenders be included in the organized screening. In this randomized study we compared vaginal self-sampling with assisted sampling by medical personnel on the cervix for HPV testing in primary screening. The first aim was to determine if the HPV prevalence is independent of sampling location (vagina versus cervix) and the person performing the sampling. The second aim was to evaluate if the two sampling strategies differed in the detection rate of CIN2+.
Methods: In total, 19,523 women were randomized into two groups, with 9,926 invited to perform self-sampling (SS arm) using the Rover VIBA-brush and 9,597 were offered assisted sampling using the cytobrush (AS arm). Samples in both groups were applied to the indicating FTA elute card and analyzed for high-risk HPV using the HPVIR real-time PCR assay.
Results: The participation in the SS arm was 52.7% as compared to 34.2% in the AS arm. All samples contained sufficient amount of nuclear DNA for a valid HPV result, with vaginal samples having a higher DNA amount than cervical samples ($p < 4.62 \times 10^{-11}$). HPV prevalence was 4.6% in the SS arm and 4.1% in the AS arm ($p = 5.5 \times 10^{-2}$), and the distribution of HPV types was similar between arms. There was no difference in the prevalence of CIN2+ per 1,000 women screened between arms ($p = 0.86$).
Conclusions: Vaginal self-sampling is an equivalent alternative to cervical sampling by medical personnel using the indicating FTA card and the HPVIR assay for identification of CIN2+.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

FAM19A4/MIR124-2 METHYLATION ANALYSIS AS A TRIAGE TEST FOR HPV-POSITIVE WOMEN: CROSS-SECTIONAL AND LONGITUDINAL DATA FROM A SCREENING COHORT

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Introduction: As primary HPV-based cervical cancer screening is increasingly being implemented in many countries, there is a high need for an accurate, objective triage tool to identify women with clinically relevant disease.
Methods: We conducted a post-hoc analysis within a Dutch population-based HPV-positive study cohort (NTR215, ISRCTN64621295) of women aged 30-60 years (*n* = 979) to evaluate the triage performance of *FAM19A4/miR124-2* methylation analysis. Bisulphite converted DNA from baseline HPV-positive cervical smears was subjected to DNA methylation analysis for *FAM19A4* and *miR124-2* genes, using the QIAsure methylation test®. Histopathologic and cytopathologic follow-up data were collected through the Dutch Pathology Registry (PALGA). Cross-sectional sensitivity, specificity, NPV and PPV and cumulative CIN3+ risks after 9- and 14-years were compared for five baseline triage strategies*: FAM19A4/miR124-2* methylation analysis, cytology, HPV16/18 genotyping, HPV16/18 genotyping with *FAM19A4/miR124-2* methylation, and HPV16/18 genotyping with cytology.
Results: *FAM19A4/miR124-2* methylation positivity proportion was significantly associated with underlying disease severity. The CIN3+ sensitivity of *FAM19A4/miR124-2* methylation analysis was equal to that of cytology (71.3% vs 76.0%, ratio 0.94, 95%CI: 0.84–1.05), at a slightly lower specificity (78.3% vs 87.0%, ratio 0.90, 95%CI: 0.86–0.94). Combining HPV16/18 genotyping with either *FAM19A4/miR124-2* methylation analysis or cytology resulted in a comparable increase in sensitivity (87.1% vs 90.6%, ratio 0.96, 95%CI: 0.92–1.01), at a decrease in specificity (58.0% vs 63.7%, ratio 0.91, 95%CI: 0.87–0.95). Equal 9- and 14-year CIN3+ risks for baseline cytology-negative women and baseline *FAM19A4/miR124-2* methylation-negative women were observed, with risk differences of -0.34 (95%CI: -2.0–1.3) and 0.05% (95%CI: -1.8–1.9), respectively.
Conclusions: *FAM19A4/miR124-2* methylation analysis has a good triage performance on baseline screening samples, equalling cross-sectional sensitivity and long-term negative predictive value of cytology triage testing. Therefore, *FAM19A4/miR124-2* methylation analysis, with or without HPV16/18 genotyping, is a promising alternative to cytology in triage scenarios in HPV-based cervical screening.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

CUMULATIVE INCIDENCE RATES OF CERVICAL NEOPLASIA STRATIFIED BY EXTENDED GENOTYPING DURING THE THREE-YEAR LONGITUDINAL PHASE OF THE ONCLARITY TRIAL

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Introduction: Evidence suggests that human papillomavirus extendedgenotyping (HPV-xGT ; beyond 16/18) is effective for risk stratification in women with normal cytology and in risk-based triage for women with atypical squamous cells-undetermined significance (ASC-US) or low-grade squamous intraepithelial lesions (LSIL) cytology. Here, 3-year cumulative incidence rates (CIR), associated with HPV-xGT,were determined for cervical intraepithelial neoplasia, grade 3 or worse (≥CIN3).
Methods: Women (N=29,513) were screened and referred to colposcopy/biopsy based on ≥ASC-US cytology or an HPV(+) result (5% normal cytology and HPV(-) controls also referred) at baseline (BL). Hierarchical ranked ≥CIN3 absolute risks(AR) values at BL, were calculated based on HPV-xGT results. Untreated women were invited for yearly follow up and had colposcopies/biopsies and treatment per protocol. Colposcopy referrals at yrs 1-3 occurred based on cytology (≥ASC-US); all women received colposcopy at yr 3. Three-year ≥CIN3CIR values, were calculated based on HPV-xGT results. Data analysis involved verification bias adjustment.
Results: Following screening with the Onclarity assay, the number of BL ≥CIN3 cases was 199 (AR: 5.3%). The three-year CIR associated with any HPV(+) result for ≥CIN3 was 7.5%. In the NILM population, three-year HPV-xGT-stratified CIR values for ≥CIN3 were: any HPV(+)=4.4%, HPV16=11.9%, HPV31=9.0% , HPV18=4.4%, HPV33/58=2.9%, HPV52=2.3%, HPV45=2.8%, HPV35/39/68=1.6%, HPV51=1.0%, HPV56/59/66=0.3%, and HPV(-)=0.1%. In the ASC-US/LSIL (combined) population three-year stratified CIR values for ≥CIN3 were: any HPV(+)=8.6%, HPV16=22.3%, HPV31=13.8% , HPV18=6.6%, HPV33/58=3.7%, HPV52=6.3%, HPV45=2.1%, HPV35/39/68=5.2%, HPV51=8.6%, HPV56/59/66=0.0%, and HPV(-)=0.8%.
Conclusions: While the three-year ≥CIN3 CIR associated with HPV16 and 31 exceeded the consensus USA risk threshold for colposcopy referral, the management of NILM associated with intermediate- or lower-risk GT results may shift based on evolving estimates or other clinical factors. HPV-xGT identified multiple three-year CIR bands for ≥CIN3 in the ASC-US/LSIL population. A follow-up period could preclude immediate colposcopy for ASC-US/LSIL cytology associated with the lowest-risk HPV GTs.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

PERFORMANCE OF SHORT-TERM REPEAT HPV TEST FOR THE TRIAGE OF HPV-POSITIVE WOMEN IN LATIN AMERICA: AN ANALYSIS WITHIN THE ESTAMPA STUDY (NCT01881659)

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Introduction: A single HPV test is highly sensitive for precancerous cervical lesions detection but has limited specificity leading to unnecessary colposcopy. Most HPV infections are transient and clear within the first year. The period between screening and colposcopy could be sufficiently balanced to allow a significant HPV clearance fraction and adequate early clinical management. We aimed to evaluate the performance of repeating the HPV test at the colposcopy visit for the triage of HPV-positive women in the ESTAMPA study.
Methods: ESTAMPA is a multicentric study in Latin America in which women aged 30-64 are screened with HPV (HC2 or Cobas) and cytology, and referred to colposcopy (with biopsy as appropriate) if any screening positive result. Cervical cells are collected using Cervix-Brush and placed in preservation medium for HPV test and additional tests. At the colposcopy visit, cervical cells are collected using a Dacron swab to repeat HPV test (same used for screening). We evaluated the performance of repeat HPV test for the detection of CIN2+ in screened HPV-positive women.
Results: Among 35,473 participants, 5028 (14%) tested HPV-positive and 4062 of them had colposcopy and a repeat HPVat that visit. The median time between screening and colposcopy visit was 1.8 months (interquartile range 1.2-2.6), and 39.3% (95%CI=37.8-40.9) of HPV-positive women cleared the infection. 610 CIN2+ cases (15%) were detected (217 CIN2, 355 CIN3, and 38 cancers). The sensitivity, specificity, and positive predictive value were 83.8% (95%CI=80.6-86.5), 43.4% (95%CI=41.8-45.1), and 20.7% (95%CI=19.2-22.4), respectively. Sensitivity (and infection clearance) improved from 82.7% (37.6%) if the test was repeated at <3.5 months to 91.3% (48.8%) if later. Performance did not vary with age.
Conclusions: Short-term repeat HPV test seems to retain acceptable sensitivity, potentially reducing the colposcopy referral to 60%. Short-term HPV persistence strategies could help to improve the acceptability of HPV-based cervical screening programs in certain clinical contexts.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

LONGITUDINAL CLINICAL PERFORMANCE OF TRIAGE STRATEGIES FOR THE RISK STRATIFICATION OF PRIMARY HPV INFECTION; AN UPDATE FROM THE PAVDAG COHORT

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Introduction: A key consideration when considering optimal triage strategies for primary HPV infection is longitudinal performance, yet few studies have assessed performance over more than one screening round. We previously reported a cross-sectional evaluation of triage strategies (cytology, cytology with dual stain, 16/18 typing) in women who routinely attended for cervical screening in Scotland. The present work describes performance over a longer 5 year period.
Methods: A subset of women (n=350) from the Papillomavirus Dumfries and Galloway (PaVDaG) study attended for routine screening, were HPV+ and had HPV 16/18 typing, LBC and p16/ki-67 dual-stained cytology (DS) at baseline. Cumulative incidence rate (CIR) of CIN2 within 66 months of the primary HPV+ test was measured and related to the various triage strategies, individually and in combination. Sensitivity, specificity, PPV and NPV for the detection of disease (@CIN2+ and @CIN3+) during follow up was measured.
Results: Over 66 months, sensitivities for cytology 16/18 typing and DS were 62.9% (50.5-74.1), 61.4% (49.0-72.8) & 74.3% (62.4-84.0) respectively, whereas specificity was 82.9% (77.0-87/1), 74.3% (68.8-79.3) & 74.3% (68.6-79.3). Women who were negative for 16/18, cytology and DS had a low risk of disease with only 4 cases detected during follow up; CIR of 2.7% (0.7-6.8)
Conclusions: Of the three technologies; DS was the most sensitive and LBC the most specific over the follow up period. Irrespective of triage strategy imposed, most cases of disease manifested within two years from the baseline HR-positive result. Around 40% of women tested negative for all triages imposed and this group had a very low risk of disease; this group could credibly be returned to (minimum) 3 yearly recall as their risk of disease over this period is less than 2%.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

COMBINED USE OF CYTOLOGY, P16 IMMUNOSTAINING AND GENOTYPING FOR TRIAGE OF WOMEN POSITIVE FOR HIGH RISK HUMAN PAPILLOMAVIRUS AT PRIMARY SCREENING

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Introduction: HPV testing is a very sensitive method of primary cervical screening, but its specificity is low. Triage tests which improve specificity, but still maintain high sensitivity are needed.
Methods: Women enrolled in the experimental arm of phase 2 of the NTCC randomised controlled cervical screening trial were tested for high risk human papillomavirus (hrHPV) and referred to colposcopy if positive. hrHPV positive women also had HPV genotyping (by PCR with GP5+/GP6+ primers and reverse line blotting), immunostaining for p16 overexpression and cytology. We computed the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for different combinations of tests, and determined potential hierarchical ordering of triage tests.
Results: 1091 HPV positive women had valid tests for cytology, p16 and genotyping, of which, 92 were histologically CIN2+ and 40 CIN3+. The PPV for CIN2+ was >10% in hrHPV positive women with HSIL+ (61.3%), LSIL+ (18.3%) and ASCUS+ (14.8%) cytology, p16 positivity (16.7%), and hierarchically for infections by HPV33, 16, 35, 59, 31 and 52 (in decreasing order). Referral of women positive for either p16 or LSIL+ cytology gave a sensitivity of 97.8% for CIN2+, and woman negative for both of these had a 3-year CIN3+ risk of 0.5%. Similar results were seen for women either p16 or HPV16 positive.
Conclusions: hrHPV+ women who were negative for p16 and LSIL+ had a very low CIN3+ rate in the next three years. Recalling them after that interval and referring those positive for either test, in each combination, to immediate colposcopy appears to be an efficient triage strategy.

ORAL SESSION 4: TRIAGE APPROACHES FOR HPV-POSITIVE WOMEN

DIAGNOSTIC ACCURACY OF P16(INK4A) IMMUNOSTAINING FOR PRIMARY CERVICAL CANCER SCREENING AND TRIAGE OF HPV-POSITIVE WOMEN

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Introduction: p16(INK4a) is an important biomarker for transforming HPV infections. We assessed the performance of p16(INK4a) immunostaining in primary cervical cancer screening and triaging the HPV positive women to colposcopy, compared to current mainstream primary and triage algorithms.
Methods: Women (N = 2,112) aged 49–69 from Shanxi, China underwent screening with p16(INK4a) immunostaining (SENYING Biology, China), liquid-based cytology (LBC) and three HPV tests including HC2 (Hybrid Capture 2), GenplexHPV (BOHUI, China) and SureX® HPV 25X Genotyping Kit (HEALTH BioMed, China). Any positive results triggered colposcopy and biopsy if indicated. p16/Ki-67 dual-stained cytology was performed for women with HC2-positive results. The diagnostic performance of p16(INK4a) immunostaining for the detection of biopsy-confirmed cervical intraepithelial neoplasia grade 3 or worse (CIN3+) was determined and compared to other primary and triage strategies.
Results: In primary screening, p16(INK4a) immunostaining was more specific (92.0%) than other methods including HC2 (81.0%), LBC with ASC-US+ cutoff (89.7%), GenplexHPV (78.3%) and SureX® HPV (77.7%) ($p<0.01$ for all); whereas the sensitivity (90.3%) was comparable to all mentioned tests ($p>0.05$ for all). Of note, p16(INK4a) immunostaining required the lowest colposcopy referral rates (10.3%) as well as the number of colposcopies per CIN3+ detected (7.5). For the triage of HC2-positive women, sensitivity of p16(INK4a) immunostaining was not significantly higher than LBC (90.0% vs. 83.3%, $p>0.05$), but higher than p16/Ki-67 dual-stained cytology (55.3%) and HPV16/18 genotyping (56.7% by GenplexHPV and 63.3% by SureX® HPV) ($p<0.05$ for all); while the specificity was comparable to LBC and p16/Ki-67 dual-stained cytology (66.6% vs 63.5% vs 72.1%, $p>0.05$), but lower than HPV16/18 genotyping by both GenplexHPV and SureX® HPV ($p<0.01$ for both).

Table 1 Performance of different primary screening tests for the detection of CIN3 + cases [n(CIN3+)=31; N=2048*]

	Test	Colposcopy referral rates(%)(n/N)	Sensitivity(%)(n/N) 95% CI	Specificity(%)(n/N) 95% CI	PPV(%)(n/N) 95% CI	NPV(%)(n/N) 95% CI	NNR
1	**p16(INK4a) immunostaining**	**10.25(210/2048)**	**90.32 (28/31) 74.25-97.96**	**91.97 (1855/2017) 90.70-93.12**	**14.74 (28/190) 10.02-20.59**	**99.84 (1855/1858) 99.53-99.97**	**7.5**
2	HC2	22.07(452/2048)	96.77 (30/31) 83.30-99.92	81.01 (1634/2017) 79.23-82.70	7.26 (30/413) 4.95-10.21	99.94 (1634/1635) 99.66-100.00	15.1
3	LBC(ASCUS+)	12.50(256/2048)	80.65 (25/31) 62.53-92.55	89.69 (1809/2017) 88.28-90.98	10.73 (25/233) 7.07-15.43	99.67 (1809/1815) 99.28-99.88	10.2
4	GenplexHPV (for 18 types#)	24.85(509/2048)	90.32 (28/31) 74.25-97.96	78.33 (1580/ 2017) 76.47-80.11	6.02 (28/465) 4.04-8.59	99.81 (1580/1583) 99.45-99.96	18.2
5	SureX® HPV (for 18 types#)	25.54(523/2048)	93.55 (29/31) 78.58-99.21	77.74 (1568/2017) 75.86-79.54	6.07 (29/478) 4.10-8.60	99.87 (1568/1570) 99.54-99.98	18.0

Note: *A total of 2,112 women were screened and 64 women were excluded due to the incomplete screening results or lost for further colposcopy examination; #GenplexHPV for 18 types including HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, 82 and 83; SureX® HPV for 18 types including HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73 and 82;

Table 2 Performance of triage for the detection of CIN3+ among HC2-positive women [n(CIN3+)=30; N=413*]

	Test	Colposcopy referral rates(%)(n/N)	Sensitivity(%)(n/N) 95%CI	Specificity(%)(n/N) 95%CI	PPV(%)(n/N) 95%CI	NPV(%)(n/N) 95%CI	NNR
1	**p16(INK4a) immunostaining**	**37.53(155/413)**	**90.00(27/30) 73.47-97.89**	**66.58(255/383) 61.61-71.29**	**17.42(27/155) 11.80-24.32**	**98.84(255/258) 96.64-99.76**	**5.7**
2	ASCUS+	39.95(165/413)	83.33(25/30) 65.28-94.36	63.45(243/383) 58.40-68.28	15.15(25/165) 10.05-21.55	97.98(243/248) 95.36-99.34	6.6
3	p16/Ki67	29.78(123/413)	53.33(16/30) 34.33-71.66	72.06(276/383) 67.28-76.50	13.01(16/123) 7.62-20.26	95.17(276/290) 92.03-97.34	7.7
4	GenplexHPV _16/18*	17.19(71/413)	56.67(17/30) 37.43-74.54	85.90(329/383) 82.01-89.23	23.94(17/71) 14.61-35.54	96.20(329/342) 93.59-97.96	4.2
5	SureX® HPV _16/18*	16.71(69/413)	63.33(19/30) 43.86-80.07	86.95(333/383) 83.15-90.15	27.54(19/69) 17.46-39.62	96.80(333/344) 94.35-98.39	3.6

Note: *A total of 452 women were tested HC2-positive, and 3 were excluded due to inconclusive histological diagnosis and 37 excluded due to lost for further colposcopy examination;

Conclusions: p16(INK4a) immunostaining, either as primary or triage method, showed a good “trade-off” between sensitivity and specificity with more efficient colposcopy referrals, which is of great importance to maximize the benefits of a cervical cancer screening program.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

A PRIMARY HUMAN PAPILLOMAVIRUS ALGORITHM WITH INTEGRATED 16/18 GENOTYPING USING THE ONCLARITY ASSAY FOR CERVICAL CANCER SCREENING: BASELINE AND THREE-YEAR TRIAL RESULTS

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Introduction: The Onclarity Trial was performed to assess the performance of the BD Onclarity human papillomavirus (HPV) assay during cervical cancer screening. Baseline and three-year longitudinal performance risk values for primary screening of women, ≥25 years of age, for cervical intraepithelial neoplasia, grade 3 (≥CIN3) are reported here.
Methods: 29,513 enrolled women had cytology and valid HPV results. We modeled the current FDA-approved algorithm for primary screening whereby HPV16/18 positive women are referred to immediate colposcopy and those positive for the other 12 high-risk genotypes are referred based on cytology triage. Performance was also determined for ASC-US triage and hybrid screening (ASC-US triage for 25-29 years and co-testing for ≥30 years). Detection of adjudicated ≥CIN3 and number of colposcopies/≥CIN3 detected were outcomes. All data analysis included verification-bias adjustment.
Results: Baseline risk for any HPV(+), HPV16, HPV18, HPV16/18, ASC-US/Other 12 HPV (+), and HPV (-) were 5.3%, 14.2%, 5.2%, 12.2%, 5.3%, and 0.1%, respectively, for ≥CIN3. Baseline sensitivity for HPV 16/18 primary screening was 72.3%; baseline sensitivity values for ASC-US triage and hybrid screening were both 53.7%. The ratio of colposcopies/≥CIN3 at baseline for HPV16/18 primary, ASC-US triage, and hybrid screening were 11.2, 11.8, and 11.8, respectively. Three-year cumulative incidence rate values for any HPV(+), HPV16, HPV18, HPV16/18, ASC-US/Other 12 HPV (+), and HPV (-) were 7.5%, 18.7%, 8.0%, 16.4%, 8.8%, and 0.2%, respectively, for ≥CIN3. Three-year cumulative ≥CIN3 sensitivity for HPV16/18 primary screening was 85.8%; three-year cumulative sensitivity for ASC-US triage and hybrid screening strategies were 52.1% and 73.1%, respectively. The three-year ratio of total colposcopies/total ≥CIN3 for HPV16/18 primary, ASC-US triage, and hybrid screening was 18.3, 15.1, and 17.7, respectively.
Conclusions: Three-year data from this trial clinically validates Onclarity for HPV16/18 primary screening to provide effective risk stratification requiring colposcopic referral, independent of cytology, under current management guidelines.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

LOW-COST POC FOR THE DETECTION AND GENOTYPING OF HIGH-RISK HPV SUITABLE FOR LOW RESOURCED SETTINGS

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Introduction: Screening for the presence of HPV infection is recommended as primary triage for cervical cancer and together with vaccination programs is having an impact upon cervical cancer rates. In resource limited settings VIA is an accepted standard for screening, however it is less clinically sensitive than HPV testing and does not address social or cultural norms.
Methods: QuantuMDx and Global Good Fund have designed and developed an assay, for the detection of 14 high-risk HPV oncotypes, that runs on the Q-POC™ platform and provides affordable genotyping results in less than 40 minutes. The assay features sufficient validity and acceptance criteria to ensure result quality and interpretability.
Results: The Q-POC™ is a battery-powered molecular diagnostic device, which utilizes a disposable test cassette, offering rapid and low cost nucleic acidic amplification based testing, overcoming known issues of POCT in resource limited settings. The HR-HPV cassette can detect and identify 14 high-risk HPV oncotypes with specimen and internal process controls. The system also features a unique specimen collection kit suitable for both provider and self-collection of cervical and cervicovaginal specimens. The swab is added directly to the specimen tube and closing the tube seals the system and releases stabilisation buffer, immersing the swab. The specimen tube easily interfaces with the test cassette allowing for controlled transfer of the specimen to the test cassette. The prototype assay is currently undergoing an external evaluation study in Peru.
Conclusions: QuantuMDx has developed a novel system for the detection and genotyping of high-risk HPV. The system provides a solution which is less invasive and can offer compatibility with self-collected specimens. Specifically designed for low resource settings and providing a turnaround time conducive to screen and treat it is envisaged that Q-POC™ HR-HPV will offer a transformative option in the detection of cervical cancer.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

THE RELATIVE IMPORTANCE OF PAST AND CURRENT HPV STATUS, EXTENDED GENOTYPING, AND CYTOLOGY IN CERVICAL SCREENING

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Introduction: A yet unresolved question for risk-based cervical screening is the relative importance of current test results and past history.
Methods: Using 1.5 million women undergoing screening at Kaiser Permanente Northern California (KPNC), we estimated the 5-year cumulative risk of CIN3+ following a visit. Risk was estimated for combinations of immediately prior HPV status (negative/positive/unknown), current HPV status, current HPV genotyping group (16, else 18, else 45, else 31/33/52/58, else other), and current cytology; risks ranged from 0.1% to 75%. To examine the importance of each factor for risk stratification, we conducted a decision tree analysis while accounting for the frequency of occurrence in screening. Because availability of prior HPV status may differ for new versus well-established HPV-based screening programmes, we repeated the decision tree analysis stratified by unknown and known prior HPV status.
Results: At the population level, HPV-status was the most important factor for risk stratification. Among those currently HPV-negative, there was relatively little information to be gained from conducting a Pap test or from eliciting prior HPV status. In screening programs new to HPV testing, cytology is more important than genotyping for managing currently HPV-positive women because of the higher prevalence of pre-existing high-grade lesions. As screening with HPV becomes more established, HPV genotyping and past history becomes more important than current cytology.
Conclusions: As HPV-based screening programmes become more established, cytology becomes less important in management of HPV-positive women than knowing the HPV genotype and whether it is a new or a persistent infection.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

XPERT HPV AS AN IMPROVED SCREENING TOOL FOR ANAL HISTOLOGIC HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HHSIL) IN WOMEN LIVING WITH HIV (WLHIV)

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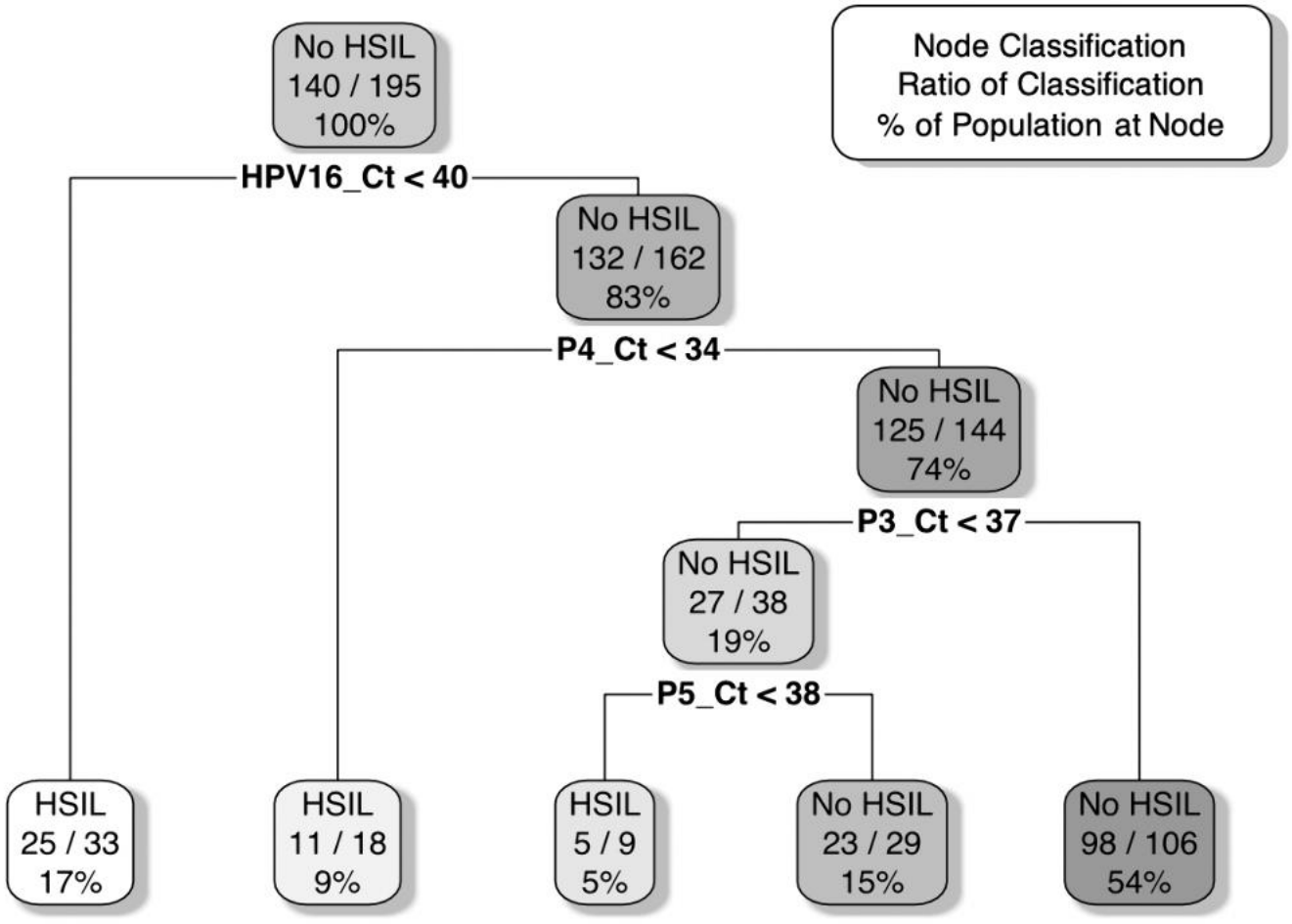
Introduction: WLHIV experience higher rates of anal cancer than the general population. Active screening using anal cytology and high-resolution anoscopy (HRA) can diagnose hHSIL, the anal cancer precursor. The low specificity of anal cytology results in high referral rates for HRA including many women without hHSIL. Screening using high-risk HPV (HR-HPV) tests may improve specificity and reduce the number of women unnecessarily referred for HRA. Xpert HPV is a point-of-care, PCR assay providing detailed HR-HPV results.
Methods: In AIDS Malignancy Consortium Protocol 084, 207 WLHIV (63% Black, 20% Hispanic) were screened for anal hHSIL using cytology, HRA with directed biopsies, and Xpert™ HPV from stored liquid cytology media. Xpert performance for predicting anal hHSIL was compared to cytology. Utilizing Xpert's 5 HPV genotypic results ((1) 16, (2) 18/45, (3) 31/33/35/52/58, (4) 51/59, (5) 39/56/66/68) and accompanying quantitative results, receiver operator curve (ROC) and recursive partitioning (RPART) analyses were used to create predictive models to improve test characteristics for hHSIL.
Results: Among the 195 WLHIV with available Xpert results, the prevalence of hHSIL and Xpert detection of HR-HPV were 28% (55) and 62% (121) respectively. The performance of unoptimized Xpert to predict hHSIL were not significantly different from cytology. Table 1 summarizes the best-performing Xpert models utilizing: (A) genotypic qualitative results and ROC analysis (see Table 2); (B) genotypic quantitative results using RPART analysis (see Figure 1). In all models, HPV 16 was strongly predictive of hHSIL. The lower abnormal screen rates of (A) and (B) reduces HRA referrals by almost half with a modest decrease in sensitivity compared to anal cytology.

	Abnormal Cytology (≥ ASCUS)	Xpert HPV	(A) Optimized Xpert Using Genotype and ROC	(B) Optimized Xpert Using Qualitative xResults and RPART
Abnormal Screen, %	61	62	34	31
hHSIL, n	45	49	42	41
Sensitivity, %	87	89	76	75
Specificity, %	49	49	82	86
PPV, %	39	41	63	68
NPV, %	90	92	90	90
Relative Change in Abnormal Screen vs Cytology, %		+2	-44	-49
WLHIV with Missed hHSIL, %	3.7	3.1	6.7	7.2

Xpert Result	Participants with Genotypic Result, n (%)	Prevalence of hHSIL in Participants with Genotypic Result, n (%)	Odds Ratio [95% CI]
16	33 (17)	25 (75)	38.5 [9.8,199.5]*
18/45	32 (16)	9 (28)	1.6 [0.2,2.0]
31/33/35/52/58	69 (35)	31 (45)	4.4 [1.8,11.2]†
51/59	32 (16)	20 (63)	4.6 [1.6,12.8]†
39/56/66/68	54 (28)	27 (50)	3.5 [1.3,9.7]†
16+31/33/35/52/58	17 (9)	12 (71)	0.1 [0.0,0.5]†
18/45+39/56/66/68	15 (8)	4 (27)	0.2 [0.0,1.5]



Conclusions: Xpert HPV is a viable point-of-care alternative to anal cytology to screen for HSIL and can be optimized to reduce the number of unnecessary HRAs performed in women living with HIV.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

EFFECT OF HPV VACCINATION IN PATIENTS WITH RECURRENT RESPIRATORY PAPILLOMATOSIS: RESULTS OF CLINICAL TRIAL IIIB

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Introduction: Recurrent respiratory papillomatosis (RRP) is a rare benign chronic disease of the larynx etiologically linked with the infection of low-risk human papillomavirus (HPV) types 6 and 11. RRP is characterized by voice changes, stridor, dyspnoea etc., tends to recur and spread throughout the aerodigestive tract. Treatment involves combination of surgical and immunomodulatory therapy, but repeated surgery often results in permanent voice disorders. As the immunotherapy presents unconvincing results, possible use of prophylactic tetravalent HPV vaccine that includes HPV 6 and 11 antigens has been studied.
Methods: Patients who signed the information consent form were included in the study (#50). Data on demographics, risk factors for RRP, and risks related to HPV exposure were collected by a questionnaire. The medical report was completed for each patient. All enrolled subjects underwent laryngostroboscopy and tissue and/or smear for HPV DNA detection and typing and blood for antibody detection were taken. The presence of HPV DNA was detected by reverse line blot hybridization, HPV-specific antibodies were detected by ELISA using individual virus-like particles as antigens. All but two patients underwent vaccination with three doses of tetravalent vaccine and were followed for 5 years. One and five years after the end of vaccination blood was taken for the detection of HPV-specific antibodies.
Results: Altogether, 42/50 patients finished the study. Most of patients were infected by HPV6. In all but 7 patients HPV6 and / or 11-specific antibodies were detected prior to vaccination. All subjects seroconverted after the 1st dose of the vaccine and the titers of antibodies increased at least tenfold. The results of the frequency of recurrences before and after the vaccination were also evaluated and will be presented.
Conclusions: HPV vaccination in adult patients with RRP has an individual benefit.

ORAL SESSION 5: VACCINES AND SCREENING IN HPV-RELATED DISEASE

IMPACT OF QUADRIVALENT HPV VACCINE DOSE SPACING ON IMMUNOLOGIC RESPONSE IN WOMEN LIVING WITH HIV

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Introduction: Vaccination schedules for HPV in the general population have changed as evidence has supported reduced dosing and extended intervals in adolescents aged <15. Girls and women living with HIV (WLWH) represent an important population in which no data on alternative dosing schedules exists.
Methods: 353 girls and WLWH received the quadrivalent HPV (qHPV) vaccine in a pan-Canadian study of immunogenicity and efficacy. Serology was performed at months 0/2/7/12/18/24. Medical and sexual history was collected at each visit up to eight years. Participants were divided into groups based on vaccine dose spacing: all three doses within 7 months (n=229), 7 months-1 year (n=56), or 1-2 years (n=22). Linear regressions were used to determine whether dose spacing had an impact on the peak geometric antibody titer achieved.
Results: 307 participants were eligible. Median age was 36 (IQR:26-44), median CD4 count was 532 cells/mm^3 (IQR:390-710), and 66% had suppressed HIV viral loads (<50 copies/ml). Median peak HPV16 log titer among dose spacing groups was 7.8 (IQR:7.1-8.4), 7.6 (IQR:6.7-8.4), and 7.2 (IQR:5.6-8.0) for within 7 months, 7 months-1 year, and 1-2 year groups, respectively. Multivariable analyses demonstrated a significant relationship between peak antibody titer and time to blood draw post last vaccine dose, naivety to the relevant HPV type, and HIV viral load for all qHPV types. There was a significant relationship between peak antibody titer and age, but only for HPV16/18. There was no significant association between the peak antibody titer and spacing of the vaccine doses.
Conclusions: Taking age, time to serology, CD4 cell count, CD4 nadir, HIV viral load, and HPV naivety into account, the spacing of the three qHPV vaccine doses did not significantly impact peak antibody titers. This is reassuring for real-world implementation of vaccine delivery in communities with high rates of HIV.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

PROGNOSTIC FACTORS OF RECURRENCE AND PROGRESSION TO MALIGNANCY IN VAGINAL INTRAEPITHELIAL NEOPLASIA: A MULTICENTER RETROSPECTIVE ANALYSIS.

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Introduction: Vaginal intraepithelial neoplasia (VaIN) is a rare premalignant condition of lower genital tract. Its natural history is still poorly understood, with most of lesions occurring in women with history of hysterectomy because of cervical precancers and cancers. The aim of this study was to investigate risk factors for recurrence and progression to invasive vaginal cancer in women diagnosed with VaIN.
Methods: Two hundred sixty-six women diagnosed with VaIN and attending the European Institute of Oncology, Milan, and the IRCCS Fondazione Policlinico San Matteo, Pavia, Italy, from January 2000 to December 2016, were included in a multicenter retrospective analysis. Principal clinic characteristics of patients, type of treatment and clinical outcome were recorded. The rates of recurrence and progression to malignancy and all potential prognostic factors were evaluated. Kaplan-Meier survival analysis was applied and a P-value <0.05 was considered statistically significant.
Results: Overall, patients had a mean age at diagnosis of 50.3 ± 13.0 years (range: 22-89) and the most were affected by VaIN3 (44.4%). After a median follow-up time of 23.0 ± 4.9 months, the rates of recurrence and progression to vaginal squamous carcinoma were 25.2% and 6.4% after a median time of 10.0 ± 3.5 and 7.0 ± 6.9 months, respectively. At univariate analysis, history of pregnancy (HR=1.68, 95% CI: 1.04 – 2.73; p=0.04), previous VaIN (HR=1.98, 95% CI: 1.14 – 3.43; p=0.02) and high-grade abnormal pap smear (HR=2.07, 95% CI: 1.24 – 3.46; p=0.005) were significantly associated to higher risk of recurrence/progression. On the contrary, concomitant CIN (p=0.04) and any kind of treatment (p=0.03) were identified as protective factors.
Conclusions: Women with VaIN are at higher risk of recurrence than progression, despite the type of treatment. A conservative management with a mandatory long-lasting follow-up could be suitable also in multiple recurrences.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

LESION-BASED ESTIMATES OF HUMAN PAPILLOMAVIRUS (HPV) PREVALENCE IN ANAL HIGH-GRADE SQUAMOUS INTRAPITHELIAL LESIONS (HSIL) IN GAY AND BISEXUAL MEN (GBM)

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Introduction: Laser capture microdissection (LCM) is an innovative approach that can be used to accurately assign HPV genotype causality to specific lesions. We analysed the prevalence of HPV infections in baseline samples of men with HSIL stratified by lesion grade and HIV status.
Methods: Samples were obtained as part of the Study of the Prevention of Anal Cancer (SPANC), a 3-year longitudinal cohort study of 617 GBM aged ≥35 years in Sydney, Australia. Participants had high-resolution-anoscopy-guided biopsy of lesions suspected to be HSIL and in those among whom HSIL was histologically confirmed, LCM was performed to excise anal intraepithelial neoplasia 2 (AIN2) and anal intraepithelial neoplasia 3 (AIN3) lesion-specific tissue. DNA extraction and HPV typing were performed using the Pico pure DNA extraction kit and HPV SPF10-LiPA25 RHA kit and SPF+ strips.
Results: At baseline, 196 (31.8%) men had histologically-confirmed anal HSIL. There was sufficient tissue for LCM and HPV genotyping in 171 men (87.2%). These 171 men had 239 distinct HSILs identified (183 AIN3 and 56 AIN2). Of these 171 participants, 84 (49.1%) were HIV-positive. Only single HPV infections were detected in HSIL (one lesion, one virus). HPV16 was the most prevalent AIN3 associate genotype (42.1%), followed by HPV58 (8.2%) and HPV31 (6.6%). HPV16 was more common in AIN3 than AIN2 lesions (42.1% vs 12.5%, $p<0.001$) while other high-risk HPV types were more common in AIN2 than AIN3 lesions ($p=0.002$) Table 1. Nonavalent vaccine types (HPV16,18,31,33,45,52,58) caused 77.1% of AIN3 and 57.1% of AIN2. HPV16 caused 27.6% of 116 HSIL in HIV-positive men and 42.3% of 123 HSIL in HIV-negative men ($p=0.017$).

		N	Any HR-HPV	HPV16	HR-HPV not 16	LR-HPV types	HPV Not Detected
			n (%)	n (%)	n (%)	n (%)	n (%)
All	HSIL	239	220 (92.1)	84 (35.2)	136 (56.9)	17 (7.1)	2 (0.8)
	AIN2	56	49 (87.5)	7 (12.5)	42 (75.0)	5 (8.9)	2 (3.6)
	AIN3	183	171 (93.4)	77 (42.1)	94 (51.4)	12 (6.6)	0 (0.0)
	p-value		*0.150*	*<0.001*	*0.002*	*0.546*	*0.054*
HIV Negative	HSIL	123	113 (91.9)	52 (42.3)	61 (49.6)	9 (7.3)	1 (0.8)
	AIN2	33	31 (93.9)	6 (18.2)	25 (75.8)	1 (3.0)	1 (3.0)
	AIN3	90	82 (91.1)	46 (51.1)	36 (40.0)	8 (8.9)	0 (0.0)
	p-value		*0.611*	*0.001*	*<0.001*	*0.442*	*0.268*
HIV positive	HSIL	116	107 (92.2)	32 (27.6)	75 (64.7)	8 (6.9)	1 (0.9)
	AIN2	23	18 (78.3)	1 (4.4)	17 (73.9)	4 (17.4)	1 (4.4)
	AIN3	93	89 (95.7)	31 (33.3)	58 (62.4)	4 (4.3)	0 (0.0)
	p-value		*0.005*	*0.005*	*0.300*	*0.027*	*0.198*

p-tests performed using chi-square test unless cell count is ≤3 in which case fishers exact was used.

Table 1. HPV types detected in 239 individual HSIL, stratified by lesion grade and HIV status

Conclusions: There were differences in the prevalence of specific HPV types in AIN2 and AIN3, with HPV16 causing over 40% of AIN3 lesions. Specific detection of some hrHPV types could be used as a screening strategy to detect AIN3.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

CLINICAL FACTORS ASSOCIATED WITH HPV CLEARANCE AND TREATMENT OUTCOMES FOLLOWING SURGICAL EXCISION OF PREMALIGNANT CERVICAL LESIONS.

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Introduction: Cervical cancer is one of the leading causes of death among African women, the human papilloma virus (HPV) is an established cause of cervical cancers. HIV positive women co-infected with HPV have a five-fold increased risk of developing cervical intraepithelial (CIN) lesions due to persistent infection and high recurrence of CIN after surgical treatment. The aim of the study was to describe clinical, viral and immunological factors associated with treatment of CIN in HIV positive women.
Methods: A prospective cohort study based in Durban, South Africa recruited women with high grade intraepithelial lesions (HGSIL) between October 2016 and August 2018. All women underwent colposcopy examination and large loop excision of the transformation zone (LLETZ) procedure at study entry. Social and behavioural data was collected using a structured questionnaire. The endpoint was treatment outcomes 12 months post-excision.
Results: Two hundred participants were recruited, of whom 149 had confirmed high grade lesions; 110 participants returned at 6 months post excision; of these 77 (68.8%) had clearance, 19 (17.0%) had treatment failure, 10 (8.9%) downgraded to low-grade lesions and 6 (5.4%) had atypical cells. Twelve months follow-up of the 77 who were clear at six months showed 10.4% (n=8) had recurrence of lesions,) continued clearance in 62.3% (n=48) and 27.3% (n= 21) were lost to follow-up. Comparison between participants with clearance, recurrence or treatment failure were statistically significant for age (38 vs 40 vs 37; p=0.0123), years on ART (3.5 vs 4.2 vs 2.5; p=0.0004) and number of HPV subtypes per participant (1 vs 3 vs 2; p=0.0452) respectively. Resection margins, CD4 count and sexually transmitted disease co-infection were non-significant.
Conclusions: Surgical resection is effective in treating precancerous cervical lesions, however recurrence is high. Infection with high number of HPV sub-types and fewer years on ART is associated with poor treatment. HPV viral load need further exploration.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

PERSISTENCE OF GENOTYPE-SPECIFIC, HPV INFECTION IS ASSOCIATED WITH INCREASED CUMULATIVE INCIDENCE RATE FOR HIGH-GRADE CERVICAL DISEASE: THREE-YEAR LONGITUDINAL DATA FROM THE ONCLARITY TRIAL.

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Introduction: *Introduction* Genotype (GT)-specific, persistent infection with high-risk human papillomavirus (HPV) is necessary for cervical precancer and cancer. The Onclarity HPV assay is capable of reporting extended GT results (beyond HPV 16, 18, and 45). The 3-year cumulative incidence rate (CIR) for ≥CIN2 associated with persistent HPV infection, was investigated.
Methods: *Methods* 29,513 enrolled women, ≥25 years, had cytology and HPV results. Abnormal cytology or an HPV(+) result (5% normal cytology controls also referred) led to colposcopy/biopsy at baseline (BL). Women treated for cervical disease were censored, but their status was carried forward in analyses. Untreated women had colposcopy referrals at Yrs1-3 based on cytology (≥ASC-US). Persistence modeling was performed by recording HPV transition states from BL to year 1 as follows: 1) no infection—HPV(-) at BL and Yr1 2) clearance—BL HPV(+) and Yr1 HPV(-) 3) new infection—BL HPV(-) and Yr1 HPV(+) 4) clearance with new infection—GT switch from BL to Yr1 5) GT persistence—the same GT at BL and Yr1. Persistence tracking was applied to remaining participants from Yrs1-2 and Yrs 2-3. Persistence was correlated with five possible diagnoses (negative, CIN1, CIN2, ≥CIN3, or treatment).
Results: *Results* 1,973 HPV transitions with corresponding diagnoses were recorded. 353 had treatment and were censored. 71.6% of treated women had ≥CIN2 pathology; of those, 90.8% had GT-specific persistence. For all transitions, the progression/maintenance ≥CIN2 rates for GT-specific persistence, any HPV positive-positive, switch-new HPV infection, HPV clearance, and no HPV were 35.1%, 8.4%, 7.0%, 0.5%, and 2.2%, respectively; excluding treatment cases at each year, the progression/maintenance ≥CIN2 rates were 15.3%, 6.6%, 5.7%, 0.4%, and 0.3%, respectively.
Conclusions: *Conclusions* GT-specific persistence closely correlates with treatment during colposcopy and had the highest ≥CIN2 CIR. Any HPV-persistence, but with a GT switch from a previous year, poses a ≥CIN2 CIR similar to HPV clearance.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

DIAGNOSIS AND TREATMENT OF CERVICAL PRE-CANCERS IN BANGLADESH

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Introduction: The Government of Bangladesh (GOB) has introduced cervical cancer screening programme through Visual Inspection of Cervix with Acetic Acid (VIA). Since 2005, VIA facilities have gradually been scaled up to 431 centres, and presently 2212 trained service providers are offering VIA to women aged 30 years and above. VIA+ve women are referred to Bangabandhu Sheikh Mujib Medical University (BSMMU) and 15 Medical College Hospitals (MCHs) for evaluation and management. This study was conducted to assess the pattern of treatment of cervical pre-cancer at the colposcopy clinic of BSMMU.
Methods: A cross-sectional and retrospective study (January 2010 to December 2018) was conducted at the colposcopy clinic of BSMMU. Women with colposcopy diagnosed high grade CIN (CIN-II and III) cases have been offered treatment by Loop Electrosurgical Excision Procedure (LEEP) or Thermal ablation during their first visit at the colposcopy clinic. Women with low grade CIN cases were advised to come for follow-up after 12 months. Selected low grade CIN I were treated. All cervical cancer cases were referred to oncology for further management.
Results: Among 1,816,802 screened women throughout the country, 85,079 (4.68%) were VIA +ve. Among them, 22,152 VIA+ve women attended the colposcopy clinic of BSMMU. Among 22,152 VIA+ve women, histologically 3,388 (17.1%) had CIN I, 966 (4.4%) had CIN II, 340 (1.5%) had CIN III, 1,617 (7.3%) had squamous cell carcinoma, and 13 (0.1%) had adenocarcinoma. During the study period, 3,308 (14.93%) women were managed by LEEP, 2,882 (13.02%) by thermal ablation and 1,663 (7.5%) were referred to oncology for further management. The positive predictive value (PPV) and negative predictive value (NPV) of colposcopy for detecting CIN II or worse lesion were 66.2% and 96.2% respectively.
Conclusions: Colposcopy is an effective way of evaluation for cervical pre-cancer and cancer. ‘See and Treat Protocol’ and thermal ablation are well accepted treatment methods.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

SEQUENCING DETECTS HUMAN PAPILLOMAVIRUS IN SOME APPARENTLY HPV-NEGATIVE INVASIVE CERVICAL CANCERS

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Introduction: Cervical cancer is caused by human papillomavirus (HPV), but some cancers may still test HPV-negative. We previously HPV tested 2850 cancer cases occurring in Sweden 2002-2011 and found that 394/2850 (13,8%) cases tested HPV-negative by PCR. Sequencing of these specimens could provide an unbiased assessment of their HPV status.
Methods: We sequenced 132 cancers: 97 HPV negative cervical cancers and 35 by PCR HPV-positive cervical cancers, matched by age and histology. Four pools of blank blocks were used as negative controls. In order to enrich for mRNAs, that may be found also in formalin-fixed paraffin-embedded specimens and is a hallmark of active viral infection, the samples were extracted, reverse transcribed, rRNA depleted and then sequenced using the NovaSeq 6000 system (Illumina, US). High quality reads were aligned to the human genome and non-human reads were queried against HPV protein.
Results: We sequenced a median of 23 million paired reads/sample. The HPV PCR results were confirmed in 31/35 HPV-positive cases. Among cases negative for HPV by PCR, 49/97 (50.5%) contained HPV sequences, with HPV 33 being the most commonly detected type, in15/49 cases. Comparison of the ratio of exon and intron sequences found that the sequenced material contained both DNA and RNA. Splice junctions were detected in 12 cases.
Conclusions: As >50% of the cervical cancers that test HPV-negative by PCR do contain HPV sequences, it appears that some late stage cancers contain HPV that it's more difficult to detect.

ORAL SESSION 6: PROGRESSION, PROGNOSTIC FACTORS AND TREATMENT IN HPV-RELATED DISEASE

REAL-WORLD EVIDENCE ON CLINICAL EFFECT OF REBACIN AS A NON-INVASIVE INTERVENTION FOR HIGH-RISK HUMAN PAPILLOMAVIRUS PERSISTENT INFECTION

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Introduction: Objectives: Our recent publication (International Journal of Cancer. 2019 Nov 15;145(10):2603-2891) has demonstrated that REBACINas a novel non-invasive therapeutic intervention can clear persistent hrHPV infections with marked efficacy. This study aims to further evaluate the clinical benefits of REBACINbased on real-world evidence collected from 9 hospitals cross 7 provinces with more than 500 patients enrolled.
Methods: 506 patients with history of persistent infection by one or more hrHPV subtypes prior to the use of REBACIN participated in the study from Febuary 2017 to July 2019. 427 of 506 had their subtypes of infections known via HPV genotyping analysis. All participants received 3-month REBACIN intervention and a follow up examination during 28-35 days after the RECABIN administration ceased. HPV infection was assessed by HC2 load or genotyping or E6/E7 transcript analysis. Viral negative conversion was counted when hrHPV infection was cleared. Effective outcome was considered when at least one subtype infection was cleared in patients with multiple-subtype infections.
Results: 352 patients out of 506 had the hrHPV infections cleared after the RECABIN regimen. The viral negative conversion rate is 69.57%. With additional 54 patients who had at least one subtype eliminated, the total effective rate was 80.24%. 158 patients of HPV16/18 infection showed the negative conversion at 77.78% and 85.37%, respectively, among those showing the best responses to the RECACIN intervention. For HPV 52/58, the two subtypes popular and persistent in Asian populations, the negative rates are over 60%. No adverse effect was detected or observed either.
Conclusions: This study by collecting real world evidence of 500+ patients in diverse geographical regions further supports that RECABIN is a safe and effective clinical regimen for hrHPV infection clearance.

ORAL SESSION 7: OROPHARYNGEAL CANCER - BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS

DIFFERENCES IN THE ORAL MICROBIOME AMONG PATIENTS WITH AND WITHOUT ORAL HUMAN PAPILLOMAVIRUS INFECTION

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Introduction: While oncogenic oral human papillomavirus (HPV) infection is known to be associated with HPV-related oropharyngeal cancer (OPC), factors that contribute to oral HPV persistence remain unclear. This study explores differences in the oral microbiome among patients with and without oral HPV infection.
Methods: Multi-institutional study of oral HPV infection. Participants ≥18 years old were recruited from multi-specialty outpatient clinics and had at least one of the following: ≥2 lifetime oral sex partners; history of anogenital dysplasia or cancer; or partner of someone with an HPV-related cancer. Saliva samples were tested for oral microbiome using 16S ribosomal RNA V4 amplification. Alpha diversity was measured by Chao 1 index (number of different species detected) and Shannon index (measure of species diversity).
Results: Participants (n=654) were predominantly male (80%) and white (67%) with a median age of 54 years (range 27-78). Oral HPV DNA was identified in 86 participant samples (13%). Several microbial species were present at significantly lower levels in HPV-positive as compared to HPV-negative individuals, including Haemophilus parainfluenzae, Neisseria subflava, Fusobacterium, Veillonella parvula and Porphyromonas (p-range <0.05-<0.001), whereas other species were higher in HPV-positive samples, including Veillonella dispar and Prevotella salivae (p<0.05 for each). HPV-positive patients had higher alpha diversity than HPV-negative patients (Chao 1 p=0.036). There were also differences in alpha diversity by number of lifetime cigarettes (Shannon p-trend=0.024), age (higher among younger versus older individuals, Chao 1 p-trend=0.049), and marital status (higher in single versus partnered participants, Chao 1 p=0.012). There was no difference by gender (Chao 1 p=0.62).
Conclusions: There are differences in the oral microbiome between individuals with and without oral HPV infection, with additional variations by age, smoking history, and marital status. Further study of the oral microbiome among individuals with oncogenic oral HPV infection may help identify risk factors for oral HPV persistence and subsequent HPV-OPC development.

ORAL SESSION 7: OROPHARYNGEAL CANCER - BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS

SPATIAL PROXIMITY BETWEEN T AND PD-L1 EXPRESSING CELLS AS A PROGNOSTIC BIOMARKER FOR OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

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Introduction: Fulfilling the promise of cancer immunotherapy requires novel predictive biomarkers to characterise the host immune microenvironment. Deciphering the complexity of immune cell interactions requires an automated multiplex approach to histological analysis of tumour sections. We tested a new automatic approach to select tissue and quantify the frequencies of cell-cell spatial interactions occurring in the PD1/PD-L1 pathway, hypothesised to reflect immune escape in oropharyngeal squamous cell carcinoma (OPSCC).
Methods: Single sections of diagnostic biopsies from 72 OPSCC patients were stained using multiplex immunofluorescence (CD8, PD1, PD-L1, CD68). Following multispectral scanning and automated regions-of-interest selection, the Hypothesised Interaction Distribution (HID) method quantified spatial proximity between cells. Method applicability was tested by investigating the prognostic significance of co-localised cells (within 30 μm) in patients stratified by HPV status.
Results: High frequencies of proximal $CD8^+$and $PD\text{-}L1^+$(HR 2.95, p=0.025) and $PD1^+$and $PD\text{-}L1^+$(HR 2.64, p=0.042) cells were prognostic for poor overall survival in patients with HPV negative OPSCC (n=31).
Conclusions: The HID method can quantify spatial interactions considered to reflect immune escape and generate prognostic information in OPSCC. The new automated approach is ready to test in additional cohorts and its applicability should be explored in research and clinical studies.

ORAL SESSION 7: OROPHARYNGEAL CANCER - BIOMARKERS FOR DIAGNOSIS AND PROGNOSIS

THE HPV SEROLOGY STANDARDIZATION INITIATIVE: AIMS AND PROGRESS TO DATE AT THE FREDERICK NATIONAL LABORATORY FOR CANCER RESEARCH

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Introduction: Protection against Human Papillomavirus (HPV) infection after vaccination is believed to be mediated by HPV-specific antibodies. Antibody responses in HPV prophylactic vaccine trials have been assessed using different methods. The lack of standardized assays, procedures, and reagents accessible to the scientific community has precluded the comparison of different studies evaluating immunogenicity of HPV vaccines. With an expected increase in the number of trials relying on immunobridging for approval of new dosing schedules or vaccine formulations, there is a critical need for standardized measurement and reporting of immunogenicity to reliably assess non-inferiority of antibody responses and improve overall comparability between studies.
Methods: The HPV Serology Standardization Initiative led by the HPV Serology Laboratory at the Frederick National Laboratory was established in January 2017, working with the National Cancer Institute (USA) and The Bill & Melinda Gates Foundation to lead standardization and harmonization efforts for HPV serological testing within vaccine trials. The main goal is to expedite serology assay standardization by developing a critical set of qualified immunoassay reagents, including secondary standards and HPV Virus-Like Particles (VLP), as well as validated assays that will be made available to the HPV scientific community. Furthermore, standard operating procedures are also accessible on our laboratory website.
Results: The HPV Serology Laboratory developed secondary standards calibrated against available WHO international standards, reference HPV VLP and a serology-based proficiency panel for the 9 HPV types included in licensed vaccines. Reference materials have been shared with 11 serology labs worldwide via Material Transfer Agreements. Luminex-based serology assays for measurement of HPV-16/HPV-18/HPV-6/HPV-11 were developed and validated (Precision (Inter-Day); HPV-16, 2.7%; HPV-18, 4.7%; HPV-6, 4.1%; HPV-11, 3.9%).
Conclusions: Achievement of these aims will enable comparisons of data across different HPV vaccines and different studies and, therefore, it will facilitate vaccine development and implementation of new vaccine recommendations and new vaccine candidates.

ORAL SESSION 8: SCREENING AND MANAGEMENT CERVIX LESIONS

YIELD OF LOOP ELECTROSURGICAL EXCISION PROCEDURE (LOOP) AMONG PATIENTS WITH AND WITHOUT KNOWN HIGH GRADE CERVICAL DYSPLASIA

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Introduction: Loop electrosurgical excision procedure (LOOP) is recommended for high-grade cervical dysplasia diagnosed on cytology and/or colposcopic biopsies. ("therapeutic" LOOP). However, the management of persistent low-grade abnormalities or human papillomavirus (HPV) positivity is not as well defined. The reported rate of occult high-grade dysplasia in a "diagnostic LOOP" (i.e., no preceding high-grade) is variable (2%-18%) and risk factors such as historical HPV status and cytology are often unavailable. The objective of this study was to determine the rate of occult high-grade in "diagnostic" versus "therapeutic" LOOPs and further risk-stratified based on prior history.
Methods: A retrospective cohort study of patients referred for LOOP at Brigham and Women's Hospital between 2008 and 2018 was performed and categorized into four groups: 1) persistent mild abnormalities (>2 years) but no history of high-grade (low risk diagnostic LOOP), 2) prior history of high-grade but now with low-grade result (high risk diagnostic LOOP), 3) newly diagnosed high-grade (low risk therapeutic LOOP), and 4) prior history of high-grade with new diagnosis of high-grade (high risk therapeutic LOOP).
Results: There were 897 LOOP procedures recorded (Table 1). The overall rates of high grade abnormalities were 13%, 22%, 59% and 62% among Groups 1 to 4 (Table 2). There is a suggestion of higher yield of diagnostic LOOP among those with a history of high-risk (Group 1 vs. Group 2, p=0.07) but minimal difference in the yield of therapeutic LOOP based on history of high-grade dysplasia (Group 3 vs. 4, p=0.37). There was a statistically significant difference in the yield of therapeutic LOOP by age where younger age was associated with increased risk of high-grade.

Table 1: Demographic Information	Group 1 (N=126)	Group 2 (N=100)	Group 3 (N=492	Group 4 (N=179)
Age at LOOP (y)				
Mean (SD)	40.1 (11.9)	42.6 (12.8)	35.4 (9.6)	35.4 (9.1)
Race-ethnicity				
Caucasian	67 (55.8%)	61 (65.6%)	272 (58.2%)	106 (63.1%)
Hispanic	21 (17.5%)	16 (17.2%)	118 (25.3%)	32 (19.0%)
African American	20 (16.7%)	9 (9.7%)	40 (8.6%)	14 (8.3%)
Asian	8 (6.7%)	5 (5.4%)	22 (4.7%)	13 (7.7%)
Other	4 (3.3%)	2 (2.2%)	15 (3.2%)	3 (1.8%)
Language				
English	99 (83.2%)	75 (79.8%)	379 (80.3%)	143 (84.1%)
Spanish	14 (11.8%)	13 (13.8%)	74 (15.7%)	17 (10.0%)
Other	6 (5.0%)	6 (6.4%)	19 (4.0%)	10 (5.9%)
Insurance				
Private	88 (71.5%)	66 (66.7%)	280 (59.7%)	114 (65.5%)
Government	34 (27.6%)	32 (32.3%)	173 (36.9%)	53 (30.5%)
None	0 (0%)	1 (1.0%)	5 (1.1%)	3 (1.7%)
Other	1 (0.8%)	0 (0%)	11 (2.3%)	4 (2.3%)
Lifetime number of sexual partners*				
1-3	33 (28.7%)	27 (31.0%)	131 (28.4%)	35 (21.1%)
3-5	31 (27.0%)	25 (28.7%)	129 (28.0%)	61 (36.7%)
7-9	30 (26.1%)	20 (23.0%)	109 (23.6%)	40 (24.1%)
10 or more	21 (18.3%)	15 (17.2%)	92 (20.0%)	30 (18.1%)
Parity				
Nulliparous	57 (46.0%)	36 (36.7%)	236 (48.1%)	85 (48.0%)
1	16 (12.9%)	21 (21.4%)	65 (13.2%)	31 (17.5%)
2	31 (25.0%)	23 (23.5%)	98 (20.0%)	37 (20.9%)
>2	20 (16.1%)	18 (18.4%)	92 (18.7%)	24 (13.6%)
Smoking history				
Never	79 (64.2%)	69 (70.4%)	284 (58.0%)	102 (57.3%)
Former	30 (24.4%)	24 (24.5%)	137 (28.0%)	54 (30.3%)
Current	14 (11.4%)	5 (5.1%)	69 (14.1%)	22 (12.4%)
HPV vaccination at time of referral among those born ≥1980				
0 doses at first visit	32 (69.6%)	26 (78.8%)	197 (79.1%)	80 (81.6%)
1-2 doses at first visit	5 (10.9%)	2 (6.1%)	18 (7.2%)	8 (8.2%)
Fully vaccinated at first visit	9 (19.6%)	5 (15.2%)	34 (13.7%)	10 (10.2%)
Year of LOOP				
2008	1 (0.8%)	3 (3.0%)	57 (11.6%)	8 (4.5%)
2009	4 (3.2%)	1 (1.0%)	39 (7.9%)	14 (7.8%)
2010	8 (6.3%)	2 (2.0%)	26 (5.3%)	12 (6.7%)
2011	11 (8.7%)	6 (6.0%)	36 (7.3%)	14 (7.8%)
2012	15 (11.9%)	8 (8.0%)	42 (8.5%)	22 (12.3%)
2013	14 (11.1%)	7 (7.0%)	34 (6.9%)	18 (10.1%)
2014	22 (17.5%)	12 (12.0%)	51 (10.4%)	17 (9.5%)
2015	16 (12.7%)	20 (20.0%)	63 (12.8%)	19 (10.6%)
2016	11 (8.7%)	19 (19.0%)	49 (10.0%)	24 (13.4%)
2017	16 (12.7%)	10 (10.0%)	60 (12.2%)	19 (10.6%)
2018	8 (6.3%)	12 (12.0%)	35 (7.1%)	12 (6.7%)

Table 2. LOOP results by group	Group 1 (Persistent mild abnormalities but no history of high risk abnormalities) N=126	Group 2 (Previously treated for high grade abnormalities but now new low risk results) N=100	Group 3 (Incident disease) N=492	Group 4 (Recurrent or persistent disease) N=179
Cancer	0 (0%)	0 (0%)	3 (0.6%)	1 (0.6%)
ACIS	0 (0%)	0 (0%)	7 (1.4%)	5 (2.8%)
SILHG	16 (12.7%)	22 (22.0%)	291 (59.1%)	111 (62.0%)
SILLG	51 (40.5%)	33 (33.0%)	59 (12.0%)	18 (10.1%)
Normal	59 (46.8%)	45 (45.0%)	132 (26.8%)	44 (24.6%)
p-value*	0.16		0.65	

Table 3: Yield by age (# High grade/Total)	Group 1 (N=126)	Group 2 (N=100)	Group 3 (N=492	Group 4 (N=179)
25-30	15% (5/33)	21% (4/19)	69% (128/185)	65% (46/71)
31-50	12% (8/67)	23% (12/53)	60% (153/256)	70% (64/92)
51-65	14% (3/21)	17% (4/24)	41% (18/44)	50% (7/14)
>65	0% (0/5)	50% (2/4)	28% (2/7)	0% (0/2)
p-value*	0.91	0.52	0001	0.12
Overall	13% (16/126)	22% (22/100)	61% (301/492)	65% (117/179)
p-value*	0.07		0.37	

Conclusions: Persistent low-grade abnormalities or HPV positivity is associated with risk of occult high-grade dysplasia of greater than 10%. This risk is further increased if the patient has had a prior history of high-grade dysplasia.

ORAL SESSION 8: SCREENING AND MANAGEMENT CERVIX LESIONS

CLINICAL EVALUATION OF ALINITY M HR HPV ASSAY IN POPULATION-BASED CERVICAL CANCER SCREENING SETTING

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Introduction: Alinity m HR HPV (Alinity; Abbott) is a novel assay that individually identifies genotypes HPV16/18/45, while reporting 11 other hrHPV genotypes in two distinct groups: HPV31/33/52/58 and HPV35/39/51/56/59/66/68. According to international guidelines, each HPV assay intended for clinical use should demonstrate predetermined thresholds of clinical accuracy.
Methods: The clinical performance of Alinity was compared to Hybrid Capture 2 (hc2; Qiagen), RealTi*m*e High Risk HPV (RealTi*m*e; Abbott) and cobas 4800 HPV Test (cobas; Roche) in a representative set of samples obtained from Slovenian women 20-64 years old attending the routine organized national cervical cancer screening program. During the 2009/2010, 4,510 women were enrolled in the baseline screening round and after 36 months women were invited to the second round, using a similar approach.
Results: The clinical sensitivity and specificity for CIN2+ of Alinity in women aged ≥30 years were 100.0% (68/68; 95% CI, 92.2–100.0%) and 92.4% (2,844/3,077; 95% CI, 91.4–93.3%), respectively and were noninferior to hc2 (all $p<0.05$). In the ≥30 years age group, women who were baseline hrHPV-negative had lower risk for CIN2+ at 3 years using Alinity (0.04%) versus those with normal baseline cytology (0.65%) and comparable risk to that of RealTime (0.04%), hc2 (0.08%) and cobas 4800 HPV (0.04%). HPV16/18 infection was associated with a significantly higher baseline and 3-year CIN2+ and CIN3+ risk versus absence of HPV16/18 or presence of other hrHPVs at baseline (all $p<0.05$). CIN2+ and CIN3+ risk at 3-years was significantly higher for HPV31/33/52/58 channel of Alinity compared with HPV35/39/51/56/59/66/68 channel (relative risk 3.5 [p=0.003] and 3.4 [p=0.03]). According to manufacturer's data Alinity's intra-laboratory and inter-laboratory reproducibility is 97.9% and 97.5%, respectively.
Conclusions: Alinity fulfils international consensus guideline criteria for primary cervical cancer screening and can be considered as clinically validated, demonstrating comparable safety to other clinically validated HPV tests.

ORAL SESSION 8: SCREENING AND MANAGEMENT CERVIX LESIONS

FIRST-VOID URINE AS AN ALTERNATIVE TO PHYSICIAN-TAKEN SAMPLES FOR HPV SCREENING

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Introduction: Cervical cancer (CC) is the fourth most common cancer in women and responsible for over 300,000 deaths worldwide. The principal causative agent of CC is infection with high-risk (HR) types of the human papillomavirus (HPV). The golden standard to test for HPV infections has been based on physician-taken smear (PTS) which is challenged by high non-attendance rates. The Colli-Pee was developed as a user-friendly device for the collection of first-void (FV) urine to enable self-sampling for screening purposes. We aim to provide consolidated data of the Colli-Pee performance compared to PTS for its potential use in HPV-based screening.
Methods: Novosanis developed the Colli-Pee for standardized and volumetric collection of 20mL FV urine. Five clinical trials were organized and reviewed to assess the potential of Colli-Pee-collected FV urine compared to PTS for the detection of HPV.
Results: A total of 1996 women who were referred to colposcopy were recruited to participate in the trials and an additional 600 will be included before the end of 2019. Twelve different institutions are involved (eight private partners, two academic institutions and three governments) covering multiple European regions. A peer-reviewed publication was published about the results on a cohort of 91 volunteers and preliminary results are available on 1056 women. The average overall hrHPV positivity in PTS and FV urine were respectively 72.3% (min:56.7%;max:86.1%) and 77.5% (min:65.4%;max:87.6%). The average agreement (kappa-values) between the two sample types was 0.78 with a minimum of 0.65 and a maximum of 0.85.
Conclusions: The results of FV urine and PTS are highly comparable. Hence, FV urine can be considered an appropriate sample type and non-inferior to PTS. Further developments involve new generation Colli-Pee devices for the collection of smaller volumes, including the first 10mL of urine, to further improve the performance for HPV testing and to enable downstream processing onto high-throughput machines.

ORAL SESSION 8: SCREENING AND MANAGEMENT CERVIX LESIONS

INTERNATIONAL QUALITY ASSURANCE OF HPV DNA GENOTYPING SERVICES: THE 2019 GLOBAL HPV DNA PROFICIENCY STUDY

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Introduction: The International Human Papillomavirus (HPV) Reference Center supports quality and order in HPV research and diagnostics. Notably, the center assigns HPV type numbers to novel HPV types, maintains a reference clone repository, and issues international proficiency panels for HPV genotyping. This international HPV DNA genotyping study issued in 2019 assesses the proficiency of the different HPV typing assays used routinely in laboratories worldwide as well as the performance of the laboratory.
Methods: Participating laboratories were asked to perform HPV typing using one or more of their usual assays on 41 coded samples composed of purified whole genomic plasmids of sixteen HPV types (HPV6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68a and 68b) in a background of human cellular DNA. Proficient typing requires detection in both single and multiple infections of 50 International Units of HPV 16 and HPV 18 DNA/ 5ml and 500 genome equivalents in 5 ml for the other types, with at least 97% specificity.
Results: The 2019 proficiency study had more than 70 participating laboratories from all over the world. The majority of participants are from countries in Europe and Asia. Participating laboratories involved public health laboratories, research laboratories, diagnostic test manufacturers and vaccine companies.
Conclusions: A continuing global proficiency program has documented an improvement in comparability and reliability of HPV genotyping assay performance worldwide.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

COMPARISON OF NEXT GENERATION SEQUENCING AND REAL-TIME PCR FOR THE EARLIER DETECTION OF HPV+ OROPHARYNGEAL HEAD AND NECK CANCER

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Introduction: The incidence of oropharyngeal squamous cell cancers caused by high-risk human papillomavirus (HPV) is increasing worldwide. Oral HPV infection precedes HPV-related oropharyngeal cancer (HPV-OPC) and is potentially amenable to earlier detection by liquid biopsy; however, the optimal assay and type of clinical sample are unknown. Next generation sequencing (NGS) and real-time PCR (RT-PCR) have been used to detect and quantify the presence of HPV. The present study compares these two methods in plasma and saliva.
Methods: 389 plasma and saliva samples, including 121 at diagnosis of HPV-OPC, were prospectively collected from 66 patients with HPV-OPC (**Table 1**). To evaluate the sensitivity of NGS and quantitative RT-PCR for the detection of high-risk HPV, primers were designed for *E6* of HPV16 and *E7* of HPV18. HPV copy number was normalized to the input of human genomic DNA. Statistical comparisons were made by either a Chi-Squared test or two-tailed Student's *t*-test.

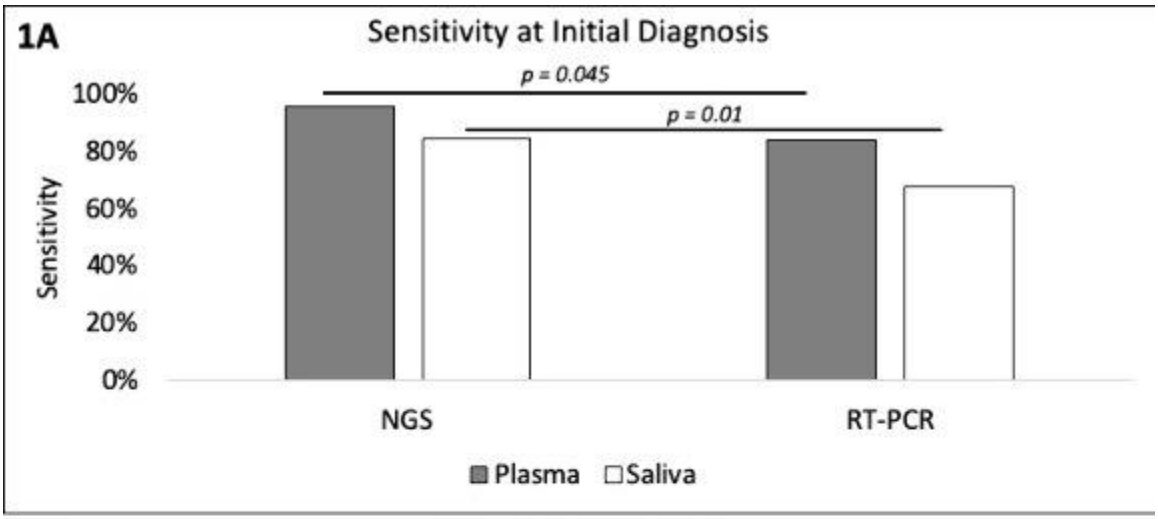
T1

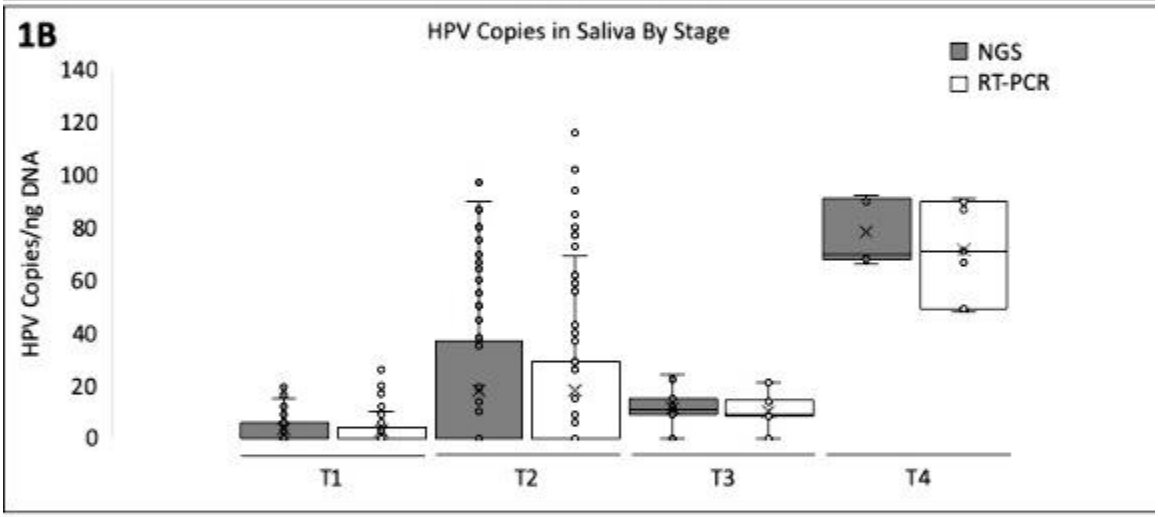
Gender (N = 66)	Number	Percentage
Male	56	85%
Female	10	15%
Race (N = 66)	**Number**	**Percentage**
Caucasian	59	89%
African American	3	5%
Not Recorded	4	6%
Age, Years (N = 66)	**Number**	**Percentage**
Mean	58.7	N/A
Median	59	N/A
Range	40-86	N/A
TNM Staging (Time of Diagnosis)	**Number**	**Percentage**
Primary Tumor (N = 64)		
T1	35	54.7%
T2	19	29.7%
T3	8	12.5%
T4	2	3.1%
Regional Lymph Nodes (N = 64)		
N0	7	10.9%
N1	13	20.3%
N2	38	59.4%
N3	5	7.8%
Distant Metastasis (N = 57)		
M0	56	98.2%
M1	1	1.8%

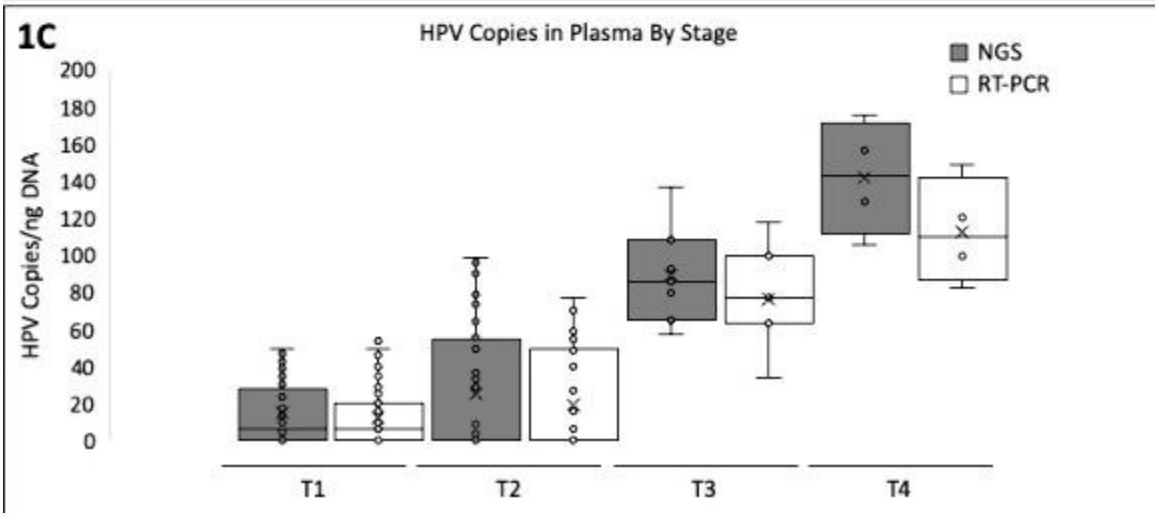
Treatment (N = 66)	Number	Percentage
Surgery Alone	25	37.9%
Chemotherapy Alone	1	1.5%
Radiation Alone	2	3.0%
Chemoradiation	4	6.1%
Surgery + Chemotherapy	0	0.0%
Surgery + Radiation	16	24.2%
Surgery + Chemoradiation	14	21.2%
Surgery + Chemoradiation + Immunotherapy	1	1.5%
Observation	3	4.5%
Length of Follow Up, Months (N= 66)	**Number**	**Percentage**
Median	50.2	N/A
Mean	50.6	N/A
Range	0.5 - 170.5	N/A
Alive at Last Follow Up	64	97.0%
Deceased at Last Follow Up	2	3.0%

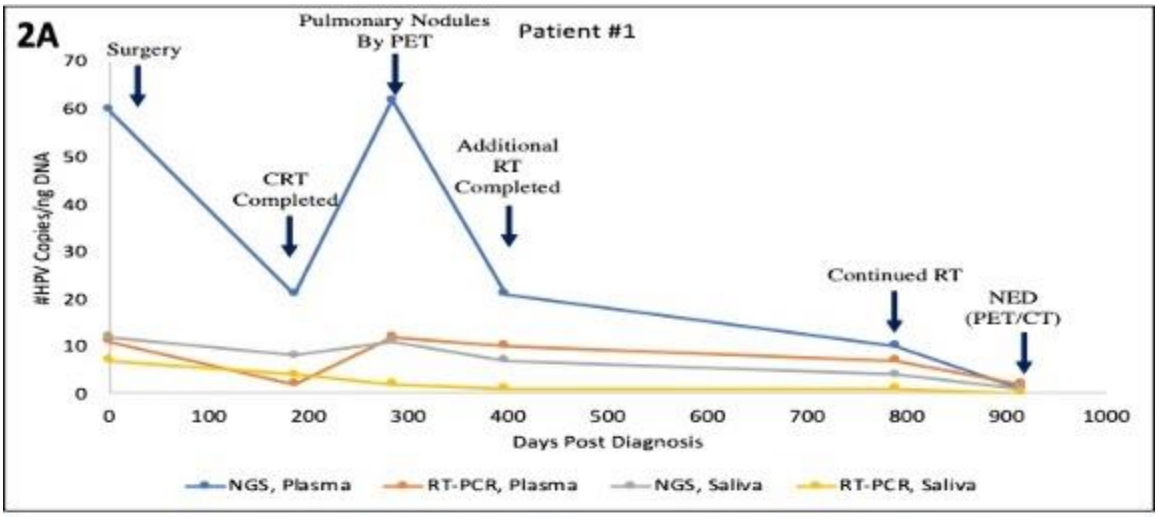
Results: Using plasma collected at diagnosis, the sensitivity of NGS was 96% (48/50) and 84% for RT-PCR (42/50, p = 0.045, **Figure 1A**). For saliva, the sensitivity of NGS was 84.5% (60/71) and 67.6% for RT-PCR (48/71, p = 0.01, **Figure 1A**). HPV copy number in both saliva and plasma increased with

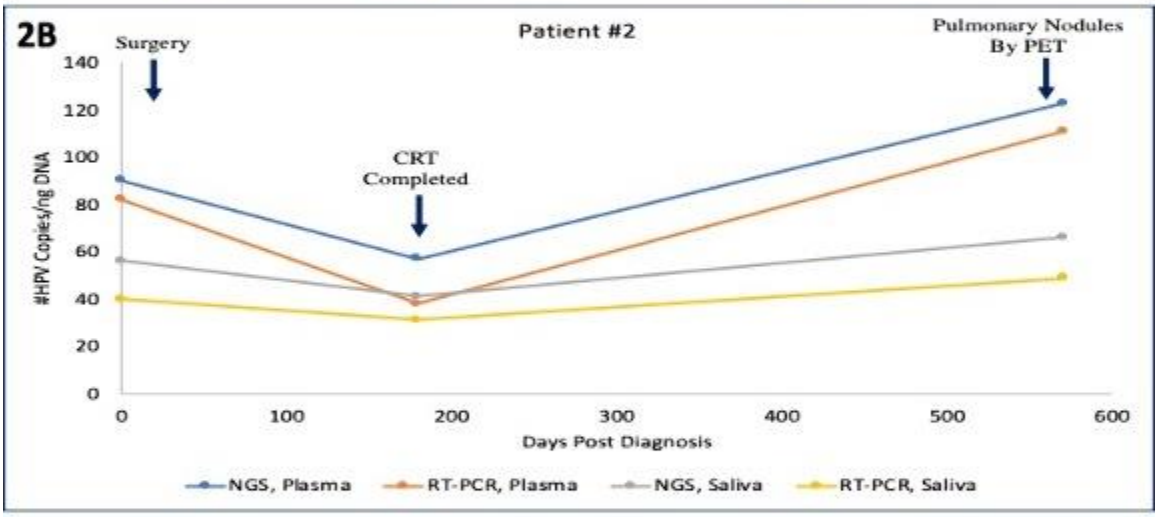
increasing tumor stage and was comparable between NGS and RT-PCR (p = 0.49, **Figures 1B-C**). HPV copy number, as measured by NGS but not RT-PCR, decreased after initial surgery and correlated with clinical status, including metastasis and further treatment with chemoradiation (CRT) and radiotherapy (RT) (**Figure 2A and 2B**). By NGS, HPV was nearly undetectable in patients showing no evidence of disease (NED, **Figures 2A and 2C**).

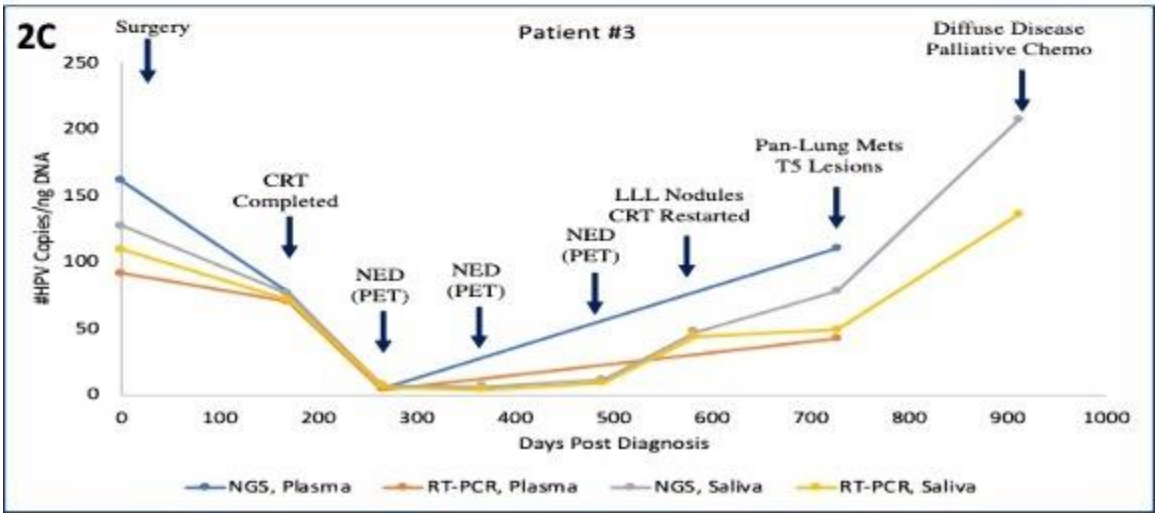

1A
Sensitivity at Initial Diagnosis
p = 0.045
p = 0.01
100%
80%
60%
40%
20%
0%
Sensitivity
NGS
RT-PCR
Plasma
Saliva


1B
HPV Copies in Saliva By Stage
NGS
RT-PCR
HPV Copies/ng DNA
140
120
100
80
60
40
20
0
T1
T2
T3
T4


1C
HPV Copies in Plasma By Stage
NGS
RT-PCR
HPV Copies/ng DNA
200
180
160
140
120
100
80
60
40
20
0
T1
T2
T3
T4







Conclusions: NGS has improved sensitivity over RT-PCR for the detection of HPV in saliva and plasma samples with plasma having superior sensitivity. NGS may have a role in monitoring patients for the

development of primary or recurrent HPV-OPC.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

PD-L1/PD-1 EXPRESSION PATTERN IN NORMAL, HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS AND SQUAMOUS CELL CANCER OF THE ANUS

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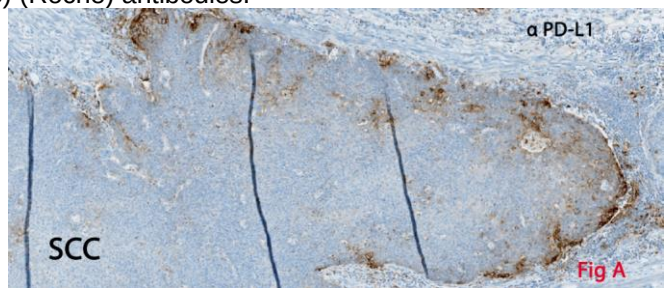
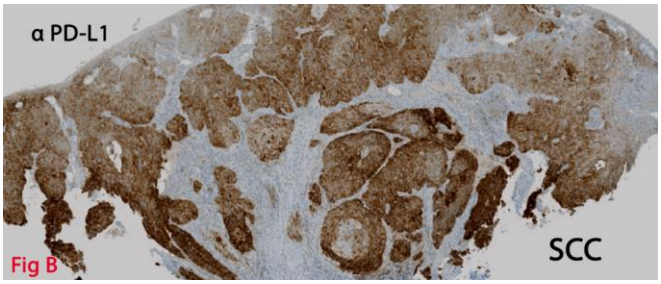
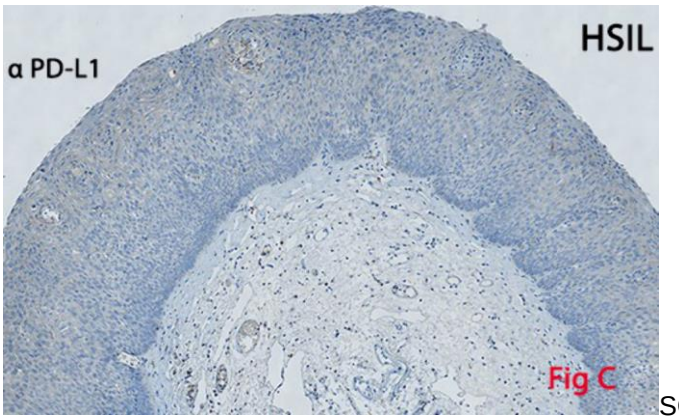
Introduction: Squamous cell carcinoma (SCC) can evade antigen-specific T-cell mediated immune immunosurveillance by co-opting the programmed cell death protein 1 (PD-1)/programmed death-ligand 1 (PD-L1) immune checkpoint pathway. Little is known regarding the expression profile and function of PD-1/PD-L1 and its role in pathogenesis of HPV-associated anal SCC. We studied PD-1 and PD-L1 expression in anal squamous epithelial cells (EC) and immune cells (IC) in normal tissue, high-grade squamous intraepithelial lesions (HSIL) and SCC obtained from HIV-positive and HIV-negative men and women.

Methods: We examined 34 SCC, 19 HSIL, 6 normal anal FFPE specimens from 36 HIV-positive (17 SCC, 14 HSIL, 5 normal) and 23 HIV-negative patients (17 SCC, 5 HSIL, and 1 normal). PD-L1 and PD-1 expression were determined by immunohistochemistry with Ventana anti-PD-L1 (SP263) and anti-PD-1 (NAT105) (Roche) antibodies.

Results:







SCC samples revealed diverse, heterogeneous PD-L1 expression patterns between tumors and within the same tumor. Membranous PD-L1 epithelial staining was seen on the tumor cells in 19/34 (56%) SCC samples, with three distinct PD-L1 expression patterns: at the periphery of the tumor nest 13/34 (38%), throughout the tumor (diffuse) 3/34 (9%), (Fig A-B) and in the center of the tumor nest 3/34 (9%). No epithelial PD-L1 staining was seen in any HSIL (Fig C) or normal tissues. PD-1 expression was observed in IC surrounding SCC tumor nests, in the sub-epithelial stroma of HSIL and infiltrating into HSIL epithelium. 4/6 (66%) normal tissues had PD-1 positive IC in the stroma. There was no epithelial PD-1 expression in any of the tissues. There was no difference in PD-L1/PD-1 expression between samples from HIV-positive and HIV-negative patients.

Conclusions: Patterns of PD-L1 and PD-1 expression varied according to severity of pathology. PD-L1 expression in EC was seen only in SCC with prominent PD-1 expression in nearby IC. PD-L1/PD-1 expression may contribute to immune-mediated pathogenesis of anal cancer.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

EVALUATION OF TWO HYBRID CAPTURE BASED HPV ASSAY WITH HPV16 AND HPV18 GENOTYPING

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Introduction: DALTONbio developed two new methods recently, DH3 and DH5 assay, which can detect 14 HR-HPV types and also HPV16/18 genotypes. DH3 detects HPV16/18 and other 12 HR-HPV types, while DH5 can detect HPV16 and HPV18 individually, just as Cobas 4800. The two HPV detection methods were evaluated in current study.
Methods: 7791 women with HPV, cytology and histological findings were included at Taizhou Central Hospital, China. The NMPA (National Medical Products Administration) approved DH3 assay was considered as a standard comparator test for HPV detection in this study. A total of 2215 cases were compared between DH3 and DH5 by using remaining specimens. HPV16 or HPV18 positive samples were further PCR amplified by using GP5+/GP6+ primers. The amplicon sequences were analyzed to confirm the HPV genotype.
Results: The sensitivity, specificity, positive and negative predictive value of DH3 to detect CIN2+ were 98.1%, 87.5%, 5.1% and 100%, respectively. In comparison, the corresponding results of cytology test were 88.7%, 93.3%, 8.3% and 99.9%. Additionally, the corresponding results of HPV16/18 were 52.8%, 96.2%, 8.6% and 99.7%. The absolute agreement of overall HPV, HPV 16/18 and other 12 HR-HPV types between DH5 and DH3 were 98.2%, 98.5% and 97.9%. In this study, 47 HPV16-positive cases and 26 HPV18-positive cases were detected by DH5. The results of NCBI BLAST suggest this new Hybrid Capture based individual HPV16 and HPV18 genotyping was highly consistent with GP5+/GP6+ PCR based DNA sequencing.
Conclusions: Compared with cytology test, DH3 assay is highly sensitive for the detection of cervical precancerous lesions. The DH5 assay demonstrated comparable analytical performance to the DH3 assay. With HPV16 and HPV18 genotyping, DH3 and DH5 assay provide new HPV genotyping method for clinical HPV screening, which will be wildly used in China with appropriate price .

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

A FIRST-IN-HUMAN PROOF-OF-CONCEPT TRIAL OF INTRAVAGINAL ARTESUNATE TO TREAT CERVICAL INTRAEPITHELIAL NEOPLASIA 2/3 (CIN2/3)

C. Trimble[1], K. Levinson[1], L. Maldonado[2], M. Donovan[3], K. Clark[1], M. Shay[1], M. Sauter[1], J. Fu[1], S. Saunders[1], P. Frantz[4], M. Plesa[5]
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Introduction: Most treatment options for cervical intraepithelial neoplasia 2/3 (CIN2/3) are either excisional or ablative, and require sequential visits to health care providers. Artesunate, a semisynthetic compound that is WHO-approved for treatment of acute malaria, also has cytotoxic effect on squamous cells transformed by HPV. We conducted a first-in-human proof-of-concept study to assess the safety and efficacy of self-administered artesunate vaginal inserts to treat biopsy-confirmed CIN2/3.
Methods: Subjects received either 1, 2, or 3 5-day treatment cycles, prior to a planned, standard-of-care therapeutic resection. Artesunate intravaginal inserts were self-administered. Safety analyses were based on patients who received at least one dose, and was assessed by the severity, frequency, and duration of reported adverse events. Tolerability was assessed as the percentage of subjects able to complete their designated dosing regimen. Modified intention-to-treat analyses for efficacy and viral clearance were based on patients who received at least one dose for whom endpoint data were available. Efficacy was defined as histologic regression to CIN1 or less. Viral clearance was defined as absence of HPV genotype(s) detected at baseline.
Results: A total of 28 patients received 1, 2, or 3 five-day treatment cycles at study weeks 0, 2, and 4, prior to a planned, standard-of-care therapeutic resection after study week 15. No local or systemic dose-limiting toxicities were observed in any study subjects. In the modified intent-to-treat analysis, histologic regression was observed in 19/28 (67.9%) subjects. Clearance of HPV genotypes detected at baseline, prior to treatment, occurred in 9 of the 19 (47.4%) subjects whose CIN2/3 lesions underwent histologic regression.
Conclusions: Self-administered intravaginal artesunate inserts were safe and well-tolerated, at clinically effective doses to treat CIN2/3. These findings support proceeding with Phase II clinical studies.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

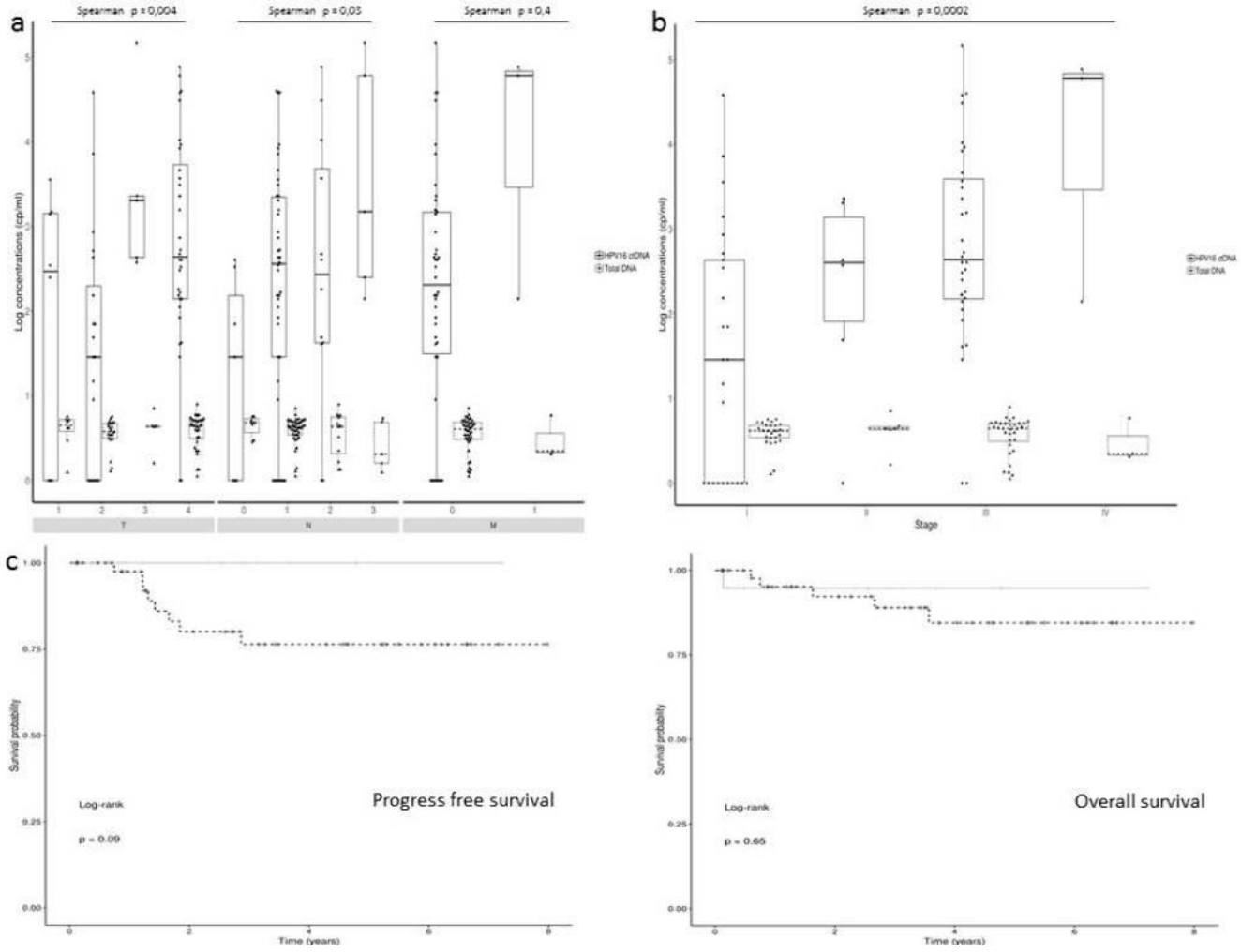
PRE-THERAPEUTIC HPV CIRCULATING TUMORAL DNA QUANTIFICATION BY DROPLET-BASED DIGITAL PCR: A PROMISING PREDICTIVE AND PROGNOSTIC BIOMARKER FOR HPV-ASSOCIATED OROPHARYNGEAL CANCERS

D. Veyer[1], M. Wack[2], M. Mandavit[3], P. Bonfils[4], S. Hans[5], H. Mirghani[4], B. Rance[2], V. Taly[6], C. Badoual[7], H. Péré[1]
[1]HEGP/APHP, Virology, Paris, France, [2]HEGP/APHP, It Department, Paris, France, [3]INSERM U970, Team 10, Paris, France, [4]HEGP, Orl, Paris, France, [5]Hôpital Foch, Orl, Suresnes, France, [6]INSERM, Umr-s1147, Ediag Platform, Cnrs Snc5014, Paris, France, [7]HEGP/APHP, Anatomopathology, Paris, France

Introduction: HPV-positive oropharyngeal squamous cell carcinoma (HPV OPSCC) constitutes a tumor entity with better prognosis and outcomes. Biomarkers are strongly needed to classify more precisely HPV OPSCC with the aim to eventually consider de-escalation in the best prognosis cases. In the last decade, the liquid-biopsy approach using the detection of circulating tumoral DNA (ctDNA) released from tumor cells and detectable in blood growing interest including in head and neck cancers. HPV-related cancers are an ideal model to monitor ctDNA by detecting HPV oncogenes particularly by ultrasensitive molecular assays such as droplet-based digital PCR (ddPCR). To determine whether pre-therapeutic assessment of HPV circulating tumoral DNA (HPVctDNA) by ddPCR could constitute a predictive and prognostic biomarker for HPV OPSCC, a mono-institutional prospective biomarker study on 66 patients with p16+/HPV16 OPSCC was conducted in European Georges Pompidou Hospital, Paris, France.
Methods: Blood samples were collected at the time of diagnosis before any treatment. Optimized digital PCR assays were used to quantify HPV16 ctDNA. ddPCR of HPV16 E6 gene was performed on a RainDrop Digital PCR System (RainDance Technologies, BioRad, Hercules, USA). To obtain absolute quantification of HPV16 ctDNA, data analysis was performed using the Raindrop Analyst software (FlowJo, Ashland, USA).
Results: Forty-seven (71%) patients showed a positive pre-therapeutic HPVctDNA at time of diagnosis. Interestingly, HPV16ctDNA quantity at baseline was significantly correlated with the T/N/M status and stages according to the 2018 new staging criteria from American Joint Committee on Cancer. Moreover, all recurrences and the majority (83%) of death reported events occurred in patients with positive HPV16ctDNA at baseline. Finally, when post-treatment blood samples were available (n=6), the kinetic of HPV16ctDNA was clearly associated with treatment success or failure.

Clinical characteristics		N (%)	Med	Min	Max
Total		66			
Sex					
	Women	20 (30)			
	Men	46 (70)			
Age at diagnosis		66	65	43	92
Number of recurrence		8 (12)			
Number of death		6 (9)			
T					
	1	8 (12)			
	2	20 (31)			
	3	5 (7,7)			
	4	32 (49)			
N					
	0	7 (11)			
	1	42 (64)			
	2	12 (18)			
	3	5 (7)			
M					
	0	42 (93)			
	1	3 (7)			
AJCC Staging					
	I	25 (38)			
	II	6 (9)			
	III	32 (48)			
	IV	3 (6)			
Tabacco					
	No	22 (38)			
	Yes	36 (62)			
HPV16 ctDNA results					
HPV16 ctDNA concentrations					
	Negative	19 (29)			
	Positive	47 (71)			
HPV16 ctDNA concentration cp/ml		66	319,4	0	147416,7
log[HPV16 ctDNA concentration] cp/ml		66	2,50	0	5,17
DNA µg/ml		66	3,34	0,122	6,93

Table 1 : Clinical characteristics of HPV16-related oropharyngeal squamous cell carcinoma and HPV16 circulating tumoral DNA (HPV16 ct DNA) results


a
Spearman p = 0,004
Spearman p = 0,03
Spearman p = 0,4
Log concentrations (cp/ml)
HPV16 cDNA
Total DNA
T
N
M
b
Spearman p = 0,0002
Log concentrations (cp/ml)
Stage
c
Survival probability
Log-rank
p = 0.09
Progress free survival
Time (years)
Survival probability
Log-rank
p = 0.65
Overall survival
Time (years)

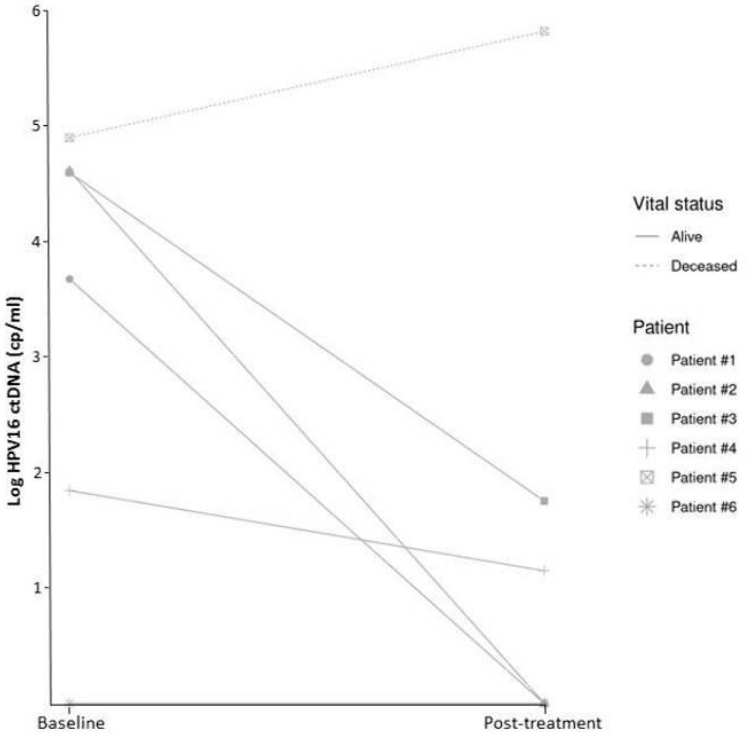


Figure 3 : HPV16 circulating tumoral DNA concentration kinetics during anti-tumoral treatment (baseline and post-treatment) in 6 patients

Conclusions: HPVctDNA monitoring by ddPCR could constitute a useful and noninvasive dynamic biomarker to select HPV OPSCC patients eligible for potential treatment de-escalation and to monitor treatment response.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

SYSTEMATIC ANALYSIS OF EIGHT DNA METHYLATION MARKERS DEMONSTRATES A COMPARABLE HIGH DIAGNOSTIC PERFORMANCE FOR CIN3 AND CERVICAL CANCER

S. Dick[1], L. Verhoef[1], L. De Strooper[1], I. Ciocănea-Teodorescu[2], J. Berkhof[2], B. Wisman[3], C.J. Meijer[1], M. Bleeker[1], R. Steenbergen[1], D. Heideman[1]
[1]Amsterdam UMC, Vrije Universiteit Amsterdam, Pathology, Cancer Center Amsterdam, Amsterdam, Netherlands, [2]Amsterdam UMC, Vrije Universiteit Amsterdam, Epidemiology And Biostatistics, Amsterdam, Netherlands, [3]University Medical Center Groningen, Gynaecologic Oncology, Cancer Research Center Groningen, Groningen, Netherlands

Introduction: By genome-wide DNA methylation profiling we have identified novel methylation markers for the detection of CIN3 and cervical cancer in HPV-positive women. This study systematically evaluates and compares the performance of eight host cell DNA methylation markers for the detection of CIN3 and cervical cancer in cervical scrapes.
Methods: HPV-positive cervical scrapes of controls (n=352) and women diagnosed with CIN3 (n=175) or cervical cancer (n=57) were tested for methylation of host cell genes *ASCL1, LHX8, ST6GALNAC5, ZIC1, GHSR, SST, FAM19A4* and *miR124-2* using quantitative methylation-specific PCR (qMSP). To evaluate their diagnostic performance, simple logistic regression was performed for single makers and LASSO logistic regression was used to build a marker panel to discriminate between controls and CIN3. Marker performance was visualized by ROC curve, and evaluated by the area under the curve (AUC) and corresponding sensitivity and specificity. Models were verified by leave-one-out cross-validation, and subsequently applied to cervical scrapes of women with cervical cancer.

Results: The methylation levels in cervical scrapes increased significantly with underlying disease severity (all markers p<0.001). AUCs from the single markers were between 0.769 and 0.886. Four markers (*ASCL1, LHX8, ZIC, FAM19A4)* showed ROC curves with cross-validated AUC>0.80. The single markers detected between 53 and 56 of the 57 cervical cancers. LASSO logistic regression resulted in a bi-marker panel consisting of *ASCL1* and *LHX8.* This panel showed the highest cross-validated AUC (0.881), and detected 80.6% of CIN3 and all cervical cancers at specificity of 84.7%.
Conclusions: All eight methylation markers showed a comparable good performance for triage of HPV-positive women using cervical scrapes. Bi-marker panel *ASCL1*/*LHX8* showed complementarity in the detection of cervical cancer. These data emphasizes the diagnostic potential of methylation analysis in HPV-based cervical screening.

ORAL SESSION 9: BIOMARKERS CERVIX AND OTHER SITES

MOLECULAR PAP SMEAR: EXTERNAL VALIDATION OF HPV GENOTYPE AND HOST EPIGENETIC MARKERS AS A PREDICTIVE CLASSIFIER OF CERVICAL CYTOLOGY

J. Shen-Gunther, A. Garcia, Q. Xia, W. Stacey, H. Asusta
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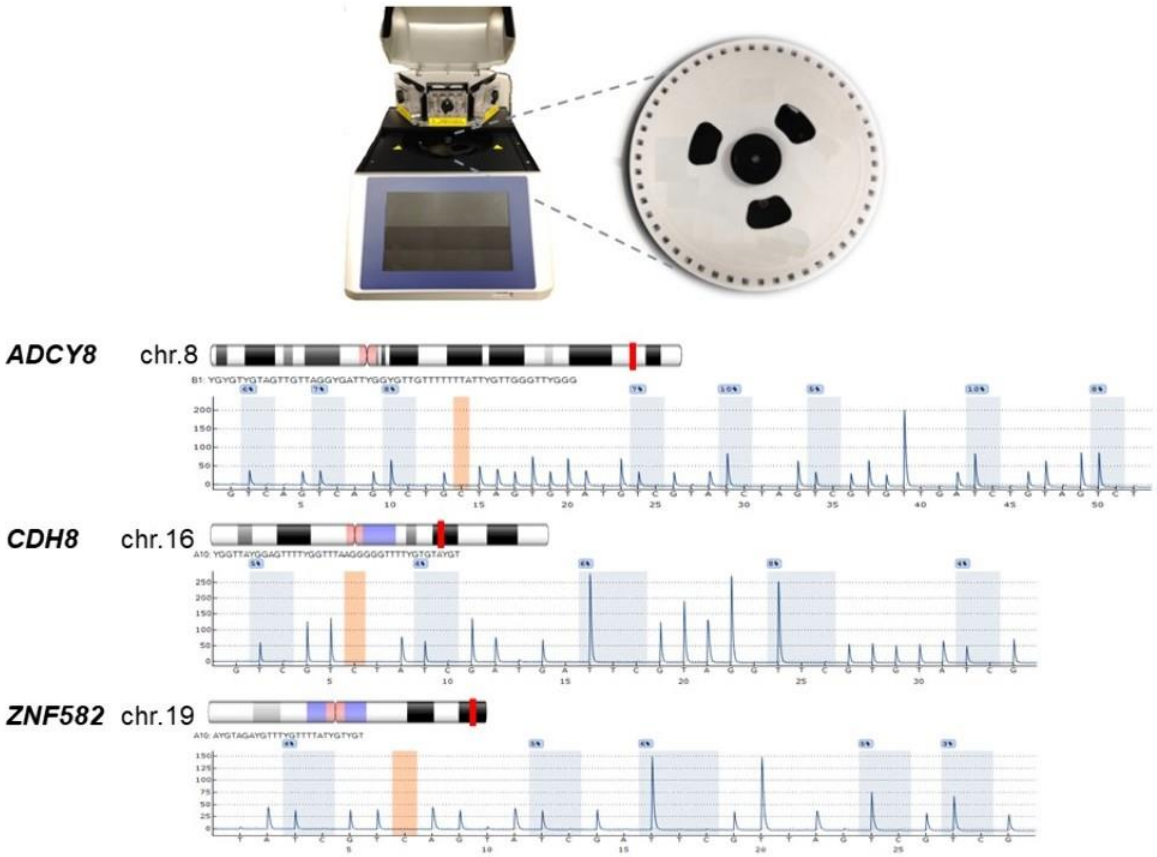
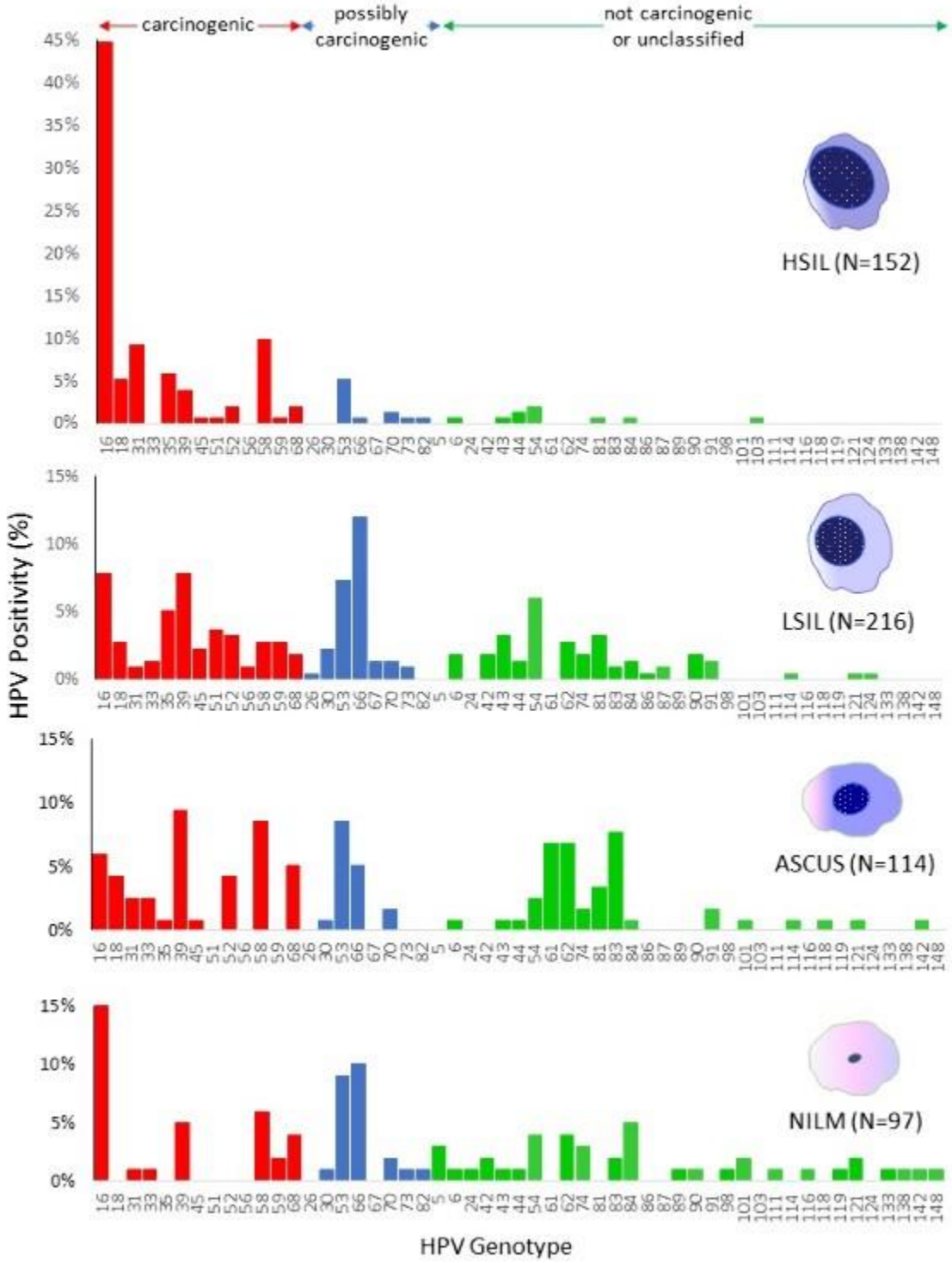
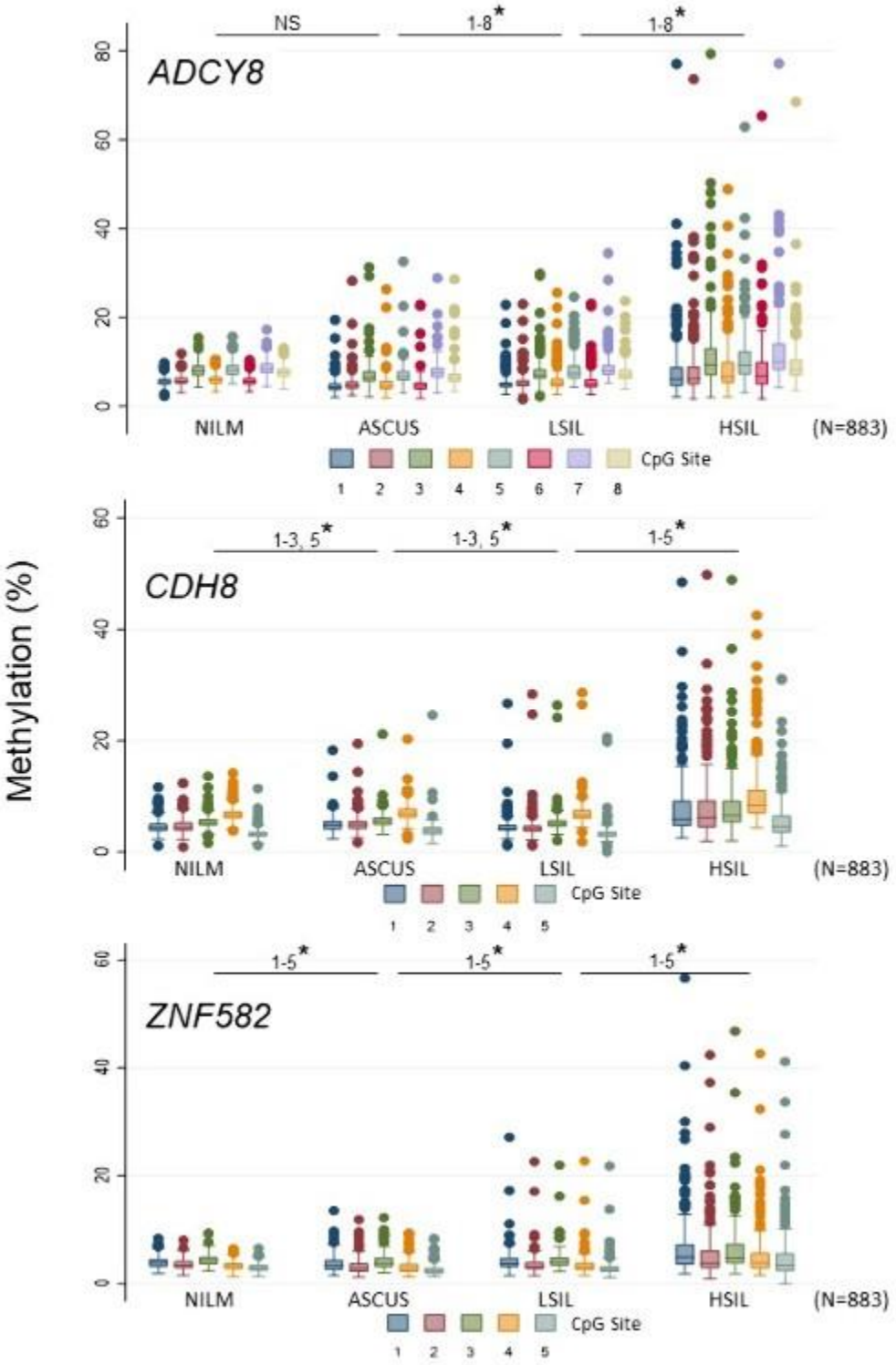
Introduction: Primary high-risk Human Papillomavirus (hrHPV) screening has recently become an accepted standalone or co-test with conventional cytology, however, hrHPV singularly lacks specificity for cytopathological grade. This study aims to validate and expand the clinical performance of a multiparametric biomarker panel named “Molecular Pap” based on HPV genotype and *ADCY8*, *CDH8* and *ZNF582* methylation status as a predictive classifier of cervical cytology.
Methods: This prospective, cross-sectional study used residual liquid-based cytology for HPV genotyping and epigenetic analysis. Extracted DNA underwent parallel PCR using 3 primer sets (MY09/11, FAP59/64, E6-E7 F/B) for HPV DNA amplification. HPV+ samples were genotyped by Sanger sequencing. Promoter CpG-methylation of 3 tumor suppressor genes was quantified by bisulfite-pyrosequencing of genomic DNA on the newest, high-resolution PyroMark Q48 platform (Fig. 1). Logistic model performance was compared using AUROC and Chi-square test. Model parameters were used to predict and classify binary outcomes.



Results: 883 ThinPrep validation samples were analyzed. HPV DNA was detected in 125/237 (53%) NILM; 136/235 (58%) ASCUS; 222/229 (97%) LSIL; and 156/182 (86%) HSIL samples. The proportion of IARC-defined carcinogenic HPV-types in sequenceable samples correlated with worsening grade: NILM 35/97 (36%); ASCUS 50/114 (44%); LSIL 94/216 (44%); HSIL 129/152 (85%) (Fig. 2). *ADCY8*, *CDH8*, and *ZNF582* methylation (%) also correlated with worsening grade (Fig. 3). The multi-marker test predicted binarized cytological outcomes better than HPV-type alone with significantly higher AUCs (P<0.05): NILM vs. >NILM (AUC 0.73 vs. 0.71); NILM/ASCUS vs. LSIL/HSIL (AUC 0.81 vs. 0.77); and <HSIL vs. HSIL (AUC 0.82 vs. 0.73), respectively.


carcinogenic
possibly carcinogenic
not carcinogenic or unclassified
HSIL (N=152)
LSIL (N=216)
ASCUS (N=114)
NILM (N=97)
HPV Positivity (%)
HPV Genotype



Conclusions: Our expanded findings validate the multivariable prediction model developed for cytological classification. The sequencing-based “Molecular Pap” outperformed HPV-type alone in predicting four grades of cervical cytology. Additional host epigenetic markers decidedly contributed to the

overall classification accuracy.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

HPV VACCINATION AFTER CONIZATION: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Introduction: HPV vaccination has become a fundamental part of prevention of cervical cancer and cervical intraepithelial neoplasia (CIN). After excisional treatment of high-grade CIN women still have an elevated risk to develop invasive cervical cancer. Therefore, a long-term reduction of this risk is important and pre- and post-conization HPV vaccination could be a possible way to achieve this.
Methods: In this meta-analysis, six pro- and retrospective studies analysing the effect of pre- or post-conization vaccination (bi- or quadrivalent vaccine) against HPV were included after a systematic review of literature. Fixed- and random-effect models were prepared.
Results: Primary end point was CIN2+ in every study. The total study population included 3060 patients (1427 vaccinations vs 1633 controls) in six studies. The meta-analysis showed a significant reduction of risk for the development of new high-grade CIN after HPV vaccination (risk rate (RR) 0.33; 95% CI [0.21; 0.52]), independent from HPV type. Due to the heterogeneous study population, multiple meta-analyses regarding the HPV type, age of patient, time of vaccination and follow-up were performed. Results for HPV 16 and 18-positive CIN2+ showed a RR of 0.41 (95% CI [0.2; 0.85]. Discrimination between younger women (age 18-26) and women of all age (age 18-45) revealed a risk rate of 0.4; 95% CI [0.21; 0.76] and 0.28; 95% CI [0.15; 0.53], respectively. After a longer period of time after vaccination (median follow-up time > three years), the relative risk was 0.33; 95%-CI [0.19; 0.59], whereas the risk for CIN2+ after a maximum time of three years of follow-up was 0.32; 95% CI [0.15; 0.69]. The relative risk of vaccination before and after operative therapy was 0.31; 95% CI [0.15; 0.65] and 0.34; 95% CI [0.19; 0.61], respectively.
Conclusions: Meta-analysis and subgroup analyses showed a significant risk reduction of developing high-grade cervical intraepithelial neoplasia after HPV vaccination and surgical excision.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

SELECTIVE PERSISTENCE OF HPV CROSS-NEUTRALISING ANTIBODIES FOLLOWING REDUCED-DOSE HPV VACCINE SCHEDULES

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Introduction: Cross-neutralising antibody (Cross-NAb) responses to phylogenetically- related non-vaccine human papillomavirus (HPV) types have been reported following 3 doses of quadrivalent (4vHPV, Gardasil®, Merck Inc.) or bi-valent (2vHPV, Cervarix®, GSK) HPV vaccine in the short-term. However, long-term data on cross-NAb responses is limited and no data is available following reduced-dose HPV vaccine schedules. In this study, we compared cross-NAb responses in girls who were either unvaccinated or had received vaccination with 1, 2 or 3 doses of 4vHPV (Gardasil®,Merck Inc.) 6 years earlier, before and 1-month after a booster dose of 2vHPV(Cervarix®,GSK).
Methods: In 2015, we conducted a cohort study in 200 Fijian girls (15-19 years old) previously unvaccinated, or vaccinated with 1-3 doses of 4vHPV 6 years earlier. Blood was taken pre- and 28 days following the 2vHPV booster dose. The NAb to HPV31, 33, 45, 52 and 58 was measured using the HPV pseudovirion-based neutralisation assay.
Results: Girls who had previously received at least 1 dose of 4vHPV had significantly higher NAb titres for HPV31 when compared with unvaccinated girls, whereas no difference in NAb titre was observed for 4 other genotypes (33, 45, 52 and 58). Following a single further vaccination with 2vHPV, NAb titres to each of the 5 tested HPV genotypes were comparable for girls who previously received 1, 2 or 3 doses of 4vHPV, and were significantly higher than for previously unvaccinated girls.
Conclusions: Vaccination with 1-3 doses of 4vHPV induced NAb to HPV31 that persisted for 6 years, but there was no persistence of NAb to HPV33, 45, 52 or 58. Our results suggest that 1 or 2 doses of 4vHPV may provide long-term protection against HPV31.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

AMC-072: 24-MONTH EFFICACY OF THE QUADRIVALENT HPV VACCINE AGAINST ANAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS IN HIV-POSITIVE MEN WHO HAVE SEX WITH MEN AGED 18-26 YEARS

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Introduction: HPV vaccination is safe and immunogenic in HIV-positive men who have sex with men (MSM), a group at high risk of HPV-related cancer. There are no efficacy data in 18-26 year-old HIV-positive MSM. These men may be less HPV-exposed than HIV-positive MSM >27 years-old, among whom the quadrivalent HPV vaccine (qHPV) has little efficacy. We performed an efficacy study with qHPV in young HIV-positive MSM with an outcome of qHPV type-attributable anal high-grade squamous intraepithelial lesions (HSIL).
Methods: 260 HIV-positive MSM 18-26 years-old were screened with high-resolution anoscopy (HRA)-guided biopsy at 15 U.S. sites. Baseline HSIL and prior HPV vaccination were exclusion criteria. Men were vaccinated with qHPV at 0/2/6 months. HRA-guided biopsies and HPV testing in mouth/penis/scrotum/anus/perianus swabs and HSIL anal biopsies were performed at 7/12/24 months. Using exact Poisson calculations, we measured efficacy as incident qHPV-attributable anal HSIL comparing men naïve for each type at baseline (seronegative and HPV DNA-negative at all sites) to “previously-exposed” men (seropositive or HPV DNA-positive at any site).
Results: 34% of men were excluded for anal HSIL at baseline. 144 men were enrolled; 138 completed all vaccinations. Enrollee mean age was 23 years. 80 (56%) were African-American, 46 (32%) were White. 18 (13%) were “other”. Median baseline CD4 count=594 cells/mL (range=237-1,520). 91% had an undetectable HIV viral load (≤400 copies/mL). 23/47/47/63% of participants were naïve at baseline to HPV 6/11/16/18, respectively. Incident-persistent infection occurred among naïve participants at 1.8/0.0/2.9/0.7 cases/100 person-years for HPV 6/11/16/18, respectively (Table). There was no incident qHPV-associated anal HSIL among naïve men (Table), compared with 10.4/1.7/8.4/2.7 cases/100 person-years of HPV 6/11/16/18-associated HSIL among previously-exposed men (p=0.01 for HPV 16).

Table. Incident persistent HPV infection and anal HSIL

	Incident persistent HPV Infection (swab from any site, persistence based on same site)				Incident anal HSIL related to vaccine type			
Exposure categories	**HPV 6**	**HPV 11**	**HPV 16**	**HPV 18**	**HPV 6**	**HPV 11**	**HPV 16**	**HPV 18**
PP: Naïve to HPV 6 n/N (%) PY Rate (per 100 PY)	1/29 (3) 55.5 1.8				0/15 (0) 25.0 0.0			
Prior exposure to HPV 6 n/N (%) PY Rate (per 100 PY)	0/15 (0) 29.0 0.0 P=0.671				9/56 (16) 86.5 10.4 P=0.064			
PP: Naïve to HPV 11 n/N (%) PY Rate (per 100 PY)		0/55 (0) 108.6 0.0				0/35 (0) 55.2 0.0		
Prior exposure to HPV 11 n/N (%) PY Rate (per 100 PY)		0/33 (0) 65.1 0.0 P>0.999				1/36 (3) 57.6 1.7 P=0.745		
Naïve to HPV 16 n/N (%) PY Rate (per 100 PY)			3/54 (6) 102.9 2.9				0/39 (0) 65.3 0.0	
Prior exposure to HPV 16 n/N (%) PY Rate (per 100 PY)			0/23 (0) 46.1 0.0 P=0.386				4/32 (13) 47.4 8.4 P=0.014	
Naïve to HPV 18 n/N (%) PY Rate (per 100 PY)				1/74 (1) 142.9 0.7				0/47 (0) 75.6 0.0
Prior exposure to HPV 18 n/N (%) PY Rate (per 100 PY)				0/23 (0) 46.2 0.0 P=0.622				1/24 (4) 37.6 2.7 P=0.166

Conclusions: A high proportion of unvaccinated 18-26 year-old HIV-positive MSM have anal HSIL. However, qHPV is efficacious in this high-risk population among those naïve to qHPV types and many could benefit from HPV vaccination.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

BENEFITS OF HPV VACCINATION AS ADJUVANT TO CERVICAL TREATMENT IN WOMEN WITH INTRAEPITHELIAL NEOPLASIA

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Introduction: Up to 25% of the women treated for high-grade cervical intraepithelial lesion (HSIL/CIN2-3) present persistent/recurrent disease. Recent studies have shown preliminary evidence that a high title of antibodies against HPV could decrease the risk of recurrence in patients treated for HPV-related lesions. We aimed to provide insight into the role of HPV vaccination of women undergoing treatment for HSIL/CIN 2-3 to decrease the risk of persistence/recurrence.
Methods: Two hundred sixty-six women treated for HSIL from July 2013 to July 2018 were included. Vaccination was recommended to all women at the moment of HSIL diagnosis. All patients were treated using Loop Electro-Excision Procedure (LEEP). First visit after LEEP was performed at 4-6 months. From then, patients were followed-up every 6 months up to 24 months with cytology (Thinprep), HPV testing (Cobas), colposcopy and biopsy if necessary. The main outcome was histological HSIL diagnosis confirmed during the follow-up visits (persistent/recurrent disease).
Results: 153 women(57.5%) underwent HPV vaccination either with 2v, 4v o 9v HPV vaccine. Seven out of the 153 vaccinated women(4.6%) received one dose, 16(10.5%) two doses, 118(77.1%) the three doses; 12 women (7.8%) could not remember the number of doses received. Cervical persistent/recurrent HSIL/CIN2-3 was observed in 6 out of 153(3.9%) of the vaccinated women, and in 13 out of 113(11.5%) of the non-vaccinated women (p=0.018). Within the vaccinated women, no association was found between number of HPV vaccine doses and prevalence of persistent/recurrent HSIL/CIN2-3 at the end of follow-up (p=0.69)
Conclusions: In conclusion, our study sustained the clinical benefit of HPV vaccination after LEEP in women treated for HSIL. The implications of these results may influence the post treatment management of HPV-related diseases to consider HPV vaccination as an adjuvant to surgical treatment. Work supported in part by Instituto de Salud Carlos III(ICSIII)-Fondo de Investigación Sanitaria and ERDF ‘One Way to Europe’(PI17/00772).

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

EFFICACY OF A SINGLE DOSE OF HUMAN PAPILLOMAVIRUS (HPV) VACCINE- FINDINGS FROM THE INDIAN COHORT STUDY

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Introduction: Elimination of cervical cancer through high coverage of the adolescent girls with Human papillomavirus (HPV) vaccination will be accelerated, if a single dose of the HPV vaccine is found to be highly protective. Present abstract reports the efficacy of a single dose of quadrivalent vaccine against incident and persistent HPV infections.
Methods: International Agency for Research on Cancer (IARC) initiated a multi-centre randomised study in India in 2009 to compare the efficacy of 2- versus 3- doses of quadrivalent vaccine in 10-18 year old unmarried girls. Suspension of vaccination in 2010 due to a Government decree led to loss of randomization with 4950 girls receiving 1 dose; 3452 receiving 2 doses on days 1 and 60; 4979 receiving 2 doses on days 1 and 180+; and 4348 receiving 3 doses on days 1, 60 and 180+. The participants were followed up over 10 years. Cervical samples were collected yearly for 4 consecutive years from 18+ year old married participants to assess incident and persistent infections. An age-matched cohort of unvaccinated married women was recruited in 2011 and yearly cervical samples were collected from them as well.
Results: The comparison of persistent infection rate in 5017 women providing at least two cervical samples with that in 1242 unvaccinated women suggests a high vaccine effectiveness in preventing persistent HPV-16/18 infections, regardless of number of doses (persistent HPV 16/18 infection rate 0.1% each in single dose, 2-dose and 3-dose groups). The rate of persistent HPV 16/18 infection was 2.3% in the unvaccinated cohort. The rates of incident HPV 16/18 infections were also significantly lower in vaccinated (2.0%) compared to unvaccinated women (8.1%), without any significant difference between the dose groups.
Conclusions: Single-dose may be as effective as 2/3 doses in 10-18 year old girls in preventing incident/persistent HPV 16/18 infections. Updated results will be presented.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

EXTENDED IMMUNOGENICITY AND EFFICACY OF THE QUADRIVALENT HPV VACCINE IN A COHORT OF WOMEN LIVING WITH HIV

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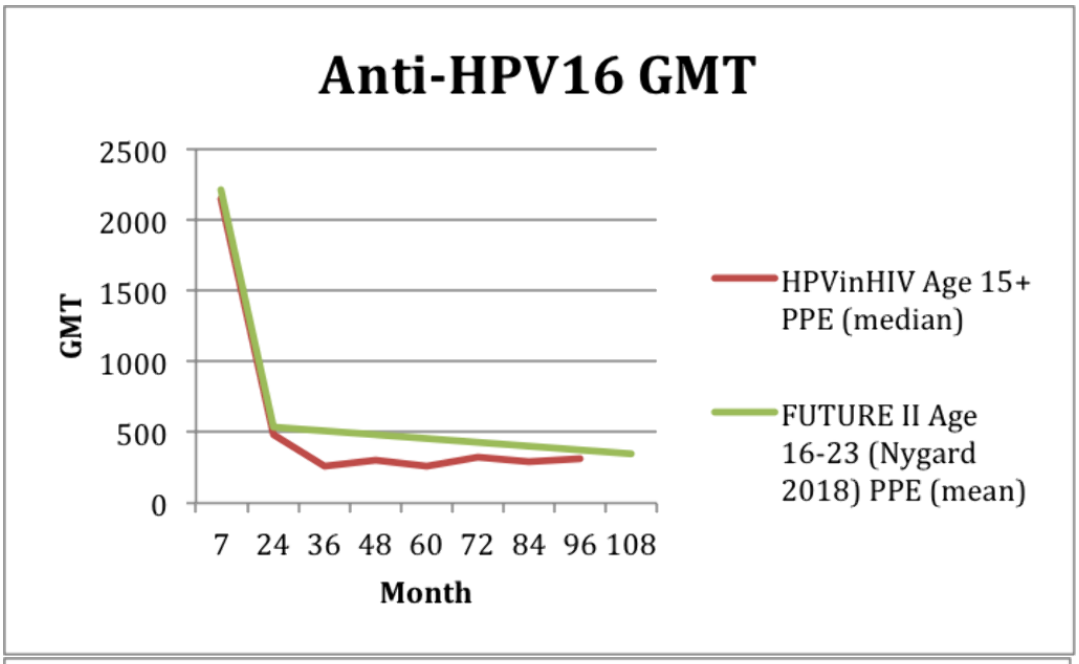
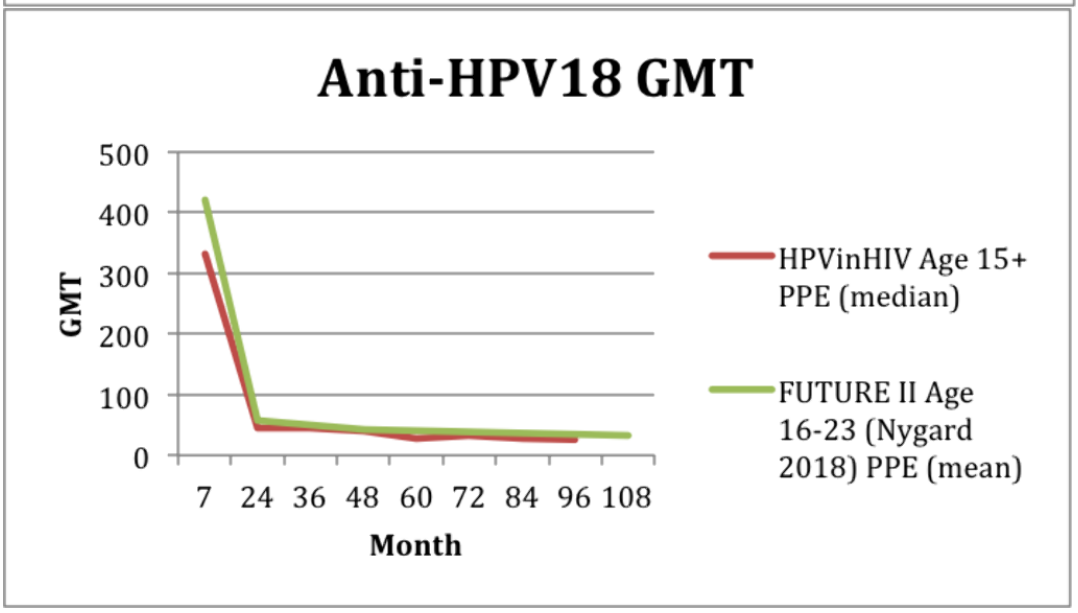
Introduction: Women living with HIV (WLWH) experience higher rates of HPV infection and associated disease. Understanding vaccine impact in this group is vital to achieving elimination of cervix cancer globally. This analysis assesses the immunogenicity and efficacy of the qHPV vaccine up to 8 years in a cohort of WLWH.
Methods: WLWH participating in a multi-centre study of qHPV vaccination were administered three doses at 0/2/6 months. Demographic and clinical data, serology (cLIA), liquid-based cervical cytology, and HPV DNA genotyping (Linear array assay) were collected at baseline and post-vaccine series q6-12 months. Immunogenicity endpoints were geometric mean titers of anti-HPV antibodies and seropositivity rates. Efficacy endpoints were persistent qHPV, genital warts, and CIN2+. Persistence was defined as new HPV 6/11/16/18 DNA persisting in samples from ≥2 consecutive visits or in the last sample.
Results: 222 women were eligible for the per-protocol efficacy (PPE) population (3 vaccine doses within 1 year, ≥1 follow-up beyond month 7, naive to the relevant qHPV type). At first vaccination, median age was 39 years (IQR: 33-45), median CD4 count was 510/mm3 (IQR: 390-700), and 73% had a suppressed HIV viral load (<50 copies/mL). Median follow-up was 5.9 years. At month 7, seropositivity rates for HPV6/11/16/18 were 98.6%, 98.9%, 98.7%, and 93.7%, respectively. At month 96, seropositivity rates were 81.8%, 87.8%, 83.7%, and 53.2%, respectively. In the PPE population, efficacy endpoints were: persistent qHPV = 0.52 per 100 person-years (95% CI: 0.19-1.13), genital warts = 0.37 per 100 person-years (95% CI: 0.10-0.94), and CIN2+ = 0 per 100 person-years. Comparisons were made to literature from women without HIV.





Conclusions: These data demonstrate low rates of infection and/or disease in this vaccinated cohort. However, as seen in other studies, there is reduced seropositivity over time especially for HPV18, such that many women are seronegative, a particular concern for this population of WLWH.

ORAL SESSION 10: VACCINES CLINICAL ASPECTS

IMMUNE RESPONSE TO QUADRIVALENT HPV VACCINE IN WOMEN AFTER HEMATOPOIETIC ALLOGENEIC STEM CELL TRANSPLANT: A NONRANDOMIZED CONTROLLED TRIAL

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Introduction: HPV infection is found in 40% of female allogeneic hematopoietic stem cell transplant survivors and can induce subsequent neoplasms. The immunogenicity of quadrivalent HPV vaccine (HPV-6/-11/-16/-18) post-allogeneic transplant is unknown.
Methods: We conducted a prospective, open-label phase 1 safety and immunogenicity study of quadrivalent HPV vaccine in clinically-stable women aged 18-50 years either on or off immunosuppressive therapy post-allogeneic transplant compared to female healthy volunteers. Participants received HPV vaccine in intramuscular injections on day 1, and 2 and 6 months later and were followed for a year after first vaccination. Anti-HPV-6/-11/-16/-18-specific antibody responses using L1 VLP ELISA were measured in serum prior to (day 1) and at months 7 and 12 post vaccination. Anti-HPV-16 and -18 neutralization titers were determined using a pseudovirion-based secreted alkaline phosphatase neutralization assay.
Results: Of 64 vaccinated women, 23 were taking immunosuppressive therapy (median age 34yr; 1.2yr post-transplant), 21 were off immunosuppression (median age: 32yr; 2.5yr post-transplant), and 20 were healthy volunteers (median age: 32yr). After vaccine series completion, 78% (18/23) of patients on immunosuppression, 95% (20/21) off immunosuppression and 100% (20/20) volunteers developed antibody responses to all quadrivalent HPV vaccine types (P=0.042, comparing the three groups). Geometric mean antibody levels for each HPV type were significantly higher at months 7 and 12 than baseline in each group (P<0.001) but not significantly different across groups. HPV-16 and HPV-18 antibody levels and neutralization titers correlated at month 7 (rho=0.92; P<0.001 for both). Adverse events were mild and not different across groups.
Conclusions: HPV vaccination induces strong, functionally-active antibody responses against vaccine-

related HPV types and can be safely administered to women post-transplant to potentially reduce HPV infection and related neoplasia. Clinicaltrials.gov identifier: NCT01092195

ORAL SESSION 11: SELF SAMPLING

SELF-SAMPLING COMBINED WITH THE COBAS HPV TEST IN A COHORT OF 13,111 WOMEN UTILIZING A MIDWIFERY NETWORK IN GREECE. FINAL RESULTS OF THE GRECOSELF STUDY.

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Introduction: The GRECOSELF study is a nationwide cross-sectional study aiming to propose a way to implement HPV-DNA testing with self-sampling for cervical cancer screening in Greece, utilizing a midwifery network.
Methods: Women between 25-60 years old, who resided in rural Greece were approached by midwives, at their place of residence, and were provided with a dry swab for cervicovaginal sampling. They were also asked to fill out a questionnaire regarding demographics and cervical cancer screening history. Each sample was tested for high-risk (hr) HPV with the cobas® HPV test, which detects HPVs 16 and 18 separately, and HPVs 31,33,35,39,45,51,52,56,58,59,66 and 68 as a pooled result. HrHPV positive women were referred to undergo colposcopy/biopsy and then to appropriate follow up/treatment according to the results.
Results: Between May 2016 and November 2018, 13,111 women were recruited. Of these 1070 (8.3%) were hrHPV positive, 224 (1.7%) and 78 (0.6%) were positive for HPV 16 and 18 respectively. Of the 1070 hrHPV positive women, 773 (72.2%) accepted to undergo colposcopy. Cervical Intraepithelial Neoplasia grade 1 (CIN1), CIN2 and CIN3 were detected in 86, 28, and 44 cases respectively. There were two cases of Vaginal intraepithelial Neoplasia (VaIN), one case of adenocarcinoma in situ, one case of adenocarcinoma, and one case of squamous cell carcinoma. CIN2+ prevalence was 0.6% within the study population and 9.7% amongst women who had colposcopy. HrHPV positivity rate decreased with age from 20.7% for women aged 25-29 to 5.1% for women 50-60. Positive predictive value of hrHPV testing and HPV16/18 genotyping ranged from 5.0-11.6% and 11.8-27.0%, respectively, in different age groups.
Conclusions: For women residing in rural Greece, hrHPV DNA detection with the cobas HPV test on self-collected cervicovaginal samples using dry cotton swabs which are provided by visiting midwives, is a promising method for cervical cancer screening.

ORAL SESSION 11: SELF SAMPLING

EVALUATION OF COBAS HPV AND SEQHPV NGS ASSAYS IN THE CHINESE MULTI-CENTER SCREENING TRIAL (CHIMUST)

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Introduction: Test two PCR-based high-risk HPV assays with self(S) anddirect(D) cervical samples in a population based cervical cancer screening trial.
Methods: 10885 women ages 30-59y women from 15 sites in 7 provinces with no cervical cancer screening for 3 years wereeligible. All participating women contributed one self-collected sample(S) and one physician-collected endocervical sample(D). The self-collected sample was first applied to the POI solid media transport card then the brush placed in 6ml ThinPrep Solution. All samples were tested with Cobas4800 and SeqHPV HR-HPV assays. Patients HPV positive (self or direct) were recalled forcolposcopy and biopsies.
Results: 10399women had complete data. The mean age was 43.9 years. 1.4% (142/10399) hadCIN2+ and 0.5%(54/10339) had CIN3+. In the liquid specimens the overall HPV infection rates were 10.8% for Cobas and 10.9% for SeqHPV in D-sample, and 13.7% forCobas and 11.6% for SeqHPV in S-sample, respectively. Thesensitivity of Cobas-D, Cobas-S, SeqHPV-D and SeqHPV-S for CIN2+ was 95.07%,95.07%, 93.6%, and 96.48%,respectively. The specificity ofCobas-D,Cobas-S, SeqHPV-DandSeqHPV-S for CIN2+ was 90.38%, 87.35%, 90.21%, and 89.53% respectively. There were no differences in sensitivity or specificity when applying the two assays to both self and direct collected samples in liquid transport media. (P>0.05).
Conclusions: Cobas 4800 and SeqHPV have similar sensitivities and specificities for diagnosingCIN 2+ in both self and direct collected liquid specimens.

ORAL SESSION 11: SELF SAMPLING

ACCEPTABILITY AND ACCURACY OF CERVICAL CANCER SCREENING USING A SELF-COLLECTED VEIL FOR HPV DNA TESTING BY MULTIPLEX REAL-TIME PCR AMONG ADULT WOMEN IN SUB-SAHARAN AFRICA

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Introduction: The cross-sectional GYNAUTO-CHAD study compared the acceptability and HPV DNA diagnostic accuracy of clinician-collected endocervical sample with swab (as reference collection) and genital self-collection method with veil (V-Veil-Up Gyn Collection Device, V-Veil-Up Pharma Ltd., Nicosia, Cyprus) in adult African women recruited from the community.
Methods: Peer educators contacted adult women living in N'Djamena, Chad, in community-churches and mosques or women association networks to participate to the survey and to come to the clinic for women's sexual health "La Renaissance Plus". A clinician performed a pelvic examination and obtained an endocervical specimen using flocked swab. Genital secretions were obtained by self-collection using veil. Both clinician- and self-collected specimens were tested for HPV and HR-HPV DNA using Anyplex™ II HPV28 genotyping test (Seegene, Seoul, South Korea).
Results: A total of 253 women (mean age, 35.0 years) were prospectively enrolled. The prevalence of HPV infection was 22.9%, including 68.9% of HR-HPV infection (HR-HPV prevalence: 15.8%, 95%CI: 11.3-20.3), with unusual HR-HPV genotypes distribution and preponderance (≈70%) of HR-HPV targeted by Gardasil-9® vaccine. Veil-based genital self-collection showed high acceptability (96%), feasibility and satisfaction. Self-collection by veil was non-inferior to clinician-based collection for HR-HPV DNA molecular testing, with "good" agreement between both methods, high sensitivity (95.0%; 95%CI: 88.3-100.0%) and specificity (88.2%; 95%CI: 83.9-92.6%). Remarkably, the rates of HPV DNA and HR-HPV DNA positivity were significantly higher (1.67- and 1.57- fold, respectively) when using veil-based collected genital secretions than clinician-collected cervical secretions by swab.
Conclusions: These observations highlight the unsuspected high burden of cervical oncogenic HR-HPV infection in Chadian women. Self-collection of genital secretions using the V-Veil-Up Gyn Collection Device constitutes a simple, highly acceptable and powerful tool to collect genital secretions for molecular testing of oncogenic HR-HPV that could be easily implemented in the national cervical cancer prevention program in sub-Saharan Africa.

ORAL SESSION 11: SELF SAMPLING

SELF-COLLECTION OR PRACTITIONER-COLLECTED EVALUATION (SCOPE) STUDY: EXAMINING WHETHER USING A COPAN FLOQSWAB IS NON-INFERIOR TO PRACTIONER-COLLECTED SPECIMENS ACROSS SIX HPV ASSAYS

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Introduction: Many countries, including most lower and middle income countries, have struggled to implement successful Pap-based cervical screening programs. One of many barriers has been that speculum-assisted practitioner collection is not feasible for cultural or logistical reasons. We now know that HPV-based cervical screening is as accurate for self-collected high vaginal samples as with practitioner-collected samples using a PCR-based HPV assay. However one of the major issues faced by laboratories is that none of the clinically validated PCR-based assays have manufacturer claims for self-collection.
Methods: Specimens were collected from 303 consenting women awaiting colposcopy at a Dysplasia clinic at the Royal Women's Hospital in Melbourne, Australia. Self-collection was undertaken using the Copan FLOQSwab (#552C) and practitioner-collected samples were collected using normal practice. Paired (self and practitioner-collected) specimens were then tested on six PCR-based HPV assays/instruments approved for use in the Australian National Cervical Screening Program (NCSP); Roche cobas 4800, Roche cobas 6800, BD Onclarity, Seegene Anyplex II, Cepheid Xpert, and Abbot m2000.
Results: HPV16/18 results had high observed agreement between self- and practitioner-collected samples on all six assays (range: 0.94–0.99), with good agreement for non-HPV16/18 oncogenic HPV types (range: 0.64–0.73).
Conclusions: Self-collection for HPV-based cervical screening shows good concordance and relative sensitivity when compared to practitioner-collected samples across accredited assays in the Australian NCSP. In Australia self-collection is being successfully implemented to reach never and under-screened women. In future it may have an important role in providing comfortable, accurate screening for all women.

ORAL SESSION 11: SELF SAMPLING

PATIENT CHARACTERISTICS THAT MODIFY THE EFFECTIVENESS OF A MAILED HPV SELF-SAMPLING KIT INTERVENTION IN A US-HEALTHCARE-SYSTEM-BASED PRAGMATIC RANDOMIZED TRIAL

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Introduction: Mailing HPV self-sampling kits to overdue women increases cervical cancer screening participation. We recently demonstrated a 50% increase in screening uptake with a mailed HPV kit intervention versus usual care Pap reminders at Kaiser Permanente Washington. To inform future health system implementation, we sought to identify patient characteristics that modified the intervention's effectiveness at increasing uptake.
Methods: From 2014-2016, we randomized 19,851 women aged 30-64 years who were overdue for Pap screening to usual care alone (n=9,891), or usual care plus a mailed HPV kit (n=9,960). Screening uptake was tracked 6-months post-randomization. Patient characteristics (age, race/ethnicity, travel time to clinic, income, BMI, tobacco use, time since last Pap stratified by enrollment history) were extracted from electronic medical records. We used intention-to-treat log-binomial regression to estimate associations between randomization arm and screening uptake, and to test patient characteristic-by-randomization arm interactions.
Results: Screening uptake was 26.3% versus 17.4% in the intervention vs. control arm (relative risk[RR]=1.51,95%CI:1.43-1.60). Although absolute differences in uptake by arm varied little by screening history (Table 1), relative effects were greater with longer versus shorter time since last Pap (No prior Pap: RRs from 1.85-3.25; ≥10 years: RR=2.78; 5-10 years: RRs from 1.69-1.86; <5 years: RRs from 1.29-1.37) (p<.001 for all interactions). No other statistically significant effect modifiers were identified; however, there were borderline-significant differences by age (p=.081), with RRs from 1.33-1.48 across 5-year age groups in women 30-54 years, versus 1.60 in women 55-59 and 1.77 in women 60-64 years.

Table 1. Effectiveness of a Mailed HPV Kit Intervention Vs. Usual Care for Increasing Screening Uptake in Underscreened Women in a U.S. Health Care System, Stratified by Select Patient Characteristics

	Intervention Arm (N=9843*)		Control Arm (N=9891)		Abs. Diff. Between Arms (%)	Intervention vs. Control RR (95% CI)	P-value for characteristic-by-arm interaction
Characteristic	**N**	**% Screened**	**N**	**% Screened**			
Age, y							
30-34	808	25.5	794	18.1	7.4	1.41 (1.16-1.70)	0.08
35-39	932	27.8	915	20.9	6.9	1.33 (1.13-1.57)	
40-44	1194	28.3	1185	20.3	8.0	1.40 (1.21-1.61)	
45-49	1380	25.4	1374	17.4	8.0	1.46 (1.26-1.69)	
50-54	1682	25.7	1707	17.4	8.3	1.48 (1.30-1.69)	
55-59	1938	24.7	1943	15.4	9.3	1.60 (1.40-1.82)	
60-64	1909	27.7	1973	15.6	12.1	1.77 (1.56-2.01)	
Race							
White	7018	28.1	7111	18.1	10.0	1.55 (1.46-1.65)	0.51
Asian	893	27.7	880	19.4	8.3	1.42 (1.20-1.69)	
Black or African American	438	27.2	431	16.5	10.7	1.65 (1.27-2.14)	
Native Hawaiian or Other Pacific Islander	151	21.2	139	15.8	5.4	1.34 (0.82-2.20)	
American Indian/Alaska Native	147	19.0	145	10.3	8.7	1.84 (1.03-3.30)	
More than one race	285	26.0	283	17.3	8.7	1.50 (1.08-2.07)	
Other	250	25.2	235	22.6	2.6	1.12 (0.81-1.54)	
Unknown	*661*	*8.2*	*667*	*7.3*			
Ethnicity							
Non-Hispanic	8710	27.6	8761	18.0	9.6	1.53 (1.45-1.62)	0.22
Hispanic	486	26.3	480	20.0	6.3	1.32 (1.04-1.66)	
Unknown	*647*	*9.4*	*650*	*7.1*			
Time since last Pap test (by length of health plan enrollment)							
Enrolled 3.4 to <5 y							
>3.4 to <5	704	37.8	710	28.5	9.3	1.33 (1.14-1.54)	<.001
No Pap test	1526	19.0	1530	10.3	8.7	1.85 (1.55-2.22)	
Enrolled 5 to <10 y							
>3.4 to <5	1519	34.9	1468	27.0	7.9	1.29 (1.16-1.44)	<.001
5 to <10	540	22.0	507	13.0	9.0	1.69 (1.29-2.23)	
No Pap test	1056	12.3	1070	5.0	7.3	2.49 (1.83-3.38)	
Enrolled ≥10 y							
>3.4 to <5	2186	39.5	2252	29.0	10.5	1.37 (1.26-1.48)	<.001
5 to <10	1143	23.8	1182	12.8	11.0	1.86 (1.55-2.23)	
≥10	475	12.6	506	4.5	8.1	2.78 (1.75-4.41)	
No Pap test	694	8.8	666	2.7	6.1	3.25 (1.94 -5.45)	
Women's census block, median household Income							
<$25,000	140	27.1	125	13.6	13.5	2.00 (1.19-3.34)	0.56
$25,000-49,999	2107	24.0	2115	15.4	8.6	1.56 (1.37-1.77)	
$50,000-74,999	3448	26.1	3439	16.5	9.6	1.58 (1.44-1.74)	
$75,000-99,999	2405	27.9	2483	19.2	8.7	1.45 (1.31-1.61)	
≥$100,000	1025	30.6	1013	20.9	9.7	1.46 (1.26-1.70)	
Unknown	*718*	*22.7*	*716*	*16.6*			
Travel time from women's home to primary care clinic							
< 10 minutes	3254	26.5	3236	16.8	9.7	1.58 (1.43-1.74)	0.53
10 - <20 minutes	4086	26.0	4048	17.8	8.2	1.46 (1.34-1.58)	
20 - <30 minutes	1407	28.3	1415	18.0	10.3	1.57 (1.37-1.80)	
≥30 minutes	1004	24.8	1072	17.4	7.4	1.43 (1.21-1.69)	
Unknown	*92*	*22.8*	*120*	*10.0*			
BMI (kg/m^2)							
<18.5	109	25.7	98	19.4	6.3	1.32 (0.79-2.21)	0.63
18.5-24.9	2238	32.6	2248	22.8	9.8	1.43 (1.30-1.58)	
25-29.9	2168	31.2	2220	21.0	10.2	1.48 (1.34-1.64)	
30-34.9	1549	28.6	1603	17.3	11.3	1.65 (1.44-1.88)	
35-39.9	1119	26.5	1080	18.5	8.0	1.43 (1.22-1.68)	
40+	1248	23.2	1184	16.0	7.2	1.45 (1.23-1.71)	
Unknown	*1412*	*9.1*	*1458*	*3.6*			
Tobacco use							
Never	5237	30.8	5232	20.9	9.9	1.48 (1.38-1.58)	0.77
Current	1276	18.5	1290	12.3	6.2	1.50 (1.25-1.81)	
Former	2041	30.6	2020	19.8	10.8	1.55 (1.39-1.73)	

Conclusions: Mailed HPV kits are effective for increasing cervical cancer screening in underscreened women within a US healthcare system. The relative effectiveness of the mailed kit outreach strategy was greatest in women with ≥10 years since last Pap or previously unscreened (highest risk for cervical cancer). Clinically important absolute improvements in uptake were observed for all women.

PUBLIC HEALTH ORAL SESSION ABSTRACTS

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

THE IMPACT AND COST-EFFECTIVENESS OF SINGLE-DOSE HPV VACCINATION IN UGANDA: A COMPARATIVE MODELING ANALYSIS

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Introduction: As data accumulate supporting similar efficacy and sustained protection for 1-, 2- or 3-doses of human papillomavirus (HPV) vaccination, uncertainties in the level and duration of a single-dose continue to exist. Model-based analyses can identify the vaccine characteristics that single-dose vaccination would need in order for it to be cost-effective. We conducted a comparative model-based analysis to evaluate the impact and cost-effectiveness of single-dose HPV vaccination compared to 1) no vaccination and 2) two-dose HPV vaccination in Uganda.
Methods: We used two dynamic model platforms (Harvard, HPV-ADVISE) that captured HPV transmission, cervical carcinogenesis, and population demographics to project the health and economic outcomes associated with routine (age 9 years) girls-only one-dose HPV vaccination (assuming 80-100% efficacy against HPV-16/18/33/35/45/52/58 infections under four waning scenarios) and two-dose HPV vaccination (assuming 100% lifelong efficacy) in Uganda. Incremental cost-effectiveness ratios (i.e., cost per disability-adjusted life year [DALY] averted) were calculated and compared against two thresholds: the Ugandan per-capita gross domestic product (pcGDP) and the World Health Organization 'Best Buys' (i.e., $100/DALY averted).
Results: Both models showed overall consistency in findings. Compared to no vaccination, single-dose HPV vaccination reached the WHO "Best Buys" threshold if protection was longer than 15 years and efficacy was ≥80%, averting between 734,000 to 2.6 million cases of cervical cancer over 100 years. Compared to 2-dose vaccination, 1-dose HPV vaccination was less costly and very cost-effective in the short-run (by 2050) when vaccine benefits were similar, but 2-dose vaccination became cost-effective (pcGDP threshold) in the long-run (e.g., over 80-90 years) as greater benefits were realized, even under optimistic single-dose vaccine characteristics.
Conclusions: One-dose HPV vaccination was considered very cost-effective compared to no vaccination, and may be preferred over two-dose vaccine under select optimistic scenarios assuming the WHO "best buys" threshold. However, two-dose was preferred from a long-term perspective provided a higher pcGDP threshold.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

GLOBAL IMPACT AND COST-EFFECTIVENESS OF ONE-DOSE VERSUS TWO-DOSE HUMAN PAPILLOMAVIRUS VACCINATION SCHEDULES: AN EXPLORATORY MODELLING ANALYSIS

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Introduction: Current World Health Organization guidelines recommend two doses of human papillomavirus (HPV) vaccine for all 9–14-year-old girls, prior to sexual debut, to protect them from oncogenic genotypes of HPV which may cause cervical cancer later in life. Although HPV vaccination was found to be cost-effective in most countries, low- and middle-income countries (LMICs) which have the highest cervical cancer incidence have been disproportionately less likely to introduce the HPV vaccine. Most LMICs are challenged with financial, logistic and supply constraints associated with delivering the two-dose regime outside the infant vaccination schedule, thus motivating alternatives such as one-dose vaccination schedules.
Methods: We synthesised results of two published models—HPV-ADVISE and Public Health England model—and compared the impact and cost-effectiveness of one-dose versus two-dose vaccination in 177 countries using the Papillomavirus Rapid Interface for Modelling and Economics model, assuming one-dose vaccination provides shorter duration of protection.
Results: We estimated the number of cervical cancer-related cases, deaths and disability-adjusted life years occurring under each scenario by time since vaccination and age for each country. Both the direct effect of vaccination with lifetime duration, and the herd and waning impact were estimated. We then compared the incremental impact of a one-dose schedule giving 10- and 20-years protection with no vaccination, and a two-dose schedule giving lifetime protection. Between 2020 to 2080, models project one-dose (with 10–20y duration) and two-dose (with lifetime duration) schedules would avert 2–15m and 14–17m cervical cancer cases respectively, with both first and second doses averting the most cases per dose in LMICs (Figure1).

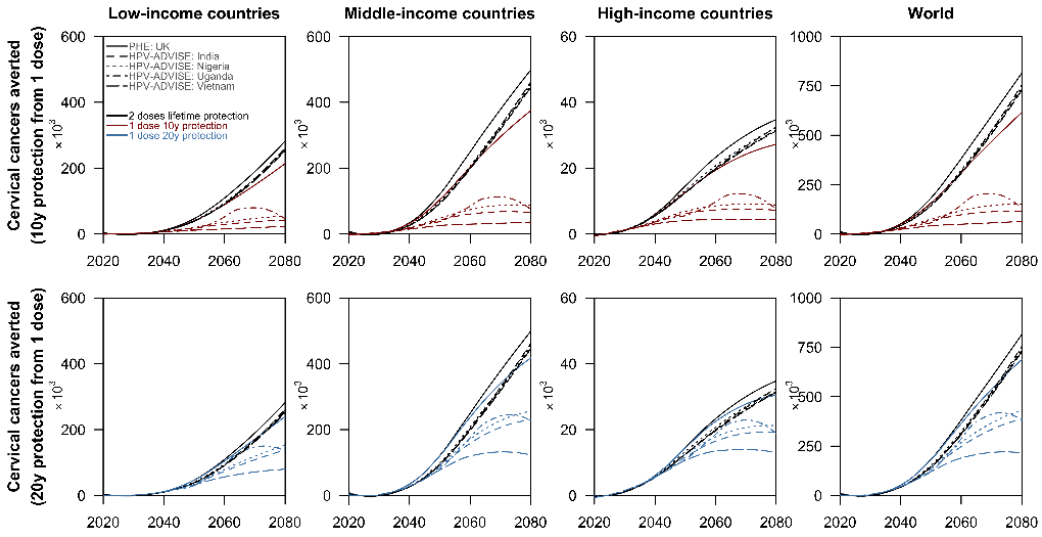

Figure1. Difference over time in impact on number of cervical cancers averted.

Conclusions: Projected impact of the vaccination is sensitive to the duration of protection offered by one dose. Results of mathematical models can guide country and global decision makers from countries with limited existing evidence in choosing optimal HPV vaccination strategies.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

IMPACT AND TRADEOFFS OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AND SCREENING CHANGES ON CERVICAL CANCER ELIMINATION IN NORWAY

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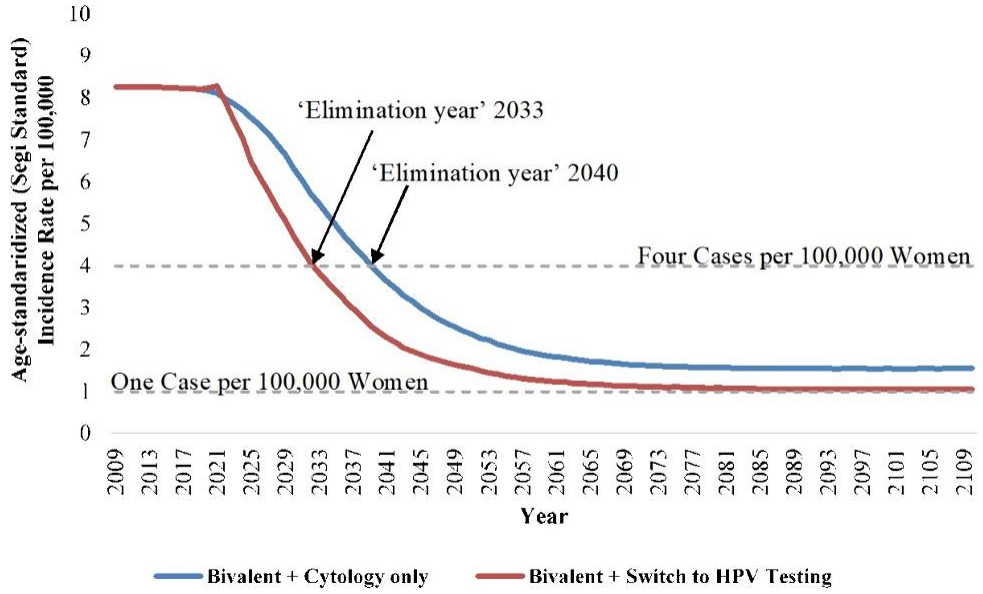
Introduction: The recent global call for action by the World Health Organization Director-General towards the elimination of cervical cancer (CC) as a public health problem requires country-specific evaluation of CC control programs. We explored the impact and tradeoffs of current and planned CC prevention programs, as well as alternative strategies, in Norway.
Methods: We used a multi-modeling approach that captured human papillomavirus (HPV) transmission, cervical carcinogenesis, and population demographics to estimate the health benefits (e.g., CC incidence rates) and resource use associated with the planned switch from cytology- to HPV-based screening compared with a 'status quo' scenario of cytology-only screening. Status quo prevention also assumed HPV vaccination at age 12 years, incorporating Norway's switch from the quadrivalent to bivalent vaccine in 2016. We also explored an alternative scenario of switching to the nonavalent vaccine in 2016, as well as the impact of alternative standard population structures.
Results: Under status-quo assumptions, CC incidence was projected to fall below 4/100,000 women by year 2040. Time to elimination was accelerated by seven years under the planned implementation of primary HPV testing for women aged ≥34 years (Figure 1). The switch to HPV testing increased colposcopy utilization compared to the status quo. Switching to the nonavalent vaccine had minimal impact on elimination timing (i.e., 1-2 years earlier) but reached a lower level of CC incidence (0.7/100,000 women, versus 1.1/100,000 with the bivalent vaccine). Different population structures led to variability in the timing of elimination (+/- 8 years).

Figure 1. Time to cervical cancer elimination in Norway.



Conclusions: CC rates in Norway may fall below 4/100,000 women by 2040 with current HPV vaccination and screening, but will be expedited with the switch to HPV-based screening. Switching to the nonavalent vaccine may lead to greater benefit but the cost-effectiveness has not yet been determined.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

THE COST-EFFECTIVENESS PROFILE OF SEX-NEUTRAL HPV IMMUNIZATION IN EUROPEAN TENDER-BASED SETTINGS

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Introduction: In many European countries, HPV vaccine uptake among preadolescent girls has remained far below target levels while vaccination cost declined because of reduced dosing schemes and tender procedures for the procurement of HPV vaccines. Yet, it remains unclear if these developments allow for a Europe-wide support for sex-neutral HPV vaccination.
Methods: We investigated the cost-effectiveness of sex-neutral HPV vaccination in European tender-based settings, focusing on prevention of cancers attributable to vaccine-targeted HPV types. Our Bayesian synthesis framework for health economic evaluation was applied to 11 countries throughout Europe, accommodating country-specific information on key epidemiologic and economic parameters. To tailor projections of herd effects, we used outcomes from three independently developed transmission dynamic models and setting-specific vaccine uptake rates.
Results: The total number of cancer cases to be prevented from vaccinating girls at current vaccine uptake varied from 350 (95% credible interval ([CrI]:280-430) cancer cases per cohort of 200,000 preadolescents (100,000 girls + 100,000 boys) in Croatia to 1,860 (1,750-1,960) cancer cases/200,000 preadolescents in Estonia. Vaccinating boys at equal coverage increased these respective numbers to 600 (530–680)/200,000 preadolescents in Croatia and to 2,300 (2,200-2,400)/200,000 preadolescents in Estonia. The incremental cost-effectiveness ratios (ICERs) of boys' vaccination compared to girls-only vaccination varied from I$3,900 (3,200-4,700)/life-year (LY) gained in Latvia to I$28,200 (23,400-33,500)/LY in Spain, remaining below country-specific per-capita GDP indicative for highly cost-effective interventions. When vaccine uptake was set at 80% in all countries, ICERs of sex-neutral vaccination remained below GDP in eight out of eleven countries.
Conclusions: Sex-neutral HPV vaccination is most likely an economically attractive intervention in European tender-based settings. Nonetheless, tender-based HPV vaccine prices need to be tailored to the country-specific income level, to ensure that boys' vaccination will remain cost-effective at universally high vaccine uptake rates.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

COST-EFFECTIVENESS OF SCALED-UP HPV VACCINATION AND SCREENING TO ACHIEVE CERVICAL CANCER ELIMINATION IN THE UNITED STATES

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Introduction: In 2019, the World Health Organization published ambitious draft coverage targets to achieve elimination of cervical cancer (CC) as a public health problem within a century. We evaluated the cost-effectiveness of increasing HPV vaccination and screening coverage in the U.S. to bring CC incidence below an elimination threshold of 4/100,000 women.
Methods: Two independently-developed models from the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium (Policy1-Cervix and Harvard) were used to evaluate the cost-effectiveness of increasing HPV vaccination coverage in 2020 and beyond to i) 90% in females at age 12; ii) 90% in females and males at age 12; iii) 90% in females by age 18; or iv) elective uptake of mid-adult catch-up to age 45, in each case with/without increasing screening coverage so that 90% of women comply with US guidelines. Both models involved a dynamic multicohort-modeling platform to capture changes over time, including herd effects from vaccination. Discounted costs and effects directly related to vaccination, screening, and sequelae were measured over the period 2020-2099.
Results: All scenarios (including status quo) reduced CC incidence below 4/100,000 before 2099. Increasing screening coverage to 90% was the most impactful intervention in terms of elimination timing and relative cancer reductions. Increasing female vaccination at 12 is likely to be cost-saving compared to the status quo, and increasing screening coverage in addition to this was very favourable (<$50,000/QALY), but additionally increasing male vaccination was highly unfavourable (>$500,000/QALY). Other strategies were less efficient than either increasing female vaccination at 12, or increasing both female vaccination at 12 and also screening coverage.
Conclusions: Although the costs of increasing coverage need to be taken into account, these results suggest that the most cost-effective strategy to hasten cervical cancer elimination in the U.S. involves increasing both female vaccination at 12 and also screening coverage.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

CERVICAL CANCER ELIMINATION IN LOW AND MIDDLE INCOME COUNTRIES: THE FLOW-ON BENEFITS OF PREVENTING THE LOSS OF A MOTHER ON THE FAMILY

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Introduction: In less developed settings, losing a mother increases the risk of death of her children due to the absence of maternal care. The Director-General of the WHO has recently called for coordinated action to eliminate cervical cancer globally. Although the impact of scaling up HPV vaccination, cervical screening and precancer/cancer treatment on global cervical cancer rates has been estimated, the additional benefits of reducing the associated childhood mortality has not been reported. In this study we aim to quantify the number of childhood deaths prevented if the WHO cervical cancer elimination targets can be reached in low and medium Human Development Index (HDI) countries.
Methods: An established platform, *Policy1-Cervix* was used to simulate cervical cancer incidence and mortality outcomes and an additional multicohort microsimulation module was developed to simulate outcomes for women and their children. Based on extensive review of the evidence after a woman's death, any of her children under 5 years of age were assumed to be subject to an increased risk of death (HR=9.86) for a 12 month period. Demographic and reproductive profiles for each country were taken into account.
Results: For each woman currently dying between the ages of 15-54 years in low and middle HDI countries, 0.04 to 0.30 child deaths are predicted (varies by country). If the cervical cancer elimination targets of 90% female HPV vaccination for ages 9-14, 70% of women screening at ages 35/45, and 90% receiving treatment for detected disease are met by 2030, 106,000 child deaths will be prevented from 2020-2070.
Conclusions: The global push for cervical cancer elimination will have far wider societal benefit than the direct impact on cervical cancer; these estimates suggest that over 100,000 children's lives will be directly saved in the next 50 years if cervical cancer elimination strategies can be successfully implemented.

ORAL SESSION 1: MODELLING I. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

POPULATION-LEVEL EFFECTIVENESS AND COST-EFFECTIVENESS OF HPV-FASTER IN TWO EXAMPLE COUNTRIES WITHOUT AN EXISTING VACCINATION PROGRAM: MODELLED EVALUATION OF CHINA AND VIETNAM

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Introduction: High effectiveness (>80%) of HPV vaccination in baseline DNA- and sero-negative females aged 26-45 has inspired the concept HPV-FASTER, which aims to accelerate the impact of vaccination in low-middle-income-countries (LMIC) by expanding the recommended age-range for vaccination. However, the benefits and cost-effectiveness of HPV vaccination in mid-adult women in LMIC has not been determined. We aimed to evaluate the impact of offering females aged 25, 35, 45 years: 1) HPV vaccination; 2) once-or twice-lifetime HPV testing; and 3) combined HPV-vaccination and once-lifetime HPV-testing, compared to no intervention. These strategies were evaluated for two Gavi-ineligible countries: China and Vietnam.
Methods: We used an extensively validated platform (*'Policy1-Cervix'*)) that accounts for herd effects from vaccination to evaluate the impact of the strategies, assuming a broad-spectrum vaccine is used, providing high protection against types 16/18/31/33/45/52/58. We assumed three-doses are required for vaccination at ages 25+ and favourable assumptions for vaccine price (US$9.80 per-dose). HPV-tests (plus delivery) were assumed to cost US$12 (worst-case assumption).
Results: For both countries, HPV vaccination at age 25, 35 or 45 years reduced the risk of cervical cancer mortality by 29-42%, 17-26% and 11-16%, respectively. Once-lifetime screening at age 35 reduced mortality by 40-45% and twice-lifetime screening at ages 35/45 reduced mortality by 62-65%. In each setting, vaccination alone at ages 25, 35 or 45 years was strongly dominated by once- or twice-lifetime screening. Screening once-or twice-per-lifetime was very cost-effective in both settings (Vietnam:ICER<US$700/LYS[WTP-threshold:1XGDP=US$2,300]; China:ICER<US$1,000/LYS[WTP-threshold:1XGDP=US$8,800]). Combined adult vaccination and once-lifetime screening delivered at ages 25, 35 or 45 years was not cost-effective in either setting.
Conclusions: HPV screening at 35 or at 35/45 is more effective and less costly than HPV vaccination for women aged 25+. Vaccination combined with HPV testing at ages 25, 35 or 45 is less likely to be cost-effective, unless vaccines are supplied at lower prices.

ORAL SESSION 2: VACCINATION I. IMPACT AND EFFECTIVENESS

LONG-TERM EFFECTIVENESS OF THE 9-VALENT HUMAN PAPILLOMAVIRUS (9VHPV) VACCINE IN SCANDINAVIAN WOMEN

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Introduction: A long-term follow-up (LTFU) extension (NCT02653118) of the pivotal 9vHPV vaccine efficacy study in young women 16–26 years of age was initiated to assess effectiveness for up to 14 years total follow-up (approximately 4 years in the base study; 10 years in the LTFU study). We report data from an interim analysis conducted at 8 years post-vaccination.
Methods: Participants from Denmark, Norway, and Sweden who received 9vHPV vaccine at the start of the base study (n=2223) and provided consent continued into the LTFU study. National health registries were used to assess those attending screening and diagnosed with cervical precancers and cancers during follow-up. Tissues from histological confirmation of cervical pathology (biopsy and definitive therapy) were retrieved for PCR analysis to detect HPV DNA and for pathology diagnosis adjudication. To assess effectiveness, the observed incidence of HPV16/18/31/33/45/52/58-related cervical intraepithelial neoplasia-2 (CIN2), CIN3, adenocarcinoma in situ, or cervical cancer ("CIN2 or worse") was compared with the estimated incidence in an unvaccinated cohort of similar age and risk level using a control chart method. Primary effectiveness analyses were conducted in the per-protocol effectiveness (PPE) population.
Results: 2029 participants continued into the LTFU study. Among those included in PPE analyses (n=1799), the median effectiveness follow-up post-Dose 1 was 6.8 years (range: 0.5, 10.0). During the LTFU study period, among 1448 PPE population-eligible participants contributing 4084.2 person-years follow-up, no new cases of HPV16/18/31/33/45/52/58-related CIN2 or worse were observed as of data cut-off (Jan 1, 2018). Over at least 6 years of total follow-up post-Dose 1, there were no signals observed in the control chart analysis that indicated waning of vaccine effectiveness in the PPE population.
Conclusions: The 9vHPV vaccine provides continued protection through at least 6 years following vaccination with a trend toward continued effectiveness for up to 8 years.

ORAL SESSION 2: VACCINATION I. IMPACT AND EFFECTIVENESS

MONITORING OF HPV GENOTYPE PREVALENCE TEN YEARS AFTER HPV VACCINE IMPLEMENTATION

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Introduction: To assess HPV genotype distribution in HPV-associated cancers from CCRs and to correlate HPV DNA presence with p16 overexpression (marker for HPV oncogene expression) in OP, rectal, and scrotal SCC.
Methods: Archived tissue from cervical, OP, anal, rectal, scrotal, and cervical carcinoma in situ (CCIS) incident cases between 2014 and 2015 were provided by CCRs in Iowa, Kentucky, and Louisiana. HPV genotyping was performed using Linear Array (Roche Diagnostics), with follow-up testing of HPV-negative samples using the INNO-LiPA HPV Genotyping Assay (Innogenetics). Weighted HPV prevalence was estimated for any HPV and the hierarchical attribution to genotypes in all vaccine formulations (16/18) and types in the 9-valent vaccine (31/33/45/52/58). P16 immunohistochemistry was performed in OP, rectal, and scrotal SCCs; percent agreement and Cohen's kappa (κ) coefficients were calculated.
Results: 363 cervical, 73 anal, 315 OP, 6 scrotal, 39 rectal, and 348 CCIS were successfully genotyped. Prevalence of HPV types were: cervical: [any HPV: 89%, 16/18: 69%, 31/33/45/52/58: 10%]; anal: [any HPV: 91%, 16/18: 85%, 31/33/45/52/58: 3%]; OP: [any HPV: 65%, 16/18: 63%, 31/33/45/52/58: 0.8%]; rectal SCC: [any HPV: 82%, 16/18: 71%, 31/33/45/52/58: 11%]; scrotal: [any HPV: 67%, 16/18: 50%, 31/33/45/52/58: 0%]; and CCIS: [any HPV: 98%,16/18: 68%, 31/33/45/52/58: 22%]. The agreement and κ coefficients between HPV and p16 for OP, rectal, and scrotal samples were 86% (κ=0.66), 92% (κ=0.75), and 83% (κ=0.67), respectively, which corresponds to substantial agreement (κ=0.61-0.80). .
Conclusions: *Conclusion*: HPV was present in over 80% of cervical, anal, rectal, and CCIS cases. Substantial agreement between HPV and p16 results was observed in OP, rectal, and scrotal SCCs, supporting the role of HPV. Monitoring HPV genotype prevalence will be important for documenting the impact of the HPV vaccine.

ORAL SESSION 2: VACCINATION I. IMPACT AND EFFECTIVENESS

NATURAL BOOSTING OCCURS IN HPV VACCINATED ADOLESCENTS: EXPOSURE, IMMUNE RESPONSE OR BOTH?

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Introduction: After natural exposure in vaccinated individuals, HPV immune responses may be enhanced ('boosted'). We aimed to evaluate whether natural boosting occurs and the associated factors up to 10 years post-vaccination in young women who received the quadrivalent HPV vaccine (QHPV).
Methods: Girls aged 9-13 years were randomized to received two or three doses of QHPV. Blood samples were collected before and at 7, 24, 60 and 120 months post-first dose and surveys were taken at baseline and each year between 60 and 120 months. Antibodies were measured by the competitive Luminex (cLIA) and total IgG (tIgG) immunoassays. A boosting event was defined as an increase in antibodies above the assay variability threshold without interval immmunization. A generalized estimating equations model with an unstructured correlation matrix was used to examine an association between antibody titres, socio-demographics, sexual behavior and HPV exposure.
Results: Of 73 participants who completed blood sampling at all time points, 17 (23.3%) showed at least one boosting event by cLIA for HPV6,11,16 or 18 during follow-up. Those with higher antibody titres during follow-up had significantly lower odds for boosting in the period thereafter. Geometric mean titres between two and three dose recipients were not significantly different, but two-dose recipients were more likely to show a boosting event during follow-up OR 3.44 (95%CI 1.07-11.11). No clear association was found with sociodemographics or sexual behavior. Eight participants (11%) showed a boosting event measured by tIgG. Evaluation of HPV DNA status in relation to increasing antibody titres is underway.
Conclusions: This study showed increasing antibody titres in 23% of adolescents vaccinated with QHPV during 10 years of follow-up. An association with boosting was found for those with lower antibody titres and for participants who received two-doses. The increase in antibody titres could reflect a response to natural exposure or maturation of the immune response.

ORAL SESSION 2: VACCINATION I. IMPACT AND EFFECTIVENESS

VACCINE PROTECTION AGAINST PREVALENT ANAL HPV INFECTION AMONG YOUNG MEN WHO HAVE SEX WITH MEN: A CANADIAN IMMUNIZATION RESEARCH NETWORK-FUNDED STUDY

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Introduction: Based on clinical trials, vaccine efficacy against anal detection of vaccine-preventable HPV types is >80% for gay, bisexual, and other men who have sex with men (gbMSM) with no prior HPV infection. Since 2015/16 in some Canadian provinces, HPV vaccine has been publicly-funded for gbMSM ≤26-years-old. We hypothesized that anal HPV prevalence would be lower among vaccinated compared to unvaccinated gbMSM soon after implementation of these programs.
Methods: Self-identified gbMSM were recruited into the Engage Cohort Study using respondent-driven sampling (RDS) in Canada's 3 largest cities (Montreal, Toronto, Vancouver) starting in 02/2017. At baseline, men 16-30-years-old self-reported HPV vaccination (≥1 dose) and self-collected anal specimens for type-specific HPV-DNA testing. We compared the prevalence of quadrivalent (HPV6/11/16/18) vaccine-preventable types between vaccinated and unvaccinated gbMSM using logistic regression.
Results: Preliminary results as of 02/2019 are based on 454 gbMSM (median age=26 years; median age at first anal sex=18 years; 4.2% HIV-positive). RDS-unadjusted vaccine uptake was 39.6% overall (50.0% in 16-26-year-olds and 27.0% in 27-30-year-olds). Among vaccinated men, 60.6% had received 3 doses. HPV6/11/16/18 prevalence was lower in vaccinated compared to unvaccinated men (21.1% vs. 27.8%). After adjustment for potential confounders (age, city, number of recent male sex partners, and lifetime history of STI diagnosis), aOR against prevalent infection was 0.69 (95%CI=0.42-1.12). Vaccination was protective in 27-30-year-olds (aOR=0.34, 95%CI=0.15-0.80) who had a longer median time since vaccination (2 vs. 1 years) and were more likely to receive 3 doses (68.1% vs. 57.5%) compared to 16-26-year-olds in whom vaccine was not protective (aOR=1.04, 95%CI=0.56-1.92).
Conclusions: Findings suggest lower anal prevalence of HPV6/11/16/18 in vaccinated compared to unvaccinated gbMSM, with better protection in 27-30-year-olds, but the timing of vaccination relative to acquisition of HPV infection was unknown. Vaccine effectiveness estimates against clinically-relevant endpoints such as persistent infection are needed for gbMSM in real-world settings.

ORAL SESSION 2: VACCINATION I. IMPACT AND EFFECTIVENESS

SIGNIFICANT DECLINES IN JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS (JORRP) FOLLOWING HPV VACCINE INTRODUCTION IN THE UNITED STATES

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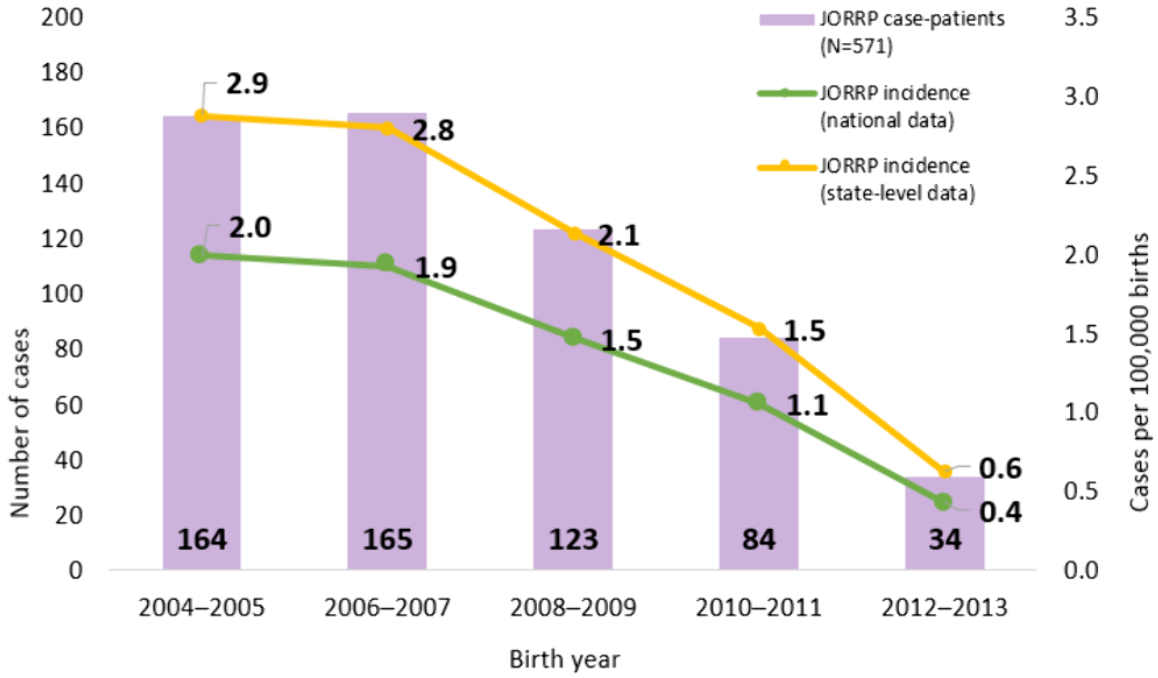
Introduction: Juvenile onset recurrent respiratory papillomatosis (JORRP) is a rare and serious disease, usually requiring specialized surgical treatment, caused by human papillomavirus (HPV) in young children. JORRP is most commonly acquired during vaginal delivery. Since 2006, HPV vaccination has been routinely recommended for U.S. females at age 11–12 years, with catch-up vaccination through age 26 years. Routine vaccination of males was recommended in 2011. We assessed trends in U.S. JORRP cases following vaccine introduction.
Methods: Case-patients were identified from 26 major U.S. pediatric otolaryngology centers. Patient demographics and clinical history were abstracted from medical records. Case-patients were grouped by year of birth rather than year of diagnosis, and birth-cohort incidences calculated using annual number of births from U.S. census data as denominator, either national or state-level birth data from the 23 states where centers were located. We calculated incidence rate ratios (IRR) and 95% confidence intervals (95% CI) over 2-year intervals.
Results: We identified 570 JORRP case-patients born in 2004–2013 in the United States. Median age at diagnosis was 3 years (interquartile range: 1–5). Number of identified JORRP case-patients declined from 173 born in 2004–2005 to 36 born in 2012–2013 (Figure). Incidence of JORRP per 100,000 births using national data declined from 2.0 cases in 2004–2005 to 0.4 cases in 2012–2013 (IRR=0.2, 95% CI=0.1–0.3); incidence using state-level data declined from 2.9 cases in 2004–2005 to 0.6 cases in 2012–2013 (IRR=0.2, 95% CI=0.1–0.3).

Juvenile-onset recurrent respiratory papillomatosis (JORRP) patients by birth year and incidence based on United States national or state-level denominator data



Conclusions: Over ten years, numbers of JORRP case-patients and incidences declined significantly. Incidences using national denominator data are likely underestimates; those using state-level data could be overestimates due to out-of-state referrals. These declines following U.S. HPV vaccine introduction are likely due to HPV vaccination. Monitoring is ongoing; HPV vaccination could lead to elimination of this serious HPV-related disease.

ORAL SESSION 3: SCREENING I. ARTIFICIAL INTELLIGENCE APPROACHES IN CERVICAL CANCER SCREENING

THE PREDICTIVE VALUE OF THE HUMAN GENE METHYLATION CLASSIFIER TO TRIAGE SELF-SAMPLING HPV POSITIVE WOMEN

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Introduction: We aimed to evaluate the human gene methylation panel to triage self-sampling HPV-positive women
Methods: The self-collected HPV cervical cancer screening cohort was conducted in 2017 in Shanxi and Inner Mongolia with 9526 women aged 30 to 64 years old. 2112 women with HPV positivity at baseline were followed up after one year. The targeted host gene(SOX17, DLX1, ITGA4,RXFP3, ASTN1 and ZNF671) methylation testing based on PCR was performed on the residual cytology sample. The optimal panel of the targeted host gene methylation for CIN2+ was explored. Then the triage clinical performance, predictive value and triage efficiency of the host gene methylation panel was compared to cytology, HPV16/18 genotyping with cytology, respectively. The feasibility of host gene as a triage method for HPV positive women was evaluated comprehensively.
Results: Host gene methylation panel remarkably decreased the colposcopy referral rate to 21.6%, which was much lower than that of cytology(44.3%, $p<0.001$) and HPV16/18 with combination of cytology(53.1%, $p<0.001$). Compared to the above two triage strategies, host gene methylation panel maintained the high sensitivity of 96.9%(95%CI:84.3%, 99.5%) for CIN3+, and with the higher specificity of 79.9% (95%CI:77.9%, 81.8%) compared to cytology(56.7%, $p<0.001$) and HPV16/18 genotyping with combination of cytology(47.8%, $p<0.001$). To detect one CIN3+ case, host gene methylation panel just needed to refer about 11 women, correspondingly, the number for cytology, HPV16/18 genotyping with combination of cytology were about 24 and 27. The CIR of CIN3+ for women with positive methylation result at baseline reached 11.9%(95%CI:8.4%, 15.4%), which was highest compared to cytology(5.9%, p=0.001), HPV16/18 genotyping with combination of cytology (5.4%, $p<0.001$).
Conclusions: The host gene methylation panel significantly decreased the colposcopy referral rate, and improved the clinical performance and triage efficiency compared to cytology, HPV16/18 genotyping with cytology.

ORAL SESSION 3: SCREENING I. ARTIFICIAL INTELLIGENCE APPROACHES IN CERVICAL CANCER SCREENING

DEEP-LEARNING-BASED EVALUATION OF DUAL STAIN CYTOLOGY IMPROVES ACCURACY AND EFFICIENCY OF CERVICAL CANCER SCREENING

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Introduction: With the advent of primary HPV testing followed by cytology for cervical cancer screening, visual interpretation of cytology slides remains the last subjective analysis step and suffers from low sensitivity and reproducibility.
Methods: We developed a cloud-based whole-slide imaging platform with a deep-learning classifier for p16/Ki-67 dual stained (DS) slides trained on biopsy-based gold standards. We compared it to conventional Pap and manually-read DS in three epidemiological studies of cervical and anal precancers from Kaiser Permanente Norther California (KPNC) and University of Oklahoma comprising 4,523 patients.
Results: In independent validation at KPNC, AI-based DS had lower positivity than cytology ($p<0.0001$) and manual DS ($p<0.0001$) with equal sensitivity and substantially higher specificity compared to both Pap ($p<0.0001$) and manual DS ($p<0.0001$), respectively. Compared to Pap, AI-based DS reduced referral to colposcopy by a third (41.9% vs. 60.1%, $p<0.0001$). At a higher threshold, AI-based DS had similar performance to HSIL cytology, indicating a risk high enough to allow for immediate treatment. The classifier was robust, showing comparable performance in two cytology systems and in anal cytology.
Conclusions: Automated DS evaluation removes the remaining subjective component from cervical cancer screening and delivers consistent quality for providers and patients. Moving from Pap to automated DS substantially reduces the number of colposcopies and achieves excellent performance in a simulated fully-vaccinated population. Through cloud-based implementation, this approach is globally accessible. Our results demonstrate that AI not only provides automation and objectivity, but also delivers a substantial benefit for women by reduction of unnecessary colposcopies.

ORAL SESSION 3: SCREENING I. ARTIFICIAL INTELLIGENCE APPROACHES IN CERVICAL CANCER SCREENING

CONSTRUCTION OF MACHINE LEARNING MODELS BASED ON RISK FACTORS, CYTOLOGY AND MOLECULAR BIOMARKERS FOR CERVICAL CANCER SCREENING AND VALIDATION ON TWO LARGE EXTERNAL COHORTS

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Introduction: Current decision for cervical cancer screening programmes resulted in increasing number of referral and unnecessary diagnostic procedures and costs. By using the machine learning method, this study aimed to develop and evaluate more accurate and cost-effective models for cervical cancer screening.
Methods: CIN2+ was the main outcome, and the following predictors in a large amount of women with normal histopathology (n=1 085), CIN (n=279) and cervical cancer (n=551) were considered to be included: demographic information, cytology, hrHPV DNA/mRNA, E6 oncoprotein, HPV genotyping, and p16/Ki-67. A basic model using age, cytology and hrHPV results and three optimized models had additional E6 oncoprotein and/or HPV genotyping results were constructed. The four models were evaluated in the baseline and 2-year follow-up data of two large screening cohorts (n=3 179 and 3 082) as external and longitudinal validation.
Results: The validation results of basic model in screening population (SP) I and II indicated sensitivities of 1.000 and 0.941, specificities of 0.845 and 0.941, AUCs of 0.978 and 0.983, and Youden indexes of 0.845 and 0.882, respectively, which were better than hrHPV and cytology alone or co-testing. The colposcopy referral rate of basic model (SPI: 17.6%; SPII: 7.4%) was lower compared to co-testing (SPI: 20.6%; SPII: 26.8%). In longitudinal validation, both basic model and co-testing yielded 100% sensitivity, while the basic model (SPI: 88.2%; SPII: 87.4%) had a higher specificity than co-testing (SPI: 85.5%; SPII: 79.4%). Optimized model containing E6 oncoprotein showed a better performance compared to basic model (Z=2.2764, P=0.02282) in follow-up.
Conclusions: Machine learning models constructed by the current cervical screening indicators increased the sensitivity and specificity, and reduced the positive referral rate. By incorporating multiple screening methods into one algorithm, we could generate a more effective and reliable screening method.

ORAL SESSION 3: SCREENING I. ARTIFICIAL INTELLIGENCE APPROACHES IN CERVICAL CANCER SCREENING

INITIAL RESULTS OF AUTOMATED VISUAL EVALUATION OF CERVICAL IMAGES FROM REAL-WORLD GLOBAL SOURCES

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Introduction: Many low- and middle-income countries (LMICs) do not have adequate cervical cancer prevention programs. Many LMIC screening programs rely on cytology; despite inconsistent implementation. Automated visual evaluation (AVE) is a new technology whereby a machine learning (ML) classifier analyzes cervical images for abnormalities. AVE does not require a lab infrastructure and has been demonstrated to provide more accurate results at the point of care (POC).
Methods: An AVE classifier was trained from a pool of histopathology-correlated digital cervical images captured with a mobile phone-based digital colposcope. The images came from providers using the Enhanced Visual Assessment (EVA) System. Histopathology of cervical intraepithelial neoplasia 2 and above (CIN2+) defined positive samples. Screening test data (cytology and human papillomavirus [HPV] testing) were also collected. Approximately 25% of the images had positive histopathology. Testing AVE on a 278-image set, a receiver operating characteristic (ROC) curve was calculated. Specified threshold values on the ROC curve were used to determine the exact sensitivity and specificity values.
Results: AVE had an area under the (ROC) curve (AUC) of 0.865. Three thresholds were selected, with a sensitivity of 0·899, 0·754, and 0·580, and a corresponding specificity of 0.560, 0.890, and 0.971. Considering only HPV+ patients, AVE Threshold 3, had specificity of 0.971, while corresponding low-grade squamous intraepithelial lesion (LSIL) cytology had a specificity of 0.841. AVE had consistent performance in different geographies; however some variations were observed with device model and auxiliary hardware.
Conclusions: This is the first report of AVE performance on real-world biopsy-correlated digital images from clinics around the world. Preliminary AVE results showed it is a highly accurate method that can be optimized for either higher sensitivity or higher specificity, while also minimizing subjectivity at the POC. Collectively these attributes show promise for different roles in cervical cancer prevention efforts across the globe.

ORAL SESSION 4: SCREENING II. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

EFFECTIVENESS OF ORGANISED PRIMARY HPV-BASED CERVICAL SCREENING OF WOMEN AGE 30-64: RANDOMISED HEALTHCARE POLICY

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Introduction: In the research setting, primary HPV-based screening results in greater protection against cervical cancer compared with cytology. The objectives of the this study were to evaluate the effectiveness of HPV-based cervical screening within a real-life screening program that offered either HPV-based or cytology-based screening, in a randomised manner.
Methods: This randomised health services trial was implemented in the context of the organised cervical screening program in the capital region of Sweden. The participants were 395,725 women aged 30-64 years, resident in the Stockholm-Gotland region of Sweden and invited to population-based cervical screening between Q3 2014 and Q3 2016. Women were randomisation to either screening with cervical cytology, with HPV triage of low-grade cytological abnormalities (cytology arm, old policy) or screening with HPV testing, with cytology triage of HPV positives (HPV arm, new policy). Detection rate of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) was the primary outcome. Secondary outcomes included screening attendance and referral to histology.
Results: In per protocol analyses, the detection rate of CIN2+ was 1.03% in the HPV arm and 0.93% in the cytology arm ($p<0.02$). There were 46 cervical cancers detected in the HPV arm (0.04% of all participating women) and 48 cancers detected in the cytology arm (0.05% of all participating women) p=ns; p for non-inferiority <0,0001). The intention-to-screen analyses found few differences. In the HPV arm, there was a modestly increased attendance after invitations to new screening rounds (68.6% vs. 67.7%; $p=0.0002$) and increased rate of referral to histology (3.89% vs. 3.53%; $p<0.0001$).
Conclusions: In this real-life, randomised health services trial of primary HPV-based screening we found comparable participation, referral, and detection rates between study arms. This suggests that HPV-based screening is acceptable and safe, already at the baseline screening round.

ORAL SESSION 4: SCREENING II. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

PERFORMANCE COMPARISON AMONG CERVICAL, VAGINAL AND URINE SAMPLES IN CERVICAL CANCER SCREENING IN CHINA

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Introduction: Cervical cancer screening practices showed certain weakness in accuracy, coverage and capacity in resource-limited areas. Urine self-sampling demonstrated potential to narrow the gaps.
Methods: Women at the age of 35-64 years old in Shanxi province were invited and provided three samples (cervical, vaginal and urine sample) after written informed consent obtained between July to October in 2015. Cervical samples were tested by careHPV and cobas4800 HPV test for triage and referral. After extraction, purified DNA samples were preserved at -80℃. The samples from 1006 women (503 HPV positive, 503 HPV negative) were detected by Isogema HPV test in July 2019 which could genotype HPV 16/18 while reported one result for another other 13 HPV types in one test. In analysis for performance evaluation, the histopathology outcome was determined by colposcopy and biopsy in 2015. Women with unsatisfactory biopsy result were excluded.
Results: There were 32.4% urine samples with hrHPV positive, and 31.4% for vaginal, 31.9% for cervical samples ($P > 0.05$) in qualified 972 women. The overall consistency was 85.2% (κ=0.659), 81.8% (κ=0.583) and 85.0% (κ=0.655) between urine and vaginal samples, urine and cervical samples, and vaginal and cervical samples, respectively. For HPV 16/18, the rates were 94.3% (κ=0.658), 93.3% (κ=0.612) and 96.0% (κ=0.76) correspondingly. Against CIN2+ detection, urine samples showed 84.2% sensitive and 69.0% specific. Meanwhile, the corresponded rates were 84.2% and 70.3% for vaginal samples, and 94.7% and 70.5% for cervical samples.
Conclusions: Urine showed comparable HPV positivity compared with vaginal and cervical samples. And the concordance achieved moderate to substantial among urine, vaginal and cervical samples. Similar clinical performance for CIN2+ detection was observed between urine and vaginal samples, but slightly lower than that for cervical samples. In summary, these findings suggest that urine-based HPV test is potential and promising in cervical cancer screening, especially in resource-limited areas.

ORAL SESSION 4: SCREENING II. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

DISCRETE EVENT SIMULATION MODELS TO SUPPORT RESOURCE AND OPERATIONAL PLANNING OF CERVICAL CANCER SCREENING PROGRAMS: A PILOT STUDY IN PERU

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Introduction: Despite many low- and middle-income countries (LMICs) adopting HPV-based screening guidelines/policies, successful scale-up of HPV testing lags farther behind. Ensuring that appropriate human and technical resources are available is essential in the initial roll-out, otherwise the programs risk early failure, undermining sustainability and scale-up efforts. However, there is little guidance available to implementers to tailor resource and operational planning decisions to their context.
Methods: To mitigate these risks, we are developing discrete event simulation (DES) models utilizing SIMIO software which replicate the processes involved in completing the continuum from screening to treatment (Figure 1). Each process consists of an activity and potential delays that can occur when moving from one activity to another. Virtual experiments compare the impact of various resource choices on key performance indicators, such as patient throughput and wait times. The results support stakeholder decisions on (1) the appropriate combination of resources to enable a given performance and/or (2) the performance possible given a fixed combination of resources. Model processes are informed by direct observation and monitoring and evaluation of the screening process in a single health network of 17 primary health facilities in Iquitos, Peru.

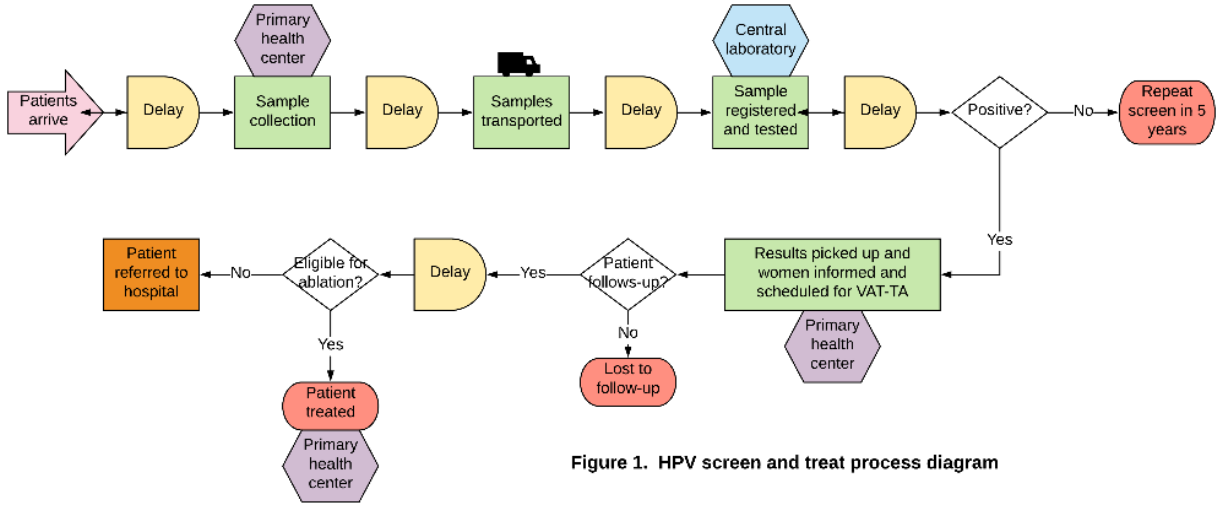

Figure 1. HPV screen and treat process diagram

Results: The DES model compares the impact of various resourcing strategies/constraints on indicators essential to the effectiveness of the screening program. As an example, we found that lab techs must work at least 20 hours per week to satisfy the constraint that all samples must be tested within 14 days of

collection if stored at room temperature (Table 1). Other examples of trade-offs in resource allocation and impact will be presented.

Table 1. Scenario: How does changing the schedule of the lab technician impact the average and maximum time from sample collection to testing?

Schedule scenario	Average time (days)	Maximum time (days)
1 hour/day, 3 days/week	11.05	23.29
2 hours/day, 3 days/week	9.28	22.37
3 hours/day, 3 days/week	7.85	20.32
4 hours/day, 3 days/week	7.24	18.27
1 hour/day, 5 days/week	9.82	22.33
2 hours/day, 5 days/week	7.45	19.35
3 hours/day, 5 days/week	5.90	15.37
4 hours/day, 5 days/week	4.81	13.29*

**Note this is the only scheduling scenario which meets the maximum allowed sample storage time of 14 days at room temperature.*

Base case assumptions: 5-hour work days, sample flow = screening target of 33 samples per day (summed over 17 primary health centers), sample transport from health centers to central lab 1x/week on Wednesday at 12pm, 2, 4-channel GeneXpert instruments operating 5 hours/day.

Conclusions: DES models offer stakeholders the ability to mitigate emergent bottlenecks in screening delivery that are otherwise difficult to anticipate. Moving forward, more general DES models are planned to enable accelerated roll-out and scale-up of screening programs across multiple resource constrained settings.

ORAL SESSION 4: SCREENING II. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

THE POSITIVE PREDICTIVE VALUE OF HPV TESTING VARIES WITH AGE AND REFLEX CYTOLOGY: FOLLOW-UP RESULTS FROM THE FIRST ROUND OF HPV PRIMARY SCREENING

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Introduction: In Australia's new HPV-based cervical screening program, HPV16/18 positive women, and women positive for non-16/18 types with ASC-H or higher reflex cytology, are referred for colposcopy. We investigated the positive predictive values (PPVs) for histologically-confirmed high-grade abnormality (HGA) among these women.
Methods: Retrospective review of 156,683 practitioner-collected primary HPV cervical screening tests submitted to a large pathology laboratory among women aged 25–74 years, in the first six months of the new program (1-Dec-2017 to 31-May-2018). PPVs were calculated from the number of HGA divided by the number of women with a positive screen, by 10-year age-groups and reflex cytology results.
Results: Colposcopy referral was recommended in 2.6% (95% CI: 2.5–2.7%; n=4006), with follow-up available for 2,261 (56.4%). HGA was detected in 555 women (513 HSIL, 16 mixed AIS/HSIL, 13 AIS, 6 AC, 7 SCC): overall PPV of 24.6% (22.8–26.4%). The PPV was highest (36.5%; 32.9–40.2%) at 25–35 years, decreasing to 6.1% (2.9–10.9%), at 65–74 years (p-trend<0.001). Among women with HSIL+ cytology, the PPV was 75.4% (70.2–80.1%), and was higher for HPV16/18 than non-16/18 positive women (79.9% [73.0–85.6%] versus 69.6% [61.1–77.2%]; p=0.039). The PPVs were high and stable, regardless of age (p-trend=0.194). Among women with negative cytology, the PPV was 6.7% (5.3–8.3%) and was highest (12.0%; 8.2–16.8%) at 25–35 years, decreasing to 1.6% (0.2–5.8%), at 65–74 years (p-trend<0.001). Among women with ASCUS/LSIL and ASC-H cytology, the PPV was 14.2% (10.9–17.9%) and 52.9% (47.5–58.2%), respectively. PPVs decreased with increasing age-groups, but this was significant only among women with ASC-H cytology (p-trend=0.09 and p-trend<0.001, respectively).
Conclusions: One in four women referred for colposcopy had underlying HGA. As expected, cytology triage increased the positive predictive value of HPV testing. A reduction in predictive value with increasing age-group, particularly among women with negative cytology, warrants ongoing monitoring.

ORAL SESSION 4: SCREENING II. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

IMPACT OF CERVICITIS ON PERFORMANCE OF PRIMARY HIGH RISK HPV TESTING FOLLOWED BY VISUAL EVALUATION IN WOMEN LIVING WITH HIV

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Introduction: The World Health Organisation recommends cervical cancer screening algorithms combining primary high-risk human papilloma virus (hrHPV) testing with visual inspection of the cervix. There is concern that cervicitis affects the accuracy of visual inspection methods. This study aimed to evaluate the impact of cervicitis on cervical cancer screening algorithms using hrHPV testing followed by either VIA or colposcopy.
Methods: A prospective cohort study of WLWH in Botswana. All participants underwent hrHPV testing. Participants with positive hrHPV underwent VIA, colposcopy and biopsy. Histopathology was the reference standard for determination of cervicitis, pre-invasive cervical disease and cervical cancer. Statistical analyses were calculated in SAS software including positive predictive value (PPV) and diagnostic accuracy (TP+FP/TP+FP+TN+FN). They were calculated for each screening algorithm based on either VIA or colposcopy and then compared between women with and without cervicitis.
Results: Among 300 women screened, 88 (29%) were hrHPV positive. Of those, 81 underwent visual evaluation and had histopathology results. 22 of 81 women (27%) had cervicitis and 28 of 81 women (35%) had high grade cervical intraepithelial neoplasia (CIN) defined as CIN2 or higher (CIN2+). For predicting CIN2+ in all subjects, positive hrHPV testing followed by VIA had a PPV of 39% [CI:24-55%] and a diagnostic accuracy of 52% [CI:41-63%]. PPV and diagnostic accuracy improved to 53% [CI:35-71%] and 58% [CI:44-70%] respectively when women with cervicitis were excluded. Positive hrHPV testing followed by colposcopy had a PPV of 47% [CI:33-62%] and diagnostic accuracy of 61% [CI:49-71%] improving to 63% [CI:46-78%] and 71% [CI:58-82%] by excluding women with cervicitis.

Table 1 Performance of visual evaluation methods of cervical cancer screening following hrHPV testing according to presence of cervicitis

	Number	Sensitivity (CI) %	Specificity % (CI)	PPV % (CI)	NPV % (CI)	Diagnostic accuracy%
All Participants						
VIA	81	58.6 (38.9-76.5)	48.1 (34.0-62.4)	38.6 (24.4-54.5)	67.6 (50.2-82.0)	51.9 (40.5-63.1)
Colposcopy	81	82.8 (64.2-94.2)	48.1 (34.0-62.4)	47.1 (32.9-61.5)	83.3 (65.3-94.4)	60.5 (49.0-71.2)
Participant Without Cervicitis						
VIA	59	63.0 (42.4-80.6)	53.1 (34.7-70.9)	53.1 (34.7-70.9)	63.0 (42.4-80.6)	57.6 (44.1-70.4)
Colposcopy	59	89.0 (70.8-97.7)	56.3 (37.7-73.6)	63.2 (46.0-78.2)	85.7 (63.7-97.0)	71.2 (57.9-82.2)
Participants With Cervicitis						
VIA	22	-	40.0 (19.1-64.0)	-	80.0 (44.4-97.5)	36.4 (17.2-59.3)
Colposcopy	22	-	35.0 (15.4-59.2)	-	77.8 (40.0-97.2)	31.8 (13.9-54.9)

Conclusions: Cervical cancer screening algorithms using hrHPV testing combined with visual inspection methods may be compromised by the presence of cervicitis. In populations with high prevalence of sexually transmitted infections, HIV and cervical cancer this represents a potential challenge for designing acceptable and effective screening programmes.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

INFLUENZA VACCINE VISITS ARE AN UNDERUTILIZED AVENUE FOR INCREASING HUMAN PAPILLOMA VIRUS VACCINATION RATES: AN AAP PEDIATRIC RESEARCH IN OFFICE SETTINGS (PROS) NETWORK STUDY

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Introduction: Missed opportunities (MOs) at primary care visits are a major contributor to low HPV vaccine coverage. Although influenza vaccination is administered often at clinician and nurse-only visits, little is known about MOs for HPV during these visits.
Methods: As part of the NIH-funded STOP HPV trial, we extracted electronic health record data from 43 practices across 18 states recruited from the AAP PROS national pediatric primary care network. We extracted all office visits from 2015-2018 in which the influenza vaccine was administered to HPV vaccine-eligible 11 to 17-year-olds. Among those visits, MOs were defined as the proportion in which an HPV vaccine was due but not given. Using descriptive statistics, we assessed the observed frequency of MOs. We also estimated incident rate ratios (IRRs) of MOs using a log-linear model clustered by practice.
Results: A total of 49,634 HPV-eligible influenza vaccine visits among 37,169 patients (median age: 12 yr., 47% female) were analyzed [Table]. Over half (58%) of these HPV vaccination opportunities were missed, and MO rates varied by practice (median: 56%, range: 26%-74%). MOs were far more common at visits during which an initial versus subsequent HPV vaccine dose was due (69% vs. 31%). MOs were also higher at acute/chronic and nurse visits versus preventive visits (75% and 81% vs. 38%). MOs were similar in males and females. In the multivariate model, MOs were significantly higher for initial versus subsequent doses (IRR: 2.39, 95% CI: 2.18-2.62) and at acute/chronic (RR: 2.08 95% CI: 1.92-2.26) and nurse (IRR: 2.21, 95% CI: 1.99-2.44) visits compared to preventive visits.

Missed Opportunities for HPV Vaccination at Visits where Influenza Vaccine was Administered at 43 Practices in 19 States

	Initial HPV Dose		Subsequent HPV Doses		Any HPV Dose	
	% MO	N (visits)	% MO	N (visits)	% MO	N (visits)
Overall	69.4%	35449	30.9%	14185	58.4%	49634
Visit type						
Preventive	48.4%	18569	7.8%	6250	38.1%	24819
Acute/Chronic	89.3%	5902	46.4%	3078	74.6%	8980
Nurse	94.3%	10978	50.7%	4857	80.9%	15835
Sex						
Male	69.7%	18862	30.4%	7443	58.6%	26305
Female	69.0%	16586	31.3%	6742	58.1%	23328
Age						
11 - 12 years	68.5%	21262	34.1%	5274	61.6%	26536
13 - 17 years	70.8%	14187	29.0%	8911	54.6%	23098

Conclusions: MOs for HPV vaccination during visits where influenza vaccine is given are frequent, particularly during acute/chronic or nurse-only visits and for the initial HPV vaccine. Efforts to increase simultaneous administration of HPV and influenza vaccines are warranted.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

TAILORING TAILORED MESSAGES? EFFECTIVENESS OF TAILORED MESSAGES TO IMPROVE BEHAVIORAL INTENT TO ACCEPT HUMAN PAPILLOMAVIRUS (HPV) VACCINATION MAY BE MODERATED BY SOCIODEMOGRAPHIC FACTORS.

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Introduction: Current guidance advises a strong, bundled recommendation for HPV vaccines, however, the most effective recommendation may not be the same for all parents. We piloted a series of brief recommendation videos for HPV vaccination, tailored to vaccine-hesitant mothers' concerns, to improve intention to accept HPV vaccination. This analysis evaluates differences in effectiveness of tailored videos compared to a traditional, bundled recommendation video within select sociodemographic groups.
Methods: We conducted a web-based, randomized-controlled trial among mothers in 27 low-uptake states who did not intend to vaccinate their 11-14-year-old child against HPV. Trial arms included: a) General, bundled-information video (“General/Control,” *n*=267), b) General video+video addressing top HPV vaccine concern (“Top Concern,” *n*=252), or; c) General video + ≥1 videos addressing all elicited vaccine concerns (“All Concerns,” *n*=243). The primary outcome was intent to vaccinate within 12 months (1=extremely unlikely; 10=extremely likely). Generalized linear models adjusted for maternal education assessed differences in mean post-test scores across intervention arms and were stratified by sociodemographic characteristics.
Results: Among 745 mothers who completed the intervention (80% white, 27% age <36 years), mothers in the All Concerns arm had significantly higher vaccination intention post-intervention than those in the General/Control arm (*p*=0.002). In stratified analyses, intention was significantly higher in All Concerns arm compared to General/Control arms among: mothers of younger (ages 11-12 years) but not older children; mothers ≤36 years but not >36 years of age; mothers with smaller (1-2 children) but not larger households; and mothers with household incomes of ≥$100,000 but not <$100,000.
Conclusions: For mothers with low intent to vaccinate, tailored messages addressing all HPV vaccination concerns may increase HPV vaccination intent more than general, bundled messages alone. However, intervention effectiveness may be influenced by sociodemographic factors. Further research is needed to better understand reasons for potential effect modification and impact on implementation in primary care.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

HPV VACCINE UPTAKE AND ASSOCIATED FACTORS IN ADULT WOMEN AGED UP TO 45 YEARS FROM 9 EUROPEAN COUNTRIES (COHEAHR-WP4 STUDY)

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Introduction: HPV vaccinated cohorts, irrespective of age, will likely reduce their subsequent screening requirements, thus opening opportunities for cost reduction in developed countries and of program sustainability in low-middle income countries. We estimated the uptake and compliance of HPV vaccination by adult women and assessed its acceptability determinants in different European countries.
Methods: Women aged 25-45 years were invited to receive free HPV vaccination in Spain, Finland, United Kingdom, Sweden, Belgium, Slovenia, Denmark, France and Germany using an opportunistic or population-based approach. Study participants completed a questionnaire on knowledge and attitudes on HPV vaccination. The determinants of vaccine uptake were explored using multilevel logistic models. A safety monitoring procedure was used.
Results: Out of 3646 participants, 2739 (range by country =50-96%) accepted vaccination and 2149 (range by country =30-93%) received the three-dose course of vaccination. Factors positively associated with vaccine acceptance were previous knowledge about adult female (OR=1.22; 95%CI=1.00-1.48) and male (OR=1.59; 95%CI=1.28-1.97) vaccination, whereas women in stable relationships (OR=0.56; 95%CI=0.45-0.69) or with higher educational level (OR=0.76; 95%CI=0.63-0.93) were more likely to refuse it. Vaccination invitation by postal mail versus convenient invitation at healthcare sites resulted in lower acceptance (OR=0.13; 95%CI=0.02-0.76), whereas vaccination coverage of adolescent girls in national public programs was a strong although borderline significant determinant of HPV vaccine uptake (OR=3.23; 95%CI=0.95-10.97). Main reasons for vaccine refusal were vaccine safety concerns (range=30-59%) and poor information on HPV vaccines (range=1-72%). No safety issues were identified in vaccinated women.
Conclusions: Acceptance and compliance rates were high despite its dependence on recruitment method used and achieved coverage of vaccination public programs, especially when vaccination is offered free of charge in healthcare settings. More information and safety reassurance continue to be relevant for informed decision making in European countries. Study results suggest that there are no major opinion barriers to vaccination of adult women.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

THE IMPORTANCE OF COMMUNITY ENGAGEMENT IN MANAGING THE RISK OF VACCINE HESITANCY IN A STUDY OF SINGLE-DOSE HPV VACCINATION

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Introduction: We implemented single-dose HPV vaccination in grade 10 girls (>15 years) in a district in South Africa, in a study measuring population-level impact of this dosing regimen. Given the potential for lower vaccine uptake in an age group older than that in the national programme (>9 years), we undertook pre- and intra-campaign community engagement and assessed this for signs of vaccine hesitancy.
Methods: In early 2019, a communications team visited all 66 public schools in the district, to meet separately with parents, educators, and Grade 10 girls, explain vaccination risks and benefits, respond to questions, and disseminate posters and information leaflets. In qualitative observations in a sub-set of schools selected for broad representativity (n=25), an observer recorded participants' concerns in information meetings and subsequent vaccination sessions.
Results: In total, 961 parents and 4790 learners attended information meetings. Most educators were supportive and actively facilitated campaign activities. Parents were mainly concerned about vaccine safety, though black parents worried that only black learners were being targeted, and lower interest was observed in more affluent schools. Learners articulated concerns about autonomy (own vs. parental consent to vaccinate), vaccine side effects (especially around contraceptive efficacy), and fear of injection pain. Many participants wanted more information about HPV and cervical cancer. Few concerns related specifically to the single-dose vaccine regimen, and there was only one instance of a parent circulating myths about vaccine safety via a social media group. We implemented ongoing training and developed an 'FAQ' on HPV vaccination for the communications team to promptly address these issues in campaign messaging.
Conclusions: Observations allowed for early identification of key stakeholder concerns and development of rapid responses to pre-empt potential spread of misinformation, likely contributing to high coverage levels in the campaign. Lessons learned will inform future vaccine introduction in cohorts involving older adolescents.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

UNDERSTANDING DATA SYSTEMS THAT ENABLE ASSESSMENT OF THE IMPACT OF HPV VACCINATION IN HIGH-INCOME COUNTRIES

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Introduction: Recently, several public health agencies have made calls to action for elimination of cervical cancer. To determine how countries progress towards this goal within the context of a complex disease requires robust data that are evaluated on a continuous basis and tracked against established targets. Such an ongoing evaluation will require data infrastructure, appropriate data collection and timely analysis. Limited information is available in peer-reviewed scientific literature regarding the characteristics of successful HPV immunization monitoring systems and their utilization to understand the impact of HPV vaccination programs. The objective of this literature review was to identify national data sources/systems that monitor the impact of HPV prevention programs (screening+vaccination). We also identified characteristics, organization, format, quality/access requirements, data linkages, and strengths/weaknesses of each dataset.
Methods: A two step methodology was applied: 1.) Pilot Review: assessed peer-reviewed and grey literature of high-income countries that may have databases, vaccination registries, HPV surveillance. 2.) Structured Targeted Review: determine characteristics, strengths/weaknesses of data sources; searches utilized PICOTS framework shown in Table 1. Search terms included combinations of keywords related to HPV, HPV-related diseases, and HPV-related outcomes. Grey literature was searched through public health agency websites.

Table 1: PICOTS criteria for study/document inclusion

	Inclusion Criteria
Population(s)	• Populations (women) eligible for cervical disease screening • Population with HPV related diseases • Populations (women and men) eligible for HPV vaccination • 10 low-, middle- and high-income countries
Interventions	Data systems used for monitoring and evaluation: • Cervical cancer screening • HPV vaccination registries • Cancer registries • Sentinel site based genital warts and RRP
Comparisons	Not applicable. The goal of the study is to evaluate the sources of data not the content of those data bases. There will be no product specific information that will be evaluated.
Outcomes	Characteristics of data systems used for monitoring and evaluating national HPV vaccination programs, HPV vaccine coverage, and/or HPV vaccine program impact/effectiveness, including: • Name of data system • Type of data system, e.g. electronic registry, paper-based registry, mixed paper and electronic system • Date data system first implemented/finished • Data system update frequency • Consent for data collection (e.g. opt-in/opt-out) • Type(s) of data collected (e.g. HPV vaccine doses administered, diagnosed cases of high-grade cervical abnormalities) • Information collected in records (e.g. date, procedures performed, ICD-10 code; i.e. what sort of data can be abstracted?) • Duration of record storage (e.g. permanent) • Representativeness of data collected • Linkage to other data sources • Method of data system performance assessment/data quality • Strengths/weaknesses of monitoring system as reported in study/document Context of data system implementation • Country/jurisdiction • World Bank income category of country
Time	• PubMed – no limit • Grey literature – 10 years for government websites (2009-2019)
Study design	Any publications or documents that provide information on relevant data systems will be included (i.e. no exclusions for study design; reports of data systems will also be scrutinized for relevant material). No language restrictions are applied.

Results: The review indicated that high-income countries offered the required infrastructure to capture HPV-related immunization data. However, there was variability in data organization. In Australia, the surveillance system is a series of linked databases. US surveillance utilizes combinations of vaccination and/or outcomes data from claims and EMR sources but has less optimal linkage. Sweden has robust linked registries with screening information. France and Canada have disparate sources of unlinked data with information on patient outcomes.

Conclusions: HPV data systems are important for addressing critical questions about the impact of HPV prevention programs. Understanding key characteristics of these datasets will help enhance existing systems and guide development of emerging systems.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

AFTER THE SUSPENSION OF THE PROACTIVE HPV VACCINE RECOMMENDATION BY THE JAPANESE GOVERNMENT; WHAT HAPPENED AND WHAT IS HAPPENING IN JAPAN?

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Introduction: Contrary to our expectations that the national HPV vaccination program targeting girls aged 12-16 years would reduce the burden of cervical cancer in the near future in Japan, our government suspended proactive recommendation of HPV vaccines in July 2013. This was due to the repeated media reports of adverse events after the vaccination. The restart of governmental recommendations for HPV vaccines is a minimum requirement to normalize the national HPV vaccine program, no official statement about that has been made for 6 years.
Methods: We investigated the related events for 6 years after the suspension of the proactive HPV vaccine recommendation by the Japanese government. They include the published new research data, epidemiological data, changes in the prevalence of HPV vaccination, the actions taken by the academic societies, and the survey about the knowledge and attitudes toward cervical cancer prevention in Japan.
Results: The prevalence of the vaccination decreased to almost near zero, and the risk of future CC prevalence has been fixed in a considerable number of unvaccinated girls. As the effectiveness and the safety of HPV vaccines were revealed, academic societies were announcing the latest information repeatedly to Japanese media. However, they expressed very little interest on the topics in contrast to their attitudes of reporting diverse symptoms such as chronic pain and movement disorder after the vaccination. Very recently, several local governments in Japan have started to notice the target citizens that HPV vaccination is still included in the national vaccine program, and the deadline for the cost-free HPV vaccination is approaching for the girls aged 16 years old.
Conclusions: Various actions for cervical cancer prevention in Japan are progressing little by little. To improve the communication between academic societies and the Japanese media, we hope that the broad notification of the global concept for cervical cancer elimination may work effectively.

ORAL SESSION 5: VACCINATION II. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

THE LONG-TERM IMPACT AND CLINICAL OUTCOMES OF FEWER VERSUS STANDARD DOSES OF HUMAN PAPILLOMAVIRUS VACCINE IN THE UNITED STATES: A DATABASE STUDY - AUTHOR REQUEST

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Introduction: Human papillomavirus (HPV)-related disease remains a significant source of morbidity and mortality, underscoring the need to increase HPV vaccination to reduce disease burden. Regardless of the number of doses needed and the age of vaccine initiation, cervical screening is still recommended. The study objective was to examine the association between number of HPV vaccine doses and risk of histologically confirmed preinvasive cervical disease (CIN II/III) and high-grade cytology (high-grade squamous intraepithelial lesions or ASC-H).
Methods: This retrospective matched cohort study used administrative data from Optum's de-identified Clinformatics® Data Mart (CDM) Database to identify females aged 9–26 years who received ≥1 quadrivalent HPV vaccine dose between January 2006 and June 2015. Cases and controls were matched on region, age, STD history, and pregnancy. All had a Pap test ≥1 year after the date of matched case's final dose. Cox proportional hazards models examined association between number of HPV vaccine doses and incidence of preinvasive cervical disease and high-grade cytology. The Kaplan Meier method estimated cumulative incidence rate at 5-year follow-up.
Results: The study included 133,082 females (66,541 vaccinated and 66,541 unvaccinated) stratified by number of HPV vaccine doses and vaccine initiation age. For females aged 15–19, the hazard ratio (HR) for high-grade cytology for the 3-dose group was 0.84 (95% CI 0.73–0.97, while HRs for histologically confirmed preinvasive cervical disease for 1, 2, and 3 doses were 0.64 (95% CI 0.47–0.88), 0.72 (95% CI 0.54–0.95), and 0.66 (95% CI 0.55–0.80).
Conclusions: Receipt of either 1, 2, or 3 doses of quadrivalen HPV vaccine by females aged 15–19 years was associated with lower incidence of preinvasive cervical disease compared to unvaccinated females, supporting the use of any HPV vaccination in reducing disease burden. Continued efforts are needed to improve HPV vaccine uptake and assess long-term protection against cervical cancer and anogenital warts.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

EVOLVING AND VALIDATING NEW TOOL FOR TRAINING PARAMEDICAL STAFF IN CANCER AWARENESS AND CERVICAL CANCER SCREENING WITH VIA AND COLLECTION OF HPV AND CYTOLOGY SAMPLES

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Introduction: Cervical cancer is the second most common cancer among women in low and low middle income countries (LMICs). The objectives were to develop and validate video based training tool for capacity building of paramedical staff in cancer awareness and screening activities, to reduce the expert time involved in the training and to reduce the duration of training.
Methods: Video based tutorials were prepared in ten modules and three languages by Tata Memorial Hospital, Mumbai, India in co-ordination with IIT, Mumbai. The health services staff were invited for training. The training which was for 12 weeks using standard methods was now planned for two weeks using new technology. Practical demonstration and micro-teaching of cancer awareness, inserting speculums, performing VIA, collection of samples for HPV DNA testing and cytology were combined with video based theory and demonstrations. The tablets pre-loaded with the video based tutorials were retained with trainees during the training period.
Results: The fifty trainees were evaluated with theory and practical evaluation. Majority scored well in theory exams. Out of twenty marks allocated for practical evaluation 49 (98%) scored above 10 marks. All trainees found training to be very informative, easy to understand and felt confident to deliver cancer awareness and perform cervical cancer screening.
Conclusions: The outcome of roll out of the cancer control programme will depend on the quality of training imparted to the health services staff. A real-world issue is relieving staff for longer duration for training and availability of expert time for training. The preparation and validation of these indigenously prepared video based tutorials has opened new avenue by which vast majority of the health services staff can be trained in relatively shorter duration. This tool will be useful in low and LMICs that are now in the process of incorporating cervical cancer screening programs.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

BARRIERS AND FACILITATORS TO CERVICAL CANCER PREVENTION AMONG HOMELESS WOMEN

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Introduction: Homeless women have disproportionately low cervical cancer screening participation and high rates of cancer. Understanding barriers and facilitators to screening provides important insights into future interventions for underserved women.
Methods: As part of a self-sampling study, we conducted interviews with providers (n=11) and patients (n=18) at an urban healthcare for the homeless program. Barriers and facilitators were coded and analyzed using the social-contextual model.
Results: Individual-level factors that made women refuse or deprioritize screening included discomfort with the procedure, competing issues, and lack of cervical cancer knowledge. Discomfort was due to histories of sexual violence, mental illness, embarrassment, transgender patients' gender identities, and procedure physical discomfort. Competing issues included substance use, chronic illnesses, care-taking responsibilities, and social concerns (ie, getting a bed each night). Lack of knowledge about cancer contributed to inaccurate risk perceptions, including not recognizing sexual activity as a risk factor. At the interpersonal level, screening became relatively low priority for providers when patients presented with pressing health concerns. Providers hesitated to offer Paps because of low confidence performing Paps or concerns about threatening the patient-provider relationship. Organizational issues included space constraints at mobile and shelter clinics, insufficient resources for immigrant populations, and accessing records from outside organizations. The social context of housing instability influenced many of the individual, interpersonal, and organizational barriers. Providers' efforts building trust and educating patients were the main facilitators. Becoming familiar with patients before offering a Pap, counseling about the benefits of screening, tailoring communication to address individual barriers, and explaining the procedure beforehand helped. Incentives for screening and designated women's health programming were important organization-level facilitators.
Conclusions: Strong patient-provider trust, communication, and education are essential to address psychosocial barriers to screening such as trauma and low perceived risk. Interventions to increase providers' ability to conduct screening and to reduce patient discomfort may also increase screening.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

META-ANALYSIS ON THE ACCURACY OF METHODS TO TRIAGE HRHPV-POSITIVE WOMEN

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Introduction: Due to the lower cross-sectional specificity of HPV-based cervical cancer screening compared to cytology screening, appropriate triage of hrHPV-positive women is crucial.
Methods: A meta-analysis on the accuracy of triage methods assessed the absolute accuracy to predict occurrence of CIN3+ and CIN2+ and included cytology, HPV genotyping, repeated hrHPV testing, over-expression of p16/Ki67, either as single tests or combination of tests performed at one or two time points. Relative accuracy was assessed using reflex cytology as comparator. We considered a strategy acceptable when the post-test CIN3 risk was >10% or <1% when triage was positive or negative, respectively.
Results: Seventy studies were included assessing 49 triage strategies. The quality of studies was very heterogeneous. One-time cytology triage at ASC-US+ had a sensitivity for CIN3+ of 75% (95% CI 66-83%) and a specificity for ≤ CIN1 of 73% (68-77%). Adding HPV16/18 genotyping when the cytology threshold remained AS-CUS+ increased the sensitivity (ratio=1.30) but decreased the specificity substantially (ratio=0.67). Among the one-time triage methods, cytoimmunostaining for p16/Ki67 and cytology at cut-off LSIL combined with typing for HPV16 were the only methods with a substantially higher sensitivity than ASC-US+ cytology (ratios of 1.23, 1.29) without loss in specificity (ratios 1.01, 1.04). Very few studies reported outcomes for two-time triage. Repeating cytology or retesting for hrHPV 6-12 months after negative reflex cytology yielded sensitivities of 96% and 100% and specificities of 67% and 35%.
Conclusions: Only two-time strategies were associated with a sufficiently low CIN3+ risk. In situations with median pre-triage CIN3+ risk of 9%, acceptable strategies were: reflex cytology with/without genotyping or HPV16/18 genotyping combined with ASCH+ cytology or p16/k-Ki67, followed by a 2nd time triage with cytology or hrHPV testing. Other strategies might be useful but were insufficiently documented. More longitudinal outcomes are needed for triage strategies.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

ESTIMATING THE EFFECTS OF AGE AT STARTING SCREENING AND SCREENING INTERVAL FROM ENGLISH CERVICAL CANCER RATES

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Introduction: In 2004 the age at first screening invitation was raised from 20 to 25 in England. Little effect on cervical cancer prevention was expected because cervical cancer is rare below age 25. This was apparently confirmed, as there was no subsequent increase in incidence at age 20-24 for the birth cohort first screened at age 25. Cervical screening from age 25 or later is now recommended in most countries.
Methods: English cervical cancer rates in 2003-2007 and 2014-2016 were compared for women aged 25-29.
Results: The annual cervical cancer incidence rate per million at age 25-29 in England has almost doubled, from 113 in 2003-2007 (women first screened at 20) to 206 in 2014-2016 (women first screened at 25).
Conclusions: Cytology screening has little effect on cancer prevention within 5 years but a large effect beyond 5 years, and this is also likely to be true for HPV screening. These English cervical cancer rates in birth cohorts invited for screening from age 20 (born 1978) and from age 25 (born 1988) reflect the effects of a 5 or 10 year screening interval from a negative HPV test at age 15, because most women are HPV negative at age 15 but HPV infection is common at age 15-24. There is no evidence that the natural history of progression from HPV infection to cervical cancer or the effects of screening are different in young women, and cervical screening coverage is high (~80%) in England. These data therefore provide the best available evidence on the effects on cancer prevention of extending the screening interval from 5 to 10 years as well as the age at which screening should begin. Predicted lifelong cancer risks with various cytology and HPV screening protocols will be presented.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

LEVELS OF ANXIETY AND DISTRESS FOLLOWING RECEIPT OF POSITIVE SCREENING TESTS IN AUSTRALIA'S HPV-BASED CERVICAL SCREENING PROGRAM: A CROSS-SECTIONAL SURVEY

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Introduction: Women have shown concerns about the extended screening interval (two to five years) and increased starting age (from 18 to 25 years of age) implemented as part of the Renewal of the Australian National Cervical Screening Program (NCSP). However, women tended to overlook the fact that there was also a change in test - from a Pap test to a human papillomavirus (HPV) test, which is the basis for many of the changes made to the program. We examined the psychosocial impact of primary HPV test results in women screened under the renewed NCSP.
Methods: Women in Australia aged 25 – 74 years who received cervical screening since December 2017 were recruited through a market research company and completed an online survey. Primary outcome measures were anxiety and general distress.
Results: 1004 women completed the survey. Most women tested HPV negative (81%), with 6% testing HPV positive; 13% did not know their result. Women testing HPV positive were more anxious (53.03 vs 43.58, $p<0.001$), distressed (3.94 vs 2.52, $p=0.004$), concerned about their test result (5.02 vs 2.37, $p<0.001$), showed greater distress about their test result (7.06 vs 4.74, $p<0.001$) and cancer worry (2.28 vs 1.73, $P<0.001$) than women testing HPV negative. Women testing HPV positive had greater knowledge of HPV (9.25 vs 6.62, $p<0.001$) and HPV testing (2.44 vs 1.30, $p<0.001$) than women testing HPV negative.
Conclusions: Receiving an HPV positive result as part of the revised NCSP significantly raised anxiety, general distress, concern and distress about test results in women. These findings suggest the need to develop ways to mitigate this impact in women receiving HPV positive test results.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

RURAL WOMEN'S PREFERENCES AND KNOWLEDGE FOR INTEGRATED, COMMUNITY-BASED SELF-COLLECTION FOR CERVICAL CANCER SCREENING IN RURAL UGANDA: THE ASPIRE MAYUGE PROJECT

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Introduction: Uganda has one of the highest incidence rates of cervical cancer in the world (47.5/100,000/year), resulting from limited screening access and weak health systems centralized in the capital. Self-collection for cervical cancer screening (SC-CCS) is a strategy to improve screening access. The objective of this study was to understand 1) women's knowledge, preferences and barriers for SC-CCS, 2) barriers and facilitators to engagement in the current screening program and 3) health system challenges to implementation of SC-CCS.
Methods: Focus group discussions (FGDs) were administered from 4 purposively selected villages in a rural district of Mayuge, Uganda. Research assistants conducted FGDs with women's groups in communities in Lusoga. FGDs were simultaneously translated to English by research assistants and audio recorded with permission, verbatim translated and transcribed. Data from FGDs were analyzed using thematic content analysis in Atlas TI.
Results: A total of 20 participants were included from 4 FGDs. Knowledge of causes and risk factors for cervical cancer were limited across participants with many comments of supernatural causes. CCS is not widely accessible despite women's desire to be screened. Facilitators to accessing CCS and treatment include decentralized care, and community engagement and education. Barriers to accessing care included lack of transportation and knowledge, long wait times, and perception of poor quality and continuity of services when treatment is required. Challenges to the implementation of SC-CCS include: lack of human resources trained in CCS, the need for specimen transport networks from communities to laboratories, and lack of infrastructure at clinics.
Conclusions: Self-collected cervical cancer screening within communities could potentially prevent the high mortality related to cervical cancer while working within the human and financial resource limitations of rural health systems. Program design must address women's preferences and break down identified barriers to care to ensure effective use of services.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

RISK STRATIFICATION IN CERVICAL CANCER SCREENING – VALIDATION AND GENERALIZATION OF A DATA-DRIVEN SCREENING HISTORY EVALUATION MODEL

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Introduction: National screening programmes in the Nordic countries have for decades generated large amounts of serial population-based data on cervical screening and disease. Machine learning has made it possible to properly use the full complexity of such data. We previously used machine-learning to construct a dynamic model capable of assessing Swedish women's future risk of invasive cervical cancer (ICC), as a function of their complete screening histories graded based on expert opinion (Baltzer et al, IJC, 2018). We here extend this investigation to the Norwegian female population, and to include a hypothesis-free search of potential predictors, to investigate if this improves model performance.
Methods: We used data from the Norwegian Cancer Registry from a total of 17981 ICC cases and 17981 healthy control women. Using the bioinformatical framework program Rosetta, we derived rules and classifiers of previous screening and treatment history to form a cumulative risk score (CRS) for ICC. We used logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI) as a function of CRS.
Results: We found good overall performance of the model (AUC of 80.7%). 31% of case women exhibited a CRS above 1, whereas 98% of control women had a CRS below 1. This translated into an 19-fold elevated OR for ICC (95% CI 18.4-20.0) for women with a CRS of 1 or higher. Factors modulating this risk level were primarily connected to delayed screening.
Conclusions: Core patterns for ICC risk prediction based on complete screening histories are functional and consistent between nations. The use of a data-driven model, rather than expert-opinion-driven such, is better. The findings may guide the way for deploying risk estimation models on a national level to adapt screening call-recall schedules for women.

ORAL SESSION 6: SCREENING III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

AUSTRALIA'S NEW CERVICAL SCREENING PROGRAM: FINDINGS FROM THE STAKEHOLDERS OPINIONS OF RENEWAL IMPLEMENTATION AND EXPERIENCES STUDY (STORIES)

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Introduction: The Australian National Cervical Screening Program (NCSP) changed from 2-yearly Pap testing to 5-yearly human papillomavirus (HPV) testing on December 1st, 2017 (referred to as the renewed NCSP). The renewed NCSP includes a self-collection pathway for never- and under-screened women and new national register. We aimed to document stakeholders' experiences in implementing the renewed NCSP, its acceptability, and their views about barriers and facilitators to implementation with a view to sharing learnings with other countries considering transitioning to HPV based screening.
Methods: Semi-structured stakeholder interviews were undertaken in 2019. Participants included: national and state and territory program managers, expert committee members, and peak body representatives; cervical screening providers; pathologists; laboratory managers and staff. Interviews were recorded, transcribed and thematic analysis performed.
Results: Forty-nine interviews were completed. While there was overwhelmingly a high opinion of, and support for, the new program, participants identified significant barriers to implementation including 1) dissatisfaction with the new register; 2) failure at the highest levels to appreciate the enormity of the program change or register build; 3) human cost due to stress and increased workload; 4) sub-optimal communication and transparency; 5) insufficient education for providers and the public; and 6) delays in offering self-collection and registry correspondence may put people at clinical risk. Facilitators identified by participants included: 1) the strong evidence base for change; 2) vocal champions of the change; and 3) a high level of goodwill from, and dedication by, key stakeholders.
Conclusions: Despite high stakeholder support for the changes, many expressed concerns about problems that occurred during implementation. Key recommendations for other countries considering transition to HPV based screening programs include the need for detailed cross sector engagement and comprehensive planning; early attention to communication, education, and regulatory issues; and transparency with all stakeholders if timelines for implementation are not on track.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

EFFECTIVENESS AND COST-EFFECTIVENESS OF POINT-OF-CARE HPV-DNA TESTING AND SAME-DAY TREATMENT IN THE HIGH-BURDEN, LOW-RESOURCE SETTING OF PAPUA NEW GUINEA

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Introduction: Papua New Guinea (PNG) has a very high estimated burden of cervical cancer. A field trial is underway to evaluate point-of-care (POC) HPV screening (using the Cepheid GeneXpert platform) and same-day treatment (visualisation of the cervix using acetic acid to guide treatment by thermal ablation; VAT) for cervical screening (ISRCTN13476702). This analysis aims to evaluate the effectiveness and cost-effectiveness of optimal strategies for screening in PNG.
Methods: A dynamic model of cervical screening ('*Policy1-Cervix*') was calibrated to cervical cancer incidence and mortality reported for PNG and used to evaluate POC-HPV-VAT and primary screening by visual inspection after acetic acid (VIA). A total of 44 scenarios were assessed, considering various screening ages and frequencies. As the test characteristics of VIA vary considerably, we assumed VIA screening provided only down-staging effects for incident cancer, but in best case analysis also considered a potential impact on cancer prevention.
Results: Compared to no intervention (ASR incidence: 29.2/100,000), the age-standardized cervical cancer incidence rates were reduced by 20%-32%, 22%-40%, and 23%-43% in once, twice, and thrice-lifetime POC-HPV-VAT screening strategies, respectively (ranges depend on different screening ages). For VIA, the impact was lower and uncertain; if only downstaging is assumed no impact on incidence but a 1% mortality reduction for thrice-lifetime screening is predicted, whereas with favourable performance assumptions, incidence rates could potentially be reduced by up to 9%-24%. Only POC-HPV-VAT was cost-effective with VIA dominated by POC-HPV-VAT strategies; up to thrice lifetime POC-HPV-VAT was still cost-effective (ICER: AUD2039/LYS vs GDPpc AUD 6287). This strategy required a number needed to screen (NNS) of 115 to prevent one cancer case, and a NNS of 164 for an averted cancer death.
Conclusions: POC-HPV-VAT was found to be very effective and cost-effective in the high-burden, low-resource setting of PNG and could be considered for other LMIC settings.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

EVALUATING THE IMPLEMENTATION OF AN HPV VACCINE SCHOOL ENTRY REQUIREMENT POLICY USING PROVIDER-VERIFIED DATA

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Introduction: Most HPV vaccination strategies in the U.S. focus on provider or clinical interventions, but policy approaches that promote expanded implementation may be effective at increasing HPV vaccination among adolescents. In 2015, Rhode Island implemented a gender-neutral one-dose HPV vaccine school-entry requirement for 7th graders. The objective of this study was to evaluate changes in provider-verified HPV vaccine uptake by age 13 for adolescents in Rhode Island compared to all other states, after school-entry policy implementation.
Methods: This study used the National Immunization Survey-Teen 2011-2017, a national telephone interview and provider-verified report of adolescent vaccination (ages 13-17). The years prior to 2015 were considered pre-implementation years, and 2015-2017 were policy-implementation years. A difference-in-differences approach, using linear probability models, compared changes in provider-verified HPV vaccination status among adolescents in Rhode Island with changes in a control group of all other states, before and after Rhode Island's implementation of the school-entry policy.
Results: Statistically significant differences by gender were observed for whether an adolescent had initiated HPV vaccination by age 13 ($F=6.38$, $p=0.01$). Compared to boys in other states, boys in Rhode Island had an increase in the probability of uptake of HPV vaccination by age 13 of nearly 14% ($b=0.139$, 95% CI[0.073, 0.205]). No such differences were observed comparing adolescent girls in RI to adolescent girls in other states ($b=0.009$, 95% CI[-0.068, 0.086]).
Conclusions: The Rhode Island school-entry requirement for HPV vaccination improved rates of HPV vaccine uptake among boys, and may be a useful option for improving HPV vaccination in other states. The lack of difference in girls may have been due to a ceiling effect, in that rates for girls in RI were already quite high. Continued evaluation of this HPV vaccine policy implementation is needed, including assessment of the impact on age of vaccination.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

THE IMPACT OF A UNIVERSAL HPV VACCINATION PROGRAM ON LOWER GENITAL TRACT DYSPLASIA AND GENITAL WARTS

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Introduction: Assess the impact of Ontario's school-based human papillomavirus (HPV) vaccination program targeting grade 8 girls on reducing rates of cervical dysplasia, utilization of colposcopy and treatment for genital warts, cervical conization, cryotherapy and laser vaporization of lower genital tract pre-invasive dysplasia.
Methods: Women born in 1995 in Ontario, Canada were the first cohort of 8th grade females to receive the quadrivalent vaccine. Uptake rates were 60%. We followed these women from age 18-23 (5-years) and identified low and high-grade pap test cytology results, attendance at colposcopy, treatment of HPV related warts and treatment of lower-genital tract dysplasia using Ontario healthcare administrative databases. We compared the incidence of these outcomes to women born in 1985, followed during the same age period of 18-23, prior to access to the HPV vaccine (considered as the unvaccinated comparison group). We calculated relative risk ratios over the 5-year period for the unvaccinated group compared to the vaccinated group. Results were stratified for income and geographic level.
Results: 100,020 women were included in the vaccinated cohort compared to 121,019 unvaccinated females. Among vaccinated women, 5.2% percent had cytologic abnormalities and 2.7% required treatment for pre-invasive disease or warts compared to 9.2% and 5.2%, respectively among unvaccinated women over a 5 year period. The relative risk of developing a low-grade cytologic abnormality if unvaccinated was 1.69 and 3.74 for high-grade abnormalities. The relative risk of requiring colposcopy if unvaccinated was 1.94 and they were 6.15 times more likely to require treatment compared to the vaccinated cohort. There were no significant differences between socio-economic groups and geographic regions.
Conclusions: Organized vaccination programs for adolescent females are effective at decreasing rates of cervical dysplasia, especially high-grade lesions and lead to reduced need for colposcopy, treatment of HPV related warts and pre-invasive disease even at early ages. With the introduction of the nonavalent formulation we anticipate even greater benefit.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

STRONG REDUCTION IN PREVALENCE OF HPV 16/18 AND CLOSELY RELATED HPV TYPES IN SEXUALLY ACTIVE ADOLESCENT WOMEN FOLLOWING THE INTRODUCTION OF HPV VACCINATION IN ARGENTINA.

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Introduction: In Argentina, the bivalent HPV vaccine was introduced in the National Vaccination Program in 2011, with a 0-1-6-month schedule, for girls ≥11 years of age.This work compares HPV DNA type-specific prevalence in sexually active unvaccinated (UV) and vaccinated adolescent (VA) girls, recruited in six public hospitals from Argentina, to provide information on the early impact of HPV vaccination.
Methods: Two cross sectional studies were conducted; the first one (2014-2015), enrolled 1,073 UV (aged 14-17), and the second one (2017-2018), 1,306 VA (aged 14-18) who had received at least one dose of the HPV vaccine. Cervical samples were taken with cytobrush and STM. DNA was extracted and purified using QIAcube system. HPV detection and typing was completed through BSGp5+/6+bio PCR - reverse line blot hybridization, which allows to identify 13 HR and 24 LR-HPVs.
Results: The general HPV prevalence decreased significantly from 56.32% (UV) to 49.75% (VA). A notorius decline of the following HPV types was found in VA: HPV16 (11.08% to 0.82%; OR 15.12), HPV 18 (5.96% to 0.41%; OR 15.44), HPV 31 (7.11% to 1.63%; OR 4.6); HPV 45 (4.60% to 0.49%; OR 9.78), HPV6 (6.69% to 3.51%; OR 1.97); HPV 33 (3.13% to 1.72%; OR 1.85); and HPV53 (6.17% to 3.84%; OR 1.64). All frequency reductions observed in VA were statistically significant ($p \leq 0.05$). A vaccine effectiveness of 93.4% (87.3%-96.6%) was estimated for protection against HPV16; 93.5% (89.7%-95.9%) against HPV18; 93.1% (88.0% -95.9%) against HPV16/18, and 84.9% (82.4%-87.0%) for HPVs 16/18/31/33/45. No genotype replacement was observed.
Conclusions: A high effectiveness of vaccination was demonstrated; likewise, the fall of non-vaccine HR-HPV genotypes (HPV31, 33 and 45) would indicate cross protection. These are the first biological monitoring data of HPV vaccination reported in a Latin American country, being of great value to sustain and optimize immunization.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

HIGH VACCINE EFFECTIVENESS AGAINST PERSISTENT INFECTIONS UP TO EIGHT YEARS POST THREE DOSES OF BIVALENT HPV VACCINATION IN THE NETHERLANDS

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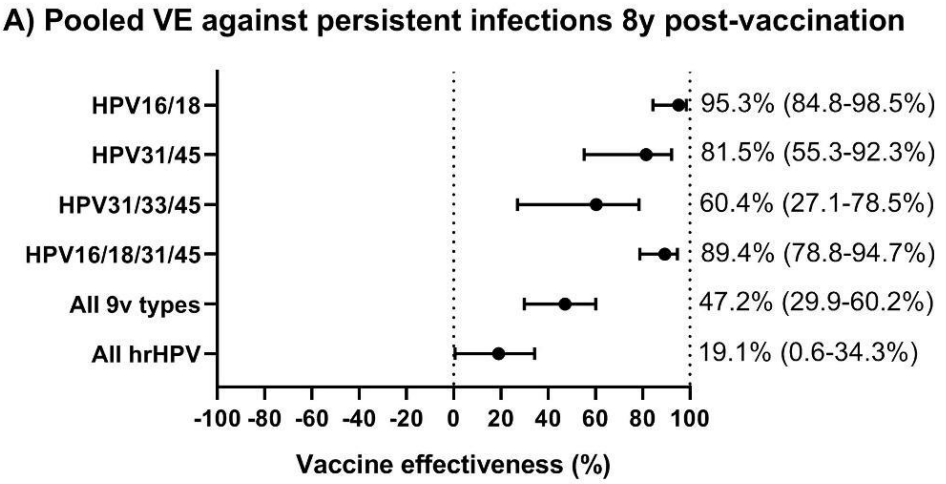
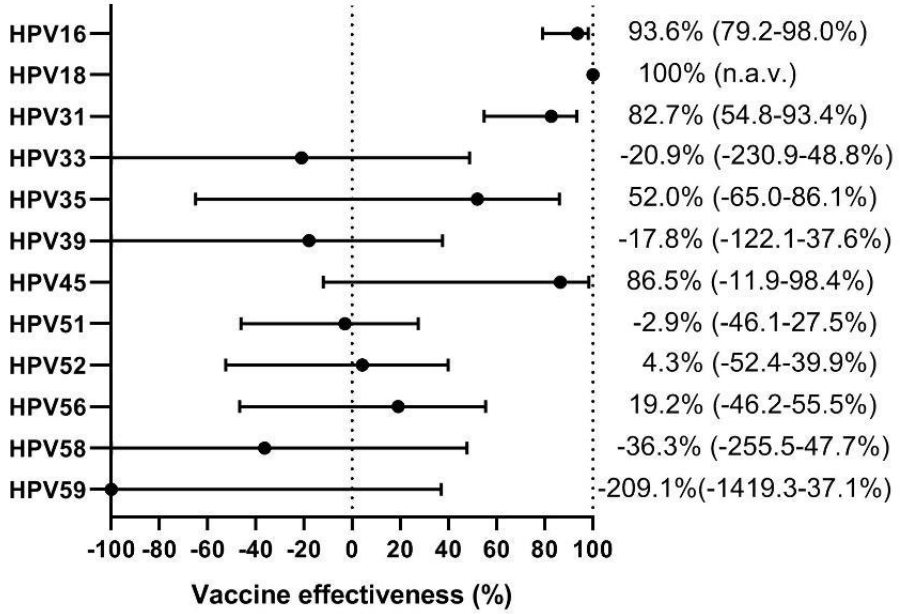
Introduction: In the Netherlands, the 2v-HPV vaccine was introduced into the NIP as a girls only vaccine in a three-dose schedule. In 2009, a catch-up campaign was initiated for birth cohorts 1993-1996 and along with this, a prospective cohort study (HAVANA) was established to monitor the HPV vaccine impact in a population setting. Here, we estimate the vaccine effectiveness (VE) against incident and 12-month persistent cervical-vaginal infections up to eight years post-vaccination.
Methods: Approximately 1800 girls who were eligible for the catch up campaign were included in the study. A baseline measurement was performed one month prior to vaccination, and thereafter a questionnaire and a vaginal self-swab were collected annually. Using the HPV-DEIA-LiPA25 platform, twenty-five HPV genotypes could be detected from the self-swabs. Using survival analysis with the Prentice Williams-Peterson total-time approach, type-specific and pooled hazard ratios were obtained. VE estimates against incident and 12-month persistent infections were calculated as (1-hazard ratio)*100%. The estimates were adjusted for age, urbanization degree, ever smoked, ever used contraception, and ever had sex (variable over time).
Results: In total, 1635 participants with baseline measurement available could be included in the analysis (53.5% fully, timely vaccinated). High VE against HPV16/18 infections was observed: 77.7% (95% C.I.: 67.0-85.0%) and 95.3% (84.8-98.5%) for incident and 12-month persistent infections, respectively (Figure 1A). In addition, statistically significant cross-protection was found against incident and persistent infections with HPV31/33/45: 56.4% (39.2-68.7%) and 60.4% (27.1-78.5%), respectively. Type-specific VE estimates (both incident and persistent infections) were statistically significant for HPV16, HPV18, and HPV31 (Figure 1B).



B) Type-specific VE against persistent infections 8y post-vaccination



Conclusions: From these results, it can be concluded that vaccine effectiveness against incident and 12-month persistent infection in a population based setting remains high up to eight years post three doses of 2v-HPV vaccination in the Netherlands. VE estimates were high against vaccine-type infections and considerable cross-protection was observed.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

DEVELOPMENT AND EVALUATION OF AN ONLINE CONTINUING EDUCATION MODULE TO INCREASE HEALTHCARE PROVIDER SELF-EFFICACY TO MAKE STRONG HPV VACCINE RECOMMENDATIONS TO EAST AFRICAN IMMIGRANT FAMILIES

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Introduction: United States (U.S.) data suggest that HPV vaccine uptake is lower among children of East African immigrants than among children whose parents are U.S.-born. Healthcare provider recommendations are associated with increased HPV vaccine uptake, but providers often lack resources to make strong, culturally-appropriate recommendations. We developed and evaluated an online continuing medical education (CME) module designed to improve provider self-efficacy to make strong HPV vaccine recommendations to East African families.
Methods: We used focus groups with providers (n = 11) and East African mothers (n =30) to identify themes and inform development of the CME. Providers serving East African families in Washington State were recruited to view the module and complete pre-/post-test surveys as well as a two-month follow-up survey. The surveys measured confidence to make strong HPV vaccine recommendations to East African families and address common parental concerns with 5-point Likert scales. We used paired t-tests to evaluate pre/post differences in responses.
Results: 202 providers completed the module and pre/post-test; 158 (78.2%) completed the two-month follow-up. Confidence to make strong HPV vaccine recommendations to East African families increased from 68.4% pre-test to 97.5% post-test. Providers' confidence to address common parental HPV vaccine concerns also increased: safety: 54.0% pre-test, 92.1% post-test; fertility: 54.7% pre-test, 89.5% post-test; child too young: 67.2% pre-test, 91.5% post-test; and pork gelatin in vaccine manufacturing: pre-test: 37.3% pre-test, 89.5% post-test. Two-month follow-up scores remained high (96.9% for overall confidence, and 93.6%-97.5% for addressing parental concerns). All pre-test/post-test and pre-test/two-month follow-up comparisons were statistically significant ($p<.001$).
Conclusions: We found that a culturally-tailored CME focused on strategies for making strong recommendations and addressing specific parental concerns was effective for increasing provider self-efficacy to recommend HPV vaccination to East African families. Similar modules could be tailored to other priority populations with suboptimal HPV vaccine uptake.

ORAL SESSION 7: VACCINATION III. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

HPV VACCINATION RATES IN A RANDOMIZED TRIAL EVALUATING A SOCIAL MEDIA CAMPAIGN WITH MOTHERS OF DAUGHTERS AGED 14-17 IN THE USA

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Introduction: Parent decisions on HPV vaccine uptake in the USA are influenced by information and misinformation about the vaccine in social media. Mothers' reports on vaccination of their adolescent daughters were examined in an evaluation of a social media adolescent health campaign.
Methods: Mothers from 34 US states (n=881) were recruited to a randomized controlled trial evaluating a social media adolescent health campaign (n=730 posts over 12 months). Eligibility criteria were: having a daughter aged 14-17, in state without a complete ban on indoor tanning by minors, using a Facebook account 1+ times a week, completing the baseline survey, and joining the Facebook group. The campaign included didactic and narrative posts some of which promoted HPV vaccination, e.g., need for vaccine, percent of adolescents vaccinated, and how HPV vaccines are decreasing infection rates. It was delivered through two Facebook private groups differing on inclusion of indoor tanning or prescription drug mis-use posts (experimental manipulation).
Results: Mothers had a mean age of 43.1 years (sd=6.6) and were 86.6% white. At baseline, 63.1% reported that their daughter had been vaccinated for HPV (49.2% received 2 or 3 doses). At the 12-month posttest, 70.9% of mothers reported that daughters had been vaccinated for HPV ($F=4.57$, $p=0.033$) and 61.0% that daughters had received 2 or 3 vaccine doses (i.e., possibly completed series; $F=9.96$, $p=0.001$). Uptake increased among older ($r=0.08$, $p=0.004$) and more educated ($r=0.06$, $p=0.021$) mothers and those with a family history of skin cancer ($r=0.09$, $p=0.001$). Mothers' reports of HPV vaccine uptake were corroborated by daughters (82.6%-87.8% correspondence, $r=0.66 – 0.76$, $p<0.001$).
Conclusions: HPV vaccine uptake increased during the 12-month social media campaign. The increase appeared to be largest in completion of the multi-dose series. Effective strategies are needed in social media to promote HPV vaccines and counter misinformation about and resistance to them.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

INTRODUCING MOBILE COLPOSCOPY TO A PUBLIC CERVICAL CANCER PREVENTION PROGRAM IN EL SALVADOR

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Introduction: Cervical Cancer Prevention in El Salvador (CAPE) is a national screen-and-treat program based on human papillomavirus (HPV) testing. Screen-positive women undergo visual assessment for treatment (VAT) triage to determine eligibility for immediate cryotherapy treatment, while ineligible women are referred to a regional hospital for colposcopy. Due to the limited number of trained colposcopists, VAT and cryotherapy are carried out by general practitioners at community clinics. To improve VAT accuracy, handheld colposcopy devices that utilize a mobile phone platform (EVA System, MobileODT, Tel Aviv, Israel) were distributed to selected clinics. The devices capture digital cervical images and upload them to a cloud-based dataset, allowing real-time remote consultations. We evaluated the feasibility of this technology for use in low and middle-income countries (LMICs).
Methods: Colposcopy devices were introduced to 30 clinics in the Oriental and Occidental regions of El Salvador. General practitioners (n=34) were trained in the use of the devices between September and November 2018. An experienced gynecologist with access to the cloud-based dataset was the designated image reviewer.
Results: Between November 2018 and August 2019, 1,351 screen-positive women underwent VAT. Providers attempted real-time remote consultation in 28% of cases (382/1,351). Real-time consultation was successful in 95% of cases (362/382), but was not possible in 5% of cases (20/282) due to lack of a stable internet connection. These images were reviewed by the gynecologist at a later time. Of all VAT cases, 236/1,351 (17%) women were referred to colposcopy.
Conclusions: The lack of trained colposcopists is a limitation in the implementation of cervical cancer prevention programs that rely on visual diagnosis or triage. Mobile colposcopy offers a method for improving program outcomes with relatively simple technology that permits remote review of cervical images by trained colposcopist.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

CESTAP: THE PILOT OF THE CERVICAL CANCER SCREEN AND TREAT ALGORITHMS STUDY USING HPV TESTING IN AFRICA

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Introduction: Cervical cancer (CC) was responsible for an estimated 311,000 female deaths in 2018, mostly from low-and-middle-income countries, although it is highly preventable using effective screening and treatment of pre-cancerous lesions. The World Health Organization recommends screening with HPV-testing with or without a Visual Inspection with Acetic acid (VIA) triage test, followed by ablative treatment. In collaboration with the University of KwaZulu-Natal, South Africa a study of CC screen-and-treat algorithms was piloted, aimed primarily to field test tools for a study examining the sensitivity of VIA to detect high-grade lesions and the comparative benefits and side-effects of HPV-testing +/- VIA triage and cryotherapy vs. a novel thermal ablation method in the context of hyper-endemic HIV.
Methods: The pilot investigation was conducted at Wentworth hospital in Durban from January to July 2018. 350 Women, 30-54 years old, were randomized in 2 arms: HPV testing+VIA+treatment or HPV testing+treatment. All HPV positive women in arm1 underwent biopsy disease verification. The GeneXpert (Cepheid) test was used
Results: The mean age was 42 (standard deviation: 7.5) with a HIV prevalence of 21%. HPV prevalence was 21% and 52%, respectively in HIV-negative and HIV-positive women. Six cervical intraepithelial neoplasia grade 2 or 3 (CIN2/3) and one invasive CC were detected. VIA detected 3 CIN2/3. Community outreach was challenging, but the screen-and-treat services were highly appreciated by the women (median satisfaction score: 8/10). Qualitative interviews determined that study procedures were also highly accepted by the study team. A stakeholders meeting extended to the local government, hospital CEOs, community caregivers and NGO's revealed strong community and local healthcare system support for phasing up this screen-and-treat approach.
Conclusions: The piloted methods and tools are feasible and acceptable for implementation in a larger research study within a resource-constrained healthcare system facing one of the largest HIV epidemic worldwide.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

PERFORMANCE OF THE CAREHPV ASSAY IN GUATEMALA AND HONDURAS

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Introduction: *care*HPV is a low-cost HPV-DNA test developed for use in cervical cancer screening programs in low-resource settings (Qiao et al. 2008). The assay is run on a specialized test system, and each test kit provides enough reagents to run 90 samples. Under the PATH Scale-Up project, the test was introduced in selected areas in Guatemala and Honduras with the objective of maximizing its application in routine use. We describe the performance of the *care*HPV test in a well-established public health screening program after 3 years of routine testing with *care*HPV.
Methods: Since 2015, Guatemala and Honduras have been using, on a routine basis, the *care*HPV test for cervical cancer screening. Tests were run in eight labs. Trained, validated lab technicians carried out the assay following manufacturer guidelines. Since 2018, results of microplate run performance were systematically recorded.
Results: Each country processed 212 test kits (10,080 tests) from December 2018 to August 2019. Out of 424 total microplate runs with a unique test kit, 21 runs (9.38%) did not produce results. Among the microplate runs that did not produce results, 42% were attributed to unknown causes, 19% to instrumentation issues, 19% to electricity failures, and 19% to various other causes. Country, laboratory, and technician, did not significantly influence the microplate runs with invalid results.
Conclusions: *care*HPV has been implemented at a large scale in multiple laboratories. However, the waste due to unsuccessful microplate runs in a routine setting remains of concern, five years after the introduction of this technology. Robust quality assurance programs and reliable technical support are required to prevent microplate failures and to resolve instrumentation issues in real time. Without these measures, countries implementing the *care*HPV assay can expect to observe continued high proportions of microplate run failures.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

OROPHARYNGEAL CANCER AND HUMAN PAPILLOMA VIRUS: TIME TO COUNSEL MEDICAL TEAMS

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Introduction: The incidence of HPV-associated oropharyngeal cancer exceeded that of HPV-associated cervical cancer in the last decade. Health professionals might feel uncomfortable discussing topics related to sexual habits and it is a problem for patient care. Objectives of this study are to assess the level of knowledge about HPV infection and cancer amongst medical team and to evaluate an educational intervention directed at health care professionals to improve potential for therapeutic discussions.
Methods: Basic levels of knowledge of oropharyngeal HPV cancer and ease to deal with patient were evaluated for general practitioners (GP), head and neck surgeons (HNS) and nurses. Each category of professional was divided into two groups, a group of participants who received the HPV training and a control group who did not receive the HPV training. The selected format was a one-hour lecture-like presentation addressing the management of oropharyngeal HPV cancer. The participants filled questionnaires about general demographic information, ease to deal with HPV patients, general knowledge of oropharyngeal HPV and an evaluation of the educational intervention itself.
Results: The final sample of 122 participants consisted of medical staff from hospitals of the Quebec province (Canada). All groups presented a significant increase of their knowledge following the training session (GP, score: 8.57 ± 0.23, at $p<0.001$; HNS, score: 8.3 ± 0.3, $p<0.05$; nurses, score: 7.6 ± 0.25, respectively different from their related control group at $p<0.001$). Post-training nurses outperformed untrained GPs ($p<0.01$). The score improvement in knowledge from the educational intervention was less marked for nurses as working experience increased. For all professional categories, the HPV training resulted in a significant increase of their perceived ease to discuss head and neck HPV infections with patients ($p<0.05$ for GPs; $p<0.05$ for HNSs; and $p<0.05$ for nurses).
Conclusions: Educational intervention with medical professional improve oropharyngeal HPV knowledge and ease of discussion.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

INCIDENCE RATES FOR OROPHARYNGEAL AND ORAL CAVITY CANCERS AMONG HIV-POSITIVE AND HIV-NEGATIVE INDIVIDUALS IN BRITISH COLUMBIA, CANADA: A RETROSPECTIVE COHORT STUDY

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Introduction: The incidence of HPV-associated oropharyngeal cancer is increasing in Canada. Despite this, little is known about the epidemiology of these cancers as it relates to HIV status, sex, and sexual behaviour.
Methods: In this retrospective cohort (1990-2015), we created a subset of ~1.2 million individuals from the Integrated Data and Evaluative Analytics (IDEAs) cohort who had tested for/been diagnosed with HIV in British Columbia (BC). HPV-associated squamous cell carcinoma of the oropharynx (tongue – base, soft palate, tonsils, mid-pharynx) and oral cavity (tongue – front 2/3, hard palate, gums, mouth floor) were assigned using ICD-O-3 codes. Follow-up began at first negative HIV test or HIV detection and ended at first oropharyngeal cancer diagnosis, HIV diagnosis (HIV-negative stratum), death, or 31/12/2015, whichever occurred first. Individuals aged >15 years with minimum 6-month follow-up time were included. Crude incidence rates per 100,000 person-years were calculated, stratified by HIV status, sex, and, among males, whether they were men who have sex with men (MSM). Incidence rate ratios, adjusted for age of cohort entry [aRR], were assessed using Poisson regression.
Results: From 1990-2015, there were 361 and 267 incident cases of oropharyngeal and oral cavity cancers, respectively. Crude oropharyngeal cancer incidence rates were highest among HIV-positive non-MSM (21.46, 95% confidence interval [95%CI]: 11.17-41.25), and lowest among HIV-negative females (0.99, 95%CI: 0.77-1.27). Crude oral cavity cancer incidence rates were highest among HIV-positive MSM (12.50, 95%CI: 6.25-25.01). HIV-positive MSM had higher rates for both oropharyngeal (aRR=2.50 (95%CI: 1.14-5.49) and oral cavity cancers (aRR=3.62, 95%CI: 1.60-8.23), compared to HIV-negative MSM. Incidence rates among HIV-positive (vs. HIV-negative) non-MSM were higher for oropharyngeal cancers only (aRR=2.93, 95%CI: 1.51-5.70).
Conclusions: Considering the paucity of evidence for oral cancer screening programs, these results highlight the importance of further research into novel methods by which to screen for these cancers, particularly among men living with HIV.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

LOW AWARENESS AND PERCEIVED RISK FOR HPV AND ASSOCIATED ANAL CANCER AMONG MEN LIVING WITH HIV RECEIVING HIV SPECIALTY CARE IN ONTARIO, CANADA

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Introduction: Our objective was to examine factors associated with human papillomavirus (HPV) awareness and perceived risk among men living with HIV, which may influence uptake of prevention strategies such as HPV vaccination and anal cancer screening.
Methods: A questionnaire assessing knowledge, attitudes, and experience with HPV-associated diseases and their prevention was administered in 2016-17 to 1702 men in the Ontario HIV Treatment Network Cohort Study, a multi-site clinical HIV cohort in Ontario, Canada. We used logistic regression to identify factors associated with men's awareness of HPV and proportional odds models to identify factors associated with increasing perceived risk for HPV-associated anal cancer.
Results: Median age was 52 years old and 80% of men identified as gay, bisexual and other men who have sex with men (gbMSM). Only 52% of men were familiar with HPV; younger men and gbMSM were more familiar with HPV (Table 1). Even among those familiar with HPV, knowledge gaps remained: 22% did not know HPV caused anogenital warts and anal cancer; 53% did not know smoking increases HPV-associated cancer risk; and 18% did not know that HIV increases risk for such cancers. Moreover, 22% of men felt they had no risk of acquiring anal cancer, 50% indicated low risk, 19% moderate risk, 5% high risk, and 4% were certain they would get anal cancer. In multivariable proportional odds models (Table 1), familiarity with HPV was positively associated with increasing perceived risk for anal cancer.

Table 1. Multivariable regression models examining factors associated with familiarity with HPV and increasing perceived risk for anal cancer.

	Multivariable Logistic Model for HPV Awareness aOR (95% CI)	Multivariable Proportional Odds Model for Perceived Risk for Anal Cancer aOR (95% CI)
Age (per 10 years)	0.75 (0.68, 0.83)	0.76 (0.70, 0.84)
Sexual Orientation (Ref: Heterosexual)		
Gay	3.28 (2.40, 4.49)	3.01 (2.24, 4.05)
Bisexual	2.16 (1.39, 3.35)	1.75 (1.15, 2.66)
Race (Ref: White)		
Indigenous	1.06 (0.68, 1.65)	0.83 (0.55, 1.26)
African, Caribbean, Black	0.37 (0.25, 0.55)	0.44 (0.30, 0.64)
South Asian	0.56 (0.36, 0.89)	0.61 (0.39, 0.84)
Multiple races	1.15 (0.55, 2.38)	1.66 (0.89, 3.14)
Other races	0.45 (0.29, 0.71)	0.64 (0.42, 1.00)
Education (Ref: less than high school)		
Completed high school	1.39 (0.89, 2.17)	0.64 (0.42, 0.97)
Some post-secondary	2.58 (1.66, 4.02)	1.09 (0.72, 1.65)
Completed post-secondary	2.97 (1.98, 4.44)	0.82 (0.56, 1.20)
Income (per $20,000)	1.17 (1.08, 1.26)	1.06 (0.99, 1.14)
Familiar with HPV	–	3.15 (2.50, 3.96)

aOR, adjusted odds ratio. CI, confidence interval.

Conclusions: Among men in HIV care, we observed low awareness of HPV, which was also associated with an inappropriately low perception of risk for HPV-associated anal cancer. This may result in a lesser uptake of HPV prevention strategies such as anal cancer screening. Increasing HPV literacy is important for men living with HIV.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

EVALUATING THE REACH AND EFFECTIVENESS OF A COMMUNITY-BASED HPV-SCREENING STRATEGY

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Introduction: Population coverage for cervical cancer prevention programs in rural and low-resource settings can be challenging, and programs need innovative solutions to screen hard-to-reach women. We employed a two-pronged community based testing approach to determine its coverage for women living in rural western Kenya.
Methods: To determine the population eligible for this screening approach, we carried out door-to-door enumeration in six communities in Migori, Kenya. Following this, community health volunteers carried out community mobilization and offered self-collected human papillomavirus testing through sequential community health campaigns (CHCs), or high-volume health fairs held in tents in central locations. After completion of the CHCs, we conducted home based testing (HBT) to reach women who did not attend campaigns. Women who screened HPV-positive were offered treatment in their nearest sub-county health facility. We examined population reach and factors related to uptake of this screening strategy.
Results: Between February and November 2018, 4,295 women were identified as eligible for screening, of which 2,297 (53.5%) screened during one of the six CHCs and 1,002 (23.3% of overall population, 50.2% of remaining unscreened population) screened via HBT, for a total population reach of 76.8%. Women screened through HBT were younger (36.8 vs 38.7 years, $p<0.001$), had lower education levels ($p<0.003$) and were more likely to be married and living with their partner compared to women screened at CHCs ($p<0.001$). There was no difference in HPV-positivity between the CHC and HBT groups (16.7% and 16.6%, $p=0.891$). Women who screened with HBT were significantly less likely to get follow-up treatment within four months (54.0% versus 27.1%, $p<0.001$).
Conclusions: A cervical cancer screening strategy employing CHCs followed by door-to-door screening resulted in a large uptake of screening in this rural community. Screening hard-to-reach women through a door-to-door campaign must be coupled with effective strategies to link women with the appropriate follow-up or treatment.

ORAL SESSION 8: SCREENING IV. IMPLEMENTATION, DISSEMINATION, AND COMMUNICATION

PRELIMINARY RESULTS OF AN ARTIFICIAL INTELLIGENCE CLASSIFIER TO DIAGNOSE CERVICAL PRECANCER

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Introduction: MobileODT has developed an artificial intelligence algorithm designed to detect high-grade cervical precancer using digital images, based on the National Cancer Institute's Automated Visual Evaluation (AVE) classifier. This algorithm was tested on data collected from 200 cases containing both images and associated histopathology.
Methods: The algorithm used here was trained on 1342 biopsy-correlated cervical images from 537 patients. For each patient, an aggregated score between 0 and 1 was determined by assigning weights to images based on their quality. We applied the trained version of AVE to a separate set of cervical images from subjects enrolled in a clinical trial in El Salvador, China and Colombia. All images were from patients with biopsy-confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+). AVE accuracy was calculated as the proportion of predictions that matched biopsy results.
Results: The algorithm's ability to identify CIN2+ varied according to threshold level. In order to map a logistic regression value to a binary category, three classification threshold (or decision threshold) were defined. For a threshold of 0.02 accuracy was 99%, for 0.13 accuracy was 95%, and for 0.5 accuracy was 81%.
Conclusions: The machine learning diagnostic accuracy in this data set was very high using the lowest classification threshold, but declined with higher thresholds. One limitation is that the data set only has positive cases, thus it is not possible to calculate sensitivity or specificity. Nevertheless, AI has great potential as a new detection method for cervical precancer.

ORAL SESSION 9: VACCINATION IV. STRATEGIES AND SCHEDULES

EFFICACY AND IMMUNOGENICITY OF A SINGLE HPV VACCINE DOSE COMPARED TO NO VACCINATION OR STANDARD TWO/THREE-DOSE REGIMENS: A SYSTEMATIC REVIEW OF EVIDENCE FROM CLINICAL TRIALS

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Introduction: Epidemiological evidence suggests that a single HPV vaccine dose may be effective against HPV infection. We systematically reviewed the literature on the efficacy and immunogenicity of single-dose HPV vaccination compared to no vaccination or multi-dose schedules among participants from HPV vaccine trials.
Methods: Medline, EMBASE, Global Health Database and Cochrane Central Register of Controlled Trials were searched for relevant articles and conference abstracts published between Jan-1999 and Aug-2018 using MeSH and non-MeSH terms for HPV AND vaccines AND (immunogenicity OR efficacy/effectiveness) AND dosage. Search results were screened against pre-specified eligibility criteria. Data were extracted from included articles, and a narrative synthesis conducted on efficacy against HPV16/18 infection and humoral immunogenicity.
Results: Of 6,523 unique records identified, seven met the inclusion criteria. Six were nested observational studies of participants randomised to receive two or three HPV vaccine doses in three large HPV vaccine trials in which some participants did not complete their allocated schedules. One small pilot study prospectively allocated participants to receive one or no HPV vaccine dose. HPV16/18 seropositivity rates were high in all HPV vaccine recipients, but antibody levels were significantly lower with one compared to two or three doses. Frequency of HPV16/18 infection was low (e.g. <1% for 12-month persistent infection) in all vaccinated participants up to seven years post-vaccination and did not differ by number of doses received ($p>0.05$ in all cases). Frequency of infection was significantly lower in one-dose recipients compared to unvaccinated controls ($p<0.01$ for all infection endpoints).
Conclusions: One HPV vaccine dose may be as effective in preventing HPV infection as multi-dose schedules in healthy young women up to seven years post-vaccination. However, there is a paucity of evidence from prospective randomised trials. Results from ongoing trials assessing the efficacy and immunogenicity of single-dose HPV vaccination versus currently-recommended schedules are awaited.

ORAL SESSION 9: VACCINATION IV. STRATEGIES AND SCHEDULES

HPV VACCINATION COVERAGE IN THREE DISTRICTS IN ZIMBABWE FOLLOWING NATIONAL INTRODUCTION OF 0,12 MONTH SCHEDULE AMONG 10-14 YEAR OLD GIRLS

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Introduction: Zimbabwe has one of the highest age-standardized incidence rates of cervical cancer in the world – 62.3 per 100,000 women. The government of Zimbabwe introduced bivalent HPV vaccine with a 0,12 month schedule to all 10-14 year old girls using a pulsed-campaign approach in May 2018 (dose 1) and May 2019 (dose 2).
Methods: We conducted a population-based, two-stage cluster survey of households with girls who were eligible for the national HPV vaccination program to determine two-dose HPV vaccination coverage in three districts of Zimbabwe. All households with girls currently aged 11 to 15 years were line-listed through a census conducted in the pre-selected clusters from each district prior to survey administration. A simple random sample of eligible households was selected from these lists to estimate HPV vaccine coverage at sufficient power with a margin of error of +/- 5%. Criteria for district selection included estimated vaccine uptake (low, medium, high), rural/urban/peri-urban, geographic area, estimated number of girls not in school, and recent natural disasters or disease outbreaks. We oversampled households with girls aged 13 or 14 years at the time of dose 1.
Results: On-time dose 1 uptake ranged from 88-94% and two-dose HPV vaccine coverage ranged from 75-86% across the three districts. Nearly all vaccinations occurred in schools, and less than 2% of girls did not attend schools. There were challenges assessing ages of girls at schools prior to vaccination – 9% of girls vaccinated were less than 10 years old at time of dose 1.
Conclusions: Zimbabwe has demonstrated that high uptake and successful completion of 2-dose HPV vaccination can be achieved with an annual dosing schedule. Efforts going forward will need to focus on minimizing dropout between doses and routinizing annual vaccinations in schools for every subsequent new cohort of 10 year old girls in the country.

ORAL SESSION 9: VACCINATION IV. STRATEGIES AND SCHEDULES

THE IMPACT OF INTRODUCING HPV VACCINE FUNDING FOR BOYS ON ACCEPTANCE AND UPTAKE: EVIDENCE FROM A NATURAL EXPERIMENT IN CANADA

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Introduction: School-based, publicly funded HPV vaccination programs were implemented Canada-wide for girls since 2007, but provinces only included boys much later. Nonetheless, uptake remains sub-optimal. To better understand this problem, we present an analysis over time of the associations between parents' knowledge, attitudes and beliefs related to the HPV vaccine, the introduction of a boys' HPV vaccination programme (policy change-where girls' programs were already well-established), and uptake of the HPV vaccine.
Methods: Canadian parents of 9 to 16 years old boys and girls residing in Quebec, Ontario and Manitoba responded to an online survey at Time 1 (T1, September 2016) and Time 2 (T2, July 2017), before and after the implementation of publicly-funded, school-based HPV vaccination programs for boys in these provinces. We used T1 and T2 data and Generalized Estimating Equations to estimate associations (AOR) over time between HPV vaccination policy change, socio-demographics, HPV vaccine attitudes (using validated scales), and HPV vaccine uptake (i.e., yes/no).
Results: Complete data from 544 parents of boys and 633 parents of girls were analyzed. Policy change was associated with increased HPV vaccine uptake in boys (AOR=1.72) and also, in girls (AOR=2.19). Older age was positively associated with HPV vaccine uptake (AOR boys =1.15; AOR girls =1.64). Increased concerns related to the affordability (AOR boys=0.50, AOR girls=0.63) and harms of the HPV vaccine (AOR boys=0.71, AOR girls=0.63) were associated with lower HPV vaccine uptake, while increased social influence (e.g., by friends, family and/or healthcare professionals) was associated with higher HPV vaccine uptake (AOR boys=4.03, AOR girls=3.44).
Conclusions: Introduction of an HPV vaccine policy change for boys surprisingly increased HPV vaccine uptake for girls and boys. Other factors (harms, affordability, and social influence) demonstrated similar influences. Vaccine funding can improve vaccine coverage and parents' attitudes towards the HPV vaccine, even beyond the intended target population.

ORAL SESSION 9: VACCINATION IV. STRATEGIES AND SCHEDULES

A SINGLE DOSE HPV VACCINATION CAMPAIGN IN GRADE 10 GIRLS IN A DISTRICT IN SOUTH AFRICA: COVERAGE AND CORRELATES

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Introduction: In early 2019, we implemented a school-based single dose HPV vaccination campaign in grade 10 girls in a district in South Africa, in a study to measure population-level impact of this dosing regimen.
Methods: We offered eligible grade 10 girls attending secondary school (n=66) in a district in the Free State, South Africa a free single HPV vaccine dose. Potential recipients were ineligible if they could not provide written assent and parental consent (if <18 years), were pregnant or breastfeeding, or reported an acute illness in the past 30 days. Data on vaccine eligibility and receipt were captured real-time into an electronic database for consenting participants. Information on school characteristics was captured from school vaccination registers. Coverage was estimated as the proportion of girls per school who received vaccination. Factors associated with coverage were assessed using linear regression.
Results: Of 66 schools, most were urban (95%), public (95%), fee-free (77%) and from the lowest wealth quintile (32%), with a median of 103 (IQR 60-137) female grade 10 learners enrolled. Out of 6673 potential recipients, 4807 (72%) received a single HPV vaccine dose. Median age of vaccine recipients was 16 (IQR 15-17) years. The primary reason for non-vaccination was lack of signed parental consent, learner assent or absenteeism (26%). A further 114 (2%) assented to vaccination but had no parental consent. Vaccine coverage varied by school and ranged from 14% to 96%. More low coverage schools were from the highest wealth quintile (39% vs. 6%, $p<0.01$). Combined or comprehensive schools, fee-free schools, and schools with high learner turnout at pre-vaccine information sessions had significantly higher vaccine coverage (p-value <0.05).
Conclusions: School-based vaccination of older adolescents at high coverage levels is achievable in this setting. More research is needed to understand barriers to parental consent, particularly in wealthier, non-fee-paying schools.

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

ASSESSING TESTOSTERONE REPLACEMENT THERAPY WITH UNSATISFACTORY ANAL CYTOLOGY AND HISTOLOGICAL HIGH-GRADE ANAL LESIONS (HHSIL) IN OLDER MEN WHO HAVE SEX WITH MEN

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Introduction: Older HIV-infected men who have sex with men (MSM) have a high prevalence of hypogonadism and testosterone replacement therapy (TRT), and anal high-risk HPV infections, histological HSIL (hHSIL), and invasive anal cancer. Transmasculine men receiving exogenous testosterone have shown higher prevalence of unsatisfactory cervical cytology. Associations between unsatisfactory anal cytology or hHSIL with TRT MSM have not been explored.
Methods: 296 HIV-infected and -uninfected MSM screened for anal hHSIL using cytology with nylon-flocked (NF) and Dacron swabs, and High-Resolution Anoscopy (HRA) with biopsy reported their TRT use. Anal cytology was evaluated as satisfactory/unsatisfactory, and histology was evaluated as <hHSIL/hHSIL using standardized procedures. Two multivariable logistic regression models compared odds of unsatisfactory cytology and hHSIL relative to current TRT use, controlling for the effects of age, race, HIV-infection, number of receptive anal intercourse (RAI) partners, and swab-collection order.
Results: Men were 55 ($\pm$11) years old, mostly White, non-Hispanic (75%) and HIV-infected (56%); hHSIL was common (43%). Current TRT use (30%) included gel (18%) and injectable (12%) forms. Historical TRT use (46%) included gel (32%) and injectable (27%) formulas. Multivariable analyses showed no association between current TRT and unsatisfactory cytology (adjOR=0.8,(95% CI: 0.4, 1.5)). NF-swab cytology showed higher odds of unsatisfactory cytology than Dacron-swab (adjOR=2.9,(1.7, 4.6)). Adjusted analyses suggested self-reported TRT use did not affect odds of hHSIL (adjOR=1.1,(0.6, 2.1)). Men reporting $\geq$2 RAI partners within 2 years of examination showed 89% higher odds of hHSIL than men reporting none (adjOR= 1.9,(1.0, 3.5)). HIV and CD4-count characteristics were not associated with (adjusted) odds of either unsatisfactory cytology or hHSIL.
Conclusions: Unsatisfactory cytology and hHSIL were not associated with self-reported TRT use. Self-reported TRT use may not closely approximate circulating serum free testosterone. Effects of exogenous testosterone in cervical tissue may differ from effects in the anus. Further research is needed.

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

TREND OF THE PREVALENCE OF HIGH-RISK HPV INFECTION AMONG RWANDAN WOMEN LIVING WITH HIV OVER 15 YEARS

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Introduction: High-risk human papillomavirus (hrHPV) causes virtually all cervical cancer as well as most other anogenital cancers and a significant proportion of oropharyngeal cancers. Cervical cancer, an AIDS-defining malignancy, is the most common HPV-related cancer. We examined the trend of the prevalence of hrHPV infection among Rwandan women living with HIV (WLWH) over a period of 15 years.
Methods: The prevalence of hrHPV DNA was measured at three different time periods in three different groups of women using three different but comparable hrHPV tests: RWISA, conducted in 2005, a MY09/MY11 PCR test, HPV Demonstration, conducted in 2010, used Hybrid Capture 2 (HC2), and U54, conducted 2016-18, used the Xpert HPV test. The trend of the prevalence of hrHPV infection was compared for the three studies and by age (30-34, 35-39, 40-44, 45-59 and 50-54 years) and CD4 cell count (<200, 200-349, 350-499 and ≥500 cells/mm^3) groups.
Results: The prevalence of hrHPV for the three studies (RWISA, HPV Demonstration, and U54) decreased over time, from 42.45% to 39.16% to 26.46%, respectively (p-trend <0.001). HrHPV prevalence decreased with increasing age (p-trend<0.001 for all studies) and increasing CD4 cell count (p-trend<0.01 for all studies). However, CD4 cell counts increased over time (p-trend <0.001), so that the percentage of WLWH with CD4 counts of ≥500 cells/mm^3 increased from 8% in 2005, 42% in 2010, and 61% in 2019. Thus, age- and CD4 count-adjusted hrHPV prevalences were much more similar over time: 31.95% for RWISA, 37.55% for HPV Demonstration, and 27.17% for U54.
Conclusions: The prevalence of hrHPV among Rwandan WLWH has been decreasing over the past decade most likely due to improving HIV care and management over time. The fact that more women are of recent having higher CD4 cell counts indicates the role ART has played in improving the quality of life for people living with HIV.

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

INCREASING BURDEN OF CERVICAL CANCER AMONG WOMEN LIVING WITH HIV IN THE CONTEXT OF ART

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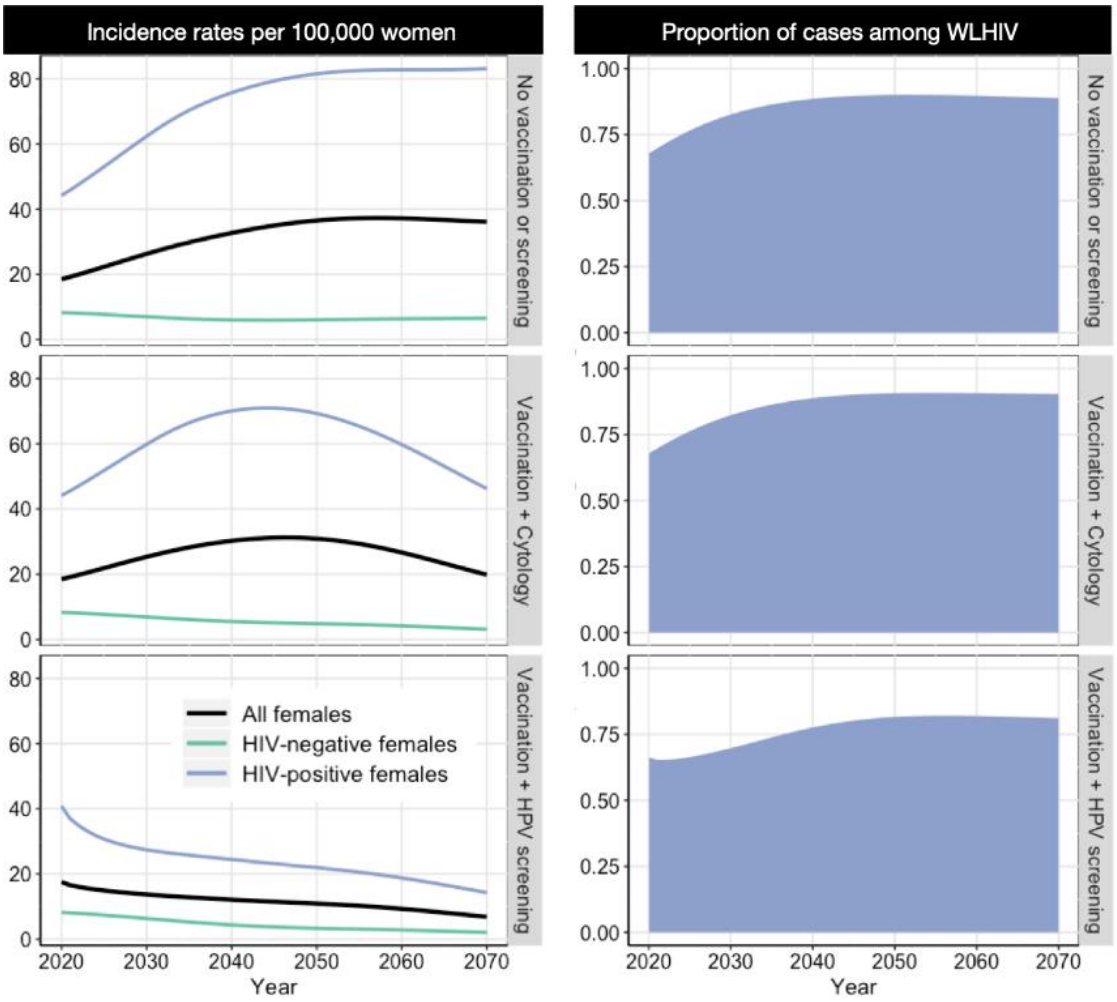
Introduction: Cervical cancer (CC) incidence in sub-Saharan Africa is more than three times higher than the global average, owing in part to high HIV prevalence. Expanded access to antiretroviral therapy (ART) could decrease cancer risk cancer for women living with HIV (WLHIV), but ART also increases survival such that more women reach the peak ages for cervical cancer incidence. Estimating the contribution of HIV to cervical cancer is important to help public health agencies anticipate prevention and treatment needs.
Methods: We developed a dynamic compartmental model of HIV-HPV coinfection dynamics in KwaZulu-Natal, South Africa, where HIV prevalence exceeds 30% in reproductive-age women. We introduced ART in 2004 with viral suppression increasing to 70% in 2030. We assumed women on ART experience lower rates of HPV clearance, but are otherwise similar to HIV-negative women. We simulated CC incidence from 2020 to 2070 with no screening or vaccination and under two scenarios with 90% routine 9vHPV vaccination and variable screening: cytology at age 35 with 48% coverage, and HPV screening scaled-up to 90% coverage in 2045 at ages 35 and 45 for HIV-negative women and every 3-years from 25-49 for WLHIV.
Results: In 2020, CC incidence was 18.5/100,000, with 68% of cases WLHIV. Without vaccination or screening, incidence increased to 36.1/100,000 in 2070, and the proportion of cases in WLHIV increased to 89%. With 90% vaccination and low-coverage cytology screening, incidence in 2070 was 19.9/100,000, with 90% of cases in WLHIV. With vaccination and high-coverage HPV screening, incidence dropped to 6.9/100,000, and 81% of cases were WLHIV.



Conclusions: WLHIV account for a disproportionate proportion of CC cases in high HIV prevalence settings. However, the full impact of HIV on cancer incidence has yet to be realized. In the context of ART, the proportion of cases among WLHIV will increase even with high-coverage vaccination and screening programs.

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

THE RISK OF HIV SEROCONVERSION FOLLOWING AN ANAL HPV INFECTION AMONG MSM

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Introduction: HIV and human papillomavirus (HPV) share acquisition risk factors and may be synergistic, each increasing the risk of the other. The objective of this study was to assess whether anal HPV infection was associated with HIV seroconversion among men from Brazil, Mexico and the USA
Methods: Nested within the HIM Study cohort, we assessed archived serum from 504 men who have sex with men (MSM) to determine if HIV-seroconversion occurred during follow-up. Serum was collected at six-month intervals and tested using the HIV-1/2 Antigen and Antibodies, Fourth Generation with Reflexes. Anal specimens were collected every six-months. HPV genotyping was done using Linear Array. Cox proportional hazards models were used to evaluate the association between HIV seroconversion and time-varying, categorized HPV infection: negative, new infection, persistent infection or cleared infection.
Results: During follow-up, 28 MSM (5.5%) seroconverted to HIV. Overall, 347 men (69%) had any HPV prevalent at baseline; 71% of the men who HIV seroconverted were infected with any HPV at baseline. Men persistently infected (infected at two or more consecutive visits) with any genotype of HPV infection were at increased hazard of HIV seroconversion relative to those who were negative (hazard ratio (HR)= 11.7, 95%CI: 3.4-39.7, Table). Relative to men who were negative for high risk HPV, men presenting with either new infections (HR= 12.2, 95%CI: 3.3-45.3), persistent infections (HR= 7.1, 95%CI: 2.6-19.6), or cleared infections (HR= 4.8, 95%CI: 1.5-16.1) had increased risk of HIV seroconversion. Men infected with types included in the 9vHPV that cleared were at increased hazard of HIV seroconversion relative to those who were negative (HR= 4.1, 95%CI: 2.7-16.5).
Conclusions: Anal HPV infections were significantly associated with increased hazard for HIV seroconversion among MSM. Further analyses adjusting for potential confounders such as concomitant STI infections and sexual practices are underway.

Table. Cox proportional hazards models the association between HIV seroconversion and time-varying HPV infection.		
		Hazard Ratio (95% Confidence Interval)
Any HPV	Negative	ref.
	New infection	3.6 (0.4-35.3)
	Persistent infection	11.7 (3.4-39.7)
	Cleared infection	1.1 (0.1-10.6)
High risk HPV	Negative	ref.
	New infection	12.2 (3.3-45.3)
	Persistent infection	7.1 (2.6-19.6)
	Cleared infection	4.8 (1.5-16.1)
Low risk HPV	Negative	ref.
	New infection	13.9 (4.6-41.4)
	Persistent infection*	
	Cleared infection	2.2 (0.4-12.2)
9vHPV	Negative	ref.
	New infection	2.6 (0.3-20.7)
	Persistent infection	6.7 (2.7-16.5)
	Cleared infection	4.1 (1.3-12.3)
4vHPV	Negative	ref.
	New infection	2.9 (0.4-23.7)
	Persistent infection	7.7 (3.3-18.0)
	Cleared infection	1.8 (0.4-8.5)
*Low Risk HPV Persistent infection was not included in the model because there were no HIV seroconversion events among participants that had a persistent LR-HPV infection		

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

HPV16 E6 SEROPREVALENCE AND TIMING OF SEROCONVERSION BEFORE ANAL CANCER DIAGNOSIS: FINDINGS FROM THE HPVC3 CONSORTIUM

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Introduction: HPV16 causes cancer at various anatomical sites. In HPV16-driven oropharyngeal cancer, seropositivity against HPV16E6 is a promising biomarker due to its high sensitivity and presence 10+ years prior to diagnosis. We aim at investigating the fraction of HPV16E6 seropositive anal cancers, timing of seroconversion, and sensitivity of E6 seropositivity in comparison with molecular HPV tumour status.
Methods: The HPVC3 consortium included 387 anal cancer cases (104 male, 283 female) and 5,814 controls from 9 cohorts (Europe, North America and Australia). Serum antibodies against HPV16 proteins (L1, E1, E2, E6, E7) were measured in all participants in at least one pre-diagnostic blood sample (median time before diagnosis: 12 years; range: 0-39 years). Of the corresponding tumour specimens, 145 (38%) will be retrieved from the JANUS cohort (Norway) to determine molecular HPV status by DNA

and RNA detection.
Results: HPV16 early antibodies were significantly more prevalent in anal cancers than controls (OR range: E7 2.0 (95%CI 1.5-2.7) to E6 32.8 (95%CI 22.6-47.7)). In anal cancer cases, HPV16E6, E1 and E2 antibodies were significantly (p-value<0.05) more prevalent in women than men (e.g. $E6_{women}$ 26.5%; $E6_{men}$ 7.7%, $E6_{total}$ 21.5%), while their seroprevalences were similar in female and male controls (p-value>0.05). Among 95 anal cancer cases with multiple pre-diagnostic blood samples, 12 (13%) were E6 seropositive in all blood draws (up to 21 years before diagnosis) and 24 (25%) seroconverted 1-18 years (median: 7.8 years) before diagnosis. Of the first 57 tumours analysed, 75% (n=43) were HPV16-driven. Seven patients (16%) with HPV16-driven tumours were HPV16E6 seropositive before diagnosis (median lead time: 14.7 years). Among twelve patients with sera drawn within 6 months prior or after cancer diagnosis, HPV16E6 sensitivity was 67% (n=8).
Conclusions: HPV16E6 antibodies are present in a small proportion of predominantly female anal cancer cases up to 21 years before diagnosis.

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ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

ELIMINATION OF CERVICAL CANCER IN SETTINGS WITH ACTIVE HIV CONTROL: THE EXAMPLE OF TANZANIA

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Introduction: WHO have set draft targets for cervical cancer elimination at 4/100,000, involving scale-up of HPV vaccination (90% coverage in females), twice-lifetime HPV screening (70% participation) and treatment of precancer/cancer (90% coverage) by 2030. Cervical cancer is more difficult to control in countries with a high prevalence of HIV, such as Tanzania (HIV prevalence 5.5%; cervical cancer incidence 59.1 cases/100,000), as HIV-positive women are at elevated risk of HPV infection, persistence and progression. Previous analysis, not explicitly accounting for HIV, predicts that meeting WHO targets will reduce age-standardised cervical cancer incidence rates to 8.4 cases/100000 women in 2099. The aim was to estimate outcomes via explicit modelling of HIV and HPV, using Tanzania as an example.
Methods: A dynamic model of HIV and HPV was used to simulate the impact of meeting the WHO targets, in the context of sustained HIV control measures (80% male circumcision prevalence; 47% viral suppression due to anti-retroviral treatment in people with HIV) in Tanzania, from 2020-2120.
Results: Without further intervention, cervical cancer incidence is predicted to decrease by 37% over 100 years (64.6/100,000 in 2020, 40.7/100,000 in 2120) due to existing HIV control measures. Compared to 2020, scaled-up HPV9 vaccination is predicted to decrease cervical cancer incidence rates by 81% by 2120 (12.1/100,000); twice-lifetime HPV testing at 35 and 45 years will increase the relative reduction to 86% (9.4/100,000). In 2099 the predicted rate with scaled-up vaccination is 10.7/100,000.
Conclusions: Scaling-up vaccination and HPV testing to meet WHO targets will substantially reduce cervical cancer incidence in Tanzania over 100 years. The findings from this analysis broadly accord with predictions from prior analysis not explicitly accounting for HIV; models that do not and do explicitly account for HIV both conclude that elimination is not predicted by 2100. Countries with high HIV prevalence may require more frequent screening to eliminate cervical cancer.

ORAL SESSION 10: HIV. NATURAL HISTORY AND PREVENTION IN HIV-INFECTED PEOPLE

THE INCIDENCE OF ANAL SQUAMOUS CELL CARCINOMA BY HIV AND MSM STATUS IN BRITISH COLUMBIA, CANADA (1990-2015)

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Introduction: Anal squamous cell carcinoma (ASCC) is an HPV-associated malignancy known to disproportionately impact people living with HIV and men who have sex with men (MSM). However, population-based incidence rate (IR) estimations that draw on precise laboratory data and MSM statuses are scarce.
Methods: The Integrated Data and Evaluative Analytics (IDEAs) Cohort includes ~1.7 million individuals who have tested or been case-reported for HIV and other infectious diseases in British Columbia (BC). We created a sub-cohort of HIV-negative and HIV-positive individuals aged 16 years and older with greater than 5 months of follow-up time. ASCC diagnoses were ascertained from the BC Cancer Registry (1990-2015). Follow-up began at first HIV test (HIV-negative stratum), first HIV detection (HIV-positive stratum), or 01/01/1990, whichever occurred last. Follow-up ended at first ASCC diagnosis, HIV diagnosis (HIV-negative stratum), death, or 31/12/2015, whichever occurred first. We assessed crude IRs of ASCC stratified by HIV status, sex, and, among males, imputed MSM status. Rate ratios, adjusted for age-at-entry into cohort, were assessed using Poisson regression.
Results: There were 245 incident ASCC cases between 1990-2015. Among 1,183,098 HIV-negative individuals (6% MSM, 34% male non-MSM, 60% female), ASCC IRs per 100,000 person-years were 2.17 (95% confidence interval [CI]: 1.26-3.73) for MSM, 1.56 (95%CI: 1.19-2.04) for male non-MSM, and 1.77 (95%CI: 1.47-2.14) for females. Among 11,840 HIV-positive individuals (46% MSM, 34% male non-MSM, 21% female), ASCC IRs per 100,000 person-years were 75.23 (56.69-99.83) for MSM, 47.75 (30.81-74.02), for male non-MSM, and 3.91 (0.55-27.73) for females. Age-adjusted IRs were higher among HIV-positive vs. HIV-negative individuals (rate ratio [RR]: 28.52, 95%CI: 21.57-37.72), particularly for HIV-positive MSM vs. HIV-negative MSM (RR=34.36, 95%CI: 18.53-63.70).
Conclusions: ASCC incidence is highest among HIV-positive MSM in BC, and much higher relative to HIV-negative MSM. These results highlight the need for implementing formalized anal cancer screening programs among people living with HIV in Canada.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

CATCH-UP VACCINATION HAS GREATER INCREMENTAL IMPACT ON CERVICAL CANCER INCIDENCE IN HIGH VS. MEDIUM HIV BURDEN SETTING

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Introduction: Women living with HIV (WLHIV) face a 2-5-fold higher cervical cancer (CC) risk than HIV-negative women due to increased HPV acquisition and progression. Catch-up vaccination to early adulthood, including WLHIV, could accelerate prevention efforts in regions with high HPV and HIV burden. However, population-level HPV vaccine effectiveness in high and medium HIV prevalence settings is unknown.
Methods: We used a dynamic compartmental model of HPV-HIV coinfection to compare the impact of catch-up vaccination on CC incidence in a setting with high female HIV prevalence (>30%) to one with medium HIV prevalence (<20%). We evaluated three scenarios: routine vaccination of 10-14-year-old girls at 90% coverage, routine vaccination with catch-up of women aged 15-29 at 50% coverage, and routine vaccination with catch-up at 80% coverage. We report the percent reduction in cancer incidence rates after 50 years in each scenario compared to no vaccination by setting and HIV status.
Results: The incidence rate was reduced by 60% with routine vaccination in the high HIV burden setting and by 71% in the medium HIV burden setting. The addition of catch-up vaccination at 50% coverage reduced incidence by 70% in the high and 78% in the medium HIV setting. Increasing catch-up to 80% led to 75% and 83% reductions in the high and the medium HIV settings, respectively. In both settings, the incremental percent reduction with the addition of catch-up vaccination was greater among WLHIV (16-17%) than HIV-negative women (10-11%).

Table 1. Percent reduction in cervical cancer incidence rates with vaccination compared to no vaccination after 50 years, by population HIV burden and HIV status.

	Routine vaccination only	Routine vaccination + catch-up at 50% coverage	Routine vaccination + catch-up at 80% coverage
High HIV burden setting			
General population	59.5%	70.0%	75.4%
HIV-positive	57.2%	68.2%	73.8%
HIV-negative	74.8%	82.2%	86.1%
Medium HIV burden setting			
General population	70.7%	78.3%	82.5%
HIV-positive	58.4%	68.8%	74.3%
HIV-negative	77.6%	83.7%	87.2%

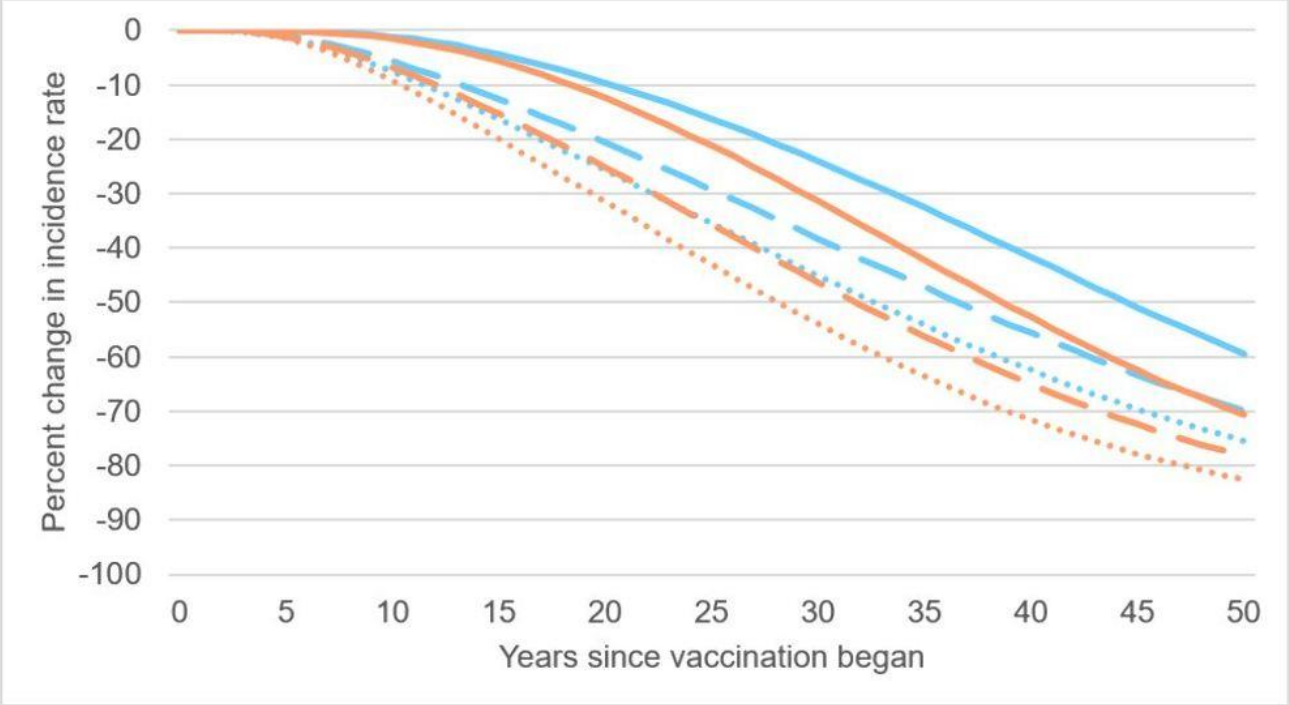

Figure 1. Percent reduction in cervical cancer incidence rates in the general population with routine vaccination at 90% coverage (solid lines), 90% routine vaccination with catch-up at 50% coverage (dashed lines), and 90% routine vaccination with catch-up at 80% coverage (dotted lines), compared to no vaccination. The blue lines represent the population with high HIV burden, and the orange lines represent the population with lower HIV burden.

Conclusions: Catch-up vaccination resulted in a larger population-level reduction of CC incidence relative to routine vaccination alone regardless of background HIV prevalence. While our model predicted a greater overall impact of vaccination in the setting with medium HIV prevalence, the incremental benefits from catch-up vaccination were higher in setting with high HIV prevalence.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

MULTI-COHORT HPV VACCINATION ENABLES CERVICAL CANCER ELIMINATION DURING THIS CENTURY FOR REGIONS WITH HIGH HIV PREVALENCE

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Introduction: Cervical cancer (CC) is the leading cause of cancer death among women in sub-Saharan Africa, and women living with HIV have 2-5 times the CC risk of HIV-negative women. HPV 9-valent vaccination prevents ~90% of CC, but effects take decades to accrue. Vaccination of older women and women living with HIV may achieve quicker reductions.
Methods: We modified a dynamic mathematical model of HPV-HIV transmission in KwaZulu-Natal, South Africa to evaluate the effect of 9-valent HPV vaccination strategies on time-to-elimination of CC as a public health issue (incidence <4/100K) and a near-term benchmark (incidence <10/100K). In the baseline scenario reflecting current coverage, 86% of girls were vaccinated at age nine. We then evaluated extending vaccination to age 14 at 86% coverage (Scenario 1). Scenarios 2-3 additionally vaccinated women living with HIV aged 15-26 at 50% and 80% coverage, while scenarios 4-5 added vaccination of all women aged 15-26 at 50% and 80% coverage.
Results: If single-age vaccination continues, CC incidence will drop below 10/100K by 2096 but will not be eliminated in the next 100 years. All enhanced vaccination scenarios make elimination possible by 2117-2119. Vaccinating girls aged 9-14 achieves incidence <10/100K by 2085. Additionally vaccinating young adult women living with HIV with 50% and 80% coverage achieves incidence <10/100K by 2084 and 2082, respectively (Scenarios 2-3). Vaccinating all women up to age 26 achieves this benchmark by 2082 and 2079 (Scenarios 4-5).
Conclusions: Multi-cohort vaccination can facilitate CC elimination during this century for settings with high HIV prevalence. Extending vaccination to age 14 decreases time to the near-term benchmark by over a decade, and vaccinating all women aged 9-26 at high coverage saves 17 years. These results support WHO and Gavi recommendations for multi-cohort vaccination, particularly in the context of high HIV prevalence.

TABLE 1. Scenario definitions. Baseline (Scenario 0) and enhanced (Scenarios 1-5) vaccination strategies.

	Vaccination regimen			
	Women without HIV		Women living with HIV	
Scenario	Ages	Coverage	Ages	Coverage
0	9	86%	9	86%
1	9-14	86%	9-14	86%
2	9-14	86%	9-14 15-26	86% 50%
3	9-14	86%	9-14 15-26	86% 80%
4	9-14 15-26	86% 50%	9-14 15-26	86% 50%
5	9-14 15-26	86% 80%	9-14 15-26	86% 80%

TABLE 2. Model predicted time to cervical cancer elimination.

Scenario	Cervical cancer incidence <10 cases per 100K (year achieved)	Cervical cancer incidence <4 cases per 100K (year achieved)
0	2096	Not achieved in 100 years
1	2085	2119
2	2084	2119
3	2082	2118
4	2082	2118
5	2079	2117

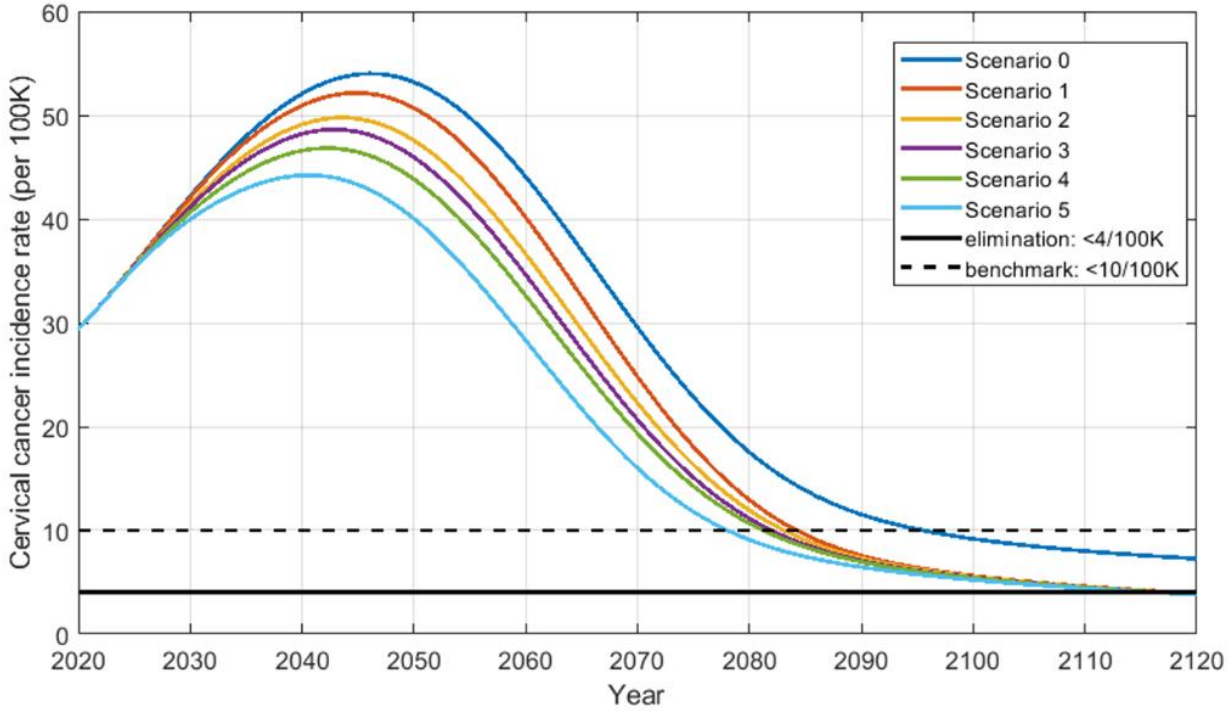

FIGURE 1. Cervical cancer incidence rates in all women over time.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

ACCEPTABLE UNIT PRICE DIFFERENCES BETWEEN HPV VACCINES FOR SEX-NEUTRAL VACCINATION ARE LOWER THAN FOR GIRLS-ONLY

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Introduction: HPV vaccines differ in their type-specific protection, which need to be translated into adjustment prices between the products in public tendering process. For each product, such adjustment price is added to the tender price to get the comparable price. The procedure is sometimes further translated to different award points. In Europe, unit price for the nonavalent (HPV9) vaccine has been 34.4 EUR/26.9 EUR higher than for the bivalent (HPV2)/quadrivalent (HPV4) vaccine in girls-only HPV programs [Qendri 2018].
Methods: A mathematical model was used to predict the HPV-related disease burden, healthcare costs and quality-adjusted life-years (QALY) lost, in a vaccinated cohort after implementation of sex-neutral vaccination program with each available vaccine (base case 80% coverage). The model was fitted with register based data about HPV diseases and cervical cancer screening in Finland from pre-vaccination era. The cervical cancer screening findings, genital warts, and other HPV associated cancers were included in the analysis. The differences in the remaining disease burden were discounted and divided for the vaccinated cohort to define the adjustment price.
Results: The adjustment prices (per dose), when comparing to HPV9 and taking into account only healthcare costs, were 13.15 EUR for HPV2 and 10.03 EUR for HPV4, of which 4.11/8.49/0.65 EUR (HPV2) and 8.80/0.00/1.23 EUR (HPV4) originated from cervical cancer/genital warts/other cancers. When also taking into account the QALYs gained, the adjustment prices were 0-8.66 EUR/dose (HPV2) and 0-7.81 EUR/dose (HPV4) at an assumed threshold of 0-10 000 EUR/QALY gained, resulting in total adjustment prices 13.15-20.96 EUR for HPV2 and 10.03-17.84 for HPV4.
Conclusions: The presented adjustment prices are lower than realized price differences in girls-only programs, which can be explained by the doubled number of vaccinated individuals of the sex-neutral HPV vaccination programs. Cervical cancer and genital warts, play still the major role even if other cancers were included the analysis.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

EXPLAINING DIFFERENCES BETWEEN DYNAMIC HPV TRANSMISSION MODELS IN PREDICTING VACCINATION IMPACT: A MODEL COMPARISON STUDY

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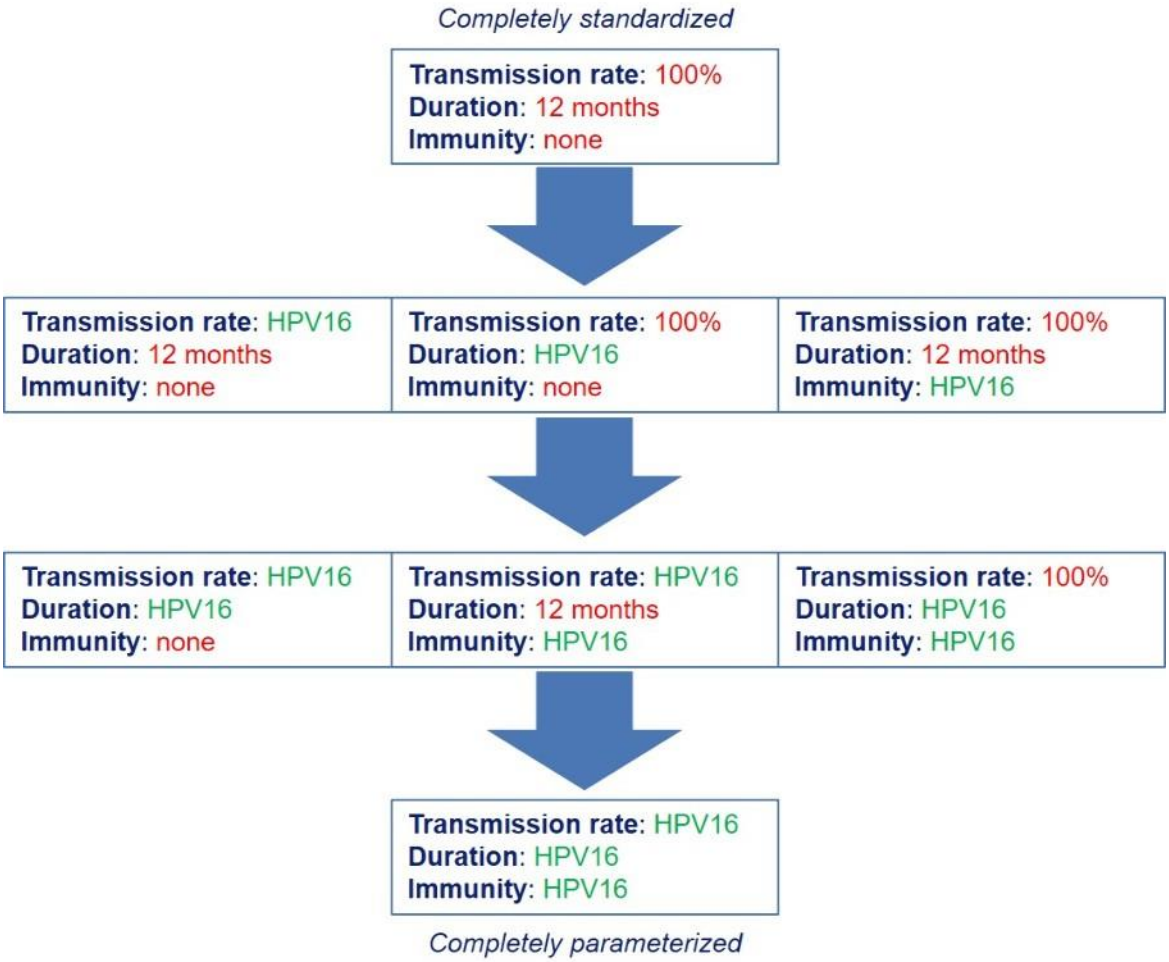
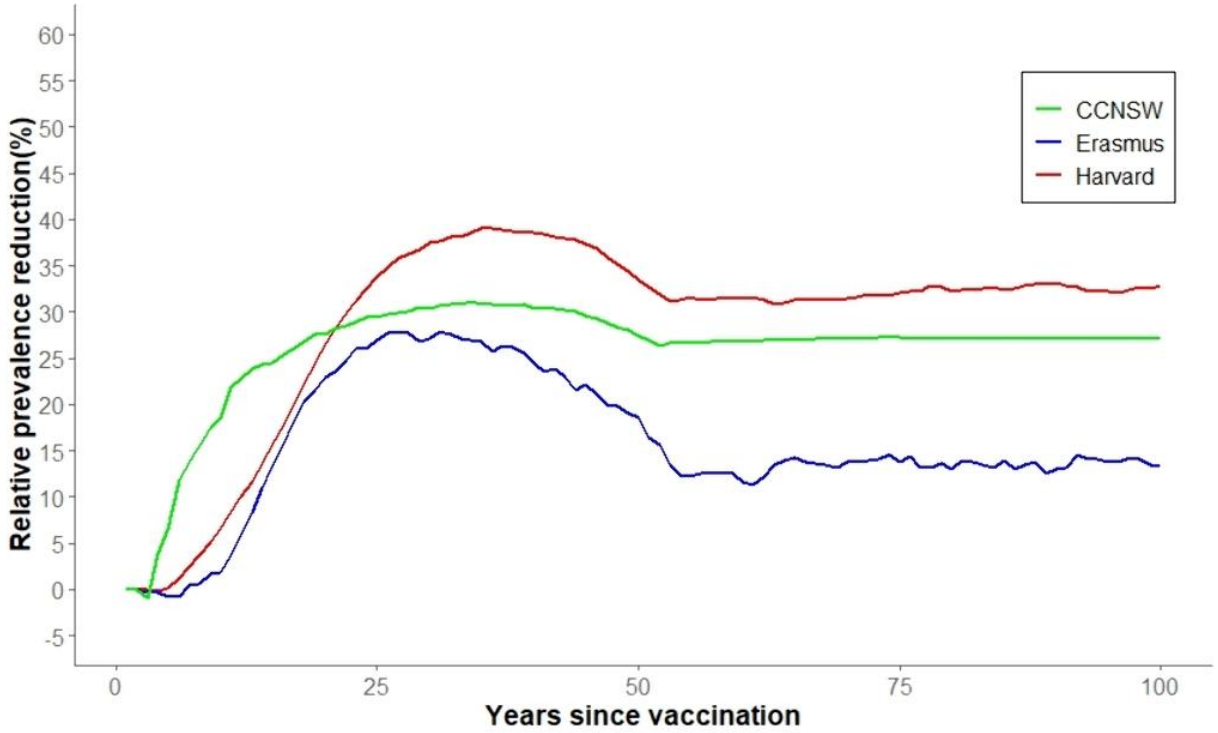
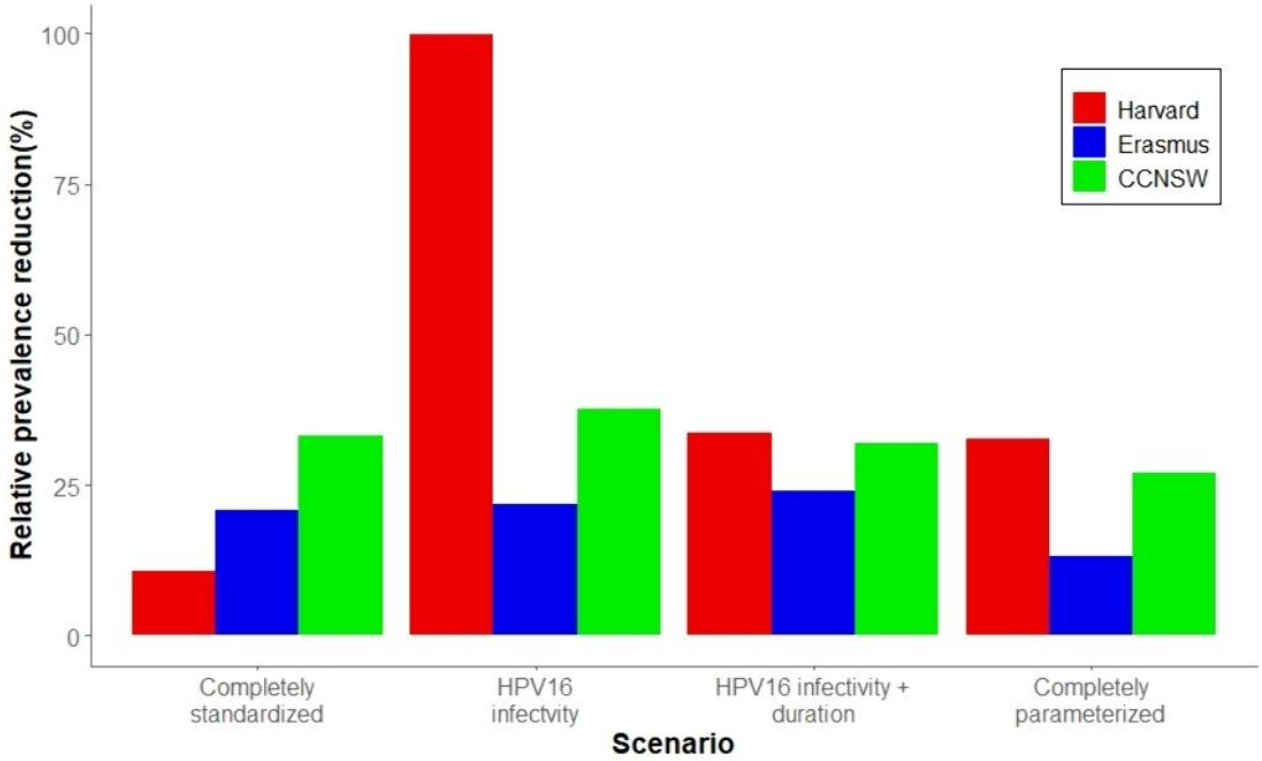
Introduction: Mathematical models of HPV vaccination differ substantially in underlying structure, assumptions, and estimated impact. Understanding their differences can help improve the interpretation of predictions. We systematically compared three independently developed Cancer Intervention and Surveillance Modeling Network (CISNET) transmission models ('CCNSW', 'Erasmus', and 'Harvard'), that reproduce similar surface-level sexual behavior (e.g. numbers of partners). We isolated the role of sexual network, transmission probability, infection duration, and natural immunity assumptions on the predicted impact of HPV vaccination.
Methods: We developed a unique stepwise comparison framework (Figure 1). Eight versions of each model were developed, ranging from 'completely standardized' generic HPV16 assumptions to 'completely parameterized' HPV16 assumptions (i.e. the original models). At each step, we compared the herd immunity effects for vaccination with 100% efficacy, at 50% uptake in females aged 12. The completely standardized scenario is a comparison of underlying networks, as the same generic infection will spread through the models. At each incremental step towards the parameterized model, we isolated how introducing model-specific rather than generic assumptions on transmission rates, duration, and natural immunity change the predicted impact of vaccination.



Results: In the 'completely parameterized' models, the equilibrium prevalence reduction in unvaccinated women ranged between 13% and 32% (Figure 2).



Even for the completely standardized model, in which only the sexual networks are model-specific, predictions were substantially different between the models (between 10% and 33%). At none of the steps in the analysis were the relative differences in prevalence reductions between models smaller than 25% (Figure 3).



Conclusions: Sexual network dynamics seem to be the main driver of discrepancies between HPV transmission models, as models completely standardized on HPV natural history give substantially different predictions. Because all models in our analysis reproduce similar surface-level sexual behavior data, deeper mechanics such as assortativeness of mixing or heterogeneities in behavior are the likely cause of differences.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

COST-EFFECTIVENESS OF COMMUNITY HEALTH CAMPAIGN STRATEGIES TO DELIVER SELF-COLLECTED HUMAN PAPILLOMAVIRUS-BASED TESTING FOR CERVICAL CANCER SCREENING IN KENYA

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Introduction: In sub-Saharan Africa, cervical cancer(CC) screening coverage is low, leading to a high CC-mortality burden in the region. Using community health campaigns(CHCs) may improve CC screening delivery when paired with access to treatment options. While HPV-based self-sampling is known to be a cost-effective screening approach, options for linkage to treatment for HPV-positive women have not been similarly evaluated. Our objective was to evaluate the cost-effectiveness of four CC screening scenarios compared to no screening, each using CHC-based HPV self-sampling: (1) followed by referral for visual assessment and cryotherapy("HPV-and-treat"), with *standard*-linkage to treatment and (2)"HPV-and-treat" with *enhanced*-linkage; and (3) followed by Visual Inspection with Acetic Acid(VIA) triage to cryotherapy("HPV+VIA-and-treat"), with *standard*-linkage and (4)"HPV+VIA-and-treat" with *enhanced*-linkage.
Methods: Screening delivery scenarios and cost data were collected from a two-phase clustered-randomized trial of the scenarios conducted in Migori County, Kenya (2016-2018). We created a decision tree to estimate disability-adjusted life years (DALYs), costs, and cost-effectiveness (cost per DALY averted) for each screening scenario, over a 6-year time horizon for women aged 25-64 years from a societal perspective. We used published literature to estimate test performance, and short- and long-term clinical outcomes. Costs were presented in 2018 International Dollar(I$). Cost-effectiveness was defined as three-times the national gross domestic product of Kenya in 2018 I$.
Results: Compared to no screening, "HPV-and-treat" with *enhanced*-linkage was the most cost-effective option at $5,492.62 I$/DALY averted. Compared to strategies that used "HPV+VIA-and-treat", "HPV-and-treat" strategies led to better health outcomes, as measured in DALYs, and were more cost-effective due to fewer missed cases of CIN2+ eligible for treatment. Deterministic sensitivity analyses showed that the proportion of women successfully linked to treatment most impacted the cost-effectiveness of "HPV& treat" options.
Conclusions: Conclusion: CHCs using HPV-based self-collection followed by "HPV-and-treat" with *enhanced*-linkage to treatment appears to be a cost-effective option for Kenya.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

BUDGET OPTIMISATION STRATEGY TOWARDS ELIMINATION OF CERVICAL CANCER UNDER AGEING, URBANISATION AND SEXUAL OPENING TRANSITION SETTINGS FROM 2015 TO 2100 IN CHINA: A MODELLING STUDY

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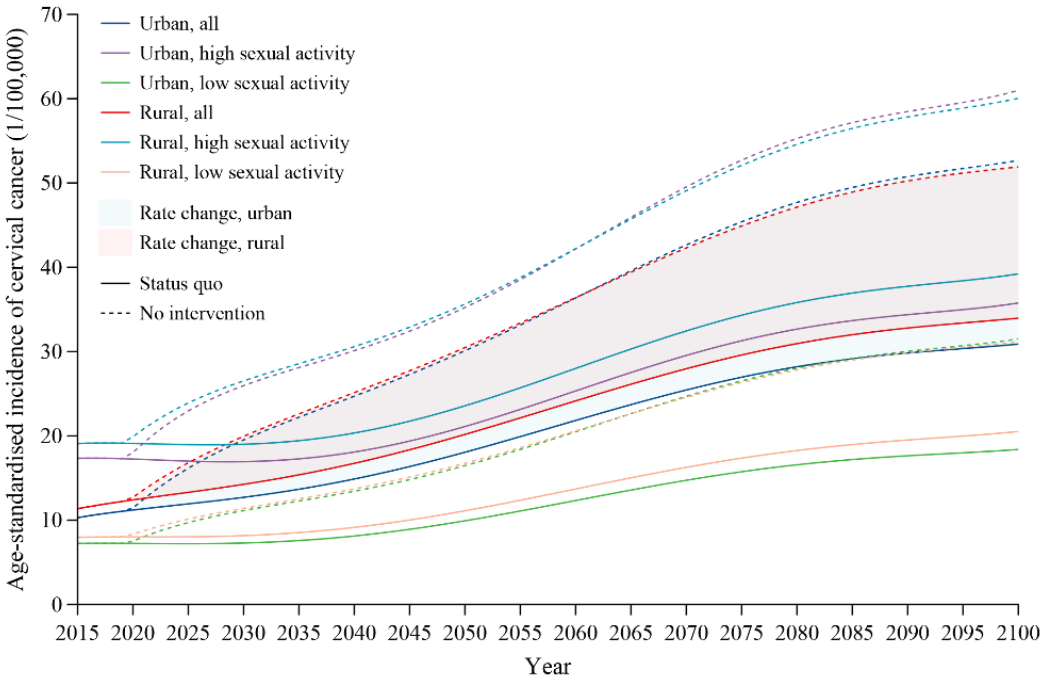
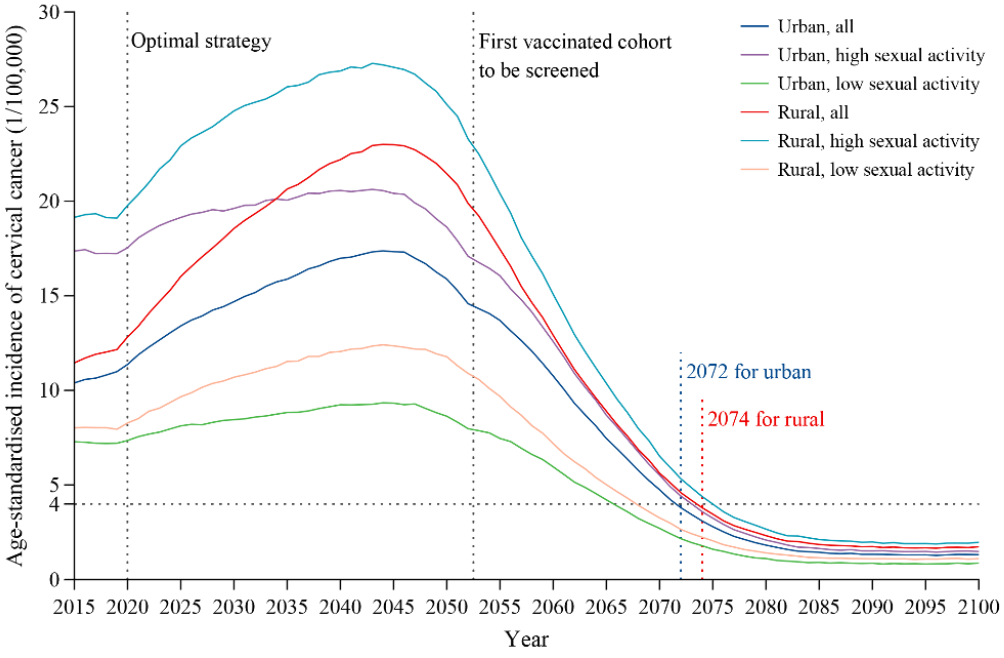
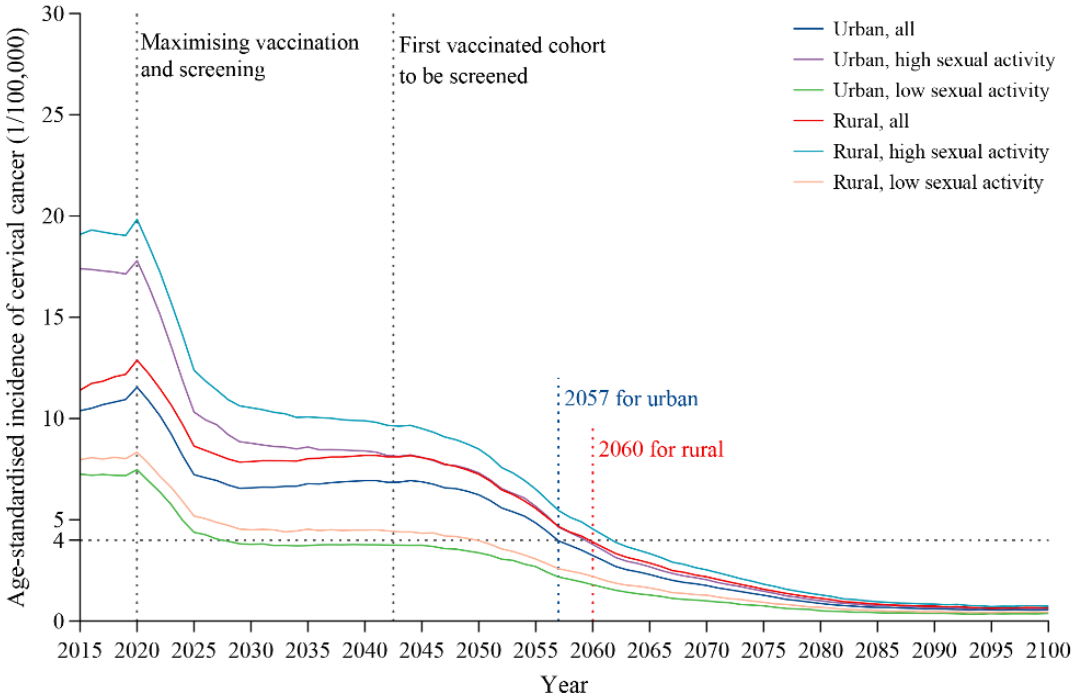
Introduction: While China delivers an unprecedented budget for cervical cancer prevention, the incidence of cervical cancer is increasing rapidly. We aim to forecast age-standardised incidence of cervical cancer in China from 2015 to 2100, and to determine the optimal strategy for eliminating cervical cancer under budget constraints.
Methods: We developed a Chinese adapted and calibrated hybrid model to estimate the incidences of cervical cancer in urban and rural China. All 1.15 billion Chinese females living in 2015–2100 under the settings of ageing, urbanisation and sexual opening transitions were considered. Varying scenarios of budget constraints, implementation of human papillomavirus vaccine, and cervical cancer screening characteristics were accessed. We employed a budget optimisation process to select the best available combinations of vaccination and screening. Primary outcomes were the incidence of cervical cancer and the year of elimination (incidence lower than four cases per 100,000 women).
Results: If current strategy remains unchanged in China, the annual incidence of cervical cancer would three times increase by 2100. But if China adopts the optimal strategy under the current budget from 2020 onwards, cervical cancer would likely to be eliminated by 2072 (2070–2074) in urban China and 2074 (2072–2076) in rural China. If the current budget were doubled, elimination would be achieved at 2063 (2059–2066) in urban China and 2069 (2066–2071) in rural China. The easiest possible year of elimination were estimated at 2057 (2053–2060) in urban China and 2060 (2057–2063) in rural China by maximizing coverages of vaccination and screening.


Urban, all
Urban, high sexual activity
Urban, low sexual activity
Rural, all
Rural, high sexual activity
Rural, low sexual activity
Rate change, urban
Rate change, rural
Status quo
No intervention
Age-standardised incidence of cervical cancer (1/100,000)
0
10
20
30
40
50
60
70
2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100
Year


Optimal strategy
First vaccinated cohort
to be screened
Urban, all
Urban, high sexual activity
Urban, low sexual activity
Rural, all
Rural, high sexual activity
Rural, low sexual activity
2072 for urban
2074 for rural
Age-standardised incidence of cervical cancer (1/100,000)
0
4
5
10
15
20
25
30
2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100
Year



Conclusions: Cervical cancer incidence in China would increase persistently under current strategy of cervical cancer prevention. Whereas, if China shifts to the budget optimisation strategy from 2020 onwards, cervical cancer could be considered to be eliminated as a public health problem by the early 2070s. Elimination would be first achieved at late 2050s by increasing the budget.

ORAL SESSION 11: MODELLING II. MODELLING AND ECONOMIC ANALYSES FOR CERVICAL CANCER ELIMINATION

COST-EFFECTIVENESS OF CERVICAL CANCER ELIMINATION IN LOW- AND MIDDLE-INCOME COUNTRIES (LMICS): EXAMPLE FROM VIETNAM

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Introduction: The World Health Organization (WHO) has developed a draft global strategy to eliminate cervical cancer as a public health problem. Draft 2030 scaleup targets include 90% vaccination, 70% twice-lifetime screening, and 90% precancer/cancer treatment coverage with a threshold for cervical cancer elimination of 4/100,000 annually. This study aimed to evaluate HPV vaccination and resource-stratified cervical screening options in Vietnam, a low-and-middle-income country, not eligible for Gavi vaccine support, and to identify the timing of elimination and whether elimination is cost-effective in this setting.
Methods: An established dynamic model of HPV vaccination and cervical screening ('*Policy1-Cervix*') was calibrated to subregions of Vietnam, and used to evaluate the impact of 2 doses of quadrivalent('HPV4'), bivalent ('HPV2') and nonavalent ('HPV9') vaccines in girls aged 12 years. We considered HPV testing under a range of burden-of-disease estimates (given gaps in registry data), triage options and age-ranges with appropriate strategies for rural and urban regions. We identified which strategies would achieve elimination and if these strategies would be cost-effective.
Results: Even with worst case burden-of-disease assumptions, a combined strategy of HPV9 vaccination and twice-lifetime screening with HPV-VAT would reach elimination and would be very cost-effective (ICER: $2164/LYS, under 1XGDP per capita: US$2215 (year 2016)). With a lower assumed burden of disease in rural regions, vaccination only (with any vaccine type) would achieve elimination. However, only combined vaccination/twice-lifetime-screening strategies would be cost-effective (ICER≤US$2130/LYS). If Vietnam achieves the WHO scale-up targets, the estimated timing for cervical cancer elimination in Vietnam would be 2061-2079, depending on the burden-of-disease in rural regions.
Conclusions: Cervical cancer in Vietnam could be eliminated by 2061-2079 if 90% coverage with a broad-spectrum vaccine and 70% twice-lifetime screening with HPV-VAT can be achieved, and this would be cost-effective.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

LONG TERM NATURAL HISTORY OF ORAL HPV OVER 8 YEARS OF FOLLOW-UP AMONG HIV-INFECTED AND UNINFECTED ADULTS

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Introduction: Short-term natural history studies have shown that most people clear oral HPV infections within 1-2 years. However, long-term natural history studies of oral HPV remain lacking.
Methods: Multicenter AIDS Cohort Study and Women's Interagency HIV Study participants were evaluated semi-annually using 30-second Scope oral rinse and gargle specimens over up to 8 years as part of a natural history study. Initially, 447 subjects were followed for four years as part of the POPS Study, and a subset of 133 showing persistent oral infections at the last POPS visit had an additional visit in the MOUTH study (median 2.5 years after last POPS sample). Extracted DNA from oral rinse/gargle specimens were amplified using PCR and type specification performed 13 types of oncogenic HPV, using PGMY09/11 primers and Roche linear array (POPS study) and SPF10 primers and LIPA (MOUTH study).
Results: The majority of oncogenic oral HPV infections cleared quickly with median time to clearance of 1.0 year [IQR=0.5-2.7]. After 7 years of follow-up, 99% of incident but only 90% of prevalent infections had cleared. At 7 years, 37 oncogenic oral HPV infections were persistently detected, representing 5.5% of infections. Most (76%) oral HPV16 infections cleared following ≤3 (HPV16+) visits. One subject tested HPV16+ at 13 visits over 7.5 years. Adjusted analyses show clearance was lower among prevalent than incident infections (aHR=0.44, 95%CI=0.35-0.55), among men (aHR=0.74 95%CI=0.60-0.91), for older participants (aHR/10 years age=0.81, 95%CI=0.73-0.89), and among people living with HIV (PLWH, aHR=0.76 95% CI=0.60-0.95). Results were similar when analyses were restricted to HPV16-infected participants, solely prevalent, and only incident infections.
Conclusions: Most oncogenic oral HPV infections cleared quickly and long-term persistence was rare in these data. Further, clearance may be lower in men, older individuals, and PLWH.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

RANDOMIZED TRIAL TO INCREASE ADHERENCE TO CERVICAL CANCER SCREENING GUIDELINES FOR YOUNG WOMEN

A.-B. Moscicki[1], H. Thiel De Bocanegra[2,3], C. Chang[4], C. Dehlendorf[5,6], M. Kuppermann[7], G. Sawaya[7,8], S. Navarro[2], F. Wyand[9], D. Guido[10], Y. Duron[11], S. Vangala[12], X. Zhou[12], D. Elashoff[12]
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Introduction: Uptake of these new cervical cancer (CC) screening guidelines has been low in the US for several reasons including women's expectation for annual tests. **OBJECTIVES** To evaluate a provider-centered intervention with and without the addition of a patient-centered education tool to promote adherence to CC screening guidelines.
Methods: The design was a clustered randomized trial using individual Family Planning, Access, Care and Treatment (FPACT) clinics. Fourteen clinics were randomized to 1 of 2 intervention arms: 1) ASCCP guideline's mobile application tool for providers only (ProvAPP), and 2) mobile APP plus patient-centered educational tool (ProvAPP+Tab). The Tab was a community-driven patient education tool using a tablet provided at the time of check-in. Each arm was compared to FPACT clinic control groups (no intervention) in a 2:1 ratio. We used Family PACT claims data for 18 months prior to and 18 months during the intervention to examine by age, the average interval between cytology specimens using a Poisson regression model. Differences in the percent change in each arm was also examined.
Results: The ProvAPP+Tab arm achieved an 18-month Pap rate of .52(95% CI, 0.37, 0.74) and the ProvAPP+Tab control group had a rate of 0.68 (95% CI, 0.53, 0.08) (p=ns). The ProvAPP arm and their control group achieved an 18-month rate of 0.44 (95% CI 0.33, 0.58) and 0.41 (95% CI 0.34, 0.51) (p=ns), respectively. The 18-month Pap rate changed from .74 to .52 (-.22) for the ProvAPP+Tab group compared to a change from .77 to .68 (-0.09) in the ProvAPP+Tab control group (p=0.02). The change in 18-month Pap rate was similar for the ProvAPP and ProvAPP control.
Conclusions: Overall, we observed a greater percent decrease in the Pap rates for the ProvApp+Tab group than its control suggesting that this patient-centered tool may be useful in educating women about new guidelines.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

EVALUATION OF ASSAYS TO MONITOR HPV-16/18 RESPONSES TO SINGLE-DOSE HPV VACCINES

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Introduction: Ongoing trials to demonstrate efficacy/non-inferiority of single dose HPV vaccination will use protection against persistent infection with targeted types as the primary endpoint, but markers of immune response are becoming increasingly important outcomes to support efficacy findings. Whether existent assays are sufficiently robust to measure the lower levels expected following single dose vaccination is unknown.
Methods: We evaluated the reproducibility/validity of assays measuring HPV-16/18 immunological responses overall and by number of doses in serum from 510 individuals receiving one, two or three doses of Cervarix (CVT) or Gardasil (IARC India) up to 36-months following vaccination. Serum was evaluated blindly in duplicate by simplex (ELISA), multiplex (LIA-4, M9ELISA, GST-L1, VLP-MIA), and high-throughput neutralization (HT-PBNA) assays. The SEAP-NA constituted the gold standard to which other assays were compared. Reproducibility was assessed by %CV. Pearson correlation (continuous) and weighted-kappa (quartiles) were used to assess validity. Determinants of seroreversion were evaluated by chi-square.
Results: HPV-16: Seropositivity range was 97.1–99.4% for single dose, 98.7–99.8% overall. Assay reproducibility (%CV) range was 4.0–18.0% for single dose, 2.9–19.5% overall. Correlation with SEAP range was 0.43–0.85 for single dose, 0.51–0.90 overall. Weighted kappas range was 0.34–0.82 for single dose, 0.45–0.84 overall.
Conclusions: These results support the utility of existent multiplex/high-throughput assays to monitor immune response following single-dose HPV vaccination. Results for individual assays will be presented.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

HPV KINETICS IN GENITAL INFECTIONS IN YOUNG WOMEN

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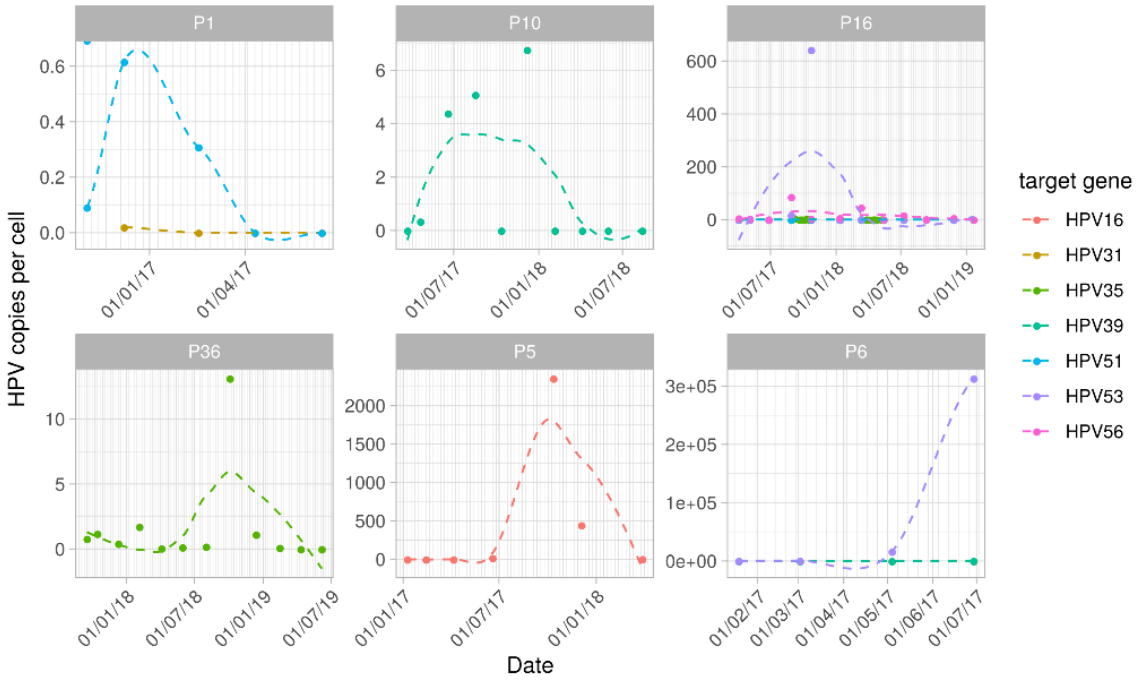
Introduction: The prevalence of human papillomavirus (HPV) genital infections is highest in young adults (age 18-25). It has been estimated that more than 90% of these infections clear naturally within three years. However, we still have a limited mechanistic understanding of the factors that drive infection clearance or persistence. Furthermore, the temporal variations of HPV virus load, also referred to as 'kinetics', are poorly known.
Methods: The PAPCLEAR clinical study conducted at the Montpellier University Hospital (France) follows longitudinally 150 young women aged from 18 to 25 in the local STI detection centre. The follow-up is still ongoing for a third of the participants. Every 2 or 4 months (depending on their HPV status), women visit the clinic for a gynaecological exam during which multiple samples are collected. In particular, in addition to HPV detection and typing, samples are used to measure local HPV viral load, quantify cytokines in cervical secretions, type the vaginal microbiota, obtain estimates of local immune cell counts and measure circulating HPV antibodies.
Results: In HPV positive participants who are not lost to follow-up early, we find consistent HPV genotype detection patterns between visits. When analysing the number of HPV copies per cell, we observe viral load kinetics patterns typical of acute infections in some participants (see original results in Figure 1). Finally, we report variations by several orders of magnitude in virus load between participants. These virus load kinetics are currently being analysed in the light of HPV antibody titres.



Conclusions: We report with unprecedented details the dynamics of HPV viral load in genital infections in young women. We show that clearing HPV genital infections exhibit kinetics patterns that are typical of acute infections. Further analyses of HPV antibody titres during the infection, local cytokines and immune cells will provide us with a better mechanistic understanding of infection clearance.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

SEQUENTIAL ACQUISITION OF HPV INFECTION BETWEEN GENITAL AND ANAL SITE AMONG MEN AND WOMEN IN LIUZHOU, CHINA: AN OBSERVATIONAL COHORT STUDY

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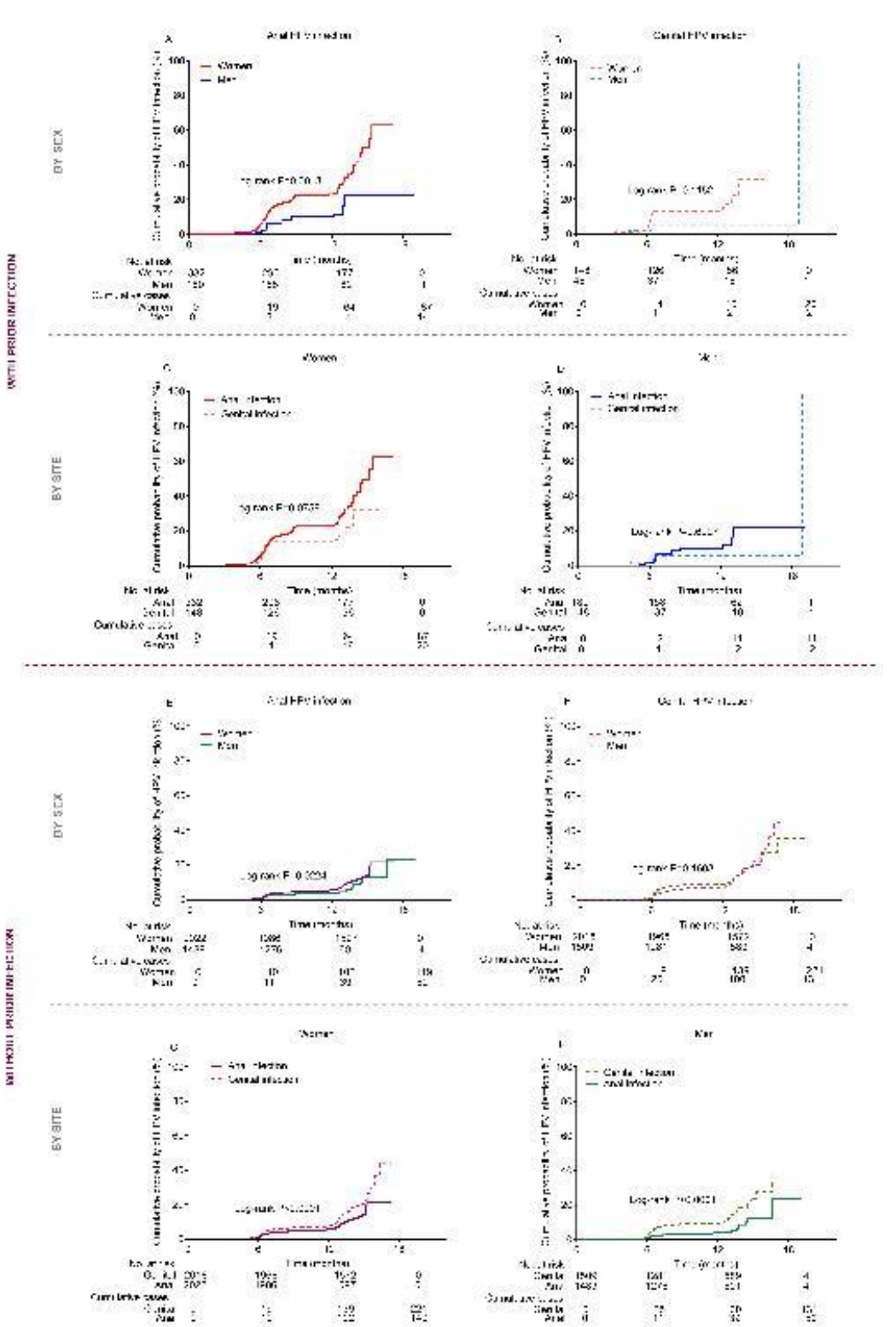
Introduction: The aim of this study was to assess the sequential risk of acquiring a concordant HPV infection in genital (or anal) site following an anal (or genital) HPV infection among men and women.
Methods: Independent specimens from 2309 male and 2378 female genital and anal sites were collected at month 0, 6 and 12. Relative ratios (RRs) and 95% confidence intervals (CIs) were calculated by Cox regression to analyze the sequential acquisition of HPV infection in genital (or anal) site following a concordant HPV infection in anal (or genital) site among men and women.
Results: The incidence rates of anal HPV infection were 8.8 (95% CI: 5.2-14.8) and 3.8 (95% CI: 2.9-4.9) per 1000 person-months in men with or without prior genital HPV infection of the same type (RR , 2.6; 95% CI: 1.4-4.6); these values were 25.9 (95% CI: 21.0-31.9) and 6.2 (95% CI: 5.3-7.3) in women (RR, 4.4; 95% CI: 3.4-5.8). Women with prior anal HPV infection also had a higher risk of subsequent genital concordant HPV infections (RR, 1.9; 95% CI: 1.2-3.1); whereas for men, significant difference was not found (RR, 0.7; 95% CI: 0.2-1.9). Among participants without prior anogenital HPV infection, the incidence rates were higher in genital site than anal site in both men and women (both $P < 0.0001$); however, among those with prior infection of the other site, females became more likely to acquire anal infection than genital infection, although the difference was not statistically significant ($P = 0.0758$, Figure



1).

Conclusions: Both men and women with prior HPV infection at genital (or anal) site had higher risk to

sequentially acquire concordant HPV infection at anal (or genital) site. Autoinoculation might play an important role for anogenital HPV infections in both sexes, especially for anal HPV infection in women.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

HIGHER RISK FOR RECENT HPV EXPOSURE AMONG VACCINATED MEN: A CANADIAN IMMUNIZATION RESEARCH NETWORK-FUNDED STUDY AMONG YOUNG MEN WHO HAVE SEX WITH MEN

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Introduction: In 2015/16, HPV vaccine was made available free of charge for gay, bisexual, and other men who have sex with men (gbMSM) aged ≤26 years in some Canadian provinces. We tested competing hypotheses that uptake in the first eligible cohort for these programs would be more likely among men at higher risk for ongoing HPV exposure ("core group") versus among those at lower risk ("worried well").
Methods: We analysed baseline data from men aged 16-26 years enrolled in the community-recruited Engage Cohort in Vancouver, Toronto, and Montreal. Self-identified gbMSM were recruited using respondent-driven sampling (RDS) in 2017-19. Men self-completed a questionnaire; underwent testing for chlamydia and gonorrhea; and self-collected anal specimens for HPV-DNA testing. Markers of possible recent HPV exposure were: (1) number of sexual partners within the past 6 months; (2) self-reported diagnosis with a sexually transmitted infection within the past 6 months; (3) laboratory-confirmed gonorrhea or chlamydia at baseline; and (4) anal infection with non-vaccine-preventable HPV types at baseline. Using chisquared tests, we compared proportions between men who received HPV vaccine (≥1 dose) and men who had not; proportions are RDS-unadjusted.
Results: Among 457 men as of 02/2019 (4% HIV-positive), vaccine uptake was 48.8%. For all risk markers (except lab-confirmed chlamydia/gonorrhea), proportions were higher among vaccinated men (Table). Notably, they had a higher prevalence of non-vaccine preventable types (45.2%) than did unvaccinated men (35.2%).

Table. Risk markers of recent HPV exposure among gay, bisexual, and other men who have sex with men, by vaccine status, among men aged ≤26 years

Marker	Vaccinated men % (n)	Unvaccinated men % (n)	P-value
Number of sexual partners in past 6 months			0.0004
One	7.6 (17)	17.1 (40)	
2-5	33.6 (75)	42.3 (99)	
6-10	24.7 (55)	17.5 (41)	
>10	34.1 (76)	23.1 (54)	
Self-reported diagnosis with an STI in past 6 months	20.6 (45)	9.0 (21)	0.0004
Laboratory-confirmed chlamydia or gonorrhea	9.0 (20)	13.8 (32)	0.1096
Anal infection with non-vaccine preventable HPV type(s)	45.2 (76)	35.2 (62)	0.0583

Conclusions: Among gbMSM in a setting with no financial barriers, early adopters of HPV vaccine were at higher risk for recent sexual exposure to HPV according to 3 of 4 markers we examined, consistent with our “core group” hypothesis. Although maximum vaccine efficacy is achieved when received prior to any sexual exposure, our findings suggest that existing programs are having success in reaching men who would benefit from protection the most.

ORAL SESSION 12: EPIDEMIOLOGY I. NATURAL HISTORY AND RISK FACTORS

EXPLORATION OF INDIVIDUAL HUMAN PAPILLOMAVIRUS (HPV) TYPES AND TYPE REPLACMENT AFTER VACCINE INTRODUCTION, OVERALL AND BY RACE, UNITED STATES

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Introduction: Type replacement with non-vaccine-targeted HPV types has been raised as a possible concern following HPV vaccine introduction. However, HPV type replacement has not been consistently observed. Routine vaccination was recommended in 2006 for U.S. females age 11-12 years and catch-up through age 26. Most vaccine used through 2014 was quadrivalent vaccine (4vHPV); 9-valent vaccine, introduced in 2015, was the only vaccine available after 2016. Differences in HPV-type specific prevalences by race have been observed in the United States. We explored type replacement overall and in non-Hispanic white (NHW) and non-Hispanic black (NHB) females.
Methods: We analyzed HPV DNA positivity from self-collected cervicovaginal specimens among sexually-experienced females 14-29 years who participated in the National Health and Nutrition Examination Survey. HPV DNA was detected using an L1 consensus PCR assay. We estimated weighted prevalences of 14 individual high-risk types (HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68) overall and for NHW and NHB females. We compared prevalences in the most recent period with available data (2013-2016) with the pre-vaccine period (2003-2006).
Results: HPV 16 and 18 prevalences were lower in 2013-2016 than in 2003-2006 overall (16: 3.4% vs 10.2%, p<0.01; 18: 1.0% vs 2.7%, p<0.01) and among NHW (16: 3.8% vs 11.6%, p<0.01; 18: 0.9% vs 2.7%, p<0.01), and NHB (16: 4.2% vs 9.9%, p<0.05; 18: 3.1% vs 4.9%, NS) (Table). Any non-vaccine high-risk type prevalences were similar in the 2 periods, overall and for each race. In 2013-2016, HPV 33 and 56 were lower overall (p<0.05); no non-vaccine high-risk type was significantly higher overall or in either race.

Table: Prevalence of high-risk (HR) HPV types among sexually experienced 14-29 year-old females, NHANES, 2003-2006 and 2013-2016

	Overall			Non-Hispanic white			Non-Hispanic black		
	Weighted Prevalence (95% CI)		P-value	Weighted Prevalence (95% CI)		P-value	Weighted Prevalence (95% CI)		P-value
HPV type	2003-2006 N = 1447	2013-2016 N = 1081		2003-2006 N = 552	2013-2016 N = 357		2003-2006 N = 423	2013-2016 N = 232	
Any 14HR	34.7 (31.6-37.9)	29.5 (26.2-33.1)	**0.03**	32.7 (29.1-36.6)	29.1 (24.0-34.8)	0.27	46.9 (40.3-53.7)	44.1 (39.3-49.1)	0.50
Any 16/18	12.3 (10.6-14.3)	4.5 (3.2-6.3)	**<0.01**	13.7 (11.3-16.6)	4.8 (2.8-7.9)	**<0.01**	13.0 (9.0-18.4)	7.3 (4.7-11.2)	**0.04**
Any non-vaccine HR	30.1 (26.9-33.6)	27.3 (23.8-31.1)	0.24	27.6 (23.9-31.7)	26.7 (21.4-32.8)	0.79	41.8 (34.6-49.3)	41.4 (36.3-46.6)	0.92
16	10.2 (8.2-12.7)	3.4 (2.3-5.0)	**<0.01**	11.6 (8.8-15.3)	3.8 (2.2-6.6)	**<0.01**	8.9 (5.9-13.3)	4.2 (2.3-7.8)[†]	**0.04**
18	2.7 (1.8-4.0)	1.0 (0.6-1.9)	**<0.01**	2.7 (1.5-4.7)	0.9 (0.3-2.4)[†]	**0.04**	4.9 (2.9-8.3)	3.1 (1.7-5.5)	0.25
31	2.6 (1.7-4.1)	2.1 (1.3-3.5)	0.53	1.8 (0.8-3.7)[†]	1.9 (0.9-4.0)[†]	0.88	3.2 (1.9-5.2)	3.5 (1.6-7.2)[†]	0.86
33	1.9 (1.0-3.7)[†]	0.5 (0.1-1.7)[‡]	**0.049**	2.0 (0.8-4.8)[†]	0.7 (0.2-3.0)[‡]	0.20	3.3 (1.4-7.3)[†]	0	**<0.01**
35	1.9 (1.2-3.0)	2.6 (1.8-3.9)	0.29	1.0 (0.3-2.9)[†]	2.6 (1.4-4.5)	0.08	6.3 (3.6-11.0)	5.6 (2.8-10.9)†	0.78
39	5.4 (4.0-7.3)	4.3 (2.9-6.4)	0.36	6.2 (4.2-8.9)	4.8 (2.7-8.6)	0.46	3.8 (2.2-6.7)	3.0 (1.7-5.2)	0.53
45	2.3 (1.6-3.5)	3.1 (2.2-4.5)	0.28	2.1 (1.0-4.2)[†]	3.6 (2.2-6.1)	0.19	3.7 (1.8-7.4)[†]	4.7 (2.4-8.9)[†]	0.63
51	5.8 (4.5-7.6)	5.8 (4.4-7.6)	0.98	5.3 (3.5-7.9)	6.1 (3.9-9.5)	0.61	9.8 (6.9-13.6)	8.4 (5.0-13.6)	0.59
52	6.7 (5.3-8.4)	4.9 (3.6-6.6)	0.09	6.2 (4.2-9.2)	3.8 (2.2-6.4)	0.12	11.6 (8.1-16.4)	11.2 (7.2-17.3)	0.90
56	4.4 (3.1-6.2)	2.6 (1.8-3.7)	**0.04**	4.4 (3.0-6.5)	2.4 (1.3-4.4)[†]	0.06	5.3 (2.9-9.6)	3.5 (1.9-6.6)[†]	0.36
58	2.4 (1.6-3.6)	2.5 (1.7-3.7)	0.82	2.5 (1.4-4.5)	2.6 (1.5-4.5)	0.92	3.2 (2.1-5.0)	4.4 (2.3-8.1)[†]	0.45
59	5.5 (3.9-7.7)	3.9 (2.7-5.5)	0.16	4.8 (2.9-7.9)	3.1 (1.4-6.7)[†]	0.33	7.6 (4.3-13.3)	6.6 (3.6-11.8)	0.73
66	5.9 (4.4-7.7)	6.0 (4.3-8.3)	0.91	4.9 (3.6-6.8)	6.7 (3.9-11.3)	0.35	8.1 (4.5-13.9)	8.3 (5.4-12.6)	0.93
68	1.8 (1.1-3.0)	2.0 (1.3-3.0)	0.78	1.4 (0.6-3.4)[†]	1.3 (0.6-2.9)[†]	0.85	3.0 (1.6-5.3)	5.4 (3.1-9.5)	0.16

NHANES, National Health and Nutrition Examination Survey
14HR, HPV types detected by clinical HPV tests: HPV 16/18/31/33/35/39/45/51/52/56/58/59/66/68
[†]Relative standard error >30% and ≤50%
[‡]Relative standard error >50%

Conclusions: Within 8 years of vaccine introduction, HPV 16 and 18 prevalences declined overall and among NHB and NHW females. Although prevalence estimates for some types not targeted by 4vHPV

appeared higher in 2013-2016, these minor differences are likely due to chance (or random variation) rather than type replacement.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

TRIAGING HPV POSITIVE WOMEN WITH LOW-GRADE CYTOLOGY: EVIDENCE FROM 10 YEAR FOLLOW-UP OF THE ARTISTIC TRIAL COHORT

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Introduction: New HPV infections often exhibit low-grade dyskaryosis but are likely to clear without intervention. Screening programmes in Europe refer these women to colposcopy without delay, but is this the best management?
Methods: The ARTISTIC trial cohort (N=24,510) were recruited in Manchester 2001-03 and traced for CIN3 and cancer incidence through national registration until December 2015. Long-term CIN3 risks associated with different triage strategies for HPV+ women with borderline and low-grade cytology were estimated.
Results: The 10 year cumulative risk of CIN3+ was much higher for women with HPV16/18 infection at baseline (19.4%, 95%CI:15.8-23.8) than for those with other HPV types (7.3%, 95%CI:5.4-9.7). Sixty percent of the women (568/944) had non 16/18 HPV infections, of which 40% cleared after 6 months. Among the 110 women with a new HPV infection, the 10 year cumulative CIN3+ risk was 6.4% (95%CI:3.1-12.9), approximately half the risk estimated from baseline (12.1%, 95%CI:10.2-14.4).
Conclusions: Immediate referral of all HPV+ women with borderline or low-grade cytology will not be cost-effective, particularly in women who have tested HPV negative in the previous screening round. The CIN3 risk is confined to women with persistent type-specific HPV so partial genotyping test assays identifying HPV16/18 as a minimum are essential for efficient risk stratification. Immediate referral to colposcopy for HPV+ women with low-grade cytology may be unnecessary and women can safely be retested to identify those with persistent HPV. Prevalent cancers, including all 10 in ARTISTIC, almost always present with high grade cytology. Of the HPV+ women with low-grade dyskaryosis referred to colposcopy in England in 2017-18, 38% showed normal colposcopic appearance and only 0.12% were diagnosed with cervical cancer. The minimal risk of invasive cancer that has progressed beyond stage 1A must be weighed against the advantages for patients and savings from reducing the number of referrals to colposcopy.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

HPV18 WHOLE-GENOME SEQUENCE DATA REVEALS IMPORTANT ASSOCIATIONS OF SUBLINEAGES WITH HISTOLOGY-SPECIFIC CANCER RISK

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Introduction: HPV18 is the second most carcinogenic HPV type and is disproportionally associated with adenocarcinoma compared to squamous cell carcinoma. HPV18 can be classified into 10 sublineages (A1, A2, A3, A4, A5, A6, B1, B2, B3, C). Little is known about the association between HPV18 lineages/sublineages and cervical cancer risk.
Methods: To assess HPV18 genetic variation with worst histologic outcome, we whole-genome sequenced viral DNA from 1,134 HPV18-positive women with CIN2 (n=206), CIN3 (n=145), SCC (n=9), AIS (n=72), adenocarcinoma (n=30), or ≤CIN1 (controls; n=672) from the NCI-Kaiser HPV Persistence and Progression cohort study using custom Ion Torrent AmpliSeq panels. Using the most common A3 sublineage as reference, we investigated the risk of all other sublineages for each histologic outcome and tested whether the risk was modified by a woman's race/ethnicity. Fisher exact tests and logistic regression were used to estimate the odds ratios and 95% confidence interval.
Results: After excluding women with HPV16 coinfections (n=162), the A1 sublineage conferred significantly increased risks of both squamous and glandular precancer/cancer (OR=1.7, 95%CI 1.0-2.7, and OR=2.4, 95%CI 1.5-4.1, respectively). A1 was previously named an Asian-American lineage because it is overrepresented in Asia. Stratified analyses showed that self-reported Asian women with A1 had increased risks of cervical cancer compared to all other women (OR=3.9, 95%CI 1.2-12.5). B2 was associated with increased risks of adenocarcinoma and SCC (OR=11.4, 95%CI 2.0-65, and OR=22.8, 95%CI 1.8-286, respectively), but not CIN3 and AIS. In contrast, B3 was associated with a decreased risk of AIS and adenocarcinoma (OR=0.15, 95%CI 0.004-0.91). We discovered a new sublineage, named here as A6, which was associated with a strong specific increased risk of adenocarcinoma only (OR=7.6, 95%CI 1.4-40.9).
Conclusions: Our data indicates that there are important precancer/cancer risk differences among HPV18 sublineages by histologic outcome.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

CIN2+ CASES MISSED BY LBC OR HPV TESTING AT 48-MONTH EXIT: HPV FOCAL CERVICAL CANCER SCREENING TRIAL

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Introduction: The HPV FOCAL Trial, conducted within an organized screening program, compared high-risk HPV (hybrid capture 2) testing to liquid-based cytology (LBC) for primary cervical cancer screening; the 48 month exit screen was HPV/LBC co-testing; and cumulative CIN2+ was a primary endpoint.
Methods: 19,009 women aged 25-65 were randomized into the HPV and LBC arms. HPV arm: baseline HPV testing and if negative, exit at 48 months. LBC arm: baseline LBC testing; if negative, LBC screened at 24 months; if negative exit at 48 months. Women diagnosed with CIN2+ during the trial exited at time of diagnosis. At exit, women were referred to colposcopy if HPV positive and/or LBC ≥ASCUS. We present case details from both arms where the LBC or HPV test failed to detect CIN2+ at the exit co-test.
Results: At exit, 25 LBC arm CIN2+ cases were missed by LBC but detected by HPV testing (LBC negative/HPV positive), while 3 HPV arm cases were missed by HPV testing (HPV negative/ LBC ≥ASCUS). Of the missed LBC arm cases, 24/25 were baseline LBC negative and one was baseline LSIL with negative colposcopy; 22/24 baseline LBC negatives were also LBC negative at 24 months. In the HPV arm, 2 of 3 missed cases were baseline HPV negative. One was baseline HPV positive/LBC negative with HPV negative/ASC-H findings at 12 months and negative colposcopy.
Conclusions: At the HPV FOCAL exit co-test, 25 CIN2+ cases were missed by cytology compared to 3 by HPV testing. During the trial, HPV testing detected CIN2+ earlier (at baseline or 12 months), leading to a lower "missed" CIN2+ rate at trial exit. In addition, multiple LBC screening rounds failed to detect some CIN2+ cases that were detected by HPV screening. These data support the higher sensitivity of HPV testing for cervix screening.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

CANCER CASES IDENTIFIED IN A RANDOMIZED IMPLEMENTATION OF HVP-SCREENING IN THE NORWEGIAN CERVICAL CANCER SCREENING PROGRAMME

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Introduction: Introduction: High risk Human Papilloma Virus (HPV) screening was implemented in a randomized controlled fashion in three counties in Norway from February 2015 until April 2018. We present detailed evaluation of the cancer cases identified.
Methods: Methods: The implementation involves women between 34-69 years in three Norwegian counties, counting approximately 285.000 women. In Norway, the follow-up algorithm after abnormal screening test has been more aggressive for HPV screening than for cytology screening, referring an increased number of women to colposcopy, and potentially earlier detection of cancers. Cancer cases are identified for both women allocated to HPV test or cytology. An early concluding cohort was used for a more unbiased comparison of the cancer cases. Descriptive analyses of screening results, screening history, FIGO-stadium and age of the cancer-diagnosed women are presented.
Results: Results: Approximately 200.000 women have been screened, half with HPV test and half with cytology. Around 124.000 women had at least 18 months follow-up, and 102 cancer cases are diagnosed so far; 63 cases after HPV screening (49 squamous cell carcinoma, 12 adenocarcinoma, 1 other cervical cancer type) and 39 after cytology screening (30 squamous cell carcinoma, 7 adenocarcinoma, 2 other cervical cancer type). Majority of the cancers are diagnosed after direct referral to colposcopy. More than 60% of the women diagnosed with cancer are under-screeners/non-screeners. Around 75% of the cancers were related to HPV16 and HPV18, and the majority of the cancers were FIGO stadium I. Updated results will be presented.
Conclusions: Conclusion: Most cancer cases identified in the enrolment represent undiscovered premalignant lesions of previous screening rounds, and the actual number of cancer cases should be comparable between the two groups. Our early concluding cohort show a slight increase in the number of diagnosed cancer cases after primary HPV test, and the number of diagnosed cases should be followed closely.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

RANDOMIZED IMPLEMENTATION OF HPV-SCREENING IN NORWAY: REAL-WORLD DATA

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Introduction: Norway is in the process of implementing highrisk human papilloma virus (hrHPV) testing every fifth year for women aged 34 to 69 years. Between February 2015 and April 2018, approximately 199 000 women, living in three counties in Norway were assigned hrHPV testing or LBC screening based on even/odd day of birth. From January 2019 a gradual and partly randomized implementation of hrHPV screening was initiated to the remaining 15 counties in Norway with the aim of completion within December 2021. The results from LBC screening is closely compared with hrHPV screening (health service study trial number 006_2014_10_RHS).
Methods: A shift of primary cervical screening from cytology to hrHPV detection introduce a major change in the technical and logistical infrastructure for screening. Comparative and descriptive analyses of screening attendance, primary screening results (cytology/HPV status/genotype), number of screening tests and biopsies and number of cervical intraepithelial neoplasia grade 2, 3 and cervical cancer (CIN2+) are reported.
Results: For the three pilot counties, screening attendance by age was similar in HPV screening and LBC screening, being 53,6% vs 52,3% after 1st and 31,8% vs 32,4% after 2nd reminder, respectively. The proportion of screeningtest positives was 5.4% in LBC screening and 6.5% in HPV screening, and declined by increasing age. HPV16/18 were detected in 28% of hrHPVpositives. Compared to LBC screening, we observed 40% more biopsies all over and 50% more CIN3+ in HPVscreening. Updated results for all counties will be presented.
Conclusions: HPV screening was well accepted and detected more precancers, suggesting that replacing LBC screening with HPV screening is a good strategy. Randomized implementation of HPV screening allows monitoring the performance of novel technology in reallife, reassuring the overall high performance of the program and mitigating the transition.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

EVALUATING COMBINED SCREENING AND TRIAGE STRATEGIES IN 4,600 WOMEN FROM THE IMPROVING RISK INFORMED HPV SCREENING (IRIS) STUDY

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Introduction: Many countries are currently switching from Pap cytology to high-risk human papillomavirus (HPV) testing as the primary cervical screening method. While a negative HPV test provides great reassurance that the risk of cervical cancer is very low over the next 5-10 years, additional triage is required to identify the subset of women with a positive HPV test who require colposcopy and biopsy. We developed the 'Improving Risk Informed HPV Screening' (IRIS) Study to evaluate screening and triage strategies in a large population from an organized screening program.
Methods: From 79,798 women ages 25-65 undergoing cotesting at Kaiser Permanente Northern California (KPNC) who were enrolled between 2016-2018, we selected cervical specimens from 4,619 women to evaluate combined screening and triage strategies. In all specimens, three HPV assays (hybrid capture 2, cobas, Onclarity) and two triage assays (cytology and p16/Ki-67 dual stain) were run. Electronic medical records provided clinical HPV and cytology as well as histology outcomes. We evaluated the positivity, sensitivity and specificity of cytology and dual stain for detecting CIN3+ for HPV positive women defined by each of the three HPV assays.
Results: The positivity of cytology ranged from 55%-56%, while the positivity of dual stain ranged from 39%-41%. The accuracy of dual stain was significantly higher compared to cytology (sensitivity of 81%-82% for cytology and 86%-87% for dual stain, respectively; specificity of 45%-46% for cytology and 61%-63% for dual stain, respectively). Overall, there were only minor variations of these estimates depending on the primary HPV assay used.
Conclusions: We demonstrate superior performance of dual stain for triage of HPV-positive women compared to cytology, with higher sensitivity and substantially reduced referral to colposcopy that did not vary depending on HPV assay. Additional biomarkers are currently being evaluated in IRIS that will inform screening, triage, and management guidelines around the world.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

PAST SCREENING HISTORY SHOULD BE CONSIDERED IN RISK BASED CERVICAL SCREENING

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Introduction: In the United States, management of abnormal cervical cancer screening results has emphasized current test results and settings (routine testing, surveillance of abnormal results, post-colposcopic follow-up of <CIN2, and post-treatment for CIN2+). The next generation of risk-based guidelines will also utilize past screening history.
Methods: Using data from 1.5 million women aged 30 to 65 undergoing routine screening with co-testing every 3 years over a period of 15 years at Kaiser Permanente Northern California (KPNC), we estimated immediate and 5-year risks of CIN3+ for each combination of current test results, screening setting, and past history. Risks for cancer/precancer were estimated using logistic regression and proportional hazards models.
Results: A single negative HPV test result was sufficient to greatly reduce risk of any subsequent abnormal test result. The immediate CIN3+ risk of testing HPV-positive with an ASC-US or LSIL cytology or with 2 consecutive HPV-positive, cytology-negatives was halved if their immediately preceding HPV test result was negative. Among women HPV-positive and cytologic high-grade, the immediate CIN3+ risk was reduced by over two-thirds if the immediately preceding HPV test was negative.
Conclusions: In the era of incorporating HPV testing into cervical cancer screening, a single negative HPV test result can strongly reduce the risk of any subsequent abnormal test result. Utilizing such past history can provide more individualized and precise management in cervical cancer screening.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

TRENDS IN CERVICAL CANCER SCREENING EVERY 3 OR 5 YEARS AS PER NEW GUIDELINES IN DAVIDSON COUNTY, TENNESSEE, UNITED STATES WOMEN DURING 2006-2017

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Introduction: Human papillomavirus (HPV) is the most prevalent sexually transmitted disease and causes most cervical cancer. We examined changes in prevalence of cervical cancer screening among Davidson County, Tennessee, United States (U.S.) women associated with 2012 guidelines, which recommend Papanicolaou (Pap) smears every 3 years for women ages 21-65 years or Pap plus HPV detection tests every 5 years for ages 30-65 years.
Methods: We identified women ages 21-65 years enrolled in the Tennessee Medicaid Program (public insurance) and one private insurance plan serving Davidson County from 2006-2017. Current Procedural Terminology codes identified Pap and HPV tests. We evaluated the prevalence of annual Pap smear (U.S. guidelines prior to 2012) and of less frequent screening per 2012 guidelines.
Results: For public and private insurance, percent of women with annual Pap screening declined in all age groups from 2006-2017 (Figure 1). Screening every 3 (Pap) or 5 (Pap+HPV) years declined from 2006-2017 in every age group (Figure 2) for both publicly-insured women: 21-29 years (78% to 61%), 30-39 years (55% to 41%), and 40-65 years (36% to 26%), and for privately-insured women: 21-29 years (77% to 67%), 30-39 years (84% to 80%), and 40-65 years (75% to 71%). Women enrolled in public insurance compared to private had substantially lower average screening in age groups 30-39 years (51% vs. 83%) and 40-65 years (31% vs. 73%).

Figure 1. Annual cervical cancer screening among private and publicly-insured women in Davidson County, 2006-2017

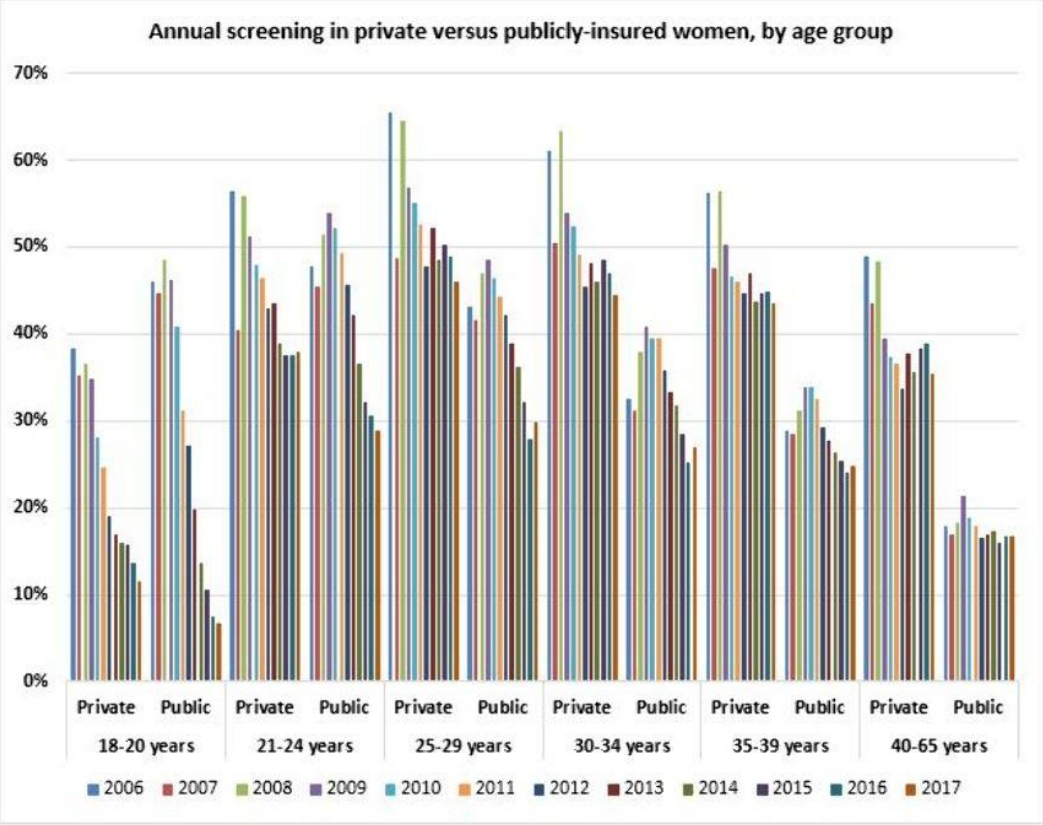
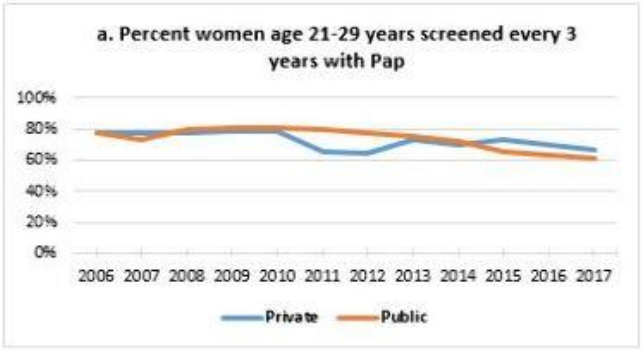
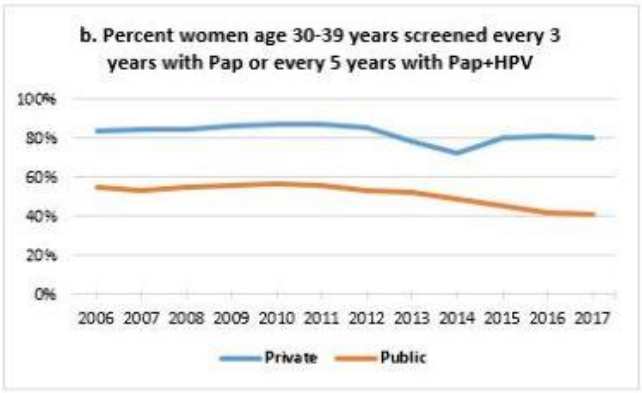
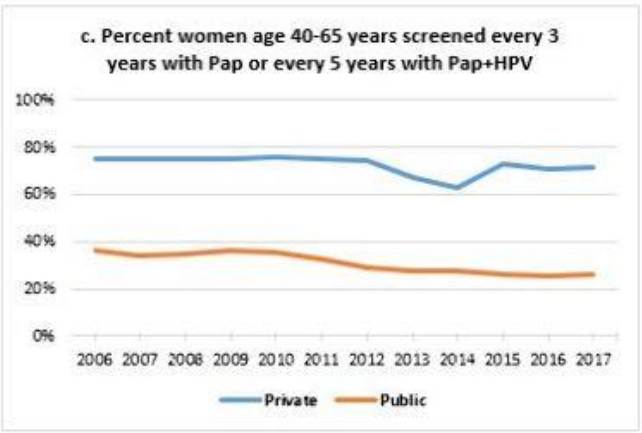


Figure 2. Cervical cancer screening among private and publicly-insured women in Davidson County, 2006-2017: a) Percent women age 21-29 years screened every 3 years with Pap, b) Percent women age 30-39 years screened every 3 years with Pap or every 5 years with Pap+HPV, c) Percent women age 40-65 years screened every 3 years with Pap or every 5 years with Pap+HPV







Conclusions: There have been declines both in annual Pap screening and in screening at the recommended less frequent intervals. Women ages 21-29 years with private and public insurance had similar screening rates. Publicly-insured women ages 30-65 years had substantially lower average screening compared to privately-insured women. By 2017, fewer than half of publicly-insured women ages 30-65 years were appropriately screened. These results highlight declines in cervical cancer screening for all ages and large disparities in screening frequency by insurance type.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

EVOLVEMENT OF CERVICAL CANCER SCREENING PROGRAMS IN LATIN AMERICA

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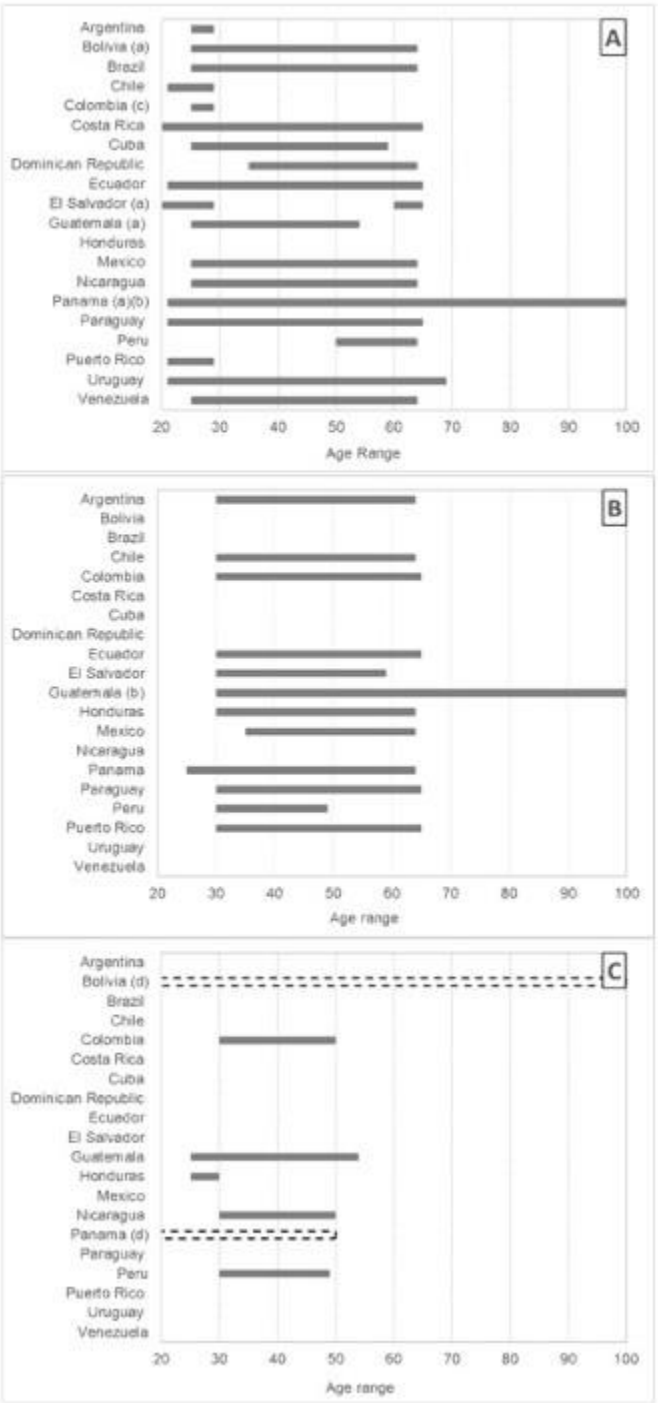
Introduction: Latin America (LA) and the Caribbean represent the region with the second highest cervical cancer mortality worldwide. Besides HPV vaccination, screening is key for WHO´s elimination plan. Cervical cancer screening started in LA in the late 1950s. Intensive research has prompted the development of new technologies and programmatic approaches for pre-cancer screening. We aimed at assessing the evolvement of screening recommendations in LA as indicator of preparedness for reducing disease burden.
Methods: Systematic review of literature and official documentation describing national programs and plans in Latin American countries. Data were triangulated with WHO-PAHO, IARC, and HPV Information Centre reports. Retrieved information on programs characteristics include screening tests, target populations, screening intervals, and program approaches. Data on contextual variables are also collected from official sources, including country income, health expenditure, and health system structure and coverage.
Results: During the last decade, 16 out of 21 countries updated their recommendations on cervical cancer screening. One country doesn't include cytology, 12 introduced HPV testing (4 consider self-sampling), and 8 are using visual inspection. Two countries recommend co-testing; however, simultaneous use of different screening tests is considered by establishing different target populations per test (by age or access to health care), or using them indistinctively. Target populations and screening intervals largely vary. Eight countries recommend screen-and-treat based on VIA (5), VIA-VILI (1), HPV-testing (1), and colposcopy (1). No differences in screening tests by income level are observed but screen-and-treat is more frequent among lower income countries.

Table 1. Latin American countries' profile

Country	Income level	Population	Cervical cancer (ASR per 100 000)		Program last update
			Incidence	Mortality	
Latin Caribbean					
Cuba	Upper middle	11 489 084	14,6	6,0	1999
Dominican Republic	Upper middle	10 882 994	17,1	9,9	2010
Puerto Rico	High	3 659 001	10,2	3,5	2007
Central America					
Costa Rica	Upper middle	4 953 201	11,2	5,6	2007
El Salvador	Lower middle	6 411 557	18,5	9,4	2015
Guatemala	Upper middle	17 245 343	21,1	11,7	2014
Honduras	Lower middle	9 417 165	19,6	12,5	2015
Mexico	Upper middle	130 759 070	11,0	5.8	2013
Nicaragua	Lower middle	6 284 763	21,2	13,3	2010
Panama	High	4 162 607	18,4	8,8	2017
South America					
Argentina	Upper middle	44 688 858	16,7	7,7	2015
Bolivia	Lower middle	11 215 667	38,5	19,0	2009
Brazil	Upper middle	210 867 959	12,2	5,8	2016
Chile	High	18 197 213	12,2	5,0	2015
Colombia	Upper middle	49 464 687	12,7	5,7	2018
Ecuador	Upper middle	16 863 427	17,8	9,0	2017
Paraguay	Upper middle	6 896 916	31,5	16,0	2015
Peru	Upper middle	32 551 811	23,2	10,2	2017
Uruguay	High	3 469 551	12,4	6,0	2014
Venezuela	Upper middle	32 381 223	23,7	10,9	N/A

Source: IARC/WHO - Globocan 2018
N/A: not available

Figure 1. Target population by screening test

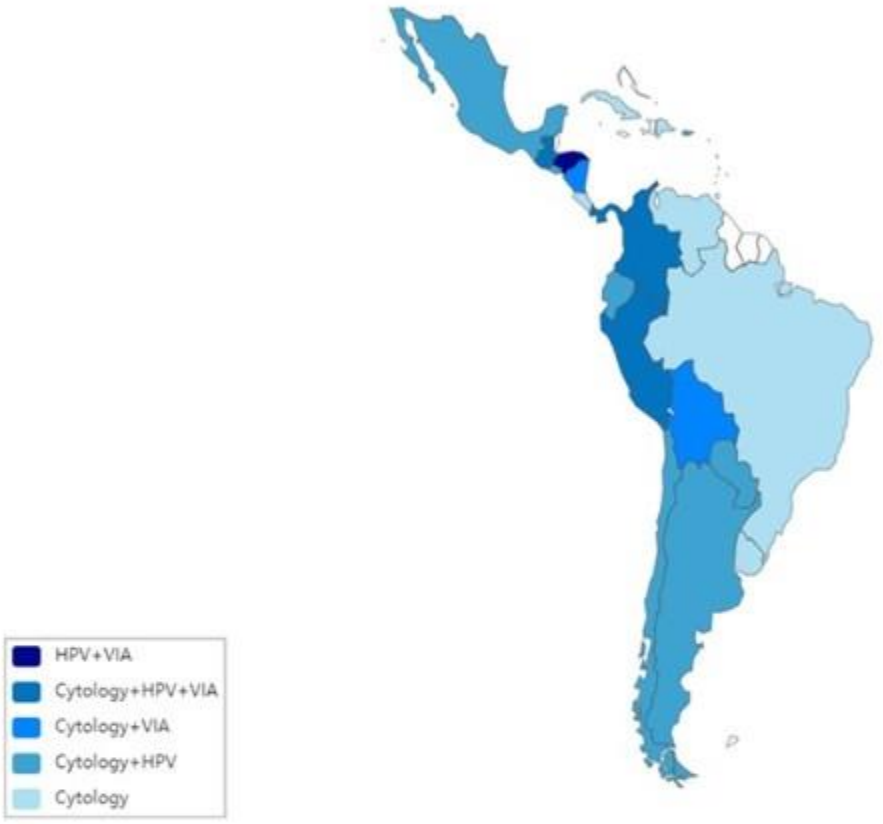


Screening tests:

A) Cytology, B) HPV testing, C) Visual inspection

(a) screening after sexual onset; (b) no age upper limit; (c) screening after sexual onset if sexual onset before 15 years old; (d) no age limits defined, Panama recommends stopping VIA after menopause

Figure 2. Cervical cancer screening tests by country



Conclusions: Cytology-based screening continues to be the most extended practice; however, screening programs have significantly evolved in LA by incorporating research results in national recommendations. Variability in target populations, screening intervals, and programmatic approaches suggest differences in

evidence assessment and the influence of contextual factors in the decision-making process. Further information on implementation status will be provided.

ORAL SESSION 13: SCREENING V. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

IMPACT OF SCALING UP HPV SCREENING IN MALAYSIA

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Introduction: In Malaysia, estimated rates of cervical cancer incidence and mortality in 2020 are 11.7 and 4.4 per 100,000 women per annum, respectively. Whilst some cytology-based screening is in place, coverage remains low, at <30%. Recently, Project ROSE, combining self-sampled HPV testing with a digital health platform, has been evaluated as a potential model by which Malaysia could scale up screening according to the WHO draft strategic target for cervical cancer elimination (70% coverage twice per lifetime).
Methods: We use an extensively validated platform (*'Policy1-Cervix'*) calibrated to Malaysia, taking into account regional variations in disease burden. We then evaluated the impact of scaling up primary HPV screening to 70% coverage with and without broad-spectrum vaccination at 90% coverage. We explored different screening frequencies, from once-lifetime to 5 yearly screening from ages 30-65.
Results: Using a combination of laboratory based HPV testing in Peninsular Malaysia and point-of-care HPV testing in East Malaysia, once-lifetime screening at age 35 results in a national reduction in age-standardised incidence and mortality rates of 27% and 32%, respectively. Increasing to twice-lifetime screening at ages 35 and 45 results in a national reduction in age-standardised incidence and mortality rates of 39% and 48%, respectively. Combining twice-lifetime screening with broad-spectrum HPV vaccination would result in long-term reductions of 91% for both cervical cancer incidence and mortality.
Conclusions: Combining vaccination and twice-lifetime screening would result in long-term cervical cancer incidence and mortality rates of 1.0 and 0.4, respectively, per 100,000 women per annum, and thus Malaysia would achieve cervical cancer elimination as a public health problem. National scale-up of Project ROSE in Malaysia with laboratory based testing across the Peninsula, in combination with point-of-care testing in more remote regions, is critical to achieving burden of disease reduction and elimination of cervical cancer in Malaysia.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

ADVANCING CERVICAL CANCER PREVENTION: THE EFFORT TO INTRODUCE HPV TESTING OF SELF-COLLECTED SAMPLES FOR CERVICAL CANCER SCREENING IN LOW AND MIDDLE INCOME COUNTRIES

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Introduction: Cervical cancer is a leading cause of cancer deaths among women in low and middle-income countries (LMIC). WHO calls for a renewed global effort to eliminate cervical cancer. HPV testing is an accurate and reproducible method that offers great potential to overcome challenges of access to screening. Jhpiego is supporting LMIC to introduce HPV testing for cervical cancer screening and main results of this effort are shared here.
Methods: In 2017-2018, Jhpiego supported a demonstration project in Botswana to assess feasibility and acceptability of introducing HPV testing of self-collected samples for women age 30-49 years, followed by treatment of HPV positive women. Following, Jhpiego continues working collaboratively with Health Ministries to building capacity for the introduction of HPV testing in LMIC.
Results: In Botswana study, of the 1022 women enrolled, 1019 (99.7%) collected samples had conclusive results, with 1018 (99.9%) receiving results. Among HIV-positive women, 230/570 (40%) tested high-risk HPV (hrHPV) positive, of whom 218 (95%) received treatment. Among HIV-negative women, 113/449 (25%) tested hrHPV positive, of whom 108 (96%) received treatment. The vast majority of participants (>95%) found it easy to do self-collection. The successful results of this project has informed the development of policy, guidelines, trainings, M&E and informational materials to support the introduction of HPV testing in country programs. On August 2019, the Botswana MOH, supported by Jhpiego, officially launched the introduction of HPV Testing into national cervical cancer screening program. Currently, Jhpiego continues working to support the expansion of this initiative to Zambia and other four additional countries.
Conclusions: Jhpiego's experience shows that introducing HPV testing of self-collected samples in LMICs is feasible and acceptable and has the potential to greatly improve access to cervical cancer screening. Main challenges are related to system strengthening especially to ensure the continuous availability of essential equipment and supplies to meet demand.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

HPV TESTING, TRIAGE AND TREATMENT FOR CERVICAL PRECANCER IN NICARAGUA WITHIN THE PUBLIC SECTOR HEALTH SYSTEM

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Introduction: In Nicaragua, cervical cancer is the leading cause of cancer death among women. Human papillomavirus (HPV) testing using self-sampling was introduced from 2014–2018 in three provinces under the BMGF-supported effort. We present indicators of screening program reach, HPV prevalence, number of women that had triage, and had treatment, and examine factors associated with follow-up completion.
Methods: We analyzed individual-level data on all women attending HPV-based cervical cancer screening at primary health care centers in 2017 in the target areas. 50,000 *care*HPV tests were allocated to the country for the year. Local guidelines stipulated that screen-positive women should be triaged with Pap or visual inspection with acetic acid (VIA) prior to treatment. Cryotherapy was the primary treatment approach for precancerous lesions. Data were de-identified and extracted from routinely collected forms. Logistic regression analysis was used to identify factors associated with receiving triage and treatment; analyses were adjusted for province, age, and sampling modality (i.e., self- or provider-collected).
Results: In 2017, a total of 44,635 women between 30–64 years of age were screened with HPV, of which 96.6% of women used self-sampling. 6,776 (15.1 %) of women were HPV positive. 3,659 (54.0%) of screen-positive women received triage (n=2,784, 76.1% with Pap, and n=874, 23.9% with VIA). A total of 1,942 (53.1%) of triage-positive women were treated. There was a significant variability between the 3 provinces in delivering triage and treatment. Triage was significantly higher among provider-collected samples and treatment was higher for women triaged with VIA compared to women triaged with Pap (aOR: 20.0, 95% CI: 12.5–25.0, p < 0.001).

Table 1. Overview of results of HPV testing, triage and treatment for cervical precancer in Nicaragua in 2017.

	N	%
Target population	141,637	
Women screened among target population	44,635	31.5
Self-collected samples among women screened	43,105	96.6
HPV-positive among women screened	6,776	15.2
Received triage among HPV-positive	3,656	54.0
Pap triage among women triaged	2,784	76.1
VIA triage among women triaged	872	23.9
Triage-positive among women triaged	915	25.0
Treated among triage-positive	486	53.1
Treated among those with positive Pap triage	132	25.7
Treated among those with positive VIA triage	361	89.8

Abbreviations: HPV: human papillomavirus; VIA: visual inspection with acetic acid.

Conclusions: Introduction of HPV testing resulted in a substantial number of women newly screened for HPV, and uptake of self-sampling was high. Management of screen-positive women remained a challenge, particularly when Pap was used for triage.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

AN INITIAL DESCRIPTION OF THE IMPROVING RISK INFORMED HPV SCREENING (IRIS) STUDY AT KAISER PERMANENTE NORTHERN CALIFORNIA

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Introduction: HPV testing alone or with cytology ("cotesting") is being introduced into primary screening. Because most HPV infections are harmless, additional triage tests must identify HPV-positive women at highest cancer risk. Many strategies for primary screening and triage are available but head-to-head comparisons within the same population are lacking. Additionally, test performance research in context of screening, colposcopy or treatment is needed. The 'Improving Risk Informed HPV Screening' (IRIS) Study was designed to evaluate candidate approaches to screening, triage and management within a large U.S. population-based screening program
Methods: Between 2016-2018 we collected discard cervical cancer screening specimens from women ages 25-65 undergoing cotesting at Kaiser Permanente Northern California. Women were selected according to cotest result. Specimens were aliquoted, stabilized, and stored. Electronic medical records (EMR) provided HPV, cytology and histopathology results as well as demographic and co-factor information. At least one follow-up specimen is collected for all participants and EMR-based follow-up is ongoing.
Results: At baseline, we collected specimens from 79,798 women (4.9% opted out). Women who opted out were slightly older (mean age 44 vs. 39) and more likely to have a negative cotest (20.2% vs. 16.7%). We sampled 55,664 of 59,094 HPV-positive, 10,360 of 16,094 HPV-negative/Pap-positive and 13,527 of 578,355 HPV-negative/Pap-negative women undergoing screening. As of August 2019, follow-up screening specimen(s) have been collected from 52,633 women and histopathology results are available for 40,405 women, including 1,824 CIN3's and 86 cancers.
Conclusions: This cohort study is a unique and highly relevant resource allowing for rigorous evaluation of candidate markers at all stages of cervical cancer screening and follow-up. Sampling of large numbers of HPV-negative women allows to weight back to the entire screening population. The availability of prior and future clinical records allows for ascertainment of previous screening, diagnostic and treatment history prior to and following cotests.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

PAVING THE WAY TO NEW LOW COST METHODS IN CERVICAL SCREENING: SELF-SAMPLED HPV TESTING AND DEVELOPMENT OF AUTOMATED VISUAL EVALUATION OF SMART PHONE IMAGES

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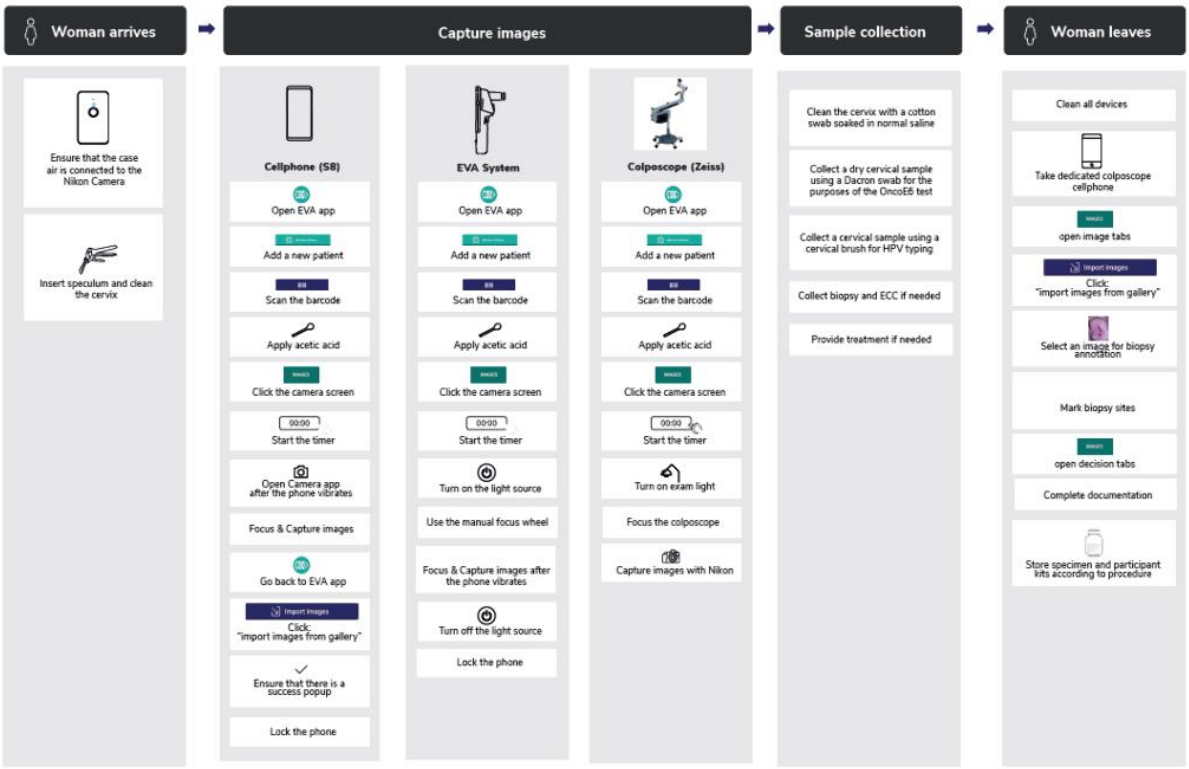
Introduction: Achieving global control of cervical cancer requires new screening strategies to detect precancer that are simple, inexpensive, fast and accurate. We present the results of a novel approach in Nigeria combining: 1) self-sampling and HPV testing with partial genotyping and 2) smart phone based deep-learning algorithm for automated visual evaluation (AVE) of the cervical images for risk based management of HPV-positive women.
Methods: Nearly 10,000 women aged 30-49 years are participating in cervical screening clinics in Ile Ife, Nigeria. Self-samples placed into Specimen Transport Medium (STM) are HPV tested. High risk HPV (hrHPV)-positive women are evaluated in colposcopy clinic, where we are comparing three automated visual triage methods based on: simple cellphone imaging, an enhanced cellphone method (MobileODT EVA System©), and colposcopic photographs. The reference standard of disease is multi-biopsy histopathology. The screening accuracy of combinations of HPV type group and AVE scores are being evaluated. **Figure1:Screening-Program Flow**

Figure2:Colposcopy-room flow



Results: With self-sampling, we were able to screen more than 150 women per day, per clinic, using only two rooms, with more than 6000 women screened to date. Infection with a hrHPV was found in 18% of women and CIN2+ and CIN3+, including 3 cancers, were identified in approximately 6.5% and 2.8% of the hrHPV-positive women, respectively, or approximately 1.2% and 0.5% of the total screening population, respectively. All three methods provided good cervical images. At the meeting, we will have completed the screening and will present the combined HPV type and AVE accuracy in finding CIN2+ and CIN3+.

Conclusions: A cervical pre-cancer/cancer screening and prevention program using HPV testing with colposcopy based triage of women positive for hrHPV is feasible in sub-Saharan Africa. Further analysis of the images obtained will help determine if the program can be improved using deep learning based AVE algorithm while avoiding the need of cytology or colposcopy.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

UPTAKE OF CERVICAL CANCER SCREENING IN ETHIOPIA BY SELF-SAMPLING FOR HPV DNA TESTING COMPARED TO VISUAL INSPECTION WITH ACETIC ACID: A CLUSTER RANDOMIZED TRIAL

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Introduction: In Ethiopia, the standard method of cervical cancer screening is using Visual Inspection with Acetic Acid (VIA). Self-collection based human papillomavirus (HPV) testing is assumed to improve the uptake of screening, especially for hard to reach populations. We investigated whether HPV DNA testing with the self-collection of cervical samples would be associated with increased uptake and adherence to procedures at the population level compared with VIA within defined rural population in Ethiopia.
Methods: A total of 22 clusters (comprising 2356 women aged 30-49 years) were randomised in two arms. Following the community mobilization, women of the clusters were invited to go either to the local health post for a self-collection-based HPV DNA testing (arm A) or Butajira Hospital for VIA screening (arm B).
Results: In the HPV arm, of the 1213 sensitised women, 1020 (84.1%) accessed the health post for self-sampling compared to the VIA arm, where 575 out of 1143 (50.5%) visited the hospital for VIA ($p<0.0001$). Of those women who attended the VIA and HPV arms, 40% and 65.4% adhered to all procedures expected after screening, respectively. Out of women positive for high risk HPV, 122 (85%) attended VIA as a follow-up test.
Conclusions: The trial demonstrated significantly higher levels of population-based uptake and adherence for self-collection HPV testing. Women were more receptive for VIA after their HPV testing result was positive. Self-collection HPV testing can be done at the local health facility and may significantly improve the uptake of cervical cancer screening in Ethiopia.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

IMPLEMENTATION OF STRATEGIES FOR THE PREVENTION OF CERVICAL CANCER IN WOMEN AGED 30 TO 64 YEARS. PARAGUAY 2014-2018 (ESTAMPA STUDY)

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Introduction: Cervical cancer is a public health problem in Paraguay, with low coverage in the national screening program. Therefore, the objective was to evaluate possible individual or combined educational strategies based on information and communication for prevention of cervical cancer in 10,082 women from 16 social territories of Itauguá and San Lorenzo, between 2014-2018.
Methods: A quasi-experimental factorial study was designed, where all the women visited during the population census of the selected social territories received some of the strategies implemented (triptych-T, direct interview-ED); then during the recruitment, sampling of PAP and HPV Test (phone calls-LT and text messages-MT). The analysis of the association between strategies and participation was performed using Chi-square and relative risk (RR) as the measure of association.
Results: There was a global average of 49% participation (4.984 / 10.082). Among the individual strategies implemented, a higher percentage of 55% participation was observed with T; followed by LT (49%); ED (44%) and MT (12%), the participation in T being significantly greater than that of MT (RR: 1.9; 95% CI 1.79-2.13). The combination of ED / LT obtained greater participation (71%) and that of MT / LT had the lowest participation (32%), RR: 2.38; 95% CI 2.18-2.59. Also, 709 women participated with additional strategies (81% were referred by third parties, 10% captured at the time of recruitment and 9% invited by local health agents). Direct contact strategies (EV, LT, ED / LT) had significantly greater participation than those of MT or T or MT / T, RR: 1.47; 95% CI 1.41-1.53. Contact difficulty was the most frequent reason for non-participation (33%).
Conclusions: This is the first local study that analyses the implementation of educational strategies. These results will serve as the basis for designing models of organized screening programs seeking to strengthen coverage in the prevention of cervical cancer.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

SELF-SAMPLING AMONG LONG-TERM NON-ATTENDERS TO CERVICAL CANCER SCREENING IN NORWAY: A PRAGMATIC RANDOMIZED CONTROLLED TRIAL

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Introduction: Attendance to the Norwegian cervical cancer screening program is suboptimal, and 1/6 of screening-eligible women have not had a screening test for at least 10 years. We test whether vaginal self-sampling for human papillomavirus (HPV) may increase cervical cancer screening attendance among long-term non-attending women in Norway.
Methods: During March-August 2019, we invited 6000 women aged 35-69 who had not attended screening for at least 10 years. They were randomized to either receiving (i) a reminder to attend regular screening (controls), (ii) a self-sampling kit, (iii) an offer to order a self-sampling kit. Women returning a positive self-sample were scheduled for follow-up at their regular general practitioner or a gynaecologist.
Results: The trial is on-going. Preliminary results suggest that 11% of women who were offered to order a self-sampling kit returned a self-sample, while 22% of women who received a self-sampling kit directly returned a self-sample. So far, all women with a HPV positive self-sample have complied to follow up. The high-risk HPV positivity rate among returned self-samples is currently 12%. We will present updated results at the conference.
Conclusions: Direct mailing of a self-sampling kit as well as offering to order a self-sampling kit affects attendance to cervical screening among long-term non-attending women, but to different degrees. Compliance to follow-up after a positive self-sample was high. The results from this study will aid decisions regarding if and how self-sampling should be offered in the context of organized screening in Norway.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

EFFECTIVENESS OF A MULTI-COMPONENT MHEALTH INTERVENTION FOR TRIAGE AFTER HPV SELF-COLLECTION: PRELIMINARY RESULTS OF THE ATICA CLUSTER RANDOMIZED TRIAL

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Introduction: High adherence to triage by HPV+ women with self-collected tests is challenging. The ATICA study (Application of Communication and Information Technologies to Self-Collection, for its initials in Spanish), is a hybrid type I trial aimed at evaluating the effectiveness/implementation of a multi-component mHealth intervention aimed at increasing triage adherence among HPV+ women with self-collected tests, compared to usual care. We report preliminary results from the clustered randomized trial.
Methods: Design: 219 community health workers (CHWs) offering self-collection during home visits were randomized (3:2) to the intervention (IG) or the control group (CG). The Multi-component mHealth intervention was weekly SMS messages for 4 weeks, notifying HPV+ women that test results were available and encouraging them to attend the health center, and an e-mail and SMS message sent to CHWs notifying them of women without cytology 60 days after the HPV-test result. Outcomes: Proportion of women with Pap at 60/120 days (post report of the HPV test) Analysis: Generalized estimating equations (GEE) approach to account for the within-CHW (cluster) correlation.
Results: The trial is underway, all women have been recruited and follow-up will finish by November 2019. By 30 June 2019, 4938 women enrolled in the study had a test result; 685 were HPV+ (13.7%) (IG: 411; CG: 274). Analysis of the 220 HPV+ women with follow-up time long enough to measure the primary outcome showed that 59.4% of women in the IG (n=133) had a triage Pap, versus 32.2% in CG (n=87) (RR: 1.78, CI: 1.26, 2.51, p-value=0.0002). Considering the 435 women with at least 60 days follow-up, 42.3% of women in IG had triage versus 24.4% in CG (RR: 1.75, CI: 1.26, 2.43, p-value=0.0002).
Conclusions: ATICA preliminary results indicate that the mHealth intervention is highly effective to increase triage among HPV+ women. Final results will be presented at the Conference.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

BEYOND SCREENING: SYSTEM GAPS RESULTING IN DELAYED DIAGNOSIS AMONG WOMEN SCREENING POSITIVE FOR CERVICAL CANCER

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Introduction: Despite scale-up of cervical cancer screening, women who present to the healthcare system for screening and early diagnosis still end up with significant morbidity and mortality. To identify the bottlenecks within the healthcare system, we evaluated the time spent at each stage from referral until definitive diagnosis among women receiving colposcopy at the gynaecology clinic in a tertiary referral centre, Nairobi, Kenya.
Methods: Screening tests, HIV status and visit dates of women reviewed at the clinic after screening positive between March and November 2014 as part of a departmental quality improvement (CQI) effort. Screening tests included visual inspection (VIA/VILI) and Pap smear. We summarized continuous variables using medians and categorical variables using proportions.
Results: Of the 102 women reviewed, the median age was 40.5 years (IQR: 32, 48). Among 92 women with a HIV status indicated,32(35%) were HIV-infected and only one was not on ART. Among 69 (68%) of the women, referral was based on VIA/VILI, 24 (24%) was based on Pap smear, 3(3%) had both VIA/VILI and Pap smear and 6(6%) of the women were referred based on indications such as menorrhagia and palpable masses. The median time spent within the system (initial referral till review of biopsy findings) was 101 days. (IQR: 74,132). Of these, 35% of the lag was patient-related i.e. time spent between referral and appointment booking at the clinic; between clinic review and colposcopy). 28% of the time was spent at pathology laboratory while 26% of the time was spent within the clinic system. This time distribution did not vary with age, HIV status or screening test.
Conclusions: The average time spent between a positive cervical cancer screening test till a definitive diagnosis of 3.5 months is too long. Strategies to improve efficiency within the healthcare system to shorten this turn-around time need to be evaluated.

ORAL SESSION 14: SCREENING VI. EVALUATION AND IMPACT OF CERVICAL CANCER SCREENING

TOWARDS CERVICAL CANCER ELIMINATION: EVALUATION OF ACCESS TO DIAGNOSTIC SERVICES FOLLOWING REFERRAL TO A SPECIALIST GYNECOLOGIST CLINIC AT A MAJOR REFERRAL HOSPITAL IN KISUMU, KENYA

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Introduction: Women in developing countries bear a disproportionate burden of cervical cancer incidence and mortality. The World Health Organization recommends screening with Visual Inspection with Acetic Acid (VIA), followed by treatment in a “screen-and-treat” approach. We evaluate access to diagnostic services following referral for VIA-positive or suspicious lesions to a gynecologist led colposcopy clinic at a major government referral and teaching hospital in Kisumu, Kenya.
Methods: Data on women referred for colposcopy at a gynecologist clinic at the Jaramogi Oginga Odinga Teaching and Referral Hospital with positive VIA from referral clinics from 2014 to 2017 were abstracted. We determined the proportion of referred women screening positive following colposcopy-based screening by a gynecologist, the proportion accessing diagnostic biopsy, and histological results following positive or suspicious lesions. Treatment ascertainment is ongoing.
Results: Four hundred and five women were evaluated following referral for positive VIA screening or suspicious lesions. Mean age was 40.2 years, mean parity was 4 children, with 53% of women self-reporting positive HIV status. Two-hundred and thirty-three (57.5%) of referred women were found to have positive or suspicious lesions following colposcopy-based screening by a gynecologist. Of these women, 147 (63%) had a biopsy done, and results were available for 110 (74.8%). Eighty-six women did not receive biopsy despite positive colposcopy, primary due to associated costs or lack of supplies. Among women with biopsy results, 25 (22.7%) were benign, 18 (16.4%) had cervical intraepithelial neoplasia grade 1 (CIN1), 9 (8.2%) had CIN2/3, 57 (51.8%) had squamous cell carcinoma (SCC), and 1 (0.9%) had nondiagnostic results.
Conclusions: While drawing from observational, paper-based clinical data with incomplete records, our evaluation demonstrates significant challenges in the cervical cancer prevention cascade at a tertiary referral hospital. This calls for strengthening facilities' ability to adequately evaluate at-risk women, remove financial barriers, as well as invest in database systems to facilitate evaluation.

ORAL SESSION 15: VACCINATION V. IMPACT AND EFFECTIVENESS

IMPACT OF HPV VACCINATION ON CERVICAL CANCER INCIDENCE IN YOUNG US WOMEN

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Introduction: HPV vaccination and HPV-based cervical cancer screening have been introduced in the United States during the last twenty years. Up until recently, no evidence of impact of these HPV technologies has been demonstrated for invasive cervical cancer. We examined cervical cancer incidence trends in young US women during 1999-2015.
Methods: We evaluated incidence rates of invasive cervical squamous cell carcinoma and adenocarcinoma among women aged 15-39 years using data from population-based cancer registries covering 98% of the US population. Trends were examined using annual percent change in cervical cancer incidence, stratified by age and histology, and were calculated using Joinpoint regression.
Results: During 1999-2015, 36,553 squamous cell carcinomas and 14,883 adenocarcinomas were reported among women aged 15-39 years. Declines in squamous cell carcinoma were observed across this age range. The largest reductions occurred in women aged 15-20 years, with a decrease of 27% per year (from 2009-2010 to 2013-2015). Adenocarcinoma incidence decreased in younger age groups but increased in women aged 30-39 years until 2007-2008, when rates stabilized.
Conclusions: For the first time since HPV vaccine introduction, both squamous cell carcinoma and adenocarcinoma incidence were shown to decline significantly among females aged 15-20 years, a group not typically screened for cervical cancer, suggesting impact of the HPV vaccine. A temporary increase in adenocarcinoma occurred in women aged 30-39 years, likely attributable to introduction of HPV-based screening methods. Timely screening and vaccination among recommended age groups could result in further declines in invasive cervical cancer.

ORAL SESSION 15: VACCINATION V. IMPACT AND EFFECTIVENESS

EFFECTIVENESS OF HPV VACCINATION AGAINST INVASIVE CERVICAL CANCER

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Introduction: Several studies have investigated the population effectiveness of Gardasil against genital warts and CIN 2/3 with promising results; however, no study to date has investigated the effectiveness of HPV vaccination against invasive cervical cancer (ICC).
Methods: Utilizing Swedish data on registration of HPV vaccination and ICC from the national Swedish Cancer Registry during 2006-2017 we investigated the effectiveness of HPV vaccination against ICC in a national cohort study of 1,427,619 women aged 15-30. HPV vaccination was considered as a time-varying exposure to estimate the incidence of ICC up to age 31. Parental characteristics including socioeconomic status, mother's disease history, and mother's county of residence were retrieved from corresponding national registers. Incidence rate ratios (IRR) of ICC, with 95% confidence intervals (CI), were estimated in Poisson regression models, controlling for attained age, birth cohort, and parental characteristics.
Results: A total of 383,694 women (26.9%) had at least one dose of HPV vaccination, and 1,043,925 (73.1%) women were unvaccinated. During the study period 19 HPV vaccinated women acquired ICC up before age 31, while the corresponding number for unvaccinated women was 538, yielding an incidence rate of 1.00 and 6.51 per 100 000 person-years, respectively. The IRR for HPV vaccinated vs. unvaccinated women was 0.50 (CI:0.32-0.80) after adjusting for age, 0.38 (CI:0.24-0.62) after additional adjustment for birth cohort, and 0.37 (CI:0.23-0.60) with additional adjustment for parental characteristics. The IRR for women vaccinated before age 17 and age 17-30 were 0.12 (0.03-0.49) and 0.48 (0.29-0.79), respectively, after adjusting for all covariates. For women vaccinated before age 20 the IRR was 0.35 (CI:0.19-0.65), and for women vaccinated age 20-30 the IRR was 0.41 (CI:0.19-0.86).
Conclusions: These results indicate that HPV vaccination is effective against cervical cancer on the population level and that young age at vaccination is a strong mediator of vaccine effectiveness.

ORAL SESSION 15: VACCINATION V. IMPACT AND EFFECTIVENESS

VACCINE IMPACT, CROSS-PROTECTION, AND TYPE REPLACEMENT EVALUATED WITH TYPE-SPECIFIC HPV-ATTRIBUTABLE CERVICAL PRECANCER INCIDENCE RATES, UNITED STATES, 2008-2015

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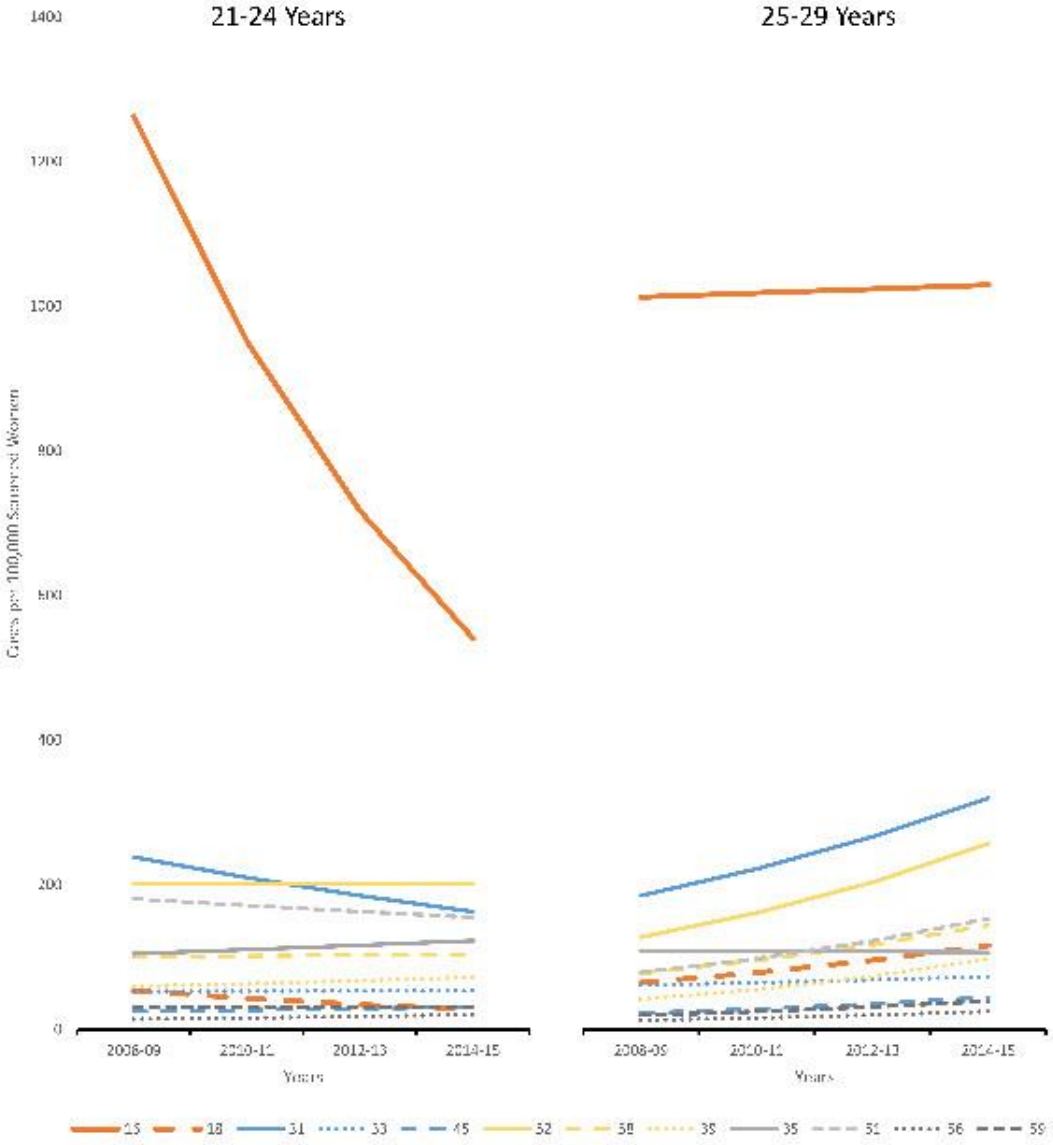
Introduction: Following HPV vaccine introduction in the United States in 2006, cervical precancer (CIN2+) incidence in screened women aged <25 years declined, whereas incidence in older ages increased, presumed due to changes in screening. To better understand trends, we evaluated rates of CIN2+ attributable to individual high-risk (HR) HPV types.
Methods: We analyzed population-based data on CIN2+ cases in women 21-39 years, from multi-site HPV-IMPACT, 2008-2015 (N=16,033). Diagnostic specimens (available for 70%) were tested for 37 HPV types, including 12 HR-HPV types. We used hierarchical attribution to assign a single HR-HPV type when >1 was detected, and applied inverse probability weights to account for un-typed cases. We calculated type-specific incidence rates per 100,000 screened women for 2-year periods by age group, and evaluated trends using average percentage changes (APC) per 2-year period and 95% confidence intervals (CI).
Results: In all age groups, highest rates were observed for HPV16-attributable CIN2+. Among 21-24 year-olds, HPV16-attributable CIN2+ declined from 1215 per 100,000 screened women in 2008-2009 to 507 in 2014-2015 (APC: –24.6, 95% CI: –36.3, –10.7) (Figure). In this age group, HPV18-attributable CIN2+ also declined significantly (51 to 27, APC: –20.3, 95% CI: –35.1, –2.1), and HPV31-attributable CIN2+ declined non-significantly (206 to 92, APC: –11.9, 95% CI: –56.6, 78.9); no type-specific CIN2+ rates increased significantly. Among 25-29 year-olds, CIN2+ attributed to HPV16 and HPV18 did not decline; CIN2+ attributed to HPV52, HPV58, and HPV39 increased significantly. Non-significant increases for most types were noted in 30-34 and 35-39 year-olds (not shown).

Figure. Trends* in type-specific rates of CIN2+ attributed to high-risk human papillomavirus types among screened women aged 21-24 and 25-29 years, HPV Vaccine Impact Monitoring Project (HPV-IMPACT), 2008-2015



*Trends were modeled using JoinPoint regression based on 2-year incidence rate estimates and standard errors, which were developed using hierarchical attribution and application of inverse probability weights.
NOTE: Orange denotes high-risk types targeted by the quadrivalent and bivalent HPV vaccines, blue denotes types identified in the literature as cross-protective, yellow denotes types identified in this analysis as having significantly increasing rates in some age groups, and gray denotes high-risk types not otherwise described.

Conclusions: Significant declines in CIN2+ attributed to HPV16 and HPV18 corroborate vaccine impact in 21-24 year-olds. A declining trend in HPV31-attributable CIN2+ is consistent with cross-protection, reported in some previous studies. No strong evidence for type replacement was observed; increases across several types in older ages suggests CIN2+ incidence increases are related to screening rather than vaccination.

ORAL SESSION 15: VACCINATION V. IMPACT AND EFFECTIVENESS

POPULATION-BASED EVALUATION OF TYPE-SPECIFIC HPV PREVALENCE AMONG WOMEN IN BRITISH COLUMBIA, CANADA AFTER 10 YEARS OF THE HPV VACCINATION PROGRAM

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Introduction: In British Columbia (BC), Canada, a publicly funded, school-based human papillomavirus (HPV) immunization program commenced in 2008 with the quadrivalent vaccine, for females born in 1994 or later in Grades 6 and 9. Assessment of province-wide HPV prevalence is included as part of the immunization program's evaluation framework. In 2010/2011, a baseline evaluation of HPV prevalence was conducted among women undergoing cervix screening. After 10 years of HPV vaccination, HPV-type prevalence was re-evaluated.
Methods: From August 2017 to March 2018, 1107 physicians were invited to return approximatley 10 cytobrushes used during routine Pap screening to the Provincial Laboratory for HPV type-specific testing. Only age or year of birth was collected. Specimens were screened for hr-HPV using Roche cobas 4800® HPV DNA Test identifying 14 hrHPV types. Other-hrHPV (OHR) positives were genotyped using Roche Linear Array. HPV type prevalence was compared for females 15-22yrs, (those eligible for the HPV school-based program) and those 23+yrs (ineligible for the program) for the 2010/2011 and the 2017/2018 data.
Results: There were 3309 valid samples received for testing; of these, 3107 had age available. For those 15-22yrs, HPV16 and 18 prevalence in 2010/11 was 8.8% and 3.7% respectively and in 2017/18 was 6.3% and 0% respectively, although the differences were not statistically significant. In those 23+, HPV16 and 18 prevalence in 2010/11 was 2.0% and 0.7% respectively and in 2017/18, 2.4% and 1.0% respectively, although the differences were not statistically significant.
Conclusions: In women eligible for school-based HPV immunization, HPV16 and 18 prevalence rates have decreased since implementation of the public program in 2008. In screened women not eligible for publicly funded HPV vaccination, no decrease in HPV16/18 prevalence was seen. Further evaluations of HPV prevalence in the province will continue for the 9-valent vaccine.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

CERVICAL PRECANCER (CIN2/3/AIS) LATER DIAGNOSED WITH CERVICAL CANCER BY SOCIODEMOGRAPHIC FACTORS, SEVERITY OF DIAGNOSIS, AND HPV-TYPE, ALAMEDA COUNTY, CALIFORNIA, UNITED STATES (U.S.), 2008-2018

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Introduction: Within an established cervical cancer screening program, cervical precancer should be identified and treated early. Understanding characteristics of precancer cases that were later diagnosed with cervical cancer may inform prevention strategies. We evaluated data from the Alameda County, California (population 1.7 million) site of a population-based cervical precancer (CIN2/3/AIS) surveillance system, HPV-IMPACT, and the statewide (population 39.5 million) California Cancer Registry (CCR).
Methods: Incident CIN2/3/AIS cases residing in Alameda County were matched with cervical cancer cases in California using Match*Pro. HPV-IMPACT data included demographics, precancer diagnosis, and HPV-typing data for a subset aged 18-39 with residual cervical tissue available. The proportions of CIN2/2-3, CIN3, AIS or AIS+CIN cases diagnosed with cancer after precancer were compared by race/ethnicity, insurance, grade/histology of diagnosis, age, and HPV type using chi-square or Fisher's exact tests.
Results: From 2008-2018, Alameda County reported 8,329 CIN2/3/AIS cases and California reported 15,020 cervical cancer cases. A total of 80 HPV-IMPACT cases matched with the cancer registry and were diagnosed with cervical cancer after their precancer. The proportion of cases later diagnosed with cervical cancer was higher in public/uninsured women than privately insured women (2.8% vs 0.4%; $p<0.001$) and varied by histology and grade of cervical precancer diagnosis: 10.0% of AIS+CIN and 6.2% of AIS-alone vs 2.0% of CIN3 and 0.3% of CIN2/2-3 ($p<0.001$). The proportion of cases later diagnosed with cervical cancer was highest (3.1%) in women aged 50+. There were no significant differences by race/ethnicity or HPV type.

Percentage of cervical precancer cases later diagnosed with cervical cancer, Alameda County, California, United States, 2008-2018

	Cervical Precancer Diagnosis	Subsequent Cervical Cancer* Diagnosis	%	p-value**
Total	8329	80	1.0%	n/a
Race (n=6153)				
Asian/Pacific Islander	1467	16	1.1%	0.073
Non-Hispanic Black	872	16	1.8%	
Hispanic	1532	26	1.7%	
Non-Hispanic White	2282	21	0.9%	
Insurance at Precancer Diagnosis (n=6767)				
Public/uninsured	1577	44	2.8%	<0.001
Private	5190	19	0.4%	
Precancer Diagnosis				
CIN2/CIN2-3	5812	20	0.3%	<0.001
CIN3	2327	46	2.0%	
AIS	129	8	6.2%	
AIS+CIN2/3	60	6	10.0%	
Age at Precancer Diagnosis				
18-29	3072	6	0.2%	<0.001
30-39	3116	23	0.7%	
40-49	1309	25	1.9%	
50+	832	26	3.1%	
HPV Type (n=3882)				
16/18	1873	12	0.6%	0.087
31/33/45/52/58	1294	3	0.2%	
Other	715	2	0.3%	

*Excluded 36 cervical cancer cases with a cervical cancer diagnosis before their incident cervical precancer diagnosis and 11 cases with a concurrent diagnosis

**Chi-square test used for all comparisons except HPV type, where Fisher's Exact Test was used due to small sample size.

Conclusions: Precancer cases later diagnosed with cervical cancer differed by insurance status and histologic type in Alameda County residents. Women may be at higher risk for a subsequent cervical cancer diagnosis if, at the time of their precancer diagnosis, they have public/no insurance or any AIS. Quality improvement efforts should focus on ensuring treatment and follow-up surveillance, especially for publicly insured/uninsured women.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

DETECTION OF SOMATIC HOTSPOT MUTATIONS IN CERVICAL PRECANCEROUS LESIONS USING CERVICAL CELLS.

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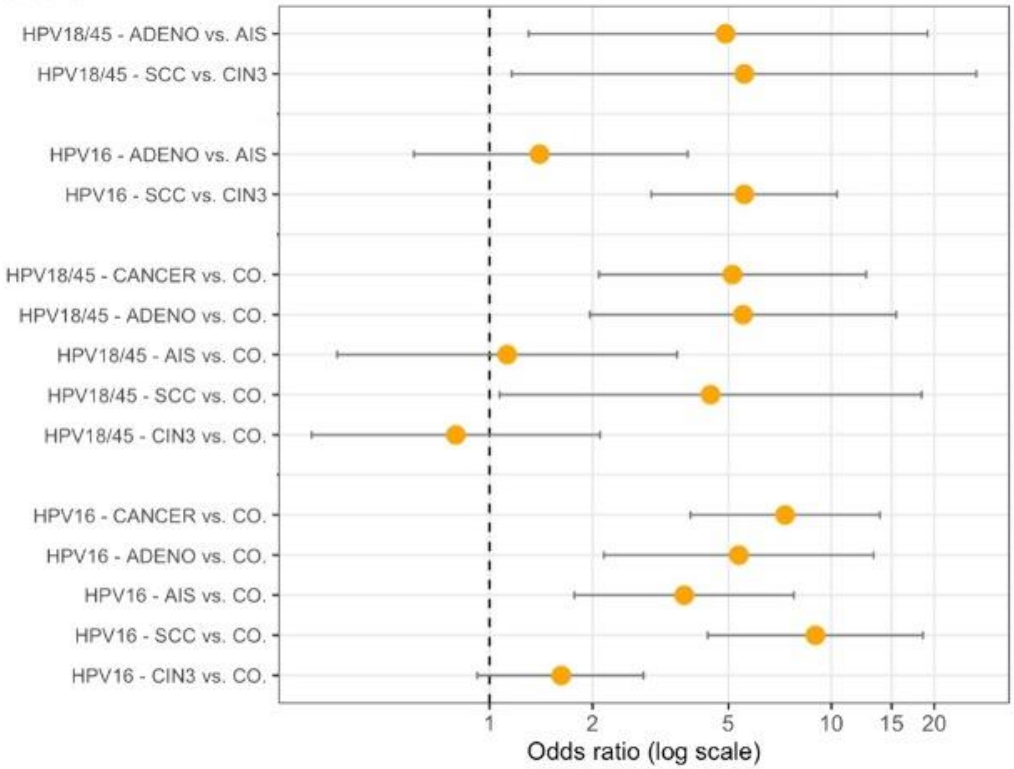
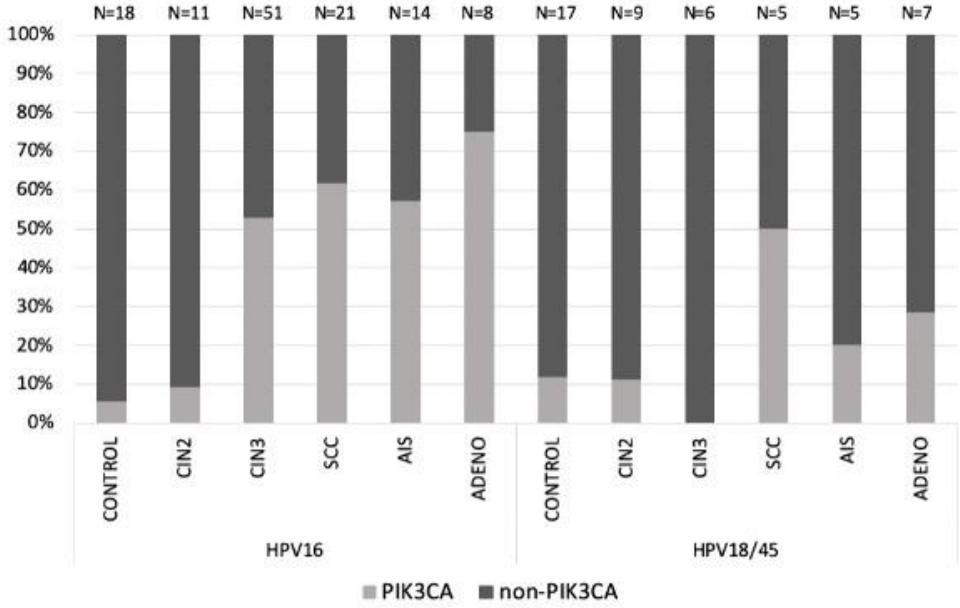
Introduction: Squamous cell carcinomas (SCC) and adenocarcinomas have distinct somatic mutational profiles, but little is known about mutations in precursor lesions (CIN2/CIN3/AIS) or the relationship to high-risk HPV-types. We investigated whether somatic mutations can be detected in precancers, and if they are influenced by HPV-type.
Methods: Using cervical cells DNA from 3,276 women with residual HPV-test specimens (obtained from the cervical canal during routine cancer screening), positive for HPV16, 18, or 45 (control benign infections, N=1,265; precancers, N=1,843; cancers, N=168) in the NCI-Kaiser PaP cohort, we sequenced 15 established cervical cancer driver genes. We evaluated known recurrent cervical cancer somatic mutations (hotspots [HS-mutations]), and calculated HS-mutation associations (odds ratio [OR]) with precancers and cancers compared to controls.
Results: Overall HS-mutation frequencies were higher in cancers (25-30%) compared to controls (6-8%;$p<0.05$), and similar between cancers and published data. HS-mutations were associated with HPV16-positive SCC (OR=5.6;95%CI=3.0-10.4) compared to CIN3; similar between HPV16-positive adenocarcinomas and AIS ($p>0.05$) (Figure 1), but higher in AIS and adenocarcinoma compared to controls (OR=4.2;95%CI=2.2-8.1). HS-mutations were associated with HPV18/45-positive adenocarcinomas (OR=4.9;95%CI=1.3-19.1) and SCC (OR=5.6;95%CI=1.2-26.6) compared to AIS and CIN3, respectively. *PIK3CA* HS-mutations were associated with cancers (OR:SCC=107,adenocarcoma=70) and precancers (OR:CIN3=17,AIS=36) for HPV16, and HPV18/45 cancers (OR: SCC=23, adenocarcinoma=10) compared to controls; non-*PIK3CA* HS-mutations were associated with SCC only for HPV16 (OR=3.44;95%CI=1.41-8.35) and adenocarcinoma only for HPV18/45 (OR=3.73;95%CI=1.21-11.50) (Figure 1). Ten out of 72 women had a HS-mutation within 2-3 years before cancer diagnosis. The HS-mutation average allele fraction, a proxy for cellular clonal expansion, was significantly lower in controls (3%) compared to precancers (8%) and cancers (15%;$p=6.7x10^{-5}$).

Figure 1. HS-mutation associations with the main histologic subtypes of cervical precancers and cancers.



CO = controls, HPV16-, HPV18- or HPV45- benign transient infections; **ADENO** = adenocarcinoma; **SCC** = squamous cell carcinoma; **CANCER** = SCC, ADENO and unknow histology; **CIN3** = cervical intraepithelial neoplasia grade 3; **AIS** = adenocarcinoma *in situ* (AIS).

Figure 2. Gene-specific HS-mutation distribution by HPV-type for controls, precancers and cancers.



CONTROL = HPV16-, HPV18- or HPV45- benign transient infections; **CIN2** = cervical intraepithelial neoplasia grade 3; **CIN3** = cervical intraepithelial neoplasia grade 3; **SCC** = squamous cell carcinoma; **AIS** = adenocarcinoma *in situ*; **ADENO** = adenocarcinoma; **cancers** = SCC, ADENO and unknow histology; **N** = number of samples with a HS-mutation; samples with both PIK3CA and non-PIK3CA were counted more than once.

Conclusions: Remarkably, we detected HS-mutations in precancers/cancers using cervical mixed cells, even before cancer diagnosis; and, provided evidence that the virus influences the somatic mutation profile. This is a novel approach using cervical cells that shows HS-mutations may help drive the transition from precancers to cancers.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

ANALYSIS OF THE RECENT INCREASE IN CERVICAL CANCER INCIDENCE IN SWEDEN

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Introduction: Sweden has had organized screening for >50 years, with high population coverage (about 80%). National guidelines mandate HPV screening since 2015, but screening is decentralized to 21 counties with 27 laboratories and some do not use the national program. Complete registers of screening history are collected into the National cervical cancer registry (NKCx), used for comprehensive audits of the screening performance. Cervical cancer incidence has declined every year until 2013 but from 2014 there is a 20% increase in incidence.
Methods: We linked the NKCx database with all smears and biopsies to all cervical cancer cases. Cancer risk by screening history, calendar time and screening laboratory were determined. National re-review of the cytology specimens reported as normal ahead of a cancer or a CIN3 diagnosis was performed. Time from high grade cytology to biopsy was measured.
Results: The incidence in nonparticipants was not increasing. There was no increase in several large regions. The increase was strongest among women with a normal smear, in particular among women with 2 consecutive normal smears. The incidence increase was strongest in women aged 30 to 50 and was seen for both AC and SCC and for both stages IA and IB. A significant increase in cancer risk among women with high-grade abnormalities appears to relate to an increased delay until follow-up (date of taking a biopsy). Re-reviews of smears found a strong time trend with an increased number of changed diagnoses before cancer in the last decade. Re-reviews before CIN3 showed large variability between labs and over time.
Conclusions: The cervical cancer incidence increase appears to relate to an increased risk of false-negative smears and increased reporting times in cytology. Adherence to the national program mandating primary HPV screening is a possible remedy to the situation.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

FOLLOW-UP OF ATYPIAL GLANDULAR CELLS: RAPID HISTOPATHOLOGY ASSOCIATED WITH LOWER INCIDENCE OF CERVICAL CANCER

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Introduction: We previously showed that atypical glandular cells (AGC) is a high-risk cytological finding, with both high proportion of prevalent cervical cancer and higher incidence of cervical cancer compared to HSIL, particularly in the first 6.5 years. We now examined whether rapid histopathological testing after AGC may be associated with improved cancer prevention.
Methods: Women with AGC as their first cytological abnormality at ages 23-60 during 2002-2016 and their first histopathology after AGC were identified from the Swedish National Cervical Screening Registry. Cases of invasive cervical cancer were identified from national databases and the Swedish National Total Population Register was used to assess death and emigration as events of censoring. Cumulative incidence of invasive cervical cancer up to 6.5 years after AGC was assessed based on the Kaplan-Meier survival function, stratified by timing of the first histopathology test.
Results:

Cumulative incidence of cervical cancer by timing of the first histopathology test

Timing of first histopathology test	No. of women	No. of CxCa cases	Cumulative incidence (95% CI) up to 6.5 years after AGC	P-value of trend test*
<1 month	911	66	7.39(5.85-9.31)	Not included
1-3 months	3565	123	3.64(3.05-4.33)	
3-6 months	1033	43	4.47(3.32-6.01)	0.0484
6-12 months	241	13	5.68(3.33-9.62)	
>12 months	293	16	5.79(3.58-9.29)	

*Log-rank trend test in Kaplan-Meier survival function.

Among 6043 women with AGC, there was a high cancer detection among those tested with histopathology within one month, probably representing rapid assessment for women having Pap test due to clinical signs or symptoms. Women having the first histopathology test after more than one month exhibited a statistically significant trend: the longer time until histopathology, the higher cumulative incidence of invasive cervical cancer.
Conclusions: Rapid histopathology after AGC in cervical screening was associated with lower incidence of cervical cancer during the upcoming two screening intervals, suggesting improved prevention of

cervical cancer.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

PREDICTING COHORT-SPECIFIC CERVICAL CANCER INCIDENCE FROM POPULATION-BASED HPV PREVALENCE SURVEYS: A WORLDWIDE STUDY

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Introduction: Predictions of cervical cancer burden, as well as potential impact of control measures, are often modelled from Human Papillomavirus (HPV) prevalence. However, model-based predictions could be improved by age-specific data on time between prevalent HPV detection and cervical cancer occurrence.
Methods: Based upon HR-HPV prevalence (IARC Surveys database) and cervical cancer incidence (Cancer Incidence in Five Continents – CI5 –Volume VIII-XI) in the same birth cohorts from 17 worldwide locations, and informed by individual-level data on age at HR-HPV detection and of sexual debut, we built a mixed model to predict cervical cancer incidence following prevalent HR HPV detection.
Results: We found a positive association between HR HPV prevalence and cervical cancer incidence in the same birth cohorts, the strength of which increased with age at HR HPV detection and time-lag between HR HPV prevalence and cancer incidence assessment. Cervical cancer predicted incidence increased significantly during the 14 years following HR HPV detection in women <35 years, e.g. from 0.02 (95% 0.003-0.06) per 1000 within 1 year to 2.8 (1.2-6.5) at 14 years, for unscreened women, but remained constant following HR HPV detection above 35 years, e.g. from 5.4 (95% 2.5-11) per 1000 within 1 year to 6.4 (2.4-17.1) at 14 years for unscreened HR HPV positive women aged 45-54 years. Age-at-sexual-debut was a significant modifier of cervical cancer incidence in HR HPV-positive women aged <25, but not at older ages, whereas screening was a significant modifier in women ≥35 years. We use our model also to predict the expected annual number and incidence of cervical cancer ten years after the implementation of the HPV prevalence surveys in countries not represented in CI5.
Conclusions: These findings can inform cervical cancer control programs, particularly in settings without cancer registries, as they allow to predict future cervical cancer burden from population-based surveys of HPV prevalence.

ORAL SESSION 16: EPIDEMIOLOGY II. BURDEN, NATURAL HISTORY AND RISK FACTORS

WHO INTERNATIONAL STANDARDS FOR HPV DNA FOR LOW-RISK TYPES HPV6 & HPV11 AND HIGH-RISK TYPES HPV31, HPV33, HPV45, HPV52 & HPV58

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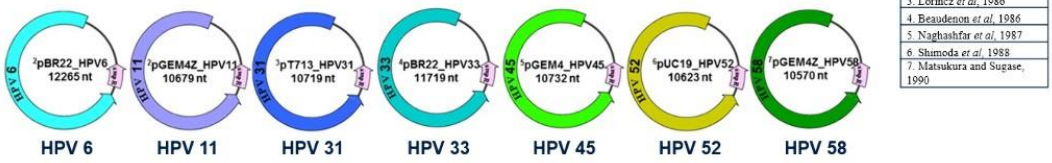
Introduction: Methods for the detection and genotyping of HPV DNA are the primary tools used to measure the burden of HPV disease and assess the impact of vaccination programs. To obtain results that are consistent, meaningful and comparable, HPV laboratories must utilize assays that are accurate, appropriately sensitive and specific. The ability of laboratories to calibrate and determine the sensitivity and specificity of their assays, is dependent upon the availability of well characterized biological reference standards for HPV. WHO International Standards (IS) are highest-order biological reference standards and are usually assigned in arbitrary International Units (IU). Their purpose is to calibrate secondary references in terms of the IU for use in assays, thus providing a uniform result-reporting system and traceability of measurements independent of the method used.
Methods: Candidate WHO ISs for low-risk and high-risk HPV types were prepared from recombinant plasmids containing full-length HPV genomes (Figure 1). Using an approach similar to that for producing ISs for HPV16 and 18 DNA, the plasmids were formulated in a background of human genomic DNA and freeze-dried. Fourteen laboratories participated in a WHO international collaborative study to determine the unitages of the candidate ISs in terms of the IU and evaluate their suitability for use in HPV DNA assays.

Figure 1. Source materials for WHO International Standards

- Plasmids containing full-length HPV genomes were provided through WHO HPV LabNet and IP owners. (Eklund et al JCM 2012)



Results: A range of HPV assays for the detection and/or genotyping of HPV DNA was used to evaluate the candidates. Genotyping assessment confirms that each candidate is monospecific for its designated HPV genotype. IU potencies estimated by endpoint dilutions from sixteen qualitative HPV assays were lower and tended to demonstrate greater inter-laboratory variability than the estimates determined from quantitative PCR assays that targeted plasmid backbone sequences (Table 1).

Table 1. Proposal submitted to the WHO Expert Committee on Biological Standardization, October 2019, for the establishment of the 1st WHO ISs for low-risk and high-risk HPV DNA Types

Panel	1st WHO International Standard for Human Papillomavirus (HPV)	NIBSC Product code	Assigned unitage (IU/ampoule)	Assigned unitage (Log_{10} IU/ampoule)	Log_{10} IU/mL when reconstituted as directed in 0.5mL water
LR HPV DNA panel	Type 6 DNA	14/256	$1x10^7$	7.0	7.3
	Type 11 DNA	14/100	$1x10^7$	7.0	7.3
other HR HPV DNA panel	Type 31 DNA	14/258	$1.6x10^7$	7.2	7.5
	Type 33 DNA	14/260	$1.6x10^7$	7.2	7.5
	Type 45 DNA	14/104	$1x10^7$	7.0	7.3
	Type 52 DNA	14/262	$7.9x10^6$	6.9	7.2
	Type 58 DNA	14/264	$7.9x10^6$	6.9	7.2

Conclusions: We report the outcome of the proposal to establish the candidates as 1st WHO International Standards presented to the WHO Expert Committee on Biological Standardization in October 2019.

ORAL SESSION 17: HEAD & NECK CANCERS. EPIDEMIOLOGY, NATURAL HISTORY AND PREVENTION

EARLY DETECTION OF HPV-DRIVEN OROPHARYNGEAL CANCER USING HPV SEROLOGY IN THE STUDY OF PREVENTION OF ANAL CANCER

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Introduction: HPV-driven oropharyngeal cancer (HPV-OPC) is rare but both incidence rate and HPV attributable fraction are increasing in many countries. Antibodies to HPV16E6 are highly sensitive and specific prospective biomarkers for HPV-OPC. However, their positive predictive value (PPV) is impaired due to the low disease incidence rate. Thus, HPV-OPC screening by HPV serology is controversial.
Methods: We performed HPV16 E1, E2, E6 and E7 serology in the Study of Prevention of Anal Cancer, an MSM cohort in Sydney (Australia), with four consecutive annual visits. At every visit, anal swabs were taken to determine anal HPV DNA, high-resolution anoscopy was performed to detect anal LSIL and HSIL, and a blood sample was taken for HPV serology.
Results: Of the 588 men enrolled, 13 had HPV16E6 antibodies, including three with anal LSIL and ten without detectable HPV16 in their anal swabs. Two men were additionally seropositive against HPV16 E2 or E7, and one was seropositive for all four antigens. These three men were among the four with the highest HPV16E6 antibody levels (>4000 MFI). The four-fold seropositive man died between enrolment and serological testing from metastatic lung cancer after a tonsillar primary tumor. The remaining 12 individuals were invited, and nine consented to a head and neck physical and visual examination and PET-CT scan. One asymptomatic man among the three described above had been persistently seropositive for 24 (E6) and 10 months (E2) and was diagnosed with a p16 positive, T1N1 base of tongue cancer. The other eight individuals were free of symptoms and scheduled for six-monthly visits, and annual PET-CT.
Conclusions: This is the first report of detection of early asymptomatic HPV-OPC using HPV16E6 serology. These data provide evidence that taking additional early antibodies, and antibody levels into account, may aid in increasing the PPV of HPV serology for HPV-OPC screening.

ORAL SESSION 17: HEAD & NECK CANCERS. EPIDEMIOLOGY, NATURAL HISTORY AND PREVENTION

UPDATE ON TRENDS IN OROPHARYNX CANCER INCIDENCE FROM CANCER INCIDENCE IN FIVE CONTINENTS

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Introduction: The etiologic role of HPV in oropharynx cancer (OPC) has been recognized for more than three decades. The epidemiology of OPC has been evolving, with trends of increasing incidence in many parts of the world. The rising rates of OPC have been attributed to a higher fraction of HPV-associated malignancy, especially in areas where the prevalence of tobacco smoking has been declining.
Methods: Data from Cancer Incidence in Five Continents (CI5) volumes VI-XI (1983-2012) were used to examine global trends in OPC incidence. Cancer registries were included in this analysis if they contributed at least 15 years of high-quality data to the latest volume of CI5. Cancer incidence rates were calculated by sex, age, time period, and country. Age-period-cohort modeling was used to evaluate the non-linear effects of period and cohort on the trends in OPC rates.
Results: OPC incidence has continued to increase globally, especially in countries with high GDP. In contrast to previous investigations, more recent data shows significantly increasing incidences of OPC in older age groups (70+) as well in many countries with strong birth cohort effects. While incidence of OPC was substantially lower among women than among men in all populations, we observed a significant rise in OPC incidence over time for women in several countries. Temporal trends for OPC incidence were coincident with positive trends in rates for oral cavity cancer among women, but not men.
Conclusions: The incidence in OPC continues to increase globally, particularly among men in high-GDP nations. In contrast to previous reports, this effect is no longer exclusive to younger individuals, with significant increases in OPC among those 70+. These data, combined with declines in tobacco-associated head and neck cancers in men, highlight the increased importance of HPV in the etiology of OPC and the concomitant need for novel disease management strategies for this malignancy.

ORAL SESSION 17: HEAD & NECK CANCERS. EPIDEMIOLOGY, NATURAL HISTORY AND PREVENTION

TIMING, NUMBER, AND TYPE OF SEXUAL PARTNERS ASSOCIATED WITH RISK OF OROPHARYNGEAL CANCER

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Introduction: Seminal case-control studies showed that HPV-related oropharyngeal cancer (HPV-OPC) is a distinct entity from HPV-unrelated head and neck cancer. These analyses from over a decade ago demonstrated that a higher number of oral sexual partners and early sexual debut were associated with HPV-OPC. Here we present an in-depth, contemporary case-control study to further characterize these and other potential risk factors for HPV-OPC by exploring differences in sexual exposure, behavior at sexual debut, and relationship dynamics.
Methods: Patients with HPV-OPC and frequency-matched controls were enrolled in a multicenter, case-control study of squamous cell carcinomas from 2013-2018. Each participant completed a survey on behavioral risk factors. Characteristics of cases and matched controls were compared using χ^2 for categorical and t-test for continuous variables.
Results: The study population included 163 cases and 345 frequency-matched controls. Timing of oral sexual initiation was associated with higher odds of HPV-OPC, including younger age of first oral sex ($p<0.001$) and oral sex debut at <18 years compared to 20 years of age (odds ratio [OR] 2.6; 95% confidence interval [CI] 1.5-4.4). Performing oral sex at sexual debut (OR=1.6, 95% CI=1.0-2.5), more than 10 lifetime oral-sex partners (OR=4.3; 95% CI 2.6-6.9), and higher oral sex intensity (number of partners per ten years; p-trend <0.001) were also found to be associated with HPV-OPC. Type of partner was also a risk factor for HPV-OPC among those who had a partner >10 years older when younger than age 23 (OR=1.6, 95% CI=1.0-2.5) or who had extramarital sex (OR=1.6, 95% CI 1.2-2.5). Those with ever-marijuana use (OR=1.8, 95% CI 1.1-2.9) and ever-cocaine use (OR=1.8, 95% CI 1.0-2.5) had increased odds of HPV-OPC.
Conclusions: Novel sexual and drug-use risk factors are associated with the diagnosis of HPV-related oropharyngeal cancer.

ORAL SESSION 17: HEAD & NECK CANCERS. EPIDEMIOLOGY, NATURAL HISTORY AND PREVENTION

THE BURDEN OF HPV IN HEAD AND NECK CANCERS - DESIGN OF THE BROADEN STUDY

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Introduction: Human Papillomavirus (HPV) is a cause of a sub-set of head and neck cancers (HNC). Based on tissue samples collected from 1990 to 2012, Castellsagué et al. estimated that 22.4%, 4.4%, and 3.5% of oropharyngeal, oral cavity, and laryngeal cancers, respectively, were attributable to HPV. Recent studies have reported an increase in the proportion of oropharyngeal cancers (OPCs) caused by HPV. This may be due to changes in sexual practices since the 1970s combined with the decrease of other risk factors particularly smoking. Evidence on the attributability to HPV for non-OPCs is very limited, as clinical guidelines do not recommend routine HPV testing for these sites. This study aims to estimate the fraction of HNCs attributable to HPV per anatomic site, in two time periods (2008-2009 and 2018-2019) in five European and two Asian countries (France, Germany, Italy, Portugal, Spain, China and Japan). This abstract describes the design of the BROADEN study, which is ongoing.
Methods: A non-interventional, cross-sectional study of patients diagnosed with HNCs will be conducted in a sample of hospitals with established local biobanks in the seven participant countries.
Results: Approximately 9,000 patients diagnosed with HNC during the two defined study periods, with HNC tissue available, will be included in the study. Tissue samples will undergo three HPV tests (detection of HPV DNA, and HPV E6*I mRNA, and assessment of $p16^{INK4a}$ expression) at a central laboratory. Analyses to estimate the country-specific, regional and global proportion of HNCs attributable to HPV will be stratified by single and grouped HNC anatomic sites (OPC vs non-OPC).
Conclusions: The results from this study will contribute to the understanding of the past (2008-2009) and current (2018-2019) involvement of HPV in HNC at OPC and non-OPC anatomic sites using a standardized methodology for HPV testing via a central laboratory.

ORAL SESSION 17: HEAD & NECK CANCERS. EPIDEMIOLOGY, NATURAL HISTORY AND PREVENTION

ORAL HPV IN AN INDIGENOUS AUSTRALIAN POPULATION

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Introduction: INTRODUCTION: Current trends suggest that oropharyngeal squamous cell carcinomas (OPSCC) associated with human papilloma virus (HPV) are on the rise. There is a clear need for greater understanding of groups known to be more vulnerable to HPV-related OPSCC. Indigenous Australians are one such group. This study aimed to estimate the prevalence of oral HPV types among Indigenous Australians.
Methods: METHODS: Eligibility included identifying as Aboriginal or Torres Strait Islander, residing in South Australia and being aged 18+ years. Saliva samples were collected, DNA extracted, and tested by PCR (HPV – MY/GP+ and beta-globin - PCO3/4). Participants provided information on socio-demographic characteristics, health-related behaviours including tobacco and alcohol use, and sexual history. Data were stratified by HPV 16 and 18 (high risk for OPSCC), other high risk HPV types (HPV 26, 31, 33, 35, 39, 45, 52, 58, 59, 68, 69, 73, 82) and low risk HPV types.
Results: RESULTS: Data for 1005 participants was obtained between Feb 2018 and Jan 2019, out of which 911 participants tested positive for beta-globin; 31.9% (95%CI: 29.1-34.8) were positive for oral HPV. The prevalence for HPV types 16 or 18 was 9.2% (95%CI: 6.5-13.0), for other high-risk HPV 9.8% (95% CI: 6.5-13.0) and for low-risk HPV 81.0% (95% CI: 76.8-85.3). These estimates were higher than other oral HPV findings in the Australian literature. A total of 46 HPV types were found, with the lowest number of participants per type being 1 and the highest being 119.
Conclusions: CONCLUSIONS: Overall prevalence of oral HPV in a large convenience sample of Indigenous Australians was high, with one-third testing positive. The prevalence of HPV types associated with OPSCC was higher than in other published estimates of oral hrHPV in Australia, although these studies are scarce and not nationally-representative.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

A LINKAGE STUDY OF HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AND PAP SMEAR CERVICAL CANCER SCREENING IN FERRARA, ITALY.

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Introduction: In Italy, HPV vaccination commenced in 2007 for 12-year-old girls, while cervical screening eligibility starts at age 25. Older cohorts, targeted by catch-up vaccination (recommended until age 18-25, and allowed afterwards), are already being screened. In this population, using routine healthcare registries, we aimed to assess the association between vaccination and screening participation and the effectiveness of HPV vaccine against screen-detected cervical abnormalities.
Methods: In a population-based cohort study, we included women residing in the Ferrara Province, born 1986-1993, screened in 2011-2018, linking data from the official vaccination and screening registries. Using logistic regression (adjusted for birth year, being born abroad, residence, number of Pap smears, and test kit), we assessed the statistical association between vaccination and abnormal cytology (LSIL+), by number of doses (received before screening) and vaccine type (bivalent/quadrivalent).
Results: Among 7,785 included women, 391 (5%) were vaccinated (3.6% with the bivalent vaccine, 1.4% with the quadrivalent), of which 212 (2.7%) with only one dose. Vaccination coverage was similar among non-screened women, at 4.8% (Chi-squared test p: 0.7). Vaccinated women (median follow up: 4.4 years) were significantly less likely than non-vaccinated ones to show abnormal cytology (adjusted odds ratio (AOR) for 1+ dose vs. none: 0.54, 95% CI: 0.35-0.83; AOR for 1 dose vs. none: 0.53, CI: 0.30-0.95). Results were similar when applying buffer periods (excluding smears within one, six, and twelve months after the first dose).

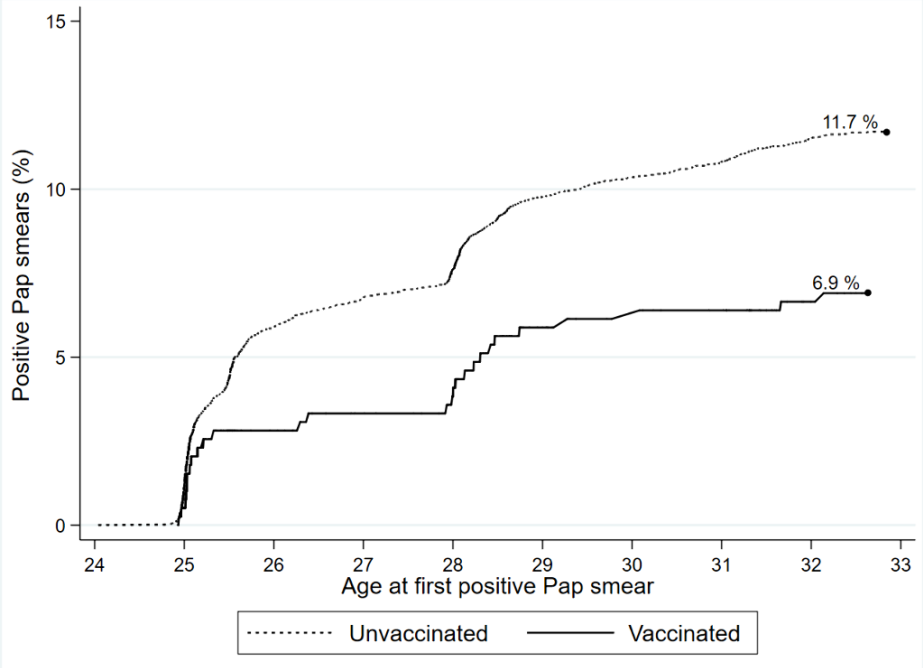
Female birth cohorts 1986-1993
n = 11,773[A]
Vaccinated = 584 (5.0%)

Excluded
Non-residents n= 1,118
Unsatisfactory Pap test n= 25
Not screened[B] n= 3,963
of which 193 vaccinated (4.8%)

Included in the study
Residents with at least one satisfactory Pap test
in 2011-2018
n = 7,785
Vaccinated[C] = 391 (5.0%)
(bivalent: 278; quadrivalent: 113)

Negative Pap smears	n = 6,892 (88.5%)
Doses no.	
0	6,528 (94.7%)
1	197 (2.9%)
2	75 (1.1%)
3	92 (1.3%)

Positive Pap smears	n = 893 (11.5%)
Doses no.	
0	866 (97.0%)
1	15 (1.7%)
2	8 (0.9%)
3	4 (0.4%)



Odds ratios of cervical abnormalities for all cohorts, by dose number.

Dose	All cohorts, OR (95% CI)	All cohorts, AOR (95% CI)
0	1	1
1	0.58* (0.34-0.99)	0.53* (0.30-0.95)
2	0.82 (0.40-1.71)	0.71 (0.32-1.58)
3	0.33* (0.12-0.91)	0.43 (0.16-1.18)
≥ 1	0.56** (0.38-0.83)	0.54** (0.35-0.83)

Conclusions: In the Province of Ferrara, a single dose of HPV vaccine reduced the likelihood of cervical abnormalities, and we found no evidence that vaccination influenced screening participation.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

USING CANCER REGISTRIES TO ASSESS HPV VACCINE IMPACT ON VULVAR, VAGINAL, AND ANAL PRECANCERS IN FEMALES UNDER 40 YEARS OF AGE, UNITED STATES 2000-2016

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Introduction: Since human papillomavirus (HPV) vaccine introduction for females in 2006, cervical precancer incidence has declined. Assessing impact on other anogenital HPV-associated precancers is challenging because few surveillance systems collect these cases. We evaluated recent US incidence trends of high grade vulvar (VIN3), vaginal (VAIN3), and anal (AIN3) precancers.
Methods: Using the Surveillance, Epidemiology, and End Results (SEER) database, we calculated incidence rates of VIN3, VAIN3, and AIN3 of squamous cell histology (ICD-O-3 8050-8084, 8120-8131) diagnosed during 2000-2016 among females aged 15-39 years. For VIN3 and VAIN3, joinpoint regression was used to calculate annual percent change in incidence. For AIN3, years of diagnosis were grouped due to sparse data into a pre-vaccination (2000-2006) and post-vaccination period (2007-2016) and rate ratios were calculated comparing incidence rates to the pre-vaccination period.
Results: We identified 6,152 VIN3, 909 VAIN3, and 425 AIN3 cases. In VIN3 cases among females aged 15-19 years, rates were stable during 2000-2006, with a significant decrease of 20.2% per year during 2006-2016. Among females 20-24 years, a significant increase of 14.1% per year during 2000-2005 was followed by significant decreases of 7.6% per year during 2005-2011 and 21.6% per year during 2011-2016. In VAIN3 cases among females 15-24 years, rates were stable during 2000-2006 followed by a significant decrease of 19.4% per year during 2006-2016. We did not observe a decrease in AIN3, but rather an increase among all age groups of females.
Conclusions: The largest declines in VIN3 and VAIN3 occurred in young females after HPV vaccine introduction. Increasing AIN3 may be a result of low numbers and detection bias, but also increased exposure. Continued monitoring of these precancers can help to further assess HPV vaccine impact

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

REDUCTION IN CIN3+ AT SECOND AND SUBSEQUENT SCREENS IN WOMEN IMMUNISED WITH CERVARIX®

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Introduction: In 2008, Scotland implemented hr-HPV immunisation with Cervarix at age 12/13 for women born in and after 1995 and catch-up immunisation for women born during 1990-1994. Immunised women have been screened since 2010, and all immunised women have had at least two rounds of screening.
Methods: Immunisation status, cervical cytology and histology results were retrieved in July 2019 for women born in 1988-1990 (un-immunised), in 1991-1994 (catch-up cohort), and in 1995-1996 (routinely immunised) and rates of CIN3+ calculated.
Results: 262820 cytology records from 437583 women have been analysed with 4454 CIN3+ events recorded during follow-up.
1271 CIN3+ events have been recorded at ages 20-23 years in all cohorts. The risk reduction relative to the cohort not offered vaccination is 51.8% (95% CI 45.6%, 56.9%) in the catch-up cohort and 89.6% (85.5%, 92.6%) in routine cohort. The risk reduction within the catch-up cohort for immunised relative to non-immunised women is 27.2% (13.6%, 38.7%).
2833 CIN3+ events have been recorded in women in the unvaccinated and catch-up cohorts with at least 6 years follow-up. Within the catch-up cohorts the risk of CIN3+ in immunised women relative to non-immunised women was reduced by 29.7% (CI 20.6 – 37.8%).
Women in the routine vaccination cohort (1995-96) have a maximum follow up of 4 years and 21 cancers have been observed at age 20-24 in all cohorts, 11 in the cohort not offered vaccination (rate 0.96/106); 10 in the catch-up cohort, (rate 1.07/106) and 0 in the routine cohort. In the catch-up cohort the rate of cancers among those fully vaccinated is 0.72/106 while among those unvaccinated the rate is 1.49/106.
Conclusions: Significant reductions in CIN3+ in both routinely immunised and catch-up cohorts are demonstrated over several screening rounds. The reduction in CIN3+ gives confidence that the predicted reduction in invasive cancers will be seen.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

DOES THE GENOTYPE-SPECIFIC CIN2+ RISK IN CERVICAL SCREENING CHANGE IN PARTLY HPV-VACCINATED COHORTS?

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Introduction: HPV vaccination will detrimentally affect the positive predictive value (PPV) of screening algorithms for high-grade cervical lesions (CIN2+) as vaccines target the most oncogenic HPV genotypes. The influence of HPV vaccination on the HPV genotype-specific PPVs is however unknown. Without herd effects, HPV genotype-specific PPVs are not expected to change but herd effects may influence type-specific PPVs by shifting the HPV infection prevalence to older age.
Methods: We used mathematical modelling to explore how the age-specific prevalence of genotype-specific HPV infection changes over time. We also assessed the implications for adding HPV genotyping to the primary HPV-based screening program in the Netherlands (5-year interval, age range 30-60 years). We focused on the bivalent vaccine types 16/18, as risk stratification according to HPV16/18 is possible with the currently used primary HPV test (i.e. Cobas 4800). Predictions were obtained for vaccine-eligible cohorts, scheduled to enter routine cervical screening at age 30 from 2023 onwards.
Results: In unvaccinated cohorts, the PPV of HPV16 for CIN2+ declined from 48% at age 30 to 26% at age 60. In vaccinated cohorts with 50 percent coverage, the post-vaccine equilibrium PPV of HPV16 for CIN2+ was 39% at age 30 and 27% at age 60. The reduced HPV16-specific CIN2+ risk at age 30 was due to a projected increase in HPV16 infection incidence among unvaccinated women above age 25. Projected effects of vaccination on the PPV of HPV18 were qualitatively similar.
Conclusions: HPV genotyping can help to alleviate the loss in efficiency of cervical screening in vaccine-eligible cohorts, but a drop in HPV genotype-specific PPV cannot be entirely prevented due to shifts in HPV infection prevalence to older age. HPV vaccination status will become an important indicator in future cervical screening programs.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

EFFECT OF HPV VACCINATION ON CERVICAL LESIONS IN OPPORTUNISTIC CERVICAL SCREENING AMONG YOUNG WOMEN IN THE NETHERLANDS

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Introduction: HPV-vaccination was introduced in the Netherlands in 2009, starting with a catch-up campaign for 13-16-year-old girls. Thereafter girls were routinely offered vaccination in the year they turned 13. The cervical screening program starts at 30 years of age. In 2023 the first girls who were eligible for HPV-vaccination, will enter the cervical screening program. However, a substantial number of young women have a cervical smear test taken before the start of the regular screening program. This study was initiated to explore possible early effects of HPV-vaccination on cervical lesions in opportunistic screening.
Methods: Cytology results of cervical smear tests from the nationwide network and registry of histo- and cytopathology in the Netherlands (PALGA) were linked to the women's HPV-vaccination status from the national vaccination registry (Praeventis). The cohort consists of girls eligible for HPV-vaccination (i.e. born from 1993 onwards) who have had a cervical smear test taken between 2009 and 2018. High-risk HPV positive tests (performed on indication) and moderate dysplasia or worse (HSIL or more) in the first cervical smear test from vaccinated and unvaccinated women were compared by using Poisson regression, corrected for age.
Results: A total of 44,820 young women did have one or more cervical smear tests during the study period. Percentages of vaccination coverage among these young women were comparable with the national vaccination coverage (45-61%). Preliminary results show that vaccinated women 16-24 years of age had a lower risk for hrHPV infection (RR: 0.84; 95%CI 0.79-0.90) and moderate dysplasia or worse (RR: 0.54; 0.44-0.66) then unvaccinated women of the same age.

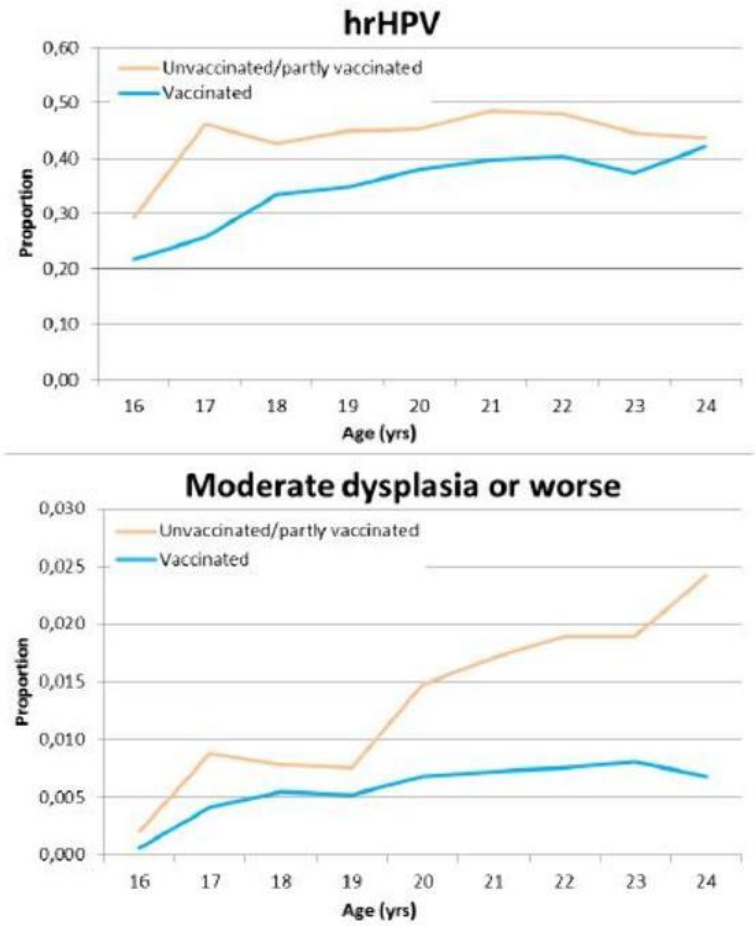

Figure: Cumulative proportion of hrHPV (upper graph) and moderate dysplasia or worse (lower graph) by age for fully vaccinated and unvaccinated/partly vaccinated women 16 to 24 years of age, 2009-2018.

Conclusions: By linking nation-wide registries on histopathology and vaccination, we were able to show significant early effects of HPV-vaccination on hrHP- infection and moderate dysplasia in young women before the start of the cervical screening program. HPV-vaccination status was not associated with uptake of opportunistic screening.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

ESTIMATING THE EFFECT OF HPV VACCINATION ON THE LIFETIME RISK OF SCREEN-DETECTED CERVICAL PRECANCER

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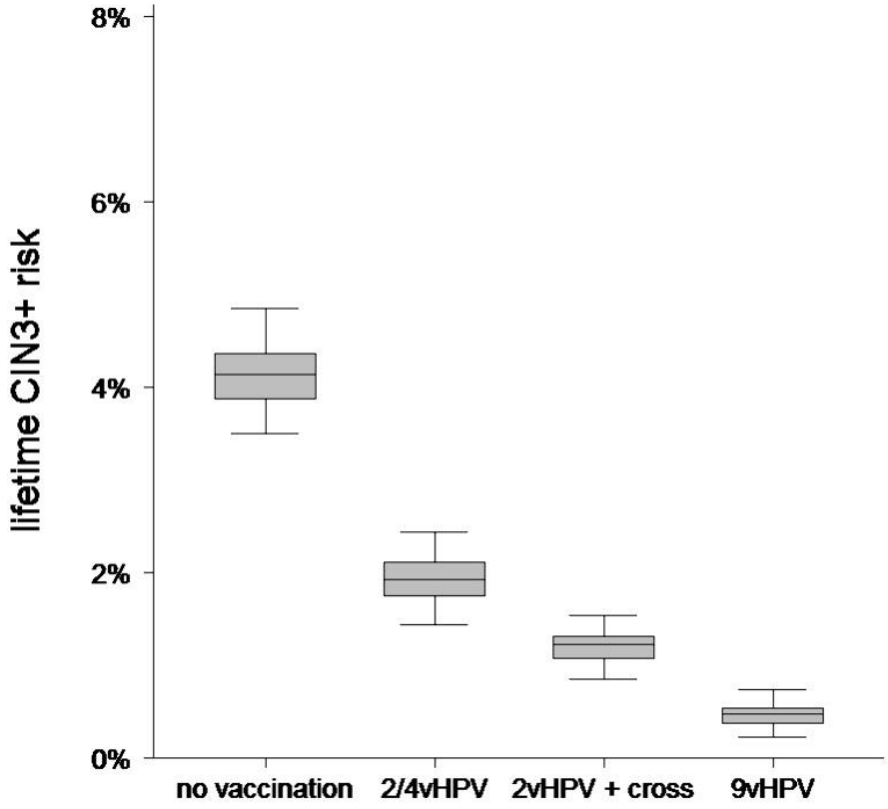
Introduction: Birth cohorts vaccinated against two or more high-risk human papillomavirus (HPV) types are now entering cervical cancer screening age. Recent data support a revision of the screening guidelines for vaccinated cohorts. Lifetime cervical (pre)cancer (CIN3+) risks are needed to assess the demand for subsequent screening in vaccinated women.
Methods: We analyzed HPV genotyping and histology data of 21,287 women participating in the POBASCAM trial, a population-based screening trial with two HPV-based screening rounds. The main outcome measure of this analysis is lifetime (screen-detected) CIN3+ risk, possibly combined with adjunct cytology under five-yearly primary HPV screening between age 30-60. We estimated HPV genotype-specific CIN3+ risks by likelihood maximization. We re-estimated the CIN3+ risk after projecting vaccine efficacy for the bivalent and the nonavalent HPV vaccines.
Results: The lifetime CIN3+ risk was 4.1% (95% confidence interval 3.5-4.9) and declined by 53.5% and 70.5% after bivalent vaccination without and with cross-protection. This risk declined by 88.5% after nonavalent vaccination, translating into a residual lifetime CIN3+ risk of only 0.5% (0.2-0.7). The corresponding CIN3+ risk after positive HPV and abnormal cytology declined to 16.9% (8.7-32.4) after nonavalent vaccination.
Conclusions: HPV vaccination will lead to a strong decline in the lifetime CIN3+ risk and the remaining absolute CIN3+ risk will be very low. Primary HPV testing combined with cytology-triage at five-year intervals still seems feasible, although unlikely to be cost-effective in women that received the nonavalent vaccine. Our results support a de-intensification of the screening programs in settings with high



vaccination coverage.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

PREDICTED IMPACT OF HPV VACCINATION AND PRIMARY HPV SCREENING ON ADVERSE PREGNANCY OUTCOMES IN AUSTRALIA 2005-2070: MODELLING IN A HIGH INCOME, HIGH VACCINATION COVERAGE COUNTRY

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Introduction: Treatment of precancerous cervical abnormalities may be associated with an increased risk of adverse obstetric outcomes (APOs). Australia introduced routine quadrivalent HPV vaccination (HPV4) in 2007, nonavalent vaccination (HPV9) in 2018, and 5-yearly HPV screening in 2017. We predicted the impact of vaccination on rates of preterm births (PTBs) and low birth weight (LBW) infants for singleton pregnancies from 2005-2070.
Methods: We estimated PTB and LBW rates in singleton births in Australia over 2005-2070 using *Policy1-Cervix*, a dynamic model platform of HPV transmission, vaccination, cervical screening and pre-cancer treatment coupled with an individual-based stochastic model of obstetric complications. We simulated a transition to five-yearly HPV screening in 2018, in addition to counterfactual scenarios assuming no HPV vaccination, and HPV9 vaccination coupled with twice-lifetime HPV screening. Our simulations estimated age-specific pre-cancer treatment rates and consequent APOs, based on age-specific probabilities of APOs in singleton pregnancies and the relative risk for APOs in women treated with large loop excision of the transformation zone (LLETZ). PTBs include births of 20-36 weeks gestation, while LBW infants includes infants with a birth weight of less than 2,500 grams.
Results: In women undergoing 5-yearly HPV screening, HPV9 is predicted to reduce PTBs by 1.5% and 2.4%, and LBWs by 2.7% and 4.3%, in 2030 and 2070 respectively, compared to what they would have been without vaccination. Changing from five-yearly to twice lifetime screening in cohorts offered HPV9 would provide a further reduction of 0.2% and 0.4% in PTBs and LBWs respectively in 2070.
Conclusions: It is predicted that HPV9 with 5-yearly HPV screening will have added benefits of a reduction in PTBs and LBW infants in Australia. Changing to twice lifetime screening in these women could further reduce APOs.

ORAL SESSION 18: VACCINATION AND SCREENING. IMPACT OF HPV VACCINATION ON CERVICAL CANCER SCREENING

HPV VACCINE EFFECTIVENESS AND CROSS-PROTECTION BY AGE AT VACCINATION, TIMING OF SEXUAL INITIATION IN RELATION TO VACCINATION, AND NUMBER OF DOSES IN A REAL-WORLD SETTING

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Introduction: The aim of this study was to examine real-world effectiveness and cross-protection after HPV vaccination by age at vaccination, timing of sexual initiation, and number of vaccine doses.
Methods: Women 13-26 years (N=825) who received quadrivalent HPV vaccine were recruited from 2009-2017. We examined detection of cervicovaginal vaccine-type (HPV6,11,16,18) and non-vaccine-type HPV (genetically related to HPV16 [HPV31,33,35,52,58,67] and HPV18 [HPV39,45,59,68,70]), by age at vaccination (≥15 vs. <15 years) and timing of sexual initiation (before vs. after vaccination), using chi-square and Fisher's exact tests. We compared vaccine- and non-vaccine-type HPV by number of vaccine doses, in all women and stratified by age at vaccination and timing of sexual initiation.
Results: Mean age of participants was 18.3 years and mean age at vaccination was 14.4 years. Detection of vaccine-type HPV was higher among those who were ≥15 vs. <15 years when vaccinated (9.5% vs. 3.6%, p=0.0004) and who initiated sex before vs. after vaccination (8.8% vs. 4.0%, p=0.0044). Prevalence of non-vaccine-type HPV related to HPV16 was higher among those ≥15 vs. <15 years at vaccination (27.4% vs. 14.6%, p<.0001) and those who initiated sex before vs. after vaccination (25.7% vs. 15.3%, p=0.0003); Vaccine-type HPV was higher among all women who received fewer doses (12.5% 1 dose, 4.5% 2 doses, 5.3% 3 doses, p=0.02) and those ≥15 years at vaccination who received fewer doses (12.8%, 4.7%, 5.3% respectively, p=0.02). Non-vaccine-type HPV related to HPV16 was higher among women who initiated sex after vaccination and received fewer doses (34.8%, 17.8%, 13.9% respectively, p=.02).
Conclusions: Among women in a real-world setting, vaccination was less effective against vaccine types and against types related to HPV16 in women vaccinated at ≥15 vs. <15 years of age and who initiated sex before vs. after vaccination. One HPV vaccine dose may be less effective and provide less cross-protection than 2 or 3 doses.

FEATURED EPOSTERS

TARGETING HUMAN PAPILLOMAVIRUS PROMOTER REGIONS AS A POTENTIAL ANTIVIRAL STRATEGY

BEST ePOSTER

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Introduction: The genomes of low- and high-risk Human Papillomaviruses (HPV) contain several guanine-rich sequences with the potential of forming stable G-quadruplex (G4) structures, particularly high-risk HPVs 16, 18, 52 and 58. G4 structures are characterized by a planar square arrangement of guanine residues (G-quartets) connected by Hoogsteen hydrogen bonds and stabilized through π-π interactions and a monovalent cation (K^+ or Na^+). These G-rich regions are present in regulatory LCR, E1, E4 regions and the L2 protein coding sequence, which may modulate viral replication and transcription processes. Thus, these motifs are potential targets for G4-targeted compound development, interfering in the regulation of gene expression.
Methods: We screened a library of seven compounds as HPV G4 stabilizing agents, using biophysical techniques such as FRET-melting assay, circular dichroism, fluorescence and nuclear magnetic resonance (NMR) spectroscopy. HPV genotypes 9, 16, 18, 32, 52, 57 and 58 were chosen due to their propensity to form G4 structures in regulatory regions. Additionally, we tested the antiviral activity of the most promising compounds in HPV16 and HPV18-infected cell lines produced by a organotypic (raft) culture system.
Results: All the compounds bind and stabilize the HPV G4 structures. Proton (^1H) NMR suggests that some compounds are able to favor the formation of G4 structures over other secondary DNA conformations such as hairpins, with potential regulatory effect on gene transcription. The antiviral activity of the compounds in infected raft cultures demonstrated the ability of one compound to decrease HPV18 viral titers by 10-fold, with pronounced HPV-dependent tissue growth inhibition at nanomolar concentrations.
Conclusions: Altogether, these results indicate that targeting HPV G4 structures may be a promising alternative route for the development of novel antiviral therapies. Acknowledgments: J. Carvalho acknowledges the fellowship from FCT, ref.SFRH/BD/122953/2016. This work was supported by projects “Ações Integradas Luso-Francesas” ref.TC-15/17, UTAustin-Portugal Program DREAM ref.UTAP-EXPL/NTec/0015/2017 and FCT ref.IF/00959/2015.

GENOME-WIDE DNA METHYLATION PROFILING IDENTIFIES TWO NOVEL GENES IN CERVICAL NEOPLASIA

BEST ePOSTER

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Introduction: We used a pan-epigenomic approach to identify new methylation markers in cervical carcinogenesis. We determined the best performing methylation markers for risk of progression along the spectrum of lesion grades. We also evaluated the correlation between methylation levels and lesion grade.
Methods: Extracted DNA from physician-collected cervical samples (54 normal, 50 CIN1, 40 CIN2, and 42 CIN3) was subjected to Illumina Infinium EPIC array analysis. CpG sites whose state of methylation correlated with lesion grade were considered (Spearman correlation analysis), and a weighted DNA methylation score was calculated, comparing normal to CIN3. Methylation markers were assessed via receiver-operating characteristic curves for sensitivity and specificity as a function of methylation. Verification of identified genes was performed using a publicly available cervical cancer dataset (GSE68339, n=270). Validation of the top selected genes was performed in an independent cohort (100 normal, 50 CIN1, 50 CIN2, 50 CIN3, 8 cervical cancers) of new patients, using targeted DNA methylation Illumina amplicon sequencing. The relationship between a combined weighted score of these markers and progression (normal to CIN grades and cervical cancer) was compared using one-way ANOVA.
Results: Our analyses revealed 7715 CpGs whose DNA methylation level correlated with progression (from normal to CIN1, CIN2, and CIN3). There was a significant trend of increased methylation with disease grade. We shortlisted a bigenic (hyaluronan synthase 1, *HAS1* and ATPase phospholipid transporting 10A, *ATP10A* corresponding to cg03419058 and cg13944175 sites) methylation marker set; r=0.55, p<0.0001. Sensitivity and specificity were both 1.00 for detection of cancer, and verification revealed a significant positive correlation (r=0.88, p<0.0001). Validation of the four most discriminating genes (*CA10*, *DPP10*, *FMN2* and *HAS1*) showed a significant correlation between methylation levels and disease progression (p-value $<2.2x10^{-16}$, adjusted R-squared=0.952).
Conclusions: Translational research of the identified genes to future clinical applications is warranted and may improve risk stratification in cervical screening.

IN VIVO MODEL FOR PAPILLOMAVIRUS INFECTION AND PREVENTION OF TRANSMISSION AND EFFECTIVE DISINFECTION

BEST ePOSTER

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Introduction: Papillomavirus transmission studies have typically used cell-free virus prepared in organotypic raft culture, or recombinant pseudo-virus isolated from monolayer 293TT cells then been investigated by quantitating viral gene transcripts after infecting reporter cells. During natural *in vivo* infection however, virions are shed from the epithelial surface in squames, and the successful transmission/infection results in new lesion formation.
Methods: We established an in vivo model, which mimics natural papillomavirus transmission/infection, and evaluated them quantitatively by utilising RNAscope to identify lesion formation microscopically and visual inspection for lesions macroscopically, in conjunction with *in vitro* infection of reporter cells using HPV16/18 raft virus and HPV16 pseudo-virus.
Results: Similar to HPV, MmuPV1 virus titre/infectivity can be quantified by RT-qPCR (E1^E4) or RNAscope (E6E7) using HaCaT cells. Virus titre/infectivity can be also quantified as periods of lesion formation *in vivo* model with a 6-log dynamic range. Up to 10 million virus particles can be produced from the surface layers of a productive lesion and transmitted with an approximate one log drop in infectivity if transmission is mediated indirectly on fomites. Virus in squames is stable following desiccation, with minimal loss of titre on fomites over 12 months. In contrast, cell-free MmuPV1 virion is not stable with loss of titre within 8 weeks. The efficacy of disinfectants was also evaluated using these in vitro/vivo models.
Conclusions: MmuPV1 *in vitro* and *in vivo* infection models using natural viruses produced from productively infected lesions are powerful methods to investigate PV transmission and susceptibility of PV for disinfectants, which can be utilised for HPV transmission. These models have demonstrated different viral shedding patterns that can affect virus stability and susceptibility for disinfectants. Importantly, we have utilised these models to demonstrate the utility of OPA in stark contrast to other studies.

LONG-TERM CERVICAL CANCER RISK FOLLOWING HPV INFECTION – 28 YEAR FOLLOW-UP OF THE MANCHESTER COHORT

BEST ePOSTER

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Introduction: The natural history of HPV infection and subsequent invasive cancer development can only be studied over long periods and in large cohorts. Decisions on implementing primary HPV testing are often based on studies with CIN2 or CIN3 as the primary outcome due to the rarity of invasive cancer.
Methods: In collaboration with over 100 general practitioners and screening clinics in the Greater Manchester area, cervical cell samples were collected from 49,655 women attending for routine cytology screening 1988-1993. There was no age restriction. HPV testing (HPV L1 MY09/MY11 consensus primers) was carried out between 1990 and 1996 on a random sample of 7278 women, 6462 of whom gave a satisfactory β-globin result. The cohort has been linked to national cancer registration for CIN3 and cancer, with a median follow-up of 26 years.
Results: Follow-up identified 1143 cases of CIN3 and 138 invasive cervical cancers. Stored samples from cervical cancers, CIN3s and random controls are being tested for HPV. A preliminary analysis included 126 cases of CIN3 and 17 invasive cervical cancers among 6215 women whose entry sample was tested for HPV in 1990-1996. The cumulative invasive cervical cancer risk 25 years after testing positive for HPV16/18 (270 women) was 2.7% (95%CI: 1.3%-5.5%: 7 cancers) and for other HR-types (169 women) was 1.2% (95%CI: 0.3%-4.7%: 2 cancers). The cumulative risk following a negative HPV test (5,776 women) was 0.13% (95%CI:0.06%-0.28%: 7 cancers). The ratio of CIN3 to invasive cancer decreased with increasing time and CIN3 was rarely diagnosed above age 45. We did not observe any additional CIN3 diagnoses beyond 13 years in women who tested HPV positive at baseline.
Conclusions: CIN3 risk declined sharply beyond 5 years after HPV detection, however the invasive cancer risk remains elevated into middle and old age. More detailed results by age and HPV status will be presented.

ATOMIC RESOLUTION CRYOEM STRUCTURE OF HPV16 REVEALS CAPSID FLEXIBILITY AND L2 RESIDUES ADJACENT TO CONSERVED L1 REGION.

BEST ePOSTER

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Introduction: Human papillomavirus (HPV) is a significant health burden and leading cause of virus-induced cancers. HPV is epitheliotropic and its replication is tightly associated with the terminal differentiation of basal cells into keratinocytes. The restricted tropism makes production and purification of high titer virus preparations for research problematic, therefore alternative HPV production methods have been developed within the HPV research community for molecular biology and structural studies.
Methods: In this study we use HPV16 quasivirus, composed of HPV16 L1/L2 capsid proteins with a packaged cottontail rabbit papillomavirus genome. We have achieved the first atomic resolution structure of a human papillomavirus by using our own cryo EM reconstruction software for icosahedral sub-volume extraction and correlative classification (ISECC).
Results: Further interpretation of the map revealed flexibility, which was quantified to show the direction and magnitude of the capsid movements. Due to the atomic resolution, we were able to build L1 un-ambiguously and identify non-L1 protein strands. This putative L2 density is incorporated adjacent to conserved L1 residues on the interior of the capsid.
Conclusions: The resulting virus structure is a promising step forward in the study of papillomavirus and will provide a framework for continuing biochemical, genetic and biophysical research for papillomaviruses. Furthermore, our approach has allowed insight into the resolution barrier that has previously been a limitation in papillomavirus structural studies.

THE PAST, PRESENT AND FUTURE IMPACT OF HIV PREVENTION AND CONTROL ON HPV AND CERVICAL CANCER IN TANZANIA: A MODELLING STUDY

BEST ePOSTER

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Introduction: Women with HIV have an elevated risk of HPV infection, and eventually, cervical cancer. Tanzania has a high burden of both HIV and cervical cancer, with an HIV prevalence of 5.5% in women in 2018, and a cervical cancer incidence rate among the highest globally, at 59.1 per 100,000. We aimed to quantify the impact that HIV control has had and may continue to have on cervical cancer in Tanzania over a period from 1995 to 2070.
Methods: A dynamic model of HIV and HPV infection and natural history was used to simulate the impact of voluntary medical male circumcision (VMMC), anti-retroviral therapy (ART), and targeted pre-exposure prophylaxis (PrEP) on HPV and HIV prevalence, cervical cancer incidence and cervical cancer mortality from 1995-2070.
Results: From 1995-2020, we estimate that VMMC has prevented 3,014 cervical cancer cases, 1,067 cervical cancer deaths, and 24,967 total deaths in Tanzania; by 2070 we predict that VMMC will have saved 1.78 million lives and have lowered cervical cancer incidence and mortality rates by 30% and 27%, respectively. We predict that ART temporarily increases cervical cancer diagnoses and deaths, due to the removal of HIV death as a competing risk, but will ultimately lower cervical cancer incidence and mortality rates by 36% and 31%, respectively, saving 1.49 million lives by 2070.
Conclusions: HIV treatment and control measures in Tanzania have an added long-term benefit to cervical cancer incidence and mortality; however, in the near term, the life-extending capability of ART has resulted in the opportunity for additional cervical cancer cases and deaths. Continued efforts towards HIV prevention will reduce cervical cancer incidence and mortality. To achieve further reductions, and to eliminate cervical cancer, scaling up HPV vaccination and cervical screening is required.

SQZ-PBMC-HPV, AN INNOVATIVE, AUTOLOGOUS THERAPEUTIC HPV-16 CANCER VACCINE ENGINEERED BY MICROFLUIDIC CELL SQUEEZING TO ELICIT ROBUST CD8+ T CELL RESPONSES

BEST ePOSTER

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Introduction: Effective antigen presentation on MHC-I remains a barrier to generating clinical effective therapeutic cancer vaccines. Most approaches rely on endocytosis. We used a microfluidics-based approach to squeeze (Cell Squeeze®) peripheral blood mononuclear cells (PBMC) and deliver antigen cytosolically. The resulting antigen presenting cells (APCs) provide enhanced antigen presentation on MHC-I and elicit robust CD8+ T cell responses.
Methods: Cytosolic antigen delivery is combined with adjuvant maturation to induce Signal 2 & 3 upregulation. Murine or human PBMCs were loaded with synthetic long peptides (SLP) containing MHC-I restricted epitopes from HPV16 E6 and E7 antigens. Studies were performed to demonstrate cytosolic delivery, cell maturation, functionality and anti-tumor efficacy (TC-1 tumor model). In the FIH study SQZ-PBMC-HPV-101 (NCT04084951), HLA A*02+ patients with HPV16+ recurrent, locally advanced or metastatic solid tumors are eligible. To generate a cryopreserved product, autologous patient leukopaks will undergo an 18 -hour manufacturing process. Study SQZ-PBMC-HPV-101 includes escalation cohorts as monotherapy and in combination with atezolizumab.
Results: In murine studies, prophylactic immunization elicited protective immunological memory. Therapeutic immunization induced tumor regression and significantly extended survival. Tumor regression correlated with an influx of E7-specific CD8 T cells (~80% of the CD8 T cells). Studies in MHC-I knockout miceconfirmed the effects were a result of direct antigen presentation by SQZ-engineered PBMCs on MHC-I.Healthy volunteer PBMCs also demonstrated intracellular SLP delivery to all major PBMC subsets in vitro with each capable of functional responses. Cell Squeeze® has been established at manufacturing scale for clinical studies.
Conclusions: Through direct cytosolic delivery of antigen, we engineered PBMCs to function as potent APCs. Our data demonstrate significant potential to generate $CD8^+$T cell responses and warrant evaluation in a FIH study in cancer patients with HPV16+ tumors.

EXTENDED IMMUNOGENICITY OF THE QUADRIVALENT HPV VACCINE IN A COHORT OF GIRLS LIVING WITH HIV

BEST ePOSTER

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Introduction: Girls and women living with HIV experience higher rates of HPV infection and associated disease. Understanding the vaccine impact is vital to achieving elimination of cervix cancer globally. This analysis assessed the immunogenicity and efficacy of the qHPV vaccine up to 8 years post-vaccination in a cohort of girls living with HIV (GLWH).
Methods: GLWH participating in a multi-centre study of the qHPV vaccine were administered three doses at 0/2/6 months. Demographic and clinical data, serology (cLIA), liquid-based cervical cytology, and HPV DNA genotyping (Linear array assay) were collected. Immunogenicity endpoints were geometric mean titers (GMTs) of anti-HPV antibodies and seropositivity rates.
Results: 41 girls were eligible for the per-protocol immunogenicity (PPI) population (3 doses of vaccine within 1 year, ≥1 follow-up beyond month 7, naive to the relevant qHPV type). At first vaccination, median age was 12 years (IQR: 10-13), median CD4 count was 701/mm3 (IQR: 540-878), median CD4 nadir was 470/mm3 (IQR: 262-598) and 61% had a suppressed HIV viral load (<50 copies/mL). Median follow-up was 6.1 years. At month 7, seropositivity rates for HPV6/11/16/18 were all 100.0%. At month 84, seropositivity rates were 82.4%, 70.6%, 88.2%, and 56.3%, respectively. Only two girls had pelvic data collected due to most not yet being sexually active or age-eligible. No cases of persistent qHPV, genital warts, or CIN2+ were observed. Comparisons to serologic response in studies of girls without HIV were made.

HAS HPV VACCINATION PREVENTED ADVERSE PREGNANCY OUTCOMES? POPULATION LEVEL ANALYSIS AFTER EIGHT YEARS OF A NATIONAL HPV VACCINATION PROGRAM IN AUSTRALIA

BEST ePOSTER

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Introduction: HPV infection, and its sequelae of precancerous cervical lesions and their subsequent treatment, have been linked with an increased risk of adverse pregnancy outcomes (APOs), including an increased risk of preterm births (PTBs) and small for gestational age (SGA) infants. Publicly-funded HPV vaccination of adolescent females commenced in Australia in 2007 with initial catch-up to age 26 years. Vaccination has been shown to reduce rates of HPV infections, anogenital warts, and cervical precancerous lesions.
Methods: Using aggregated data from the Australian Institute of Health and Welfare National Perinatal Data Collection, we compared rates of PTBs and SGA infants born in Australia between 2000 and 2015. We used generalised linear models (GLMs), assuming a Poisson distribution and log link function, with single-year categories of infant birth year, maternal age, and age-year-specific HPV vaccination coverage as independent variables.
Results: For every 20% increase in HPV vaccination coverage in the maternal cohort, there was a relative incidence rate reduction of 1.0% (95%CI: 0.4%-1.5%) for PTBs and 1.8% (95%CI: 1.2%-2.4%) for SGA births, after adjusting for infant's birth year and maternal age. In the maternal cohorts with 60-80% HPV vaccination coverage achieved in Australia, the vaccination program within this period is estimated to have resulted in a reduction of 3.2% (95%CI: 1.1%-5.3%) in PTB and 9.8% (95%CI: 8.2%-11.4%) in SGA infants. We estimated that about 370 PTBs and over 1000 SGA births may have been prevented in Australia in 2015.
Conclusions: Although data were aggregated and we were unable to fully adjust for potential confounding by smoking behaviour and other factors, this study provides preliminary population-level evidence of a reduction in APOs in cohorts of women who have been offered HPV vaccination. These findings from Australia, the first country to introduce HPV vaccination, indicate broader benefits than have been documented to date.

HIGH PREVALENCE AND CONCORDANCE OF ANAL AND CERVICAL HPV GENOTYPES

BEST ePOSTER

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Introduction: The incidence of anal cancer is increasing by 2% each year in all genders. High-risk (HR) Human Papillomavirus (HPV) genotypes associated with cervical cancer can also induce anal cancer and its precursors (AIN). Women with history of CIN have a 10-fold increased risk of anal dysplasia. This study explores the correlation between cervical and anal HPV infection as well as the development of cervical and anal dysplasia.
Methods: Women with gynaecological clinical indication (HPV/cytology/histology) were recruited. Initially, anal cells were collected using swabs for HPV testing and cytological examination, followed by a cervical smear to prevent contamination between the smears taken. Anal HR-HPV positive women were followed up and underwent high-resolution anoscopy (HRA). Anal and cervical smear tests were repeated after 12 months. Women becoming anal HR-neg. completed the study, anal HR-HPV positive but HRA inconspicuous women had a final examination after 48 months.
Results: So far, 69.7% (n=53) women had ≥1 anal HR-HPV type and HPV-positivity at the cervix (visit 1). From these, 84.9% (n=45) had ≥1 identical HPV type at cervical and anal sites. Cervical examination demonstrated 25 low-grade and 8 high-grade dysplasia. The anal smear tests showed no clinical indication. 26 women underwent HRA with no clinical findings (no AIN n=25, non-valid result n=1). Anal HR-HPV and cervical HPV-positivity was detected in 60% (n=12), including 9 women with ≥1 identical HPV type cervical and anal. Five women had persistent co-infections (from V1-V3), whereas 7 women either had new co-infections or loss of HPV-genotypes.
Conclusions: HPV infection at the anal region in women with cervical clinical indication and with HPV infection is common. The concordance between cervical and anal HPV is prominent (69.7%). Despite this very high anal infection rate, the rate of anal dysplasia is low as compared to cervical sites.

POSTER VIEWING

HUMAN PAPILLOMAVIRUS CORRELATES OF HIGH GRADE CERVICAL DYSPLASIA AMONG HIV-INFECTED WOMEN IN NIGERIA

CLINICAL RESEARCH / MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

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Introduction: The immunosuppressive state induced by Human immunodeficiency virus (HIV) potentially increases HPV acquisition, persistence, and development of cervical cancer. Persistent hrHPV infection is higher among women living with HIV/AIDS thus increasing their risk for cervical cancer. We evaluated the virological and immunological correlates of cervical dysplasia in HIV-infected women.
Methods: A cohort of 220 consenting women attending the antiretroviral clinic of the Federal Medical centre, Keffi, Nigeria was tested for cervical HPV infection using nested PCR. The prevalent HPV genotypes were determined by DNA sequencing. CD4+T count and type specific HPV was correlated with cervical cytology. Descriptive and inferential statistical analysis of the data was done using the statistical package for social sciences (SPSS) version 20 (SPSS Inc, Illinois, USA) for analysis after validation.
Results: Overall HPV prevalence was 119 (54.1%) while the hrHPV prevalence was 79 (35.9%). HPV 35 was the most frequent 12 (20.5%), with multiple HPV infections seen in 25 (21.0%) samples. Premalignant and malignant lesions were observed among 54 (25.3%) participants with CIN II being the predominant type lesion. Majority (72.0%) of the premalignant and malignant lesions were observed among participants with CD4+T counts that ranged from 200 to 300 cells/mm^3 A statistically significant association was observed between cervical premalignant lesions and CD4+ count (X^2 =24.747, P value =0.001) as well as hrHPV infections (X^2 = 46.800, P <0.001).
Conclusions: High risk HPV infection is an independent risk factor for cervical precancerous lesion. Additionally, HIV positive women with low CD4+T count are at a higher risk of cervical precancerous lesions. The high prevalence of precancerous lesions in the HIV-infected sub-population justifies the need for routine targeted screening of HIV-infected women to reduce morbidity and mortality from cervical cancer.

MINION NANOPORE SEQUENCING AND ASSEMBLY OF A COMPLETE HUMAN PAPILLOMAVIRUS GENOME

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: The MinION™ sequencer (Oxford Nanopore Technologies) belongs to the third generation sequencing technology that allows the generation of long reads of up to 200 kb. Therefore, the Minion may be useful for rapid sequencing of full-length viral genomes from papillomaviruses, instead of using time-consuming and low-throughput methodologies such like Sanger sequencing.
Methods: The Oxford MinION Technology has been used to sequence the whole genome of HPV_ICB2 (7441 bp) from a skin swab, that has been recently isolated by our laboratory. DNA library preparation was carried out according to the 1D PCR barcoding amplicons SQK-LSK109 protocol. In order to identify the best strategy for obtaining an accurate sequencing of the whole viral genome, we have performed; (protocol A) three consecutive MinION runs of 12 hours each and, (protocol B) a single MinION run of 48 hours starting from a pool of three barcoded DNA libraries. A bioinformatics workflow was developed for the reconstruction of the viral genome.
Results: The protocol A generated a total of 9,354,933 reads. More than 89% of the reads passed the QC filtering. Read length N50 ranged between 7,316 and 7,355 nucleotides over the three sequencing runs. Although the number of active nanopores was limited (n=560), the protocol B produced 3,255,879 reads, among which 70.1 % passed the QC filtering. Read length N50 was 7260 nucleotides. More than 85% of the reads generated by both protocols were identified as HPV-ICB2 sequences. Bioinformatics analysis showed that the whole genome of HPV-ICB2 can be reconstructed from both protocols, with a percentage of pairwise identity of up to 99%.
Conclusions: These results support the fact that this new technology can be applied for sequencing of full-length genomes from papillomaviruses, thus constituting an important tool for rapidly characterizing HPV genomes.

UNDERSTANDING THE RELATIONSHIP BETWEEN ONCOGENIC HUMAN PAPILLOMAVIRUS (HPV) STATUS, CLINICAL CHARACTERISTICS AND HPV PSYCHOSOCIAL BURDEN IN WOMEN WITH ABNORMAL CERVICAL CYTOLOGY

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: The use of HPV testing in cervical screening and triage has been associated with increased psychosocial burden and perceived risk of cancer. This study aim was to identify and describe clinical, demographic and psychosocial variables that influence HPV burden (the psychosocial impact of an HPV infection) following HPV results disclosure.
Methods: This prospective pilot study examined 128 women referred with abnormal cytology to a large Toronto colposcopy clinic between December, 2013 and September, 2014. Demographic and clinical characteristics, and standardized measures for HPV Burden [(HPV Impact Profile (Mast et al, 2009)], were collected via survey and chart audit at two points in time: 1) at initial colposcopy consultation, and; 2) 4 to 6 weeks following initial consultation.
Results: Mean HPV burden scores were 37.5 and were higher among HPV positive and untested compared to HPV negative women [24.9 (HPV negative), 44.0 (HPV positive), and 38.1 (HPV untested), ($p<0.01$)]. Psychosocial characteristics of women with higher HPV burden included lower self-efficacy (B=-0.31, 95% CI=-0.48 to -0.14), p=0.01), higher perceived risk of cancer (B=1.77, 95% CI= 0.67 to 2.88, $p<0.01$), greater baseline anxiety (clinical cut-off; B=5.51, 95% CI= 0.64 to 10.38, p=0.03), higher cancer-related distress (clinical cut-off) (B=11.91, 95% CI=6.55-17.28, $p<0.01$), and those who were HPV positive (B=11.36, 95% CI=1.65-21.06, p=0.02).
Conclusions: Results from this study indicate that a number of factors influence HPV-related burden, highlighting the potential for the use of HPV testing, knowledge of one's HPV status, and self-efficacy to decrease HPV burden for those most at risk. Future work is needed to establish anticipated clinical ranges for HPV related burden, determinants of HPV burden and strategies to assist women to appropriately cope.

NEGATIVE ATTITUDES TOWARDS HUMAN PAPILLOMAVIRUS VACCINATION AMONGST CAREGIVERS RESULT IN LOW VACCINATION UPTAKE IN AGE-ELIGIBLE GIRLS ATTENDING PRIVATE SCHOOLS IN SOUTH AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The South African (SA) government provides free vaccination against cervical cancer for public sector school girls aged ≥9 years in Grade 4. While public sector first dose human papillomavirus (HPV) vaccination coverage is >80%, no data on vaccination coverage or factors associated with HPV vaccination uptake are available on age-eligible girls attending private sector schools. This study investigated if caregivers' knowledge of and attitudes towards HPV vaccination predict HPV uptake in age-eligible girls attending private schools in SA.
Methods: A link to an online survey (Survey Monkey®, USA) on HPV vaccination coverage and caregivers' HPV vaccination knowledge and attitudes was circulated to caregivers via an email sent to school principals of all private schools in four provinces enrolling girls in grades 4-7. Following a poor post-reminder response, a paid Facebook survey-linked advert targeting SA Facebook users aged ≥25 years nationally was run for 4 days, and placed on the SA Vaccination and Immunisation Centre's Facebook page for 20 days. Epi Info™ was used for descriptive and inferential statistical analysis. Institutional ethical clearance and informed consent from respondents were obtained.
Results: In total 615 responses (448 post-Facebook advert) were received, with 413 providing HPV vaccination data and 455 completing the knowledge and attitudes tests. Only 19.4% of the girls were vaccinated, while 76.5% of caregivers had good knowledge and 45.3% had positive attitudes towards HPV vaccination. Daughters of caregivers with negative attitudes were statistically significantly less likely to be vaccinated (OR 0.2; 95% CI: 0.1-0.3).
Conclusions: This survey suffers from selection bias, since the majority of respondents were Facebook users. The results are nevertheless concerning, and suggest that a HPV vaccination advocacy campaign is urgently needed, and while this needs to be directed at all stakeholders, caregivers of girls attending private schools need to be specifically targeted.

EVALUATION OF FOLATE RECEPTOR-MEDIATED DETECTION AS AN ALTERNATIVE DIAGNOSTIC TOOL FOR CERVICAL INTRAEPITHELIAL NEOPLASIA 2+

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: *FRD ® (Folate Receptor-mediated Detection) has been proposed as a reliable method to screen cervical intraepithelial neoplasia 2+ (CIN2, CIN3, and cervical cancer). This study investigates the clinical significance of FRD ® by comparing the accuracy of FRD ® with that of HPV Testing and Thinprep Cytology (TCT).*
Methods: *From March 2019 to April 2019, 81 patients in the gynecology clinic of the Second Hospital of Jilin University received screening with FRD ®, TCT, and HPV examinations upon visiting the clinic. If any of the three tests provided a positive result, colposcopy was performed with biopsy being the gold standard for pathological diagnosis.*
Results: *The sensitivity of FRD ®, TCT, and HPV in the diagnosis of cervical intraepithelial neoplasia 2+ (CIN2, CIN3, Cervical Cancer) were 72.22%, 72.22%, and 83.33% respectively. The specificity of FRD ®, TCT, and HPV in detection of CIN2+ was 65.07%, 60.31%, and 25.39% respectively. The accuracy of FRD ®, TCT, and HPV in diagnosis of CIN2+ was 66.67%, 62.96% and 38.27%. The positive predictive value (PPV) of FRD ®, TCT, and HPV in diagnosis of CIN2+ was 37.14%, 34.21% and 38.27% respectively, while the negative predictive value (NPV) was 89.13%, 88.37% and 84.21% respectively.*
Conclusions: *FRD ® provided high values of sensitivity, specificity and accuracy. FRD ® has advantages in detection speed (< 60 seconds), economic cost, and patient compliance. FRD ® can be an effective and advantageous tool for the primary screening of cervical intraepithelial neoplasia 2+ (CIN2, CIN3, Cervical Cancer), especially in regions with hard-to-reach patients. FRD ® could also provide significant value as a co-test with HPV Testing.*

CERVICAL CANCER INCIDENCE IN YOUNG WOMEN IN AUSTRALIA BY VACCINATION STATUS: A NATIONAL LINKED DATA ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Quadrivalent HPV vaccination commenced in 2007 in Australia, with a 3-year catch-up program vaccinating >50% of females 12-26 years. The median age of sexual debut is 16-17 years, meaning many vaccinated women were already HPV-exposed. Australia maintains registries of HPV vaccination and cancer.
Methods: The Australian Institute of Health and Welfare linked data using name-based probabilistic methods between the HPV vaccination register and the Australian cancer database. National cancer data depend upon timely data from 8 jurisdictions and was only available up to 2012 at linkage. Following the methods of Luostarinen et al 2018, we compared the incidence of cervical cancer in young women, as well as breast and thyroid cancer as control cancers, by HPV vaccination status between April 2007-Dec 2012. The population cohort comprised 6.4 million females born 1 Jan 1981- 1 January 2000 (oldest age 26 in 2007, youngest 12 in 2012). We also evaluated cancer type and vaccination history of all women diagnosed with cervical cancer after vaccination.
Results: Crude incidence rates of cervical, breast and thyroid cancer were low and comparable between fully vaccinated and unvaccinated women (cervix 1.6 vs 2.2, breast 1.8 vs 2.1, thyroid 3.9 vs 3.6). Cervical cancer incidence increased over time with cohort ageing; in 2012 rates were 2.5 (95%PoissonCI 1.7- 3.4) and 5.9 (95%PoissonCI 4.6-7.4) per 100,000 amongst fully vaccinated and unvaccinated women respectively. Of 102 cases of cervical cancer diagnosed in vaccinated women 2007-2012, only two cases, of non-HPV associated clear cell adenocarcinoma, occurred in women unlikely to have been sexually active prior to vaccination (as determined by age, screening history and dose dates).
Conclusions: Six years follow-up is too early to observe a population level decline in cervical cancers in Australian women who received catch up HPV vaccination. However these data suggest that significant reductions may be commencing.

HUMAN PAPILLOMAVIRUS TYPES CAUSING RECURRENT RESPIRATORY PAPILLOMATOSIS IN ZIMBABWE

CLINICAL RESEARCH /RECURRENT RESPIRATORY PAPILLOMATOSIS

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Introduction: Recurrent respiratory papillomatosis (RRP) caused by human papillomavirus (HPV) is preventable through vaccination. This study was motivated by the recent thrust of the Zimbabwean government to reduce incidence of HPV related cervical cancer in Zimbabwe through vaccination against HPV. We therefore set out to type HPV genotypes causing RRP in Zimbabwe. We also describe for the first time, the demographics of Zimbabwean RRP patients, the characteristics of patients with different HPV types and possible risk factors of HPV infection in our setting.
Methods: We conducted a prospective, hospital based study were patients were recruited from two national otorhinolaryngology hospitals in Zimbabwe. All patients diagnosed with RRP during a twenty four month period were included in the study. A questionnaire was administered per patient to collect both demographic and clinical variables. HPV DNA was extracted from formalin fixed paraffin embedded laryngeal tissue. The extracted HPV DNA was amplified using polymerase chain reaction and next generation sequencing was used to genotype the HPV types.
Results: A total of 52 patients all aged 14 years and under were recruited into the study. Only Juvenile onset RRP cases were observed over the two year period and 64% of the patients were HPV positive. HPV types 6 and 11 were the dominant types observed constituting 85% of all HPV types. The remaining 15% constituted of HPV 16 and HPV 18. 27% of the patients had coinfection with at least two different HPV types. There were no statistically significant differences between the characteristics of HPV positive and HPV negative patients. No statistically significant risk factors were observed.
Conclusions: HPV types 6 and 11 were the predominant genotypes causing RRP in Zimbabwe. Thus the use of quadrivalent or even nonavalent HPV vaccines may play an important role in the prevention and management of RRP in Zimbabwe.

MRNA BIOMARKER IN ANAL CYTOLOGY: A FEASIBLE APPROACH FOR ANAL CANCER SCREENING IN MEN WHO HAVE SEX WITH MEN LIVING WITH HIV

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: There is growing interest in anal cancer screening strategies. However, cytological/molecular evaluation of anal samples is challenging. We aimed to determine the feasibility of detecting, in anal liquid-based cytologies, the expression of biomarkers involved in the cell cycle disturbance elicited by human papillomavirus (HPV). The accuracy of this approach in the identification of high-grade squamous intraepithelial lesions/anal intraepithelial neoplasia grade2-3 (HSIL/AIN2-3) was also evaluated. 215 anal cytologies from men having sex with men living with human immunodeficiency virus were evaluated.
Methods: For this cross-sectional study, anal cytology samples, collected in the Anal Cancer Prevention Unit from January to December 2016 from men who have sex with men living with HIV, were retrieved from the Department of Pathology of the Hospital Clinic. Patients showing concordant cytological and anoscopy-directed biopsy diagnosis were selected: 70 with negative cytology and HPV test, 70 with low-grade SIL (LSIL/AIN1) cytology and biopsy, and 75 with cytology and biopsy of HSIL/AIN2-3. CDKN2A/p16, MKI67 and TOP2A mRNA expression was analyzed. HPV detection was performed with Xpert HPV Assay (Cepheid, Sunnyvale, CA). The data were analyzed with the SPSS program (Version 24.0).
Results: The mRNA expression was significantly higher in HSIL compared with LSIL and negative samples for the three biomarkers: TOP2A ($p= 0.043$ and $p=0.030$, respectively), MKI67 ($p=0.011$ and $p<0.001$, respectively) and CDKN2A/p16 ($p=0.011$ and $p<0.001$, respectively). The specificity for HSIL/AIN2-3 detection for a sensitivity established at 70% was 44.7% (95%confidence interval [CI] 36.5-53.2) for TOP2A and MKI67 and 54.5% (95%CI 46.0-62.8%) for CDKN2A/p16.
Conclusions: mRNA detection of cell biomarkers in anal liquid-based cytology is feasible. Further studies are warranted to confirm if strategies based on mRNA detection have any role in anal cancer screening.
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COMPARISON OF COPAN URISPONGE TO COLLI-PEE FOR THE COLLECTION OF URINE FOR HPV DETECTION WITH MOLECULAR ASSAYS

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Urine collection is non-invasive and accepted by patients comparing to vaginal, cervical or urethral self-collection for HPV screening at point of care or at home. Easy-to-use, and leak-proof devices are essential for HPV screening programs. The Copan UriSponge (TM) (US), can be used for the collection of urine for culture and molecular assays, has a leak proof-tube with a screw cap containing a plastic stick with sponges attached that absorb and retain the urine sample during transport. The objective of this study was to compare the UriSponge (TM) (US) to the Colli-Pee (CP) (Novosanis) urine devices for self-collection of first-void-urine (FVU) for the detection of HPV with the Seegene Anyplex II HPV28 assay.
Methods: FVU were collected in steriale containers by 63 patients with a recent diagnosis of cervical dysplasia, attending the Gynecology Clinic. In the laboratory one urine aliquot was used to saturate the UriSponge and 20 ml were added to a CP. Nucleic acids were extracted by NucliSENS easyMAG (bioMérieux) from US and CP urine samples and HPV detection was performed using AnyplexII™ HPV28 Assay. Sample cellularity was evaluated with a real-time PCR detecting human CCR5 gene.
Results: In 64 urines tested in duplicate for HPV, 36 (56.3 %) were positive for HR, 13(20.3%) for LR and 14 (21.9%) were negative in US and CP samples. Adequate and comparable cellularity was present in both samples with a mean value of 2.09E+06. Optimal concordance for all HR HPV type compared to cervical sample was demonstrated for both urine devices.
Conclusions: Data obtained in this study demostrated that the UriSponge(TM) detected all the HR-HPV positive and good cellularity compared to cervical swab and to Colli-Pee using the Anyplex II HPV28 assay. The UriSponge(TM) is easy-to-use for urine self-collection, it's not bulky, can be shipped by mail, and cost less comparing to the Novosanis Colli-Pee.

MOTHERS' KNOWLEDGE AND ATTITUDES TOWARDS THE HUMAN PAPILLOMAVIRUS (HPV) VACCINATION IN CHILDREN: A NATIONWIDE CROSS-SECTIONAL SURVEY FROM CROATIA

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Although the prevention of cervical cancer is one of the priorities in global health, related knowledge on human papillomavirus (HPV) and vaccination might represent a barrier to vaccine acceptance. Since Croatia is a country with low HPV vaccine uptake, we designed a survey to address the knowledge and attitudes towards HPV and HPV vaccination specifically in mothers.
Methods: This nation-wide, cross-sectional study consisted of 743 mothers who volunteered to participate in the survey. The questionnaire that was used encompassed seven groups of questions informed by the literature, appraising demographic data, basic HPV knowledge, basic HPV vaccine knowledge, attitudes towards HPV vaccination and other pertinent HPV issues. Statistical significance was set at $p<0.05$.
Results: The study has showed satisfactory basic knowledge regarding HPV and related diseases in the majority of respondents (91%), but the basic HPV vaccine knowledge was satisfactory in only 45% of them. Residence (*i.e.* rural or urban) did not influence mothers' decision to vaccinate their sons ($p=0.103$) and daughters ($p=0.174$). However, mothers were significantly more prone to opt for vaccination if they parented daughters ($p<0.001$). There were two interesting, perhaps counterintuitive findings in our study; first of all, mothers with elementary and high-school education were significantly more prone to vaccinate both their sons ($p<0.001$) and daughters ($p=0.001$) when compared to mothers with higher education. In addition, despite better overall HPV knowledge in mothers with medical background, there were no differences in the decision to vaccinate when compared to mothers without medical background ($p=0.249$ for female children; $p=0.157$ for male children).
Conclusions: Our results show that, although mothers had adequate basic information on the virus, the education regarding HPV vaccination is lacking. The latter should be tackled by modifying educational approaches to ensure the success of vaccination programs in countries with low vaccination rates.

HPV DETECTION IN URINE SAMPLES COLLECTED USING COPAN'S URISPONGE™ VERSUS CLINICIAN-COLLECTED CERVICAL SAMPLES

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Urine collection is a non-invasive sampling procedure, especially in pregnant women, for HPV screening. Copan UriSponge™ is a device that prevent bacterial overgrowth during transport and supports microbial detection by culture and/or molecular assays. The objective of this study was to compare UriSponge™ first-void-urine (FVU) to clinician-collected cervical samples (CS) for the detection of HPV with the AnyplexII™ HPV28 assay (Seegene).
Methods: Urine and cervical samples were obtained from 104 women with a diagnosis of cervical dysplasia, attending a Colposcopy clinic. FVU was collected in sterile containers, CS were collected using the L-Shaped Endo/Esocervical FLOQSwab® in 20ml ThinPrep solution (Hologic). Two/three UriSponge™ were saturated with urine and room temperature (RT) stability after 1-week and 4-weeks was evaluated. Nucleic acids were extracted from 1ml of FVU and CS using NucliSENS easyMAG (bioMérieux). HPV detection was performed using AnyplexII™ HPV28 Assay. Sample cellularity was evaluated with a quantitative real-time PCR detecting human CCR5 gene.
Results: In the 104 women tested, CS HPV positivity rate was 63% for HR and 44.2 % for LR while FVU positivity rate was 66% for HR and 52% LR. The positivity rated of UriSponge™ RT stability after one and four weeks was 66.7% for HR and 45% for LR, and 53.4% for HR and 36.4% for LR respectively. Ggood concordance was obtained for HR HPV detection in urines as compared to cervical samples, HPV HR types 16, 18, 51 and 31 were most detected. Comparable cellularity was demonstrated in both sample types with mean values of 2.09E+06 and 3.16E+06 cells/sample for FCU and CS respectively.
Conclusions: Data obtained in this study confirmed a good concordance in HR HPV detection in both CS and FVU collected with UriSponge™. CS and US cellularity showed comparable results. UriSponge™ RT stability was good after 1-week with a minor loss after 4-weeks.

MEDICAL STUDENT KNOWLEDGE AND ATTITUDES OF HPV AND THE HPV VACCINE

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The most significant influence on HPV vaccination uptake is receipt of an effective healthcare provider recommendation. As future providers, comprehensive training on how to offer effective vaccine recommendations is essential for medical students. However, such training has not been thoroughly assessed among medical students in the U.S.
Methods: An electronic survey assessing demographics, HPV and HPV vaccine knowledge, attitudes, vaccine status, and vaccination intentions was distributed to all undergraduate medical students at a College of Medicine in the U.S. Scales were developed to assess composite HPV and HPV knowledge scores and HPV vaccination intentions. Cronbach's alpha was used to assess internal consistency reliability for each scale. Mean Total Scores for each scale were compared across groups using Analysis of Variance (ANOVA) models with Welch correction for unequal sample sizes and variances. Data analyses were conducted in SAS Version 9.4.
Results: Data were analyzed from 127 respondents (response rate = 42.8%). Of those age-eligible, 32.1% reported completion of the HPV vaccine series while 15.2% reported partial completion. Knowledge gaps were observed across all years regarding cancers associated with HPV. However, HPV and HPV vaccine knowledge overall significantly increased with program year ($p<0.0001$ and $p=0.0069$, respectively). Positive attitudes toward HPV vaccination also increased with program year ($p=0.0003$).
Conclusions: Given the importance and interdisciplinary nature of HPV vaccination, these data indicate a need to include more education and training on HPV, HPV vaccination, counseling within the undergraduate medical curriculum. Opportunities should particularly be integrated into the first two years of the program. Modules and interactive workshops with sub-topics such as vaccine hesitancy, are critical to preparing students for their impending role as advocates and potential immunizers. Streamlined approaches to this training should also be considered such as development of expert content by centralized organizations such as the National HPV Vaccination Roundtable.

GENOTYPING OF HPV16 IN FIRST LINE IN THE SCREENING OF CERVICAL CANCER (CC): AN ESSENTIAL TEST.

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Screening based on the HPV test confers 60-70% more protection against CC than cytology-based screening. The finding that women with normal cytology and presence of 16 or 18 have a higher risk of having or developing a CC or precancer (HSIL/CIN2 +) compared to other genotypes HPV supports the need to incorporate the genotyping 16/18 in the first line screening.
Methods: CRYGEN study compared 10 different screening protocols. For that, 1988 women of 35 years old were included in the study. All were tested for HPV and cytology. The HPV test used was Roche Cobas 4800 HPV test®, wich detects 14 HR genotypes, genotyping specifically 16/18 and mantaining the remaining 12 HR-HPV as undifferentiated.
Results: 26 CIN2 + lesions were diagnosed when HPV genotyping is performed in the first line with direct shunt to colposcopy compared to the 20 CIN2 + diagnosed if it is not genotyped and the shunt depends on the result of triage cytology. HPV 16 was present in 17 of the 26 HSIL/CIN2 + detected after biopsy (65.38%), having been 6/26 reported as normal cytology rep resenting 23.07% of all HSIL/CIN2 + lesions detected and 35,29% (6of17) of HSIL/CIN2 + lesions with positive HPV16. Moreover, 14.63% of all women with positive result to HPV 16 and normal triage cytology had an HSIL/CIN2 + lesion. These women would only be diagnosed in that round of screening if all positive HPV16 are directly referred to colposcopy.

Table: Crossing the HPV Profile with the results of the cytology, in biopsy samples with a result of HSIL/CIN2+

No. of infections	HPV Profile	Normal	ASCUS	LSIL	HSIL	ASC-H
Infections with 1 positive	*HPV-16*	4	2	2	4	-
	HPV-18	-	-	-	-	-
	hrHPV (not HPV-16 not HPV-18)	-	3	3	3	-
Infections with 2 positives	*HPV-16 + HPV-18*	-	-	1	-	-
	HPV-16 + hrHPV	2	-	1	-	1
	HPV-18 + hrHPV	-	-	-	-	-
Infections with 3 positives	*HPV-16 + HPV-18 + hrHPV*	-	-	-	-	-

Table: Relationship of the HPV Profile with the results of the biopsy HSIL/CIN2+. Complete sample (n = 79)

	Descriptive: Frequency (%)	
HPV Profile	**HSIL/CIN2+ biopsy**	**NO HSIL/CIN2+**
HPV-16	12 (46.2)	12 (22.6)
HPV-18	–	3 (5.6)
Other HPV	9 (34.6)	32 (60.3)
HPV-16 + HPV-18	1 (3.8)	–
HPV-16 + Other HPV	4 (15.4)	4 (7.5)
HPV-18 + Other HPV	–	2 (3.7)
HPV-16 + HPV-18 + Others	–	–

Conclusions: Cytological triage yields low sensivity due to high rate of false negatives compared to HPV test. It is considered essential to include the genotyping of HPV16 in the first line of screening and direct shunt to colposcopy if this specific genotype is detected, since it significantly increases the detection rate (in 23,07%) of HSIL/CIN2 + lesions.

HPV ETIOLOGY IN THE RECURRENT CHRONIC CYSTITIS

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: The recurrent chronic cystitis is still difficult problem in clinical urological practice. It's hard to treat, the quality of life of patients is reduced for a long time. Although the bacterial nature of cystitis has been well studied, we guess that its etiology is not fully disclosed. We suggest a viral etiology of this pathology, in particular, the HPV etiology.
Methods: 62 women represent the sample. All of them had two or more recurrences of cystitis in a year. No one of them had any anatomical and functional abnormalities of the urinary tract, bacterial infections detected using microbiological culture methods, sexually transmitted disease detected by PCR. For the purpose of the study, we used cystoscopy with a biopsy. Then using PCR we detected DNA of chlamydia, mycoplasmas, herpes simplex virus types I and II, cytomegaloviruses, Epstein-Barr virus and human papillomavirus in the urethral swabs, urine and bladder biopsy.
Results: We detected the DNA of HPV in 56.5 % cases of the middle portions of urine and 69.4 % cases of specimens of bladder. Most often, 16 and 18 types of HPV were found. Regardless of the etiology, signs of chronic inflammation were found in all patients. Foci of squamous metaplasia of the epithelium were found in all samples, and in 69.4 % of cases it was combined with focal hyperplasia of the basal cells. In all cases, signs of the presence of HPV were detected: koilocytosis, keratosis, pyknosis. In most samples we've found binuclear cells. In 37 % of cases, the morphological picture of PVI was formed by an inverted condyloma, represented by sections of ectocervix covered with stratified squamous or metaplastic epithelium with coilocytosis, papillomatosis, acanthosis and dyskeratosis against lymphocytic infiltration.
Conclusions: One of the causes of recurrent chronic cystitis can be HPV.

HPV-18 E5 ONCOPROTEIN COOPERATES WITH E6 AND E7 TO PROMOTE A MALIGNANT PHENOTYPE IN HACAT CELLS.

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: It is known that a persistent infection with a high-risk human papillomavirus (HR-HPVs), especially with types 16 and 18, may lead to cancer development in the cervix uteri. The viral oncoproteins (E5, E6, and, E7) of HR-HPVs play a fundamental role in the process of cell transformation. E5 has been the least studied of the three oncogenes with scarce literature regarding its cooperation with E6 and E7. In this work we attempt to understand how HPV-18 E5 cooperates with E6 and E7 to promote carcinogenic traits in HaCaT cells.
Methods: Three HaCaT cell lines were generated by lentiviral transduction expressing the following combination of oncogenes: HaCaT E5, HaCaT E6/E7 and HaCaT E5/E6/E7. Cell viability, proliferation, migration and invasion were evaluated by MTT assay, cell counting growth curve, scratch assay, and a transwell invasion kit (ECM551|QCM™ Collagen Cell Invasion Assay, Millipore, Germany). Finally, we employed a protein array kit (Human XL Oncology Array Kit, R&D Systems, USA) to determine which cancer markers were up or downregulated in each of the cell lines. Non-transduced HaCaT cells were used as a control in all experiments.
Results: The cell line expressing E5/E6/E7 showed a significant higher cell viability (P <0.001) and displayed the lowest doubling time (DT=22.38 h) of all cells in the growth curve. Interestingly, cells transduced with E6/E7 and E5/E6/E7 exhibited greater migration capacity than the control assessed by scratch assay. As for the invasion potential, E5/E6/E7 showed the highest invasion capability with respect to the control (P <0.001). The protein array showed that four proteins related to carcinogenic processes (CapG, Enolase 2, Fox01 and HMOX1) were upregulated in E5/E6/E7 expressing cells.
Conclusions: This is the first study that provided evidence of an in vitro cooperation among HPV-18 viral oncoproteins (E5, E6, and E7) and the induction of a more malignant phenotype on HaCaT cells.

CHARACTERIZATION OF OVARIAN CANCER FOR HPV INFECTION AND EVALUATION OF BIOMARKERS USING QUANTIGENE® PLEX 2.0 ASSAY

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: Ovarian cancer is the most lethal malignancy of the female genital tract. Approximately 23% of gynecological cancers are ovarian in origin, and 47% of all deaths from cancer of the female genital tract occur in women with ovarian cancer. In addition, this malignancy lacks clear symptoms, which prevents early diagnosis and treatment. Hence, finding specific and sensitive biomarkers for diagnosis and follow up of this malignancy is of crucial significance. Currently, a theory has been postulated regarding the participation of human papillomavirus (HPV) in the development of ovarian cancer. The aim of this study was to detect the presence of HPV genotypes by oncogene expression and determine the expression levels of tumor suppressor genes, biomarkers of cell proliferation, stem cell biomarkers, oncoproteins in selected histological types of ovarian cancer patients as compared to control groups.
Methods: The detection of HPV genotypes and cellular biomarkers such as P16, STMN1, MCM2, TOPO2A, Mki67, P63, CD63, ALDH1A1, ALDH1L1, SOX2, NANOG, POU5FI, BIRC5, TERT, P53, AGR2, KRT7, KRT17, GDA and MMP7; was performed using a multiplex mRNA expression quantitation assay (QuantiGene® Plex 2.0 Assay). Sensitivity, specificity and the receiver-operating characteristic curve (ROC) for parameters investigated alone and in combinations were performed. Moreover, correlations between the biomarkers tested were established.
Results: A retrospective study on archived FFPE of human ovarian tumor tissues was performed. FFPE material was sliced with consistent cleaning and mock sections in between experimental FFPEs as a precaution to avoid cross-contamination. When evaluated by ROC analysis for the ability to distinguish various ovarian cancer histotypes from a non-cancer control some biomarkers such as MCM2, mKi67 and KRT7 showed a high AUC (0.903 -0.923), and high sensitivity and specificity (95-100%).
Conclusions: These data may be used in the evaluation of the usefulness of these biomarkers in diagnosing ovarian cancer and in the discrimination of various histotypes.

COMMUNITY HEALTH VOLUNTEERS INVOLVEMENT IN CERVICAL CANCER SCREENING AND TREATMENT IN KISUMU COUNTY KENYA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Globally, cervical cancer is estimated at 530,000 new cases in 2012, and 7.5% of all female cancer deaths (WHO, 2006). More than 270,000 deaths occur every year, and 85% in less developed regions. In sub-Saharan Africa, 34.8 new cases of cervical cancer are diagnosed annually, and 22.5/100,000 women die (WHO, 2006). Kenya has a screening rate of 3.2%; and cervical cancer prevalence has not been established (DHIS2; 2015). Community Health Volunteers (CHV) are required to create demand for screening in the community and capture this in the Ministry of Health (MOH) reporting tools. KMET implements cervical cancer project dubbed 'See and Treat' in Kisumu County with the goal of decreasing the overall incidence rate of cervical cancer. The objectives are to screen women between the ages of 24 to 49 with 100% patient participation in cryotherapy/ thermo coagulation treatment and/or follow-up treatment and identify, strengthen deficits within the already established "See & Treat" clinics and achieve operational sustainability for cancer management in Kisumu County.
Methods: The County Health Management team identified 11 facilities for the implementation of the see and treat project in Kisumu County. Facility entries and team engagement clarified, service providers trained on cervical cancer screening and treatment. The community health volunteers (CHVs) were identified and trained as cancer screening demand champions in cancer messaging and reaching women using the see and ask model. The trained CHVs were equipped with education job aids and a support system put in place to continuously build their knowledge and a formal referral system.
Results: 1,791 women were referred by CHVs for cervical screening , 50% (896) received screening in health facility. 4,889 screened (May 2018 –May 2019), 135 received cryo and thermo coagulation treatment .
Conclusions: CHVs are key in the community its time to invest in them as first preventive machinery.

FEASIBILITY OF A CERVICAL CANCER PREVENTION PROGRAM IN HAITI WITH SELF-COLLECTED HUMAN PAPILLOMAVIRUS (HPV) SCREENING TESTS AND THERMAL ABLATION TREATMENT

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Haiti has one of the world's highest cervical cancer mortality rates. Two non-profit organizations, Basic Health International and Family Health Ministries, in partnership with Haiti's St. Luke's Foundation, began a two-year study to determine the feasibility of a screen-and-treat cervical cancer prevention program in urban and rural settings (n=3,000). Patient and provider acceptability data will be collected.
Methods: The study launched April 19, 2019. Women aged 30 to 49 years are recruited in Port-au-Prince (urban) and Tom Gato (rural). Consented women respond to a questionnaire and are instructed in self-collection of a low-cost human papillomavirus (HPV) test (careHPV, Qiagen, Gaithersburg, MD). Women perform self-collection in a private space and subsequently complete an acceptability survey. Screen-positive women return for a pelvic exam and, if eligible, undergo thermal ablation treatment (women ineligible for ablation are referred to colposcopy). Treated women are instructed to return in 1 year for provider-collected HPV re-testing.
Results: To date, the study has enrolled 1,215 women (549 urban, 666 rural). These preliminary data reveal differences between urban vs. rural areas in never having been screened (396/549 [72.13] vs. 533/666 [80%], $p<.001$) and HPV positivity (96/549 [17.48%] vs. 121/666 [18.16%], $p<.001$). More urban than rural patients reported willingness to recommend self-sampling to a friend (331/549 [60.29%] vs. 227/666 [34.08%], $p<.001$).
Conclusions: Urban and rural women in Haiti differ in screening history and HPV positivity. Self-collection of HPV tests was acceptable to over half of urban women but most rural women either did not respond or expressed lower acceptability. The 6 local providers report high acceptability of thermal ablation. Missing data at both sites reflects the challenges of adequate data collection in a low-resource setting; however, the study will shed light on cervical cancer prevention strategies that may be feasible in Haiti.

DETERMINATION OF THE OPTIMAL FIRST-VOID URINE COLLECTION VOLUME FOR THE DETECTION OF VIRAL AND HOST BIOMARKERS, AND EVALUATION OF AN INTERNAL CONTROL

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The goal of the CASUS project is to develop the first fully molecular integrated cervical cancer screening approach, based on first-void (FV) urine as an easily accessible and non-invasive source of biomarkers. This study focused on the development of next generation Colli-Pee FV urine devices to determine the optimal volume for the detection of viral and host biomarkers. The validation of an appropriate control to monitor sample transport, storage and extraction was done in parallel.
Methods: For this study, 25 women (≥18 years old) diagnosed with a high-risk (hr) HPV infection in the past six months, provided three consecutive FV urine samples with a minimum time interval of 2h. Each sample was collected at home, using Colli-Pee devices with collector tubes that differ in size, prefilled with preservative (Urine Conservation Medium (UCM)) and spiked with an internal process control in a 2:1 urine preservative ratio. This allowed us to collect an average of 2.67 mL urine, 6.67 mL urine and 13.33 mL urine in 4 mL, 10 mL and 20 mL tubes respectively. On each sample, DNA extraction was performed followed by real-time RT-PCR to obtain Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and internal control threshold cycle (Ct) values.
Results: from the three samples collected by 25 different hrHPV positive women will be presented at the IPV conference. These include (1) comparison between different FV urine collection volumes, (2) comparison of four different extraction methods performed on the 20 mL FV urine sample and (3) evaluation of the internal control.
Conclusions: The results of the first objectives in the CASUS study regarding the determination of the optimal FV urine volume to be collected and evaluation of the internal control will be the first step towards development of the first fully molecular integrated cervical cancer screening approach based on first-void urine.

ADAPTING HEALTH DECISION SCIENCE MODELS FOR EVALUATION OF PRIMARY HPV SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Control of cervical cancer will require cost-effective strategies that can be adapted across settings. We hypothesize that the most cost-effective options for prevention are prophylactic HPV vaccination of young girls and screening with primary HPV testing (including self-collection). For HPV-positive women, triage tests— e.g., automated visual evaluation (machine learning applied to visual triage methods)— will need to minimize overtreatment while ensuring safety.
Methods: We are developing an evidence-based framework for health decision models that will be used to evaluate screening strategies across different resource settings. The natural history framework is based on a simple multi-stage causal pathway of cervical carcinogenesis: acquisition of a carcinogenic HPV infection; viral persistence; progression to precancer; and invasion. Health state transitions vary depending on the immune status of the target population, requiring at least 3 distinct natural history models: immunocompetent women (Model 1); partially immunocompromised women due to environmental conditions (e.g., chronic parasitosis) (Model 2); and women living with HIV (WLHIV) (Model 3).
Results: We will provide an update on development of the 3 natural history models. Extensive data are available to inform HPV type- and time-dependent health state transitions in Model 1, which represents populations with an initial peak HPV prevalence around sexual initiation followed by a secondary peak of precancer some years later. More longitudinal data are needed to inform transitions in Model 2, which represents populations with less of an age-related decline in HPV prevalence, likely due to reduced viral clearance. Model 3 is characterized by a lifelong loss of HPV control, requiring different strategies of screening and treatment; for WLHIV we hypothesize that programmatic success will hinge on the ability of treatment to interrupt the transition from precancer to cancer.
Conclusions: Novel screening technologies require advances in health decision models. Model development is underway.

HUMAN PAPILLOMAVIRUS (HPV) TYPES PREVALENCE IN FEMALE SEX WORKERS COMPARED TO THE GENERAL POPULATION IN BOGOTA-COLOMBIA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human papillomavirus (HPV) infection is the most significant risk factor of the development of cervical cancer. The distribución of HPV prevalence and genotype varies widely between regions. In this study, it aimed to investigate the prevalence and genotype distribution of HPV in female sex workers (FSWs) compared to the general population in Bogotá-Colombia.
Methods: HPV genotyping and cytology data were analysed from routine Pap smear tests that were collected from both FSWs and the general population (100 and 302 for each group). Within the laboratory database, all FSWs were matched 1:1 for age and testing date to determine of hrHPV genotypes, DNA and cytology outcome.
Results: Prevalence of HPV in FSWs and general population was 42% and 34% respectively. In the two populations analyzed, 95% and 63% respectively were positive for hrHPV DNA. The high-risk genotypes with the highest and lowest frecuency detected were 45,18,16,51,52,58,53,53,59,73,35,39,66,31,33,68 in FSWs and 16,39,53,31,45,52,58,59,66,68,73,33,18 in general population. It was found that in women 25-29 years in the two populations had the highest percentage of genotypes of hrHPV DNA followed by women of general population of 45-49 years. In both groups, HPV 16 was the 3th (FSWs) and 1th (general population) in prevalent. While HPV18 ranked 2nd in FSWs and 13th in general population.These differences between the presence of HPV16 or HPV18 genotypes or other HPV AR and population group become more evident when disaggregated by age groups; women under 25 with paid sexual activities have 16.67 times higher risk of infection compared to women over 30 years and 9.29 times more in women 25-29 years, compared to women over 30 who perform paid sexual activities.
Conclusions: It is necessary to include molecular tests that allow the identification of hrHPV DNA in groups of women aged 25 to 29, in particular of differential population groups such as FSWs in Bogota-Colombia

PREVALENCE OF HIGH-RISK ANAL HPV INFECTIONS IN ZIMBABWEAN WOMEN LIVING WITH HIV: BASELINE RESULTS OF A COHORT STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Anal cancer is a rare outcome of persistent anal HPV infection. Understanding the factors related to persistence and clearance of anal HPV infections may help to inform anogenital cancer prevention strategies. We sought to characterise anal HPV infections in a cohort of women living with HIV (WLH) in Harare, Zimbabwe.
Methods: We enrolled 113 women in an ongoing cohort study on factors associated with persistence, clearance and genotype distribution of anal HPV infections in WLH presenting for care at an opportunistic infections clinic. Eligible women were HIV-positive, 18 years and older, with no previous or current diagnosis of anal cancer. Informed consent was obtained from each participant. Demographic, social, medical and sexual history was recorded through an interviewer-administered tool. Data on CD4 counts and HIV viral load were extracted from medical records. Anal canal swab samples were collected from each participant for HPV genotype testing in an Ampfire HPV assay (Atila Biosystems, Mountainview, California).
Results: Mean age was 39.5 years (range 20-71). Majority (58/110; 51.3%) were married. Cigarette smoking and alcohol intake were low in this cohort (0% and 4% prevalence respectively). Median CD4 count was 500cells/mm^3(IQR 358-650). Of 82 patients with viral load data (87%) were virally suppressed. Ninety six (85%) had been sexually active in the preceding 3 months with 5 having engaged in receptive anal intercourse. Of 110 valid anal swabs tested, 45(40%) were high-risk HPV positive. The most commonly detected high-risk HPV were HPV-66(13%), HPV-39(12%) and HPV-51(8%). Prevalence of HPV-16 and HPV-18 was 7% and 2%, respectively whilst 23% participants had >1 high-risk HPV.
Conclusions: Anal high risk HPV infections at baseline in Harare WLH are common and consist of a wide spread of HPV types. HPV-16 and HPV-18, which are most directly implicated in anal cancer, were uncommon in this cohort.

COMPARISON OF HUMAN PAPILLOMAVIRUS DETECTION AND GENOTYPING ASSAYS: CLINICAL AND EPIDEMIOLOGICAL LIMITATIONS

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: As HPV is recognized as the causative agent of cervical cancer and associated with anogenital non-cervical, head and neck cancers, the characterization of the HPV types circulating in different geographic regions is an important tool in screening and prevention, as a diagnostic complement and evaluation of the effectiveness of the vaccines available. In this context, this study compares four methodologies for HPV detection and genotyping: HPV-HR+GT 16/18 test on cobas® 4800 HPV System (real-time PCR based), nested-PCR followed by conventional Sanger sequencing, High+Low PapillomaStrip kit (reverse hybridization based) and rolling circle amplification (RCA) followed by next generation sequencing (NGS) at Illumina HiSeq2500 platform.
Methods: Cervical samples from 2,076 patients followed at the Family Health Strategy from Juiz de Fora, Minas Gerais, Brazil were collected and analyzed for HPV infection using cobas HPV test. Of those, 114 samples were randomly included in this study and grouped according to the results obtained by cobas. Sanger sequencing was performed on a nested MY09/GP05 PCR fragment, reverse hybridization using High+Low Risk PapillomaStrip kit was based on a PCR of HPV *E6-E7* genes to identify 37 HPV types and NGS was performed from RCA product.
Results: Our data shows heterogeneity among the four methods used for HPV identification with concordance rates ranging from 66.7 to 100%. Reverse hybridization and cobas showed limitations for genotyping as they restrict the HPV types identified based on probes or type-specific primers, however they were more efficient to identify the presence of high-risk HPVs with clinical relevance. On the other hand, Sanger sequencing and NGS preceded by non-biased assays would be indicated for HPV prevalence and genotyping studies because they can identify each HPV type present in the samples, including novel HPVs.
Conclusions: The four methodologies studied have advantages and disadvantages, and their use should vary according to the purpose of each study.

ACCEPTABILITY OF ANORECTAL SWAB SAMPLING FOR HPV AMONG HIV-POSITIVE WOMEN

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: HPV testing is emerging as a valuable triage and/or complementary modality for assessing anal cancer risk. During a study on persistence and clearance of anal HPV infections in HIV-positive women, participants completed an anorectal swab collection acceptability questionnaire at baseline. Anorectal swab collection was a novel procedure for most participants involved in our study.
Methods: Women 18 years and older, presenting to two opportunistic clinics in Harare, Zimbabwe for routine HIV care, were enrolled in a study aiming to complete 3 visits over a 12-month period. At each visit, a standardized risk assessment tool was administered followed by collection of an anorectal swab for HPV testing and typing. A questionnaire specific for the anorectal swab experience was completed by each participant at baseline. It included Likert 5-point responses to questions on procedural pain, embarrassment, fear of passing flatus, perianal cleanliness, and willingness to have a repeat procedure in future or recommend the procedure to others.
Results: Of 113 women enrolled in the study, 104 completed the post-procedure questionnaire. Responses were as follows: 29% were neutral or found the procedure to be painful or very painful; 41% were embarrassed; 30% worried about passing flatus during examination; 30% had concern about perianal uncleanliness; 76% were willing to have a repeat examination at the appropriate time but 23% would not recommend the examination to a friend or relative.
Conclusions: Overall, anorectal swab collection is both feasible and acceptable to Zimbabwean HIV-positive women for the purpose of HPV testing. To enable sustained uptake of anorectal HPV testing, there is need to explore some of the reasons behind the negative perceptions demonstrated in this survey.

PUBLIC HUMAN PAPILLOMAVIRUS IMMUNIZATION PROGRAMS AND VACCINATION COVERAGE RATES IN CANADA: A HISTORICAL ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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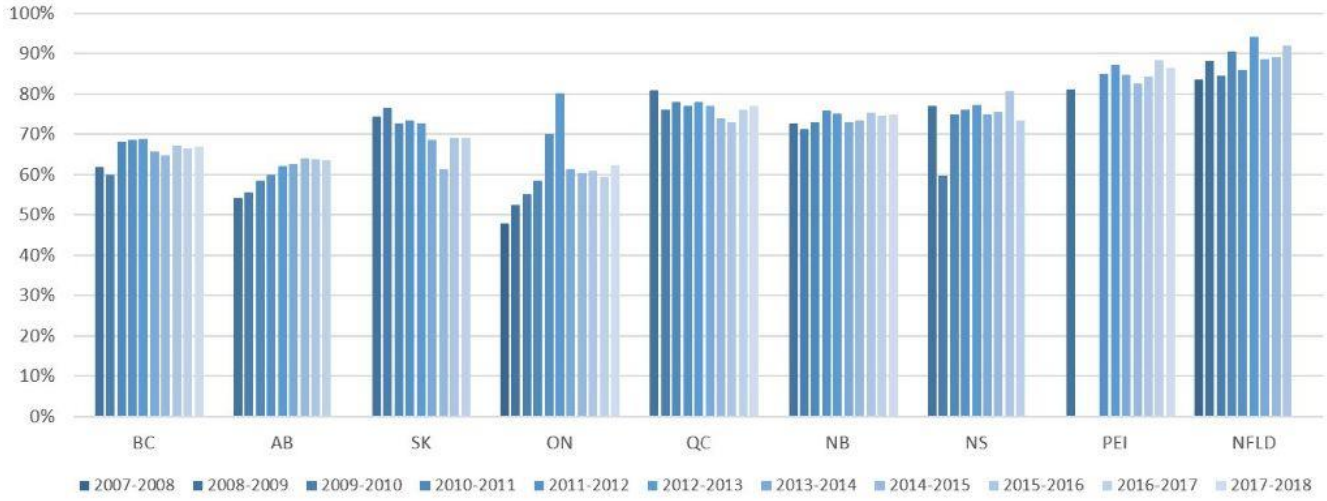
Introduction: Canada was one of the first countries to implement a publicly funded human papillomavirus (HPV) vaccination program. Since their implementation in girls in 2007, provincial programs have undergone multiple policy changes, gradually increasing population protection via inclusion of boys and high-risk mid-adults, making Canada one of the world leaders in the fight against HPV related cancers/diseases. Over time, policy changes have reflected the evolving science on HPV vaccination and funding support at the provincial/territorial level. Given that program information is scattered across multiple data sources and reported typically at provincial level, having one reference that summarizes the evolution of HPV vaccination policies across Canada will be a valuable resource.
Methods: We conducted a targeted literature review on HPV vaccination programs in Canada, focused on governmental databases and statistics, informal reports and PubMed. We extracted publicly available information on current and historical public HPV vaccination programs, cohorts eligible for vaccination by age and gender, and vaccine coverage rates (VCRs) by Canadian jurisdiction.
Results: Between 2007 and 2010, all provinces/territories implemented publicly funded routine HPV immunization programs for girls with 4vHPV vaccine. In 2013, Prince Edward Island was the first province to include boys in the school-based program. By 2018, all provinces/territories had adopted gender-neutral HPV vaccination programs. Transition from a 3-dose to 2-dose schedule and the switch to 9vHPV vaccine occurred between 2013 and 2018, depending on the province/territory (Figure 1). VCRs ranged between 48% and 94% in girls who received full schedule depending on the province/territory and school

Province	School grade of vaccination		2007-2008	2008-2009	2009-2010	2010-2011	2011-2012	2012-2013	2013-2014	2014-2015	2015-2016	2016-2017	2017-2018	2018-2019
British Columbia	*Grade 6*	Girls												
		Boys												
Alberta	*Grade 6*	Girls												
		Boys												
Saskatchewan	*Grade 6*	Girls												
		Boys												
Manitoba	*Grade 6*	Girls												
		Boys												
Ontario	*Grade 7*	Girls												
		Boys												
Quebec	*Grade 4*	Girls												
		Boys												
New Brunswick	*Grade 7*	Girls												
		Boys												
Nova Scotia	*Grade 7*	Girls												
		Boys												
Prince Edward Island	*Grade 6*	Girls												
		Boys												
Newfoundland and Labrador	*Grade 6*	Girls												
		Boys												
Yukon	*Grade 6*	Girls												
		Boys												
Northwest Territories	*Grade 4-6*	Girls												
		Boys												
Nunavut	*Grade 6*	Girls												
		Boys												

Three doses 4vHPV
Two doses 4vHPV
Three doses 9vHPV
Two doses 9vHPV
9vHPV + 2vHPV

year (Figure 2).



Conclusions: While school-based vaccination programs have been implemented across the country since 2007, there is heterogeneity between provinces/territories in the adoption of different policies and in current/historical VCRs. These data may assist Canadian health authorities to address disparities in access and coverage of HPV vaccination with a view of eliminating cervical cancer.

STRUCTURAL VIOLENCE AND HPV-ASSOCIATED CERVICAL CANCER AMONG A MINORITY POPULATION IN CHICAGO

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Despite being preventable, cervical cancer (CC) remains a public health challenge in the United States. Annually, 13,170 new cases of invasive CC are diagnosed and 4,250 women die. Hispanic and African-American women are disproportionately affected. Vaccine uptake and screening reduce incidence and death. Approximately, 95% of CC is caused by human papillomavirus (HPV). Most HPV clears naturally. The association of HPV genotypes with race and neighborhood-level factors is not explored. We aim to explore the link between structural violence as expressed by exposure to residence in high stress, violence, poverty and HPV prevalence in 24 Chicago neighborhoods.
Methods: After obtaining IRB approval, we established a database of 13,466 patients residing in 24 Chicago neighborhoods who underwent 41,378 cervical screening tests over five years (Jan 2013 - Dec 2018). Data was imported into RedCap from an enterprise data warehouse (EDW). The main dataset will be critical in linking patient medical information to neighborhood-level epidemiological information. Preliminary analysis of 4,763 patients completed and full analysis to be finalized by December 2019.
Results: Of 4,763 patient records coded, 3,502 women underwent HR-HPV tests and 708 tested positive for HR-HPV (20.2%). African Americans made up 50.1% of the 4,763 coded cases and 55.2% of the HR-HPV positives. HR-HPV prevalence ranges from 36.4% in Fuller Park to 3.9% in West Elsdon. Correlation analysis shows that HR-HPV is associated with CC death, but not incidence. It is also associated with percentage African American. Chlamydia, gonnorhea, syphillis and HIV are associated with HR-HPV as are poverty and homicide. These latter factors may cause increased cortisol that facilitates HR-HPV resilience and progression to CC.
Conclusions: Our study examines the distribution of HPV across neighborhoods in a large urban setting. Correlation of HPV with demographic and neighborhood-level data, particularly structural violence factors, may help better understand likely facilitators of HPV and CC.

MEDIATING ROLE OF PARENTAL AWARENESS ABOUT HUMAN PAPILLOMAVIRUS AND THE HPV VACCINE IN UNDERSTANDING THE ASSOCIATION BETWEEN PHYSICIAN RECOMMENDATION AND PARENTAL INTENT TO VACCINATE ADOLESCENTS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Physician recommendation plays an important role in human papillomavirus (HPV) vaccination. It also increases the awareness of the parents about HPV and the vaccine and thereby increasing the likelihood of vaccine acceptance. The current study sought to understand the mediating role of parental awareness about HPV and the vaccine in the association between physician recommendation and parental intent to vaccinate unvaccinated adolescents.
Methods: National Immunization Survey (NIS) – Teen survey 2011 data were used in this study. Parents of unvaccinated adolescents was the population of interest (n = 14552). Physician recommendation (exposure of interest), parental awareness of HPV and the HPV vaccine (mediator of interest), and parental intent to vaccinate their adolescents with the HPV vaccine (outcome of interest) are all binary (Yes / No) variables. Logistic mediational models were used to estimate the total effect, direct effect, and the indirect (mediation) effect. The bootstrap method was used to calculate the 95% confidence interval of the mediation effect. All analyses accounted for the complex sampling design of the NIS-Teen data.
Results: Physician recommendation was significantly associated with parental intent to vaccinate their adolescents with the HPV vaccine (Adjusted Odds Ratio 2.67 (95% CI: 2.27 - 3.16). Physician recommendation was also significantly associated with awareness of the parents about HPV and the vaccine (Adjusted Odds Ratio 5.97 (95% CI: 2.96 - 12.04). The estimated mediated effect suggests that only about 7 percent of increased odds ratio of parental intent to vaccinate unvaccinated adolescents who received physician recommendation is attributable to awareness of the parents about HPV and the vaccine (Adjusted Odds Ratio 1.07 (Bootstrap 95% CI: 0.84 - 1.36).
Conclusions: Findings highlight the need for physician communication in addition to recommendation to educate parents about the benefits of the HPV vaccine. This may further improve uptake of the HPV vaccine.

PREVALENCE OF HIGH-RISK HPV AND GENOTYPIC DIVERSITY IN CERVICOVAGINAL SAMPLES WITHOUT NEOPLASIA AND CERVICAL CANCER OF THE YUCATAN PENINSULA, MEXICO

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Worldwide, HPV16 is the most common genotype in patients with cervical cancer (CeCa) and samples negative for intraepithelial lesions or malignancy (NILM). Although HPV18 is the second in frequency in most countries, there are regions where the frequencies of other genotypes are higher than HPV18, both in CeCa and NILM. The frequency of HPV genotypes has been poorly studied in the Yucatan Peninsula (southeastern Mexico). This geographical region has particular characteristics, such as a significant population of Mayan origin.
Methods: One thousand three hundred and ninety-seven cervicovaginal samples of women who attended the IMSS cervical cancer screening program were HPV testing by Hybrid Capture 2® (HC2). The genotyping of positive samples was done by HPV direct-Flow Chip system. The cervical cancer samples were Formalin-Fixed Paraffin-Embedded and genotyped by Inno-Lipa HPV Genotyping Extra.
Results: We found that 26.7% of samples were positive for HPV. The frequency of HPV decreased according to age: in the group under 24 years, the frequency was 44% and in women >= 50 years the frequency was 17.4%. The genotypes identified in the screening samples were (in descending order): HPV51, 52, 59, 58, 31, 66, 16, 18, 45, and 39. While in the cervical cancer samples, the genotypes identified were (in descending order): HPV16, 18, 39, 52, 58, 35, 45, 31, and 51. Interestingly, in CeCa, HPV39 was as frequent as HPV18 (20%), while HPV52 and HPV58 were particularly frequent (17% and 9%).
Conclusions: Although HPV16 and HPV18 were the most common genotypes in women with CeCa from the Yucatan Peninsula, they were not the most frequent genotypes in screening samples. HPV52 and 58 were particularly frequent in this Mexican population. Interestingly, these two genotypes are also common in some regions of Asia.

LESSON LEARNED FOR DEVELOPING AND TRANSFERRING AMPFIRE CERVICAL CANCER SCREENING TECHNOLOGY TO LOW MIDDLE INCOME COUNTRIES (LMIC)

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: AmpFire HPV screening assay designed and developed with the developing world in mind. The assay demonstrated that is very simple to run and very inexpensive, and good for dry brush transport to be used with self-collected vaginal samples. Self-collection can become an important addition to population based cervical cancer screening programs as the primary screen in LMIC. Objective of this presentation is to share the evolution of designing and developing the AmpFire HPV screening technology suitable for LMIC and lesson learned for how to transfer the AmpFire technology to LMIC.
Methods: The AmpFire Multiplex HR HPV Screening assay detects 15 HR HPV and simultaneously genotypes HPV 16 and 18 in one reaction with isothermal real time fluorescent detection. Simple assay protocol by adding 1ml buffer to the dry brush sample tube with vortexing and waiting for 20 minutes at room temperature, the sample is then ready for detection. The HPV results are automatically reported by AmpFire detection system within an hour.
Results: In resource-limited environments, self-collection and dry brush samples overcome many of the barriers comparing to use of alcohol-based liquids for cervical cancer screening. AmpFire HPV assay was used in Inner Mongolia to screen 1400 women in two days with an overall positive rate of proximately 18% on self-collection dry swabs. The workflow will be discussed and experience and lesson learned to transfer AmpFire HPV assay to LMIC will be shared.
Conclusions: AmpFire HPV assay is suitable for being used in LMIC for large population screen. It is affordable at a fraction of the cost of common assays. To use dry swab sampling is much easy to collect. The test is simple to perform with minimal training. Sample to result is about an hour that is fast enough to enable treatment of the patient during the visit.

FUNCTIONAL ANALYSIS OF A PEPTIDE SELECTED BY PHAGE DISPLAY IN HEAD AND NECK TUMOURS

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Head and neck cancer is the sixth most common cancer type worldwide with an estimated incidence of 630,000 new cases and almost 400,000 deaths/year. Human papillomavirus in one of the risk factor in head and neck tumors and the overall incidence of HPV related tumors is increasing. By Phage Display technology, we isolated a specific peptide able to distinguish between head and neck tumors derived-cell lines (both HPV positive and negative) from normal oral cells. This specificity is conferred by binding to *stratifin* (or 14-3-3σ), which is differentially expressed in these cell lines. *Stratifin* play important roles in a wide range of physiological and pathological process and several studies have shown that 14-3-3 σ expression is dysregulated in human cancers, including head and neck cancers.
Methods: By immunohistochemistry, we have shown the binding of our peptide and the expression of 14-3-3 in tissues from a series of head and neck cancer. Using CRISPR/Cas9 technology we silenced 14-3-3 σ in several head and neck tumor cell lines to assess growth, invasivity and tumorigenicity.
Results: The knockout was evaluated through DNA sequencing and western blot analysis.
Conclusions: Additionally, we aim to check the biological activity of this peptide in the modulation of 14-3-3 σ.

OPTIMIZATION OF A HANDHELD THERMAL ABLATION DEVICE FOR THE TREATMENT OF CERVICAL PRECANCER IN LOW AND MIDDLE-INCOME COUNTRIES

CLINICAL RESEARCH /TREATMENT OF PRECANCER IN LOW-RESOURCE SETTINGS

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Introduction: Thermal ablation is a potentially game-changing cervical precancer treatment that uses high temperatures to destroy lesions. However, the conventional device is not well-suited for use in limited-resource settings. We have collaborated with the manufacturer to develop a handheld model that meets the needs of low and middle-income countries (LMICs).
Methods: The C3 thermal ablator (WiSAP, Brunnthal, Germany) weighs 2lb, includes a sliding sheath to prevent vaginal burns, and operates with electricity or a rechargeable battery. The efficacy and safety of this device are being evaluated in a randomized clinical trial comparing thermal ablation to gas-based cryotherapy and a non-gas cryotherapy device. We present preliminary data on patient pain and side-effects of these treatments. Experiences from this study have been used to further optimize the device. The new model will include interchangeable probes with tips in various shapes and sizes that will be evaluated in a different, upcoming trial.
Results: The ongoing trial has randomized 566 women. Preliminary findings show that pain levels (min. =0, max.=10) are higher during thermal ablation than gas-based cryotherapy or non-gas cryotherapy (3.41 vs. 2.97 vs. 2.31, $p<.004$, respectively), but pain declines across arms immediately after treatment (0.11 vs. 0.41 vs. 0.38, $p<.34$, respectively). Cramping and vaginal discharge at 6-weeks post-treatment have been reported, respectively, by 52% and 96% of women treated with thermal ablation, 48% and 95% of women treated with gas-based cryotherapy, 43% and 88% of women treated with non-gas cryotherapy. There are no significant differences across arms (cramping = $p<.72$, discharge = $p<.79$).
Conclusions: Treatment with the C3 thermal ablator results in tolerable pain and comparable side effects to cryotherapy. An optimized device will be utilized in an upcoming randomized trial to compare single-tip and two-tip techniques against cryotherapy. Results will help standardize thermal ablation guidelines for the treatment of cervical precancer.

EVALUATION OF POLYETHYLENIMINE (PEI)-BASED TRANSFECTION METHODS FOR HPV L1L2 VLP PRODUCTION IN MAMMALIAN CELLS FOR USE IN SEROLOGY ASSAYS

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Currently licensed HPV vaccines are based on HPV L1 virus-like particles. HPV VLPs are used extensively in HPV research and as critical reagents in the assessment of HPV-induced immune responses. There are a variety of available methods to produce HPV VLPs for use in immunoassay testing; however, transfection methods are expensive and time-consuming. With the aim of reducing costs and saving time in VLP production while maintaining robust HPV particle assembly and similar performance in assays, we have investigated different transfection approaches in a mammalian-based HPV L1L2 VLP production system.
Methods: HEK293TT transfection procedures were optimized for two transfection reagents, polyethylenimine (PEI) and Transporter™ 5 (T5), in the context of final HPV-6 and HPV-18 L1L2 VLP output as compared to Lipofectamine 2000 (Lipo). XTT cell viability assay, GFP transfection efficiency, HPV-6 and HPV-18 ELISA, and electron microscopy were performed to evaluate and to optimize the HPV-6 and HPV-18 L1L2 VLPs produced.
Results: Transfection efficiency and cell viability were used to define optimal transfection reagent ratios (Lipo, 3:1; PEI and T5, 4:1). The average concentration from three transfection experiments for HPV-6 and HPV-18 L1L2 VLPs were as follows: HPV-6 (Lipo, 1.7 mg; PEI, 1.6 mg; T5, 1.8 mg) and HPV-18 (Lipo, 0.72 mg; PEI, 0.6 mg; T5, 1.3 mg). Furthermore, the ELISA antibody levels obtained using HPV-6 and HPV-18 VLPs produced by each transfection method were similar when evaluating a set of samples with a wide range range of HPV VLP antibody responses.
Conclusions: Results demonstrate PEI and Transporter™ 5 are as efficient as Lipofectamine 2000 in producing assembled particles. The use of these reagents will add alternative methods for VLP production and help reduce overall production cost.

TRAINING OF HEALTHCARE PROVIDERS FOR THE IMPLEMENTATION OF A NATIONAL CERVICAL CANCER PREVENTION PROGRAM IN EL SALVADOR

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical cancer is the leading cause of cancer death for women in El Salvador. In 2012, human papillomavirus (HPV) testing was introduced to the country as part of Cervical Cancer Prevention in El Salvador (CAPE), a primary HPV-based screen-and-treat demonstration project. The success of CAPE led to its adoption by the Ministry of Health (MOH) and a subsequent national scale-up that is currently underway. Each step required rapid training of healthcare workers across the country. The CAPE training model can serve as a blueprint for other cervical cancer prevention programs in low and middle countries (LMICs).
Methods: The training model divided healthcare providers into three categories based on the MOH's existing workforce (physicians, nurses, and community health promoters). The model included preparation of educational materials, training of healthcare workers, and monitoring of program implementation. Results from the regional expansion of CAPE and preliminary findings from the national scale-up are presented here.
Results: Training curricula were developed by Basic Health International (BHI) and the MOH with technical support provided by international agencies and experts. Specific materials were designed for each of the three categories of healthcare workers. Training took place over 3 months in the Paracentral region of the country. During this stage, CAPE trained 223 doctors, 360 nurses, and 610 health promoters. The regional expansion screened and treated 17,795 women over 24 months. The national scale-up has subsequently trained an additional 608 doctors, 920 nurses, and 1,534 health promoters in 3 months, while 30,000/100,000 projected women have been screened.
Conclusions: CAPE successfully trained public healthcare workers to implement a population- based cervical cancer screening program in a LMIC. Some of these workers are now capable of providing trainings to new members of the local workforce. The CAPE training model is a sustainable strategy to strengthen in-country capacity.

A SIMPLE, RAPID, MULTIPLEX, AMPFIRE ISOTHERMAL AMPLIFICATION ASSAY FOR DETECTION AND GENOTYPING OF HUMAN PAPILLOMAVIRUSES IN FORMALIN-FIXED PARAFFIN-EMBEDDED OROPHARYNGEAL CANCER TISSUES

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: Rapid and accurate detection and identification of human papillomavirus (HPV) is important for both clinical management and population screening. Detection of HPV DNA from formalin-fixed paraffin-embedded (FFPE) specimens has been a challenge as it usually requires lengthy and inefficient sample process. This presentation describes the simplest and fastest HPV detection methods from FFPE oropharyngeal cancer tissue samples
Methods: The AmpFire HPV assay (Atila Biosystems Inc, Mountain View, CA, USA) incorporates a multiplex isothermal amplification to detect and genotype 15 high-risk (HR) HPV genotypes directly from raw FFPE samples without needing to extract or purify the DNA. The whole detection process requires couple pipetting steps and can be completed within 2.5 hours. We performed analytic validation of Atila AmpFire Multiplex HPV assays on FFPE cervix/vulva and oropharynx diagnostic tissue samples.
Results: Limits of detection determined by plasmids cloned with HPV genotype-specific sequences were 2 copies/reaction for HPV16, HPV18, and some HR HPV genotypes, and 20 copies/reaction for the remaining HR HPV genotypes. The performance of the AmpFire assays in clinical samples was evaluated using 214 FFPE specimens. The AmpFire assay failed in one clinical specimen for an invalid rate of 0.5%. The AmpFire assay detected HPV in clinical samples with positive percent agreements of 100.0% for HPV16, 100.0% for HPV18, and 94.7% for non-16/18 HR-HPV, and 100% negative percent agreements for HPV16, HPV18 and non-16/18 HR-HPV. Qualitative detection agreement was obtained in the reproducibility study.
Conclusions: In summary, the Atila AmpFire HPV assay demonstrated excellent analytic sensitivity and specificity for detection and genotyping of 15 HR HPV genotypes. Assay parameters of simple specimen processing, small sample size requirement, rapid turnaround time and being near instrument-free render it well suited for HPV detection and genotyping in FFPE specimens.

HIV IS A DRIVEN FACTOR OF HUMAN PAPILLOMA VIRUS AMONG WOMEN IN YAOUNDÉ-CAMEROON

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: HPV is the leading cause of cervical cancers, with an increasing risk associated to HIV in developing countries. This study aimed at comparing HPV positivity, circulating genotypes and its determinants among women following their HIV status.
Methods: A comparative study was conducted in 2012 at the Chantal BIYA International Reference Centre, among 278 women enrolled consecutively in two reference hospitals of Yaoundé. HPV genotyping, , HIV serological screening, HIV viral load and CD4-count were performed.. Statistical analyses were performed using Microsoft Excel 2016 and Graph Pad version 6.0 software; with $P<0.05$ considered statistically significant.
Results: Globally, mean age was 37 ±3 years; median CD4-count for HIV+ was 414 cells/mm^3 [IQR: 264.75-588] and median viremia was 50 RNA copies/mL [IQR: <40-8288]. Following HIV status, HPV rate was 43.47% (80/184) among HIV+ vs. 28.72% (27/94) among HIV- (OR: 1.937; p<0.0142); HPV genotypes among HIV+ vs. HIV- were respectively distributed as follows: genotype 16 (3.75% vs. 0.00%, p=0.57), genotype 18 (3.75% vs. 3.70%, p=1.00), co-infection 16 and others (8.75% vs. 7.40%, p=1.00), co-infection 18 and others (8.75% vs. 11.11%, p=0.71), co-infection 16, 18 and others (2.50% vs. 0.00%, p=1.00) and other genotypes (72.50% vs. 77.78%, p=0.80). Among HIV+ participants, HPV rate following CD4 was 62.88% (61/97) for CD4<500 vs. 35.71% (20/56) for CD4≥500 (OR: 3.05; p=0.0012) while HPV rate following HIV viremia was 42.71% (41/96) with <1,000 RNA copies/ml vs. 66.00% (33/50) with >1,000 RNA copies/ml (OR= 0.384; p =0.009).
Conclusions: In Yaoundé, HPV rate was very high, with higher rates of genotypes other than 16 and 18 in circulation. In the event of HIV infection, the risk of HPV positivity is two times higher, favoured by immunodeficiency and high HIV-viremia. Thus, HIV-infected women should be closely monitored to prevent the emergence of cervical cancer.

DIFFERENCES IN FUNCTIONAL ACTIVITIES OF HPV-18 NATURAL VARIANTS

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Extensive analysis of HPV-18 genome variability resulted in important findings regarding phylogeny, evolution, and natural history of infections. However, the functional impact of HPV-18 nucleotide variability is unknown. For instance, epidemiological studies revealed that whereas Amerindian (As+AI) and European (E) variants are more prevalent in adenocarcinoma and adenosquamous carcinoma, African (Af) variants are mainly detected in invasive squamous carcinoma. Our aim was to extensively characterize primary human keratinocytes (PHK) immortalized by E6/E7 of two different variants of HPV-18.
Methods: PHKs pools were transduced with E6/E7 from HPV-18 Af and As+AI variants. Cells were continuously grown and considered immortalized when p30 was reached.
Results: We did not observe a clear “crisis” for all transduced PHKs, independently of the variant analyzed. As+AI PHKs reached the endpoint significantly sooner than Af PHKs. However, after immortalization (p30) there were no significant differences regarding the proliferation of variants. Both HPV-18 As+AI and 18 Af showed epithelial differentiation alterations in rafts cultures comparable to HSIL. Although HPV-18 Af PHKs formed a larger number of colonies in the clonogenic assay, HPV-18 As+AI PHKs formed bigger and more compact colonies. HPV-18 As+AI PHKs also formed a higher number of colonies in soft agar. Additionally, HPV-18 As+AI transducing PHK were more efficient in invading through a collagen matrix. Other analysis is underway and will be presented.
Conclusions: The results obtained so far attribute to the HPV-18 As+AI variant a higher in vitro oncogenic potential compared to the Af variant. This study is unique in analyzing the function of the E6/E7 oncoproteins in the context of the natural host which are the epithelial cells. Financial Support: Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Grants numbers 15/26345-0 to LS; 15/26346-6 and 2018/14697-7 to EMN).

AWARENESS AND ATTITUDES ON ANAL CANCER AND ANAL CANCER SCREENING AMONG MEN WHO HAVE SEX WITH MEN (MSM) LIVING WITH HIV

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: Human papillomavirus (HPV)-associated anal cancer is emerging as a leading cause of non-HIV-related death in men who have sex with men (MSM) living with HIV. Anal cancer rates in HIV-positive MSM are up to 100-times higher than the general population. There are no universally-accepted guidelines for anal cancer screening. We sought to describe awareness and attitudes on anal cancer and anal cancer screening among HIV-positive MSM.
Methods: The HPV Screening and Vaccine Evaluation (HPV-SAVE) Study is a Canadian study on screening of anal cancers and pre-cancers and treatment of anal precancers in HIV-positive MSM. HIV-positive MSM were invited to have anal cytology testing in their physician's office. Prior to the test, men were interviewed with a self-administered questionnaire, in which they were asked about anal cancer and anal cancer screening.
Results: Of 332 men who underwent anal cancer screening (67% white, median age: 50 years), more than half (52%) were diagnosed with abnormal anal cytology. Seventy-eight percent were not aware that anal cancer screening was available to them prior to their participation in the study. Eighty-nine percent of participants reported that receiving an anal cancer exam was important, and 73% were moderately concerned or very concerned about anal cancer. Eighty-seven percent reported that they were comfortable discussing anal health with their HIV doctor and 91% of participants met with their HIV doctor at least every six months; however, only 35% had ever discussed anal cancer with any health professional.
Conclusions: Anal cancer is a concern to MSM living with HIV, yet many are unaware of anal cancer screening options and have not discussed anal health with their doctor, despite the fact that they are well-connected to health care. These findings suggest a pressing need to develop anal cancer educational and screening programs for MSM living with HIV.

HPV SELF-SAMPLING AS A ROUTINE OFFER TO 58,673 SCREENING NON-ATTENDERS IN THE CAPITAL REGION OF DENMARK.

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: In the Danish organized cervical screening programme a key challenge is the slowly declining participation which today is 73 %. To address this issue, the Capital Region of Denmark is offering all non-attending women a routine HPV self-sampling test as an alternative.
Methods: Through 2017-2018, 58,673 screening non-attenders were invited for HPV self-sampling in the Regional Opt-In programme by letter, phone, E-mail or web-platform. Invitation reminders were mailed after 8 weeks and women opting-in and receiving an HPV self-sampling kit were reminded after 8 weeks. Self-sampling brushes were analyzed using the BD Onclarity HPV assay. If HPV positive, women were recommended for a doctor taken cytology sample. Women with negative HPV self-sampling were returned to routine screening.
Results: 27 % (15.962) of all invited women opted-in for HPV self-sampling, and 60 % of these returned the brush for analysis resulting in an 16 % overall participation (9.629 participants). Around 60 % of the responders used the web-platform for opt-in, 30% answered by letter and 10 % by Email/phone. The HPV prevalence in women accepting self-sampling was 16 %. Off these, 88 % completed the recommended follow-up. In addition, 11 % of the invited women chose a regular cytology sample after receiving the invitation for self-sampling. In total, the overall intention to treat participation rate was 27 %.
Conclusions: Here we report the first large scale operational experience from the general Danish roll-out of the HPV self-sampling to non-attending women. The HPV self-sampling was well-received by the Danish women with 27 % responding to the offer with a high follow-up rate. The web-platform was the most often used method of replying and the reminders had a large effect on the participation rate, underling the importance of timely communication. In conclusion, HPV self-sampling offer is a promising initiative to improve the participation in organized screening.

APPLICATION OF INTERNET-COMMUNITY MODEL FOR CERVICAL CANCER SCREENING

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: To evaluate the application of an internet-community cervical cancer screening model using self-sampling HPV tests as the primary screening.
Methods: A population based cervical cancer screening program was conducted in suburb Shenzhen, China, from July 2014 toJuly 2017. Women 25-60 years of age with no pregnancy were eligible for participation. Participants could registerfor screening by logging in www.mcareu.com with the assistance of local medical providers. Name, ID, telephone number, and address were the required personal identification information for registration. Samplers were shipped to registered participants and the self-collected vaginal specimens were shipped via commercial logistic service to the lab for HPV test. Testing results were reported on the website and phone calls were given to all the positives to instruct themfor management. Positive women could visit any hospital for management or be managed locally bya team of doctors assigned by Peking University Shenzhen Hospital every 3 month.
Results: 12,699 women registered for screening at 46 primary medical services. 10,792 samplers were shipped out and 10011 women shipped their samples to the lab.99.5% (9960/10011) of the personal identification information were correct (retractable). No reverse event was reported. 1.1% specimens were unqualified for tests.
Conclusions: When self-sampling HPV testing is used as the primary testing, internet -community screening model facilitates more participation of community women, therefor potentially benefits the screening coverage.

EVALUATION OF AN ISOTHERMAL AMPLIFICATION HPV DETECTION ASSAY (AMPFIRE) FOR PRIMARY CERVICAL CANCER SCREENING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: To evaluate the performance of Ampfire HPV technology, a new isothermal amplification assay for primary cervical cancer screening, using both self- and clinician-collected samples.
Methods: This is a sub-study from the Chinese multi-center screening trial (CHIMUST). The self-collected and direct collected samples obtained from 3 of the 6 study sites (stored in PreservCyt at -4°C) were used. 6619 women participated in the trial from these three sites. Samples from women with complete data were tested with the Ampfire assay. These women had been previously tested with Cobas and SeqHPV assays, and the clinician-collected samples were also tested with cytology. In CHIMUST all patients, HPV positive (self- or clinician-collection assayed on Cobas or SeqHPV) were recalled for colposcopy and had directed and/or random biopsies plus ECC.
Results: Preliminary analysis includes 1,941 women with a mean age of 42.8 from 1 of the 3 sites. CIN 2 was 0.82% (16/1941); CIN 3 was 0.51% (10/1941); cervical cancer 0.1% (2/1941). The sensitivity of Ampfire for CIN2+ of self-collections and clinician-collections both were 92.9%; specificity was 92.9% and 93.2% respectively. The sensitivity of Cobas for CIN2+ of self-collections and clinician-collections both were 96.4%; specificity was 92.4% and 93.6% respectively. The sensitivity of SeqHPV for CIN2+ of self-collections and clinician-collections were 100% and 96.43% respectively; the specificity was 93.5% and 93.6 respectively. The sensitivity and specificity for CIN2+ were similar among the three assays.
Conclusions: The Ampfire HPV showed similar sensitivity and specificity to Cobas and SeqHPV for CIN2+ on both self- and clinician-collections($P > 0.05$). The speed, cost, and simplicity and ability to do full genotyping as well as a full STD panel, will make the Ampfire assay particularly suited for middle and low resource settings. It's accuracy with self-collection makes it applicable for mass screening programs. The full data will be reported.

A SYSTEMATIC REVIEW OF THE IMPACT OF SCHOOL-BASED EDUCATIONAL INTERVENTIONS IN MIDDLE ADOLESCENTS ON SEXUAL RISK BEHAVIOURS, PERCEPTIONS AND KNOWLEDGE OF HPV AND ASSOCIATED CANCERS. -- AUTHOR REQUEST

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: The American Academy of Paediatrics (AAP) divides adolescence into early (12-14 years), middle (15-17 years), and late (18-21 years) stages. Despite the implementation of school-based HPV vaccination programmes, supporting educational interventions are inconsistent and largely directed at parents of early adolescents during vaccination. As the average age of first sexual intercourse is 15-17 years old in developed countries, a second educational intervention for middle adolescents could have a strong impact on HPV prevention. This poster appraises literature relating to the impact of school-based educational interventions in 15-17yrs on sexual risk behaviours, perceptions and knowledge of HPV and its associated cancers. .
Methods: Randomised controlled trials (RCTs) and quasi-experimental designs (QEDs) from 2007-2019 were included if they delivered a school-based educational intervention for 15-17 year olds, and the outcome measures included; knowledge of HPV and associated cancers; perception of HPV; attitude regarding self-protection against HPV; or future sexual behavioural intention after the educational intervention. Systematic searches of the following databases were conducted: Medline, EMBASE, Scopus, CINAHL, PsycInfo, AMED and Cochrane Reviews. 322 articles were assessed for eligibility. Fifteen studies met the inclusion criteria; all being deemed of moderate or high quality using the Quality Assessment Tool for Quantitative Studies. All studies demonstrated a statistically significant improvement in at least one major outcome measure despite a wide variety in the design and implementation of interventions.
Results: School-based HPV interventions for 15-17 years olds are uncommon but have the potential to improve HPV-associated knowledge, perception and future associated intentions.
Conclusions: Long-term longitudinal studies are needed to ascertain whether this translates to reduced HPV acquirement and/or uptake of HPV associated screening. Regular gender and age adapted school interventions could reverse the falling cervical screening uptake, and lead to a reduction in the acquirement of HPV and associated cancers.

THE MYB-RELATED RESTRICTION FACTOR MYPOP AS A NOVEL TUMOR SUPPRESSOR

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: The Myb-related protein MYPOP has been recently identified as a novel intrinsic host restriction factor of the oncogenic human papilloma virus. On the one hand, MYPOP functions as a transcriptional repressor, that directly binds to the consensus Myb response element (MRE), which is present in multiple copies within the Long Control Region (LCR) of HPV16-transformed (SiHa) and HPV18-transformed (HeLa) cancer cell lines. Furthermore, MYPOP interacts with the viral capsid protein L2, and thereby seems to reduce the expression of HPV early genes and the infection rate over all (Wüstenhagen et al., 2018). On the other hand, Western blot assays with SiHa and HeLa cell lines could show that HPV infection reduces MYPOP protein amounts, most likely through degradation processes via the early viral protein E7. Re-expression of MYPOP, in turn, significantly reduced cell proliferation, when analyzing only transfected cells through selection with neomycin, suggesting MYPOP as a promising candidate for treatment of HPV induced cancer.
Methods: Therefore, we used HPV16 capsid for MYPOP-gene transduction.
Results: Indeed, using this approach, we were able to re-express MYPOP in HeLa cells and to reduce cell proliferation in a significant manner without using selection drugs.
Conclusions: Together our data show that MYPOP level controls cell proliferation and that MYPOP-gene therapy might be a novel anti-cancer tool.

USE OF ROUTINE ELECTRONIC MEDICAL RECORDS TO EVALUATE THE PERFORMANCE AND IMPACT OF CERVICAL CANCER PREVENTIVE ACTIVITIES, THE CASE OF CATALONIA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In the absence of dedicated information systems, routinely-collected electronic medical record data are an increasingly used resource to evaluate real-world effectiveness and impact of cancer control programs. However, as non-targeted information, its use faces several challenges. We aimed to explore current public e-health data system to evaluate opportunistic cervical cancer screening and HPV vaccination program in Catalonia, Spain.
Methods: The Information System for the Development of Research in Primary Care (SIDIAP) contains all primary care clinical information managed by the Catalan Health Institute (ICS), the main Catalonian primary health care provider (covers 74% of the resident population). The SIDIAP database provides anonymised longitudinal patient information on socio-demographic characteristics, morbidity, clinical variables, laboratory tests and treatments since 2008.
Results: We obtained individual records (per visit) for all HPV prevention-related procedures (cytology, HPV test, colposcopy, biopsy, HPV vaccine), clinical diagnoses (ICD10 codes) and treatments. A set of basic screening indicators could be estimated with a high degree of confidence: screening coverage, cytology consumption, distribution of cytology results, and adherence to screening interval in regular and underscreened women as HPV vaccine coverage, trends in genital warts incidence and vaccine effectiveness. Completion rate for test results of cytology and HPV was 77% and 81% respectively. However, due to lack of structured electronic forms, use of free text fields, and referral to specialized care centers with an inadequate record linkage between databases, referral rates to colposcopy and histology results could not be assessed adequately. Only 43% of indicated colposcopies were registered in the system and, for these, completion rate was 55% on colposcopy results and 59% on related biopsy procedures and diagnoses.
Conclusions: Evaluation of cervical cancer prevention programs can be done using non-dedicated national electronic health records systems. However, number of estimable indicators will largely depend on the systems' design, structured information available and data linkage feasibility.

CHARACTERIZING HIGH-RISK HPV E7 ONCOPROTEIN AMONG PATIENTS WITH OROPHARYNGEAL CANCER

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: High risk type human Papillomavirus (hrHPV), particularly HPV16 accounts for approximately half of all oropharyngeal carcinomas (OPC). Due to the high prevalence and the transient nature of HPV infections, the detection of hrHPV genotypes in samples obtained from OPC tissues does not necessarily speak of an HPV-driven tumor. Detection of high level of hrHPV oncoproteins may be helpful in optimally distinguishing HPV-driven oropharyngeal cancers from HPV-positive but HPV-independent OPCs. With this study, we aim to characterize an ELISA-based detection of hrHPV E7oncoprotein among patients with histologically confirmed OPC.
Methods: Tumor surface brush samples (digene® HC2 DNA Collection Device, Qiagen, Hilden, Germany) were immersed in a 20ml vial containing the fixative medium PreservCyt (Hologic, Bedford, MA). For the detection of HR-HPV E7-oncoprotein a sandwich ELISA tests system (recomWell HPV 16/18/45, Mikrogen, Neurid, Germany) was used. Results are presented as optical density (OD) with a limit of detection set at 0.5pg of protein per well. P16 immunohistochemistry was also conducted.
Results: A total 46 patients – median age 64,9 years, 87% males – with histology confirmed OPC were included in the study. Twenty-one patients (45,7%) were positive for E7 oncoprotein. Twenty (57.1%) out of 35 individuals with valid P16 immunohistochemistry results showed p16 overexpression. E7 oncoprotein positivity was significantly associated with p16 positivity: OR (95% CI) = 5.12 (1.18-22.2), P= 0.03.
Conclusions: A sensitive detection hrHPV oncoprotein speaks specifically of HPV-associated pathology as compared to p16 detection which is rather a sign of cell cycle deregulation.The significant association between high level of hrHPV E7 oncoprotein positivity and p16 overexpression indicates that ELISA-based high-risk HPV oncoprotein detection may be an easy and cost-effective option in precisely identifying HPV-driven OPCs. Since HPV-driven and HPV-independent OPCs are two different entities with different therapeutic and prognostic consequences, this preliminary finding seems to be of non-negligible clinical value.

AGE-STRATIFIED CELLULARITY IN SELF-COLLECTED VAGINAL SAMPLES AND FIRST VOID URINE SAMPLES.

CLINICAL RESEARCH /HPV SELF-COLLECTION

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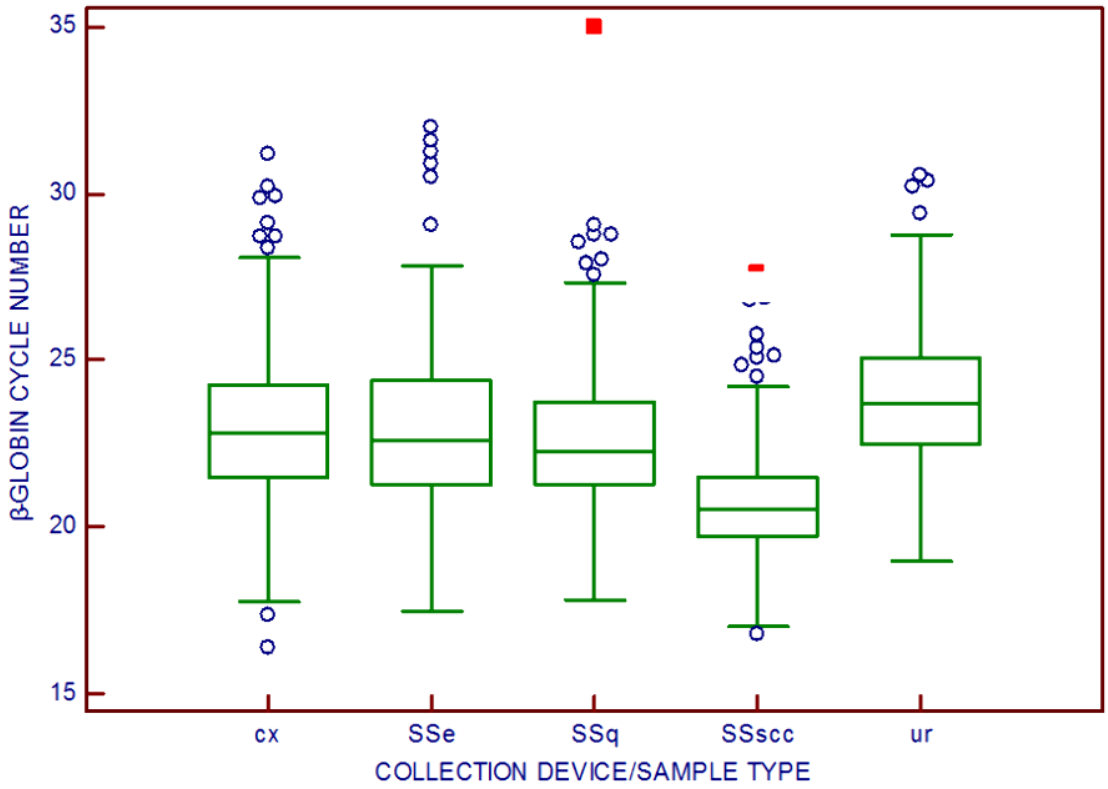
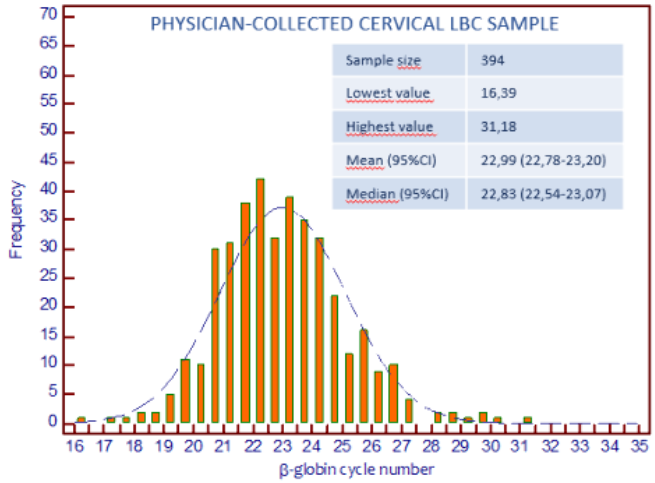
Introduction: High-risk HPV (hrHPV) DNA testing on vaginal self-samples using clinically validated PCR-based tests demonstrated acceptable performance in previous meta-analyses. Urine might be an alternative sample type in cervical cancer screening. Assessing sample cellularity is of critical importance to ensure sample quality. This analysis aims to assess cellularity in urine and vaginal self-samples collected with different devices in relation to patient´s age.
Methods: Sample cellularity was evaluated in vaginal self-samples [Multi-Collect swab (Abbott), Evalyn (Rovers) and Qvintip (Aprovix)] brushes , and physician-collected cervical samples from 394 patients referred for colposcopy enrolled in the VALHUDES study, using the the m2000 RealTime High Risk HPV assay (Abbott). Multi-Collect swabs were transferred in 2.5ml of Cervi-collect medium (Abbott), whereas the other specimens were transferred into 20ml of ThinPrep (Hologic). Cellularity was assessed by the cycle number for ß-globin amplification and categorized as high (CN<22), intermediate (22-26), low (>26) Age was grouped in <30 years; 30-50 years; >50 years. Differences in average CNs were assessed by ANOVA.
Results: Sample cellularity was similar for vaginal and cervical samples, but was significantly higher in swabs and lower in urine (Fig.1). Lowest cellularity was found with vaginal Multi-Collect swabs (0.7%), followed by cervical (8.1%), vaginal brushes (10.9%), and urine (11.2%).Kolmogorov-Smirnof analysis confirmed normal distribution of Cn frequencies for cervical and urine samples, but not for self-collected vaginal samples (Figure 2).
Cellularity increased by age in cervical, decreased by age in vaginal brushes, while Multi-Collect vaginal swab and urine did not vary significantly by age (Fig.3).

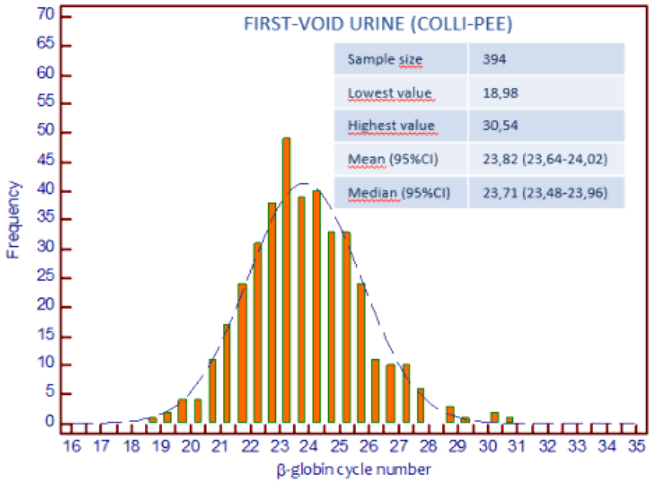
Fig1: BOX-WHISKER PLOT OF CELLULARITY IN DIFFERENT SAMPLE TYPES

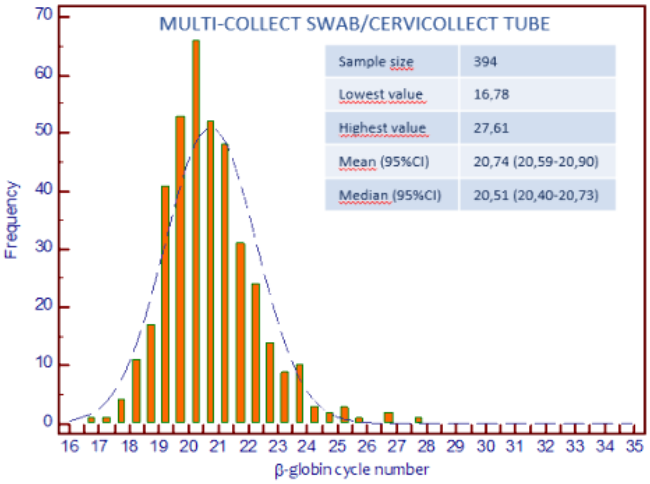


cx = physician-collected cervical LBC sample – SSe = vaginal self-sample Evalyn/LBC – SSq = vaginal self sample Qvintip/LBC – SSscc = vaginal self sample Multi-Collect swab/Cervi-CollectTube – ur = first-void urine (Colli-Pee) in buffer

Fig2: DISTRIBUTION PLOT β-GLOBIN SIGNAL







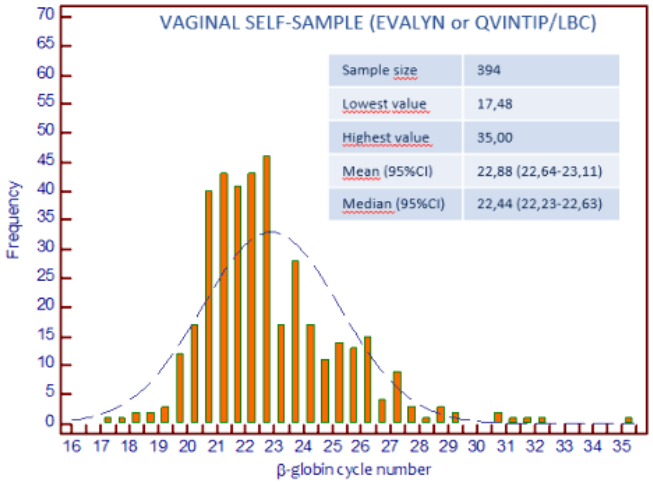
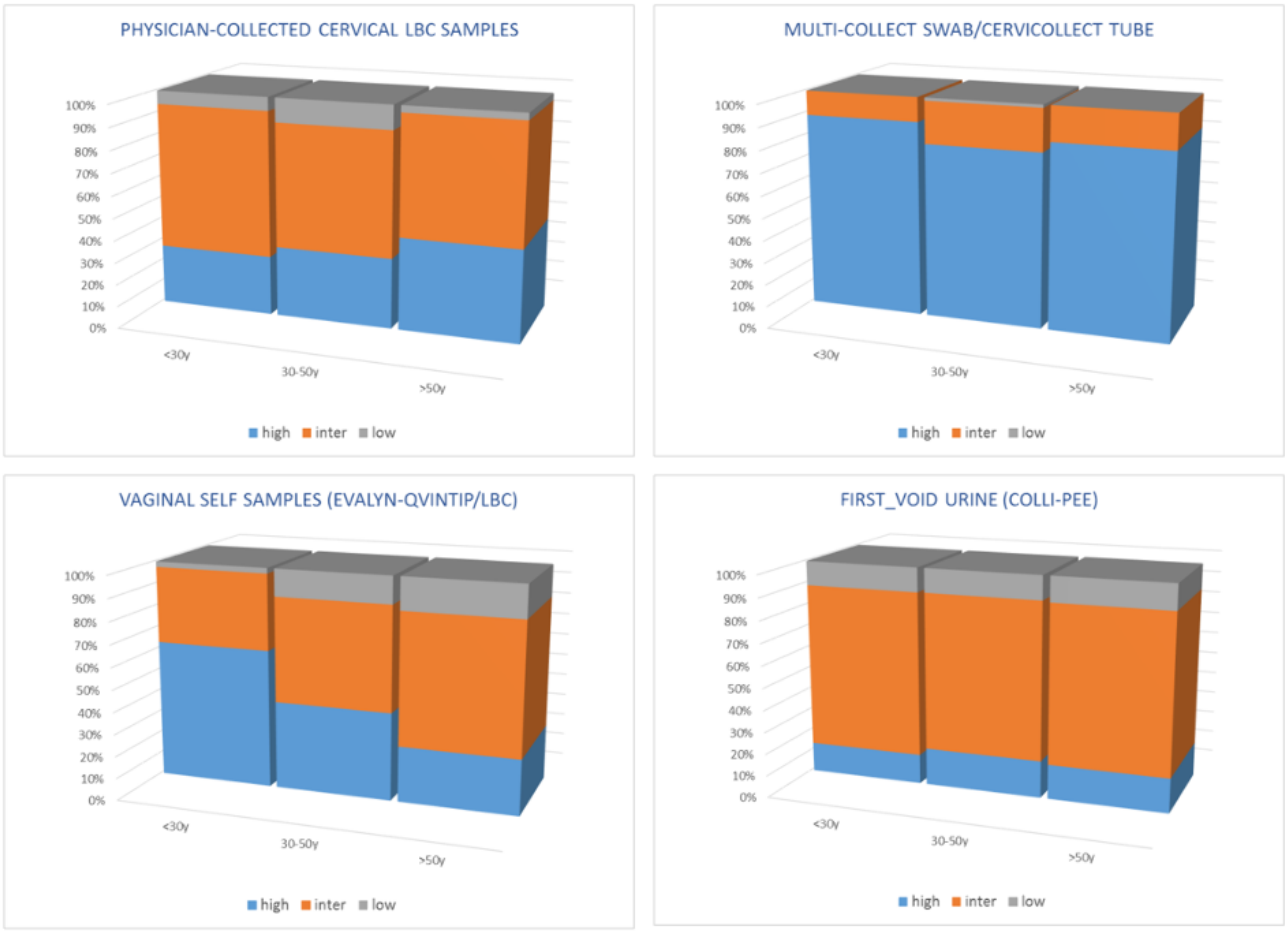


Fig3: CELLULARITY IN FUNCTION OF WOMANS AGE



Conclusions: Cellularity varied by collection procedure. Higher cellularity in the Cervicollect samples can be explained by the lower volume (and composition) of transport medium. The practical impact of cellularity in different samples on analytical viral and clinical accuracy requires further research which is ongoing in the VALHUDES study.

EVALUATE THE SOLID TRANSPORT MEDIA FOR DETECTING HR-HPV IN VAGINAL SELF-SAMPLES COMPARED TO LIQUID TRANSPORT MEDIA

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: To evaluate a new solid media transport card to detect HR-HPV in self-samples compared to liquid transport madia
Methods: The solid transport media is a small size card that allows fast, easy DNA extraction from a variety of biological samples. 10885 women between the ages of 30-59 with no screening for 3 years were enrolled. The self-collected sample was first applied to a new solid media transport card (Labeled as SS) then the brush placed in6 ml ThinPrep liquid (Labeled as SL). Then a physician collected a direct endocervical specimen into ThinPrep liquid (Labeled as DL). Samples were tested with Cobas 4800 and the SeqHPV NGS assay for HR-HPV. Patients positive on any test were recalled for colposcopy and biopsy.
Results: 10,339 participants had complete data. The mean age was 43.9years. CIN 2+ rates were 1.4% (142/10339). The overall agreements of Hr-HPV detection were 95.1% (Cobas SL vs DL), 96.2% (Cobas SS vs DL),96.8% (Cobas SSI vs SL), 98.1% (SeqHPV SL vs DL), 98.3% (SeqHPV SS vs DL) ,99.5% (SeqHPV SS vs SL). For both HR-HPV assays, the sensitivities and specificities were similar for the two self-sample media (SL, SS). Tested with Cobas, the sensitivity for CIN 2+ of self-card was 94.37% (95%CI 88.83-97.36), and for the physician-collected sample was 95.07% (95%CI 89.72-97.82), Tested with SeqHPV, the sensitivity for CIN2+ of self-card was 95.77% (95%CI 90.63-98.27), and for physician -collected sample was 93.66%(95%CI 87.96-96.88)
Conclusions: The solid transport media when used with self-collected vaginal samplesis as accurate as liquid transport media assayed by two different PCR based HR-HPV tests.The solid transport media is a suitable medium for collecting and storing vaginal self-samples

DETECTION OF HPV 16/18 E6 ONCOPROTEINS IN CARCINOMA OF THE OROPHARYNX AND IN NECK CARCINOMA OF UNKNOWN PRIMARY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: The human papillomavirus (HPV) oncogenic role in patients with oropharyngeal squamous cell carcinoma (OPSCC) and neck lymph node metastasis of squamous cell carcinoma from unknown primary tumor (NSCCUP) is increasingly acknowledged and rapidly rising in Western Countries. The identification of clinically relevant transforming HPV infections is crucial for staging, prognostication and enrollment in clinical trials. The aim of this study was to determine the feasibility and accuracy of the detection of HPV 16/18 E6 oncoprotein in cytological specimens from primary carcinomas and neck metastases.
Methods: In addition to tissue biopsies for histological diagnosis, cytological specimens from primary tumors and neck metastases were collected by fine needle aspiration from 34 patients with OPSCC with lymph node involvement or NSCCUP and tested with a commercial lateral flow test (OncoE6, Arbovita) detecting HPV16 and 18 E6 oncoproteins. Sera were also collected at diagnosis. Results were compared to presence of HPV-DNA together with $p16^{INK4a}$ overexpression or HPV DNA together with HPV E6 seropositivity as reference method.
Results: Eighteen of 29 OPSCC (62%) and 3 of 5 NSCCUP (60%) were HPV-driven according to our reference method. The HPV 16/18 E6 oncoprotein test had a sensitivity of 94% (95% CI: 70%-100%) and a specificity of 100% (95% CI: 66%-100%) on primary tumor, and a sensitivity of 88% (95% CI: 64%-99%) and a specificity of 100% (95% CI: 74%-100%) on neck metastases. Test agreement between the E6 oncoprotein lateral flow test and the clinical reference method was excellent both for primary lesion and neck metastases (Cohen's kappa value 0.92 and 0.88 respectively).
Conclusions: In this study, we found the detection of HPV 16/18 E6 oncoproteins to be a feasible, highly reliable and low-invasive method to assess HPV status in OPSCC and NSCCUP.

ITERATIVE DEVELOPMENT OF MSAADA: A MOBILE PHONE APPLICATION TO SUPPORT COMMUNITY HEALTH VOLUNTEERS DURING CERVICAL CANCER SCREENING IN WESTERN KENYA.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: There are more than 500,000 new cases and 265,000 deaths from cervical cancer each year. Recent work by Huchko et al. in Migori, Kenya has demonstrated cervical cancer screening via HPV self-collection led by community health volunteers (CHVs) is acceptable and well attended. However, CHVs cited a desire for improved counseling/protocol support tools, and evidence supports a need for education among Kenya women regarding cervical cancer. This study sought to iteratively develop the mSaada mobile phone application prior to pilot testing. mSaada was designed for use by CHVs and repackages routinely utilized clinical tools and educational materials into an efficient, streamlined platform for use during cervical cancer screening.
Methods: Six feedback sessions were conducted in Migori and Kisumu, Kenya over four weeks with a convenience sample of 19 individuals with varying engagement in the cervical cancer screening process. Participants took part in introductory focus groups, in which the features of the app were explored through simulation activities, and a semi-structured interview, to provide a more detailed review of the app. Sessions were audiotaped and transcribed for thematic analysis.
Results: Participants found the features of mSaada and overall layout to be appropriate and comprehensive. Most participants found the usability and responsiveness to be high and thought the app was easy to learn and use. Although app graphics were well received, participants recommended further consideration of their relevance in both rural and urban settings. While participants applauded the simple, direct language used for client education, they suggested translating the information into local languages, working to ensure phrasing of statements were reflective of the area. Feasibility concerns were raised, including charging, the need for internet connection, and the importance of reliable technical support.
Conclusions: While the mSaada mobile app was considered user-friendly and comprehensive, continued work is needed to tailor its content for use in Western Kenya.

THE STRUCTURE OF CLINICAL MANIFESTATIONS OF PATIENTS WITH HPV INDUCTED RECURRENT UNCOMPLICATED URINARY TRACT INFECTION

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: The role of opportunistic flora in the development of recurrent uncomplicated urinary tract infection (rUTI) is well studied. Little is known about the viral etiology of this pathology. In addition to revealing the involvement of HPV in development of UTI, we described the features of the clinical course.
Methods: 62 women with rUTI represent the sample. The average age was 39.5 years. All of them had symptoms of lower urinary tract infection, severe recurrent clinical course. No one of them had any anatomical and functional abnormalities of the urinary tract. They had negative results of cultural urine analysis. We used cystoscopy with a biopsy. Then using PCR we detected DNA of HPV types. A gynecologist and pelvic helped to exclude other pathologies.
Results: PCR and biopsy analysis detected HPV in all samples. Most often, 16 and 18 types of HPV were found. All females had pain, dysuric symptoms and sexual dysfunctions. Localization of the pain was in the perineum (77.4% of cases), the suprapubic region (72.6 %), on the threshold of the vagina (37.1 %). >50 % had two or more localizations of the pain. 22.6% subjects had painful frictions. Sexual disorders: libido had damaged in 51.6 % subjects, sexual arousal – in 61.3 %, orgasm – in 40.3 %. Lack of satisfaction from sexual intercourse had 50 % of women, insufficient moisture of the vagina – 25.8 %.
Conclusions: Virus, in particular, HPV, may induct RUTI. In addition to pain and dysuria, 100% of patients with viral cystitis report sexual dysfunctions.

FEATURES OF HPV INFECTION OF INFERTILE MEN, DEPENDING ON THE TYPE COMPOSITION OF THE COMBINATIONS

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: The last two large meta-analyzes showed: HPV is a risk factor for infertility. There is little information about the effects of HPV combinations, the deepening of pathological processes, depending on their type composition.
Methods: 71 infertile men aged between 22 and 44 years diagnosed with HPV were included in the study. Patients with any another risk factors weren't included. The material for the study was the ejaculate. Evaluation of the fertilizing ability of the ejaculate was carried out in accordance with the recommended WHO (2010) in the clinical diagnostic laboratory. To identify the type of virus we used PCR. Statistical data processing was carried out using STATISTICA 6.1 (StatSoft Inc., USA).
Results: The analysis of the ejaculate: asthenozoospermia was detected in 56% cases, asthenoteratozoospermia – 21%, oligoasthenoterozoospermia – 16%, oligoastenozoospermia – 6 %. Pathozoospermia in most cases combined with 16, 18, 33 types of HPV. The number of virus types has a statistically significant weak correlation with sperm motility ($r = -0.267$; $p = 0.0244$). The types of pathospermia and their degree are partially explained by the presence of specific combinations of HPV types. The combination of types 31 and 33 significantly reduced the total sperm count and sperm count in 1 ml. A combination of type 6 and 11 significantly reduced overall and progressive sperm motility. The results were evaluated 12 months after the treatment with Viferon®: pregnancy was observed in 36.6%.
Conclusions: This study found the percentage of sperm pathology, the most common types of HPV in the cohort. A significant trend was revealed: pathospermia is determined not only by the presence of HPV, but also by the number of its types in semen. Combinations of different types of virus have not same pathogenic potential. Limitations: a large number of measured parameters that can lead to an accidental false-positive result.

AGE-SPECIFIC CERVICAL HPV INFECTIONS AMONG UNVACCINATED WOMEN IN THE COSTA RICA HPV VACCINE TRIAL (CVT)

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Human papillomaviruses (HPVs) are common sexually-transmitted infections. We aim to describe HPV incidence and prevalence in the decade after approximate sexual debut among unvaccinated women in the Costa Rica HPV Vaccine Trial (CVT) and the associated long-term follow-up (LTFU), spanning ~11 years.
Methods: We conducted our analysis in 3735 women (aged 18-25 at enrollment) from the control arm of CVT who were followed for 4-6 years. We also included an additional group of 2460 unvaccinated women from the same birth cohort and geographical regions who were enrolled at year 4 of CVT and followed for up to 7 years (LTFU). Cervical samples were collected and tested for HPV annually in CVT, then biennially in LTFU, using either SPF10-LiPA or TypeSeq (both validated methods have similar sensitivity and specificity). HPV incidence refers to HPV infections detected for the first time and not at prior study visit; HPV prevalence refers to HPV infections detected at the study visit of interest. We used generalized estimating equations, using a logistic-link and assuming an independent correlation matrix, to estimate prevalence/incidence and the 95% confidence intervals (CIs) with adjustment for genotyping assay (and, for incidence, interval between study visits).
Results: Annual/biennial incidence (10.2%, 95% CI:8.2-12.6%) and prevalence (26.7%, 95% CI:24.7-28.8%) for any oncogenic HPV peaked at age 23. Highest incidence was observed at age 20 for HPV16/18 (3.3%, 95% CI:2.3-4.7%) and HPV31/33/45 (3.3%, 95% CI:2.2-4.9%), which are HPV types prevented by the bivalent vaccine directly or indirectly through cross-protection. After age 20, HPV acquisition gradually declined with age (HPV16/18: 0.6%, 95% CI:0.2-2.2%; HPV31/33/45: 1.1%, 95% CI:0.4-3.5% at age 37, oldest in our population), and the decline was statistically significant ($p_{trend}<0.05$).
Conclusions: Consistent with HPV literature, we observed high incidence of oncogenic HPVs in young women that showed a gradual decline at older ages.

GENITAL HPV PREVALENCE ACCORDING TO SEXUAL PRACTICE IN POP-BRAZIL STUDY PARTICIPANTS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: HPV infection has a high prevalence. Horizontal transmission occurs mainly through the sexual act but few studies assessed HPV infection related to sexual intercourse type. Therefore, we aimed to present data on the HPV infection prevalence according to sexual practice types of Brazilian young adults.
Methods: POP-Brazil is a cross-sectional study conducted among 2016-2017 with sexually active unvaccinated individuals, aged 16-25, from all Brazilian capitals. Individuals were submitted to a face-to-face interview with sociodemographic and behavioural questions, and provided biological samples from cervical/penile regions. Linear Array® Test (Roche) was used for HPV detection and genotyping. Analysis were weighted by sex and the capitals population size.
Results: Most participants are female (63.6%), brown (57.0%), class C (55.5%), attending or completed high school (55.9%), and currently dating (39.9%). From the 4879 participants, 32.9% performed vaginal sex exclusively, 60.3% had oral sex (except anal), 3.4% practiced anal sex (except oral) and 3.3% had vaginal, and oral, and anal sex. The prevalence of overall HPV was 49.7% in participants with exclusively vaginal sex, 54.7% in oral sex, 48.5% in anal, and 58.5% in those who practiced all types of sex (p=0.3156). High risk HPV prevalence was 31.1% in those with exclusively vaginal sex practice, 37.7% in individuals who practiced oral sex, 35.7% in anal sex and 39.9% in all types of sex (p=0.144). Prevalence of more than one type of HPV was 26.6% in those with exclusively vaginal sex practice, 32.8% in oral sex, 31.8% in anal sex and 40.5% in all types of sex (p=0.089).
Conclusions: There was no significant difference in HPV prevalence among different types of sexual practices. This new information enables health professionals to better counsel patients on risky sexual behaviors, contributing to the individuals integral health promotion.

NATIONAL CERVICAL CANCER SCREENING PROGRAMS AND COVERAGE WORLDWIDE

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Both the Sustainable Development Goals and the WHO call for cervical cancer elimination include screening coverage in adult women as a monitoring indicator. However, global estimates are still unavailable. We aim to produce comparable global/regional standardized estimates of cervical screening coverage, and to assess current achievements and gaps and their potential impact for monitoring global disease reduction.
Methods: We run a systematic review on national cervical screening programs, with support from professional translators. Retrieved information includes program characteristics and age-specific screening coverage rates. Data are further cross-checked with WHO, IARC, and HPV Information Centre databases. Women grouped by one-year age and country strata are assigned with a 2019 screening coverage rate, applied to United Nations population estimates and pooled to obtain global rates. Imputation algorithms adapted to the complexity of cervical screening are being developed, including predictive mean matching and other missing-data treatment techniques.
Results: As of July 2019, 58 countries have been reviewed. We are reporting on the first two areas completed (Arab-speaking (AS-countries) and post-Soviet states (FSU-countries). Most AS-countries lack national screening programmes, except for the Maghreb region. Most FSU-countries have cytology-based screening, and half send personal invitations. Less than 20% of women aged 30–49 in AS-countries have ever been screened, while over 65% in FSU-countries have. At the meeting, detailed results on program characteristics and global coverage estimates will be presented.
Conclusions: This work will answer essential questions for global health governance and monitoring of the elimination campaign such as the extent and characteristics of screening programs worldwide, or the number of women that will need to be screened for the first time in the next 5-years. Main challenges are the variability and complexity of screening data. Adaptation of a previously developed methodological approach to produce global HPV-vaccination coverage estimates may prove useful to quantify global screening practices.

IMMUNE MEMORY RESPONSES FOLLOWING REDUCED-DOSE QUADRIVALENT HPV VACCINE IN ADOLESCENT FIJIAN GIRLS

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: Data on immunological memory following reduced-dose human papillomavirus (HPV) vaccine schedules are limited. Immune memory cells such as memory B cells (Bmem) and T-follicular helper T cells (Tfh) are important for generation of long-term memory responses. We examined Bmem and Tfh 1-month following a booster dose of 2vHPV (Cervarix®, GSK) in girls who were previously unimmunised or received 1, 2 or 3 doses of 4vHPV (Gardasil®, Merck Inc.) 6 years earlier.
Methods: We conducted a cohort study in 200 Fijian girls (15-19 years old) previously unimmunised, or immunised with 1-3 doses of 4vHPV 6 years earlier. Blood was taken pre- and 28 days following the 2vHPV booster dose. To determine HPV vaccine type immune memory cells, we conjugated HPV16 or 18 pseudovirions with a fluorescently-labelled probe (Alexa Fluor® 488), and then measured the HPV-specific response by flow cytometry using the following markers for Bmem (CD19, CD27, CD38, IgM, IgG) and Tfh (CD4, CXCR5, CD278 and CD279) responses.
Results: Following a dose of 2vHPV, there were similar proportions of $CD27^+IgG^+HPV16^+/18^+$ populations in girls who were previously immunised with 1, 2 or 3 doses of 4vHPV 6 years earlier. All were higher than unimmunised girls, although this was not significant. A weak correlation was found between $CD27^+IgG^+16/18^+$ and HPV16/18 neutralising antibodies when the data were pooled ($r=0.22$, $p=0.03$). Analyses for the comparison of other cell populations ($CD27^+IgM^+16/18^+$; memory IgM B cells, $CD27^+CD38^+$; plasmablast, $CD4^+CXCR5^+PD\text{-}1^+ICOS\text{-}1^+$; Tfh) are ongoing.
Conclusions: Prior immunisation with 1, 2 or 3 doses of 4vHPV generated similar levels of $CD27^+IgG^+16/18^+$ Bmem after a booster dose of 2vHPV, suggesting that 1 dose may efficiently prime immunological memory responses. Additional analyses of specific immune memory cell populations will provide a better understanding of the potential usefulness of single dose HPV schedules in the long-term.

THE HPV E4 IS A CANDIDATE BIOMARKER IN CERVICAL INTRAEPITHELIAL NEOPLASIA GRADE 2

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: HPV E4 protein is synthesized as a E1^E4 fusion protein as a result of mRNA splicing. The knowledge regarding the functions of E1^E4 during the viral life cycle remains incomplete. We think it is safe to suggest that the protein is involved in virus release and transmission and that it is a marker of the onset of productive infection. However, the potential role of E4 as a tool to stratify cervical intraepithelial neoplasia (CIN), and to detect HPV-associated lesions that may progress towards CIN2+, has been reported in multiple publications recently. The management of CIN2 is still controversial, prompting us to investigate the correlation between E4 expression and prognosis of lesions classified as CIN2.
Methods: We carried out a retrospective cohort study using the medical and histopathological records of 115 patients with CIN2 treated at Keio University Hospital. E4 was detected as described previously (Griffin et al., 2015). Regression was defined as negative cytological and histological result for more than one year. Progression was defined as the appearance of histologically confirmed CIN3 during follow-up. We built Kaplan-Meier curves for progression/regression groups and compared unadjusted survival statistics using Log-rank test.
Results: The median follow-up was 557 days, ranging from 91 to 1933 days. The cases were 28, 67, and 20 for regression, persistence, and progression, respectively. Kaplan-Meier curves showed that E4 expression was significantly difference between progression and regression (Log-rank test=$p<0.001$). CIN2 progressed in the E4 negative cases and regressed in the E4 positive cases.
Conclusions: The E4 expression was correlated with progression/regression of CIN2. These data suggest that the HPV E4 expression is a candidate biomarker for prognosis of CIN2.

ONE-YEAR FOLLOW-UP AFTER THERMAL ABLATION TREATMENT OF PRE-NEOPLASTIC CERVICAL LESIONS IN HONDURAS

CLINICAL RESEARCH /TREATMENT OF PRECANCER IN LOW-RESOURCE SETTINGS

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Introduction: Affordable and robust precancer treatment methods are essential for an effective cervical cancer prevention program. Challenges associated with cryotherapy treatment—most notably the need for refrigerant gas—have resulted in poor treatment coverage. Thermal ablation has emerged as a compelling option in low-resource settings (Dolman et al. 2014; Randall et al. 2019). We present the assessment of lesion disappearance at one year after thermal ablation treatment of HPV- and visual inspection with acetic acid (VIA)-positive women with histology-confirmed lesions.
Methods: The study enrolled 319 women with combined positive HPV and VIA evaluations who were eligible for ablative treatment in four health centers in the Metropolitan Region of Francisco Morazán, Honduras, between May and September 2018. Eligible and consented women received between one and three applications of thermal ablation with the Liger Medical Thermocoagulator (Liger Medical LLC, Lehi, UT), which had high acceptability. At one year, all women with a positive biopsy (CIN2-3) and a sample of women with negative biopsy (<CIN2) at enrollment were re-tested for HPV and evaluated with VIA. Biopsies were taken in VIA-positive women. A Pap smear was taken in HPV-positive, VIA-negative women. Follow up will be completed by the end of October 2019.
Results: Out of 317 women with histological diagnoses at baseline, 76 women (24%) had CIN2-3. At one year, 52 women with CIN2-3 at baseline have completed follow-up evaluation to-date, among whom 40 (76.9%) are HPV negative and 34 (65.4%) are VIA negative. Among women who completed follow-up evaluation, 50 (95.7%) show no evidence of CIN2-3, as described in Table 1.

Table 1. Clinical outcomes to-date among women with CIN2-3 at baseline; follow-up will be completed by October 2019.

Clinical outcome	Number	%
No evidence of CIN2-3 *Women who are HPV negative and VIA negative;* *HPV negative, VIA positive, with normal/CIN1 biopsy results; or* *HPV positive, VIA negative, with negative/normal cytology results.*	44	84.2
No evidence of CIN2-3, but signs of persistent (low-grade) infection *Women who are HPV positive, VIA positive, with normal/CIN1 biopsy results; or* *HPV positive, VIA negative, with ASCUS, AGUS, or LSIL cytology results.*	6	11.5
Evidence of CIN2-3 *Women who are HPV positive, VIA positive, with CIN2+ biopsy results;* *HPV positive, VIA negative, with HSIL cytology results; or* *HPV negative, VIA positive, with CIN2+ biopsy results.*	2	3.9
Total	52	100.0

Abbreviations: CIN: cervical intraepithelial neoplasia; VIA: visual inspection with acetic acid; ASCUS: atypical squamous cells of undetermined significance; AGUS: atypical glandular cells of undetermined significance; LSIL: low-grade squamous intraepithelial lesions; HSIL: high-grade squamous intraepithelial lesions

Conclusions: Our preliminary findings indicate that cure levels of thermal ablation are high at one year. HPV testing may be the most indicative test for successful treatment.

PUBLIC HEALTH/EPIDEMIOLOGY SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT THE ROLE OF PATIENT ADVOCATES IN HPV SCREENING IN KENYA: A 3 YEAR CASE STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: PUBLIC HEALTH/EPIDEMIOLOGY Screening for HPV-related Disease: Implementation, Evaluation and Impact THE ROLE OF PATIENT ADVOCATES IN HPV SCREENING IN KENYA: A 3 YEAR CASE STUDY **Background and Aims** Grassroots level advocacy is a powerful tool for impacting health seeking behavior and disease outcomes in underserved communities. This is particularly important in Kenya where cervical cancer incidence is 5250 and mortality is 3286 annually. There is virtually no documented evidence on the impact of patient advocates in reducing cervical cancer prevalence in Kenya. This paper documents a 3 year case study by a patient advocate with an aim of bridging evidence, practice and policy.
Methods: Methods Data was collected primarily by observation and document review over a 3 year period. The patient advocate convened patient advocacy sessions in 10 counties in Kenya. Baseline information on knowledge and perceptions was documented by interviews and focus groups. Observations were made on proactive screening and choice of method for screening.
Results: Results Most individuals were optimistic about cervical cancer screening after advocacy with a mean of 60% of attendants proactively seeking screening immediately. A mean of 14% of participants proactively sought screening within one month of advocacy. 16% of participants were completely opposed to screening while 10% remained indifferent over the 3 year period. There was little variance observed across the counties. The most preferable screening method was HPV DNA testing with 80% of participants and the least preferable was VIA VILI. Over 38% of participants were previously aware of Pap smear but had never proactively sought screening.
Conclusions: Conclusion Based on the national guidelines for management of cervical cancer, there is need to include patient advocates as an integral part of the health system as well as recommend HPV self-testing as the primary method of screening.

HPV VACCINE EFFECTIVENESS IN THE AREA OF INFANTA LEONOR UNIVERSITY HOSPITAL-MADRID: PRELIMINARY RESULTS.

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In Spain, HPV systematic vaccination began in 2007 in 14-year-old girls. In 2019, they turn 25, the age of onset of cervical cancer screening. Published studies on vaccine effectiveness indicate that in countries with systematic vaccination programs there is a reduction in the prevalence of HPV infection, genital warts and in the rate of cytological alterations.
Methods: HPV test with genotyping (CLART-HPV2 / Genomica) and cytology is performed on 800 women born in 1993 and 1994 comparing prevalence of infection, rate of cytological alterations and incidence of genital warts among the group that adequately received 3 doses of tetravalent vaccine and the unvaccinated group. Preliminary results obtained at 50% of recruitment are presented (415 cases).

Results: 415 women, 226 vaccinated and 189 unvaccinated are included. The overall prevalence of HPV infection was 41% in unvaccinated vs 35.1% in vaccinated group. Among vaccine genotypes, significant differences were found only for HPV16, 7.4% in unvaccinated versus 1.76% in vaccinated ($p < .05$). Of the 4 positive HPV16 cases detected in the vaccinated population, 3 of them were vaccinated after sexual intercourse. No significant differences were observed in the rate of cytological alterations or in the incidence of genital warts yet.

Contingence table: HPV16 detection. Vaccine yes/no

Recount

		Detection HPV 16		Total
		No	Si	
Vaccine si/no	No	175	14	189
	Si	222	4	226
Total		397	18	415

Contigence table: Vaccine yes/no * Cytology

Recount

		Cytology				Total
		Negative for lesion or malignity	ASCUS	LSIL	HSIL	
Vaccine yes/no	No	149	16	15	5	185
	Yes	176	24	17	3	220
Total		325	40	32	8	405

Contigence table: HPV test * Vaccine yes/no

Recount

		Vaccine yes/no		Total
		No	Yes	
HPV test	Negative	111	144	255
	Positive	77	78	155
Total		188	222	410

Conclusions: Halfway through the planned recruitment, a significant reduction in the prevalence of HPV16 infection in the vaccinated population is observed. There are no statistically significant differences in the overall HPV infection rate, presence of other vaccine genotypes, incidence of genital warts or cytological alterations, possibly due to the low number of alterations obtained. It would be necessary to wait until the end of the recruitment for further analysis. *This study has been funded by MSD.*

DIAGNOSTIC ACCURACY OF HPV-DNA/P16INK4A DOUBLE TESTING IN NON-OROPHARYNGEAL HEAD AND NECK CANCER: RESULTS FROM THE ICO INTERNATIONAL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: For the diagnosis of HPV-driven non-oropharyngeal head and neck cancer (HNC), tests or test algorithms have not been validated so far.
Methods: Formalin-fixed, paraffin-embedded cancer tissues of oral cavity (OCC), oropharyngeal (OPC), and laryngeal (LC) cancer were collected from pathology archives in 29 countries. All samples were subject to histopathological evaluation, DNA quality control, and HPV-DNA detection. HPV-DNA positive and a random sample of HPV-negative samples were subject to HPV E6*I-mRNA detection and $p16^{INK4a}$ immunohistochemistry. Three different cut-offs of intense nuclear and cytoplasmic staining were evaluated for $p16^{INK4a}$ overexpression: >25%, >50% and >70%. Accuracy of HPV-DNA/$p16^{INK4a}$ double testing was assessed by estimating the sensitivity, specificity, odds ratios, and area under the curve (AUC) taking as gold-standard E6*I-mRNA positivity, by HNC site.
Results: 169 OCC, 431 OPC and 129 LC out of 3680 HNC with valid HPV-DNA results were tested for $p16^{INK4a}$ and E6*I-mRNA. HPV-DNA/$p16^{INK4a}$ double testing showed higher AUC than $p16^{INK4a}$ alone in OPC for all cut-offs (p-values < 0. 05), due to an increase of specificity. In OCC and LC, the increase of specificity was also observed, although not being statistically significant. Sensitivities of HPV-DNA/$p16^{INK4a}$ and $p16^{INK4a}$ alone were much lower for LC compared to OCC and OPC (56.3%-59.4% versus 80.9% and 85.5%, respectively). When restricting the analysis to HPV16-positive cases, an improvement for HPV-DNA/$p16^{INK4a}$ double testing than $p16^{INK4a}$ positivity alone was observed in OPC for all cut-offs (p-values <0.001) and in OCC, although not reaching the statistical significance in this case neither (p-value 0.139).
Conclusions: HPV-DNA/$p16^{INK4a}$ double testing may be useful for HPV-driven OCC diagnosis although more experiments with higher number of cases are needed. Considering only HPV16-positive cases may improve the test accuracy. When assessing HPV-role on non-oropharyngeal HNC, a distinction between OCC and LC must be made.

THE USA HPV VACCINATION PROGRAM: POLICY, IMPLEMENTATION AND IMPACT

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccine was introduced into the national USA immunization program in 2006; vaccination policy has evolved as additional HPV vaccines were licensed and new data became available. Vaccination coverage is increasing although consistently lower than for other adolescent vaccinations. Routine safety monitoring and projects for impact evaluation are being conducted.
Methods: We reviewed recommendations from the Advisory Committee on Immunization Practices, vaccination coverage data from the annual National Immunization Survey-Teen, and reports from several safety and vacccine impact monitoring systems, including the National Health and Nutrition Examination Survey.
Results: Routine HPV vaccination was recommended at age 11-12 years in 2006 for females and in 2011 for males, with catch-up through age 26 for females and age 21 for males. Catch-up recommendations were harmonized through age 26 in 2019. Most vaccine used through 2014 was quadrivalent vaccine (4vHPV). 9-valent vaccine (9vHPV), introduced in 2015, was the only vaccine available after 2016. At least 1-dose and up-to-date coverage among 13-17 year-olds in 2018 was 70% and 54% among girls; 66% and 49% among boys. Vaccination coverage has been increasing; between 2017 and 2018 coverage increased only among boys. There are various reasons for low coverage; efforts are ongoing to increase vaccine uptake. Through June 2019, about 43 million 9vHPV doses were distributed in the United States; 9vHPV safety profile is similar to 4vHPV. 4vHPV-type HPV prevalence in self-collected cervicovaginal swabs declined 86% between the prevaccine era and 2013-2016 among 14-19 year-olds and 71% among 20-24 year-olds. Declines also have been observed in anogenital warts and cervical precancers.
Conclusions: The United States was the first country to introduce HPV vaccine and currently has a gender-neutral vaccination program. The vaccine safety profile has been well established by 12 years of monitoring. Given moderate vaccination coverage, impact on HPV prevalence and HPV-associated outcomes has exceeded expectations.

DIFFERENCES IN RISK BETWEEN VACCINATED AND UNVACCINATED WOMEN AGAINST HUMAN PAPILLOMAVIRUS AND HERD IMMUNITY: TOWARDS A PERSONALIZED SCREENING APPROACH

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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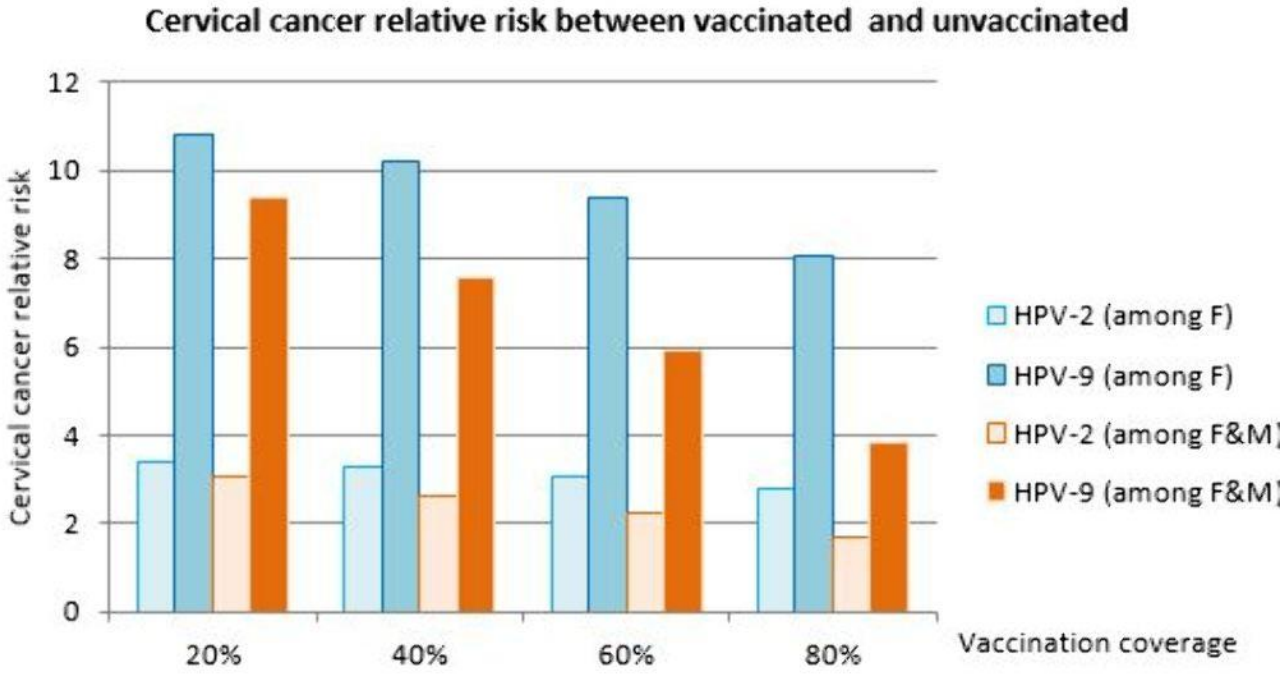
Introduction: With increased uptake of the vaccination against human papillomavirus (HPV) oncogenic types and increased herd immunity over time, HPV vaccine will provide protection also for unvaccinated women, depending on the vaccination coverage. The resulting difference in cancer risk will determine the price of universal screening for vaccinated and unvaccinated women, in terms of over- and under-screening and highlight the importance of a personalized screening approach.
Methods: We used STDSIM, a stochastic microsimulation model to investigate the herd immunity progress over time in unvaccinated women. We estimated differences in HPV-prevalence rate and cervical cancer risk between vaccinated and unvaccinated women aged 15 to 64 years of the same cohort. Application of the bivalent and the nonavalent vaccination under different coverages among females alone vs females and males were considered.
Results:



In the steady state situation, which is reached after more than five decades under all scenarios, the relative cervical cancer risk for unvaccinated compared to vaccinated women ranged from 1.7 to 10.8, depending on the vaccination strategy. The relative risk was higher in lower vaccine coverages, using the nonavalent vaccine and when vaccinating females only.

Conclusions: We found notable differences in the risk of developing cervical cancer in unvaccinated compared to vaccinated women under all vaccine coverage assumptions. Since the disease risk is one of the most important variables that determines an optimal screening program, we aim to incentivize thinking towards personalized cervical cancer screening, dependent on the vaccination strategy.

NATURAL HISTORY OF NON-HPV16/18 INFECTIONS AMONG HPV-NAÏVE WOMEN PROTECTED AGAINST HPV16/18 IN THE COSTA RICA VACCINE TRIAL (CVT)

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Our understanding of co-factors for oncogenic-HPV persistence and progression derive largely from natural history studies dominated by HPV16/18. We aimed to evaluate co-factors for persistence and progression of non-HPV16/18 infections in HPV16/18-vaccinated women.
Methods: This analysis included 2,154 18-25-year-old women enrolled in CVT who were HPV-DNA-negative for all types at baseline or self-identified as sexually naïve, received a minimum of 1-dose of Cervarix, and were followed for up to ~11 years. Persistence of infection was defined as 2+ HPV-DNA positive results for the same HPV type over 1-year without intervening negative results; multiple persistent infections within-woman were counted as separated events. CIN2+ diagnoses were based on histological findings by expert pathologists. GEE Poisson regression was used to evaluate time-dependent factors (age, smoking, sexual behavior, contraceptive use and BMI) and risk of persistence and progression, clustered by individual and adjusted for relevant confounders. Cumulative incidence (CI), relative risk (RR) and 95% confidence intervals (95%CI) are reported.
Results: Eleven-year CI of any non-HPV16/18 infection was 61% (1311/2154); 18% persisted for 1-year and 12% persisted for 2-years. Eleven-year CI of any carcinogenic non-HPV16/18 infection was 45% (978/2154); 11% persisted for 1-year and 7% persisted for 2-years. Eleven-year CI of CIN2+ was 2% (42/2156). Non-statistical associations were found for age, smoking (duration/intensity), sexual behavior, most contraceptive use variables, and BMI and the risk of persistence of any non-HPV16/18 infection (p-values>0.05). Intrauterine device use (IUD) was associated with an increased risk persistence of any non-HPV16/18 infection (former [RR=3.5 (95%CI=1.9-6.3)] and current [RR=2.9 (95%CI=1.2-7.3)] vs no-use). Analysis for progression to CIN2+ are ongoing and will be presented.
Conclusions: In an HPV16/18-vaccinated naïve cohort, commonly known co-factors were not associated with persistence of non-HPV16/18 infections, except for IUD. As more countries adopt HPV vaccination, understanding the natural history of non-HPV16/18 infections is important for successful control of cervical cancer.

INFILTRATING T-CELL MARKERS IN CERVICAL CARCINOGENESIS: A SYSTEMATIC REVIEW AND QUALITATIVE AND META-ANALYSIS

BASIC RESEARCH / VIRUS – HOST INTERACTIONS"

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Introduction: The host adaptive immune response is important in determining which cervical HPV infections persist and progress to precancer and cancer. Systematic characterization of T cell infiltration will help inform key steps in cervical carcinogenesis.
Methods: We conducted a systematic review of infiltrating T cells positive for the following markers in normal cervix, low-grade lesion, high-grade lesion, and invasive cancer epithelial, stromal, and total tissues: CD3 (total T cells), CD4 (helper), CD8 (cytotoxic), FoxP3 (regulatory), CD25 (regulatory), and the CD4:CD8 ratio. We conducted a quantitative meta-analysis of cells/mm2 for marker-disease-tissue type combinations with sufficient data for pooling and a qualitative analysis for those without (Figure 1). A qualitative review was undertaken of longitudinal data on associations between infiltrating T cells and cervical disease persistence, regression, progression, or prognosis.

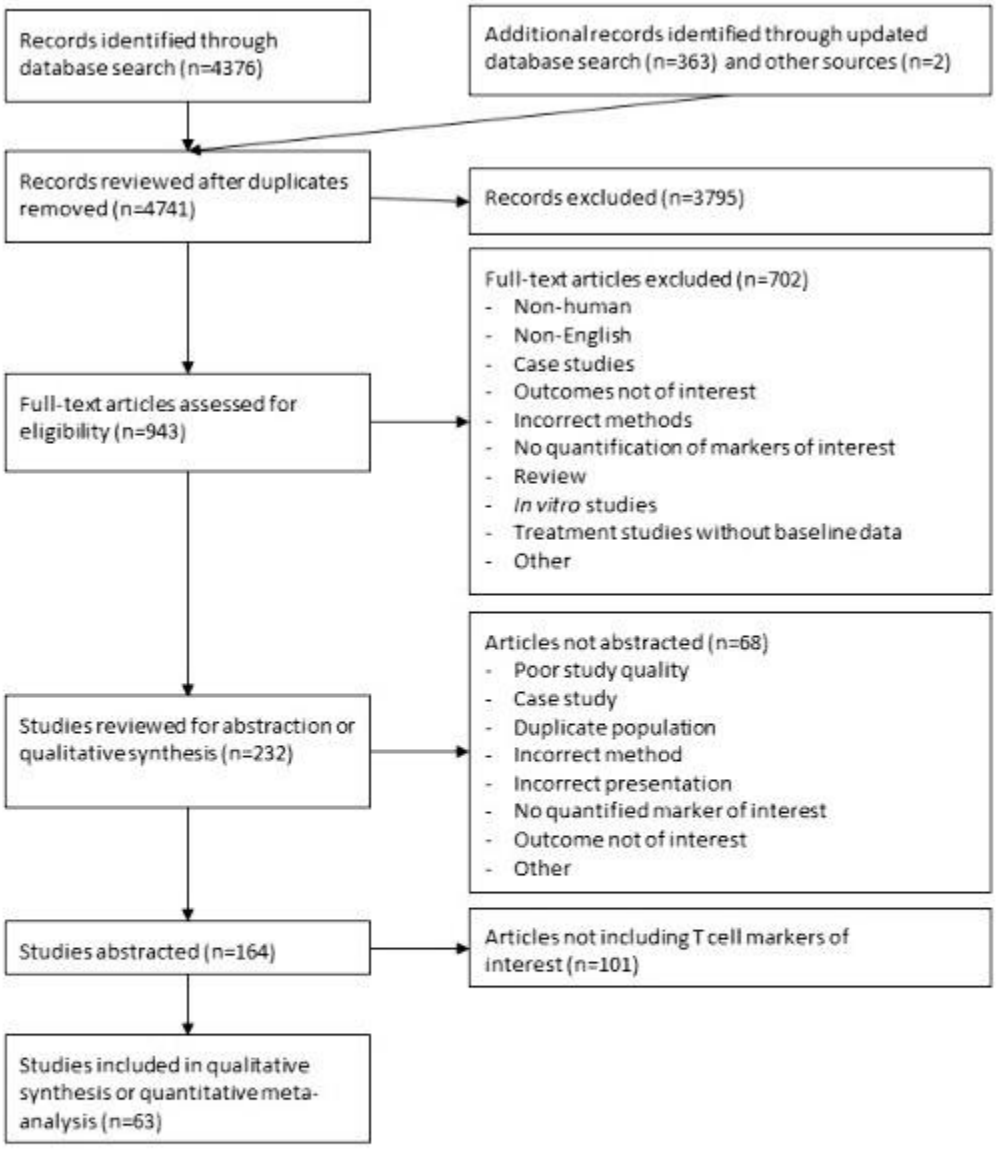

Figure 1: PRISMA Diagram. The initial and updated PubMed searches plus two additional records identified during the full text review resulted in total of 4741 records reviewed. After title and abstract review, 3795 records were excluded leaving 943 for full text review. The full text review excluded an additional 702 records, leaving 232 records for potential abstraction. Of these, 68 were not abstracted for the reasons indicated and 164 were abstracted. After limiting to the T cell markers of interest, 63 records remained for inclusion in the quantitative meta-analysis or qualitative summary of infiltrating T cells in cervical tissue.

Results: There were fewer CD3+, CD4+, and CD8+ cells in cervical lesions and more cells in cancers compared to normal epithelium (Figure 2). Taken together, FoxP3 and CD25+ quantitative and qualitative analyses suggest that regulatory T cell infiltration is high in persistent and precancerous lesions, and

longitudinal data show improved outcomes with lower regulatory T cell levels.

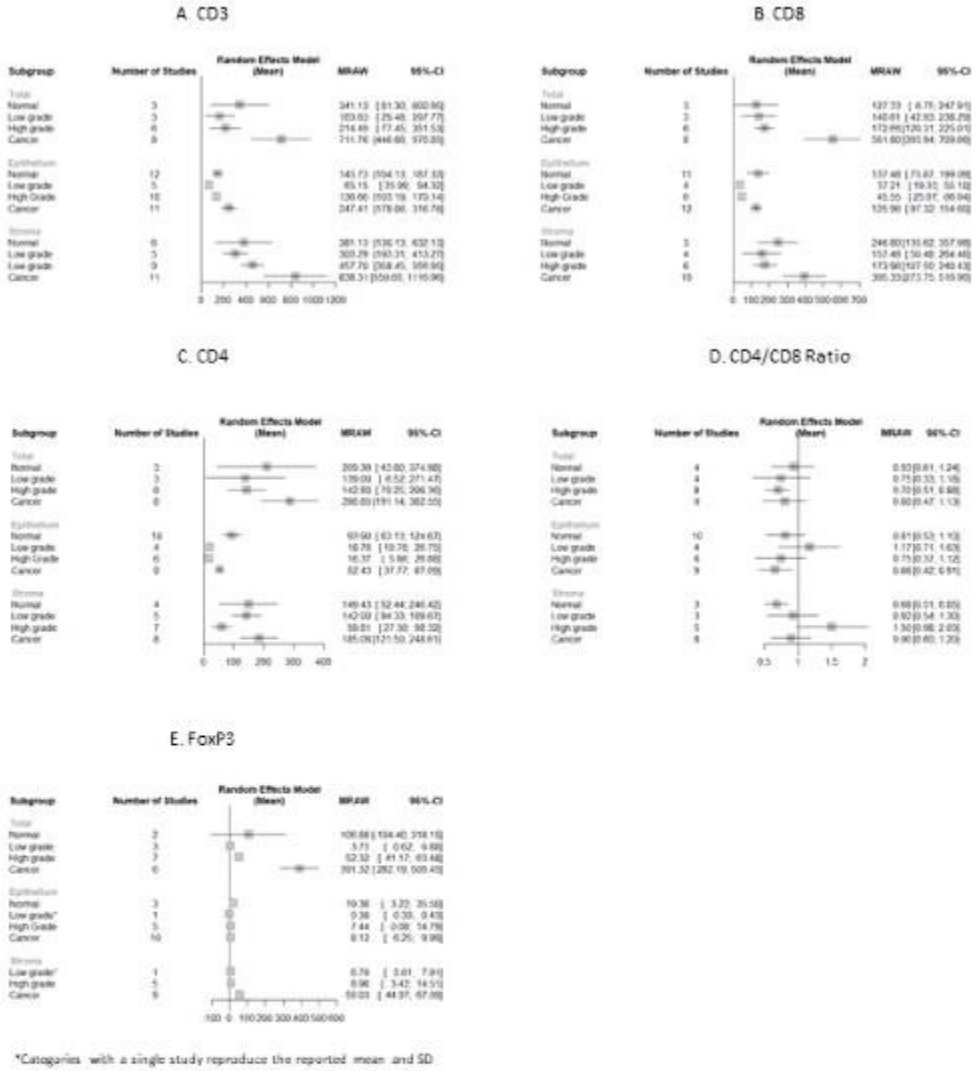

Figure 2. Forest plots of T cell infiltrate quantitative meta-analyses. Forest plots of meta-analyses of infiltrating T cell markers across cervical disease stages in total tissue, epithelium and stroma expressed as mean cells/mm^2 with 95% confidence intervals for the following markers: A. CD3, B. CD8, C. CD4, D. CD4:CD8 ratio, E. FoxP3. There were no stromal normal FoxP3 reports, so this category is absent. Abbreviations: CIN, cervical intraepithelial neoplasia; LG, low grade; HG, high grade; MRAW, raw (untransformed) mean; CI, confidence interval.

Conclusions: Successful immune evasion may reduce T cell infiltration in HPV infected and precancerous epithelium, while invasive cancers are highly immunogenic causing increases in all T cell

subsets (Figure 3). Inhibition of the adaptive immune response, characterized by high regulatory T cell infiltration, contributes to cervical disease persistence and progression. Understanding these factors may have prognostic value and could aid in the development of novel treatments and the determination of which patients require immediate treatment. However, the published data are heterogeneous and inconsistent, leaving important gaps to be filled by further tissue analyses.

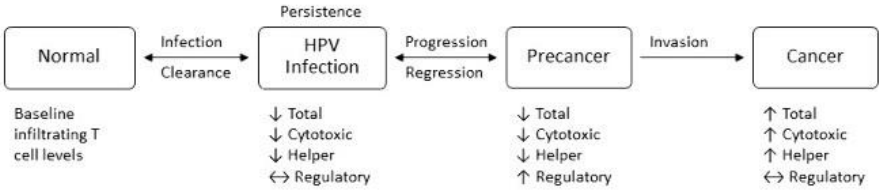

Figure 3. Conceptual model of infiltrating T cells in cervical carcinogenesis. Normal cervical tissue is infiltrated by T cells and T cell subsets that respond to infection as part of the adaptive immune response. When HPV infection becomes established and is not immunologically cleared, it evades immune detection with reduced total (CD3+), cytotoxic (CD8+), and helper (CD4+) T cell infiltration. It is unclear whether regulatory (CD25+, FoxP3+) T cell infiltration is affected. When HPV infections persist and progress to cervical precancer, pro-immune T cell subsets continue to be suppressed and regulatory (inhibitory T cells) are increased. If the lesion progresses to invasive cancer, a highly immunogenic state is reached with high levels of total, cytotoxic, and helper T cells. Regulatory T cells may be relatively high, resulting in a worse prognosis, or low, resulting in a better prognosis.

ROLE OF HUMAN PAPILLOMAVIRUS INFECTION IN HEAD AND NECK CANCER IN ITALY: THE HPV-AHEAD STUDY.

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Literature on the incidence and prognostic value of HPV in head and neck cancer (HNC) in Italy is limited, especially for non-oropharyngeal tumours. Within the context of the HPV-AHEAD study, we aimed to assess the diagnostic and prognostic value of different tests or test algorithms judging HPV carcinogenicity in HNCs, as well as factors related to HPV-positivity.
Methods: We conducted a retrospective cohort study of patients diagnosed with a primary HNC at the European Institute of Oncology in 2000-2010. Formalin-fixed, paraffin-embedded cancer tissues were subjected to histopathological evaluation, DNA quality control, HPV-DNA detection, and $p16^{INK4a}$ immunohistochemistry. All HPV-DNA positive and a random sample of HPV-DNA negative cases were subjected to HPV-E6*I-mRNA detection. Demographic, tobacco/alcohol use, clinical and follow-up data were collected. Multivariate models were used to evaluate factors associated with HPV-positivity. Proportional-hazards models were conducted to assess the risk of death and recurrence among HPV-driven and non-driven HNC.
Results: A total of 698 cases were included in the analyses (166 oral cavity (OC), 110 oropharyngeal (OPC), 401 laryngeal (LC) cancer cases). The percentage of HPV-driven cases (considering E6*-mRNA positivity) was 1.8%, 40.9% and 2.2% for OC, OPC and LC cases, respectively. Double testing for HPV-DNA/$p16^{INK4a}$ showed strong diagnostic accuracy for the three HN sites, although the estimates were based in low number of cases. Being non-smoker or former smoker or diagnosed at more recent calendar periods were associated with HPV-positivity in OPC. HPV-driven OPC cases showed better overall survival, but not HPV-driven OC and LC cases as compared to HPV- non-driven ones.
Conclusions: The percentage of HPV-driven cases was higher in OPC than in OC and LC as reported in other studies. HPV prevalence in OPC was observed to be increasing in recent years in our setting as it happened two decades ago in areas where nowadays most of OPC cases are HPV-related.

KNOWLEDGE, BELIEFS AND BARRIERS ABOUT THE HUMAN PAPILLOMAVIRUS (HPV) VACCINATION AMONG THE PARENTS OF CHILEAN SCHOOL GIRLS.

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The persistent infection by human papillomavirus (HPV) is the leading cause of cervical cancer, which is one of the primary causes of cancer related mortality in women. The vaccination against HPV represents an effective public health strategy to reduce the morbidity and mortality that it causes. Since 2014, the Chilean Ministry of Health has been providing the HPV vaccine to fifth grade girls. Vaccination against HPV is obligatory however it has the highest rate of rejection in the National Immunization Program due to opposition from some parents. This study is the first to concurrently evaluate HPV vaccine knowledge, beliefs and barriers in Chilean parents for their school-aged daughters.
Methods: We recruited parents who accepted and rejected the HPV vaccination of their daughters to participate in focus group discussions. The participants were predominantly women of middle-income, belonging to different districts of the Chilean Metropolitan Region. Qualitative data were analyzed using thematic and discourse analysis.
Results: Parents have limited knowledge about HPV, cervical cancer, and the HPV vaccine. Several barriers were revealed: some parents perceived low risk for HPV-related diseases; others believed that HPV vaccine is a new vaccine with potential unknown side effects and others worry that the vaccine could promote an early or high-risk sexual behavior. Parents do not talk to their children about sexual health issues, they prefer that health professionals or teachers educate their daughters about this topic.
Conclusions: There is a clear need to develop primary prevention strategies and health care providers and teachers should be prepared to provide parents with basic cervical cancer prevention knowledge and how to talk to their daughters about these topics. Additionally, prevention strategies should also consider the socioeconomic and cultural context and the role that schools play in the teaching about sexual education.

AN ASSESSMENT OF THE FACTORS THAT CONTRIBUTE TO RESILIENCE IN HPV VACCINATION SYSTEMS AROUND THE WORLD: A LITERATURE REVIEW

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In recent years, shocks, or external stresses or challenges to vaccination systems (e.g. vaccine hesitancy, safety concerns), have resulted in drops in vaccination rates of routinely recommended vaccines. Furthermore, these shocks have led to the resurgence of previously well-contained vaccine-preventable diseases. The capacity of health entities and local stakeholders to effectively respond to such shocks, maintain core functions when shocks arise, and quickly adapt to changing circumstances helps to demonstrate a health system's resilience. This study assessed the factors that may impact vaccination systems' resilience within the context of HPV vaccination.
Methods: A targeted literature review was conducted to identify peer-reviewed, grey literature, and web publications from 2011-2019 related to health or vaccination systems' resilience and HPV vaccine-related safety concerns and/or crises introducing unanticipated shocks to systems.
Results: We screened 143 publications, of which 107 were included for full review. Several publications focused on factors that support or erode health systems' resilience in the face of shocks, but few focused specifically on impacts to vaccination systems. Several highlighted recent shocks to HPV vaccination programs in Japan, Ireland, India and Denmark, which were attributed to alleged vaccine safety concerns and led to subsequent vaccine hesitancy. Denmark's multi-stakeholder response to the shock demonstrated concepts associated with resilience (e.g. adaptability and coping), enabling post-shock recovery of vaccination rates. Conversely, the Japanese government ceased proactively recommending the vaccine, which has led to a vaccination rate of around 1% in females born after 2001.
Conclusions: A comprehensive understanding of the factors associated with vaccination systems' resilience is important for addressing vaccine hesitancy. Using recent HPV vaccine-related shocks as a case study highlights the imperative for vaccination system stakeholders to work to instill trust and maintain vaccination coverage rates, while adapting and responding to the political, social, and economic impacts that unanticipated shocks can produce.

VARYING SIGNAL-TO-CONTROL HRHPV-DNA AND HRHPV-E6/E7-MRNA (HRHPVE6/E7) POSITIVITY CUT POINTS PREDICT ANAL HISTOLOGICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HHSIL) FOR ADULTS LIVING WITH AND WITHOUT HIV.

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

D. Wiley[1], H. Hsu[1], L. Flowers[2], M. Moran[1], S. Young[3], N. Joste[4], R. Detels[5], O. Martinez-Maza[6], R. Mitsuyasu[7], E. Chiao[8], E. Stier[9], E. Rodriguez[1], T. Brown[10], G. D'Souza[11], S. Reddy[12], F. Jenkins[13]
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Introduction: Improving the specificity and accuracy for anal hHSIL screening minimizes healthcare costs.
Methods: 431 HIV-infected/-uninfected MSM (332), cis-women (96) and transfemine-women (3) were evaluated using Dacron-cytology (aCyt), hrHPV-DNA, hrHPVE6/E7, and HRA/biopsy to predict histological HSIL (hHSIL). Sensitivity, specificity, and area under Receiver-Operating Characteristic (AUC) curves were evaluated for chemiluminescence compared to control (hrHPV-DNA=RLU/Co and hrHPVE6/E7=S:CO) as positivity cut-points: $\geq$2, $\geq$4, $\geq$6, $\geq$8, $\geq$10 S:CO or RLU/Co, respectively, compared to manufacturer recommended cut-point, $\geq$0.5 S:CO and $\geq$1 RLU/Co. Gender- and HIV($\pm$)-adjusted logistic regression models estimated odds of hHSIL for each cut-point. Statistical contrasts evaluated differences between cut-points, overall.
Results: Mature adult (54.6 (σ=11.4) years), ever-smokers (61%) comprised the cohort; 44% reported HIV-infection. Men showed 2-fold higher odds of $\geq$ASC-US cytology ($p<0.05$) and nearly 3-fold higher prevalence of hHSIL than women (45% vs. 16% $p<0.0001$). Adjusted analyses showed aCyt sensitivity to predict hHSIL at any alternative cut-point did not significantly vary using either test across these cut-points ($p>0.05$). However, using either hrHPV test, at all cut-points, specificity for hHSIL was statistically significantly greater than aCyt: hrHPV-DNA=69%-83%; hrHPVE6/E7=77%-82% vs. 51%. All single-test hrHPV-DNA cut-points $\geq$4 RLU/CO showed higher specificity than $\geq$1 RLU/CO (78%-83%, p-values <0.02). Single-test hrHPVE6/E7 specificity improved for cut-points $\geq$8 vs. $\geq$0.5 S:CO (81%-82% vs. 73%, p-values$\leq$0.05).

Test Characteristics to Predict hHSIL for Two Molecular hrHPV Test Strategies in Comparison to Anal Cytology Across 7 to 8 Alternative Positivity Cut-points and Manufacturer-Specified Cut-Points.

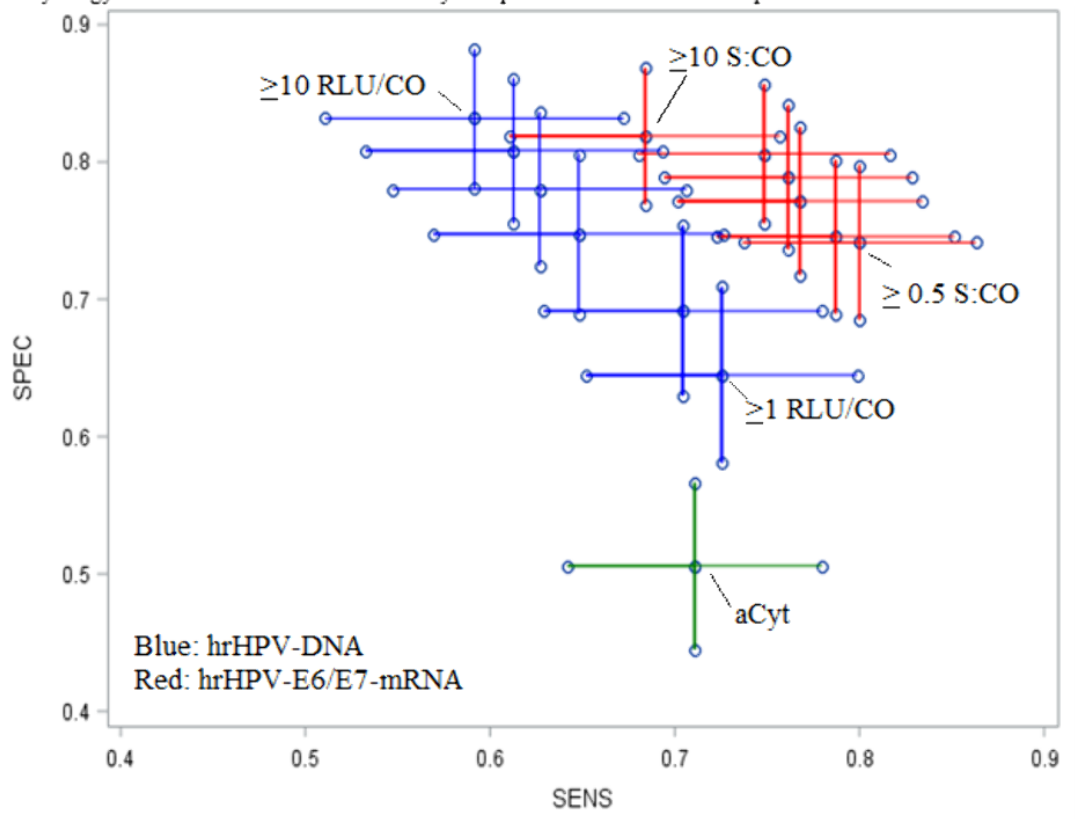

Table: Sensitivity and Specificity For hrHPV-DNA And hrHPVE6/E7 Over Incrementally Increasing Chemiluminescence Signal-to-Control Positivity Cut-Points in Comparison to Anal Cytology and Contrasts Across Positivity Cut-Points Within Molecular Assays for 431 Adults Evaluated Using High-Resolution Anoscopy and Biopsy.		
	Sensitivity % (95% Confidence Interval)	Specificity % (95% Confidence Interval)
hrHPV-E6/E7 (S:CO)		
≥0.5[£]	81% (74%, 87%)	73% (67%, 79%)**
≥1	80% (74%, 86%)	74% (69%, 80%)*
≥2	77% (70%, 83%)	77% (72%, 83%)*
≥4	79% (72%, 85%)	75% (69%, 80%)*
≥6	76% (69%, 83%)	79% (74%, 84%)*
≥8	75% (68%, 82%)	81% (76%, 86%)*[a]
≥10	68% (61%, 75%) [a]	82% (77%, 87%)*[b]
hrHPV-DNA (RLU:CO)		
≥1[£]	73% (65%, 80%)	64% (58%, 71%)*
≥2	70% (63%, 78%)	69% (63%, 75%)*
≥4	65% (57%, 73%)	75% (69%, 81%)*[a]
≥6	63% (55%, 71%)	78% (72%, 84%)*[d]
≥8	61% (53%, 69%)	81% (76%, 86%)*[e]
≥10	59% (51%, 67%)	83% (78%, 88%)*[e]
Anal Cytology	71% (64%, 78%)	51% (44%, 57%)
[£] Manufacturer-specified cut-point (referent for within-assay comparisons) Contrasts comparing each molecular assay at 6 hrHPV-DNA and 7 hrHPV-E6/E7 positivity cut-points vs. aCyt, *p*-values: *<0.0001, **<0.05 Contrasts comparing sensitivity and specificity within each assay, employing positivity cut-points greater to recommended positivity cut-points vs. manufacturer-specified cut-points: *p*-values: [a]≤0.05, [b]<0.02, [c]<0.005, [d]<0.0006, [e]<0.0001)		

Conclusions: Adjusting positivity cut-points for anal hHSIL screening using hrHPV-DNA or hrHPVE6/E7 assays improves specificity appreciably over aCyt, while retaining similar sensitivity. Employing molecular tests as a primary screen for anal hHSIL opens opportunities to evaluate targeted, cost-effective population-based cancer prevention strategies.

IMPLEMENTATION OF HPV VACCINATION IN GEORGIA (THE COUNTRY)

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical cancer is the fourth most common cancer among women in Georgia and it's responsible for 200 deaths annually. It has been only 2 years since free and voluntary HPV vaccination has been implemented by Global Alliance for Vaccines and Immunization and it includes 9-year-old girls and not adults (it's quite expensive for other age groups). We decided to conduct a research which analyzes current situation and focuses on the goals which will improve total coverage of vaccination.
Methods: 1) Researching/analyzing statistical data about HPV vaccination in 9-year-old girls;
2) Questioning of patients and doctors about HPV and HPV vaccination;
3) Analyzing the results; figuring out the reasons of low activity and finding ways to improve the situation.
Results: Analyzing the statistics of voluntary HPV vaccination of 9-year-old girls, which took place in 4 different cities, demonstrated the following: In the first year, the best results were seen in Batumi where 80% of girls were vaccinated. In Kutaisi data shows 50% and Tbilisi (the capital) showed the lowest results - 36%. (The results of the fourth city – Sukhumi – is not known). Unfortunately, for the second year, the numbers decreased in every city. Questioning of focus groups and analyzing the results have shown that:
(1) Informative campaign was poorly planned;
(2) Patients and their parents still don't have clear knowledge about the necessity and advantages of this vaccination;
(3) Medical personnel is passive and sometimes prefers not to get their patients vaccinated;

Conclusions: The research showed that there is a lack of information in patients and even in medical personnel. Statistics of HPV vaccination is not satisfactory and major increase of informative campaigns is needed to improve the current situation. Besides, it will cause a tremendous change if the vaccine will get mandatory for children aged 10, 11 and 12 years old.

DIAGNOSIS AND MANAGEMENT OF CERVICAL PRECANCERS IN A RESOURCE-POOR SETTING IN NORTHERN NIGERIA

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Human Papillomavirus (HPV) is a necessary cause of cervical cancer (CC) in which 80% of the disease burden occurs in developing countries where organized screening programmes are not available and, as such, still opportunistic. This study aims to review the opportunistic screening methods used in our centre, and the treatment methods offered for high grade abnormalities.
Methods: A ten-year review (January 2009- December 2018) was carried out on records of patients that had opportunistic screening for CC in our centre. The methods of diagnosis, histological results, treatment methods and follow up of these patients were recorded.
Results: A total of 11,597 clients had cervical cancer screening during the study period. In 18% of cases, pap smear was done using liquid-based cytology and 72% using conventional cytology. A total of 98 smears were inadequate, more with the conventional (89%). Immunohistochemistry for P16/Ki67 was not routinely done, except for research purposes. No single case of high risk HPV deoxyribonucleic acid testing (hrHPVDNA) or visual inspection was done. The histology result showed CIN II/III or HSIL on cytology in 8.6%, CINI or LSIL in 5.6%, negative/inflammatory in 79% and atrophic in <1%. Ninety-two percent had colposcopy and biopsy after diagnosis of HSIL with an 83 percent concordance of cytology and histology. Of these, 70 (76.9%) had hysterectomy, 11 (12.1%) had cone biopsy, and 9 (9.9%) had cryotherapy. One client had no treatment at all / no treatment record was seen. No client had loop electrosurgical excision procedure (LEEP). Treatment method largely depended on fertility desire, availability of treatment options, and coexisting pathologies. There was no defined follow up pattern for these clients.
Conclusions: The availability of organized screening using HPVDNA testing and treatment using LEEP excision in resource poor settings will go a long way in reducing the burden of cervical cancer.

IMMUNOGENICITY, SAFETY AND EFFECTIVENESS OF THE HPV VACCINE IN PEOPLE LIVING WITH HIV (PLHIV): A SYSTEMATIC REVIEW AND META-ANALYSIS.

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Effectiveness or duration of protection of HPV vaccination may be different in PLHIV. We systematically reviewed current evidence on the immunogenicity, safety and effectiveness of HPV vaccines among PLHIV.
Methods: We searched MEDLINE, PubMed, Embase, clinicaltrials.gov and WHO ICTR for data published by April 2019. Studies reporting data on vaccine safety, effectiveness or immunogenicity of a licensed HPV vaccine among PLHIV were included. We pooled estimates using random-effects model. Here, we report immunogenicity results (i.e. seropositivity and time trends for geometric mean titres (GMT) after 1st vaccine dose) for HPV-16 and HPV-18.
Results: We included 15 independent clinical trials (from 3,293 items identified). These focused on the quadrivalent(n=13) and bivalent(n=3) vaccine. Trials were conducted in the Americas(n=6), Europe (n=4), Africa (n=2), South East Asia (n=1). Studies reported on immunogenicity(n=13), safety(n=11) and effectiveness (n=5). Seropositivity among baseline seronegative individuals was high 4 weeks after the last dose of the vaccination schedule (e.g. for 3 doses, 28 weeks since the first dose, HPV-16: 98%(95%CI:97-99%); HPV-18: 93%(95%CI:90-96%)). Seropositivity declined over time, especially for HPV-18 (table).

Table: Seropositivity following 1st HPV vaccine dose in PLHIV who were HPV seronegative for the HPV type at baseline*

HPV	Doses	Timing measurement**	Vaccine	Sex	Seropositivity (95%CI)	I2	Number of estimates pooled (N)
HPV 18	3 doses	28 weeks	Quadrivalent	Both	93(90-96)	66%	8
		48-96 weeks	Quadrivalent	Both	74(65-83)	79%	7
		48 weeks	Bivalent	Both	98(92-100)	0%	1
		> 100 weeks	Quadrivalent	Both	57(40-73)	0%	2
	4 doses	96-100 weeks	Quadrivalent	Both	90(70-100)	90%	2
		>100 weeks	Quadrivalent	Both	76(68-83)	0%	2
HPV16	3 doses	28 weeks	Quadrivalent	Both	98(97-99)	22%	8
		48-96 weeks	Quadrivalent	Both	96(93-99)	67%	8
		48 weeks	Bivalent	Both	100 98 -100)	0%	1
		> 100 weeks	Quadrivalent	Both	86(72-95)	0%	2
	4 doses	96-100 weeks	Quadrivalent	Both	100(97-100)	53%	2
		>100 weeks	Quadrivalent	Both	98(96-100)	0%	2

** Seropositivity among type specific HPV negative was determined using the cLIA test (n = 36), or other type of immunoassay (n = 8)*
*** Number of weeks after receiving the 1st dose in the vaccination schedule. 28 is approximately 4 weeks after the last vaccination dose in the 3-dose and 4-dose regimes.*
**** Measure of heterogeneity.*

GMT increased substantially above the assay cut-off for seropositivity at 28 weeks, and declined thereafter but remained above the seropositivity cut-off across studies (figure 1 and 2). GMT levels were substantially higher for HPV-16 than HPV-18 over time across studies.

Figure 1: GMT titres over time for HPV 18 following vaccination with the quadrivalent vaccine in PLHIV who were initially seronegative for HPV−18

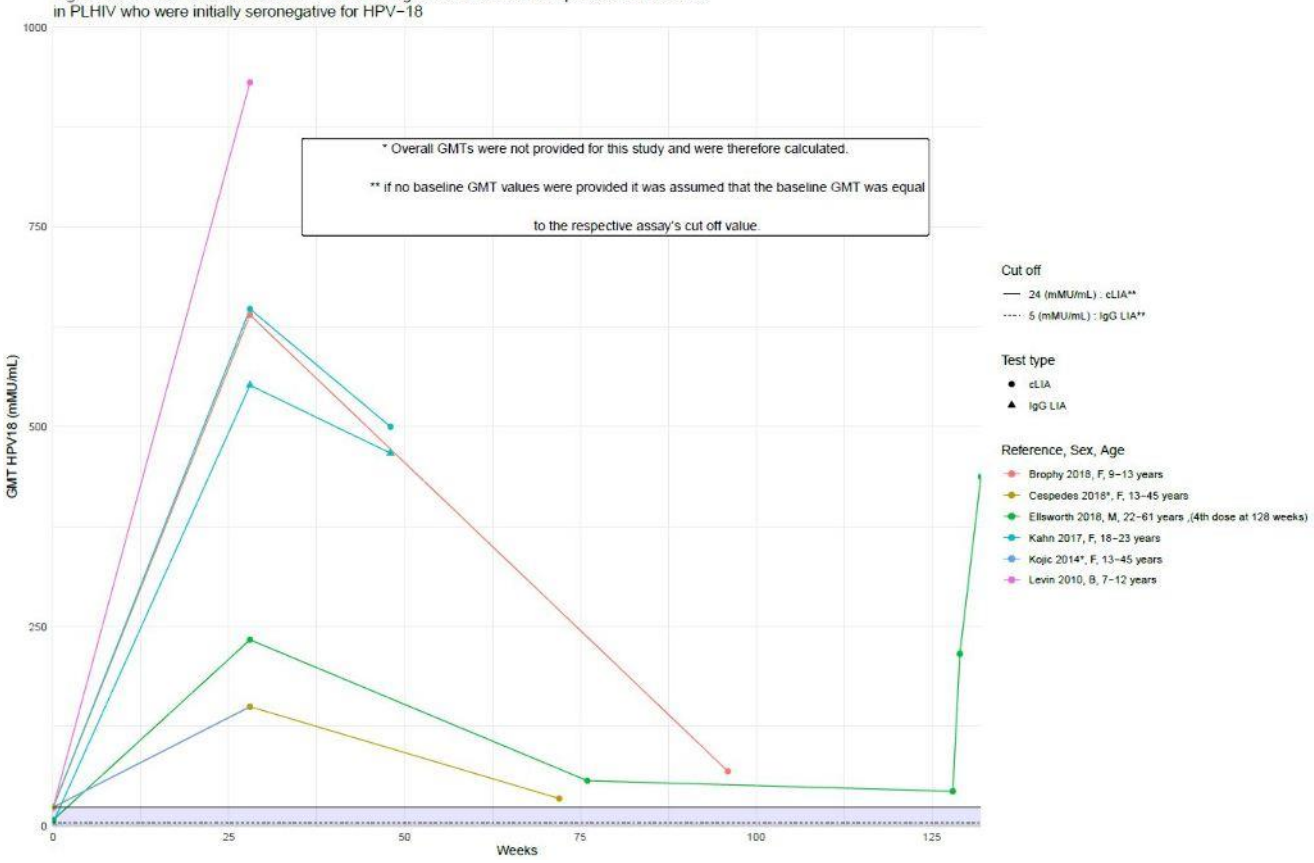
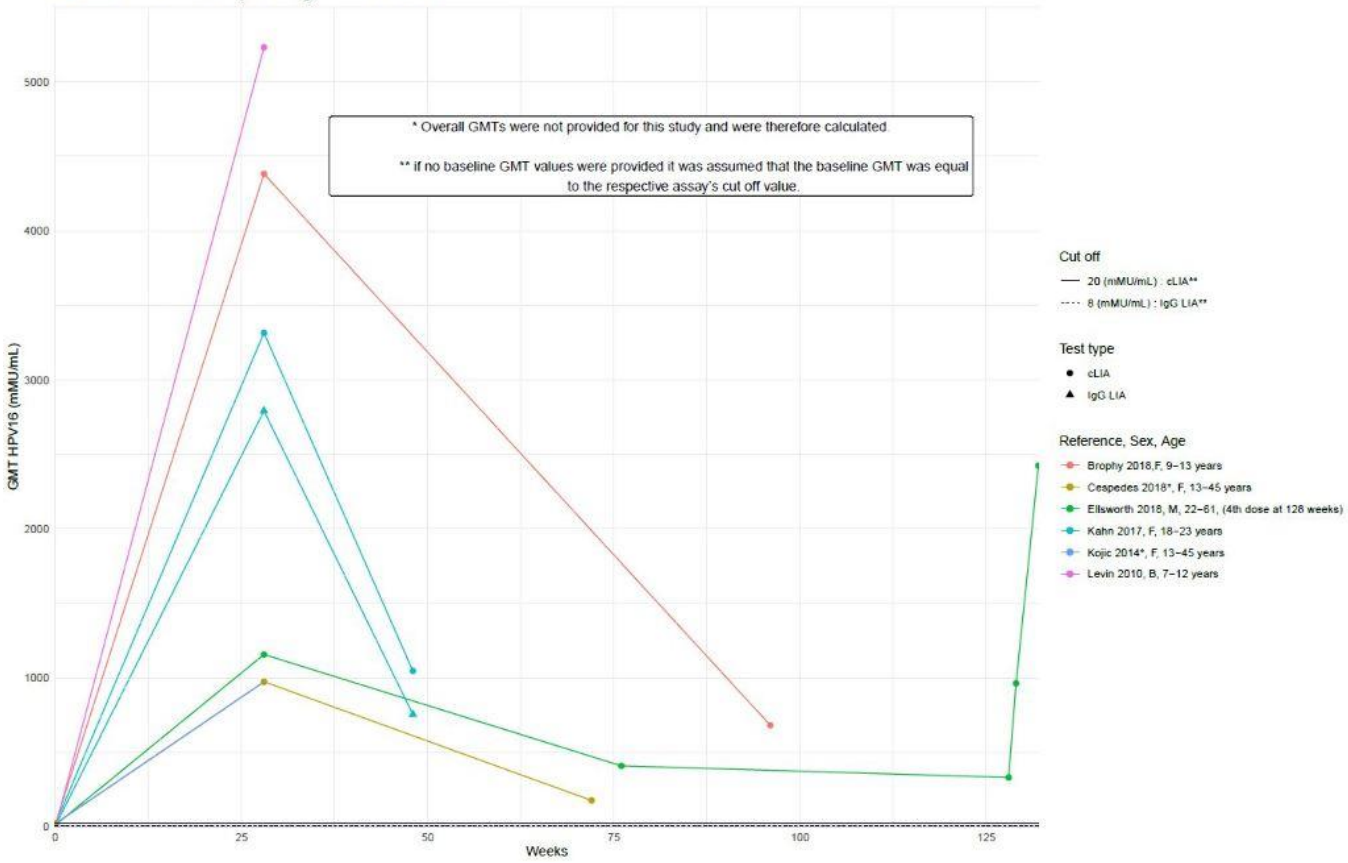


Figure 2: GMT titres over time for HPV 16 following vaccination with the quadrivalent vaccine in PLHIV who were initially seronegative for HPV-16



Conclusions: There is a robust antibody response in PLHIV following vaccination, especially for HPV-16. GMT levels remain above the seropositivity threshold suggestive of protection, which may be similar or weaker than for HIV-uninfected individuals who may achieve higher GMT levels. Future analysis will summarise the influence of patient characteristics (e.g. CD4 count, sex, age) on immunogenicity, safety results, and effectiveness results to determine if there is evidence that the antibody response translate into sustained protection against HPV infection in PLHIV.

IMPLEMENTATION OF HPV-BASED SCREENING FOR CERVICAL CANCER PREVENTION IN PERU: LESSONS AND CHALLENGES OF MOVING POLICY TO PRACTICE

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The Peruvian Ministry of Health (Ministerio de Salud or MINSA) has adopted HPV testing as a primary screening strategy in their National Cancer Control Plan since 2016. The MINSA, in collaboration with multiple technical support teams, is striving toward practice-based evidence to ensure rapid roll-out of sustainable and regionally-adapted HPV-based screening programs.
Methods: HPV screening in Peru targets women 30-49 years, which represents a total population of 4.48 million women spread across 25 geographically and culturally diverse regions. The two pilot projects, Tumbes and Loreto regions, have tested implementation of community-based and health system-based screening programs, with and without diagnostic triage prior to treatment. Key performance indicators, such as percent of population screened, percent testing HPV positive, and operational logistics such as time from sample collection to testing and result delivery were monitored. Among positives, percent attending next levels of care were monitored as critical program effectiveness performance indicators. Screening registries were developed independently for each pilot study and are evaluated for utility at a national level.
Results: HPV testing was broadly acceptable in both pilot studies and offers a significantly reduced time spent in the screening continuum compared to Pap-based programs. Where colposcopy and anatomic pathology resources are limited, direct treatment of HPV-positive women with ablative therapy is feasible and acceptable, reducing significant loss to follow up. Key programming decisions are in progress, and being aided by national and international experts on the topic. However, programming decisions are also hindered by HPV test costs, difficulty obtaining technical information relevant for community-level implementation, among other challenges.
Conclusions: Peru is committed to meeting cervical cancer elimination goals by accelerating the adoption and scale-up of sustainable HPV-based screening programs in women 30-49 years. Regional adaptability of HPV-based screening implementation strategies is essential to meet these goals, and this is facilitated by partnership with technical advisory teams.

ASSOCIATION OF CYTOKINE GENE POLYMORPHISMS WITH PERSISTENT HPV INFECTION IN THE CERVIX

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: In precancerous lesions of the cervix and in cervical cancer (CC), a state of immunosuppression has been identified, characterized by an increase in the expression of type II interleukins (IL-4, IL-10, suppressors of the cellular immune response) and a concomitant reduction of interleukins type I (IL-2, INF-γ), which favors the persistence of HPV infection. The objective of this study was to evaluate the association of genetic polymorphisms of the -590C>T (IL-4); −573G>C (IL-6); −592C>A, −819C>T and −1082A>G (IL-10); −509C>T (TGF-β1); −308G>A (TNF-α) and -1615C>T (IFN-γ) with persistence and clearance of HPV in the cervix.
Methods: Dynamic cohort study in 267 HPV positive women in the cervix and who were included in the baseline study and evaluated at 12 months to determine persistence or viral clearance. HPV molecular test and evaluation of allelic discrimination polymorphisms with Taqman probes in peripheral blood mononuclear cell samples was realized. Bivariate and logistic regression analysis was performed to determine the statistical association of these polymorphisms with persistence and clearance-HPV adjusted by potential confusers.
Results: We found to be a carrier of polymorphisms -573G>C (IL-6), -380G>A (TNF-α), -1615C>T (IFN-γ) is a risk factor for persistence of HPV infection, while being carriers of polymorphisms -590C>T (IL-4) and -509C>T (TGF-β1) confer protection against persistence and elimination of HPV infection, respectively.
Conclusions: The associations found for the polymorphisms of IL-6, TNF-α and IFN-γ suggest that these SNPs are potential predictors of persistent HPV infection in the cervix. It is necessary to evaluate its potential use and thus reduce the current care burden of diagnosis and treatment of premalignant lesions and CC.

IDENTIFICATION OF TRANSCRIPTOMIC PROFILES IN HPV-POSITIVE AND HPV-NEGATIVE PENILE CANCER OF PUERTO RICAN MEN

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: Penile cancer (PeCa) is a rare but highly morbid disease. A significantly higher incidence and mortality rate among Puerto Rican men has been shown in comparison to other Caucasian, African American or Hispanic US populations. The objective of this study is to determine the genome-wide expression profiles in HPV^+ and HPV^- PeCa.
Methods: PeCa fresh tissue was obtained from surgery cases. The global gene expression profile was analyzed using the Affymetrix GeneChip® Human Gene 2.0 array. Gene set enrichment analysis (GSEA) of the clinical dataset (11 HPV^+ samples, 17 HPV^- samples) was performed. For each sample we collected clinical information (age, HPV status, p16 staining, tumor stage, tumor type, histology grade, lymph node status and metastasis).
Results: Several categories of pathways were enriched for HPV cases: (1) Out of the 50 Hallmark gene sets of the MSigDB Collections, pathways involved in cell division were enriched for HPV^+ PeCa. They include genes involved in mitotic spindle assembly, G2/M checkpoint, cell cycle targets of E2F transcription factors, and genes regulated by MYC. (2) Out of the 50 Hallmark gene sets, there were pathways involved in DNA damage response and p53 function, consistent with the activity of the HPV E6 oncoprotein to induce degradation of the tumor suppressor protein p53 via the ubiquitin pathway. (3) Out of the 50 Hallmark gene sets, estrogen response genes were enriched for HPV^+ cases (p-value < 0.05). (4) Out of the 1329 Canonical Pathways gene sets, the top enriched pathway was Notch signaling pathway of KEGG (p-value = 0.00192). (5) Compared with HPV^+ cases, fewer pathways were found enriched in HPV^- cases.
Conclusions: Our transcriptomic data revealed extensive signaling changes associated with HPV in PeCa among Puerto Rican men. Our results can help in the development of diagnostic and prognostic biomarkers for HPV^+ and HPV^- PeCa.

HPV INFECTIONS AND CYTOLOGIC ABNORMALITIES IN VACCINATED WOMEN 21-34 YEARS OF AGE: THREE-YEAR LONGITUDINAL RESULTS OF THE ONCLARITY TRIAL

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccination programs have led to reduced HPV infections and high-grade cervical disease in many countries. Comparatively, vaccination rates in the United States (where vaccination is largely opportunistic) are lower and vaccination often occurs at an older age. However, baseline data from the Onclarity trial suggest that “catch-up” vaccination is effective in reducing HPV infection. Here we provide three-year cumulative prevalence values for HPV genotypes and cervical intraepithelial neoplasia grade 2 or worse (≥CIN2) in vaccinated and unvaccinated women enrolled in the trial.
Methods: 33,858 subjects, ≥21 years, were screened by cytology and the Onclarity HPV Assay. Those with abnormal results underwent colposcopy/biopsy. Women who had colposcopy and a random selection of others were invited for yearly follow-up for three years. HPV and ≥CIN2 cumulative prevalence values were compared in a subset (N=14,153) of women 21-34 years of age stratified by vaccination status and age group (21-24 yrs, 25-29 yrs, and 30-34 yrs). Mantel-Haenszel analysis was performed to determine the association between vaccination status and prevalence/odds ratio (OR), adjusting for age.
Results: The three-year cumulative prevalences of overall HPV, HPV16, 18, 31, and 33/58 were all lower in vaccinated women across age groups; significant (all $p<0.005$) lower prevalences were observed with 16 (OR: 0.28), 18 (OR: 0.15), 31 (0.54), and 33/58 (0.67) in vaccinated compared to unvaccinated women (all ages combined). In addition, reduced HPV 16/18-associated ≥CIN2 prevalence was observed in vaccinated women compare to unvaccinated women (OR: 0.38; $p<0.001$).
Conclusions: Consistent with the baseline results, the three-year follow-up data show that HPV vaccinated women have a lower prevalence of any high-risk HPV, HPV 16, 18, 31, and 33/58; and of HPV 16/18-associated ≥CIN2 compared to unvaccinated women. A lower HPV prevalence in older, vaccinated women suggests that “catch-up” vaccination provides benefit.

GENITAL VS ANAL CANAL VS ORAL HPV PREVALENCE IN THE HPV INFECTION IN MEN (HIM) STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Human papillomavirus (HPV) is a known cause of anogenital cancers and a subset of oropharyngeal cancers among men across the globe. Little is known about simultaneous prevalence of HPV in genital, anal canal, and oral anatomic sites among men. In this study, we assessed the pairwise association of HPV infection in these three sites and the age distribution at each site.
Methods: Participants of the HPV Infection in Men (HIM) cohort study who had data for anal, genital, and oral HPV prevalence in the same study visit were included (N = 739). Genital and anal canal HPV was genotyped using Roche Linear Array whereas oral HPV was genotyped using the SPF_{10} PCR-DEIA-$LiPA_{25}$ assay. Pairwise association of HPV infection between the three anatomic sites and their age distributions were assessed using log binomial models.
Results: Prevalence of any HPV infection in genital, anal canal, and oral sites was 41.8%, 25.7%, and 10.1% respectively, and high-risk HPV infection was 32.2%, 19.1%, and 7.4% respectively. Anal infection was significantly associated with genital infection for HPV types 16, 39, 45, 51, 56, 58, 59, 6, 11, 53, 54 and 66. Oral infection was significantly associated with genital infection for HPV types 51, 56, 59, and 66 whereas significant association with anal infection was observed for HPV types 35 and 6. Any and high-risk genital HPV prevalence generally decreased with increasing age whereas anal HPV prevalence first decreased with age but then increased among men aged 51-73 years. Oral HPV demonstrated unimodal distribution, with peak prevalence among men aged 31-40 years.
Conclusions: Occurrence of simultaneous anal and genital HPV infections was observed for more HPV genotypes than oral-genital or oral-anal sites. Different HPV types were co-detected at oral-anal sites compared to anal-genital and oral-genital sites. Age-pattern of HPV prevalence differed between the three sites.

LOWERING THE AGE FOR SCREENING AND USING HPV TESTING OPTIMIZES CERVICAL CANCER OUTCOMES AMONG WOMEN LIVING WITH HIV: INSIGHTS FROM A MATHEMATICAL MODEL

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: Cervical cancer incidence among women living with HIV is 2-5 times higher than HIV-negative women. Many settings with high HIV prevalence have low cancer screening coverage, in which context once-per-lifetime screening could be high-yield for cervical cancer prevention. However, due to higher rates of HPV progression with HIV co-infection, the optimal age for once-per-lifetime screening is likely to differ by HIV status.
Methods: Using a dynamic compartmental model of HIV and HPV transmission and disease progression, we evaluated the ages at which cervical cancer screening and treatment minimize cancer incidence and mortality by HIV status. Our model is parameterized to KwaZulu-Natal, South Africa, a region with high HIV and cervical cancer incidence. We modeled scenarios with observed 86% coverage of school-based HPV vaccination and 70% coverage of one-time screening at ages ranging from 20-70 in 5-year increments. To test the impact of different screening modalities, we compared scenarios using cytology (CIN2+ sensitivity 57%) and HPV testing (CIN2+ sensitivity 88%). We present the range of screening ages that resulted in reductions in cancer incidence and mortality within 10% of optimal over a 50-year time-horizon from 2020-2070.
Results: Among HIV-negative women, cervical cancer incidence was minimized with screening between ages 50-60. Cancer mortality was minimized with screening between ages 55-60. Among women living with HIV, incidence and mortality were minimized with screening between ages 40-50 and 45-55, respectively. HPV-based screening increased by three-quarters the prevention gains for both groups, and the relative impact of screening was higher for women living with HIV.

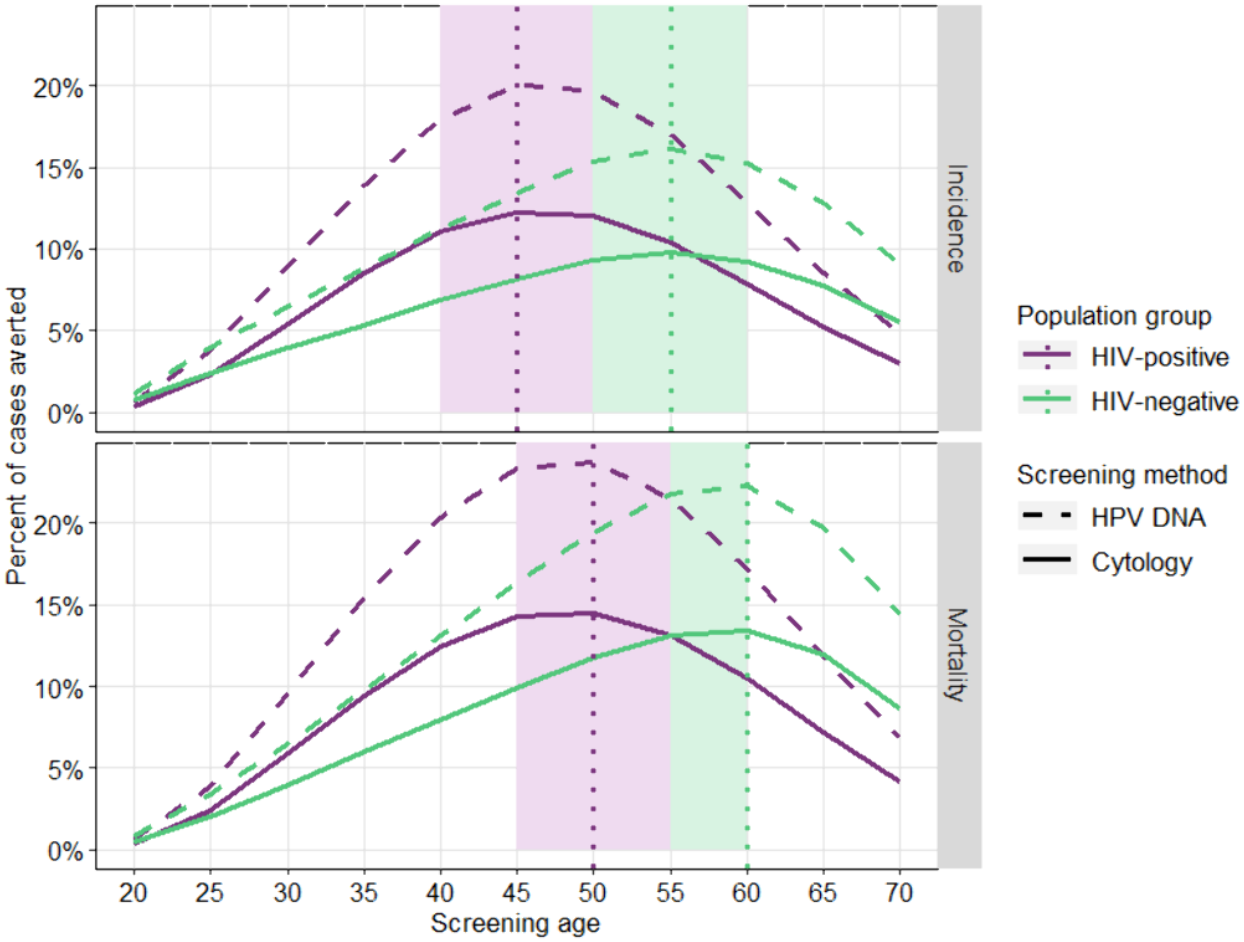

Table 1. Optimal screening ages and impact on cervical cancer incidence and mortality by HIV status and screening modality

	HIV-negative		HIV-positive	
	Optimal age (range[a])	Percent of cases/deaths averted[b]	Optimal age (range[a])	Percent of cases/deaths averted[b]
Incidence				
Cytology	55 (50-60)	9.78%	45 (40-50)	12.3%
HPV testing	55 (50-60)	16.1%	45 (40-50)	20.0%
Mortality				
Cytology	60 (55-60)	13.4%	50 (45-55)	14.5%
HPV testing	60 (55-60)	22.2%	50 (45-55)	23.7%

[a]Range of evaluated ages that result in a percent reduction within 10% of the optimal
[b]With screening at the optimal age, relative to a scenario with no screening

Conclusions: Our model indicates that even once-per-lifetime screening could have a substantial impact on cervical cancer outcomes over the coming decades, particularly with use of HPV-based testing in settings with high HIV prevalence. Screening efforts should target women up to age 60, with a focus on

younger ages for women living with HIV.

LABORATORY QUALITY MANAGAMENT IN THE CONTEXT OF CERVICAL CANCER PREVENTION PROGRAMS: THE ARGENTINEAN MODEL

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2012, Argentina implemented the Human Papillomavirus (HPV) test as primary screening method for 30-year-old women and above. Cytology is used for *triage*. At present, eleven HPV laboratories from eight provinces process HPV samples from women attending the public health system. In order to achieve high quality diagnosis in these laboratories, the National Program on Cervical Cancer Prevention (PNPCC-INC, by its initials in Spanish) designed a laboratory quality control model.
Methods: The main components of the Argentinean quality control model for HPV laboratories were systematized based on criteria proposed by “Quality Management System in the Laboratory” handbook (WHO, 2011).
Results: The main components of the Argentinean quality control model for HPV laboratories are: 1) centralization of HPV test processing as part of a centralized HPV-cyto-pathology service; 2) adaptation of laboratory physical space for storage of samples/reagents, and processing of HPV tests; 3) staff training; 4) development of protocols for transport, and conservation of samples and supplies, processing and reporting of unexpected events and results; 5) implementation of SITAM (the national screening information system); 6) design and monitoring of diagnostic quality outcomes using specific indicators: HPV positive percentage (<9% and >15%), reasons for non-processing/rejection of samples, unsatisfactory cytologies percentage (>10%), ASCUS/ASCH cytologies percentage (<5%), HSIL cytologies percentage (2%), and cyto-histological correlation percentage (<60%); 7) implementation of external audits *in situ* by the National and Regional Reference HPV Laboratory (Global HPV LabNet, under the authority of ANLIS-Malbrán); 8) organization of workshops/meetings to exchange experiences and on-site training for the continuous improvement of work processes.
Conclusions: This model has been applied at population scale in programmatic contexts in Argentina, allowing to improve processes to optimize diagnostic quality.

HPV VACCINATION FOR BOYS IN ADDITION TO GIRLS-ONLY VACCINATION IS COST-EFFECTIVE IN FINLAND: ANALYSIS BASED ON NATIONAL HEALTH REGISTERS AND MODELING

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In Finland, a country with one of the lowest cervical cancer incidence, HPV vaccination for girls started in 2013. Whether also boys should be included into the program is not obvious, since girls' HPV vaccination, with 65-75% coverage, already create herd effects into both males and females.
Methods: HPV related disease burden, including cervical cancer and a number of other HPV associated cancers (e.g., anogenital, head and neck), were estimated based on data from nationwide health registers. Besides numbers of cases, the disease burden consists of screening and treatment costs, and of life-years (LY) and quality-adjusted life-years (QALY) lost. A dynamic transmission model, calibrated to data from pre-vaccination era, was used to predict how the age-specific disease burden in a population (birth cohorts of 60,000) changes in time under different HPV vaccination strategies (base case 70% coverage). For evaluating the cost-effectiveness of sex-neutral vs girls-only HPV vaccination, we followed the population after onset of vaccination. We also assessed the annual disease burden in the pre- and post-vaccination steady-states.
Results: For sex-neutral vs girls-only vaccination, the cost per LYs/QALYs gained was 0-39/0-23 kEUR with vaccine prices of 10-40 EUR per dose and 3% discount rate. In the new steady state, sex-neutral vaccination prevented annually approximately 300 cancer cases and saved about 1700/2500 LYs/QALYs compared to 200 cases and 1200/1900 LYs/QALYs by girls-only vaccination (undiscounted). The annual undiscounted treatment costs were 4.1 MEUR less for sex-neutral than for girls-only vaccination, of which 2.6 MEUR originated from cervical cancer and its screening, while the annual vaccination costs increased 0.5-1.8 MEUR with the assumed vaccine prices.
Conclusions: Sex-neutral HPV vaccination in addition to girls-only vaccination is likely cost-effective with current European tender based vaccine prices in the Finnish setting. Cervical cancer and its screening play still major roles in the benefits.

INTRODUCTION OF HPV VACCINATION IN ZIMBABWE – EXPERIENCES WITH MULTI-AGE COHORT VACCINATION DELIVERY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The World Health Organization (WHO) recommends human papillomavirus (HPV) vaccine for girls aged 9-14 years for cervical cancer prevention and encourages vaccinating multi-age cohorts in the first year to maximize impact. In 2018-2019, HPV vaccine was introduced nationwide in Zimbabwe through an annual, school-based campaign to a multi-age cohort (ages 10-14) in the first year and a single-age cohort (grade 5 girls in-school and age 10 girls out-of-school) in the second year. This overlapping approach was used so the first-year cohort's second dose was concurrently delivered with the second-year cohort's first dose.
Methods: We reviewed country documents and interviewed key informants at the national level from May–September 2019 regarding decision-making, planning and implementation of HPV vaccine introduction. Materials reviewed included policy/strategy documents, introduction plans, readiness reports, country presentations and implementation tools. Key informants included focal persons from government health and education ministries, in-country immunization partners, and HPV Strategic Advisory Group members.
Results: Respondents identified high cervical cancer burden, political will, vaccine availability, financing from Gavi, The Vaccine Alliance, and the successful pilot program as factors driving the decision to introduce HPV vaccine nationally. A school-based delivery strategy was chosen due to high primary school enrollment (97.5%) and health staff presence in most schools. Annual dosing schedule (with an overlapping age cohort) was selected to minimize cost. The first national HPV vaccination campaign achieved 89.7% administrative coverage. Interviewees perceived the school-based delivery strategy positively and attributed successful introduction to strong collaboration between health and education sectors and high vaccine demand. Challenges with insufficient funding and heavy staff workload during campaigns were reported.
Conclusions: High coverage was achieved through Zimbabwe's first multi-age cohort school-based HPV vaccination campaign. Further evaluation is needed to understand actual costs, feasibility, and sustainability of this strategy, as well as document successes and challenges with vaccinating overlapping target age cohorts.

DUAL STAINING FOR P16/KI-67 TO DETECT HIGH-GRADE CERVICAL LESIONS: RESULTS FROM THE SCREENING TRIAGE ASCERTAINING INTRAEPITHELIAL NEOPLASIA BY IMMUNOSTAIN TESTING (STAIN-IT) STUDY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: We compared clinical performance of p16/Ki-67 dual-stained cytology and HPV genotyping, via different algorithms, alone, or in combination with cytology, to identify CIN2+ in women referred to colposcopy at three university-affiliated hospital clinics.
Methods: The STAIN-IT study included 492 (134 normal, 130 CIN1, 99 CIN2, 115 CIN3, 6 CIN2/CIN3, 8 cancers) randomly selected specimens out of 1158 with valid conventional cytology, HPV and biopsy results. Cervical specimens were transferred to PreservCyt solution and tested for presence of high-risk HPV, hrHPV (cobas® 4800 HPV Test). Dual staining (CINtec® PLUS assay) was retrospectively performed; each slide was read by a cytologist and confirmed by two pathologists. Slide readers were blinded to cytology, biopsy, and genotyping results. Accuracy (correct classification rate), sensitivity and specificity (restricted to lesion-free women) and 95% confidence intervals (in parentheses below) of dual-staining to detect CIN2+ were compared with other screening tests available for the same women (HPV, cytology, and combinations), overall and by age (≤30/>30 years).
Results: hrHPV and HPV16/18 positivity were detected in 321 (65.2%) and 139 (28.3%) women, respectively. The overall positivity rate for dual staining was 56.7%; increasing with histological severity from 30.6% in normal, 41.5% in CIN1, 72.7% in CIN2, 87.8% in CIN3 to 87.5% in cancer cases. Dual-stained cytology and hrHPV positivity had similar accuracy [71.8% (67.6-75.7)] in predicting CIN2+; superior to cytology [ASC-US: 65.0 (60.6-69.3); LSIL: 66.7 (62.3-70.8)]. Dual staining alone had lower sensitivity [80.7% (75.0-85.6) vs. 89.9% (85.3-93.5)] and higher specificity [69.4% (60.9-77.1) vs. 64.9% (56.2-73.0)] for CIN2+ compared with hrHPV testing. Combining dual-stained cytology with an ASC-US abnormality threshold, sensitivity increased to 96.1% (92.6-98.2) whereas specificity decreased to 40.3% (31.9-49.1). Corresponding values considering an LSIL threshold were 91.7% (87.3-94.9) and 53.0% (44.2-61.7). Comparable performance patterns were observed between age groups.
Conclusions: Dual-stained cytology and HPV testing had relatively similar performance in predicting CIN2+.

ORAL HPV PREVALENCE ASSESSMENT BY LINEAR ARRAY VS. SPF10 PCR-DEIA-LIPA25 SYSTEM IN THE HUMAN PAPILLOMAVIRUS INFECTION IN MEN (HIM) STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Oral human papillomavirus (HPV) attributable oropharyngeal cancers are on the rise in many countries. Studies of oral HPV natural history are needed to fill gaps in knowledge. In studies to date, oral HPV infections are commonly detected using oral gargle samples. However, the optimal method for HPV genotyping oral gargle specimens has not been previously evaluated.
Methods: Oral gargle samples from 1455 HPV Infection in Men (HIM) study participants were HPV genotyped using two different methods: Linear Array and the SPF_{10} PCR-DEIA-$LiPA_{25}$. The sensitivity of the two tests for detecting individual HPV types and grouped HPV types, high-risk HPV, low-risk HPV, grouped 4-HPV-vaccine types, and grouped 9-HPV-vaccine-types, and the degree of concordance between the two tests were assessed. We also examined whether socio-demograhpic and behavioral factors were associated with concordance between the two assays.
Results: The sensitivity of SPF_{10} PCR-DEIA-$LiPA_{25}$ was higher than Linear Array, with the exception of HPV 70, for the detection of oral HPV. The prevalence ratio of SPF_{10} PCR-DEIA-$LiPA_{25}$ to Linear Array varied between 1 and 9 for individual HPV genotypes, excluding HPV 70, and between 3.8 and 4.4 for grouped 4-valent and 9-valent HPV vaccine types, respectively. There was no association between socio-demographic and behavioral factors and discordance in results between the two tests for oral HPV 16 detection.
Conclusions: SPF_{10} PCR-DEIA-$LiPA_{25}$ was more sensitive than Linear Array for detecting HPV in oral gargle samples. Given the growing importance of detecting oral HPV infection for oral HPV natural history studies and vaccine effectiveness evaluation, we recommend using methods with higher sensitivity such as SPF_{10} PCR-DEIA-$LiPA_{25}$ for detecting HPV in oral gargle samples.

PREVALENCE AND RISK FACTORS FOR HUMAN PAPILLOMAVIRUS INFECTION AMONG FEMALE SEX WORKERS IN HANOI AND HO CHI MINH CITY, VIETNAM: A POTENTIAL TARGET FOR VACCINATION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Cervical cancer caused by persistent infection with high-risk human papillomavirus (HPV) is the fourth leading cause of cancer mortality among women worldwide. Female sex workers (FSWs) and their clients play key roles in sustaining HPV transmission in the general population, particularly in many low-income/middle-income countries. However, FSWs are rarely considered in screening and vaccination strategies in many countries, partly due to concern that they may already be HPV-infected.
Methods: In a community-based, cross-sectional study, conducted in Hanoi and Ho Chi Minh City (HCMC) between December 2017 and May 2018, we surveyed and screened 699 FSWs aged ≥18 for infection with both low-risk and high-risk HPV genotypes, risk behaviours, and abnormal cytology. We performed multivariable modified Cox regression to determine risk factors for high-risk HPV infection.
Results: Overall prevalences of any HPV (26.3%), high-risk HPV (17.3%), and HPV-16/18 (4%) infection were moderate and similar between two cities (figure 1&2). However, FSWs in insecure settings—divorced, widowed, living alone—were associated with higher prevalence of high-risk HPV infection. Among those who had HPV DNA, the proportions of infection with any high-risk HPV type, HPV-16, HPV-18, HPV-52, multiple infection were 66.8%, 11.4%, 5.4%, 27.7%, and 69.0%, respectively. An abnormal Papanicolaou test results were observed in 12.7% of the FSWs. Squamous cell carcinomas was identified in a 33-year-old FSW, with a prevalent infection with only HPV-31. **Figure 1. Prevalence of high-risk and low-risk HPV types among FSWs.**

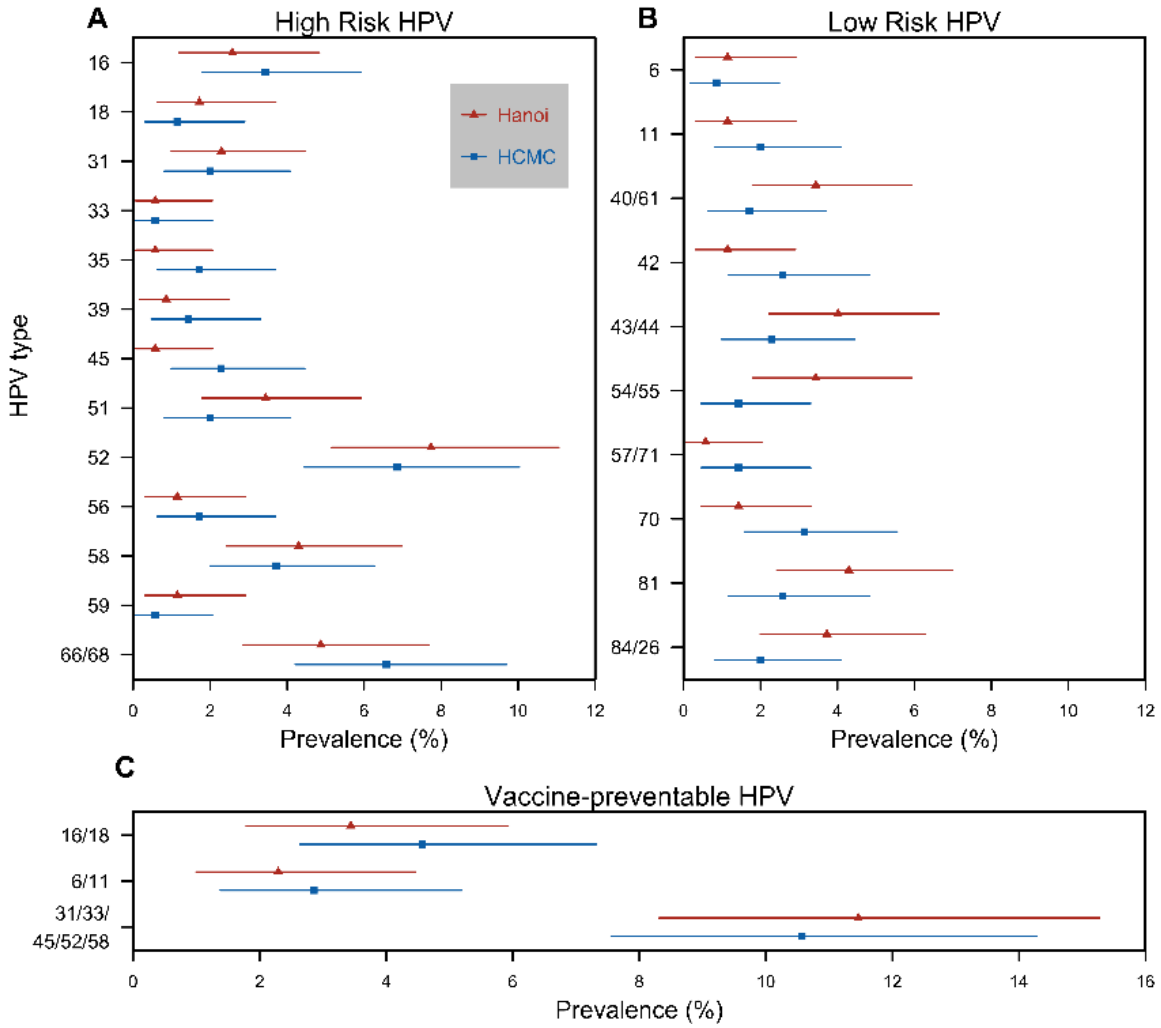
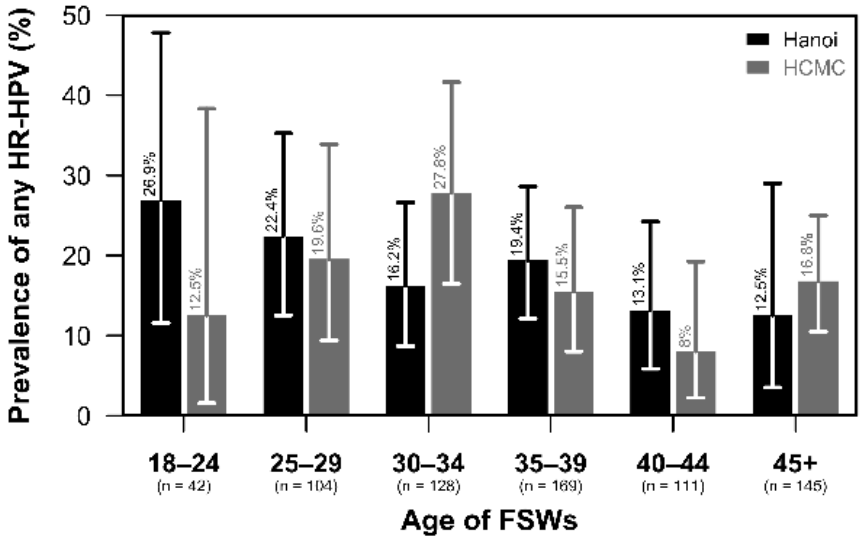
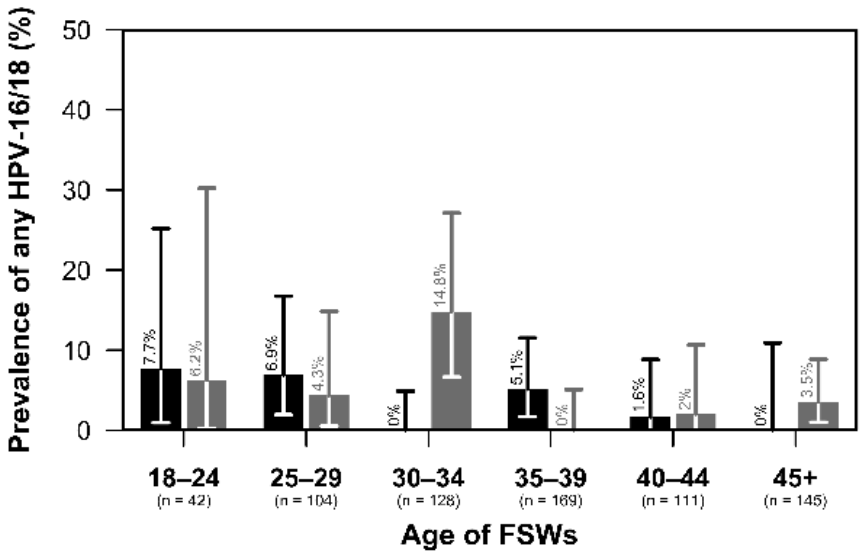


Figure 2. Prevalence of any high-risk HPV and HPV-16/18 by age of FSWs.





Conclusions: The moderate prevalence of the high-risk oncogenic HPV types among FSWs in both Hanoi and HCMC suggest that they can still benefit from screening and vaccination. Such strategies may hasten cervical cancer elimination in Vietnam and other countries with similar epidemiology, both through direct protection of women at high risk, and through the generation of herd immunity.

POTENTIAL BIOMARKER OF CERVICAL AND ANAL CANCER IN VULNERABLE POPULATIONS (HIV-POSITIVE AND QUILOMBOLA WOMEN)

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Some populations are more vulnerable to the development of anogenital cancer due to HR-HPV infection, such as HIV+ individuals and those who have limited access to health services as ethnic and racial groups, who live in semi-isolated Brazilian territory (quilombola communities). The incidence of cervical cancer remains high in the Brazilian population despite control actions adopted (cytopathology and vaccination 4vHPV), while there are no clinical trials to provide suitable screening for anal cancer. Therefore, biomarkers emerge as promising tools for anogenital cancer screening. We aimed to investigate whether the viral load corresponding to nonavalent vaccine (9vHPV) types is related to cervical and anal lesions in vulnerable populations (MSM and women HIV+, and quilombola women). This study obtained approval by the Ethical Research Council of the Federal University of Espírito Santo, Brazil.
Methods: Viral DNA was extracted from 267 cervical and anal samples (QIAamp DNA Mini Kit™-QIAGEN). HPV was screened with sets of PGMY09/11 primers and genotyped by Reverse Line Blot (RLB). The viral load of HR-HPV was determined by Real-time PCR (TaqMan® protocol) from 158 patients wihout lesions, 62 with LSIL and 47 with HSIL.
Results: The median viral load was always higher for HIV+ than for HIV- individuals. The HR-HPV 16/18 viral load was significant in HSIL for HIV- patients (p=0.02), but not for HIV+. HPV16-infected HIV- individuals had always low viral load (≤10 copies/cell) in cases of normal cytology, and at least moderate (>10 copies/cell) in cases of the lesion (p=0.04). HPV16 and HPV31 viral load behaved differently regarding HIV serological status: it was statistically significant in cases with lesion for HPV16 in HIV- (p=0.002), and for HPV31 in HIV+ (p=0.001).

Conclusions: The median viral load increased according to the “no lesion”, “LSIL” to “HSIL” cytology, regardless of HIV serological status. HPV16 and HPV31 viral load behaved differently according to HIV serological status.

DIFFERENTLY EXPRESSED GENES IN SQUAMOUS CELL CARCINOMA OF THE UPPER AERODIGESTIVE TRACT ASSOCIATED WITH HIGH-RISK HUMAN PAPILLOMA VIRUSES.

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: High-risk human papillomavirus (HPV-HR) has emerged as an important risk factor for Head and Neck Squamous Cell Carcinoma (HNSCC) due to the increase in the number of associated cases, and it has predictive value in global survival and loco-regional control (followed by smoking rate and tumor stage). Therefore, HPV-HR-positive HNSCC is now considered as a distinct biological and clinical entity from HPV-HR-negative HNSCC. In this context, it is necessary to analyze molecular alterations associated with HPV-HR because this is one of the most relevant biological factors in the clinical response to date.
Methods: Clinical-pathological data and biological material were obtained from 145 cases with HNSCC. The presence of HPV-HR (Inno-Lipa), as well as immunohistochemical detection of p16 (E6H4™), were determined. Twenty-six samples were analyzed in the Affymetrix HTA 2.0 expression microarray and Transcriptome Analysis Console. We identified differentially expressed genes (DEG) between HPV+/p16+ and HPV-/p16- tumors.
Results: We found the presence of HPV-HR in 19.3% of cases, and overexpression of p16 in 33.1%. Different frequencies of HPV+/p16+ were observed depending on the anatomical site: oropharynx, 26.8%; oral cavity, 20.0%; and larynx, 16.8%. We identified 24 differentially expressed genes (mRNAs and ncRNA) between HPV+/p16+ and HPV-/p16- (Fig. 1, Table 1). Interestingly, CD44 was down-regulated in HPV+/p16+. It is noteworthy that low expression of CD44 has been reported in cervical-uterine cancer and has been associated with better overall survival. We also found the presence of several non-coding RNAs (e.g., SCARNA14 and MIR3182).
Conclusions: HPV-HR infection seems to be associated with the deregulation of 24 genes, which could serve as biomarkers related to the presence of HPV-HR. The identification of ncRNA in HNSCC could contribute to the molecular classification associated with pathological characteristics and clinical outcome, as well as the other molecular signatures before proposed on HNSCC.

A "STORYTELLING CLOTH" APPROACH TO MOTIVATING CERVICAL CANCER SCREENING IN MALI

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: A powerful motivation to screen for cervical cancer (CC) is personal awareness of risk. Previous studies shows that in Mali, a country suffering from both low levels of literacy and high rates of CC, knowledge about CC and the underlying risk factor, infection by Human Papillomavirus (HPV) is low. This interventional study evaluated the impact of an initiative by GAIA Vaccine Foundation (GAIA VF) to improve cervical cancer (CC) awareness utilizing a “storytelling” textile design for a community awareness campaign and offering free CC screening in Bamako, Mali.
Methods: During the six-month campaign, healthcare providers and community health workers led weekly education sessions on CC, the connection between HPV and CC, and the HPV vaccine, in health clinics and surrounding communities while dressed in a “storytelling” cloth. The cloth print illustrates the connection between viral infection of HPV and the development of CC in a colorful West African wax print style. Effectiveness of the campaign was assessed by surveying women seeking CC screening at the partnering clinics.
Results: CC screening during the campaign increased fivefold. Survey results show that 52% of women cited the education sessions where the storytelling cloth was displayed as their reason for visiting the clinic more often than any other form of outreach. Participants’ desire for vaccination (of girls) was high and overwhelmingly driven by knowledge obtained through the storytelling cloth campaign. The cost of the intervention was $33 per woman screened, and 3,271 women successfully completed screening during the six-month period.
Conclusions: This culturally relevant, visually based approach for improving health literacy could be applied to future health campaigns by linking educational outreach to diagnostic and treatment services.

THE IMPACT OF IMAGE CAPTURE DEVICE ON ACCURACY OF AVE AI-DIAGNOSTIC FOR CERVICAL CANCER SCREENING

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Automated Visual Evaluation (AVE) is a diagnostic method using artificial intelligence (AI) to identify dysplasia using a visual image of the cervix. Following published work by the National Cancer Institute of the US and Global Good, AVE has emerged as a promising real-world implementation of an AI algorithm for cervical cancer screening. While encouraging results emerge from lab studies, the reproducibility and consistency of those results across devices deploying the algorithms need further exploration.
Methods: Data captured on MobileODT's EVA System offers a controlled case study opportunity given the consistency of measurable illumination, magnification and smartphone device type used by each generation of the product. Approximately 40,000 EVA System biopsy-validated images were used to train MobileODT's AVE. An analysis was performed on MobileODT's anonymized biopsy-correlated image database to understand differences in AVE algorithm performance between device models. The two device types tested were the EVA 3.0 and the EVA 3+ using a Samsung J500 and J530 smartphone, respectively. The test parameters included neural network performance given the test parameters of smartphone type, polarizer, light source.
Results: Distinct quantifiable differences in AVE prediction outputs were observed between devices when testing several deep neural networks and with varying levels of complexity.
Conclusions: An AVE developed on images from one smartphone based imaging system cannot be automatically transferred to another imaging system. Even if a model can be trained to predict for multiple devices, it would require enough data to prove efficacy per device. When compared to other medical imaging modalities (e.g. X-rays, etc.), AVE is highly uncontrolled, being affected by a multitude of external acquisition factors.

SINGLE PROTOCOL VALIDATION OF AUTOMATED DNA EXTRACTION IN DIFFERENT TYPES OF BIOLOGICAL SAMPLES REFERRED FOR HPV TYPING

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: A high quality of nucleic acid is crucial for the execution of experiments in order to obtain reliable results. The standardization and validation of pre-analytical steps are imperative to this.
Objectives: The aim of this study was to optimize a unique automated DNA extraction protocol for different types of biological samples.
Methods: Methods: Samples from cervical, penile, anal and oral collection were included in the validation. The collection method was performed with FLOQswab™ kit (penile and anal samples), oral rinse with mouthwash solution (oral) and Digene® HC2 DNA Collection Device kit (cervical). We personalized pre-processing step of each sample type to uniform the volume of sample added in the automated extraction protocol to 500µL. HPV DNA extraction was performed using Magna Pure Platform (Roche Diagnostics) and Total Nucleic Acid Kit High Performance with the program Total NA HS500. DNA concentration and purity were measured using the NanoK spectrophotometer (Kasvi).
Results: Results: To achieve the best result in DNA concentration/purity we optimize the follow conditions in pre-processing protocols: Oral samples, centrifuged at 2.000 rpm for ten minutes two times, discard the supernatant and resuspended in 2 mL of PBS 1X solution and repeat the procedure; Anal and penile, agitated for 45 minutes in low rotation and added 1 mL of PBS 1X solution and cervical, agitated to 10 seconds and resuspended in 1mL of PBS 1X solution. The average DNA concentration between the 4 types of samples extraction procedures was 47.6ng/µL for cervical, 37.4ng/µL for anal, 24.2 ng/µL for penile and 44.0 ng/µL for oral samples. Purity of all samples was around 1.25.
Conclusions: Conclusions: This automated extraction protocol was initially offered to blood and serum extraction and we achieved very good results to different samples to be used in the detection and genotyped of HPV with Linear Array HPV Detection and Genotyping Kit.

TEMPORAL DYNAMICS OF PERSISTENT HIGH-RISK HUMAN PAPILLOMAVIRUS (HPV) AND ITS RELATIONSHIP TO VAGINAL MICROBIOTA AMONG AFRICAN AMERICAN WOMEN IN THE UNITED STATES: LONGITUDINAL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: To examine the temporal dynamics of HPV in relation to the vaginal microbiota among a cohort of women in the United States.
Methods: This analysis used data from a longitudinal study of 1365 women followed for 12 months every two months apart from six locations across the US. HPV genotyping was performed using quantitative PCR using TaqMan probes in a customized plate (ThermoFisher Scientific). Bacteria flora were identified by 16S rRNA gene sequences from the V3-V4 region using high-throughput pyrosequencing.
Results: We report on 3 time-points for 80 African-American women with mean age was 21.4 years (SD: 2.11), with 81.2% graduating high school. 36.3% (95%CI: 25.8%-47.8%) remained clear of HrHPV throughout the three visits, 11.3% (5.3%-20.2%) had an incident infection, 37.5% (26.9%-49%) had persistent infection, 1.3% (0.03%-6.7%) had a recurrent infection. 13.8% (7.1%-23.3%) had HrHPV at previous visit and were able to clear the infection at subsequent visit. 23.8% had different HrHPV types at different time-points. Persistent HrHPV types included 6,11,16,18,52, and 58. While all women had BV at baseline, 61.3% had BV, 21.3% had intermediate flora and 17.5% were healthy at the third time-point. Concurrent HrHPV and BV was found among 25% at the third time-point.However, there was no significant difference in the prevalence of any HrHPV among women with and without BV at any time-point. Among women with persistent HrHPV, 8.3% had community state type (CST) I, 37.5% had CST III and 54.2% had CST IV-B; women who cleared HrHPV, 45.5% had CST III and 54.5% had CST IV-B, the control group who remained HrHPV free throughout follow-up had CST III (31.0%), CST IV-A (3.5%) and CST IV-B (65.5%).
Conclusions: This longitudinal study suggests that single round of HrHPV screening may lead to overtreatment and unnecessary referrals. Conducting type-specific HPV re-testing will be necessary in the management of HrHPV infections.

GEOSPATIAL ANALYSIS OF WOMEN WITH CERVICAL PRE-CANCER IN DAVIDSON COUNTY, TENNESSEE, UNITED STATES 2008 – 2017

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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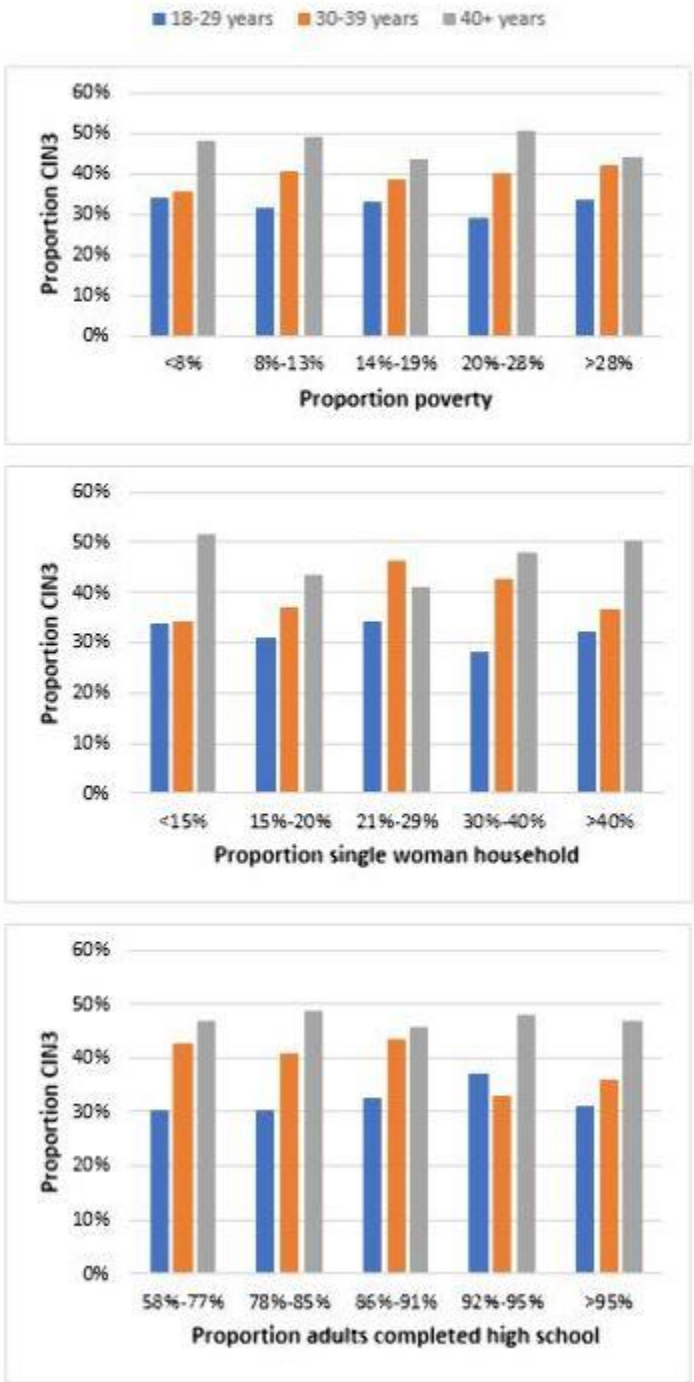
Introduction: Human papillomavirus (HPV) is the most prevalent sexually transmitted disease and causes cervical pre-cancer (cervical intraepithelial neoplasia [CIN]) and cancer. CIN2+ (CIN grades 2, 2/3, 3 and adenocarcinoma in-situ [AIS]) and cervical cancer are reportable conditions in Tennessee (TN), United States. Information on women diagnosed with CIN2+ is collected under public health surveillance. We aimed to determine if area-level characteristics were associated with presenting with CIN3 versus other pre-cancers (CIN2, 2/3 and AIS).
Methods: The data for this analysis includes Davidson County, TN, United States women ages 18 years and older diagnosed with CIN2+, 2008-2017. Women with CIN2+ were assigned a Federal Information Processing Standards (FIPS) code based on their address. The Integrated Public Use Microdata Series GeoMarker database generated area-level data associated with the FIPS code. Area-level data includes: proportion of the population in poverty, proportion single woman households, and proportion of adults who completed high school. This analysis identified the proportion of all women with CIN2+ that were classified as CIN3. The variables analyzed were ages (18-29, 30-39, and 40+ years) and area-level data that were organized into quintiles for analysis.
Results: The proportion of all women with CIN2+ presenting with CIN3 increased with age: 32% for 18-29 years, 39% for 30-39 years, and 47% for 40+ years. Across each age group, these proportions were stable throughout all quintiles of the 3 area-level factors examined including: poverty, single woman household status, and education.

Figure 1. Proportion of pre-cancers that were CIN3 based on area-level characteristics, by age group, a) Proportion CIN3 stratified by poverty level, b) Proportion CIN3 stratified by % family households headed by a single woman, c) Proportion CIN3 stratified by % adults who completed high school



Conclusions: The proportion of women with CIN2+ who presented with CIN3 was strongly associated with age. Almost 50% of women 40 years and older with cervical pre-cancer presented with CIN3. Overall, the proportion of women with pre-cancer presenting with CIN3 was not associated with area-level

characteristics including proportion of households in poverty, proportion of households headed by a single woman, and proportion of adults completing high school.

HPV SELF-COLLECTION IMPLEMENTATION IN TUCUMAN, ARGENTINA: ANALYSIS OF ADHERENCE TO CYTOLOGY TRIAGE

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: HPV self-collection has been shown to reduce access barriers to screening. When using HPV self-collection, triage tests are a key step in cervical cancer prevention process. However, in middle income settings high adherence to triage has been difficult to obtain. The aim of this study was to measure adherence to triage by HPV positive women with self-collected tests in Tucuman province, Argentina.
Methods: We analyzed data on screening/triage/diagnosis/treatment from women aged 30+ who performed self-collection between 2015 and 2017, in the public health system in Tucuman, Argentina. Data source was the national screening information system (SITAM). We calculated: 1) % of adherence to triage, 2) % Adherence to colposcopy, and 3) Time between HPV self-collection and cytology triage.
Results: In the province of Tucuman programmatic, population based self-collection was implemented in 2015. Between 2015-2017, a total of 15,765 women aged 30 and older were HPV-screened through self-collection (40.1% of total HPV-testing). Mean age of screened women was 43 (range 30-86), 16.2% had a record of previous PAP-based screening and 55.2% had public health insurance. In total, 2391 women with self-collected tests were HPV positive (15.2%) and among them 1120 (46.8%) completed cytology triage. The percentage of women completing cytology triage within 120 days was 30.9% in 2015, 19.9% in 2016 and 23.4% for 2017. Among women with an abnormal cytology, 60.0% performed a colposcopy, of which 72.2% resulted in pathological results. The number of CIN2+ cases confirmed by histology was 78.
Conclusions: Our results showed that adherence to triage by women with self-collected tests is challenging. Special efforts should be devoted to increase adherence to follow up among these women.

GEOGRAPHICAL DIFFERENCES IN THE PREVALENCE OF HIGH-RISK HPV IN MEXICAN WOMEN ATTENDING THE IMSS CERVICAL CANCER SCREENING PROGRAM

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPV detection is one the main screening strategies for cervical cancer. Worldwide, 12% of women with a normal cytology are HPV-positive. In the Caribbean and Eastern Africa, such prevalence is high (35%), whereas in North America the prevalence is low (4%). In Mexico high-risk HPV-HR prevalence is around 14%. Differences in the sensitivity of the detection methods used could be the reason for potential differences between populations.
Methods: Cervical scrapes from patients who attended the IMSS cervical cancer-screening program from different regions in Mexico were analyzed, including Puebla, Veracruz, Morelos, Guerrero, Mexico City, Campeche, and Quintana Roo. The samples were collected in PreservCyt medium and processed with CobasÒ4800 HPV Test. The clinical data were collected. Descriptive statistics were performed in the IBM SPSS program.
Results: 2526 samples were collected. 20.1% were positive for HPV-HR and only 0.3% were invalid. The presence of HPV-HR was more frequent in Campeche (25.3%), followed by Morelos (23.8%), Veracruz (21.5%), Quintana Roo (18.3%), Mexico City (17.5%), Puebla (16.7%), and Guerrero (15.0%). Of the valid samples, 3.6% of the cases were HPV16, 2.0% HPV18 and 17% positive for other high-risk genotypes. Regarding the HPV16 positive samples, 55% were identified as single genotype, 42.6% in multiple infection with other genotypes. Multiple infections of HPV16 with HPV18 were uncommon (2.2%). The frequency of HPV-HR seems to decrease with age, from 35% in the group <= 24 years of age to 14% in the group of >=50 years of age.
Conclusions: Our results indicate that there are differences in the prevalence of HPV-HR in the populations studied, which could be associated to changes in the risk factors of particular regions in the Mexican territory. It is important the access to molecular HPV test for improve cervical cancer screening.

TRENDS OF UNINDICATED CERVICAL CANCER SCREENING IN ADOLESCENT FEMALES: 2012–2018

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Cervical cancer is exceedingly rare in adolescents. In 2009, U.S. guidelines discouraged screening in young immunocompetent women <21 years of age. This study aims to ascertain the trends and factors associated with unindicated screening in adolescents.
Methods: Cervical cancer screening tests performed in females <21 years from 2012–2018 were reviewed from Yale New Haven Health System. The final diagnosis, the results of HPV testing, and the clinical indications for the procedure were extracted using Natural Language Processing. Each screening test was adjudicated as either indicated or unindicated based on the logic presented in the guidelines. The biannual rate of unindicated screening was calculated as the ratio of unindicated cases to the total number of <21 years patient visits completed by a given provider during a 6-month interval for the overall sample, for each practice setting, and for provider degrees.
Results: Data from 118 providers and 797 women (N=906 Paps) were included. Characteristics of patients are detailed in Table 1. The reasoning for performing screening was not given for 62% of the reports. The most common reasons listed were "routine clinical care" (63%) or "history of prior cervical abnormalities" (23%). Although most adolescents had an unindicated pap, 8% had a follow-up pap after receiving an abnormal result on a prior unindicated pap. During the study period, 49 colposcopies and 3 conizations were performed in women <21 years. Although the incidence of unindicated screening was more than twice as high among community-based providers, the rate of reduction was greater in the community than in the academic setting during the study period (Table 2).

Table 1. Patient-Level Characteristics

	Overall		Practice Setting: Community		Practice Setting: Academic			
	N=	902	N=	625	N=	277	OR*	p-value
Age, median (IQR), y	20	(14-20)	20	(16-20)	20	(15-20)	0.69	0.01
Race, No. (%)								
White	574	(64%)	446	(71%)	128	(46%)	referrence	
Hispanic	84	(9%)	40	(6%)	44	(16%)	3.83	<0.01
Black	141	(16%)	65	(10%)	76	(27%)	4.07	<0.01
Other+	33	(4%)	21	(3%)	12	(4%)	1.99	0.06
Multiple	34	(4%)	19	(3%)	15	(5%)	2.75	1.36
Unknown	36	(4%)	34	(5%)	2	(1%)	-	-
Pap smear diagnosis								
NIEL	694	(77%)	496	(79%)	198	(71%)	referrence	
ASCUS	109	(12%)	76	(12%)	33	(12%)	1.08	0.71
LSIL	88	(10%)	46	(7%)	42	(15%)	2.30	<0.01
ASC-H	4	(0%)	2	(0%)	2	(1%)	2.50	0.36
HSIL	4	(0%)	2	(0%)	2	(1%)	2.50	0.36
Unsatisfactory	3	(0%)	3	(0%)	0	(0%)	-	-
Indication of screening								
Pap unindicated	834	(92%)	598	(96%)	236	(85%)	0.26	<0.01
HPV test unindicated	73	(8%)	40	(6%)	33	(12%)	1.90	0.04
Outcomes								
Colposcopy +/- biopsy	49	(5%)	16	(3%)	33	(12%)	4.55	<0.01
Conization/curettage	3	(0%)	0	(0%)	3	(1%)	-	-

+Other Race/Ethnicity: Non-Hispanic American Indian, Asian and Native Hawaiian
*OR= odds ratio, using logistic regression where the outcome is coming from an academic setting
NIEL: negative intraepithelial lesion
ASCUS: atypical squamous cells of undetermined significance
LSIL: low-grade squamous intraepithelial lesion
ASC-H: Atypical squamous cells, cannot exclude HSIL
HSIL: high-grade squamous intraepithelial lesion

Table 2. Biannual Incidence Rate and Trends of Unindicated Cancer Screening

	Incidence Rate per 1,000 Encounters				Average Biannual Change			
	IR	95% CI	IRR	p-value	Trend	95% CI	Trend Ratio	p-value
Community	24.09	(16.91 to 31.27)	reference		-2.01	(-3.39 to -0.63)	reference	
Academic	10.73	(8.99 to 12.46)	0.45	<0.01	0.11	(-0.34 to 0.56)	-0.05	<0.01
Community								
Physicians	23.94	(17.18 to 36.71)	reference		-2.03	(-4.23 to 0.16)	reference	
Non-Physicians	39.32	(3.85 to 74.79)	1.64	<0.01	-10.32	(-16.89 to -3.75)	5.08	0.30
Academic								
Physicians	24.28	(16.70 to 31.85)	reference		0.18	(-1.79 to 2.14)	reference	
Non-Physicians	8.10	(0.65 to 15.55)	0.33	<0.01	-1.99	(-3.47 to -0.51)	-11.26	<0.01

Conclusions: Nearly a decade has passed since the release of the current cervical cancer screening guidelines in the US, yet unindicated screening of adolescents remains a challenge. More research is

needed to identify better strategies to reduce the overutilization of screening.

THE RANK/RANKL AXIS ASSOCIATES WITH HPV INFECTION AND PERINEURAL INVASION IN PENILE CANCER

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Penile cancer is a rare neoplasm and 30-50% of cases are associated with HPV infection. The receptor-activator of NF-kB (RANK) and its ligand (RANKL) have been associated with tumour aggressiveness and metastasis in various types of cancer but remains poorly characterized in penile cancer. This study aimed to evaluate the involvement of the RANK / RANKL axis in penile cancer and its correlation with tumor behavior.
Methods: Fifty-nine penile cancer cases collected from hospitals in the Brazilian state of Maranhão were stored at the local Tumor & DNA Biobank. Sociodemographic data were obtained through a questionnaire; clinical and histopathological data were collected from medical records. Nested PCR was used to detect HPV using primers PGMY09/11 and GP+5/6 followed by automated sequencing for viral genotyping. Quantitative real-time PCR was used to study the expression of RANK (*TNFRSF11A*), RANKL (*TNFSF11*) and osteoprotegerin (*TNFRSF11B*).
Results: 47% and 58% of patients reported the use of tobacco and alcohol, respectively. 32% of patients reported over 10 sexual partners, 68% were uncircumcised, 44% never used a condom, and 44% indicated previous sexually-transmissible infections. HPV was detected in 73% of cases; HPV16 and HPV11 were the most common types. Histologically, the usual subtype predominated (34%). *TNFRSF11A* expression was higher in HPV-positive tumours particularly in those with high-risk HPV (p=0.043) and was associated with perineural invasion (p=0.025) and tumour ulceration (p=0.045). *TNFSF11* expression was higher in tumours with low-risk versus high-risk HPV (p=0.016).
Conclusions: The differential expression of genes involved in the RANK/RANKL axis suggests its involvement in the pathogenesis of HPV-associated penile cancer. While high-risk HPVs seem to up-regulate RANK expression, low-risk types seem to depend on RANKL up-regulation. RANK/RANKL seems to promote tumour aggressiveness via perineural invasion. Further studies are needed to clarify the significance of these findings.

HPV AND TERT PROMOTER MUTATION PROFILE IN VULVAR CANCER

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Activating mutations in TERT promoter gene have shown to irreversibly re-activate telomerase expression and cell senescence evasion in many tumor types. The oncoprotein E6 encoded by high risk human papillomaviruses (HPV), besides other oncogenic functions, promotes cell immortalization by transactivation of TERT promoter causing telomerase expression. We analyzed the presence of HPV DNA and E6 and E7 mRNAs in vulvar squamous cell carcinoma (SCC) as well as TERT promoter mutations and telomerase expression to identify significant molecular events in the telomerase activation relevant for vulvar cancer development.
Methods: Sixty-two cases of vulvar SCC were analyzed for TERT promoter mutations and HPV DNA by PCR and direct sequencing analysis. The expression levels of TERT gene, HPV16 E6 and E7 as well as p53-related genes was analyzed by qPCR in 19 fresh-frozen tissues of vulvar SCC and non-tumor biopsies
Results: Recurrent mutations in TERT promoter at nucleotide positions -124G>A and -146G>A were identified in 45.1% of vulvar SCC. HPV DNA was found in 37.1% of vulvar SCC with HPV16 representing 78.3% of all infections. TERT promoter mutations were more frequent among HPV negative (51.5%) than positive (38.9%) cases. Telomerase mRNA expression was 2-fold higher in TERT promoter mutated versus not-mutated vulvar SCC. Expression profile of p53-related genes showed a significant down-regulation of the anti-angiogenic ADGRB1 gene, among cancer cases overexpressing telomerase.
Conclusions: TERT promoter mutations were very frequent in vulvar SCC and associated with increased telomerase expression compared to non-tumor tissues, irrespective of HPV16 E6 levels. The increased levels of telomerase in vulvar SCC caused the activation of non-canonical pathways affecting the expression of ADGRB1 tumor suppressor.

CERVICAL CYTOLOGY TEST, HPV TEST, AND BIOPSY OUTCOMES BY HPV VACCINATION STATUS IN FOUR U.S. HEALTH CARE SYSTEMS DURING 2010-2014

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: While studies have consistently shown benefit of HPV vaccine for those vaccinated at younger ages, results for those vaccinated at older ages have been mixed. We examined the distributions of outcomes from cervical cytology tests, HPV tests, and biopsies by vaccination status in a large cohort of women from four U.S. healthcare systems who were primarily vaccinated at older ages.
Methods: The study included 638,493 vaccine-age-eligible women (ages 18-34) in the Population-Based Research Optimizing Screening through Personalized Regimens (PROSPR I) consortium. HPV vaccination histories and all cervical cancer test and biopsy results from 2010-2014 were obtained from clinical and administrative data sources. We compared outcomes between vaccinated and unvaccinated women for 863,086 cytology tests, 273,364 HPV tests, and 57,285 biopsies, stratified by age at first vaccination, and women could contribute multiple tests and/or biopsies.
Results: Among those vaccinated, only 3.8% were vaccinated before age 15 and 35.6% before age 18. Compared to unvaccinated women, we observed a 60% lower prevalence of HSIL+ for those vaccinated before age 18 but only a 35% lower prevalence for those vaccinated at 18 or older. Unexpectedly, the proportion of HPV+ results was greater among the vaccinated than unvaccinated, regardless of age of vaccination. Compared to unvaccinated women, there was a 42% and 25% lower prevalence of CIN2+ for those vaccinated before 18 and at 18 or older, respectively.
Conclusions: In this large U.S. cohort, we found that the association with HPV vaccine was age dependent—the greatest association (lower prevalence of HSIL+ and CIN2+) was observed in women vaccinated at the youngest ages, closest to the target age of 11-12 years. Confounding by sexual behavior may contribute to the higher HPV prevalence observed in the vaccinated group compared to the unvaccinated group in this cohort primarily vaccinated at older ages.

CLINICAL CHARACTERISTICS AND GENOTYPIC CHARACTERIZATION OF HUMAN PAPILLOMAVIRUS IN PATIENTS WITH RECURRENT RESPIRATORY PAPILLOMATOSIS IN SAO LUÍS, MARANHÃO, BRAZIL

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Human papillomavirus (HPV) is a non-enveloped virus that infects skin and mucosal epithelium. Recurrent respiratory papillomatosis (RRP) is caused by HPV types 6 and 11 in 90% of cases. Although benign, RRP tends to have an aggressive clinical course in children and can be fatal due to its high recurrence and tendency to spread throughout the respiratory tract.
Methods: This work aimed to describe the sociodemographic and clinical profile of patients with RRP treated at a referral hospital in São Luís, Maranhão, Brazil, from July 2013 to August 2018 and to evaluate the prevalence and genotypes of HPV in these lesions. We performed a prospective cross-sectional study with 11 fresh samples of laryngeal papillomatous lesions collected during surgery and stored in RNA Latter™. Sociodemographic and clinical data were obtained from the patients' medical records. For HPV analysis, sample DNA was extracted and subjected to polymerase chain reaction (PCR) with PGMY09/11 primers. Positive samples were submitted to automated sequencing technique for viral genotyping.
Results: 54.55% of the patients were female and the average age at diagnosis was 12.63 years. Vaginal delivery was the most frequent among patients (81.8%). Juvenile RRP was the most prevalent (63.6%) disease presentation. Among the clinical manifestations, most patients presented dysphonia (90.9%), 63.6% had dyspnea and 27.7% had dysphagia. Recurrence of the disease was also common (72.7%). The presence of HPV was detected in 100% of the cases, being type 6 the most prevalent in this population.
Conclusions: The evaluated population had mostly juvenile-RRP, were female and HPV was present in all samples, with type 6 being the most prevalent. Clinical knowledge of RRP is essential to reach the correct diagnosis of the disease. There is currently no definitive cure for PRR and surgical removal remains the main treatment.

CROSS-TALK BETWEEN STAT3 AND P65 NFKB AND IMMUNE EVASION IN CERVICAL CANCER

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Several soluble molecules are secreted by cells in the complex tumor environment. These molecules may reach the circulation and signal to other tissues in the body, with various effects, including modulation of immune responses.To better understand the effects of such molecules, we sought to characterize the activation status of signaling pathways involved in cell proliferation, inflammation and immune responses in cervical high-grade lesions and cancer.
Methods: We studied a cohort of patients with high-grade and invasive cancer, and a control group of voluntaries. We investigated, through flow cytometry, the expression of key proteins in signaling pathways involved in cell proliferation and survival, as well as inflammation and immune responses: Akt, CREB, STAT3 and p65 NFkB, where we used phosphorylation as an activation putative marker. In patients, we investigated protein expression in cervical biopsies and peripheral blood mononuclear cells (PBMCs), and in controls, PBMCs. We then studied the effect of IL-6 and G-CSF neutralization or STAT3 pharmacological inhibition, using the drug NSC74859, in mice inoculated with TC-1 tumor cells.
Results: In patients, although we have not observed robust changes in protein expression related to lesion grade, we did observe positive correlation among proteins of most analyzed pathways in tumor cells, but not in leukocytes. In PBMCs, on the other hand, we observed a signficant increase in STAT3 expression, both total and activated forms, according to lesion progression, while we observed the opposite regarding p65 NFkB. Neutralization of IL-6 and G-CSF, known to be secreted by cervical cancer cells, in TC-1 tumor bearing mice, inhibited tumor growth and increased T cell tumor infiltration and p65NFkB activation in the spleen. Similar results were observed by blocking STAT3 signaling. These effects were partially lost if p65 NFkB was also blocked.
Conclusions: STAT3 signaling interferes in NFkB activation leadind to immune evasion by cervical cancer.

FACTORS ASSOCIATED WITH ANY, HIGH RISK, AND LOW RISK ORAL HUMAN PAPILLOMAVIRUS PREVALENCE: THE HPV INFECTION IN MEN (HIM) STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Given the rise of HPV-attributable oropharyngeal cancers across the globe, especially among men residing in high-income countries, it is important to understand the risk factors of oral HPV infections. We utilized a multinational sample of men residing in Brazil, Mexico and the US to examine factors associated with oral HPV prevalence separately for high-risk and low-risk HPV, and by country of residence.
Methods: DNA was extracted from adequate oral gargle samples collected from men enrolled in the HPV Infection in Men (HIM) study (N=3,127) and HPV genotyped using the SPF_{10} PCR-DEIA-$LiPA_{25}$ system. Log-binomial multivariate models were fit separately for vaginal/anal sex and oral sex variables, after adjusting for age, country of residence, marital status, pack-years of cigarettes smoked, and history of bleeding gums.
Results: Reporting more than 19 lifetime number of sexual partners was significantly associated with any [aPR: 2.9 (1.8,4.6)], high-risk [aPR: 2.8 (1.6,4.8)], and low-risk HPV [aPR: 3.3 (1.3,8.2)] compared to reporting two or less partners. Reporting 25 or more oral sex partners in the past 6 months was significantly associated with any [aPR: 1.7 (1.2,2.5)] and high-risk [aPR: 1.7 (1.1,2.7)] HPV compared to reporting no oral sex partners. Similarly, reporting 3 or less number of days since last oral sex was significantly associated with any [aPR: 2.0 (1.1,3.5)] and high-risk [aPR: 2.2 (1.2,4.3)] HPV compared to reporting never having had oral sex during their lifetime.
Conclusions: Lifetime number of sexual partners was independently significantly associated with both high-risk and low-risk oral HPV prevalence while oral sex related variables were significantly associated with only high-risk HPV prevalence. These different risk-factor profiles of high-risk and low-risk oral HPV prevalence warrant further study.

EVALUATION OF AUTOMATED CLINICAL AND DIAGNOSTIC HUMAN PAPILLOMAVIRUS (HPV) TESTING BY RNA ISH AGAINST COMBINED P16 IHC AND DNA ISH IN OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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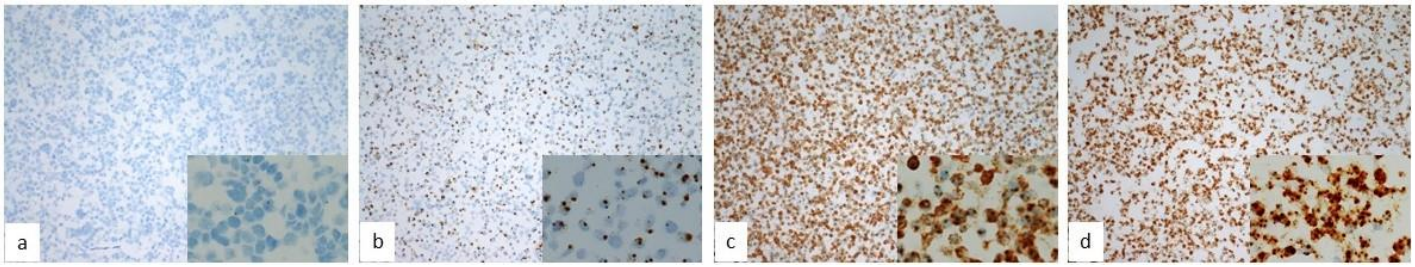
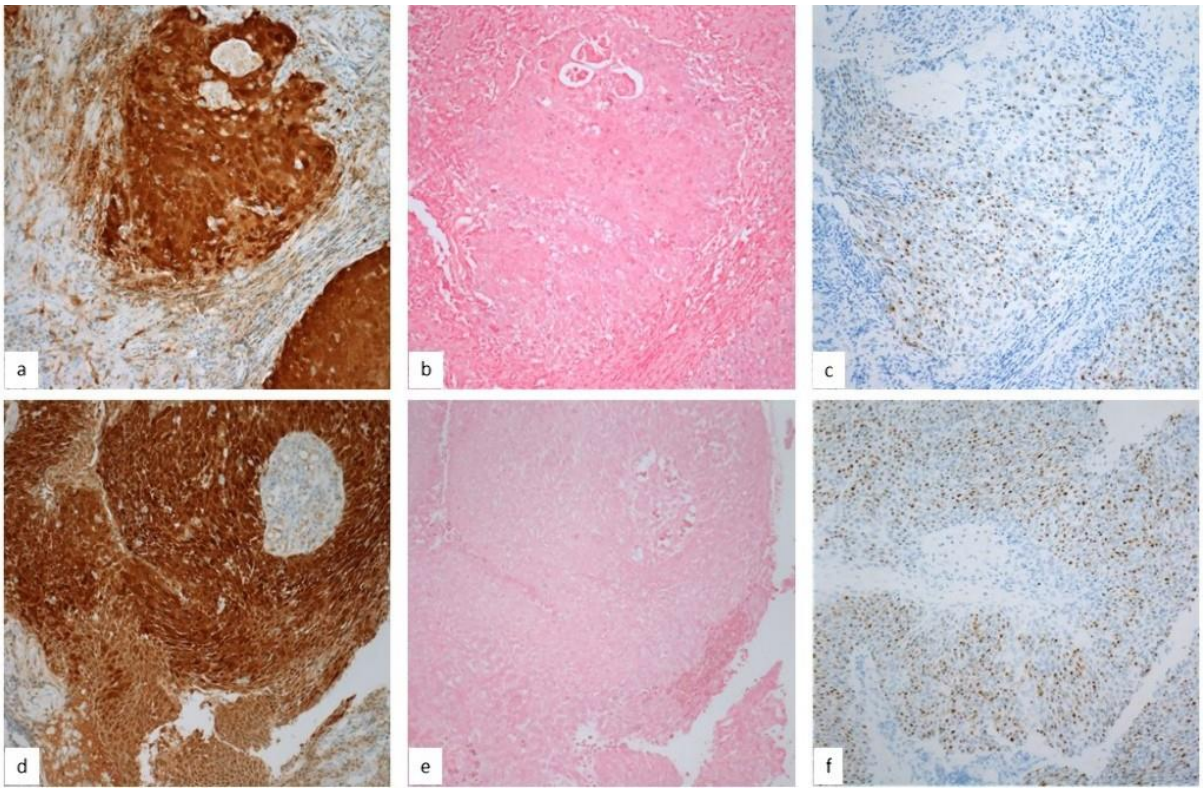
Introduction: Current diagnostic methods for detecting high-risk HPV in oropharyngeal squamous cell carcinoma (OpSCC) is via a two-stage algorithm, namely p16 immunohistochemisty (IHC) followed by HPV DNA in-situ hybridisation (ISH) if the former is positive. Within this context, there have been recent calls for a single-step HPV laboratory diagnostic test with a view to greater clinical effectiveness. This study evaluated the clinical utility of automated RNAISH as a single-step alternative to the two-stage algorithm within a routine diagnostic histopathology setting.
Methods: 38 p16+/DNAISH+, 42 p16- and 20 p16+/DNAISH- were randomly selected from the diagnostic archive of the Head & Neck Pathology Department, Guy's Hospital. High-risk HPV RNAISH was undertaken on all cases on an automated clinical platform. Manufacturer recommended and on-slide p16/HPV positive and negative controls were used (Figure 1). Test quality assurance and diagnostic RNAISH were independently assessed by two observers. Initial discordant cases were re-evaluated. A consensus diagnosis was reached in the presence of a third observer on remaining discordant cases. All RNAISH results were then correlated against p16 +/- DNAISH status.



Results: 12 cases required re-testing and initial evaluation revealed 16 discordant cases. The 16 disagreements along with 12 randomly selected additional cases were reassessed leaving 5 discordant cases (Table 1, kappa=0.90, p<0.001). There was full concordance between RNAISH and p16 +/- DNAISH status (Figure 2a-c). Of the 20 p16+/DNAISH- tumours, RNAISH was positive in 18 and negative in 2 cases (Figure 2d-f).

Table 1: Re-evaluation of cases

	Observer1 positive	Observer1 negative
Observer2 positive	57	0
Observer2 negative	5	38



Conclusions: Automated RNAISH is a viable alternative to current two-stage HPV testing for OpSCC in routine diagnostic histopathology and is likely to increase clinical effectiveness. Our study also indicates diagnostic RNAISH interpretation requires a degree of training and experience. Furthermore, on-slide HPV analyte controls are important for interpretation of RNAISH staining.

P16INK4A AS A TARGET FOR T CELL-BASED CANCER IMMUNOTHERAPY

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: For development of effective cancer vaccines, tumor antigens need to be identified that are either tumor-specific or selectively overexpressed in tumors. The cyclin-dependent kinase inhibitor $p16^{INK4a}$ may be an almost ideal target structure, because it is strongly overexpressed in human papillomavirus (HPV)-induced cancers, but is barely detectable in normal tissue. Moreover, $p16^{INK4a}$ is not only expressed in HPV dependent tumors, but also in a large fraction of non-HPV-related tumor entities such as colorectal cancer and small cell lung cancer, marking $p16^{INK4a}$ as a broad tumor antigen.
Methods: In order to develop a $p16^{INK4a}$-based vaccine, two different mouse models were used: 1) C57Bl/6 mice were vaccinated with murine $p16^{INK4a}$-derived peptides to evaluate the induction of humoral and cellular immune responses and 2) FoxP3-DTR mice were immunized with $p16^{INK4a}$-derived peptides after depletion of Tregs and challenged with HPV-induced, $p16^{INK4a}$-expressing TC-1 cells to analyze the anti-tumor effect.
Results: Antibodies as well as $CD4^+$ and $CD8^+$ T cell responses were induced by immunization of C57Bl/6 mice with $p16^{INK4a}$-derived peptides showing that there is no or no complete tolerance against the murine self-antigen $p16^{INK4a}$. A more vigorous $CD8^+$ T cell response against $p16^{INK4a}$ was obtained in Treg-depleted FoxP3-DTR mice resulting in partial rejection of TC-1 tumors.
Conclusions: These data demonstrate for the first time that a $p16^{INK4a}$-positive tumor can be eradicated by $p16^{INK4a}$ vaccination, provided that the immune response is of sufficient strength. The generation of effective anti-tumor responses against $p16^{INK4a}$ could lead to a new therapeutic approach for HPV-induced cancers as well as for tumors overexpressing $p16^{INK4a}$ independent of an HPV infection.

PSYCHOSOCIAL IMPACT OF POSITIVE HUMAN PAPILLOMAVIRUS TESTING IN JUJUY, ARGENTINA RESULTS FROM THE PSYCHO-ESTAMPA STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: HPV-testing can have a negative impact on women lives including fear of cancer, disease denial and worries about sexuality. This study was aimed at measuring the psycho-social impact of HPV-positivity among HPV-tested women from Jujuy, Argentina.
Methods: In this cross-sectional study carried out between 2015 and 2016, the psycho-social impact of HPV-positivity was measured using the Psycho-Estampa Scale, specifically designed and validated to be used in Latin American settings. We measured mean scores for each of the five scale domains, and the total Impact score (Values from 1: No impact to 4: Heavy impact). We also compared scores according to Pap triage diagnosis using ordinal logistic regression.
Results: A total of 163 HPV-positive women were included in the study sample. Mean age was 38 years (SD = 8 years). Most women had higher (53.4%) or secondary (36.8%) level of education. 124 women (76.1%) had negative Pap smears. Total Impact score was 2.53, SD:0.65. The domain Worries about cancer and treatment had the highest score (mean: 3.6, SD:0.5), followed by Sexuality domain (mean:2.5; SD:1). The Domain “Uncertainty about information provided by health providers” had the lower score: mean 2.14, SD:0.73. Moderate values were observed in domains referred to Repercussions on the family (mean:2.27, SD:2.3) and Emotional symptoms (mean:2.3; SD:0.82). The odds of having higher negative psychosocial impact among women with abnormal Paps was 2.9 (95%CI:1.43- 6.07 p=0.0036). One unit increase in age (year) was associated with a reduced likelihood of having a higher total psycho-social impact (OR:0.95; p=0.036, CI=0.92-0.99). No statistically significant differences were found in scores of specific domains according to cytology results.
Conclusions: As the psycho-social impact of HPV-positivity can not only result in reduced quality of life but it can also influence women adherence to follow-up and treatment, specific counseling interventions to reduce it are needed.

UTERINE CERVIX INFECTION WITH ONCOGENE HUMAN PAPILLOMA VIRUS AT GABRIEL TOURÉ TEACHING HOSPITAL.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: The cancer of the cervix especially remains true public health problems in the developing countries. It constitutes the 4th cancer at the woman in the world; whereas it occupies the 2nd position in the developing countries, especially in south sahara Africa
Methods: we carried out a cross sectional study in Bamako at Gabriel Teaching hospital from January 1st 2009 to june 30th 2015. Were included in the sample the patients admitted for routine cervical cancer screening or for management of precancerous lesions and accepting a molecular testing for oncogenic HPV presence using the Abott Real Time PCR technique.
Results: we performed 755 HPV tests. The global prevalence of oncogenic HPV was 16%. Type specified prevalence were: HPV 16: 2.4% (18/755), HPV 18: 1.6% (12/755) and another oncogenic HPV 14.2% (107/755). HPV prevalence decreased with age. It increased with polygamy or vaginal infection ($p < 0.05$). The positivity rate of molecular testing was 15.9% (62/391) during routine cervical cancer screening. After management of precancerous lesions, the positivity rates of HPV testing for CIN1, CIN2 and CIN3/carcinoma in situ were respectively of 13.3%, 21.3% and 34.9%. oncotypes HPV 16 and HPV 18 were more associated with CIN2/CIN3 than CIN1.
Conclusions: whatever the mode of use of the molecular test. There was a high prevalence of non 16 and non 18 HPV types; thus, the interest of a complete characterization of the full range of oncogenic HPV types in Mali to better understand the epidemiology of this infection in our context.

PARENT ATTITUDES REGARDING VACCINATION IN THE ORAL HEALTHCARE SETTING

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In the United States, uptake of the HPV vaccine remains far below the goals of public health programs. Involvement of healthcare professionals beyond the traditional pediatric clinic setting can help to remove barriers to vaccination. Oral healthcare providers are stakeholders in prevention of high-risk HPV-associated oropharyngeal cancer and therefore dental clinics are a logical alternative setting for vaccination.
Methods: We surveyed parents/guardians whose children were receiving care at a pediatric dental clinic to ascertain their receptivity to vaccination in the oral healthcare setting. Adults were approached in the clinic reception area and completed the short survey anonymously.
Results: Adults ages 22 to 61 (median, 36) participated in the study. The majority were women (70%) and self-identified as a racial/ethnic minority (63%). Participants' children ranged in age from infant to 34 years and included 18 boys and 11 girls at the target ages for HPV vaccination. Most respondents (62%) believed that an oral health professional is a trusted source of information about vaccines, but while 71% would trust a vaccine recommendation from a dentist, only 36% would trust the recommendation of a dental hygienist. Correspondingly, 75% would allow their child's dentist to administer vaccines. Adults who would refuse to allow a dentist to vaccinate their child were no different in age or education level from those who would accept the vaccine. A higher proportion of women (31%) than men (17%) reported that they would refuse vaccination of their child by a dentist, though this difference was not statistically significant. Many respondents (79%) expected that their child's dentist should inform them of primary prevention strategies for head and neck cancer, while only 18% expected that this responsibility fell solely on their child's pediatrician.
Conclusions: Parents are generally receptive to discussing and obtaining vaccines for their children from their child's dentist.

HPV IN OROPHARYNGEAL CANCER AMONG U.S. VETERANS LIVING WITH HIV

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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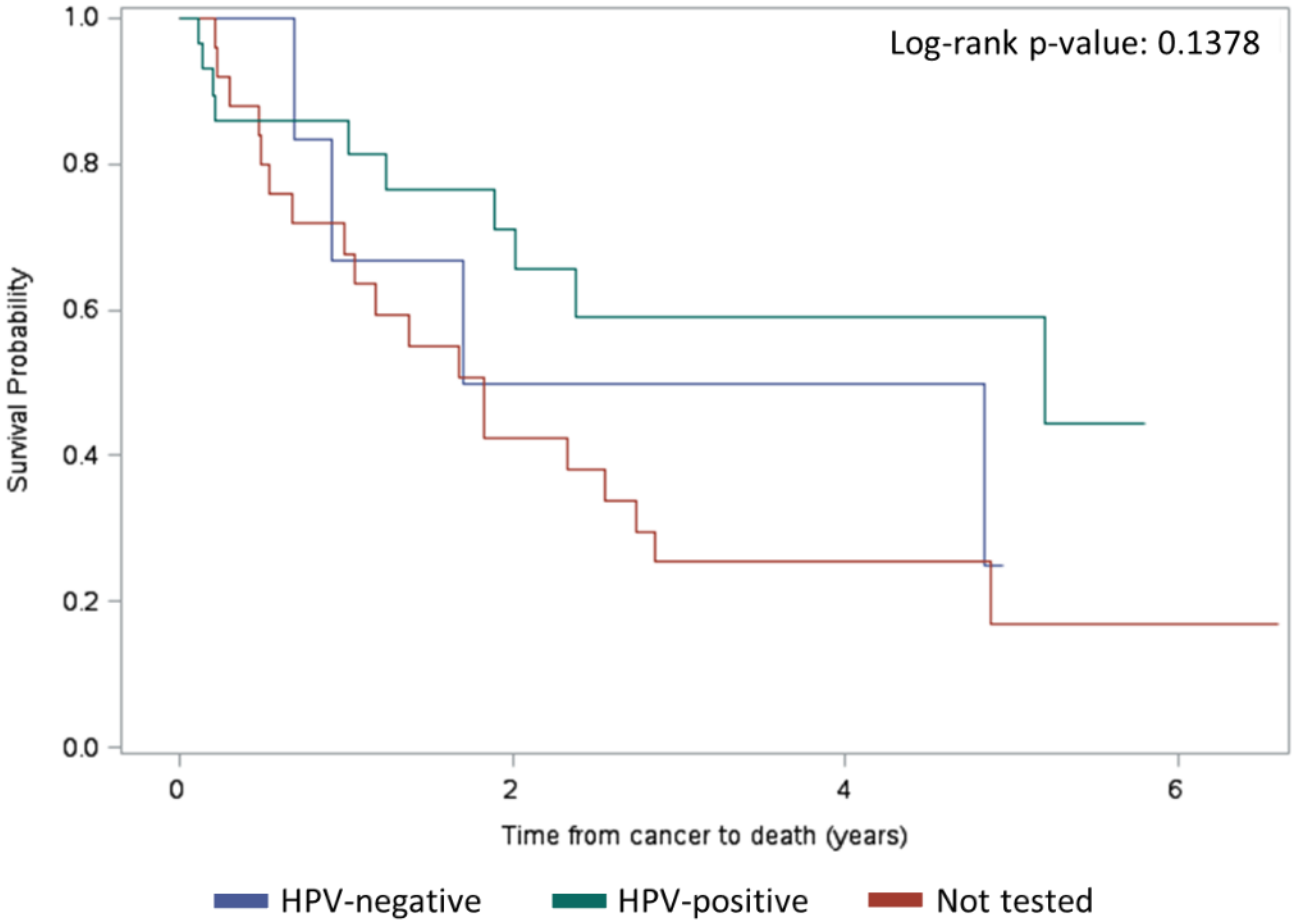
Introduction: Human Papillomavirus (HPV)-positive oropharyngeal cancers squamous cell carcinoma (OPSCC) is the most common cancer caused by HPV. People living with HIV/AIDS (PWH) have an excess risk of OPSCC compared to the general population. Given the promising treatment deintensification clinical trials, understanding HPV-positive OPSCC among people living with HIV is exceedingly pertinent.
Methods: We performed a retrospective cohort study using individual-level patient data from the national VA Corporate Data Warehouse (CDW) and the VA Central Cancer Registry (CCR) of OPSCC among PWH diagnosed from 2010 to 2016. We conducted chart review to determine HPV status based on p16 or High Risk HPV testing. We used a chi-square test to compare the factors among HPV-positive, HPV-negative, and untested oropharyngeal cases and calculated the survival for each group.
Results: Of the 62 OPSCC cases among PWH that met our inclusion criteria, 40.3% (n = 25) were not tested for HPV. Of those tested, 30 (80.1%) were positive and 7 (11.3%) were negative (Table 1). There was no difference in age between HPV-positive (Mean: 46.9 years; standard deviation (SD): 7.4) and HPV-negative (Mean: 47.6 years; SD: 9.9) OPSCC. Older smokers and recently diagnosed HIV cases were less likely to be tested. Although not statistically significant, HPV-positive OPSCCs had better survival (Figure 1; 5-year survival: 57%) than HPV-negative (5-year survival: 17%) and untested OPSCCs (5-year survival: 20%) in PWH. Table 1. Descriptive statistics of OPSCC among PWH.

	HPV-positive n = 30	HPV-negative n = 7	Not tested n = 25	p-value
Age				
< 40	7 (23.3%)	2 (28.6%)	0	0.04
40-59	21 (70.0%)	4 (57.1%)	18 (72.0%)	
60 and above	2 (6.7%)	1 (14.3%)	7 (28.0%)	
Race				
Black	15 (50.0%)	6 (85.7%)	12 (48.0%)	0.24
Other/Unknown	2 (6.7%)	0	0	
White	13 (43.3%)	1 (14.3%)	13 (52.0%)	
Smoking				
Ever or unknown smoker	23 (76.7%)	7 (100.0%)	25 (100.0%)	0.01
Lifelong non-smoker	7 (23.3%)	0	0	
Alcohol				
No	13 (43.3%)	3 (42.9%)	5 (20.0%)	0.17
Yes	17 (56.7%)	4 (57.1%)	20 (80.0%)	
CD4 Count				
<=200	16 (53.3%)	3 (42.9%)	14 (56.0%)	0.83
>200	14 (46.7%)	4 (57.1%)	11 (44.0%)	
Viral load % undetectable				
< 40%	30 (100.0%)	7 (100.0%)	25 (100.0%)	NaN
40-80%	--	--	--	
> 80%	--	--	--	
Year first HIV				
Before 1996	10 (33.3%)	3 (42.8%)	5 (20.0%)	0.34
1996-2000	8 (26.7%)	2 (28.6%)	8 (32.0%)	
2001-2005	5 (16.7%)	2 (28.6%)	2 (8.0%)	
2006-2016	7 (23.3%)	0	10 (40.0%)	

Figure 1. Kaplan-Meier curves for oropharyngeal cancer by HPV-status.



Conclusions: Survival is still lower for HPV-positive OPSCC among PWH than the general population (5-year survival: 85%). However, HPV-positive OPSCCs have better survival than HPV-negative among PWH. Even with the recommendation for HPV testing, a large proportion is still untested and that there is a disparity in which older smokers were less likely to be tested. Additional research is needed to address the knowledge gaps about interactions between HIV and HPV-associated cancers.

HPV-16 MEMORY B-CELL RESPONSES POST-DOSE THREE OF THE QUADRIVALENT HPV VACCINE AMONG MID-ADULT AGED MEN

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Strong quantitative and functional antibody responses to the quadrivalent HPV vaccine were previously reported in mid-adult aged men, but there are very limited data on the direct cellular response of B-cells following vaccination, especially in males. Here, we assessed HPV-16 B-cell responses via ELISPOT at Day 1 (prior to vaccination) and 1- month post-dose three of the vaccine in mid-adult aged men.
Methods: Sera and peripheral blood mononuclear cells (PBMC) at Day 1 and month 7 were obtained from 32 men, ages 27-45, from Tampa, FL, USA, who received Gardasil at 0, 2, and 6 months. Following stimulation, PBMCs were plated in triplicate at 300,000 or 100,000 cells/well in ELISPOT plates pre-coated with HPV-16 L1 VLPs. IgG spots were enumerated on the Cellular Technology Limited (CTL) Immunospot® instrument. Data were expressed as # of spots/10^6 cells and % of HPV16- specific IgG memory B cells.
Results: The memory B-cell response was induced following vaccination and followed a similar pattern for both types of analysis, # of spots/10^6 cells (2.8 spots/10^6 cells at Day 1 versus 150.0 spots/10^6 cells at Month 7) and % of IgG specific cells (0.001% of HPV-16 IgG specific cells at Day 1 versus 0.357% of HPV-16 IgG specific cells at Month 7). No significant correlations were observed between the HPV-16 ELISPOT results and anti-HPV-16 IgG ELISA or avidity responses.
Conclusions: Gardasil induces an increase in HPV-16-specific memory B-cell responses following three doses of vaccine in mid-adult aged men, along with increases in antibody levels and avidity. However, there appears to be a lack of correlation between quantity and strength of antibody responses and memory B-cell responses. Future studies are needed to better understand the role of memory B cells and antibody responses in HPV efficacy.

"YOU CANNOT IGNORE THE PROBLEM WHEN IT IS PRESENTED SO CLEARLY": VISUALIZING THE SYSTEM TO UNDERSTAND AND IMPROVE CERVICAL CANCER SCREENING PROGRAMS

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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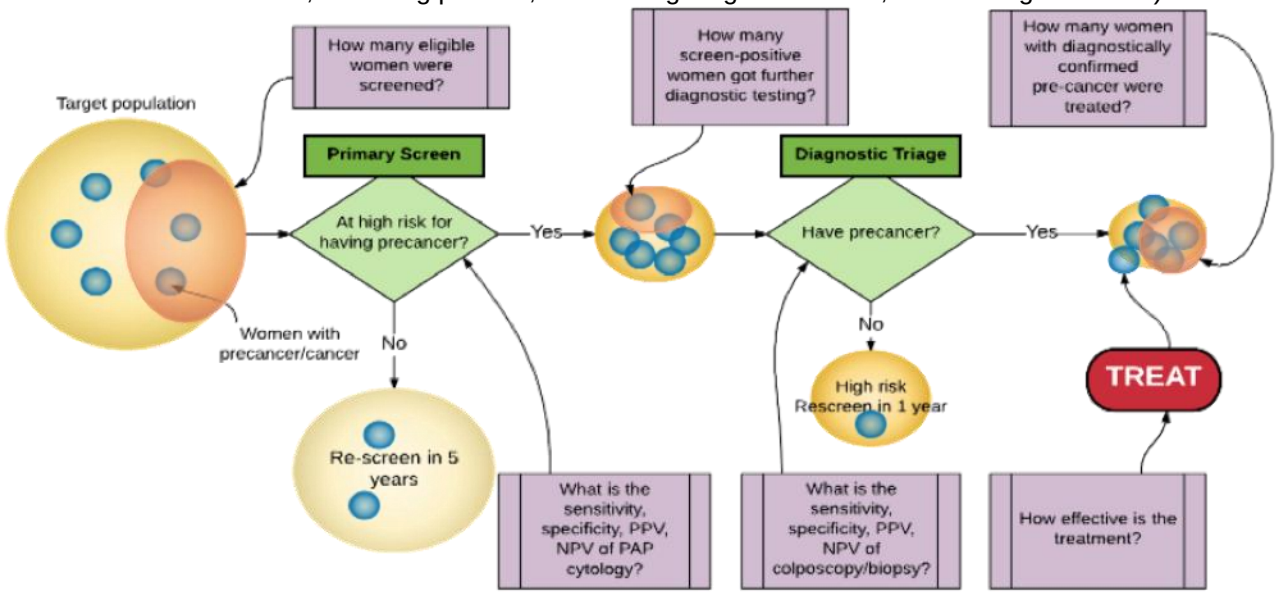
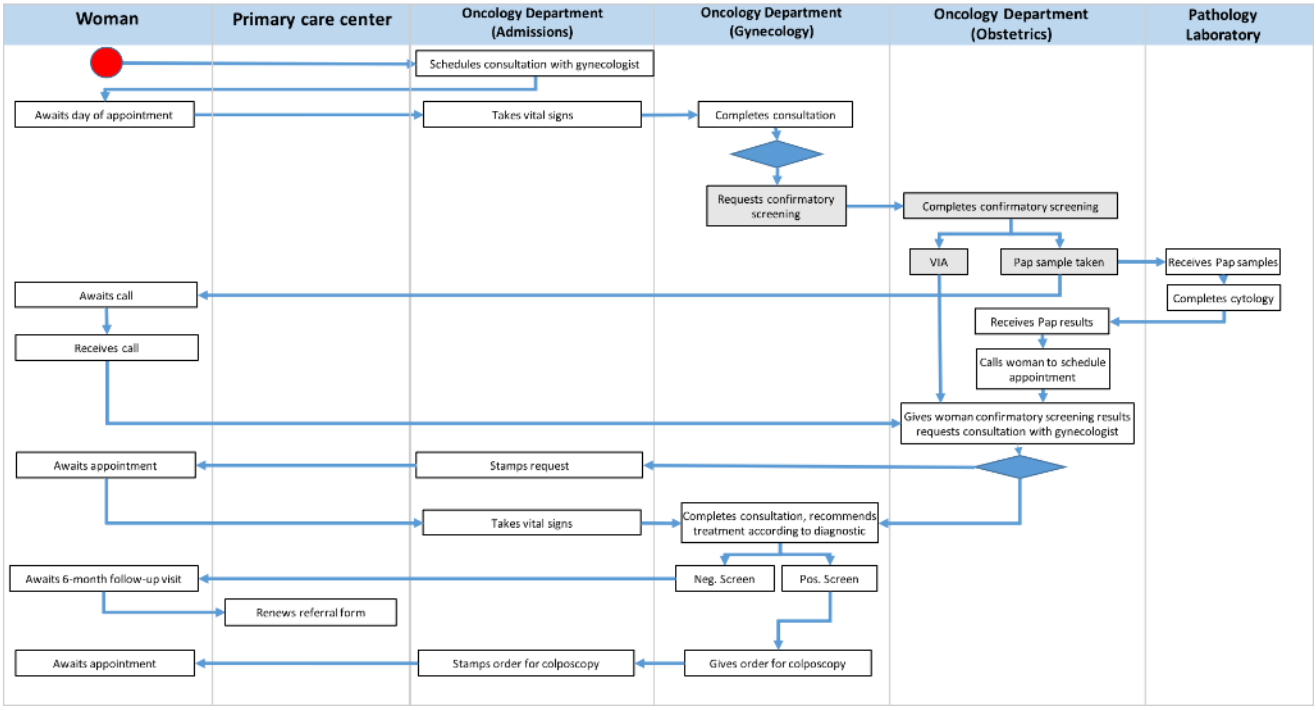
Introduction: of more sensitive screening technologies (e.g., HPV testing) is expected to reduce cervical cancer burden, but only if tests are deployed into a strong and well-integrated screening system.
Methods: Using soft systems methodology, purposive sampling, and strategic assumption surfacing and testing, we conducted 23 key informant interviews and 15 working group meetings of representative stakeholders in the screening system in Iquitos, Peru to understand the elements involved in cervical cancer screening (people, institutions, policies) and how they interact. Stakeholder groupings maximized the similarity of experience within the group and the differences in experience between the groups. Interviews were guided by a common mental model of screening (Figure 1). The data were organized into two types of visual process maps: thematic flowcharts representing overall processes and swim-lane diagrams representing patient/data flow through different sectors of the health care system. Health record review of screening, diagnosis, and treatment was performed to assess current system performance (e.g., percent of women screened, % testing positive, % receiving diagnostic exam, % receiving treatment).



Results: The shared screening process visuals were presented in a design workshop which brought together representatives across the stakeholder spectrum. The effectiveness of current screening program was poor (32.7% screening coverage, 3.9% screen-positive, 37.5% attending colposcopy). System-level inefficiencies were identified including lack of standardization in process and registration of

screening activities, duplication of screening in different health sectors, and excessive administrative procedures required prior to care. A lack of standardized monitoring, particularly at the hospital level, was revealed in medical record review.



Conclusions: Understanding the perspectives of the screening system purpose and operation across a range of stakeholders unearthed several screening test-independent problems in screening delivery. Participatory engagement of stakeholders to strengthen current system function before introduction of new technologies is essential for successful implementation of primary HPV screening.

HPV-RELATED BEHAVIOURAL RISK FACTORS AND CLINICAL SYMPTOMS AMONG MEN LIVING WITH HIV: EARLY RESULTS FROM THE HPV SCREENING AND VACCINE EVALUATION (HPV-SAVE) STUDY

CLINICAL RESEARCH / MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

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Introduction: Men who have sex with men (MSM) living with HIV are disproportionately affected by human papillomavirus (HPV)-associated anal cancer. In the absence of anal cancer screening guidelines in Canada, clinical research that comprehensively assesses known risk factors, including lifestyle behaviours and symptoms, is necessary.
Methods: The HPV-SAVE Study is a set of studies in three Canadian cities, including an anal cancer and HPV screening study among MSM living with HIV. Participants are invited to undergo anal cytology testing in their physician's office, followed by high resolution anoscopy (HRA) and anal biopsies if high-grade abnormalities, graded per Bethesda classification, are present. Self-reported demographic, sexual behaviour, and HPV-related risk factors are assessed at each study visit. Survey data are presented using descriptive statistics.
Results: Of 351 participants (median age=50), most were white (67%), born in Canada (61%), and had completed at least some college/university (79%). Current and former cigarette use was reported by 19% and 31% of participants, respectively. HPV infection-related disease was prevalent: 52% of 302 satisfactory anal cytology tests were abnormal; dysplasia and anal/genital warts were reported among 40% of participants. Only 13% reported having had the HPV vaccine. Symptoms reported in the past 3 months varied, with the most common being anal/rectal bleeding (33%), anal itching (29%), and anal/rectal pain or soreness (27%). Over half of the participants (58%) reported having >50 lifetime male sexual partners and 23% reported having 5 or more sexual partners in the past 6 months. Condomless sex in the past 3 months was reported by 35% of participants.
Conclusions: Early results from our study indicate that a significant proportion of MSM living with HIV endorse numerous behavioural and symptom-related risk factors for HPV infection. Complemented by biospecimen-based screening activities, these findings can help inform future anal cancer and HPV screening interventions among those at highest risk.

THE IMPACT OF CHANGING NATIONAL GUIDELINES ON CERVICAL SCREENING INTERVAL ADHERENCE: A POPULATION-BASED EVALUATION FROM THE UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Recent U.S. Preventive Service Task Force guidelines recommend 5-yearly HPV testing-based cervical screening, alone or with concurrent cytology ("co-testing"). To assess adherence to 5-yearly co-testing or 3-yearly cytology screening intervals as recommended in 2012, we conducted a state-wide retrospective cohort investigation of 510,834 unique women in New Mexico, U.S.A.
Methods: Median screening interval from 2008 to 2018, and the percentage of women screened at 1-, 2-, 3-, 4-, 5-, and >5-year intervals by type of screening (co-testing or cytology alone) in 2012, 2015, and 2018 were estimated in women aged 25-64 years undergoing routine cervical screening after a previous negative screen.
Results: For all age groups across 2008-2018, the percentage of women screened decreased approximately two-fold, while the screening intervals lengthened. Nearly one-third of women aged 25-29 years and one-fifth of women aged 30-64 years who received co-testing were screened at a one-year interval in 2018. There was also a trend across time for an increasing number of women to be screened at >5-year intervals. For those women aged 30-64 years with an antecedent negative co-test, the percentage of women screened at an interval >5-year intervals rose from 2.3% in 2012 and 3.0% in 2015 to 5.5% in 2018 ($p_{trend}<0.0001$). For those women aged 30-64 years with antecedent negative cytology, the percentage of women screened at an interval >5-year intervals rose from 2.5% in 2012 to 10.0% in 2015 and 16.0% in 2018 ($p_{trend}<0.0001$). In any given year, less than 15% of women with an antecedent negative co-test and less than 25% with an antecedent negative cytology received cervical screening at the recommended 5-year and 3-year screening intervals, respectively.
Conclusions: Many women are over-screened, increasing the harms of screening, while an increasing number of women are being under-screened which could potentially result in increases in cervical cancer incidence. Call/recall interventions are needed.

GENITAL WARTS AND PRECANCEROUS LESIONS IN HPV VACCINATED YOUNG WOMEN IN GERMANY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: HPV (Human Papillomavirus) vaccination has been available in Germany since 2006 and was recommended by the Standing Committee on Vaccination (STIKO) in 2007 for girls and in 2018 for boys. The vaccine should be given before the first sexual contact in order to exclude a prior exposure to the infection. The HPV vaccine is considered highly effective and safe. Data from Australia, where vaccination rates are at 80%, show a marked reduction in the rates of genital warts and precancerous lesions of the cervix uteri in vaccinated young women. In Germany, 44.6% of 17-year-old girls were fully vaccinated in 2015, while vaccination rates were lower in Bavaria.
Methods: We assessed data of legally insured girls from the database of the Bavarian Association of Statutory Health Insurance Physicians (KVB). Vaccination coverage trends were evaluated cross-sectionally and longitudinally. Age at vaccination and type of vaccine administered were investigated. Trends regarding diagnosis of genital warts (ICD-10: A63.0) and precancerous lesions of the cervix uteri (ICD-10: N87.1, N87.2 and D06) between vaccinated and unvaccinated young women were also evaluated.
Results: More than 350,000 girls were vaccinated against HPV in Bavaria from 2008 until 2018. The overall vaccination rate was 46.7%. In 2017, 51% of 18-year old girls were vaccinated at least once against HPV. The number of pediatricians delivering vaccination showed a significant increase in comparison to gynecologists and general *practitioners*. The vaccination rates increased significantly over the years, but with strong regional differences within Bavaria. A reduction in genital warts as well as precancerous lesions is already visible in young women who have been vaccinated against HPV.
Conclusions: The first evaluations on the use of HPV vaccine in Bavaria show a promising decline in the diagnosis of genital warts and precancerous lesions in vaccinated young women. However, a clear increase in vaccination rates is necessary.

PROTOCOL FOR A CASE-CONTROL STUDY ON OROPHARYNX CANCER AND HPV IN BRAZIL: STOP-HPV STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: The incidence of oropharynx cancer induced by Human Papillomavirus (HPV) infection is increasing in many countries. There are a small number of studies about the role of this infection in oropharynx cancer in Brazil, where a different distribution of HPV types was described. To study the relation of HPV and oropharynx cancer can bring important information to support decisions in public health such as HPV vaccination.
Methods: This is a case-control study, composed by 622 individuals with oropharyngeal cancer from 5 different regions of Brazil and their controls aimed to evaluate the association of HPV infection and oropharynx cancer. Samples will be collected in different sites such as oral cavity, genital and anal regions, as well as tumor tissue. An analysis of the expression of oncoproteins will be performed and the immune response will be evaluated in a serum sample. Participants will be interviewed about their sexual behavior and other possible confounders of the association between HPV and cancer such as eating habits, alcohol use, family history of cancer, oral hygiene, and smoking. The screening, selection and inclusion of individuals and the collection of data and biological samples will be performed by trained and certified researchers. Samples will be processed and analyzed at the study's central laboratory. Strict quality control will be performed using different procedures, such as training and certification of health professionals responsible for data acquisition, monitoring visits, and test-retest.
Results: The information about the magnitude of the association of HPV infection and oropharynx cancer and identification of the main types enrolled in cancer development becomes decisive for decision making both in terms of preventive public policies and oncological therapeutic options.
Conclusions: The data collected in this study will therefore have an important impact in public health and clinical decision making.

DIRECTIONALITY OF HPV INFECTION TRANSMISSION WITHIN HETEROSEXUAL COUPLES: A SYSTEMATIC REVIEW AND META-ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Greater female-to-male (F-M) relative to male-to-female (M-F) HPV transmission rates has been suggested. We verified this differential transmission rate hypothesis in couple-based studies by conducting a systematic review and meta-analysis.
Methods: We searched MEDLINE, EMBASE, Scopus, and Cochrane Library databases (inception- June 10, 2019). Studies were eligible if they included heterosexual couples aged 18+, genital samples collected from couples, and reported transmission rates of alpha-HPV types. We examined directionality of absolute transmission by calculating pooled estimates of F-M and M-F transmission rates, and rate differences per 100 person-months along with corresponding 95% confidence intervals (CI) using a random-effects model based on the number of transmission episodes and person-time. We identified and counted occurrences of directionality preponderance (F-M or M-F) for each HPV type in studies that reported incidence/transmission rates by sex and HPV type, considering the incidence rates in males and females to infer directionality under the assumption that HPV transmission occurred between study partners.
Results: Of 834 identified records, the full-text of 23 potentially relevant publications was obtained, of which 7 studies published between 2008 and 2019 were considered eligible. Data from 752 couples were used. The pooled estimate for F-M transmission rates was 3.01 (CI: 1.19-7.64), whereas that for M-F was 1.60 (CI: 0.86-2.98). The corresponding I^2 statistics were 97% and 89%. The overall rate difference between F-M and M-F transmission rates was 0.61 (CI: -0.27-1.49); I^2=75%. Only three studies provided incidence/transmission rates by sex and HPV type. Two favoured a preponderance of F-M transmission (F-M>M-F for 16 genotypes vs M-F>F-M for 11 genotypes; F-M>M-F for 29 genotypes vs M-F>F-M for 6 genotypes), and one study favored a M-F transmission (F-M>M-F for 6 genotypes vs M-F>F-M for 14 genotypes).
Conclusions: Our findings provide moderate evidence for a differential transmission rate with higher F-M compared to M-F transmission, with substantial statistical heterogeneity.

CERVICAL HSIL STANDARD OF CARE EFFECTIVENESS AND SAFETY OUTCOMES BY HPV-16/18 VS. OTHER GENOTYPES IN THE UNITED STATES – A RETROSPECTIVE COHORT STUDY

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: Clinical management of cervical high-grade squamous intraepithelial lesions (HSIL) has resulted in lower cervical cancer incidence rates over decades. However, surgical treatment of cervical HSIL is associated with recurrence of lesions and adverse outcomes, including pre-term birth. This U.S. population-based study reports the effectiveness and safety outcomes of the current standard care for cervical HSIL.
Methods: From a health insurance claims database representing approximately 5% of the US population, we derived a retrospective study cohort comprised of women aged 18+ years with claims for biopsy-confirmed cervical HSIL from 2008 through 2018. The cohort was divided into women who were initially managed with treatment (TX), watchful waiting (WW), and those who began with WW but were subsequently treated (i.e. delayed-treatment, DTX). Women with available data were further classified according to HPV-16/18 vs. other genotypes.
Results: There were 66,327 women with cervical HSIL in the cohort. Among those women, 71.9% received TX initially, while 28.1% were managed by WW. Among those initially managed with WW, 21.6% had DTX. Consistent with clinical guidelines, women managed with WW tended to be younger than women treated (mean age 32.2 versus 34.5 years) and were more likely to have a history of pregnancy in the six months preceding diagnosis (6.1% versus 2.8%). HPV-16/18 status is available for approximately 2% of the cohort. Among women with HPV-16/18 status available and initial management with WW, 34% of HPV-16/18 positive and 18% of HPV-16/18 negative women received DTX.
Conclusions: This large cohort with cervical HSIL will add beneficial new information to the field by enabling the assessment of effectiveness and safety outcomes associated with current standard of care management of cervical HSIL. Ongoing analyses will assess occurrence of several outcomes, including cervical HSIL recurrence, HPV clearance, pre-term birth, and perinatal mortality, comparing management cohorts and HPV genotypes.

*Note: Timothy Herring and Katherine Hughes are co-first authors, and Prakash Bhuyan and John Seeger are co-senior authors.

PREVALENCE OF HIGH-RISK HUMAN PAPILLOMAVIRUS IN FEMALE SEX WORKERS IN BOGOTA-COLOMBIA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Although female sex workers (FSWs) are a well-known high-risk group for Human Papillomavirus (HPV) infections, few tailored intervention programmes for HPV have been established worldwide. Lack of data on the prevalence of HPV-HR and cervical lesions in this population make it difficult to establish based evidence intervention programs.The objective of this study was the molecular identification of high-risk HPV genotypes in a group of FSWs in the city of Bogota.
Methods: HPV genotyping and cytology data were analysed from routine Pap smear tests that were collected 100 samples of FSWS between November 2018 and February 2019. Within the laboratory database, all FSWs were matched 1:1 for age and testing date to determine of hrHPV DNA genotypes and cytology outcome
Results: Overall prevalence of HPV was 42% and prevalence of hrHPV DNA in FSWs was 95%. The highest positivity of hrHPV was detected in women between 25-29 years. The most prevalent hrHPV genotypes were 45,**18**,**16**,51,52,58,53,53,59,73,35,39,66,31,33,68. 22% of the FSWs presented cytological abnormality and 59% of them presented hrHPV DNA.
Conclusions: FSWs have a significantly higher prevalence of hrHPV and more abnormal Pap smears in Bogota-Colombia. The prevalence of hrHPV in FSWs is similar to that reported in the literature. Screening with molecular tests for HPV-AR becomes a fundamental tool considering that this population group in Bogotá

PATIENT COMFORT WITH DISCUSSING HPV AND NON-HPV RISK FACTORS FOR OROPHARYNGEAL CANCER WITH DENTAL PROVIDERS

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: Introduction: Recent studies show that the human papillomavirus (HPV) is now the leading cause of oropharyngeal cancer (OPC). Although tobacco and alcohol use were historically known to be risk factors for OPC, 70% of all cases are now caused by HPV. Dental providers are critical to the prevention of HPV-related OPC, and previous research indicates that they have embraced their new role in HPV prevention. The purpose of this study was to assess patients' comfort with discussing HPV as a risk factor for OPC with dental providers.
Methods: Methods: Perspectives of US adults ages 18 to 45 (n=298) regarding the acceptability of dental providers' role in HPV-related OPC prevention were assessed through anonymous surveys completed via Qualtrics. Paired sample t-test and two-way ANOVA were conducted to assess patient comfort levels discussing HPV versus non-HPV related risk factors for OPC with dental providers. Comfort levels were also analyzed by provider role. All analyses were conducted in SPSS 25.
Results: Results: Participants were more comfortable discussing non-HPV related OPC risk factors (alcohol, tobacco, sun damage) than discussing HPV with dental providers (p=.003, η^2=.0287). For non-HPV related OPC risk factors, participants were most comfortable discussing tobacco (p=0.003, η^2=.0289) and least comfortable discussing sun damage (p=0.038, η^2=3.805) with dental providers. Participants were still less comfortable discussing HPV with dental providers, regardless of the non-HPV related OPC risk factor. These findings were consistent across dentists (p=0.017, η^2=.0189) and dental hygienists (p=0.006, η^2=.0254).
Conclusions: Conclusions: This study adds a critical dimension to the prevention of OPC in dental offices, indicating that patients may be less comfortable discussing HPV with dental providers compared to non-HPV related risk factors. Given that dental providers are aware of their unique role in HPV prevention, future research should explore patient and provider preferences for HPV-related communication.

MODELLING THE EFFECTS OF THE OPTIMAL CERVICAL CANCER SCREENING STRATEGY IN A PARTLY VACCINATED POPULATION AGAINST HUMAN PAPILLOMAVIRUS

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: The nonavalent vaccine contains additional high-risk HPV types, compared to the other two vaccines that have been used against human papillomavirus and it can potentially prevent up to 93% of cervical cancers. In the coming decades, vaccinated women will reach the screening age for cervical cancer, and this will result in a mixed population of vaccinated and unvaccinated women eligible for screening.

Methods: A HPV-type-specific microsimulation model (MISCAN) was calibrated to epidemiologic data from the United Stated to project the health benefits, harms and costs associated with different screening strategies in women vaccinated with the nonavalent vaccine under a 50% coverage. In our screening strategies, we varied the primary screening test, including cytology, HPV-test, and combined cytology and HPV "cotesting"; triage screening tests; age of screening initiation and/or switching to a different test; and interval between screens. Outcomes included lifetime cancer risk, life expectancy, lifetime costs and incremental cost-effectiveness ratios. The strategies were evaluated according to a threshold range of $50 000 to $200 000 per quality-adjusted life-year (QALY) gained.

Results: Among partly vaccinated women with the nonavalent vaccine, strategies that incorporated either HPV-test or HPV-genotyping are more cost-effective than those with cytology alone or cotesting. For the primary HPV-test strategies, the optimal strategy involves screening every 3 years from the age of 35 with $51 005 per QALY gained. Strategies with HPV-genotyping as a primary test at the age of 21, involving increased frequency, range from $97 056 for a 10 years screening interval to $159 246 for a 4 years screening interval.

Conclusions: Our study suggests high effectiveness of primary HPV screening among women vaccinated with the nonavalent vaccine. Screening effectiveness was higher if the primary test included also genotyping in addition to HPV-test alone. Vaccination coverage is an important variable in determining the optimal screening strategy for a population.

MAILED SELF-SAMPLE HUMAN PAPILLOMAVIRUS (HPV) TESTING KITS AMONG UNDER-SCREENED WOMEN IN A SAFETY NET HEALTH SYSTEM: PROTOCOL FOR A RANDOMIZED CONTROLLED TRIAL

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Mailed self-sample HPV testing kits have been demonstrated to increase cervical cancer screening among under-screened women in numerous organized screening programs. However, to our knowledge, they have not been evaluated in the context of U.S. safety net health systems that provide services to predominantly racial/ethnic minority, medically underserved populations.
Methods: We designed a randomized controlled trial (RCT) to evaluate the effectiveness and cost-effectiveness of mailed self-sample HPV testing kits alone and in combination with telephone-based education/instructional support (i.e., patient navigation). Working with leadership, we integrated key components of the intervention into health system processes.
Results: Under-screened women (i.e., no Pap in 3.5 years or no Pap/HPV co-test in 5.5 years) (N=2,268) will be randomized to one of three arms: 1) standard-of-care recall to clinic-based Pap screening (control); 2) mailed self-sample HPV testing kit (intervention); or 3) mailed self-sample HPV testing kit + patient navigation (intervention plus). Mailed kits consists of low-literacy printed educational/instructional materials, a Hologic Aptima® vaginal swab collection kit, and a pre-paid return envelope addressed to the health system laboratory. Kits will be tested using the Aptima HPV assay, with reflex testing for HPV 16, 18/45. Results will be communicated through the electronic medical record to healthcare providers for clinical follow-up of high risk-HPV positive patients. Effectiveness will be evaluated by comparing the proportion of women in each arm who participate in primary screening (self-sampling or attendance for clinic-based screening) and the proportion of screen-positive patients who attend for clinical follow-up. Cost-effectiveness will be evaluated using RCT data and decision-analytic modelling.
Conclusions: To our knowledge, this trial is the first to evaluate the effectiveness and cost-effectiveness of mailed self-sample HPV testing kits in a U.S. safety net health system. If cost-effective, this approach may represent a practical strategy for increasing cervical cancer screening among under-screened minority populations.

BARRIERS AND FACILITATORS OF HPV VACCINATION OF GIRLS ELIGIBLE FOR VACCINATION IN 2012-2014, AND THEIR PARENTS: A POPULATION-BASED CROSS-SECTIONAL STUDY IN MANIZALES, COLOMBIA

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2012, Colombia attained 80% coverage of a new school-based HPV vaccination program targetting nine-year-old girls. Following a mass psychogenic event in 2014 in Carmen de Bolivar, a town of the Caribbean region, vaccination dropped to 20% in 2016. This study aims at identifying barriers and facilitators of HPV vaccination among girls eligible for vaccination in 2012 to 2014, and their parents in a town of the Andean region of Colombia.
Methods: All households of two-stage random sample of blocks of high, medium and low socio-economic status (SES) were visited (September 2017-February 2019) for girls born in 2003, 2004 and 2005. Girls and responsible adults were interviewed separately using structured questionnaires designed upon a previous qualitative survey. Vaccination was defined by combining self-report with the Expanded Program of Immunization registry.
Results: 1.277 of 1.299 girls recruited were eligible, and completed survey and informed assent. Refusal participation was high (20%) in high SES levels, 99% were school-registered and 97% lived in the urban area. 78%, 57% and 31% of 2003, 2004 and 2005 birth cohorts completed the 2-dose series vaccination. 80% and 50% of vaccinated or non-vaccinated girls were aware of HPV vaccine. Regardless vaccination status, majority of girls believed vaccine prevents HPV infection and cervical cancer and half that it is dangerous. Around 30% vaccinated girls mentioned teachers, medical staff or the media recommendation as facilitators. The frequency of main barriers was non-school-based vaccination (31%), news about Carmen de Bolivar event (30%) or of other adverse events (15%) and recommendation against vaccination by parents/friends (20%). 50% of non-vaccinated girls mentioned they received little or none information about HPV vaccine prior to vaccination campaigns.
Conclusions: In this representative sample, the causes of vaccination decline seem to be multiple. Independent correlates of vaccine acceptability for girls and their parents will be presented at the conference

HPV ONCOPREDICT: A NOVEL DIAGNOSTIC TOOL ALLOWING ACCURATE DETERMINATION OF SAMPLE CELLULARITY AND NORMALIZED GENOTYPE-SPECIFIC VIRAL LOAD

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Cervical cancer (CC) kills 330,000 people annually and requires persistent infection with high-risk Human Papillomavirus (hrHPV) for its development. European guidelines advocate the use of hrHPV DNA tests for CC prevention in women over the age of 30 years. Most presently available hrHPV tests however do not provide quantitative sample cellularity assessment, as a measure of sample adequacy, or hrHPV viral load. The aim of this study was to evaluate the relationship between normalized HPV type-specific viral load and cervical cytology grade using HPV OncoPredict, a new in-vitro diagnostic tool allowing accurate quantitative sample cellularity assessment and hrHPV genotype-specific viral load (E6/E7 DNA) determination, developed as part of a Horizon 2020 SME Instrument Project (SME Instrument Grant GA 806551).
Methods: Clinician-collected cervical (CCC) samples were collected from 100 women referred to colposcopy at San Gerardo Hospital, Monza, Italy, for a diagnosis of precancerous cervical disease, classified by cytological stage (undetermined, low or high grade [ASCUS, LSIL, HSIL] squamous intraepithelial lesions). CCC were collected using L-Shaped FLOQSwabs (Copan) and resuspended in 20 mL of ThinPrep (Hologic). Nucleic acid extraction from 1 mL of sample was performed using NucliSENS easyMAG (bioMérieux), further eluted in 100 µl of buffer. HPV OncoPredict prototype (Hiantis) was used to determine samples' cellularity and normalized hrHPV genotype-specific viral load.
Results: Preliminary data using HPV OncoPredict indicate an adequate cellularity for all samples (mean human cellularity values of 6.78E+04, 1.06E+05, 7.02E+04 cells/mL for ASCUS, LSIL and HSIL respectively). Mean normalized viral loads overall ranged from 1.27E+02 (ASCUS) to 1.85E+02 (HSIL) GU/human cell, with differences in viral loads observed among different hrHPV genotypes.
Conclusions: HPV OncoPredict preliminary evaluation has shown promising results, allowing the possibility to accurately define normalized genotype-specific viral loads. Differences in viral loads observed between hrHPV suggest that further studies are required to determine normalized genotype-specific clinical cut-off values.

BARRIERS AND FACILITATORS TO THE IMPLEMENTATION OF THE HPV SCHOOL-ENTRY VACCINE POLICY IN PUERTO RICO: A CONSOLIDATED FRAMEWORK FOR IMPLEMENTATION RESEARCH ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2018, Puerto Rico (PR) enacted a Human papillomavirus (HPV) vaccine school-entry policy for student's ages 11 to 12 years. Using Consolidated Framework for Implementation Research (CFIR), we aimed to identify potential barriers and facilitators, and understand multiple contexts that may influence implementation. Key informants (KI) interviews were conducted to document the factors that facilitate or impede a successful HPV vaccine school-entry policy implementation in PR.
Methods: We conducted 40 KI interviews with stakeholders in the PR Department of Health (DOH), school system, healthcare organizations, and coalitions from July 2018 to September 2019. The interview guide was developed by the research team using the CFIR model. The interviews were transcribed verbatim, coded and analyzed to identify barriers and facilitators.
Results: The CFIR construct most cited, as a facilitator, was engaging (key stakeholder) due to the role of nurses from health and school fields to take the message to adolescents/parents and educate about the vaccine and its school-entry mandate. Another facilitator identified was cost (coverage of the vaccine by health insurers), access to knowledge and information (training and education from DOH and external agents to school nurses). The CFIR construct most cited as a barrier was parents' needs and resources, due to the misinformation (in relation to the mandate and HPV vaccine) among those parents of children impacted by the policy expressed by KIs. Other barriers mentioned included the constructs of complexity (problems with doses completion), access to knowledge and information (principals and teachers were detached from the implementation process) and available resources (lack of staff-school nurses).
Conclusions: Findings from this study can be used for improving implementation (adaptations/modifications) and can inform other countries in earlier stages of consideration of the adoption of similar immunization policies.

AKNA EXPRESSION IS ALTERED IN HPV POSITIVE OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Human Papillomavirus (HPV) is now recognized as a causative agent of oropharyngeal squamous cell carcinoma (OSCC) which is associated to a better prognosis and affects young men mostly. Among the different mechanisms involved in clinical outcome of OSCC, a deregulation in the immune response avoids the recognition and elimination of neoplastic cells. AKNA, an AT-hook transcriptional factor, is regulated by HPV, nevertheless, little is known about AKNA status in HPV positive OSCC.
Methods: Through the analysis of tumor biopsies from the National Cancer Institute from Mexico, a retrospective study was conducted to determine the levels and localization of AKNA by Immunohistochemistry Image Analysis.
Results: The results indicated only a 17.9% of positivity to HPV. AKNA expression was heterogeneous in tumor cases being positive in the nucleus in a 46%. After Kaplan Mayer analyses, the presence of HPV did not show an impact in overall survival, whilst AKNA nuclear localization was close to significance, indicating that AKNA could be active in these tumors.
Conclusions: The results suggest that loss of AKNA might be contributing to a better overall survival. Still, it is necessary to determine the significance of HPV in the modulation of AKNA levels in OSCC.

USER-DRIVEN COMMENTS ON FACEBOOK GENERATED FROM ONLINE MEDIA COVERAGE IN RESPONSE TO HUMAN PAPILLOMAVIRUS VACCINE AS A SCHOOL-ENTRY POLICY IN PUERTO RICO

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Using social media to identify and gauge public concerns on a variety of issues, including vaccination and mandatory vaccination policy, has been increasing. The accessibility to express opinions in these platforms, offers a unique opportunity to impact the perception and attitudes towards vaccination in other users. Since August 2018, the HPV vaccine is on the list of required immunizations for school-entry among adolescents aged 11 to 12 years in Puerto Rico (PR). The aim of this study was toevaluate public sentiments discussed on social media about the HPV vaccine and its implementation as a mandatory school-entry vaccine in PR, using as reference the Facebook comments.
Methods: The summary of Facebook comments derived from news articles related to the HPV vaccine and the mandate between January 2017 and December 2018. A total of 600 Spanish-language comments related to HPV vaccines and the school-entry policy made by 389 users were included. Sentiments expressed in the comments were categorized as either positive, negative or neutral. Thematic analysis was used to classify users' comments. Significant assessment of the association of sentiments and comments by sex was performed using the Chi-Square distribution.
Results: Overall, 75.6% of the users expressed negative sentiments in relation to the new policy. Three-fourths of the comments (77.9%) were written by women. The most popular concern among women were side effects (28.6%); whereas males' primary discussion was conspiracy theories (13.0%). Females were more likely to share a personal story in their comments compared with males ($p<0.01$).
Conclusions: Given the high proportion of negative responses observed, responsible agencies and stakeholders should use social media as promotion venues to educate the public. In particular, efforts targeting vaccine safety and media hoaxes should be considered in the promotion of the vaccine and this new mandate.

HUMAN PAPILLOMAVIRUS TYPE 197 IS NOT ASSOCIATED WITH SKIN TUMORS

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: Human papillomaviruses (HPV) of the genus gammapapillomavirus (γ-PV) represents the most rapidly growing HPV genus. Recently, a role of HPV197, a γ-PV type, in the pathogenesis of cSCC was postulated. Using whole genome amplification and type-specific real-time PCR, HPV197 was detected in 34 of 91 non-melanoma skin tumors in a previous study. Our aim was to investigate a potential etiologic link between HPV197 infection and skin carcinogenesis.
Methods: 258 skin tumor biopsies of immunocompetent patients including actinic keratoses, Bowen´s disease, cutaneous SCC, microcystic adnexal carcinomas, basal cell carcinomas, keratoacanthomas, atypical fibroxanthomas, and dermatofibromas were analyzed for HPV197 DNA prevalence. Additionally, skin swabs of 442 HIV-positive men and healthy male controls were investigated and viral load was determined with type-specific real-time PCR and expressed as HPV197 copies per beta globin gene copy.
Results: We could only detect HPV197 in one Bowen´s disease sample with a very low viral DNA load of 0.001 HPV197 copies per beta-globin gene copy. Neither of the other tumors was HPV197- positive. In 442 forehead swabs of HIV-1 positive (HIV+) patients and HIV-1 negative (HIV-) controls, HPV197 was found significantly more frequently on the skin of HIV+ (25/205; 12.2%, 95% confidence interval (CI) 8.4 - 17.4%) compared to HIV- men (8/237; 3.4%, 95% CI 1.7 - 6.5%) ($p<0.001$; Chi-square test, 2-sided). However, HPV197 DNA loads were similar in HIV+ and HIV- men (median load HIV+ 0.022 (interquartile range (IQR) 0.006 - 0.153) versus 0.055 (IQR 0.015 - 0.156) in HIV- ($p=0.374$, Mann-Whitney-U-test).
Conclusions: We conclude from our data that HPV197 is not associated with non-melanoma skin tumors, because it was undetectable by qPCR in almost all lesional biopsies analyzed. HPV197 was found on the surface of normal forehead skin of both immunocompetent and immunosuppressed individuals, and thus could be part of the human skin virome.

BETA-HUMAN PAPILLOMAVIRUS INFECTION OF KERATINOCYTE CARCINOMAS ASSOCIATED WITH CUMULATIVE ULTRAVIOLET RADIATION EXPOSURE AT THE TUMOR LEVEL

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: Growing evidence suggests that cutaneous human papillomavirus (cuHPV) infection, particularly beta-HPV, may play an etiological in keratinocyte carcinoma (KC) development, in concert with ultraviolet radiation (UVR) exposure, although information available at the tumor level is sparse. We examined the presence of cuHPV DNA in KC tumors and its association with solar elastosis in the adjacent normal tissue, a measure of cumulative UVR damage, among skin cancer screening patients enrolled in the Viruses in Skin Cancer (VIRUSCAN) prospective cohort study.
Methods: Pathological characteristics were documented for 575 KC tumors arising in 364 VIRUSCAN participants, including anatomic site, histology, and degree of solar elastosis (SE) in normal tissue adjacent to KC tumors (levels 0-3). Viral DNA corresponding to 46 beta-HPV types and 52 gamma-HPV types was measured in formalin-fixed, paraffin-embedded KC tumors using a Multiplex PCR/Luminex assay, and associations with pathologic characteristics were examined.
Results: Of 315 squamous cell carcinoma (SCC) and 257 basal cell carcinoma (BCC) tumors tested, 19% and 8% were positive for at least one beta-HPV type, respectively (p=0.001), whereas no difference in gamma-HPV prevalence was observed by histology (6% SCC; 4% for BCC; p=0.30). KC tumors arising on the head and neck were more likely to be beta-HPV positive than those arising on the torso or limbs, and both SCC and BCC tumors arising in skin exhibiting the highest degree of solar elastosis were significantly more likely to be beta-HPV positive (20%) compared to those with less cumulative UVR damage (14%, p=0.01). No difference in gamma-HPV DNA positivity of KC tumors was observed by anatomic site or solar elastosis.
Conclusions: Beta-HPV infection is more common in SCC than BCC and in KC tumors arising in sun-exposed and sun-damaged skin, supporting the hypothesis that beta-HPV infection and UVR exposure may be co-factors in the development of KC.

INTERNATIONAL HPV AWARENESS DAY AND ITS IMPACT ON UNIVERSITY NURSING STUDENTS: A PRIMER FROM CROATIA

PUBLIC HEALTH / EPIDEMIOLOGY / ELIMINATION

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Introduction: International HPV Awareness Day campaign was inaugurated in 2018 as an annual focal point for global conversations about human papillomavirus (HPV) and associated malignancies - not only online, but also in universities, in the public, and among families around the world. Right from the start, University North in Croatia joined this global initiative as an Operating Partner of the International Papillomavirus Society (IPVS).
Methods: Two events were organized by the Operating Partner at this Croatian public university in 2018 and 2019, respectively, where university lecturers, national and international invited speakers, and student representatives joined the local event based on IPVS campaign tools and resources. Although interested public and media were present, both of these events primarily targeted student population. A total of 102 and 114 of undergraduate nursing students participated in the first and second instalment of the International HPV Awareness Day, respectively. Participating students took a written knowledge test on HPV and completed an evaluation form about their prospective professional career interests before and after the event.
Results: A significant increase in test scores has been observed in almost all categories after the event, and significantly more students were prepared to consider a future career in gynaecology, or continuing with their graduate studies in nursing management and/or public health. This study shows that a one-day professional event envisioned as a hub for exchanging information, expertise, key media messages and know-how on HPV can improve their knowledge level and encourage them for certain career choices.
Conclusions: Our results form the basis for recommending the integration of HPV Awareness Day (and similar initiatives) into the undergraduate nursing curriculum as a part of an elective course on sexually transmitted diseases. Additional evaluation will inform how exactly this event and nursing curriculum can be further improved for the benefit of future student generations.

HUMAN PAPILLOMAVIRUS TYPING IN PAIRED FRESH-FROZEN AND FORMALIN-FIXED, PARAFFIN-EMBEDDED COMMON WART TISSUE SAMPLES

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Formalin-fixed, paraffin-embedded (FFPE) tissue specimens are an invaluable source for research and diagnostic purposes when fresh clinical samples are unavailable and their prospective collection is not feasible. However, nucleic acids extracted from FFPE tissues are often degraded and chemically modified making the molecular studies challenging. In order to evaluate the use of FFPE specimens in etiological studies of common warts (CWs) a total of 128 paired fresh-frozen and FFPE tissue specimens of histologically confirmed CWs were analyzed.
Methods: Following DNA extraction from fresh and FFPE CWs, using a Qiagen DNA Mini Kit, all samples were tested using type-specific quantitative multiplex RT-PCR, allowing sensitive detection and differentiation of HPV2/27/57 infection in a single PCR reaction, and three different type-specific quantitative *Mu*-PV RT-PCRs.
Results: Single HPV infections were found in 72/128 (56.3%) fresh-tissue CWs, of which the concordant single HPVs (HPV1, 2, 27, 57 in 2, 8, 21 and 33 specimens, respectively) were also detected in 64/72 (88.9%) paired FFPE samples. HPV DNA was not detected in 8/72 (11.1%) FFPE samples, in which low concentrations of single HPV types (HPV1 or 63) were previously found in fresh CWs. Additionally, multiple HPV infections were detected in 51/128 (39.8%) fresh tissue samples, of which concordant results (double infections with HPV1, 27, and 57 in 11 cases and triple infection with HPV1, 27, and 57 in a single case) were found in 12/51 (23.5%) paired FFPE samples, most probably due to low viral loads in fresh tissues. In 5/128 (3.9%) CW samples HPV1/2/27/57/63/204 DNA was not detected, even though the DNA extraction was successful from all samples according to amplification of the housekeeping gene.
Conclusions: FFPE samples can be used for HPV detection in CWs in which high viral load is present, but may be less suitable for detecting multiple HPV infections.

MULTIPLEXED MOLECULAR PROFILING BY QUANTIGENE 2.0 FROM PRIMARY CERVICAL SMEAR SAMPLES DETECTS DYSPLASIA WITH HIGH PRECISION

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Persistent infection by Human Papillomaviruses (HPV) is characterized by viral oncogene expression and upregulation of cellular proteins that can be regarded as biomarkers for transformation. The oncoproteins E6 and E7 have pleiotropic effects and interact with cellular proteins regulating proliferation, tumor suppressors, (cancer) stem cell markers, and tumor markers. The strength of expression correlates to dysplasia stage and progression.
Methods: A multiplexed mRNA quantifying assay based on Luminex/QuantiGene 2.0 technology platform (Thermo Fisher Scientific) was developed. It combines detection of the E7 oncogene of 18 HPV genotypes and 18 cellular biomarker expression, routinely used for diagnosis, markers for cancer stem cells, tumor markers and housekeeping genes for normalization. All mRNA species are detected simultaneously from a crude lysate of a cervical smear sample taken into Thinprep/PreserveCyte. In a prospective trial 1400 consecutively collected samples were measured and data used for logistic regression and ROC analyses.
Results: The assay has a high sensitivity detecting less than 40 CaSki or HeLa cells. It genotypes 18 HR-HPVs and detects leading types in multiple infections with highest E7 expression. Logistic regression identified E7 expression strength as most informative biomarker discriminating low grade and high grade (CIN2+) dysplasia. P16, proliferation associated markers (Ki67, MCM2, Stathmin), and tumor markers (ALDH1A1, BIRC5, hTERT) contributed to detection and differentiation of dysplastic stages. Accuracy by ROC analysis to detect CIN3+ from the initial screening sample was 90%.
Conclusions: Multiplexed mRNA quantification of viral and cellular biomarkers by QuantiGene 2.0 Plex assay detects HPV infection and dysplasia with high accuracy. The assay could be used as a triage to colposcopy after primary HPV screening. The assay procedure is simple and robust and maybe used in LMIC settings to reduce further triage and avoid overreferral.

GENOTYPE-CONCORDANCE OF CERVICAL AND ANAL HPV INFECTION AMONG HIV POSITIVE WOMEN IN SOUTH AFRICA.

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Human Papillomavirus is associated with cervical, anogenital and oropharyngeal cancers. Multiple subtypes, persistent and concurrent HPV infections are common among HIV+ women.However, there is a paucity of data regarding the concordance of HPV genotypes between the cervical and anal region. Therefore, this study aims to investigate the association of cervical HPV infection, with genotype-concordant anal HPV infection among women with CIN in Durban South Africa.
Methods: A longitudinal cohort of 148 women aged 18-65 years with high grade cervical CIN at King Edward Hospital, Durban South Africa were followed-up prospectively from October 2016- March 2017. Behavioural, clinical and demographic data were collected. Cervicovaginal and rectal swab samples were collected from women (n=30) over the age of 30 years to detect DNA of 37 HPV subtypes using Roche Linear array. Descriptive statistics and multivariable regression to describe the relationship between genotype-concordant HPV infection identified from anal and the cervical region.
Results: Majority of participants 97% (n=145) were African black women, with an average age of 38 years. Of which 94.6% (n=140) were HIV positive with a mean CD4 count of 481. Participants Anal HPV infection was 93.3% (n=28), with HPV 16 and 18 detected in 64.3% (n=18). Overall, oncogenic HPV subtypes were concordant between the two anatomical sites, with an avergare genotype specific concordance of 45.6%; HPV16 was 55% and HPV 18 31.2,% respectively.
Conclusions: In this population of women cervical and anal HPV infections occur consecutively. The high degree of genotype-specific concordance, therefore, suggests that the cervix and anus may serve as reservoirs for HPV infection at other either anatomical site. Thus more studies are needed to further explore this phenomenon to eliviate the burden of HPV-related disease. This data may have implications in informing public health guidelines, advocacy for cervical and anal screening of HIV positive women.

CUMULATIVE RISK OF CIN IN BASELINE HPV+ CYTOLOGY NORMAL WOMEN: SYSTEMATIC REVIEW AND META-ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Most human papillomavirus (HPV)+ women do not have any cytological abnormalities, but are at increased risk of developing cervical intraepithelial neoplasia (CIN). To inform their screen management, we conducted a systematic review and meta-analysis of the cumulative risk of CIN in HPV+ cytology normal women.
Methods: We searched MEDLINE, Embase, and Scopus for prospective studies measuring the cumulative risk of histologically-confirmed CIN in women who were HPV DNA+ and cytology normal at baseline. We estimated the cumulative risk of CIN2+ and CIN3+ using a generalized linear mixed effects meta-regression model assuming exponential survival, with time and study-level variables as predictors of risk. We used the meta-regression model to calculate pooled 1- and 5-year risks of CIN3+ and hazard ratios.
Results: We screened 4,035 abstracts, and included 162 records reporting cumulative risks of CIN in HPV+ cytological normal women. The pooled predicted 1- and 5- year cumulative risks of developing CIN3+ were, respectively, 3.7% and 7.9% for any high risk HPV type, 4.7% and 12.2% for HPV16/18, and 2.8% and 3.1% for high risk types excluding HPV-16/18, with HPV type a significant predictor of progression risk ($p<0.0001$). Women with persistent infections had a hazard ratio of 3.8 (95%CI 2.4-16.8) for progressing to CIN3+ compared to women whose infections' persistence was not ascertained. Population age, HPV test type (commercial vs research), and study calendar year did not significantly predict progression to CIN3+. There was a substantial heterogeneity in the background risk of CIN3+ across studies, with a 95% credibility interval of 0-12.7% for the baseline risk.
Conclusions: We found substantial variation in the background risk of CIN3+ across populations that is not accounted for by the examined study-level variables. This suggests cumulative CIN3+ risk estimates for HPV+ cytology normal women may not be transportable between populations for risk-based screen management.

QUANTIGENE-BASED HPV E7 AND CELLULAR BIOMARKER MRNA DETECTION INCREASES SPECIFICITY OF HPV SCREENING IN ETHIOPIA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: A cluster randomized cervical cancer screening study was performed in Butajira, south central Ethiopia, where acceptance of self-sampling for HPV DNA testing was compared to visual inspection with acetic acid. (1) As adjunct study, persistently HPV-positively tested women were retested with an innovative assay based on the QuantiGene 2.0 technology platform (Thermo Fisher). The aim was to compare feasibility and precision in detection of dysplasia.
Methods: Women self-sampled cervicovaginal smears using the Evalyn brush (Rovers Medical Devices, Oss, The Netherlands) and multiplexed genotyping (MPG) was performed on extracted DNA. HR-HPV positive women underwent VIA for triage and resampling into Thinprep/PreserveCyte 4-8 months later. MPG retesting and QuantiGene assay were performed on Thinprep samples for detection and quantitation of E7 oncogene and cellular biomarker mRNA expression (e.g. p16, Ki67, Stathmin/oncoprotein 18, MCM2, ALDH1A1, Birc5/Survivin).
Results: Out of 1020 women accepting self-sampling and HPV testing 144 (14.1%) tested HR-HPV positive and 122 attended VIA triage of whom 110 gave a second Thinprep sample. Upon retesting 4-8 months later 84 (76.4%) women had cleared the original HR-HPV genotype and 26 (23.6%) were persistently HR-HPV genotype positive. Colposcopy showed dysplastic changes in 2 women with CIN2+ alterations while the third had a TZ3. QuantiGene test analysis including strength of E7 mRNA and cellular biomarker expression identified these 3 samples with markedly increased expression. The relative screening burden by HPV test (110 positives) versus Quantigene mRNA detection (3 positives) was 36 fold reduced.
Conclusions: Acceptance of self-sampling and HPV screening was high. Clearance of prevalent HPV infections within appx. 6 months was high posing a problem for triage and follow up. Repeated HPV testing rounds may reduce over referral. QuantiGene-based mRNA detection including biomarker evaluation, which is a simple and robust technique, enhanced specificity remarkably. References 1) Gizaw M, et al., Cancer Prev Res 2019 (9):609-616

UNITED STATES ORAL HEALTH STUDENTS' WILLINGNESS TO TRAIN AND ADMINISTER THE HPV VACCINE IN DENTAL PRACTICES

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: HPV oropharyngeal cancers have now surpassed cervical cancer rates in the United States. Dental providers' engagement in HPV education and vaccination efforts may help reduce the burden of HPV oropharyngeal cancers. We examined factors associated with oral health students' willingness to train and administer the human papillomavirus (HPV) vaccine in dental settings.
Methods: United States students in 15 oral health programs participated in an online survey in 2016. Unadjusted and adjusted multivariable logistic regression were conducted and odds ratios (OR) and 95% confidence intervals (CI) were reported. Analyses were conducted in SAS Version 9.4. Data from a total of N = 306 students were analyzed to examine sociodemographic, educational, practice, and attitudinal factors associated with willingness to train and administer the HPV vaccine.
Results: Majority of the participants were female (70.3%), nonHispanic/Latino (90.8%), and White (62.1%). Perceiving that HPV vaccination recommendation (OR = 1.95, 95% CI = 1.14–3.35) and administration (OR = 3.79, 95% CI = 1.63–8.81) was in the dental professional's scope was positively associated with outcome measures when other factors were held constant. Students with greater patient contact time (OR = 4.47, 95% CI = 1.14–17.58) and lower role conflict (agreed that HPV vaccine administration was in the dental professional's scope) had higher odds of willingness to administer the HPV vaccine when other factors were held constant (OR = 5.9, 95% CI = 2.27–15.3).
Conclusions: The major barrier to engaging oral health students in HPV vaccination efforts was role conflict. Professional organizations and oral health programs should strongly support the role of oral health professionals in HPV oropharyngeal prevention. Additional training of oral health providers is needed to improve HPV vaccine and HPV-related cancer prevention education and HPV vaccine receipt among oral health patients at routine dental health visits at ages 9-26 years.

USING THE HEALTH BELIEF MODEL TO UNDERSTAND WOMEN'S PERCEPTION REGARDING HPV, CC, AND PAP TRIAGE IN ARGENTINA.

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: Completion of triage by women with HPV self-collected tests (HPV-SC) is challenging. We analised how women´s knowledge, perception and attitudes related to HPV/cervical cancer (CC) may influence the screening/diagnosis process. This analysis is part of a mix-method study to evaluate the effectiveness/implementation of an mHealth intervention to increase triage adherence among HPV+ women with self-collected tests (ATICA Project).
Methods: During January 2017, six focus groups (FG) were carried out in the province of Jujuy (n=48 women, both with HPV positive and negative results), stratified by rural/urban residence. Inclusion criteria: being aged ≥30 and having performed HPV-SC. Thematic analysis was carried out using constructs from the Health Belief Model: Perception about HPV risk (susceptibility/severity), benefits/costs of triage, self-efficacy (confidence in ability to perform triage), and cues to action (mobile phone text messages –SMS- as reminders to increase adherence to triage).
Results: Misinformation regarding HPV and cervical cancer prevention was common. Participants considered that their HPV risk was low and an inevitable part of being a woman; many of them were not aware of the importance of continuing follow-up if HPV+. Comfort and privacy offered by HPV-SC was highlighted as a main benefit. Women had negative views about clinician-collected screening/triage: they rejected the gynecological consultation (“like a torture”), which was also perceived as producing an economic impact (transport/time to attend health centers). Lack of help from family/friends was considered an important obstacle to perform triage. Women highly accepted and valued receiving SMS to be notified about HPV result availability and to remind them about the need to attend the health center for triage if HPV+. No differences were found among rural/urban FG participants.
Conclusions: Misinformation about HPV/CC, lack of awareness about the importance of triage, and rejection of the gynecological consultation are obstacles to complete triage. SMS reminders can be useful to increase triage.

RATES OF NEW HPV DETECTION AND LOSS OF DETECTION AMONG MIDDLE-AGED WOMEN IN THE US: ATTRIBUTION TO RECENT ACQUISITION VS NEW DETECTION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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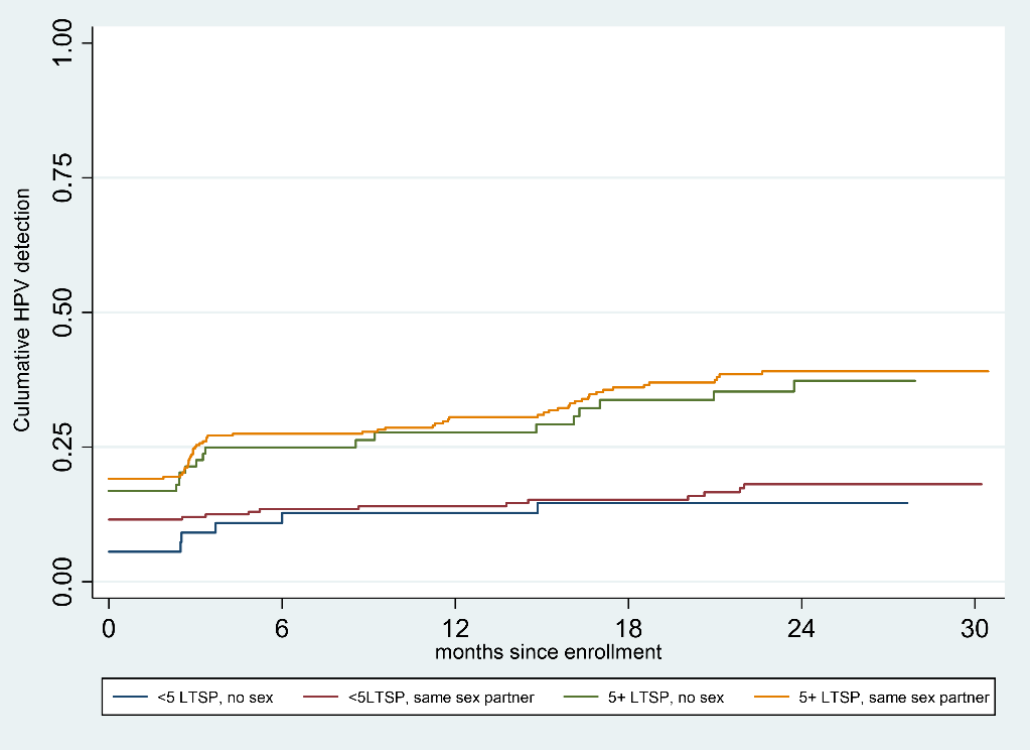
Introduction: The United States Advisory Committee on Immunization Practices (ACIP) does not recommend routine HPV vaccination for persons over age 26 years but allows vaccination up to age 45 if a benefit to the patient is perceived. Assuming that benefit is gained predominately through prevention of acquisition of new infection (versus reactivation of latent infection), we estimated the fraction of new HPV detections due to new acquisition vs. redetection/reactivation among 731 women aged 35-60 years in Baltimore, MD.
Methods: During 2008-2011, a cervical brush sample was collected for HPV testing by a trained study physician or nurse and participants completed health and sexual behavior questionnaires at baseline and every 6-months over a 2-year period. Rates of new HPV detection were calculated using Kaplan-Meier methods, stratified by recent and past sexual behavior. Population attributable fractions (PAFs) of new HPV detection due to new acquisition vs. redetection were estimated.
Results: Rates of new detection were highest in women reporting a new partner regardless of sexual history, however rates of new detection were over 2-fold higher in women with 5+ lifetime sex partners (LTSP) compared to women with <5 LTSP (Table 1, Figure 1). Of the 67 new HPV detections, 18% occurred in women with <5 LTSP and no new partner, 63% in women with ≥5 LTSP and no new partner, and 19% in women with a new partner. The PAF of new HPV detection due to new acquisition was 17.0% versus 34.3% due to having 5+ LTSP.

Variable	Woman-months of follow-up	Number of new detection events	New detection rate per 1000 woman-months (95% CI)	unadjusted HR (95% CI)	adjusted HR (95% CI)*	PAF
< 5 LTSP (no new partner and no sex)	5,450	12	2.2 (1.3, 3.9)	1.0 (ref)	1.0 (ref)	
≥ 5 LTSP (no new partner and no sex)	7,582	42	5.5 (4.1, 7.5)	2.5 (1.3, 4.7)	2.2 (1.2, 4.2)	34.3
New partner (< 5 LTSP and ≥ 5 LTSP)	483	13	26.9 (15.6, 46.4)	12.6 (5.8, 27.7)	8.1 (3.5, 18.6)	17.0



Conclusions: Recent and past sexual behavior independently affects the risk of having a new HPV type detected in this mid-adult population, suggesting that new detection reflects both recent acquisition and recurrent detection of previously acquired infection. These results may be useful in counseling older women undergoing routine HPV-based cervical screening and considering HPV vaccination.

RECIPROCAL PDX AND ORGANOID MODELS OF CERVICAL CANCERS TO IDENTIFY NEW THERAPEUTIC AGENTS

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Human papillomaviruses are prevalent pathogens of the ano-genital epithelia and the oro-pharyngeal airway cells. Persistent infections by the mucosotropic high-risk (HR) HPV types can progress to cancers. Virtually all cervical cancer is caused by over-expression of the HR HPV viral E6 and E7 proteins that destabilize p53 and pRB tumor suppressors, respectively. Advanced and metastatic cervical cancers are recalcitrant to the available chemo-radiation therapies, with high recurrence rates. Tumor heterogeneity is a leading contributor to drug resistance and tumor recurrence. The US National Cancer Institute has recommended to establish patient-derived tumor xenografts (PDX) in Severe Combined Immune Deficiency (SCID) mice as drug screening platforms, because they are the most physiologically relevant preclinical models. In recent years organoid/tumeroid cultures emerged as alternative strategy for drug screening, because evaluation in PDXs is time consuming and expensive.
Methods: We established PDX from cervical cancer. We also developed organoid raft cultures (ORCs) from cervical cancers as a novel tumor model in vitro.
Results: We demonstrated that ORCs can be used to develop PDX and, conversely, the PDX tissues can be grown as ORCs. ORC and PDX derived from the same cervical cancers share similar histology and a number of key biomarkers. The organoids responded to inhibitors of pathways known to be activated by the HPV oncogenes. We are comparing the two systems in molecular detail with the objective to demonstrate that ORC provide a faithful, economical and convenient in vitro model with which to identify new therapeutic drugs.
Conclusions: PDX derived ORC can be used to evaluate efficacy of drug candidates in vitro. The method is economical, and results could be verified in PDX models prior to clinical trials.

WORLDWIDE BURDEN OF CERVICAL CANCER IN 2018

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: The knowledge that persistent human papillomavirus (HPV) infection is the main cause of cervical cancer has resulted in the development of prophylactic vaccines to prevent the HPV infection and HPV assays that detect the virus Given the recent call from WHO to scale up preventive, screening and treatment interventions to eliminate cervical cancer as a public health problem during this century, it is timely to assess the current burden of the disease as a baseline from which to assess the impact of the global initiative.
Methods: Visual and tabular descriptions of national estimates of cervical cancer incidence and mortality in 2018 are presented from GLOBOCAN, the recently compiled database from IARC of cancer estimates for 185 countries.
Results: There were an estimated 570,000 cases of cervical cancer and 311,000 deaths from the disease in 2018. It is the fourth most common female cancer ranking after breast cancer (2.1 million cases), colorectal cancer (0.8 million cases) and lung cancer (0.7 million). The incidence of cervical cancer varies widely among countries with estimated world-age-standardised rates ranging from less than 1 to 75 per 100,000. Cervical cancer is the leading cause of cancer-related death among women in Eastern, Western, Middle and Southern Africa. The highest incidence rate is estimated in the Kingdom of Eswatini, with ~ 6.5% of women developing cervical cancer before the age of 75. China and India contribute over one third of the global cervical burden with 106,000 and 97,000 cases and 48,000 and 60,000 deaths, respectively. More than the other major cancers, the disease affects women <45 years.
Conclusions: Cervical cancer continues to be a major public health problem affecting young women particularly in low and middle-income countries. The global scale-up of HPV vaccination and HPV-based screening – including self-sampling – may make cervical cancer a rare disease in the decades to come.

PATIENT AGE AND CERVICAL LESION SEVERITY BY HIV-STATUS AND TREATMENT COMPLETION: THE FIRST 8-MONTHS OF VIA AND CRYOTHERAPY IMPLEMENTATION IN NAMIBIA

CLINICAL RESEARCH /TREATMENT OF PRECANCER IN LOW-RESOURCE SETTINGS

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Introduction: Recommendations for cervical cancer screening initiation in HIV-positive women varies internationally with little published data available. In March 2018, the Namibian Ministry of Health and Social Services finalized cervical cancer prevention guidelines setting first screening for HIV-positive women at age 20 years because of high HIV prevalence (15.7%) and average age of 16 years at sexual debut. Analysis of program data compared visual inspection with ascetic acid (VIA)-positivity at age of first screening by HIV status to inform and strengthen screening practices.
Methods: Program data from the first 8 months (October 2018–June 2019) of VIA and cryotherapy implementation in Namibia's Khomas region compared rates of VIA-positivity by age at self-reported first ever screening, lesion severity, and HIV status. Chi-square tests examined the significance of differences in VIA-positivity and lesion severity percentages by HIV status, and compilation of age-stratified cryotherapy treatment and large loop excision of the transformation zone (LLETZ) referral data compared percentages by HIV status.
Results: Of 1,102 women screened, 287 (26%) were HIV-positive. Overall, 161 (15%) had pre-cancer lesions, 52 of whom were HIV-positive (18% VIA-positivity). [Table 1]. VIA-positivity in ages 20-24 years was 40% in HIV-positive compared to 15% in HIV-negative women. The proportion of HIV-positives with VIA-positivity was significantly higher (18% and 13%, p=0.04) and the proportion of HIV-positives with large lesions ineligible for cryotherapy was higher, although not significant (31% and 21%, p=0.08). [Tables 1, 3]. Completion of cryotherapy treatment was 80%. [Table 2].
Conclusions: Young HIV-positive women in Namibia had high VIA-positivity. Age stratified cancer incidence data could distinguish Human Papillomavirus infections likely to self-clear from true pre-cancer lesions in young women. Additionally, cost-benefit analysis of potential overtreatment and cancer cases averted in young women could guide resource allocation. Treatment completion rates are high in Namibia despite inadequate human resources and carbon dioxide supply chain challenges.

Table 1. VIA findings at first screening by age, lesion severity, and HIV status in Namibia (October 2018-June 2019)

		Age (years)						
	Total	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**
HIV+								
VIA-screened	287	1	15	30	40	73	71	53
VIA-positive	52 (18%)	0 (0%)	6 (40%)	8 (27%)	8 (20%)	11 (15%)	13 (18%)	5 (9%)
Cryotherapy Eligible	30 (58%)	0 (0%)	4 (67%)	2 (25%)	4 (50%)	9 (82%)	8 (62%)	2 (40%)
Cryotherapy Ineligible	16 (31%)	0 (0%)	2 (33%)	5 (63%)	3 (38%)	2 (18%)	3 (23%)	1 (20%)
Suspected cancer	6 (12%)	0 (0%)	0 (0%)	1 (13%)	1 (13%)	0 (0%)	2 (15%)	2 (40%)
HIV-								
VIA-screened	774	6	78	271	155	118	73	67
VIA-positive	102 (13%)	2 (33%)	15 (19%)	38 (14%)	22 (14%)	13 (11%)	3 (4%)	9 (13%)
Cryotherapy Eligible	77 (75%)	2 (100%)	12 (80%)	33 (87%)	16 (73%)	9 (69%)	2 (67%)	3 (33%)
Cryotherapy Ineligible	21 (21%)	0 (0%)	3 (20%)	5 (13%)	4 (18%)	4 (31%)	1 (33%)	4 (44%)
Suspected cancer	4 (4%)	0 (0%)	0 (0%)	0 (0%)	2 (9%)	0 (0%)	0 (0%)	2 (22%)
HIV Unknown								
VIA-screened	41	0	4	11	10	6	5	2
VIA-positive	7 (17%)	0 (0%)	0 (0%)	2 (18%)	2 (20%)	1 (17%)	1 (20%)	0 (0%)
Cryotherapy Eligible	5 (71%)	0 (0%)	0 (0%)	2 (100%)	1 (50%)	1 (100%)	1 (100%)	0 (0%)
Cryotherapy Ineligible	1 (14%)	0 (0%)	0 (0%)	0 (0%)	1 (50%)	0 (0%)	0 (0%)	0 (0%)
Suspected cancer	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Abbreviations:
VIA-Visual inspection with ascetic acid

Table 2. Treatment and referral of VIA-positive all screening types by age at first screening and lesion severity

		Age (years)							
	Total	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**50+**
VIA-positive	161	2	21	48	32	25	17	14	2
Cryotherapy eligible	112	2	16	37	21	19	11	5	1
Cryotherapy performed	90 (80%)	1 (50%)	11 (69%)	30 (81%)	18 (86%)	15 (79%)	9 (82%)	5 (100%)	5 (100%)
Cryotherapy ineligible & referred for LLETZ	38	0	5	10	8	6	4	5	0

Abbreviations:
VIA-Visual inspection with ascetic acid;
LLETZ-Large loop excision of the transformation zone

Table 3. VIA-positivity and cryotherapy ineligibility by HIV status in Namibia (October 2018-June 2019)

	Yes	No	Total	Results of Chi-square test
VIA-positive				
HIV-positive	52	235	287	$\chi2=4.1$ $p=0.04$
HIV-negative	102	672	774	
Total	154	907	1061	
Cryotherapy ineligible				
HIV-positive	16	30	46	$\chi2=2.9$ $p=0.08$
HIV-negative	21	77	98	
Total	37	107	144	

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INVESTIGATING INTRA-HOST GENOMIC EVENTS OF HPV 31, HPV33 AND HPV45 POSITIVE CERVICAL SAMPLES USING DEEP SEQUENCING

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: Recent studies have revealed extensive intra-host nucleotide variation in the human papillomavirus (HPV) genomes. The variation differs between HPV types and morphologies, and there are indications that HPV acquires some of this variation through mutagenic processes, including APOBEC, which fuels intra-host viral evolution and adaptation. This study aims to investigate the nature and extent of the intra-host genomic events of HPV31, HPV33 and HPV45, broadening our understanding of the less frequently studied HPV types, using deep sequencing technology.
Methods: HPV31 (n=117), HPV33 (n=104) and HPV45 (n=66) positive cervical samples, categorized into the four diagnostic categories normal/ASCUS/LSIL (n=55), CIN2 (n=51), CIN3 (n=170) and ICC (n=11), were sequenced using the HPV whole genome deep sequencing TaME-seq protocol to allow simultaneous study of nucleotide variation, genomic deletions and chromosomal integrations.
Results: In total, 241 samples had a mean coverage more than 300× reads and were included in the analyses. Preliminary results indicate that HPV31 positive samples have the largest proportion of integration sites and that the number of integrations per sample increases with lesion severity. In addition, we observe clear mutational signatures of APOBEC activity in some of the samples, as well as differences in HPV nucleotide variation.
Conclusions: Intra-host genomic events analyses of HPV31, HPV33 and HPV45, showed distinct type-specific and morphology-specific profiles. These results are important for understanding differences in biology and pathogenicity of the lesser-studied oncogenic HPV types relative to HPV16/18 and broadens our understanding of the molecular mechanisms behind HPV-driven carcinogenesis.

CERVICAL CANCER TREATMENT AND REFERRAL COMPLETION RATES BY HIV STATUS: THE FIRST 8-MONTHS OF VIAC IMPLEMENTATION IN NAMIBIA

CLINICAL RESEARCH /TREATMENT OF PRECANCER IN LOW-RESOURCE SETTINGS

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Introduction: Women in Namibia experience geographic and other barriers in accessing cervical cancer screening and treatment services. In 2018, the Ministry of Health and Social Services introduced a screen and treat approach with visual inspection with acetic acid and cryotherapy (VIAC). Namibia has high HIV prevalence (15.7% among women aged 15–64 years) and increasing cervical cancer mortality rates. A review of the literature found no studies in Namibia, or generally, comparing treatment rates in women with cervical pre-cancer lesions stratified by HIV status. To address this gap, we compared cryotherapy completion rates in HIV-positive and HIV-negative women who screen VIA-positive in Namibia.
Methods: Routine program data from the first 8 months (October 2018-June 2019) of Namibia's VIAC implementation in the Khomas region at CDC-funded facilities were used to analyze cryotherapy completion rates and large loop excision of the transformation zone (LLETZ) referral between HIV-positive and HIV-negative women. A chi-square test was performed to examine whether the difference in the cryotherapy completion percentages between HIV-positive and HIV-negative women was significant.
Results: More HIV-positive women (86%) completed cryotherapy than HIV-negative women (75%) across age groups (Table 1), however the relationship was not statistically significant (p=.0581) (Table 2). All women screened ineligible for cryotherapy were referred for LLETZ treatment, however, LLETZ completion data are not available at this time.
Conclusions: HIV-positive women with cervical pre-cancer lesions in Namibia were not significantly more likely to complete cryotherapy treatment. Further analyses with a larger and more diverse samples from other regions in Namibia are needed to confirm these findings. Additional data are needed to identify strategies to improve cryotherapy treatment completion rates among all eligible women. Specific areas for further exploration include comparing women's comfort level with healthcare system interactions, readiness to accept medical diagnoses, and healthcare worker engagement and prioritization of HIV-positive women.

Table 1. Treatment and referral of women with cervical pre-cancer lesions by age at first screening, lesion severity, and HIV status in Namibia (October 2018-June 2019)

		Age (years)							
	Total	**15-19**	**20-24**	**25-29**	**30-34**	**35-39**	**40-44**	**45-49**	**≥50**
HIV-positive									
VIA-positive	146	0	6	7	19	38	48	22	6
Cryotherapy eligible	73	0	4	2	11	24	24	5	3
Cryotherapy performed	63 (86%)	0 (0%)	3 (75%)	2 (100%)	10 (91%)	16 (67%)	22 (92%)	7 (140%)*	3 (100%)
Cryotherapy ineligible & LLETZ referred	73	0	2	5	8	14	24	17	3
HIV-negative									
VIA-positive	170	2	19	60	35	23	12	17	2
Cryotherapy eligible	128	2	15	48	26	17	9	9	2
Cryotherapy performed	96 (75%)	1 (50%)	11 (73%)	37 (77%)	21 (81%)	12 (71%)	6 (67%)	6 (67%)	2 (100%)
Cryotherapy ineligible & LLETZ referred	42	0	4	12	9	6	3	8	0

**Cryotherapy performed among HIV-positive women 45-49 includes two referral cases whose screening data had not been captured at referring facility and not captured at receiving facility to avoid double counting*

Abbreviations:
VIA-Visual inspection with ascetic acid;
LLETZ-Large loop excision of the transformation zone

Table 2. Cryotherapy completion by HIV status in Namibia (October 2018-June 2019)

	Cryotherapy completed			
	Yes	**No**	**Total**	**Results of Chi-square test**
HIV-positive	63	10	73	$\chi^2=3.592$
HIV-negative	96	32	128	$p=0.0581$
Total	159	42	201	

GLOBAL LEARNINGS FROM HPV VACCINE INTRODUCTIONS AT SCALE

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2018 record number of low and middle income countries (LMIC) introduced HPV vaccine. Most introductions happened at scale and in different contexts afforded opportunities for learnings to inform other countries with national introductions. Jhpiego, a Johns Hopkins University affiliate, with funding from Gavi-The Vaccine Alliance and in collaboration with partners, supported HPV vaccine introductions in Tanzania, Ethiopia and Sikkim state of India in 2018.
Methods: We analyzed and mapped publically available coverage data against the program review findings to generate learnings that can inform subsequent national HPV vaccine introductions.
Results: With countries adopting facility based, school based and community outreach vaccine delivery approaches, majority states/regions achieved >70% coverage for the first dose of HPV. However, the coverage for the second dose was suboptimal, with majority of regions/states, though not all, reporting <50% coverage. For the first dose, denominators used for calculating coverage were much lower than the actual coverage, making it difficult to use coverage data for decision-making. Data-systems did not capture coverage data for out of school (OOS) and HIV+ girls, limiting the understanding of equitability of coverage.
Conclusions: Achieving high coverage with both doses of HPV vaccination needs meticulous planning and appropriate operational strategies. There are examples of some regions like Iringa and Sikkim achieving high coverage with two doses in these countries, demonstrating the feasibility of achieving the same for other regions with strategic planning and strong execution. Simple, unambiguous definition of eligible population along with use of appropriate denominators for evaluating coverage of vaccination is important for meaningful use of data for decision-making. Achieving high absolute coverage should not take away attention from achieving equitable coverage. There is a need for measurement of coverage among vulnerable groups like OOS and HIV+ girls to ensure understanding and intentional planning for reaching them.

SOCIODEMOGRAPHIC CHARACTERISTICS OF YOUNG ADULTS WITH HOMOSEXUAL RELATIONSHIPS IN THE POP-BRAZIL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Same-sex marriage was declared legal in Brazil in 2013 and since then, epidemiological characteristics about this population received more attention. Furthermore, these individuals still having higher barriers in accessing healthcare and are more susceptible to sexually transmitted infections. This study aimed to evaluate sociodemographic characteristics and prevalence of HPV among men and women (16-25 years) with same-sex relationships in Brazil.
Methods: A cross-sectional study conducted with 7,694 individuals from public primary care units of all country (POP-Brazil) collected data on sociodemographic and behavioral characteristics, and trained health professionals collected genital biological samples. HPV detection and genotyping were performed using Linear Array. Individuals who reported same-sex partnerships in the last 5 years were considered having same-sex relationships. Socioeconomic class was analyzed by using the ABEP Criteria. Data were weighted by sex and population of each capital.
Results: Valid data were obtained from 6,666 participants. Of these, 7.62% reported same-sex relationships, with higher proportion in men (11.90%) than women (3.65%; $p<0.001$). Being married was more frequent in women with heterosexual (45.66%) than same-sex relationships (24.17%) ($p<0.001$). Among men, only 3.25% of same-sex relationships individuals were married compared to 28.92% of heterosexual. Both men and women in same-sex relationships have higher educational level than heterosexuals (39.45% vs. 21.36% among men and 39.98% vs. 18.94% among women, $p<0.001$). Regarding social class, women with same-sex partners are more frequently from higher social classes A-B (20.21%) compared to those with heterosexual relations (12.29%, $p<0.016$). There was no differences in social class among men. Regarding the prevalence of overall HPV, there was no significant difference between same-sex (54.08%) and heterosexuals (57.26%, $p=0.566$) relationships.
Conclusions: Even with known differences in sexual behavior among same-sex relationships, HPV prevalence was similar to heterosexual individuals. The important difference found in sociodemographic and behavioral data can be used to establish and direct evidence-based interventions.

PREVALENCE OF HUMAN PAPILLOMAVIRUS INFECTION AND OTHER SEXUALLY TRANSMITTED INFECTIONS (STIS) IN WOMEN FROM THE BRAZILIAN STATE OF MARANHÃO

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Sexually transmitted infections (STIs) can contribute to Human papillomavirus (HPV) infection persistence and cervical lesion progression. Therefore, this study aimed to evaluate the presence of HPV, Chlamydia trachomatis, Neisseria gonorrhoeae, and Trichomonas vaginalis in women of São Luís - MA.
Methods: This is a descriptive and cross-sectional study of 353 women treated at a gynecology service of Basic Health Units. All women agreed to participate in the study by signing an informed consent form and answered a sociodemographic questionnaire. Samples of cervical swabs were collected and analyzed by PCR to detect HPV (primers PGMY09/11 and GP5+5/+6) and the microorganisms *Chlamydia trachomatis* (KL1/KL2), *Trichomonas vaginalis* (TVA5/TVA6) and *Neisseria gonorrhoeae* (HO1/HO3). HPV positive samples were submitted to automated sequencing for viral genotyping.
Results: Of the 353 women evaluated, 211 (59.7%) had HPV infection. Among HPV positive women, the presence of co-infections (147/69.6%) was higher than HPV infection alone (64/30.3%). In women who had HPV/STI co-infection, HPV was associated with one secondary infection (93/63.3%) ($p<0.05$). Among women who had T. vaginalis infection, 73.5% also had HPV ($p<0.005$). In women with HPV only, HPV16 (15.6%) was predominant, followed by HPV11 (14.06%) and other low-risk types (12.50%). In women with HPV/STI co-infections, HPV16 (14.2%), HPV18 (6.8%) and other high-risk types (13.6%) were predominant. The population profile was 35-44-year-old women with an income below one minimum wage, married/stable union, reported no previous STIs, and reported not using condoms during sexual intercourse.
Conclusions: High prevalence of HPV was observed, as well as other STIs among the women participating in this study. In women who presented co-infections, a high prevalence of high risk HPV was observed.

PERSISTENT HPV AS A CLINICAL INDICATOR OF THE PRESENCE OF PRECANCER REQUIRING LEEP TREATMENT

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Current clinical standard usually requires histologic confirmation of precancer before treatment. We investigated if persistent HPV in women aged 18-39 without prior biopsy confirmation yields similar rates of underlying precancer as those with prior biopsy confirmation, as a potential clinical indicator for LEEP.
Methods: In the Costa Rica Vaccine Trial, 7466 women were randomized to HPV or control vaccine and followed annually 4 years. HPV-vaccinated participants were invited to long-term follow-up (LTFU) for 6 more years at two-year intervals. Additionally, 2,836 unvaccinated women from the same areas and cohorts were enrolled as a new control group. All women were followed with cytology and HPV tests. When screening resulted in biopsy confirmed cervical precancer; women were offered LEEP. In the absence of biopsy confirmation, after discussion of individual cases, we performed diagnostic LEEPs on women with persistent HPV infection or high-grade colposcopy impression. Here, we included all women with a LEEP regardless of the indication (histologic CIN2+, persistent HPV infection, other [i.e. high-grade cytology or colposcopy]), and compared the percentage of women with CIN2+ on the diagnostic LEEP specimen to therapeutic LEEP (i.e. biopsy-confirmed). We further estimated disease recurrence post-LEEP.
Results: 47.5% of those with LEEP had CIN2+, regardless of preceding biopsy suggesting CIN2+ (46.5%,), persistent infection without evidence of HSIL/CIN2+ (54.3%;), or other reasons (45.0%;). Among diagnostic LEEPs in women with persistent HPV, the proportion with underlying precancer was significantly higher for women with persistent HPV16/18/45 compared to persistent non-HPV16/18/45 (75.5% vs 36.5%; p=<0.0001) regardless of presence of histologically confirmed CIN2+. Recurrence after LEEP was low in all groups (Table).

Table 1. Final diagnosis on women who had LEEP and recurrence of HSIL+/CIN2+ post-treatment.

					Reasons for LEEP					
		Irrespective of HPV type			Persistent HPV16/18/45 infection (immediately preceding or at LEEP)			Persistent non-HPV16/18/45 infection (immediately preceding or at LEEP)		
	Total	CIN2 + in biopsy	HVP persistent in Absence of HSIL/CIN2+ in biopsy	Other reasons	CIN2 + in biopsy	Absence of HSIL/CIN2+ in biopsy	Other reasons	CIN2+ in biopsy	Absence of HSIL/CIN2+ in biopsy	Other reasons
	(n=885)	(n=729)	(n=116)	(n=40)	(n=280)	(n=53)	(n=6)	(n=449)	(n=63)	(n=34)
Final Consensus Diagnosis										
Review incomplete	**27 (3.1%)**	**26 (3,5%)**	**0 (0,0%)**	**1 (2,5%)**	7 (2.5%)	0 (0.0%)	0 (0.0%)	19 (4.2%)	0 (0.0%)	1 (2.9%)
<CIN2	**438 (49.5%)**	**364 (49.9%)**	**53 (45,6%)**	**21 (52,5%)**	96 (34.3%)	13 (24.5%)	1 (16.7%)	268 (4.2%)	40 (63.5%)	20 (58.8%)
CIN2+	**420 (47.5%)**	**339 (46.5%)**	**63 (54,3%)**	**18 (45%)**	177 (63.2%)	40 (75.5%)	5 (83.3%)	162 (36.1%)	23 (36.5%)	13 (38.2%)
Recurrence of HSIL+/CIN2+										
No follow-up	**51 (5.8%)**	**42 (5,8%)**	**4 (3,4%)**	**5 (12,5%)**	8 (2.9%)	2 (3.8%)	2 (33.3%)	34 (7.6%)	2 (3.2%)	3 (8.8%)
Follow-up <HSIL and CIN2	**804 (90.8%)**	**664 (91,1%)**	**108 (93,1%)**	**32 (80%)**	263 (93.9%)	49 (3.8%)	4 (66.7%)	401 (89.3%)	59 (93.7%)	28 (82.4%)
HSIL+ and/or CIN2+	**30 (3.4%)**	**23 (3,1%)**	**4 (3,4%)**	**3 (7,5%)**	9 (3.2%)	2 (3.8%)	0 (0.0%)	14 (3.1%)	2 (3.2%)	3 (8.8%)

Conclusions: In the absence of histologic confirmation of high-grade disease, our data support diagnostic LEEP in the presence of persistent HPV infection, particularly for HPV 16/18/45 infections. LEEP remains a highly effective treatment with low recurrence.

A NEW PEPTIDE MOTIF TARGETING HPV16 E6 ONCOPROTEIN

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Although prophylactic vaccination prevents HPV infections, there is no specific treatment for infected individuals. Thus, targeting high-risk HPV E6 and E7 oncoproteins, which play essential roles in HPV infection and progression to carcinogenesis, represents a promising therapeutic approach. Since E6 has low similarity with cellular proteins and its silencing leads to apoptosis, specific targeting of this protein seems an ideal strategy to treat HPV-dependent tumors. Here we used phage display to identify a new peptide motif that may help achieve such goal.
Methods: Recombinant HPV16 E6 (carrying no cysteine mutations) fused to gluthatione-S-transferase (GST) protein (GST-E6) was purified by affinity chromatography, immobilized (1µg) on 96-well plates and utilized for phage display selection. Two phage libraries were used: X6 and CX8C, whereas X = any amino acid; C = cysteine. To minimize selection of unwanted peptides, libraries were pre-cleared against GST prior to selection on GST-E6. After three rounds of biopanning, we sequenced DNA from individual clones to identify the corresponding displayed peptides, and tested them for specificity against GST-E6, GST or controls (E7 and BSA).
Results: We observed significant phage enrichment after three rounds of selection using both libraries: 3,300x (X6) and 38x (CX8C). DNA sequencing of individual clones revealed four distinct peptides containing a common motif selected from the X6 library. Curiously, three of them were longer than six amino acids. All four peptides bind specifically to GST-E6 ($p<0,0001$) and competition with soluble GST-E6 but not GST prevented all individual phages binding to GST-E6, further confirming their specificity toward the E6 domain of the fusion protein. We have not yet validated peptides from the CX8C library.
Conclusions: In sum, we have successfully identified and validated a new HPV16 E6 binding motif, which might be an important lead for developing more specific and less toxic therapies for HPV.

EFFECTIVENESS OF INFRARED COAGULATION FOR THE TREATMENT OF HIGH-GRADE ANAL DYSPLASIA IN HIV-INFECTED WOMEN AND MEN. RETROSPECTIVE COHORT STUDY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: To assess risk factors for recurrence after anal dysplasia treatment in an HIV-infected population

Methods: Longitudinal retrospective single-centre study with descriptive analysis of our recurrence results after the treatment with infrared coagulation of high-grade anal intraepithelial neoplasia (HGAIN) in a HIV-infected population from 2012 and 2015.

Results: From our HIV-population of 665 patients, 81 were treated for HGAIN (80% Men and 20% Women, 43,1years). 20 patients recurred (25% women and 24.6% men), median recurrence time of 4 months (2-19m). HPV16 was more frequently found in women's cytology (55% vs. 40%, p=0.147), also in the cytology where recurrence was identified (100% vs. 47%, p=0.147). Women had also higher rate of dysplasia in cytology (ASCUS 6%, LSIL 31%, HSIL 63%) comparing to men (ASCUS 8%, LSIL 59%, 34% HSIL) (p=0.1), even in biopsy (63% AIN2, 37% AIN3 in women vs. 79% AIN2, 21% AIN3 in men, p=0.158). Every woman that recurred in their anal dysplasia had at least one abnormal cervical cytology in their gynaecologic history (25% ASCUS, 25% LSIL and 50% HSIL, p=0,062).
Conclusions: Although recurrence after treatment is similar between genres, women have higher prevalence of HPV16 infection and higher rates of dysplasia comparing to men. A careful follow-up is needed in these patients.

REACHING UNDER-SCREENED/NEVER SCREENED INDIGENOUS PEOPLES: HPV SELF-TESTING

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Indigenous and minority peoples face a greater burden of cervical cancer morbidity and mortality than non-indigenous/non-minority peoples. These inequities are unjust and unacceptable. In New Zealand, the National Cervical Screening Program (NCSP) (standard cytology), is failing indigenous Māori women, with 33% under-screened compared to 24% of European women. Māori women are twice as likely to die of this preventable cancer. Self-collected specimens for HPV testing provide screening comparable to clinician-collected specimens. He Tapu Te Whare Tangata (sacred house of humankind), a community based RCT, offered HPV self-testing to under-screened Māori women in partnership with Māori communities and primary care aiming to increase cervical screening coverage.
Methods: Inclusion criteria were Māori women aged 25-69 years, with no cervical smear in 4 years or more. Six rural primary care clinics were randomised to intervention (offer of HPV self-test) or control (usual offer of cervical smear). Recruitment was March 2018 to August 2019 inclusive. HPV genotyping used the Abbott Real-time HPV assay distinguishing HPV16 and 18 from other high-risk types and negative samples. For analysis, NCSP data was obtained with cervical screening history for both groups. Logistic regression enabled comparisons of acceptance rate by intervention versus control.
Results: Of 519 eligible women in the intervention group, 310 (59.7%) were screened by HPV self-test (n=226, 72.9%), HPV self-test and smear (n=38, 12.3%) or smear only (n=46, 14.8%). Of 451 eligible women in the control group 97 (21.5%) had a cervical smear. Overall screening risk ratio for intervention vs control was 2.8 (95% CI: 2.3-3.4) p-value $<2.2 \times 10^{-16}$.
Conclusions: HPV self testing has the potential to half the number of under-screened Māori women. Utilising outreach health workers contributed to the high uptake. HPV self-testing could substantially decrease cervical cancer disparities for Indigenous peoples in high- income countries and should be urgently introduced as a routine standard of care.

SUPERIOR ACCURACY IN CERVICAL DYSPLASIA DETECTION BY MULTIPLEXED HPV ONCOGENE AND BIOMARKER EXPRESSION QUANTITATION USING QUANTIGENE PLEX 2.0 ASSAY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Cervical cancer and pre-malignant dysplasia are caused by HPV-infections and accompanied by cellular biomarker upregulation. Screening programs switch from cytology to HPV-based testing. While HPV-tests have a higher sensitivity (95% vs. 50%), the specificity is unsatisfactorily low (<40%). The addition of expression quantitation of cellular progression-associated biomarkers enhances specificity and allows for diagnosis of dysplastic stages. A combination of both methods provides the QuantiGene 2.0 platform, enabling efficient multiplexed mRNA quantitation.
Methods: A multiplexed QuantiGene 2.0 assay (QuantiGene-Molecular-Profiling-Histology, QG-MPH) individually quantifying oncogene (E7) mRNA of 18 high-risk HPV-genotypes, cellular housekeeping genes, and 10 well established cellular biomarkers was designed. On a referral population Logistic Regression and ROC-analyses were performed and risk scores and related cut-off values were calculated for disease stages CIN2+, CIN3+, and CxCa. A nested sample set (550 patients) of a population-based cohort (MARZY real-world study, Mainz, Germany) was reanalysed. The risk score results were compared to standard screening methods (PAP, LBC, HC2, GP5+/6+-PCR) and four different co-testing variants (PAP+HC2, PAP+PCR, LBC+HC2, LBC+PCR). Histological endpoints CIN2+ and CIN3+ were evaluated.
Results: 61 women (all peculiar plus 5% randomly selected healthy women) of the MARZY study population had a histology result. Of those, nine CIN2+ and six CIN3+ were histologically confirmed. Sensitivity and specificity for detection by QuantiGene risk scores was 67% and 83% for CIN2+ and 83% and 82% for CIN3+, respectively. Cytology was less sensitive (PAP: 33%; LBC: 40%) and similarly specific (PAP: 80%; LBC: 80%) for the detection of CIN3+. The HPV-tests and the four co-testing strategies had similar sensitivities (83%) but lower specificities (range 27-67%).
Conclusions: Due to significantly higher specificity and equal sensitivity compared to all HPV- and co-testing approaches in group CIN3+, the QuantiGene-based QG-MPH assay presents an attractive method for cervical cancer screening. These data warrant further assay evaluation in lager screening cohorts.

IMPLEMENTATION OF HPV SCREENING IN IQUITOS, PERU

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: We used a participatory action research approach to select a feasible cervical cancer screening program for a single micronetwork (N=20,000 screen-eligible women 30-49 years) in the District of Loreto, Iquitos Peru. HPV-based testing followed by visual assessment for ablative therapy (VAT) was implemented in ministry primary health clinics in July 2019.
Methods: Women aged 30-49 years were screened for high-risk HPV using either clinician-collected or self-collected swabs tested with the GeneXpert HPV assay from July 2019. Screening coverage was estimated for HPV testing as the monthly average needed to screen 20,000 women over 5 years (N=333 per month) and for VIA/Pap as the monthly average needed to screen 20,000 women over 3 years (N=555 per month).
Results: In 2018, the Iquitos South micronetwork screened 1282 women aged 30-49 years by VIA or Pap, 19% of the total screen-eligible population and 27% of WHO elimination goals of 70% of the population screened. Beginning in July 2019, the health system implemented a HPV-based screen-and-treat program. In the first 6 months of the HPV-based program, the system screened 303 women per month (90% coverage). 18% of were positive for HR-HPV, and as of January 1, 2020, 41% had a visual inspection with 80% treated by thermal ablation and 20% referred for alternative treatment at the hospital level.
Conclusions: Using a strategy of systems thinking and participatory action research to prepare the health system for a new screening strategy, we moved screening coverage from 19% to 90% in the first 6 months of implementation (~56% self-collected and 44% clinician collected samples). Details on provider and patient satisfaction with the new screening system will be presented. Our experience provides a blue print for health system strengthening prior to implementation of new screening technologies in low- and middle-income countries.

ELEVATED PGE2 LEVELS IN HPV16+ HEAD AND NECK CANCERS AND AUTOLOGOUS PBMC THAT NORMALIZES FOLLOWING SUCCESSFUL TREATMENT: A BIOMARKER FOR THE BEST USE OF NSAIDS?

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Head and neck cancer is the 7th most common cancer worldwide causing >1.5% of all cancer deaths in the USA. $HPV16^+$ oropharynx cancer in the US rose from 16.3% (1980s) to >72.7% (2000s). Despite a better prognosis for $HPV16^+$ vs. HPV^- tumors, substantial morbidity and poor quality of life is the same for both groups since both groups are treated similarly. Reducing treatment intensity for $HPV16^+$ tumors may increase mortality. One third of patients have *PI3KCA* gene amplification/gain-of-function point mutations, results in increased tumor COX-2 expression. Additionally, patients with elevated PI3K activity taking NSAIDs had improved outcomes. In this study we asked whether patients with HPV+ oropharyngeal cancers had elevated plasma PGE_2 levels, and whether it correlated with tumor COX-2 expression.
Methods: Plasma PGE_2 was measured by ELISA. *COX2* and *PGE_2 synthase* mRNA expression was measured by q-PCR in tumor and contralateral tissues of patients and normal tonsils, and in PBMC of patients and controls.
Results: One third of $HPV16^+$ patients had elevated plasma PGE_2 levels when compared to $HPV16^-$ patients or controls. Repeat measurement of a subset of patients with elevated plasma PGE_2 showed that levels dropped to normal 1-3 years after successful treatment. PBMC from $HPV16^+$ patients expressed more *COX-2* and *PGE_2 synthase* than the tumors or contralateral clinically normal issues, or control PBMC.
Conclusions: Elevated PGE_2 levels in $HPV16^+$ HNC patients returned to normal in patients free of disease following treatment. PGE_2 may thus be a biomarker of patients who could best benefit from NSAIDs and thereby personalize their care. Lower PGE_2 expression by $HPV16^+$ tumors/contralateral tissues vs. PBMC suggests that elevated tumor PI3K activity in patients with oropharynx cancer may cause elevated PBMC PGE_2 expression, suggesting that NSAIDs may not only impact tumor growth or survival, but modulate systemic immune functions in these patients.

HUMAN PAPILLOMAVIRUS INFECTION PREVALENCE, GENOTYPE DISTRIBUTION AND RISK FACTORS IN FEMALE SEX WORKERS IN BAMAKO (MALI), WEST AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: This study aimed to: (1) estimate the prevalence and genotype distribution of HPV among FSWs; (2) evaluate factors associated with low-risk (LR) and high risk (HR) HPV types.
Methods: We analyzed baseline data of 353 FSW aged ≥18 years recruited during a prospective cohort study in Bamako (Mali) from 2017 to 2018. The Linear Array HPV genotyping test was used to identify the HPV genotypes. The cross-reactivity between HPV52 and HPV-33, 35 or 58 was further tested with a real-time PCR assay specific for HPV52. Descriptive statistics and multivariate log-binomial regression were used. Adjusted prevalence ratio (APR) with 95% confidence intervals (95%CI) were estimated.
Results: The mean age was 26.78 years and the age at first sexual intercourse was 15.3 years. HIV prevalence was 20.4%, while 35.1% of the FSWs had at least one other curable sexually transmitted infection. Bacterial vaginosis (BV) prevalence with Nugent score ≥ 7 was 23.5%. HPV data were available for 350 FSWs. We found that 62.3% of the FSWs were positive for at least one HR-HPV, whereas 55.4% of FSWs were positive for at least one LR-HPV. The most frequent HR-HPV types were: HPV16 (15.7%), HPV51 (14.3%), HPV52 and HPV35 (12.3% each), HPV58 (23.3%), HPV45 (11.7%). The most frequent LR-HPV types were: HPV62 (15.1%), HPV61 (12.9%), HPV84 (10.6%), HPV81 (9.7%) and HPV83 (8.6%). The main two factors associated with HR-HPV infections were HIV infection (APR = 1.31; 95%CI:1.09 – 1.57) and BV (APR = 1.22; 95%CI: 1.02 – 1.45). The same factors were associated with LR-HPV: HIV infection (APR = 1.59; 95%CI: 1.31 – 1.93), and BV (APR = 1.33; 95%CI: 1.09 – 1.62).
Conclusions: We found a high prevalence of HPV infection in FSWs in Mali. HPV16 was the predominant one in this group. These finding suggest the necessity of cervical cancer prevention in this population.

SQUAMOUS INTRAEPITHELIAL LESIONS AND RISK FACTORS ASSOCIATED AMONG FEMALE SEX WORKERS IN BAMAKO (MALI), WEST AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: There is no data on precancerous lesions of cervix in female sex workers (FSW) in Mali. This work aimed to estimate the prevalence and risk factors of cervical precancerous lesions among FSW in Mali.
Methods: We analyzed baseline data from a cohort study between November 2017 to February 2018 in Mali. Screening for cervical cancer was performed with Papanicolaou test. HIV and syphilis serology, and nucleic acid amplification tests for gonorrhea and chlamydia were also carried out. The Linear Array HPV genotyping test was used to identify the HPV genotypes. Risk factors of low grade squamous intraepithelial lesions (LSIL), and high grade squamous intraepithelial lesion (HSIL) were identified using polytomous logistic regression. Adjusted odd ratios (AOR) with 95% confidence intervals (95%CI) were estimated.
Results: A total of 353 FSWs were enrolled. The prevalence rates of high-risk HPV and low-risk HPV were respectively 62.3% and 55.4%. About 20.4% were HIV seropositive, whereas 35.1% had other sexually transmitted infections (STIs). These STI were: trichomoniasis (3.7%), chlamydia (14.0%), gonorrhea (24.4%), and syphilis (3.1%). Fifty-eight FSWs had abnormal cytology (17.4%) and only 8.8% of FSW had at least one cervical screening test in the past year. About 2.7% of FSWs had an ASCUS, while 11.3% and 3.3% had respectively LSIL and HSIL. Risk factor of LSIL was mainly HPV35 (AOR = 1.65; 95%CI: 1.05 – 2.59). Factors associated with HSIL were gonorrhea (AOR = 3.00; 95%CI: 1.03 – 8.77, current syphilis (AOR = 9.84; 95%CI: 2.20 – 44.08) and self-reported previous STIs (AOR = 3.60; 95%CI: 1.06 – 12.30).
Conclusions: Very high level of other STIs in FSWs are associated with cervical intraepithelial lesions prevalence. Better STI management strategies in this specific group is needed, which can help to prevent HPV infection and cervical lesion.

PERSISTENCE OF HPV IS ASSOCIATED WITH HIV INFECTION IN KENYAN WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: As opposed to other HIV-associated malignancies, the incidence of cervical cancer has not declined in the era of anti-retroviral treatment (ART). A longitudinal study was initiated in Kenya to investigate associations of factors associated with persistent detection of HPV.
Methods: HIV-uninfected women (n=106) and HIV-infected women (n=116) without cervical dysplasia were enrolled in a longitudinal study. Demographic/behavioral data and cervical swabs were collected at enrollment and annually for two years. HPV typing was performed on swabs (Roche Linear Array). Women attending at least one of the two follow-up visits were included in an analysis of HPV persistence, defined as having the same type-specific HPV detected for at least two visits (Enrollment, Year 1, or Year 2). Two sets of logistic regression models were fit: one based on type-specific HPV detection records, and one based on study participants, to examine associations between HPV persistence and HIV infection. All logistic regression models were adjusted for demographic and behavioral characteristics.
Results: The analytical sample consisted of 82 HIV-uninfected and 101 HIV-infected women; HIV-infected women were older, less likely to be married and to own a home, and had more lifetime sexual partners. At enrollment, all HIV-infected women were receiving ART (from medical records); CD4 counts and HIV viral loads are shown in Table 1. In regression models, persistent HPV detection was significantly associated with HIV infection for any HPV type, oncogenic HPV types, IARC-classified oncogenic HPV types, and non-oncogenic HPV types (Table 2).

Table 1. CD4 and HIV viral loads for HIV-infected women

CD4 Count (cells/μL)

Visit	N of women in analysis	N of women with available CD4	CD4 for women with available CD4		
			Median	25% Percentile	75% Percentile
Enrollment	101	98	538	379	771
1st Annual	92	90	598	438	715
2nd Annual	86	60	620	453	891

HIV Viral Load (copies/mL)

Visit	N of women in analysis	N of women with available HIV viral load	N of women with undetectable HIV viral load	N of women with detectable HIV viral load	Viral load for women with detectable HIV viral load		
					Median	25% Percentile	75% Percentile
Enrollment	101	101	74	27	5739	140	23091
1st Annual	92	90	81	9	4013	218	7081
2nd Annual	86	77	73	4	90	48	5698

Table 2. Logistic regression analysis of associations of persistent HPV detection with HIV status and characteristics of Kenyan women

Variables	Any HPV[1]		HR HPV[2]		IARC HR-HPV[3]		LR-HPV[4]	
Analysis based on type-specific HPV detection records (n=6771)[5]	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
HIV-infected	4.01 (2.16-7.45)	<.001	2.44 (1.29-4.63)	0.006	2.53 (1.25-5.12)	0.010	26.99 (3.58-203.66)	0.001
Age	0.97 (0.94-1.00)	0.033	0.94 (0.90-0.98)	0.003	0.94 (0.89-0.99)	0.012	1.01 (0.96-1.06)	0.769
Married	0.60 (0.33-1.10)	0.096	0.59 (0.32-1.11)	0.100	0.45 (0.22-0.92)	0.028	0.60 (0.22-1.58)	0.299
More than secondary school education	0.69 (0.30-1.56)	0.369	0.60 (0.22-1.70)	0.339	0.53 (0.16-1.81)	0.313	0.77 (0.21-2.85)	0.695
Home ownership	0.71 (0.35-1.48)	0.366	0.91 (0.42-1.99)	0.822	1.17 (0.50-2.75)	0.718	0.46 (0.14-1.52)	0.201
Walking distance to health care ≥60 mins	1.27 (0.74-2.17)	0.391	1.05 (0.54-2.02)	0.888	0.86 (0.36-2.02)	0.722	1.62 (0.72-3.64)	0.245
Number of lifetime sex partners	1.00 (1.00-1.01)	0.377	0.99 (0.97-1.01)	0.308	1.00 (0.98-1.01)	0.548	1.01 (1.00-1.01)	<.001
Age of first sex	1.07 (0.98-1.16)	0.129	1.04 (0.94-1.16)	0.442	1.10 (0.97-1.24)	0.144	1.11 (0.99-1.24)	0.071
Analysis based on women participating in study (n=183)	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
HIV-infected	4.03 (1.85-8.76)	<.001	2.71 (1.21-6.08)	0.016	2.72 (1.12-6.61)	0.028	26.96 (3.29-220.64)	0.002
Age	0.97 (0.91-1.03)	0.292	0.94 (0.89-1.00)	0.055	0.94 (0.88-1.00)	0.052	1.03 (0.95-1.11)	0.463
Married	0.51 (0.24-1.08)	0.078	0.54 (0.24-1.21)	0.137	0.36 (0.14-0.87)	0.024	0.35 (0.12-1.06)	0.063
More than secondary school education	0.91 (0.30-2.76)	0.861	0.70 (0.21-2.38)	0.567	0.56 (0.14-2.24)	0.414	1.49 (0.30-7.33)	0.626
Home ownership	0.89 (0.36-2.18)	0.797	1.01 (0.39-2.59)	0.989	1.29 (0.47-3.57)	0.620	0.61 (0.15-2.52)	0.497
Walking distance to health care ≥60 mins	1.19 (0.45-3.12)	0.730	0.97 (0.35-2.67)	0.953	0.67 (0.22-2.10)	0.494	1.60 (0.47-5.39)	0.448
Number of lifetime sex partners	1.02 (0.97-1.07)	0.379	0.98 (0.94-1.03)	0.534	0.99 (0.95-1.03)	0.647	1.03 (0.98-1.08)	0.302
Age of first sex	1.09 (0.97-1.23)	0.137	1.06 (0.93-1.20)	0.385	1.13 (0.99-1.29)	0.081	1.15 (0.96-1.37)	0.121

[1]Any HPV: HPV 16,18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39
[2]HR-HPV (High-Risk HPV): HPV 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 67, 68, 69, 70, 73, 82, IS39
[3]IARC HR-HPV: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66
[4]LR-HPV (Low Risk HPV): HPV 6, 11, 40, 42, 54, 55, 61, 62, 64, 71, 72, 81, 83, 84, CP6108
[5]Each women participated in study had 37 type-specific HPV "detection records" of HPV persistence, therefore there was a total of 183×37=6771 type-specific HPV detection records

Conclusions: Persistent detection of oncogenic and non-oncogenic HPV types was strongly associated with HIV infection in Kenyan women without cervical dysplasia. Further studies are needed to identify immunological defects in HIV-infected women taking ART and have satisfactory CD4 counts and HIV viral loads, as these women still suffer from a high burden of cervical cancer.

REDUCED COVERAGE OF HPV VACCINE TYPES IN CERVICAL PRECANCER AMONG HIV-INFECTED; A POPULATION-BASED REGISTRY STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: We wished to study to which extent cervical precancer (CIN2+) in women living with HIV (WLWH) is caused by HPV types targeted by vaccination. The Swedish National HIV registry (InfCareHIV) includes all WLWH in Sweden and these women have an increased risk of CIN2+ (Carlander et al. IJC 2016) and of treatment failure of CIN2+ (Carlander et al. AIDS 2018). All cervical tissue blocks in this cohort and a control group were retrieved from archives and HPV-genotyped.
Methods: InfCareHIV, the Swedish Population Registry and the Swedish National Cervical Screening Registry were linked. We identified all WLWH with CIN2+ (68% migrants), living in Stockholm or Gothenburg sometime between 1983 and 2014. For each WLWH we randomly selected two HIV-negative women with CIN2+, matched for country of birth. Archived cervical tissue blocks were HPV-genotyped. HPV prevalence ratios (PR) were calculated with Poisson regression.
Results: 130 WLWH and 234 HIV-negative women had valid HPV genotype results. WLWH were less likely to have single or multiple HPV16 infections in CIN2 (13 vs. 40%, PR 0.3, 95% CI 0.15-0.78) but not in CIN3 (50 vs. 53%, PR 0.9, 95% CI 0.7-1.2). WLWH with CIN3 were four times more likely to have single or multiple HPV35 (11% vs. 3%, PR 4.4, 95% CI 1.3-14.3) and these women were mainly born in sub-Saharan Africa (>70%). HPV types targeted by the 9-valent vaccine were significantly less common in WLWH with CIN3 (63% vs. 88%, PR = 0.7, 95% CI 0.6-0.8) and significantly less common in immunosuppressed WLWH (CD4 count continuous, cells/µl, Ptrend= 0.003).
Conclusions: WLWH with cervical cancer in situ to a lower extent had HPV types targeted by vaccination, mainly driven by a higher prevalence of HPV35 in WLWH born in sub-Saharan Africa. Cervical screening remains important in WLWH, even when vaccinated.

HIGH PREVALENCE OF HUMAN PAPILLOMAVIRUS (HPV) TYPE 66 IN LOW-GRADE CERVICAL LESIONS OF MEXICAN WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: HPV-66 was originally detected in a biopsy of a 38 year old patient with squamous-cell carcinoma of the uterine cervix. Several papers have reported a variable prevalence of HPV-66, predominantly in premalignant lesions. HPV-66 is an α-PV from species 6 and belonging to a third phylogenetic branch unrelated to types 16 and 18. Indeed, E6 and E7 proteins from type 66 have been shown to degrade p53 and RB cellular proteins, with lower efficiency than other HR-HPV types. The aim of this study was to analyze the prevalence and possible associations between HR-HPVs in cervical lesions as well as the risk factors related with HR-HPV infections in Mexican women.
Methods: Cross-sectional study using 362 cervical samples collected between 2016 and 2017. Fourteen HR-HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) were detected by highly sensitive PCR amplification followed by reverse hybridization. Bivariate and multivariate analyses were performed to investigate the association between HPV types and risk factors among lesions
Results: Most samples were HR-HPV positive (83.43%). HPV-16 was the most prevalent among negative for intraepithelial lesions or malignancy (78.6%), high-grade squamous intraepithelial lesions (50%), and cervical cancer (58.2%). HPV-66 showed an unexpected high prevalence in atypical squamous cells of undetermined significance (50%), low-grade squamous intraepithelial lesions (45.7%), and only found 3.6% in cervical cancers. HPV-16 was significantly prevalent among women between 30-39 years, whereas types 66 and 52 were significantly associated when previously sexually transmitted disease had occurred ($p < 0.05$).
Conclusions: HPV-66 might be indicative of cervical lesions that will not progress to cancer. HPV-66 prevalence was unusually high in low-grade cervical lesions, in co-infection with HPV-51. HPV genotyping results obtained by methods that grouped type 66 with other HR-types should be interpreted with caution.

HPV 16/18-SPECIFIC MEMORY B-CELL RESPONSES IN WOMEN 8 YRS AFTER VACCINATION

BASIC RESEARCH / IMMUNOLOGY

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Introduction: HPV vaccines generate long-lasting immunity and persisting anti-VLP antibody levels up to 10 years post-vaccination. Long-term antibody production is dependent on immunological priming leading to long-lasting plasma cell responses. There is uncertainty about the optimal number of HPV vaccine doses, and the need for/timing of booster doses. This study was designed to develop and validate a previously described memory B-cell ELISpot to measure HPV-16/18-specific memory B-cells in HPV-vaccinated women.
Methods: METHODS Asymptomatic healthy HPV-vaccinated women aged 18-21 years attending a sexual health clinic were included. Blood was drawn for peripheral blood mononuclear cells isolation. ELISpots were conducted according to a Mabtech B cell protocol for total and antigen-specific IgG with antigen-down wells coated with either HPV 16 or 18 VLPs @12.5mg/mL. $1x10^5$ stimulated cells were applied to VLP-coated wells and cultured for 18-24hr @ 37°C 5% CO_2. Spots were manually counted and numbers adjusted to represent $1x10^5$ cells. Results are expressed as percentage VLP-specific spots/total IgG spots.
Results: RESULTS Eleven women were tested for responses to HPV-VLPs 16 and 18. All had received Cervarix; 7 were certain of 3 doses, 1 of 2 doses and 3 were unsure. All subjects had antigen-specific responses. In 10/11 cases B-cell responses to HPV-16 VLPs were higher than to HPV-18 VLPs (16 VLP response: range = 0.37 – 1.59, median = 0.93; 18 VLP response: range = 0.18 – 1.04, median = 0.36, Mann-Whitney U-test p=0.02).
Conclusions: CONCLUSIONS This community-based sample demonstrate HPV 16/18-specific memory B-cell responses at a median 8 years post-vaccination. This is the longest interval of HPV memory B-cell responses post-vaccination measured to date. The only comparable data is from 3-dose qHPV vaccinated 9-13 yr old girls measured at 7 months. 7.5 years later our levels are ~ 60% (HPV16) and ~ 40% (HPV18) of those, attesting to long-lasting HPV vaccine induced B-cell immunity.

PREVALENCE OF HUMAN PAPILLOMA VIRUS TYPES IN WOMEN WITH ABNORMAL CERVICAL CITOLOGY IN ZENICA-DOBOJ CANTON, BOSNIA AND HERZEGOVINA – FIRST REPORT

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: Determination of human papillomavirus (HPV) types in women is the key in preventing cervical cancer. Although there was (once) cytology-based cervical cancer screening programme, HPV-typing was unavailable in Zenica-Doboj Canton (ZDC) until 2018, and data about circulating HPV types from ZDC and Bosnia – Herzegovina (B&H) as a whole, are still missing and scarce, respectively. The aim was to determine prevalence of HPV types in abnormal Pap smear samples.
Methods: Cervical samples of 95 women admitted to our institution with abnormal Pap smear test (18 inflamation, 38 CIN 1, 32 CIN 2, 6 CIN 3 and one with unknown citology) (using Bathesda system) were analyzed for the presence and HPV-types, during the January 2018 to December 2019. Typization of high-risk HPV (HPV -16, HPV-18, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-56, HPV-58, HPV-59, HPV-66,HPV-68) was performed using Real-time PCR.
Results: A total of 79 samples were positive for HPV: 16 inflamation, 33 CIN 1, 24 CIN 2, 6 CIN 3, and one of unknown citology. Mean age of women was 46.5 years. HPV-16 was the most frequently detected, in 49 (62%) samples, mostly in co-infection with HPV-39, in (79.6%) cases. HPV-39, HPV-31 and HPV-18 were detected in 16 (20.3%), 14(17.7%)and 13 (16.5%) samples, respectively
Conclusions: This is the first report on HPV prevalence in ZDC. The reason for small number of analyzed patients is the high cost of HPV-typing analysis. In ZDC and in B&H, HPV screening programs from public health institutions are lacking, therefore, data about circulating HPV types in this geographical area are not unified and available. We report HPV-16 as most frequent type, in co-infection with HPV-39. It is important to provide and continue HPV prevalence monitoring, and to confirm co-infection patterns. In B&H no vaccination programme is available yet and one cannot evaluate the impact of HPV vaccine on genotype prevalence.

SCREENING OF HIGH RISK HPV GENOTYPES IN A UNIVERSITY HOSPITAL, ANKARA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Human papillomaviruses have been established as a risk factor for invasive carcinoma of the uterine cervix. HPV DNA detection provides an efficient method of screening and by real time PCR analysis oncogenic HPV types can be detected easily. In the present study, we aimed to screen the genotypes of HPV retrospectively in women with or without gynecological symptoms who admitted to a tertiary care university hospital in Ankara.
Methods: Totally 3782 cervical swab samples of women aged 18-68 years were sent to Medical Virology Laboratory from January 2017 to October 2019. Cervical swab samples were collected in Cell Collection Medium (Roche, Switzerland). Nucleic acid extraction and amplification of samples were done by an automated system (Cobas®4800, Roche, Switzerland). The test can detect 14 high-risk HPV (HR-HPV) types in a single analysis by providing individual results on the highest-risk genotypes, HPV 16 and HPV 18 and pooled results on other high-risk genotypes (OHR-HPV) (31,33,35,39,45,51,52,56,58,59,66,68).
Results: HPV DNA positivity was detected in 13% (490/3782) of the samples in 3 years. HPV type 16 and type 18 were detected in 2.1% and 0.8% of the samples, respectively. OHR-HPV types were found in 7.9% of the samples. Of the 1.6%, 0.4% and 0.1% samples had mix types with type 16+OHR-HPV, type 18+OHR-HPV and type 16+type18+OHR-HPV, respectively.
Conclusions: The results of this study presented the rates of high risk HPV genotypes of a university hospital in Ankara, in a 3 year process. It was observed that positivity rate of OHR-HPV (7.9%) was higher than the rates of type 16 (2.1%) and 18 (0.8%). This finding shows that other HPV types beside 16 and 18 are increasing. HPV vaccines are not in the national immunization program in Turkey yet, however they are available and the vaccination rates of women are increasing.

REPURPOSING FENOFIBRATE, AN ANTI-HYPERLIPIDEMIA DRUG, FOR HPV+ HEAD AND NECK SQUAMOUS CELL CARCINOMA

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Human papillomavirus-associated head and neck squamous cell carcinoma (HPV+ HNSCC) is now recognized as a distinct disease with unique biological underpinnings. Repression of p53 and pRb by viral oncoproteins E6/E7 is a critical mechanism of HPV+ HNSCC. Effective drugs to target E6/E7 or their major targets p53 and pRb, however, are not currently approved for clinical use.
Methods: A panel of inducible E6E7-targeting shRNA HPV+ cancer cell lines were generated. KEGG pathway analyses were performed to identify druggable signaling pathways modulated by E6E7 with temporal resolution. The impact of E6E7 repression and pharmacological modulation of selected downstream pathways was evaluated in vitro and in vivo.
Results: E6E7 knockdown significantly reduced in vitro and in vivo (>90% inhibition, $p<0.001$, n=7) tumorigenicity confirming E6E7 addiction in our model system. KEGG analyses revealed that Wnt and PPAR pathways are altered in response to E6E7 silencing. Due to their established roles in HNSCC, reciprocal regulation, and multitude of target genes, these two identified pathways were deemed good candidate drug targets. Wnt antagonist, FH535, and PPAR agonist, fenofibrate, showed significant anti-proliferative effects in three HPV+ cancer cell lines. In UMSCC47 and CaSki cell lines, fenofibrate mirrored the effects of E6E7 knockdown and augmented p53 protein levels in a dose-dependent manner. Additionally, fenofibrate impaired xenograft tumor growth ($p<0.01$, n=7) and, in combination with cisplatin, achieved regression or complete response in a majority of mice ($p<1.0x10^{-7}$, n=7).
Conclusions: Our work reveals that fenofibrate boosts p53 levels and mimics phenotypic effects of direct E6E7 repression. Moreover, fenofibrate shows excellent therapeutic potential for HPV+ HNSCC as monotherapy or in combination with cisplatin. Since fenofibrate is FDA-approved for cardiovascular indications, re-purposing this drug for HPV+ HSNCC in the clinical setting should be prioritized.

TARGETED TUMOR CELL KILLING BY AN HPV VLP-IR700 DYE CONJUGATE INDUCES POTENT AND LONG-LASTING T CELL-MEDIATED ANTI-TUMOR IMMUNITY.

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Introduction: AU-011 (Belzupacap Serotalocan) is an HPV16 L1/L2 VLP-IR700 dye conjugate that targets specifically modified heparan sulfate proteoglycans found on the surface of many tumor types. Upon local activation with near-infrared light, a single administration of AU-011 causes rapid, necrotic cell death. It is currently being tested in a Phase II clinical trial for treatment of choroidal melanoma. This study examined the ability of AU-011 to induce immunogenic cell death and elicit protective anti-tumor immunity.
Methods: Methods: Human and murine tumor cells were treated with AU-011 either in vitro or in vivo and damage associated molecular patterns (DAMPs) were measured. In vivo TC-1 tumor treatments were performed using AU-011 alone or in combination with anti-CTLA-4. T-cells were depleted at the time of treatment or during subsequent secondary tumor challenge to determine a role for adaptive immunity in tumor control.
Results: Results: AU-011-mediated cell killing in vitro was pro-immunogenic, resulting in the release of DAMPs such as DNA, ATP and HMGB-1, surface re-localization of calreticulin and HSP70, and activation of caspase-1. In vivo, calreticulin surface expression and caspase-1 activation were observed, implicating the induction of an immunostimulatory tumor microenvironment. Combination of AU-011 with anti-CTLA-4 doubled therapeutic efficacy, resulting in 80-100% tumor-free animals 100 days post-treatment. AU-011 alone, or with anti-CTLA-4, resulted in protection from secondary tumor challenge in a majority of the surviving animals. Depletion of CD4+ or CD8+ T-cells, either at the time of AU-011 treatment or secondary tumor challenge of regressor mice, indicated that both populations are vital to AU-011's primary efficacy and for induction of long-lasting tumor protection.
Conclusions: Conclusions: These data support the conclusion that AU-011 both directly kills tumor cells and induces potent long-term anti-tumor immunity alone, or in combination with anti-CTLA-4, and further supports its use as an anti-tumor therapy in the current and future clinical trials.

INTEGRATED HPV-DNA AS INDIVIDUALIZED BIOMARKER FOR THE DETECTION OF RECURRENT CIN2/3 DURING POST-TREATMENT SURVEILLANCE --- FIRST RESULTS OF THE HPV-INT-CX STUDY GROUP

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Due to relapse in up to 10% of cases post-treatment follow-up after CIN3 surgery is mandatory. Standard follow-up is based on co-testing (cytology and hrHPV-DNA). This procedure has high sensitivity but limited specificity. False-positive tests result in unnecessary follow-up and anxiety in patients. Aim of the study is to show that an individualized viral-cellular-junction test (vcj-PCR) combined with cytology has superior specificity compared to standard co-testing for the prediction of recurrent CIN2/3.
Methods: HPV-INT-CX is a German prospective multicenter observational study (DRKS00010435) adhering to the guidelines for post-conisation monitoring. First cervical sampling was done pre-surgically. This sample served for the identification of HPV16/18 integration sites by next-generation-sequencing (NGS). Three follow-up exams including cervical sampling were performed at 6, 12 and 24 months post-surgery or up to the time point of recurrence. All samples were evaluated by cytology, hrHPV-DNA and the patients´ individual HPV-integration sites (vcj-PCR on the basis of NGS).
Results: In 50 of 447 eligible patients HPV integration sites could be identified by sequencing and individualized vcj-PCR assays were established. Integration frequency of 11.2% (95%CI:8.5-14.5%) was thus considerably lower than anticipated. Of these 50 patients, 42 had attended at least the first follow-up visit 6 months post-surgery and 38 could be followed over 2 years (median). In 33 patients without recurrence specificity was 82% (95%CI:65-92%) for standard hrHPV/cytology at 6 months compared to 88% (95%CI:72-96%) for vcj-PCR/cytology, respectively (McNemar p=0.5). Five patients developed histologically confirmed recurrences (≥CIN2) during follow-up. Standard testing by hrHPV/cytology was positive in all and vcj-PCR/cytology in four patients with recurrences. Vcj-PCR alone discovered 2 of 5 recurrences and was negative for all 33 cases without recurrence.
Conclusions: Although highly specific on its own our individualized biomarker test for the detection of recurrent CIN lacks sensitivity. Possible reasons may be multifocal lesions, incident CIN and/or intratumoral heterogeneity.

SURVEILLANCE OF YOUNG HPV-POSITIVE WOMEN BELOW AGE OF 30 BY FAM19A4/MIR124 METHYLATION: A MULTI-CENTER EUROPEAN COHORT STUDY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: The majority of CIN2 and CIN3 lesions in young HPV-positive women <30yr regress spontaneously even though these are positive for cytology or HPV16/18. Classical histopathology cannot discriminate between regressive and transforming CIN lesions. This leads to considerable overtreatment. The burden of overtreatment is cumbersome because these women are in childbearing age. Therefore markers are needed to better predict high-risk for transforming disease in young HPV-positive women. DNA methylation status is associated with increasing CIN grade and regression or progression of CIN2. The FAM19A4/miR124-2 methylation test has a very high sensitivity for cancer and advanced transforming CIN with a high short-term progression risk for cancer. The clinical performance of the FAM19A4/miR124-2 methylation test in HPV-positive women (<30yr)was determined in a multicenter study to evaluate whether the test can guide the clinician in the management of CIN disease.
Methods: 1097 HPV-positive scrapes of women (15-29 years) originating from screening and referral settings from five countries (Scotland,Slovenia,Denmark,Germany,Spain) were tested locally for FAM19A4/miR124-2 methylation (QIAsure Methylation Test). Sensitivity for histology was determined for methylation and HPV16/18 genotyping. 127 CIN2/3 lesions were immuno stained for $p16^{INK4a}$,Ki67 and HPV-E4. HPV-E4 is a biomarker of productive HPV infections. The study is part of the Valid-screen project performed within the European Horizon2020 program.
Results: In total 98% (1071/1097) of the samples yielded valid methylation test results. Sensitivities for CIN2,CIN3 and cancer for methylation were 28.1%(47/167),61.2%(126/206) and 100%(1/1). Specificity for ≤CIN1 and referral rates were 79.1%(551/697) and 29.9%. Methylation-negative CIN2/3 were significantly more positive for HPV-E4(p=0.0003).
Conclusions: The FAM19A4/miR124-2 methylation test has a good clinical performance in women aged <30 years in different European settings and is particularly sensitive for transforming CIN lesions, which are considered to have a high short-term progression risk to cancer. The test can provide markedly better clinical management of young HPV-positive women by reducing overreferral and overtreatment.

MORTALITY REDUCTIONS AND LIVES SAVED ON THE PATH TO ELIMINATING CERVICAL CANCER IN 78 LOW AND LOWER-MIDDLE INCOME COUNTRIES: A COMPARATIVE MODELLING ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / ELIMINATION

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Introduction: WHO will present a Global Strategy to achieve cervical cancer elimination as a public health problem at the World Health Assembly in May 2020. This proposes an elimination threshold of 4 cases per 100,000 woman-years and includes '90-70-90' triple-intervention coverage targets for HPV vaccination, cervical screening, and invasive cancer treatment. The WHO Cervical Cancer Elimination Modelling Consortium (CCEMC) involves three independent dynamic models and has found that elimination by 2120 is possible in 78 LMIC if girls-only vaccination is combined with twice-lifetime screening. The aims here were to project the impact of achieving the 2030 'triple-intervention' targets on cervical cancer mortality and deaths averted over the next century.
Methods: The CCEMC models projected results over time in 78 LMIC for three core scenarios: girls-only vaccination of 9-year-olds with catch-up for ages 10-14 years; girls-only vaccination, plus once-lifetime HPV screening at ages 35 and cancer treatment scale-up; and girls-only vaccination, plus twice-lifetime screening at 35/45 and cancer treatment scale-up.
Results: By 2030, vaccine-only strategies would have minimal impact on mortality, but adding twice-lifetime screening and cancer treatment would result in a 2030 mortality rates of 8·5(8·2-10·8) per 100,000 women, a 34·2%(23·3-37·8)% reduction, averting 200,000(200,000-300,000) deaths, mainly due to improved access to cancer treatment. By 2070, vaccination only would lead to mortality rates of 5·0(4·5-5·4) per 100,000 women, a reduction of 61·7%(61·4-66·1)%, averting 4·4M(3·7-4·5)M deaths. Adding twice-lifetime screening and cancer treatment scale-up would reduce rates to 1·0(0·9-1·6) per 100,000 women, a 92·3%(88·4-93·0)% reduction, averting 14·0M(13·4-14·0)M deaths. By 2120, the triple-intervention strategy would lead to rates of 0·2(0·2-0·5) per 100,000 women [98·6(96·5-98·6)% reduction], averting 61·4M(60·9-61·6)M deaths.
Conclusions: The implementation of WHO's triple-intervention strategy would reduce cervical cancer mortality rates by almost 99% and prevent over 60M deaths by 2120. These findings have directly

informed the draft WHO strategy for cervical cancer elimination.

PALLIATIVE CARE IS ASSOCIATED WITH LESS AGGRESSIVE CARE AT THE END OF LIFE FOR PATIENTS WITH CERVICAL CANCER

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Advanced cervical cancer may lead to severe symptoms that interfere with quality of life, yet few studies have examined the rate of palliative care referral in this population. The purpose of this study was to examine palliative care referral rates in patients with cervical cancer and assess whether the referrals affect care at the end of life (EOL).
Methods: We conducted a retrospective review of deceased women treated for cervical cancer at two tertiary institutions from 2000-2013. We examined clinical variables including the presence, timing and setting of palliative care and hospice referrals as well as measures of aggressive EOL care. Data were analyzed with univariable and multivariable parametric and non-parametric testing.
Results: We identified 217 cervical cancer decedents, 52 of whom were lost to follow up and 12 of whom died of other causes. Seventy-six percent of the 153 cervical cancer decedents were stage III or IV by the 2018 FIGO staging system. The median overall survival for the cohort was 2.1 years and average time from palliative care referral to death was 5.6 months. Palliative care referrals were made for 46% of the cohort. Palliative care referral was significantly associated with hospice referral (OR 10.7, $p<0.001$) and death in hospice (OR 8.1, $p<0.001$). Patients who received a referral had a decreased rate of ICU admissions (OR 0.25, $p<0.02$) and an increased rate of code status discussions (OR 7.23, $p<0.001$) in the last 30 days of life. Palliative care referral was negatively associated with death in an acute care setting (OR 0.07, $p<0.001$).
Conclusions: Less than half of women with end-stage cervical cancer received formal palliative care referrals and those patients underwent fewer measures of aggressive care at the EOL. Further study to understand the barriers of referral to palliative care will be crucial for integrating palliative care into general cervical cancer care.

PILOT STUDY ON DETERMINING BASELINE KNOWLEDGE AND ATTITUDES OF YOUNG PAKISTANI GIRLS ON HUMAN PAPILLOMAVIRUS INFECTION AND HUMAN PAPILLOMA VIRUS VACCINE.

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Cervical cancer is the fourth most common malignancy causing mortality and morbidity in women. It is one of the leading causes of cancer deaths among women In Pakistan, cervical cancer screening is not routine, and the burden of Human papillomavirus(HPV) infection remains unknown. The poor health-seeking behaviours may be primarily due to the poor awareness of Pakistani women on the disease, the screening test, and the presence of a vaccine. The aim of the study was to determine the baseline knowledge and attitudes of selected Pakistani girls on HPV and HPV vaccine.
Methods: We conducted a small scale, exploratory survey that is envisioned to be upscaled into a more robust, quantitative-qualitative study design in Pakistan. Our study participants were young girls attending different schools and colleges in Islamabad /Rawalpindi. The survey instrument was an online questionnaire with 6 closed-ended questions designed to evaluate the knowledge and attitude of young female respondents towards HPV infection and vaccine.
Results: A total of 41 females completed the survey. The majority of the respondents 80% (n=33) were from the age group 16-25 years old. Out of 41 respondents who participated in the survey, (68%) were not aware of cervical cancer, and 64% were not aware of the disease burden. Two-thirds (63%) of the girls were unaware of the vaccine, however, most of the girls (90%) wants to benefit from the vaccine.
Conclusions: A significant number of girls are unaware of HPV and the vaccine, however, there is broad and positive interest in receiving the vaccine. The data generated was inconclusive and highlights the need for a large-scale study to estimate the level of awareness.

TREATMENT OF BENIGN CERVICAL DISEASES ASSOCIATED WITH HPV INFECTION USING HIGH INTENSITY FOCUSED ULTRASOUND (HIFU)

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: HPV of high carcinogenic risk is recognized as a central etiological factor of intraepithelial cancer and pre-cancerous neoplastic cervical lesions. Early detection and effective treatment of pre-cancer cervical lesions associated with HPV is a real possibility of reducing the incidence of cervical cancer. **Objective:** is to avaluate the effectiveness and safety of non-invasive focused ultrasound in the treatment of recurrent HPV-associated cervicitis.
Methods: Clinical examination of 112 women with benign (non-oncological) cervical diseases and verified HPV was conducted. At the first visit, an "ABNORMAL" result was obtained for all patients after an optoelectronic intraepithelial cervical screening (TruScreen). Also all patients underwent liquid cytology and study of the vaginal microbiota. The treatment was performed with the high intensity focused ultrasound (HIFU). All patients were interviewed by phone after 7 days and re-examined 3 months after ultrasound therapy to assess the safety and effectiveness of this method.
Results: All patients received ultrasound therapy well tolerted and not one had severe complications. Occasional minor vaginal excretions were in the first 7 days in 71.4% of patients. Without any intervention, they disappeared 2 weeks after US therapy. Other symptoms of patients were significantly alleviated after US therapy, including 93.5% of patients who had pre-procedure excretions, 82.9% with post-genital bleeding and 94.4% with pelvic pain. The indicator "NORMAL" according to the results of optoelectronic intraepithelial cervical screening (TruScreen) was observed in 85.7% of patients, cytological examination showed that the damage disappeared in 83% of patients. Subsequent HPV tests showed that 78.6% of patients had negative results on HR-HPV infection after treatment.
Conclusions: Non-invasive focused ultrasound therapy is safe and effective in treating patients with non-cancerius cervical diseases associated with HPV.

HIGH-RISK HPV PERSISTENCE AND INCIDENCE FOLLOWING ONE ROUND OF HRHPV-BASED SCREENING AND TREATMENT IN WOMEN LIVING WITH HIV IN BOTSWANA

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Cervical cancer is the leading cause of cancer death in women in Botswana. The burden of cervical cancer in Botswana is impacted by the high prevalence of HIV in reproductive aged women (20.3%). Botswana recently implemented primary high-risk human papilloma virus (hrHPV) testing. The effectiveness and implementation of a primary hrHPV cervical cancer screening strategy in populations with high HIV prevalence is unclear.
Methods: We conducted one-year follow-up of a prospective cohort of women living with HIV in Botswana. At baseline participants underwent cervical cancer screening using primary hrHPV testing and treatment based on colposcopy results. At one-year follow-up, all participants underwent repeat hrHPV testing.
Results: Of 300 HIV-infected women screened at baseline, 88 (29%) had a positive hrHPV test, of which 15 had HPV type 16, 21 had HPV 18/45, and 66 had other hrHPV (prevalence 5%, 27%, 22%, respectively). Treatment with loop electrosurgical excision procedure (LEEP) was performed in 45 (51%) of the women who were hrHPV positive. At one-year follow-up, 206 (69%) women were available for re-testing, and 43 (21%) were hrHPV positive, which was a significantly lower prevalence than baseline (p=0.04). Prevalence for hrHPV types 16, 18/45 and other hrHPV was 2.9%, 1.0%, and 18.4% respectively at follow-up testing. Among the 43 hrHPV positive women at follow-up, 28 (45.9%) had persistently positive hrHPV results (including 14 of 28 who had undergone LEEP and were re-tested). The incidence of newly detectable hrHPV infection was 10.3% (15 new infections among 145 women seen in follow-up who had baseline negative hrHPV results).
Conclusions: One year after primary hrHPV testing and targeted treatment, the overall prevalence of hrHPV among HIV-infected women was modestly but significantly reduced. The high incidence of newly detectable hrHPV infection in this population warrants further investigation into the dynamics of hrHPV acquisition and shedding in women living with HIV.

HUMAN PAPILLOMAVIRUS VACCINE-RELATED EMBARRASSMENT: GENDER DIFFERENCES AND INTENTIONS TO RECEIVE THE HPV VACCINE AMONG UNVACCINATED YOUNG ADULTS

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: Embarrassment has been identified as a potential barrier to multiple cancer preventive behaviors. However, human papillomavirus (HPV) vaccine-related embarrassment has not been examined quantitatively. The aims of the current study were to examine: 1) the extent to which unvaccinated young adults may feel embarrassed about HPV vaccine-related discussions and behaviors; 2) potential gender differences in embarrassment; and 3) relationships between HPV vaccine-related embarrassment and intentions to receive the HPV vaccine.
Methods: Unvaccinated men and women (*n*=202) aged 18-26 years attending a public university responded to nine 5-point items assessing the extent to which they would be embarrassed to: 1) discuss the HPV vaccine with their parents, friends, or providers; 2) receive a vaccine recommendation from their parents, friends, or providers; 3) ask a provider for the vaccine; 4) make an appointment to receive the vaccine; and 5) receive the vaccine. Participants also reported their intentions to receive the HPV vaccine. Descriptive, t-tests, and correlational analyses were conducted.
Results: Participants generally reported low levels of embarrassment that did not differ by gender, with one exception. Women reported significantly greater embarrassment than men about discussing the HPV vaccine with friends, $t(199)=-2.60$, $p=.01$. Among men, greater HPV vaccine intentions were related to lower levels of embarrassment about asking a healthcare provider for the vaccine ($r=.32$, $p<.01$) and receiving the vaccine ($r=.33$, $p<.01$). Among women, greater HPV vaccine intentions were related to lower levels of embarrassment about receiving the vaccine ($r=.20$, $p=.02$). Other forms of embarrassment were unrelated to HPV vaccine intentions in men and women.
Conclusions: Embarrassment about HPV vaccine-related behaviors was, on average, low in college men and women. Men and women with less embarrassment regarding HPV vaccine receipt reported greater intentions to receive the vaccine. Future intervention research should examine whether reducing embarrassment promotes HPV vaccination receipt among young adults.

DEVELOPMENT OF NOVEL MOLECULAR TECHNOLOGY USING UNIVERSAL LFA (LATERAL FLOW ASSAY) ARRAY FOR HPV GENOTYPING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPV infection is a primary cause of cervical cancer. HPV genotypes are very important factors to predict the progress and treatment of cervical cancer. We developed novel genotyping technology based on universal array called MPCR-ULFA (Multiplex PCR- Universal Lateral Flow Assay). The new technology was evaluated for HPV genotyping with cervical swab samples in clinical laboratory.
Methods: The genotyping technology is combined multiplex PCR with nucleic acid lateral flow assay. Type-specific primers with linker sequences were designed for the amplification of 20 different HPV types, which includes 14 high risk, 2 probably high risk, and 4 low risk HPV types. Multiplex PCR uses for amplification of HPV types modified with universal linker and biotin. Amplified target products are combined with Streptavidin-conjugated nanogold and hybridized with universal probes immobilized on NC membrane through lateral flow. The 271 cervical swab samples were tested for HPV genotyping with the designed method and compared with the results of real-time PCR methods.
Results: When amplified HPV DNAs were hybridized with universal probe by lateral flow, the brown lines appeared on the membrane in 10 to 15 minutes. Our data show that sensitivity and specificity using 271 cervical swab samples in Seoul Clinical Laboratories are 97.42% and 100% respectively.
Conclusions: High-Risk HPV detection is considered the best cervical cancer screening methods. The MPCR-ULFA array is the proprietary chimeric technologies that combine with molecular and immune diagnostics. This technology is very sensitive, specific, fast and affordable method that are especially appropriate for applications in not only low resource settings but Point of Care Testing (POCT).

REDUCTION IN DOMESTIC HPV VACCINE PRICE ENABLES GOOD ECONOMIC RETURNS FOR CERVICAL CANCER PREVENTION IN CHINA: A COST-EFFECTIVENESS ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Coinciding with the first and recently released Chinese domestic human papillomavirus (HPV) vaccine, Innovax, and the substantial advancements in cervical cancer screening technology, we evaluated the cost-effectiveness of universal schoolgirls vaccination with Innovax and several cervical cancer screening programmes and identified the cost-effectiveness threshold for the vaccination cost in China.
Methods: We developed a Markov model of cervical cancer to evaluate the incremental cost-effectiveness ratios (ICERs) of sixty-one intervention strategies, including a combination of various screening methods at different frequencies with and without vaccination, and also vaccination alone, from a healthcare system perspective. We conducted univariate and probabilistic sensitivity analyses to assess the robustness of the model findings.
Results: Compared with 'no intervention', all intervention strategies resulted in an ICER less than 3-time Chinese per-capita gross domestic product (GDP) (ranging from cost-saving to US$24,302/quality-adjusted-life-year (QALY)), except 3-yearly liquid-based cytology+Hybrid Capture-2 screening. With a willingness-to-pay (WTP) threshold of 3-time per-capita GDP, 5-yearly *care*HPV screening alone would be the most cost-effective strategy with an ICER of US$16,447/QALY compared with the lower-cost non-dominated strategy on the cost-effectiveness frontier, and the probability of it being optimal (42%) outperformed other strategies. Strategies that combined screening and vaccination were only more cost-effective than screening alone strategies when the vaccination cost was below US$100/3 doses at the current WTP.
Conclusions: Five-yearly *care*HPV screening is the most cost-effective strategy. Reduction in domestic HPV vaccine price is necessary to ascertain a good economic return for the future vaccination programme.

ROLE OF HEALTHCARE PROVIDERS IN HPV VACCINATION PROGRAMS

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Despite the availability of safe and effective HPV vaccines, there remains a number of challenges to tackle in order to ensure the smooth implementation and sustainability of the HPV vaccination program. Healthcare providers (HCPs) play a critical role in ensuring the delivery of accurate information and stable communication to support implementation and sustainability of the vaccination program
Methods: The HPV Prevention and Control Board (www.hpvboard.org) organizes technical and country meetings, where experts exchange experiences and insights to strengthen countries' efforts to secure HPV prevention and control programs [1–8]. On May 15–16, 2018, the sixth meeting in the series was held in Bucharest, Romania. This technical meeting targeted the role of healthcare providers in prevention programs, with a focus on HPV vaccination and cervical cancer screening.
Results: The table below summarises certain key aspects to enhance the impact of HCPs on improving HPV vaccination coverage.

Key Aspects	Recommendation and Sustainability
Training	Training HCPs with: Training modules Improve curriculum (pre-service training) Centralizing and coordinating educational materials including availability in local language
Communication	Working with media: will help HCPs to answer queries in time. Training on Announcement approach Making effective HPV recommendations Announce and in case of hesitancy connect, clarify and counsel
Building Confidence	HCP are part of the public Increase HCP norms of getting vaccinated Set up an information portal for HCPs to clarify their doubts, and boost confidence in vaccination Allow sufficient time to focus on training and learning modules

Conclusions: It is clear that HCPs play a critical role in HPV immunization programs. Therefore, it is important to train HCPs and equip them with adequate knowledge and skills to educate the public and strategies for effective communication to ensure the sustainability of the program.

HPV16'S MOLECULAR VARIANTS AMONG MEN ENROLLED IN THE HIM STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Human papillomavirus 16 is the cause of multiple cancers in women and men. Since HPV-16 variants have been associate with differences in risks for persistent cervical infections and cervical lesion development, it is unknown as to whether or not this may apply to the men's genitalia.
Methods: Genital samples collected from men enrolled in the prospective HIM (HPV Infection in Men) Study that were previously typed as HPV-16 positive by Linear Array were included in this study. HPV-16 molecular variants were classified into lineages and sublineages as previously described (Chen *et al*., 2013). In addition, specimens from genital warts or lesions were also evaluated for lineage of HPV-16.
Results: We classified the lineage of 170 previously identified HPV-16 positive genital samples from 88 men across multiple study visits: 52 samples from 9 men enrolled in the United States, 108 from 75 men enrolled in Brazil, and 10 from 4 men enrolled in Mexico. Overall, most HPV-16 sequences were of the A1 lineage. While the A1 isolate was the most frequently detected lineage in the American, Brazilian, and Mexican samples, A2, B1, C1, D1, D2 and D3 lineages were only identified in the Brazilian population. Among men with persistent HPV 16 infection, most were positive for the same variant at each study visit. Furthermore, some inconclusive samples demonstrated signals in the chromatogram that could implicate co-infection of multiple variants warranting further investigation. Among the nine specimens derived from genital warts or lesions, all harbored the same variant detected in the other penile swabs from the same individual, with the exception of 2 swabs which were PCR negative using type-specific primers.
Conclusions: HPV-16 variant characterization is still ongoing, and data will be presented. At the moment, the Brazilian population has a more diversified distribution of HPV-16 variants.

QUADRIVALENT HPV VACCINATION AFTER EFFECTIVE TREATMENT OF ANAL INTRAEPITHELIAL NEOPLASIA IN HIV+ MSM (VACCAIN-P TRIAL)

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: High-grade anal intraepithelial neoplasia (HGAIN;AIN2/3) is highly prevalent among HIV-positive men-who-have-sex-with-men(MSM). Treatment of HGAIN to prevent cancer is frustrated by high recurrence rates (50%). In a non-concurrent, non-blinded cohort study quadrivalent human papillomavirus(qHPV) vaccination significantly (HR=0.50) reduced recurrence among HIV-negative MSM successfully treated for AIN. The current study is a multicentre, double-blind, placebo-controlled, randomised trial investigating the effectiveness of qHPV vaccination in preventing HGAIN recurrence in HIV+ MSM after successful treatment. As deblinding of the trial took place in October 2019, we have late breaking data to present.
Methods: From 2014 until 2017, in three Amsterdam clinics, HIV+ (CD4 count>350 cells/µl) MSM with in the past year successfully treated intra-anal HGAIN were randomised for qHPV or placebo (vaccinations at 0,2,6 months). At inclusion, high-resolution anoscopy (HRA) was performed independently by two experienced anoscopists to rule out recurrent HGAIN. HRA was repeated at 6,12 and 18 months. Primary endpoint was cumulative, biopsy-proven HGAIN recurrence at 18 months (12 months after last vaccination). Secondary endpoints were: safety, causative HPV-type in the recurrent HGAIN and HPV-type specific serological response.
Results: All 126 included participants received all three vaccination and two participants were lost to follow-up in both arms. qHPV vaccination gave an adequate serological response (significant increase of antibody concentrations for HPV16 and 18). At baseline 64% was already seropositive, while 100% was seropositive at three months after last vaccination. We found no difference(p=0.38) in HGAIN recurrence rates between the qHPV (65.6%) and placebo group (58.1%) in the intention-to-treat analysis and a similar recurrence risk (RR=1.13 (95%CI: 0.858–1.489); ARR=-7.5 (95%CI:-24.5–9.3)). This was similar in the per-protocol analysis (complete follow-up). In both arms a similar percentage(≈40%) of recurrences were caused by vaccine HPV-types. No vaccine-related SAEs occurred.
Conclusions: qHPV vaccination after successful treatment for HGAIN does, despite adequate serological response, not prevent HGAIN recurrence in HIV+ MSM.

FZD4, FZD9, RYK, AND ROR1 RECEPTORS: POTENTIAL BIOMARKERS IN CERVICAL CANCER

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Cervical cancer (CC) is the fourth most common neoplasm in women worldwide. Involves uncontrolled cell division and tissue invasiveness of the cervical epithelium. Its major risk factor is human papillomavirus (HPV) infection. However, other molecular modifications are necessary for its development, such as an aberrant activation of the WNT/β-catenin signaling pathway. Although the cytosolic events that occur during the pathway activation have been widely studied, little is known about the participation of the WNT receptors in CC development and their possible use as biomarkers or therapeutic targets.
Methods: The mRNA and protein expression of the FZD1-FZD10, RYK, ROR1-2 and VANGL2 receptors was determined by qPCR and flow cytometry, respectively in HPV infected CC-derived cell lines (HeLa and SiHa) compared with non-tumorigenic immortalized keratinocytes (HaCaT); in HaCaT keratinocytes that express E5, E6 or E7 from high (-16 and -18) or low risk (-84) HPVs; as well as in cervical samples from women without cervical lesions, cervical intraepithelial neoplasia or CC. The Attune flow cytometer and the "Attune Cytometer Software-vs2.1" were used to acquire the data, acquiring 20,000 events per sample. The “FlowJo-vs10” program was used to graph the results. The statistical analysis was performed with IBM-SPSS Statistics-vs25.
Results: The majority of the receptors, except FZD3 and FZD4, were highly expressed in cell lines (<50% positivity), a differential expression was identified between non-tumorigenic cells and cells derived from CC in FZD4, FZD9, RYK and ROR1 receptors, data that correlate with the results observed in cervical samples. VANGL2 was found absent in cell lines derived from CC compared to HaCaT keratinocytes.
Conclusions: It was shown that the FZD4, FZD9, RYK, and ROR1 receptors are overexpressed, both in CC-derived cell lines, and in cervical samples from women with CC, compared to keratinocytes without malignancy characteristics.

TRENDS IN CIN2+ DIAGNOSES BETWEEN 2013 AND 2018 IN WOMEN 18 TO 45 YEARS OLD– RESULTS FROM A GERMAN STATUTORY HEALTH INSURANE CLAIMS DATA ANALYSIS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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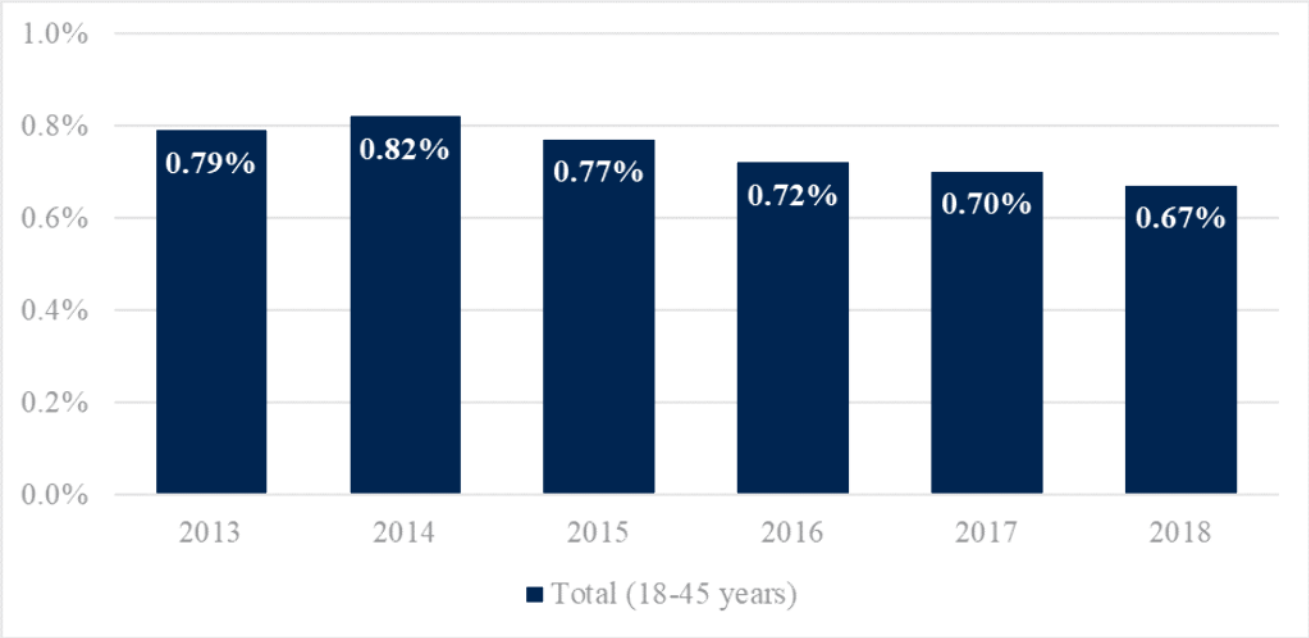
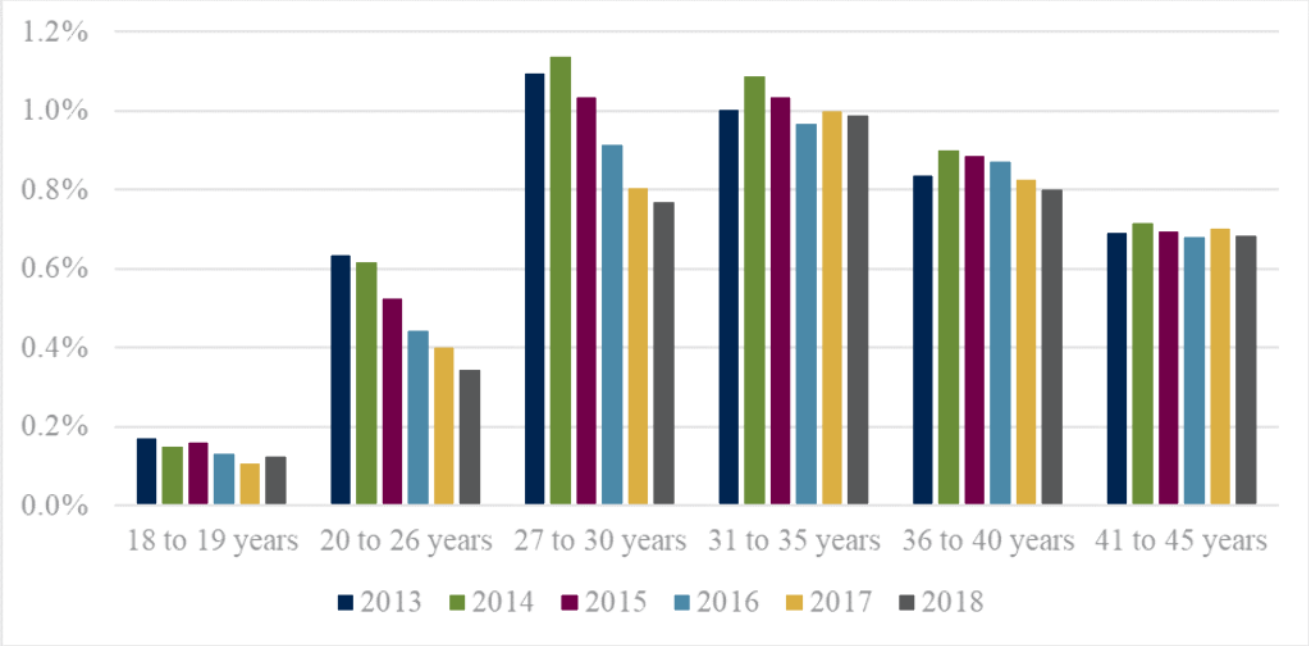
Introduction: Cervical intraepithelial neoplasia (CIN) are a consequence of Human Papillomavirus (HPV) infection. CIN diagnosis and treatment present a considerable burden to patients through surgical procedures (e.g. cervical conization for CIN2+) and psychosocial consequences, and can be prevented through HPV vaccination. Currently, information on trends in CIN2+ diagnoses in Germany is sparse. The objective of this study was to estimate the annual proportion of women aged 18-45 with CIN2+ diagnoses in Germany from 2013-2018.
Methods: We conducted a retrospective cross-sectional claims data analysis using the “Institut für angewandte Versorgungsforschung Berlin GmbH“ (InGef) research database, which covers approximately 4 million lives and is representative for the German population regarding age and gender. The annual proportion (2013-2018) of women aged 18-45 years with CIN2+ diagnoses (CIN2 / CIN3) was calculated as the number of women with at least one ICD-10-GM record for CIN2+ in the inpatient (main/secondary diagnosis) or outpatient setting (verified diagnosis), divided by the total number of women from the respective year in the database. The analysis was stratified by age.
Results: The overall proportion of women with CIN2+ diagnoses was 0.79%, 0.82%, 0.77%, 0.72%, 0.70% and 0.67% in 2013, 2014, 2015, 2016, 2017, and 2018, respectively (figure 1). The share of 20-26 year-olds in CIN3 diagnoses decreased from 18% in 2013 to 9% in 2018, and 80% of diagnosis was among women ≥27 years. Age-group-stratified results are provided in figure 2. Women aged 31-35 had the highest proportion of CIN2+ in 2018.





Conclusions: Observed decreases in CIN2+ diagnoses from 2013-2018 were driven by younger women, with greatest declines in proportion of CIN2+ diagnosis between 20-30 years, possibly driven by the HPV vaccination, with trends subject to changes in underlying screening practices. The most substantial share of the CIN2+ burden remains among women ≥27 years.

HPV VACCINATION IMPACT AT THE GLOBAL, REGIONAL AND NATIONAL LEVELS: PRIME MODELLING STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: The Papillomavirus Rapid Interface for Modelling and Economics (PRIME) has been used around the world to assess the health impact and cost-effectiveness of HPV vaccination in girls. We updated PRIME with new data and methods for demography, disability weights and cervical cancer burden, and generated revised estimates of the health impact of HPV vaccination at the global, regional and national levels for 177 countries.
Methods: PRIME was updated with population demography of the United Nations World Population Prospects (UNWPP) 2019 revision, disability weights of the Global Burden of Disease (GBD) 2017 study, and cervical cancer burden from the Global Cancer Incidence, Mortality and Prevalence (GLOBOCAN) 2018 database. We estimated the lifetime health benefits for bivalent/quadrivalent and nonavalent vaccination of 9-year-old and 12-year-old girls at 90% coverage during 2020-2029 in 177 countries.
Results: When the health impact of vaccination of 9-year-old girls was compared to the counterfactual scenario of no vaccination, the bivalent/quadrivalent HPV vaccine averts 15 cases, 12 deaths and 243 DALYs per 1000 vaccinated girls, while the nonavalent HPV vaccine averts 19 cases, 14 deaths and 306 DALYs per 1000 vaccinated girls. The health benefits of vaccination of 12-year-old girls are similar but relatively lower in comparison to vaccination of 9-year-old girls. HPV vaccination may have an even greater impact and be more cost-effective than predicted here, because of a number of conservative assumptions in PRIME, such as the exclusion of herd effects and cross-protection against non-vaccine HPV genotypes.
Conclusions: The updated PRIME estimates suggest that HPV vaccination will have higher health benefits in comparison to prior forecasts, and thereby being more cost-effective. The demography update of population ageing is the major driver for the change in the health impact estimates. The WHO African region is expected to gain the highest relative health benefits and should be prioritised for HPV vaccination. **Reference:** Abbas KM, van Zandvoort K, Brisson M, Jit M. Effects of demography, disability weights and cervical cancer burden on HPV vaccination impact estimates at the global, regional and national levels: PRIME modelling study. The Lancet Global Health, 2020. (In press)

THE EPIDEMIOLOGY OF HPV IN YOUNG SEXUALLY ACTIVE WOMEN IN ENGLAND HAS BEEN CHANGED RADICALLY BY 10 YEARS OF HIGH COVERAGE HPV VACCINATION

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The National HPV Vaccination Programme was introduced in the UK in 2008 with the vaccine offered routinely to 12-13 year-old females and a catch-up programme up for females up to 18 years old. Initially the bivalent vaccine was used; since 2012 the quadrivalent vaccine has been used.
Methods: Since 2008, we have conducted surveillance using residual vulvovaginal swab (VVS) specimens from 16-24 year-old females attending for chlamydia screening to monitor the epidemiology of HPV. Samples are linked to demographic data and chlamydia result prior to anonymisation. Anonymised specimens are tested for type-specific HPV-DNA infection using an in-house multiplex PCR and Luminex-based genotyping system. We present results to end 2018 (n=2,354 pre-vaccination in 2008, and 18,780 post-vaccination between 2010-2018).
Results: Steep declines in the prevalence of HPV16/18 infection have been seen in all age-groups (17.6%/16.9%/15.3% for ages 16-18/19-21/22-24 years old in 2008 to 8.2%/14.0%/16.4% in 2010/11 to 0.0%/0.7%/2.6% in 2018). The prevalence of HPV16/18 among 16-18 year-old females (with highest coverage) has been consistently below 2% since 2014. Reductions are strongly associated with known and estimated HPV vaccination coverage but are also substantial in unvaccinated females. The prevalence of HPV31/33/45 has also declined among the younger age-groups (6.5%/8.6% for ages 16-18/19.21 years old in 2010/11 to 1.9%/2.8% in). There was no evidence of increases in other high-risk HPV types.
Conclusions: In a population with high vaccination coverage, we have shown declines in high-risk HPV types that demonstrate high levels of direct (including cross) and indirect protection in young females in England. These findings validate, if not exceed, expectations and increase confidence in predicted reductions in cervical (and other) cancers.

CERVICAL PAP TESTING AMONG FEMALES LIVING WITH HIV IN THE UNITED STATES AND PUERTO RICO: MEDICAL MONITORING PROJECT GYNECOLOGICAL CARE AND REPRODUCTIVE HEALTH DATA, 2010-2017

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical cancer is the only human papillomavirus (HPV)-related gynecologic cancer that has a screening test, and one of only a few cancers that are preventable when detected and treated early. Yet, females living with HIV (FLWH) are three times more likely to be diagnosed with cervical cancer compared to HIV-negative females. In this study, we examined cervical Pap testing among FLWH.
Methods: The Medical Monitoring Project (MMP) is a public health surveillance system designed to assess the experiences and needs of people living with HIV. Gynecological care and reproductive health data from MMP HIV surveillance reports (2010–2017) were used to describe annual Pap testing among FLWH and integration of HIV and gynecological care. From 2010–2014, the MMP sample only included FLWH currently engaged in HIV care. Beginning in 2015, the MMP included all FLWH within their sample. Bivariable tables and Chi-square tests were used to compare annual Pap testing (2010 vs. 2014 and 2015 vs 2017) and integration of care (2010 vs. 2014).
Results: Bivariate results show between 2010 and 2014, annual Pap testing among FLWH engaged in HIV care decreased marginally from 79% (CI: 74.8 – 82.8) in 2010 to 76.0% (95 CI: 71.8 – 80.3) in 2014, p=0.713. Utilization of HIV care co-located in a gynecological clinic was low, however increased significantly from 21% (95% CI: 14.6 – 26.4) in 2010 to 28% (CI: 21.0 – 34.9) in 2014, p<0.001. Between 2015 and 2017, annual Pap testing among FLWH (regardless of HIV care status) remained stable (70.3% [66.4-74.1%] vs. 68.6% [64.4-72.8%], p=0.409). Integration of HIV and gynecological care was not assessed after 2014.
Conclusions: Cervical cancer screening adherence among FLWH falls below the United States' Healthy People 2020 goal of 93.0%. Offering evidence-based cervical cancer screening services in community-based, non-clinical settings may reduce structural and other healthcare access barriers among FLWH.

POSSIBLE ETIOLOGIC ROLE OF HUMAN PAPILLOMAVIRUS IN VULVAR SEBORRHEIC KERATOSIS

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF GENITAL AND SKIN WARTS

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Introduction: Background The presence of HPV-DNA in vulvar seborrheic keratosis (vSK) detected through polymerase chain reaction (PCR) has been refuted as evidence of an etiologic involvement of HPV, as PCR does not specifically locate the virus to the cell of interest.
Methods: To augment the evidence on this association, we performed a combination of methods, i.e. whole tissue section(WTS)-PCR, immunohistochemistry, and laser capture microdissection (LCM)-PCR, on a series of vSKs. p16 and E4 are considered as surrogate markers of HPV-activity, and LCM-PCR allows HPV-detection from specific lesional cells, with a higher precision than WTS-PCR.
Results: Fifteen vSKs from 13 patients with median age of 52 years were included. Strict histologic criteria were used for case selection, to avoid inclusion of the common differential, condyloma acuminata, which is an HPV-related lesion. HPVs were detected in 73% (11/15) of vSKs through WTS-PCR (SPF10-PCR-DEIA-LiPA25); the detected genotypes included HPV44 (n=4), HPV6 (n=4), HPV42 (n=2), HPV53 (n=1), and an untypable genotype (n=1). Patchy p16-positivity was noted in 82% (9/11), and E4-positivity was noted in 36% (4/11) of HPV-positive vSKs. LCM-PCR was performed on seven areas selected from four HPV-positive vSKs. Of these areas, six were lesional (two p16+/E4+ and four p16+/E4-), and one was from adjacent normal epithelium (p16-/E4-). HPV-DNA was detected from all lesional areas by LCM-PCR; in all cases the results were concordant with WTS-PCR. HPV-DNA was detected from the intermediate and basal epithelial layers in lesional areas, whereas, the area of normal epithelium was HPV-negative. This strongly argues against false-positivity due to contamination from resident flora.
Conclusions: Detection of HPV-DNA from specific lesional cells through LCM-PCR, and immunohistochemical expression of p16 and / or E4 imply a pathogenic involvement of HPV in a proportion of vSKs. Further expanded studies can help us better understand their natural history.

HPV 31 BASELINE PERFORMANCE AND RISK DETERMINATION FOR HIGH-GRADE CERVICAL DISEASE BY ONCLARITY DETECTION AND VIRAL LOAD

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Determine performance results in women, ≥25 years, for a screening that involves HPV16/18/31 primary screening or HPV 16/18/31$_{NILM}$; that latter of which sends women with NILM cytology to colposcopy based on HPV31 DNA load (HPV16/18/31$_{NILM}$).
Methods: 29,513 women had valid cytology and HPV results. Models for primary screening were evaluated whereby (1) HPV16/18/31 positive women are referred to immediate colposcopy or (2) for HPV16/18/31$_{NILM}$, NILM cytology was stratified by DCt scores; for both models, women positive for the other 11 high-risk genotypes had cytology triage. Positive likelihood ratio values were calculated for the optimal sensitivity-versus-specificity cut-point across HPV31$_{NILM}$ DCt scores. Detection of adjudicated ≥CIN3 and number of colposcopies/≥CIN3 detected were outcomes.
Results: Inclusion of HPV31 into an HPV16/18 primary screening improved ≥CIN3 sensitivity from 76.3 to 85.6; but required 212 more colposcopies (colpo/≥CIN3 ratio for HP16/18 and 16/18/31 was 10.5 and 10.8, respectively). Significantly higher ≥CIN3 association, compared to ≤CIN1 (p=0.04), was observed with high HPV 31$_{NILM}$ DNA-load. Restricting inclusion of HPV31$_{NILM}$ values (above the cut point) into the HPV16/18 screening algorithm resulted in higher sensitivity (83.2%), but only increased colposcopies by 127 with no decrease in PPV.
Conclusions: Inclusion of HPV 31 in an HPV 16/18 screening algorithm improves sensitivity for ≥CIN3 detection but results in more colposcopies and reduced PPV. Stratification of HPV31-NILM by DNA load in the HPV16/18/31 strategy, however, facilitates increased sensitivity, reduced burden of colposcopy, and no reduction in PPV. HPV16/18/31 and HPV16/18/31$_{NILM}$ inclusion might be effective for optimizing an HPV primary screening strategy.

PERFORMANCE OF CONVENTIONAL CERVICAL CYTOLOGY IN LATINO AMERICA: AN ANALYSIS WITHIN THE ESTAMPA STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In HPV-based cervical screening, cytology represents the immediate triage of HPV positive women because of the available installed capacity in many countries, particularly in Latin America. We evaluated the role of cytology to detect CIN2+ among HPV positives within the ESTAMPA study (Multicentric study of cervical cancer screening triage with HPV testing, NCT01881659).
Methods: In nine Latin American countries, 50,000 women are being screened with cytology and HPV; those with ASCUS+ or being HPV+ have colposcopy, biopsy and treatment as needed. Women without disease are those with negative screening, negative colposcopy, or negative/CIN1 histology. Cytology was processed/read in 10 laboratories: six routine/public and four private; in four laboratories pathologists read 100% of smears and in five they only read ASCUS+ (based on cyto-technicians interpretation), and in one routine laboratory only smears of HPV+ are processed/read. Sensitivity and specificity of cytology for CIN2+ detection among HPV+ were estimated overall and by laboratory characteristics.
Results: Among 5,104 HPV+ women included in the analysis, 658 CIN2+ were detected. Overall, the ASCUS+ rate was 17.8 (range: 8.7%-20%); the sensitivity: 48.5% (95%CI 44.6-52.4; range: 28.1%-71.4%) and specificity: 87% (95%CI 85.9-88.0) to detect CIN2+. No differences in sensitivity between routine and private laboratories were observed, but laboratories where pathologists read 100% of slides had significantly higher sensitivity than those where they only read ASCUS+ (51.1% vs 35.7%, p=0.003). The highest ASCUS+ rate (20.0%) and sensitivity (56%, 95%CI 49.2-62.5) were observed in the laboratory where only HPV+ smears were processed/read. Specificity was similar across laboratories.
Conclusions: Cytology sensitivity for CIN2+ detection among HPV+ was limited. However, the highest sensitivity was observed where only HPV+ slides were read. This suggests that cytology performance may be improved when HPV status is known and supports the use of cytology as triage of HPV+ until better/accessible biomarkers are available.

PLANNING TOOL TO OPTIMIZE CERVICAL PRECANCER SCREENING AND TREATMENT APPROACHES IN LOW- AND MIDDLE-INCOME COUNTRIES

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: Cervical cancer is a largely preventable disease, yet kills about 260,000 women each year, mostly in low- and middle-income countries (LMICs). Cervical screening is a proven technique for reducing the incidence of cervical cancer, but only if screen-positive women receive timely, effective precancer treatment. As planning efforts to scale up cervical precancer screening and treatment programs to reach more women are occurring in many high-burden countries, tools to determine what and how much equipment to procure and how to deploy it are needed.
Methods: To assist decision-makers, PATH developed the Cervical Precancer Planning Tool. This scenario-based Excel model is designed to help countries determine what screening approach(es) are most appropriate and what treatment equipment to procure and how best to deploy it. Baseline data for 13 countries were gathered from a literature review, global databases, and PATH fieldwork, and the tool can be used by any other LMIC using commonly available data. The screening component of the tool provides the number and outcome of screened women based on screening test accuracy and the associated costs for four different screening approaches (visual inspection with acetic acid, human papillomavirus (HPV) testing, and HPV testing with two different triage options). The treatment component provides number of women treated, treatment equipment needed by type, and the associated costs for five different equipment deployment scenarios.
Results: The tool aims to increase access to lifesaving screening and treatment while optimizing the use of scarce resources. Dashboards, including graphs and data tables, help the users weigh the tradeoffs of patient convenience and access, test accuracy, and efficient utilization of equipment, skilled personnel, and financial resources.
Conclusions: Results from the tool can inform national cervical precancer program strategies and decisions about device procurement and deployment. After consultation with stakeholders, the tool will be available on path.org in March 2020.

HPV AND CERVICAL CANCER PROGNOSIS: A NARRATIVE REVIEW

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Several factors such as clinical stage at diagnosis, lymph node involvement and access to treatment influence cervical cancer survival, yet it is unknown whether HPV status (+ or -) is related to cervical cancer prognosis. We conducted a narrative review to synthesize the available evidence and assess the methods used to evaluate the influence of HPV status on cervical cancer prognosis.
Methods: We searched Medline on June 12, 2019 to identify studies that evaluated the impact of HPV status on cervical cancer prognosis. We extracted data on HPV detection, patient and tumor characteristics, and clinical outcomes.
Results: Of 4,447 abstracts and 236 full-text articles reviewed, 60 studies were included. Almost half (46%) of the studies evaluated HPV status and prognosis in <100 patients while four studies had >500 patients. In 88% of the studies, more than half of the patients were diagnosed as stage I/II. Most (86.7%) tested for HPV in cancer tissue collected once at baseline. Thirty percent of studies used more than one detection method to test for HPV. Most studies (83%) used PCR, of which 60% used consensus primers. Forty-two percent of studies tested for fewer than 14 HPV types. The prognosis outcomes evaluated included lymph node involvement (32%), recurrence (27%), as well as disease-free (22%), progression-free (5%) and overall (62%) survival. Of 37 studies that evaluated the impact of HPV status on overall survival, twelve (32%) reported a statistically significant association; all studies except for one found that HPV positivity favourably impacted survival. However, only five out of these 12 studies adjusted for other variables such as age or cancer type.
Conclusions: This review indicates that HPV detectability in cervical cancer is associated with better prognosis but that the available evidence is heterogeneous.

LONGITUDINAL DETECTION OF CIRCULATING HPV DNA IN THE BLOOD OF WOMEN WITH CERVICAL DYSPLASIA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Circulating HPV DNA has been previously described in women with advanced stages of cervical cancer. Furthermore, it has been recently demonstrated in animal models that blood infected with papillomavirus could induce cancer formation in tissue not normally associated with the virus. These results suggest that human blood could be a potential source of HPV infection and subsequent cancer at distant sites. The aim of this study was to investigate the presence of high-risk HPV (hrHPV) in cervical and plasma samples of women with a recent history of cervical dysplasia and to evaluate its persistence in bloodstream after 6/12 months.
Methods: Blood and cervical samples were obtained from women referred for colposcopy at San Gerardo Hospital, (Monza, Italy). All samples were extracted using NucliSENS easyMAG (bioMérieux). In cervical samples HPV detection was carried out using AnyplexII HPV28 (Seegene). HPV16, 18, 31, 33, 45, 51 and 52 DNA detection in plasma was performed using sensitive "in house" real-time PCR assays.
Results: At baseline, 91 paired cervical and plasma samples were tested. Positivity for one or more hrHPV tested was demonstrated in 70.3% (64/91) of cervical samples, with the most prevalent genotypes identified being HPV16 and HPV31. Fifteen women (15/91; 16.5%) were found to be HPV DNA positive in plasma. HPV16 and HPV51 resulted the two most common hrHPV types detected in plasma. Presently, 58 of these women have returned for a follow-up visit. HPV DNA was detected in the blood sample of 10 (17.2%; 10/58) women and three (3/10; 30%) of them had also shown a previous hrHPV positivity at baseline.
Conclusions: These preliminary results confirm that hrHPV DNA can be detected in plasma samples of women with cervical dysplasia. However, future studies are necessary to better understand the possible role of hrHPV DNA in the bloodstream.

URGENT CALL FOR REALISTIC GLOBAL HEALTH PRIORITIES AND ACTIONS: TOPICAL THERAPEUTIC DRUGS ARE ESSENTIAL TO HPV MANAGEMENT

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: HPV vaccines are safe and effective at blocking infections. However, anticipation that prophylactic vaccines would substantially reduce the staggering burden of HPV diseases has been unfulfilled. Less than 1.5% of the global population is vaccinated, primarily in high-income countries, whereas LMIC bear >85% of the burden of life-threatening HPV diseases. Population growth is outstripping vaccination by 10-fold. Behind this disappointing uptake are bottlenecks in manufacturing and delivery, high cost, lack of public health infrastructure, anti-vaccine efforts, and competing economic and medical issues. Over-zealous support for vaccination has crippled efforts at alternative and practical approaches to HPV management. Pathological evaluations and surgical interventions are out-of-reach in much of the world. Immunotherapies have proven elusive. In contrast, small molecule pharmaceuticals are the gold-standard of care for most infectious diseases. .
Methods: Our lab created a 3-dimensional epithelial tissue culture model that supports a robust HPV-18 productive infection cycle.
Results: We identify host cell targets on which all HPV genotypes depend for replication, then repurpose existing drugs developed for completely different indications. The lab validated anti-HPV agents of different pharmaco-chemical classes which are now or soon to be in clinical trials: ODE-Bn-PMEG (Antiva); Vorinostat (HDAC inhibitor of replication); Novan1000 (nitric oxide releasing macromolecule); and Chk1 inhibitor MK-8776, with others under investigation.
Conclusions: Medically and economically, treatment of HPV as an STI must be the prime clinical priority, with the correlative consequence of avoiding risk of future neoplastic progression. Elimination of active lesions and long-term suppression of persistent infections require early and repeated screening for both non-oncogenic and oncogenic HPV infections using molecular tests. Positive diagnoses should be followed immediately with self-administered topical treatments using safe, effective, well-tolerated, affordable, available and socially acceptable small molecule antivirals. This is most realistic integrated approach to diminish health disparities in HPV diseases that disproportionately impact economically challenged communities and countries.

AFRICAN AMERICAN PATIENTS WITH P16+ HEAD AND NECK CANCER HAVE DISTINCTLY POOR TREATMENT OUTCOMES

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: HPV+ HNSCC is generally associated with a favorable prognosis. At oropharyngeal sites, positive p16 immunohistochemistry, an established surrogate marker for HPV+ HNSCC, confers such favorable outcomes that treatment de-escalation has been explored. Growing evidence indicates that African Americans (AA) with HNSCC represent a subgroup with poor treatment outcomes. The reason for this survival disparity and whether this extends to p16+ HNSCCs remain unclear.
Methods: We analyzed data from all patients diagnosed with p16+ HNSCC between 2010 and 2017, who received treatment at our academic medical center. Associations between ethnicity, age, gender, various clinical variable, time to treatment initiation (TTI), and overall survival (OS) were investigated.
Results: In this cohort, AA (n=49) had dramatically worse 5-year OS compared to CA (n=418); AA=35.2%, CA=68.4% (log-rank, $p<0.0001$). This difference remained when the analysis was limited to oropharynx cases only; AA=51.4%, CA=71.4% (log-rank, $p=0.007$). AA tended to be diagnosed with more advanced disease, with 66% diagnosed at T3/4 compared to 46% of CA ($p=0.009$). However, differences in T stage at time of presentation did not fully explain the disparate outcomes since multivariate Cox regression analysis revealed ethnicity (HR 2.17 (0, 1.37), $p=0.001$) and T stage (HR 2.32 (1.6, 3.4), $p<0.001$) as independent prognostic biomarkers with similar impact on OS. TTI, a surrogate measure for access to care, was not statistically different between AA and CA patients (mean TTI; AA=39.1 days, CA=38.4 days, $p=0.922$).
Conclusions: Despite a generally favorable prognosis for p16+ HNSCC patients, our analysis shows surprisingly poor outcomes among AA in this group and, moreover, argues that AA patients are poor candidates for treatment de-escalation. Disparities in HNSCC outcomes were not fully explained by any of the clinical co-variates examined including TTI, and thus the contribution of biological differences between these two ethnicities warrants further investigation.

AN EVALUATION OF A NOVEL HPV GENOTYPING ASSAY FOR CERVICAL CANCER SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: With increasing HPV tests emerging on the market, it is important that tests are evaluated to ensure they are eligible for purpose. In the present study, a novel HPV test – The SureX® HPV genotyping test targeting the E6 and E7 genes of HPV was compared with Hybrid Capture 2 (HC2) in a population-based screening settings.
Methods: Women (N = 2,112) aged 49–69 from Shanxi, China underwent screening with liquid-based cytology (LBC) and HPV tests including HC2 (Hybrid Capture 2) and SureX® HPV 25X Genotyping Kit (HEALTH BioMed, China) which provides individual genotyping information for 25 HPV types, including 14 high-risk types (HR-HPV: 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68), four medium-risk types (MR-HPV: 26, 53, 73 and 82) and seven low-risk types (LR-HPV 6, 11, 42, 43, 44, 81, and 83). Any HR-HPV positive or cytology abnormal results triggered colposcopy and biopsy if indicated. The accuracy of the SureX® HPV test for the detection of cervical intraepithelial neoplasia grade 2 or worse (CIN2+) was determined relative to HC2.
Results: Overall HR-HPV positivity by HC2 and SureX® HPV were 21.4% and 21.0%, with overall agreement of 93.5% (95%CI: 91.8-94.0, kappa value: 0.81, 95% CI, 0.78-0.84). The sensitivity and specificity for CIN2+ by SureX® HPV (14 HR-HPV types) were 94.5% (95%CI: 83.5-98.8) and 80.9% (95%CI: 79.1-82.6), both of which were comparable to those of HC2 (relative sensitivity: 0.96, 95%: 0.91-1.02; relative specificity: 0.99, 95%CI: 0.98-1.00). Combined screening strategy using SureX® HPV16/18 with reflex cytology(ASC-US+) offered comparable sensitivity and superior specificity than HC2 primary screening alone (relative sensitivity: 0.98, 95%: 0.94-1.02; relative specificity: 1.08, 95%CI: 1.06-1.10) with more efficient colposcopy referrals.
Conclusions: Our results suggest that SureX® HPV assay offers applications for cervical cancer screening while providing genotyping information that may be useful for better risk stratification.

THE PAPILLOMAVIRUS EPISTEME

BASIC RESEARCH / TAXONOMY

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Introduction: The Papillomavirus Episteme (PaVE) is a database of curated papillomavirus genomic sequences, accompanied by web-based sequence analysis tools. Database URL: http://pave.niaid.nih.gov/
Methods: The papillomavirus genomes within PaVE now include the major spliced mRNA transcripts. Viral genes and transcripts can be visualized on both linear and circular genome browsers. Evolutionary relationships among PaVE reference protein sequences can be analyzed using multiple sequence alignments and phylogenetic trees. PaVE also contains an image library containing gross clinical and histopathological images of papillomavirus infected lesions.
Results: We are continually updating the database tools and content. Updated in January 2020, the PaVE currently contains 655 annotated papillomavirus genomes (including 226 Non-reference genomes), 7247 genes and regions, 5310 protein sequences, and 74 protein structures, which users can explore, analyze or download.
Conclusions: The seamless integration of the data and the analytical tools is designed to assist in accelerating scientific progress and in ultimately our understanding, detection, diagnosis, and treatment of diseases caused by papillomaviruses.

SCHOOL-BASED HPV VACCINATION COVERAGE IN CHILE, YEARS 2014 – 2019

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Chile has a strong, mixed health-center and school-based vaccination program that dates back to 1950. School-based HPV-vaccination started in 2014 only for 4Th-school-grade girls (9-10 years old), with a two-dose scheme. The second dose is given 12-month apart in 5Th grade. A catch-up vaccination was undertaken in 2015-2016 for 6th and 7th grade girls. Vaccine rejecters can be vaccinated the following years in health centers or in schools. Gender neutral vaccination was started in 2019. The objective of this contribution is to describe the vaccination coverage between 2014 and 2019.
Methods: A review of the annual coverage numbers held by the Immunization Department of the Chilean Ministry of Health was undertaken. For 2019, only preliminary data until December 2019 was available.
Results: Mean coverage rates for 2014-2019, for 1st/2nd doses together, was 81,75% (71-91%). For 1st dose, the mean coverage was 85,4 % (77-91%) and for 2nd dose 76,6 % (71-87%). Fig 1 shows coverage by doses and years, and the tendency 2014-2019. (without catch-up) In 2019, first year of gender-neutral vaccination, a 1st dose coverage rate of 91% for girls and 89% for boys was obtained. The vaccination coverage by birth cohorts 2005-2007 (including rejectors), is shown in fig. 2. Most girls from 2005 cohort were vaccinated in 2014, but others have been vaccinated even until 2018. The 1st dose rejection rate for 2014, 2016 and 2018 was 2,4% 5,7 %, and 1,8 % respectively.

Fig. 1
School-based HPV Vaccination Coverage, Chile 2014-2019

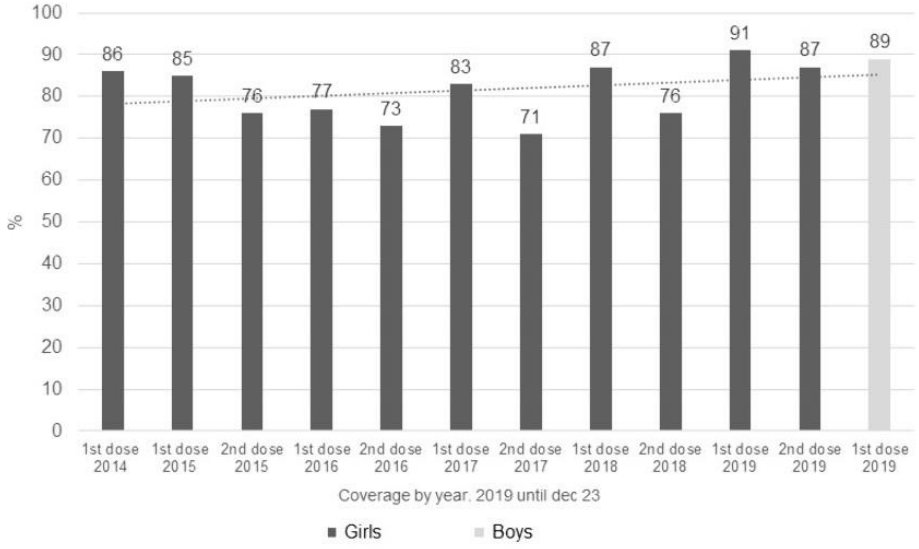
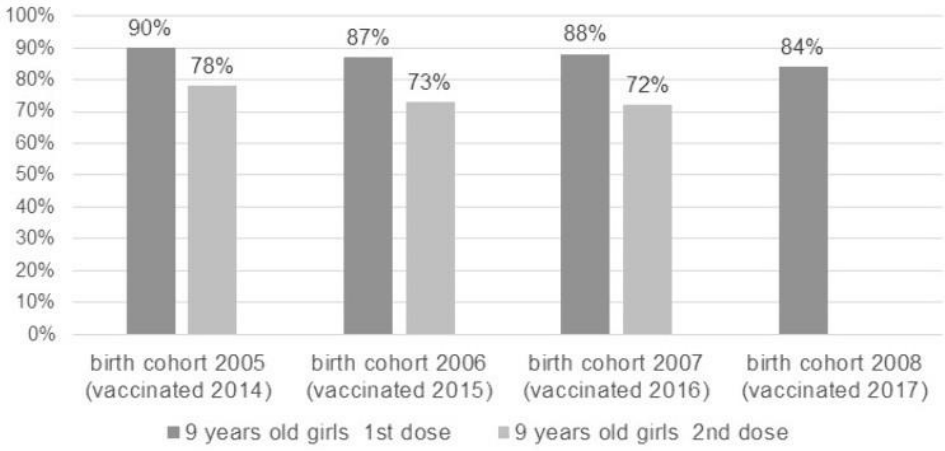


Fig. 2
School-based HPV Vaccination Coverage by birth cohorts, Chile 2014-2017 (*)



(*) Preliminary data since vaccine-rejecters can still be vaccinated

Conclusions: The drop in vaccination coverage in 2016/2017 and the higher rejection rate for year 2016 were explained by a strong anti-vaccination campaign undertaken by several anti-vaccination groups, mainly through social media. Since then, a high number of educational events, both for health/education professionals as for general public have been undertaken, leading to a growing tendency in vaccination coverage. Gender-neutral HPV-vaccination has been widely accepted in Chile.

THE HPV PREVENTION AND CONTROL BOARD: MULTIDISCIPLINARY GUIDANCE TO SUPPORT THE IMPLEMENTATION OF HPV PREVENTION AND CONTROL PROGRAMS.

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: HPV Prevention and Control Board, created in 2015 is an independent, international, multidisciplinary group of experts that provides evidence based reflection and guidance on strategic, technical, and policy issues that will occur as we move forward in the implementation of HPV prevention and control programs.
Methods: The HPV Board (www.hpvboard.org) operates by arranging two meetings per year: 1) a technical meeting covering topics such as vaccine characteristics, vaccine safety, screening technologies and landscape, treatment strategies, dealing with anti-vaccine messages, etc, 2) a country meeting covering SWOT analysis of a country or region.
Results: THE HPV board has succeeded with arranging 8 technical meeting and country meetings: Kick-off meeting – December 2015 Prevention and control of HPV and HPV related cancers in Denmark: lessons learnt and the way forward - Copenhagen, November 2016 'Barriers in HPV vaccination & cervical screening programmers' - Antwerp, June 2016 Building Trust, Managing Risk: Vaccine Confidence and Human Papillomavirus Vaccination, 7-8 June 2017, London, UK Prevention and control of HPV and HPV related cancers in Ireland and the UK: lessons learnt and the way forward, 30 November - 1 December 2017 The role of HCP in HPV vaccination and screening programme implementation - Prevention and control of HPV and HPV related cancers in Romania, 15 & 16 May 2018 Prevention and control of HPV and HPV related cancers in Colombia: Lessons learnt and the way forward - 15 & 16 November 2018 HPV Vaccination of Adults: Impact, Opportunities and Challenges - 14 & 15 November 2019
Conclusions: The HPV Prevention and Control Board has been actively playing a role in the prevention and control of HPV and HPV related cancers. Therefore, it's essential to maintain a platform that brings together different key stakeholders in order to effectively contribute towards cervical cancer elimination.

ANALYSIS OF PREVALENCE OF HUMAN PAPILLOMA VIRUSES OF HIGH CARCINOGENIC RISK IN WOMEN CO-INFECTED WITH HIV-1 AND M. TUBERCULOSIS IN THE CONTEXT OF HIV/TB-ASSOCIATED PATHOLOGIES

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Cervical cancer caused by human papillomavirus of high carcinogenic risk (HR-HPV) is one of the most common pathologies in HIV infection. Out of HR HPV infections and cervical inflammation 67% cases are associated with tuberculosis (TB). The goal of the work was to study the prevalence of HR-HPV types in women co-infected with HIV-1 and TB in the context of HIV/TB-associated pathologies.
Methods: The study enrolled 58 patients with HIV/TB co-infection treated at two big medical TB centres. For the HPV-detection cervical smears were collected with further DNA isolation and PCR analysis using commercial kit detecting HPV types 16,31,33,35,18,39,45,52,56,58,59,66(AmpliSens® HPV HCR genotype-EPh,InterLabService). Material was amplified with specific primers, and regions encoding E6 and E7 were sequenced.
Results: The median age of patients was 25 years(21÷60). Most patients had infiltrative tuberculosis(37.8%) followed by disseminated pulmonary tuberculosis(27.1%). Upon submission patients were ART-naive (n=26) or treated for<1 month (n=8), the rest (n=24) received ART and anti-tuberculosis therapy for≥3 months. Over the period of 4-6 months the majority (79.3%;46) had one sexual partner. Only 13.8%(8) reported no sexual activity. HR-HPVs were detected in 58.6% cases: HPV16 in 22(37.9%), and other HR-HPVs in 12(20.7%). Twelve patients(20.7%) were infected with multiple HR-HPVs. There was no difference in HPV16-detection rate in ART-, ART+anti-TB-treated and naïve individuals. However, the rate of other HR-HPV types and multiple HR-HPV infections increased in HIV/TB-patients on ART/TB-treatment compared to untreated individuals (75% vs to 25%, p=0.01).
Conclusions: TB infection in HIV-positive women is characterized by high prevalence of infection with HPV16 and multiple HR-HPV types. The high rate of HR-HPV types other than HPV16 seems to increase in patients on ART, whereas prevalence of HPV16 is not influenced by ART or TB treatment. Altogether, this indicates multiple/repeated HR-HPV infections and low rate of spontaneous HPV clearance. Study was supported by RFBR grants 17_54_30002 and 20-04-01034.

DEVELOPMENT OF HPV18 RT-QPCR FOR A POTENTIAL USE AS TRIAGE TEST FOR HPV18 DNA+ WOMEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Since January 2020, cervical cancer precursor screening in Germany is recommended for women above 35 years and includes DNA testing of oncogenic HPV and cytological co-testing every three years. This change in the routine screening program increases the need for triage tests. A promising option is the detection of HPV16 RNA patterns predicting the presence of mild (≤CIN1) versus severe cervical abnormalities (≥CIN3). However, this assay is specific for HPV16 and not suited for cervical lesions driven by HPV18. Aim: To develop a high-throughput quantitative reverse transcriptase (qRT-)PCR assay for the detection of three HPV18 spliced transcripts (E6*I, E1^E4, E1C) as previously reported for HPV16.
Methods: In vitro RNA transcripts were generated from HPV18 plasmids and quantified by specific primers and probes in qRT-PCRs using the Cobas Z 480 system.
Results: The HPV18 spliced transcripts E6*I, E1^E4 and E1C were specifically and sensitively quantified in qRT-PCRs. There was no cross-reaction observed with the corresponding full-length transcripts, or between the spliced transcripts. Detection limits were determined using ten-fold serial dilutions of RNA transcripts and 10 to 100 copies per PCR could be successfully detected with an efficiency of 1.93-2.12. To identify HPV18 RNA patterns discriminating mild from advanced lesions, collection of cervical smear samples stored in PreservCyt from a colposcopy clinic is ongoing. Among 72 HPV18 single positive samples collected so far, we identified 12 histologically normal, 10 CIN1, 22 CIN2, 18 CIN3, 2 invasive squamous cell carcinoma, and 1 adenocarcinoma; 7 were analysed by cytology only (3 ≥ PapIIID).
Conclusions: We developed sensitive and specific HPV18 RT-qPCRs for the detection of three potentially diagnostically relevant RNA transcripts. Validation experiments in cervical smear samples to test HPV18 RNA patterns as triage test for non-HPV16-positive lesions are ongoing.

POPULATION DIFFERENCES BETWEEN USERS OF THE HRHPV SELF-SAMPLING TEST AND THE CLINICIAN-COLLECTED TEST IN THE NETHERLANDS

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In the first two years of the new high-risk Human Papillomavirus (hrHPV)-based cervical cancer screening programme in the Netherlands, differences between the clinician-collected test and the self-test in hrHPV positivity and CIN2+ detection were observed. We investigated whether these differences could be explained by population characteristics.
Methods: Using data from the Dutch national pathology database (PALGA), all primary screening tests were selected from women eligible for screening in 2017 and 2018. Data on socioeconomic status, migration background, number of people in the household, household income and position in the household from Statistics Netherlands were securely linked via a trusted third party to PALGA data in an individual-level. Data was linked in October 2019. Proportions of women within each category were calculated for each variable and by test type. Further statistical analysis will be performed.
Results: There was a higher proportion of young women (<40 years) amongst self-test users (27.6%) than amongst clinician-collected users (22.3%). A slightly higher proportion of self-test users were Dutch (83.3%) compared with clinician-collected testing (80.5%). A higher proportion of self-test users live in 1- or 2-person households (47.5%) compared with clinician-collected testing (40.0%). Similar proportions of participants were employed (self-test: 77.6%; clinician-collected: 78.8%) and had higher household incomes (self-test: 37.4%; clinician-collected: 38.3%) across both tests. A higher proportion of self-test users were the main breadwinner in the household (38.6%) compared with clinician-collected testing (34.7%).
Conclusions: A higher proportion of self-test users are younger, are Dutch, are the primary bread winner in the household and live in smaller households, although the latter two factors may be related to age. However, the differences users of the two tests are small. Our results indicate that the differences observed between the self-test and clinician-collected testing cannot be explained by population differences, but are probably due to technical reasons.

THE STRENGTH OF THE ASSOCIATION OF BACTERIAL VAGINOSIS AND HPV INFECTION DIFFERS ACCORDING TO THE GENOTYPE

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: There is good evidence that vaginal dysbiosis, specially bacterial vaginosis (BV) is associated with HPV infection. Less is known about the strength of these relations according to the genotypes involved.
Methods: Post-hoc analysis of data collected for the validation of a molecular test for the diagnosis of vaginitis. All women had a vaginal sample collected for Nugent score. The women who had an HR-HPV test (cobas® HPV) performed as part of their routine care or because they were under follow-up for a previous positive HPV test/abnormal Pap test were selected for analysis.
Results: Out of 761 women enrolled, 308 had an HR-HPV test performed. Women with BV were more likely to be HPV positive. These differences were statistically significant when the outcomes were: any HPV infection, HPV18 or HPV16/18. For HPV16 and genotypes other than 16/18, there was a trend, but not significant. Women with BV had a relative risk of having HPV18 of 2.47 (1.39-4.37); the risk of having any HR-HPV was 50% higher if BV was present.

	BV (Nugent score)			
	Positive	Negative	p	RR
HPV any	45.7% (37/81)	32.2% (73/227)	0.032	1.51 (1.05-2.19)
HPV16	12.3% (10/81)	7.9% (18/227)	0.262	1.41 (0.82-2.41)
HPV18	6.2% (5/81)	1.3% (3/227)	0.032	2.47 (1.39-4.37)
HPV16/18	18.5% (15/81)	8.4% (19/227)	0.021	1.83 (1.19-2.82)
HPV others	39.5% (32/81)	27.8% (63/227)	0.068	1.46 (1.01-2.13)

Conclusions: While the sample was small, it showed a clear association between BV and HPV infection (50% increased risk). The association was disproportionately elevated for HPV18. It is uncertain if the dysbiosis is a risk factor for the acquisition and persistende of the HPV infection, or a consequece of it. Further studies are needed to evaluate the role of the treatment of dysbiosis as part of the prevention of acquisition of HPV infection in women at risk, and in those already infected.

HPV INFECTION AND VACCINATION: AWARENESS AND KNOWLEDGE AMONG UNVACCINATED PATIENTS ATTENDING SEXUALLY TRANSMITTED INFECTION CLINICS IN PUERTO RICO.

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Research shows that lack of HPV knowledge varies by gender and is associated with low HPV vaccine uptake. This study assessed awareness and knowledge of HPV infection and vaccination among unvaccinated patients attending sexually transmitted infection (STI) clinics in Puerto Rico.
Methods: Data from an ongoing cross-sectional study (November 2018-present) among men and women receiving services at STI clinics in the San Juan metropolitan area of Puerto Rico was analyzed. HIV-negative, sexually active individuals aged 21-49 years are eligible for this study and participate in an interviewer-administered questionnaire that collects information on sociodemographic and lifestyle characteristics. Unvaccinated patients were included in the current analysis.
Results: Of 98 patients, 59.2% were men; mean age was 32.0±7.6 years. Most participants were single (66.3%), 60.2% reported having public insurance, and 36.5% reported ≥21 lifetime sexual partners. More than three quarters (82.5%) reported having heard about HPV infection, and only 43.8% have heard of the HPV vaccine. More women than men were aware of the HPV vaccine (60.0% vs. 32.8%, $p<0.05$). Most participants knew that HPV causes cervical (100.0%), anal (100.0%), and oral (97.0%) cancer. Many erroneously thought that HPV could disappear without treatment (64.2%) and that infected individuals usually know (82.7%) and always present symptoms (69.1%). More than two-thirds (64.2%) believed that HPV infection is uncommon, and almost half of them (48.2%) mentioned that condom use always prevents HPV transmission. The main reasons for not having the HPV vaccine included vaccine unawareness (38.7%), having limited knowledge about it (16.0%), and concerns about its side effects (9.3%). There were no differences in HPV knowledge between men and women, although vaccine awareness was higher in women.
Conclusions: STI clinics represent an important venue to raise awareness and knowledge of HPV infection and vaccination among high-risk adults in Puerto Rico (NIDCR Grant R21DE027226-02).

NON-SPECULUM CLINICIAN SAMPLINGTO INCREASE CERVICAL SCREENING UPTAKE IN OLDER WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: The speculum can become uncomfortable after the menopause which may reduce screening uptake in older women. Self-sampling is an obvious solution but 50%-70% of women worry about not taking a good sample. HPV testing on clinician-collected vaginal samples without a speculum (non-speculum) is another possibility and may particularly appeal to older non-attendee women who prefer the reassurance of a clinician-taken sample but find the speculum uncomfortable.
Methods: An RCT offering non-speculum HPV testing was carried out at 10 GP practices in London (UK) between Aug18-Nov19 to assess feasibility in the target population. Eligible women were aged 50-64 who were overdue screening by >1y and had attended at least once in the past 15-years (i.e. lapsed attenders). Women were identified using GP electronic records and were randomised (1:1) at a single timepoint to either an Intervention arm (sent letter offering the choice of booking an appointment for a non-speculum clinician sample or ordering a self-sampling kit); or Control (usual care). Study samples were collected using a flocked swab (Copan 552C), transported dry, resuspended in ThinPrep prior to analysis using Roche Cobas4800.
Results: A total of 809 women were randomised (intervention n=404, control n=405). Overall uptake in the intervention arm was 18% (73/404) and was highest for SS (10.9% (44/73) SS vs 7.2% 29/73) NS). Analysis is ongoing and will be updated (including data on screening uptake (including conventional screening) at 4m and 12m after randomisation in both arms, attendance to follow up after for HPV positive on a NS or SS).
Conclusions: Preliminary data show that non-speculum clinician sampling for HPV testing is a viable option which appears to enhance uptake in older women, over and above the impact of self-sampling alone.

CERVICAL CANCER SURVEILLANCE AMONG WOMEN IN DAVIDSON COUNTY, TENNESSEE, UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Human papillomavirus (HPV) is among the most prevalent sexually-transmitted diseases, and the cause of most cervical cancer. The annual incidence of cervical cancer per 100,000 women is 8.0 in the United States, 8.4 in Tennessee (TN), and 6.2 in Davidson County. Most cervical cancer is preventable through HPV vaccination and/or through screening.
Methods: We identified 350 Davidson County women with cervical cancer diagnoses from 2008-2018 through the TN Cancer Registry. We completed medical record review on 107 women for: age, race, insurance, histology, symptoms, immunocompromised and smoking status, social barriers to screening and screening status (Table 1). We compared these variables among women with Stage I versus Stages II-IV cancers.
Results: The 107 women were 55% White, 29% Black and 11% Hispanic. Most (63%) were ages 40-64 years, had squamous cell carcinoma (70%), presented with symptoms (82%), and had one or more social barriers to screening (57%). There were 13% of women who were uninsured including 7% with Stage 1 and 20% with Stages II-IV. Almost all (96%) women with Stages II-IV presented with symptoms versus 70% of women with Stage I. Overall, 60% of women lacked appropriate screening, 17% had delayed follow-up after an abnormal screening test and only 12% had a false negative screening test that contributed to delay in diagnosis. More (71%) women Stages II-IV failed to be screened versus only 50% of women with Stage I. Furthermore, 23% of women with Stage I failed to follow-up versus 10% with

Table 1: Cervical Cancer Surveillance: Stage I vs Stages II-IV		Stage I	Stages II - IV	All Stages
		N=56	N=51	N=107
Age Groups	18-39	34%	10%	22%
	40-64	52%	75%	63%
	65+	14%	16%	15%
Race/Ethnicity	White	63%	47%	55%
	Black	21%	37%	29%
	Hispanic	13%	10%	11%
	Other/Unknown	4%	6%	5%
Health Insurance	Private	43%	29%	36%
	Public	48%	51%	50%
	Uninsured	7%	20%	13%
	Unknown	2%	0%	1%
Cancer Histology	Squamous cell carcinoma	63%	78%	70%
	Adenocarcinoma	34%	18%	26%
	Adenosquamous carcinoma	2%	0%	1%
	Other carcinoma	0%	4%	2%
	Unknown carcinoma diagnosis	2%	0%	1%
Presenting Symptoms[a]	Yes	70%	96%	83%
	No	27%	2%	15%
	Unknown	4%	2%	3%
Immunocompromised	Yes	9%	2%	6%
	No	89%	98%	93%
	Unknown	2%	0%	1%
Smoking Status	Yes	46%	53%	50%
	No	52%	45%	49%
	Unknown	2%	2%	2%
Social Barriers[b]	Yes	57%	57%	57%
	No/Unknown	43%	43%	43%
Screening Classification[c]	Failure to be screened	50%	71%	60%
	Failure to follow up	23%	10%	17%
	Failure of screening test	13%	12%	12%
	Cannot be determined	14%	8%	11%

Presenting Symptoms[a]: vaginal bleeding, pelvic pain, pain with intercourse
Social Barriers[b]: language, lack of insurance, substance abuse, serious mental illness, obesity, incarceration, and homelessness
Screening Classification[c]: failure to be screened (no Papanicolaou [Pap] test in 3 years or no Pap and HPV co-test in 5 years prior to diagnosis), failure of follow-up (greater than one-year lapse between abnormal screening test and follow-up), and failure of the screening test (appropriate screening and/or follow-up yielded false-negative results)

Stages II-IV.

Conclusions: In the age of the HPV vaccine era, women still develop cervical cancer. Overall, most women progressed to cancer in our county due to lack of screening. These results emphasize the importance of routine screening and appropriate follow-up, and more education on cervical cancer screening guidelines.

ACCEPTABILITY OF CLINICIAN-TAKEN SAMPLES WITHOUT A SPECULUM FOR CERVICAL SCREENING IN OLDER WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: in the UK women aged 65+ account for 20% of cervical cancer incidence. Most are in women inadequately screened when aged 50-64y. The speculum can become a significant barrier to screening postmenopause. Self-sampling is an obvious solution, but many women worry about taking their sample correctly. Clinician sampling without a speculum(non-speculum) is another possibility and may appeal to women who prefer the reassurance of clinician-sampling.
Methods: A questionnaire was included in an RCT of non-speculum clinician sampling in women aged 50-64 who had not attended screening in the last 6y (but at least once in the past 15-years). Eligible women at 10 GP practices in London were randomised(1:1) to either Intervention (sent letter offering the choice of a non-speculum clinician sample or ordering a self-sampling kit); or usual care. Recruitment took place from Aug 2018-Nov 2019. Questionnaires were either given to women at clinic (non-speculum) or included in the self-sampling kit. Questions were mainly closed (Likert scales) and inquired about experiences of the test and future screening preferences.
Results: Preliminary results (analysis ongoing): A total of 29 women had a non-speculum clinician sample (NS) and 44 women self-sample (SS). Response rate was high 83% (61/73), but lower in the women who chose NS (66% (19/29) vs SS 95% (42/44)). Unsurprisingly both NS and SS scored highly in measures of acceptability, with no obvious differences between approaches. Confidence that their sample was taken correctly was higher for NS (83% vs 72% reported being either “very confident” or “fairly confident”. A high proportion of women (88% (SS) and 70% (NS)) in both groups either “agreed” or “strongly agreed” that it was important to have a choice between the two tests.
Conclusions: Non-speculum clinician sampling may be a valuable supplement to self-sampling and that including a choice, could be beneficial.

EVALUATION OF COLLECTION DEVICES FOR HPV DIAGNOSIS IN MEN

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF GENITAL AND SKIN WARTS

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Introduction: The awareness of human papillomavirus (HPV) infections in men is on the rise which goes along with an increasing demand for HPV testing. Hence, there is a need for the evaluation of a sampling device for the genital, anal, and pharyngeal region using standardized procedures. Aim of the present study was to compare the FLOQSwab® 5E046S (Copan Italia Spa) with the brush from the PapilloCheck® Collection Kit (Greiner Bio-One GmbH) in symptomatic and asymptomatic male patients for different sampling areas in order to assess the most adequate collection device.
Methods: For the evaluation of the optimal collection device, duplicate specimens from 200 male patients were collected with both, brush and FLOQSwab® in a randomized order and standardized procedure. Penile, perigenital, pharyngeal and anorectal specimens were tested for HPV at the Outpatient´s Centre for Diagnosis of Infectious Venero-dermatological diseases by using the PapilloCheck®, a microarray-based assay which allows the detection and identification of 18 high risk (hr) and 6 low risk (lr) HPV genotypes.
Results: Out of 200 duplicates a positive HPV result was achieved in 99 (49.5%) samples collected with the FLOQSwab® and 100 (50.0%) with the brush**.** Invalid results with the FLOQSwab® (14/200) were significantly lower (p-value 0.009) compared to the brush (26/200). For 75 (37.5%) duplicates discrepant results were achieved, with the FLOQSwab® being more likely to detect multiple infections compared to the brush.
Conclusions: It has been shown that the FLOQSwab® has an approximately 50% lower rate of invalid results and detects more HPV genotypes in men (p-value 0.021) compared to the brush from the PapilloCheck® Collection Kit. Therefore, the FLOQSwab® can be recommended as a sampling device for HPV diagnosis in men under standardized procedures.

STRIDES: STUDYING RISK AND DISPARITIES IN CERVICAL CANCER SCREENING IN MISSISSIPPI. BASELINE RESULTS FROM A NEW STATEWIDE COLLABORATIVE INVESTIGATION WITH THE U.S. NATIONAL CANCER INSTITUTE.

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Mississippi has the highest mortality rate from cervical carcinoma in the United States, with Black women dying at two times the rate of Whites. We developed a statewide cohort and biospecimen collection of women undergoing cervical cancer screening, to study natural history, precancer risk, and biomarker performance in a diverse, understudied population.
Methods: From 12/23/2017 to 12/22/2019, 20,831 women underwent cervical cancer screening at the Mississippi State Department of Health (MSDH) and University of Mississippi Medical Center. Screening was based on HPV-cytology cotesting. The current analysis was restricted to 17,899 women with Black or White race. HPV results are shown for a subset of 4,384 women from MSDH undergoing cotesting at age 30+ and ASC-US triage <30. We computed contingency tables and chi-square tests for baseline population characteristics.
Results: This population included 12,395 Black women (69.2%) and 5,504 White women (30.8%). No significant differences of cytologic categories by race were observed. HPV positivity in women <30 years with ASC-US was 61.6% in Blacks versus 51.9% in Whites (p=0.08). In women 30+, no significant differences in HPV positivity by race were observed (19.3% in Blacks and 19.3% in Whites; p=0.95). However, the genotype distribution differed significantly by race. Black women had fewer HPV 16/18 (20.1%) compared to White women (28.1%). Conversely, Black women had more HR 12 types compared to White women, 79.9% versus 71.9%, (p=0.015).
Conclusions: Black women have a significantly higher proportion of HR 12 and a lower proportion of HPV 16/18 among all HPV infections compared to White women. Possible biological differences that contribute to lower HPV 16/18 in Blacks require additional study, like extended genotyping. Our prospective cohort will evaluate a novel next-generation sequencing extended genotyping assay, dual stain, and viral methylation, among other assays.

ADJUNCTIVE TESTING BY CYTOLOGY, P16/KI67 DUAL-STAINED CYTOLOGY OR HPV16/18 E6 ONCOPROTEIN FOR THE MANAGEMENT OF HPV16/18 SCREEN-POSITIVE WOMEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPV16/18 genotyping is unable to discriminate non-progressive HPV infections from those that will progress to high-grade cervical lesions and cervical cancer. Therefore, the use of further tests based on progression markers might help to prevent potential harms and unnecessary costs by reducing colposcopy referrals. The present study assesses if additional testing either with cytology or the putative progression markers p16/KI67 and HPV16/18 E6 oncoprotein can improve the prediction of cervical precancer and cancer in women referred to colposcopy for HPV16/18 infections.
Methods: Women attending colposcopy after positive results to HPV16/18 genotyping within the FRIDA hrHPV-based screening study in Tlaxcala, Mexico, underwent further testing with liquid-based cytology (LBC), p16/ki67 dual-stained cytology (DS) and HPV16/18 E6 Oncoprotein (E6). Histologically-confirmed cervical intraepithelial neoplasia grade 2 or higher (CIN2+) and grade 3 or higher (CIN3+) were used as disease outcomes.
Results: 475 women of 739 HPV16/18 positive women had complete results for all adjunctive tests. Triage positivity rates were 14.1%, 18.5% and 24.4%, for LBC, E6 and DS, respectively. Of the women who attended colposcopy, 67 CIN2+ and 45 CIN3+ were detected. Five invasive cancers were identified and, none were missed by DS or E6, but four were cytologically normal. Compared to LBC, DS had higher sensitivity (24.4% vs 60.0%) although lower specificity (87.0% vs 79.3%) for CIN3+ ($p<0.001$), whereas E6 had a sensitivity of 37.8% and a specificity of 83.5%. Similarly, DS had significantly higher sensitivity for CIN2+ (55.2%) than either LBC (23.9%) or E6 (31.3%). Furthermore, DS triage of HPV16/18 positive women was able to reduce colposcopy referrals by almost 75% and allowed for the least number of colposcopies (n=4.3) per CIN3+ detected.
Conclusions: We show that adjunctive testing of HPV16/18 positive women with DS may greatly reduce unnecessary colposcopy referrals within HPV-based screening employing HPV16/18 genotyping while retaining good sensitivity for CIN2+ and CIN3+.

COST-EFFECTIVENESS OF HPV VACCINATION IN GIRLS LIVING IN LATIN AMERICAN COUNTRIES: A SYSTEMATIC REVIEW

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: Our objective was to synthesize the results of cost-effectiveness studies on HPV vaccination of girls under 18 years of age living in Latin America.
Methods: We systematically searched MEDLINE, EMBASE, the Cochrane Library, LILACS and Web of Science until October 2019. Two reviewers independently selected articles and extracted data. We extracted data related to the population, intervention, control, model, and results. Incremental cost-effectiveness ratios (ICERs) were assessed with data converted to international dollars (I$) and inflated to 2018 value using the Consumer Price Index. We assessed risk of bias with the Consensus on Health Economic Criteria (CHEC) checklist for economical evaluation.
Results: We screened 325 articles from all databases and found 20 cost-effectiveness studies of HPV vaccination in Latin America. Age at vaccination ranged from 9 to 12 years. Most studies compared 3 doses of HPV vaccine plus screening against screening alone, cytology being the most common screening method. Eight studies considered anogenital warts as well as cervical cancer. There were four dynamic models, two hybrid, and the rest static; the most common perspective was of the health care payer, six studies assessed the bivalent vaccine, ten the quadrivalent vaccine, and seven did not differentiate between them. Discount rates ranged from 3% to 6%. There was great heterogeneity between studies in the assumed vaccine efficacy, screening sensitivity, coverage rates both for the vaccine and the screening, and willingness to pay threshold. Only two studies concluded that HPV vaccination was not cost-effective. Inflated ICERs ranged from cost-saving to I$146,459. The mean ICER for the bivalent vaccine was I$15,927 and I$8,775 for the quadrivalent vaccine. The societal perspective had a mean ICER smaller than the health care payer perspective, I$ 4,838 and I$16,265, respectively.
Conclusions: HPV vaccines and screening were cost-effective compared to screening alone in most Latin American studies.

INCIDENCE AND RISK FACTORS FOR HIGH-RISK HPV TYPES IN MAYUGE DISTRICT, UGANDA (ASPIRE MAYUGE): RESULTS FROM ARM 1

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Uganda has one of the highest cervical cancer incidence rates in the world (54.8 per 100,000) as a result of limited screening access and infrastructure. The ASPIRE Mayuge trial uses a pragmatic, sequential, cluster randomized trial design to compare the effectiveness of two cervical cancer screening models for self-collected HPV testing: 1) community health worker recruitment (door-to-door); and 2) community health meetings. The aim of this study was to determine incidence of high-risk HPV (HR-HPV) types and explore risk factors for HR-HPV infection among arm 1 participants.
Methods: Data presented are taken from the arm 1 (door-to-door) study sample. Women are eligible to participate if they have no previous history of hysterectomy or treatment for cervical cancer or pre-cancer and are aged 25-49 years. Samples are tested for HR-HPV using GeneXpert point of care testing. Test results were summarized and association between demographics, and medical/obstetric history was assessed using a multi-level logistic regression model with cluster as a random intercept.
Results: Between August 7, 2019, and December 31, 2019, 1060 women were recruited to participate in arm 1 and 5 were lost to follow-up. The incidence of any HR-HPV infection was 28.1% (296/1055) with strains 31, 33, 35, 52, and 58 being most common (118/296; 11.2%). HPV 16 (50/296; 4.7%) and HPV 18 (73/296; 6.9%) incidence was low. Independent associations with positive HPV status included: younger age, unmarried, lower primary education, and younger age at first childbirth. These are interim results as the study is ongoing.
Conclusions: High-risk HPV infection was common among this eastern Ugandan population and dominated by types that are not impacted by use of the quadrivalent vaccine, the only available HPV vaccine in the country. Secondary prevention through ongoing screening will be critical in achieving the World Health Organization’s target of cervical cancer elimination. Trial registration: ISRCTN12767014; NCT04000503.

MIXED MS2-L2 VLPS PROTECT AGAINST AN HPV TYPE ASSOCIATED WITH UP TO 66% OF GENITAL WARTS AND RECURRENT RESPIRATORY PAPILLOMATOSIS

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: Current human papillomavirus (HPV) vaccines protect against HPV types associated with ~90% of cervical cancers and are expected to protect against a percentage of HPV-associated head and neck cancers. We had previously developed an L2 candidate HPV vaccine based on bacteriophage MS2 virus-like particles (VLPs) *(Zhai et al., Antiviral Research, 2017 and 2019)*. The candidate vaccine consists of a mixture of two MS2-L2 VLPs displaying: i) a concatemer of L2 peptide from HPV31 (epitope 20-31) and from HPV16 (epitope 17-31); ii) a consensus L2 peptide representing epitope 69-86. Mixed MS2-L2 VLPs protected mice against genital infection with nine different HPV types (HPV11, 16, 18, 31, 33, 45, 53, 56, and 58) and also protected mice against oral infection with five HPV types (HPV16, 35, 39, 52, and 58).
Methods: Mice were intramuscularly immunized with mixed MS2-L2 VLPs and serum was collected at two weeks/one-month intervals after the last immunization. Antibody titers in serum were assessed by peptide ELISA and mice were challenged with HPV pseudovirus types 5, 6, and 51. To formulate the VLPs into a powder, mixed MS2-L2 VLPs were mixed with MTDL. The mixture was spray-freeze dried (SFD) into a powder and stored at 37º C for two months. The powder was then reconstituted in a buffer and the integrity & immunogenicity of the VLPs were assessed.
Results: Recent data show that antibody titers against HPV16 and HPV31 peptides (epitope 17-31) and against a consensus HPV peptide (epitope 69-86) last up to 4 months (ongoing study). Additionally, mixed MS2-L2 can protect mice against three additional HPV types, one of which is associated with up to 66% of genital warts and recurrent respiratory papillomatosis. Furthermore, SFD mixed MS2-L2 powder is thermostable at 37º C for two months and is immunogenic.
Conclusions: Mixed MS2-L2 VLPs is a candidate HPV vacine.

HEALTHY MALE UROGENITAL TRACT MICROBIOME COMPOSITION BY AGE, HIV AND HPV INFECTION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Studies about circumcision role in prevention of HIV and human papillomavirus (HPV) infection have suggested the potential relevance of urogenital microbiota. The objective of this study was to explore the association of penile microbiota composition with age, HIV and HPV infection.
Methods: Public data of penile microbiota (glans, coronal sulcus, and shaft) from healthy heterosexually-active Black South African men were analyzed. Sequencing data (V3-V4 region, Illumina MiSeq), penile asymptomatic papillomavirus (HPV) infection (Roche Diagnostics) and clinical data submitted by the University of Cape Town (August 2019) were accessed from the European Nucleotide Archive (https://www.ebi.ac.uk/ena/browser/view/PRJNA559354). Amplicon sequence variants were obtained (DADA2 R package, silva 132 database). Association study was performed (Phyloseq R package). Simpson's diversity index was compared (Wilcoxon or Kruskal-Wallis rank sum test, generalized linear model, $p<0.05$). Compositional analysis was performed (Selbal R package).
Results: We selected 242 samples out of 288 (patients sharing circumcision information, good quality sequencing data). Mean age was 38.5 years (22-67). Prevalence of HIV, any HPV and HPV16/18 infection were 38.4%, 55.6% and 12.5%, respectively. The most abundant Phylum were *Actinobacteria, Firmicutes and Bacteroidetes*. The most abundant Genus were *Corynebacterium, Finegoldia, Anaerococcu*s and *Corynebacterium*. In the studied population, alpha diversity increased with age (p = 0.024 unadjusted, p=0.067 adjusted by sequencing library). Alpha diversity was not associated with HIV, HPV or HPV16/18 infection. Shifts in two taxa abundance were associated with age: A higher relative abundance of *Brevibacterium* and a lower relative abundance of *Cutibacterium or Micrococcus* were found as age increased (30% cross validation, unadjusted or adjusted by sequencing library or HIV infection).
Conclusions: Age may influence penile microbiota in healthy men. Further studies would be necessary to replicate these findings. It could be interesting to assess the association between urogenital microbiota and persistant HPV penile infection and its impact on men health.

DETECTION OF ALPHA, BETA, GAMMA AND UNCLASSIFIED HUMAN PAPILLOMAVIRUSES IN CERVICAL CANCER SAMPLES FROM MEXICAN WOMEN

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: Cervical cancer (CC) is associated to high-risk-HPV infections. Accurate HPV genotyping is crucial for patient surveillance and treatment. However, to date, most HPV diagnostic tests are focused on Alphapapillomavirus (α-PVs) genus and little attention has been paid to cervical infections with other HPV genotypes, like those of the Betapapillomavirus (β-PVs) and Gammapapillomavirus (γ-PVs) genera. The aim of this study was to determine the HPV genotypes from different genera in women with CC.
Methods: The study comprised 48 CC samples analyzed by Linear Array HPV-Genotyping test and individually sequenced with 454 Next-Generation-Sequencing (NGS) using PGMY09/11 and FAP primers. The sequences obtained were compared with HPV-L1 gene reference sequences from the Papillomavirus Episteme database (PaVE).
Results: Among the forty-eight CC samples, 51 different HPV genotypes were detected, of which 7 are still unclassified, 28 belong to *α-PVs* (6, 11, 16, 18, 26, 30, 33, 35, 39, 42, 43, 44, 45, 51, 52, 53, 54, 59, 62, 66, 68, 69, 70, 71, 74, 81, 102, 114), 10 to *β-PVs* (5, 12, 21, 37, 38b, 47, 80, 107, 118, 122), and 6 to *γ-PVs* (101, 103, 123, 135, 147, 214). Moreover, 79.2% of the samples consisted of multiple HPV infections, whereas the remaining 20.8% consisted of a single genotype. Among all samples HPV16 was the most prevalent genotype (54.2%), followed by HPV18 (16.7%), HPV38b (14.6%), and HPVs 52/62/80 (8.3%).
Conclusions: This study reports for the first time the presence of Beta- Gamma- and still unclassified papillomavirus specifically in CC samples detected by NGS. The high prevalence of *β-PVs* genotypes 38b and 80 may suggest their possible role as carcinogenetic co-factors. The direct relation of hr-HPVs in CC has been widely studied, but future work must focus on the role of *β-* and *γ- PVs* during malignant progression and the significance of papillomavirus coinfections.

HIGH-RISK HUMAN PAPILLOMAVIRUS SCREENING RESULTS USING ROCHE COBAS® 4800 HPV TEST AT TWO SITES IN THE SURQUILLO DISTRICT IN LIMA, PERU

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical cancer (CC) is a leading cause of death among women worldwide with 85% of deaths occurring in low-resource countries. High Risk HPV (HR-HPV) testing has gained increased usage for CC risk screening. HR-HPV testing was used for primary screening among general population and a sex worker cohort attending the Surquillo Health Center (SHC) and triage screening at the Instituto Nacional de Enfermedades Neoplásicas (INEN). This is the first instance of HR-HPV testing and reporting of HR-HPV prevalence for Surquillo.
Methods: Women who met the inclusion criteria were screened using Roche cobas® HPV test, which reports pooled results for HR-HPV genotypes and individual results for the highest-risk genotypes, HPV 16 and HPV 18.
Results: At INEN 374 women were recruited, 45% (167) were HR-HPV positive with prevalence highest for women 30–39 (32%). HPV16 accounted for 36% (60), HPV18 for 4% (8), and other HR-HPVs for 60% (100). At SHC 626 women were recruited, 312 from the general population and 314 from a cohort of sex workers. In the general population, 21% (65) were HR-HPV positive with prevalence highest for women 20–29 (42%). HPV16 accounted for 23% (15), HPV18 for 8% (5), and other HR-HPVs for 69% (45). In the sex worker cohort 27% (86) tested HR-HPV positive with prevalence highest for women 20–29 (67%). HPV16 accounted for 16% (14), HPV18 for 6% (5), and other HR-HPVs for 78% (67).
Conclusions: HR-HPV prevalence in Surquillo surpasses global average (10%) in both the general population (21%) and sex workers (27%). HPV 16 and 18 were comparable among the cohorts with other HR-HPVs accounting for the increase. We observed the highest HR-HPV prevalence among women undergoing triage at INEN (45%). Together these observations suggest a need for improved screening and interventions.

CROSS-SECTIONAL AND PROSPECTIVE EVALUATION OF A REFERRAL POPULATION WITH SUSPECTED CERVICAL DYSPLASIA BY QUANTIGENE-MOLECULAR PROFILING HISTOLOGY BIOMARKER ASSAY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Current non-invasive cervical dysplasia screening and triage methods have limited accuracy for diagnosis of underlying disease stage. The innovative QuantiGene-Molecular Profiling Histology (QG-MPH) assay combines HPV oncogene and biomarker expression and calculates risk scores for high grade dysplasia from a cervical LBC smear. A referral subpopulation of the MOLTRIAGE study was analyzed by QG-MPH assay for detecting underlying disease and its prospective development.
Methods: Risk scores and related Cut-Off values for the QG-MPH had been developed with data from a large referral population for the disease stages CIN2+, CIN3+ and CxCa. Women referred to colposcopy were recruited. Clinical data was collected from medical health records including cytology, histology and standard HPV-test results. QG-MPH assay (QuantiGene 2.0 platform, ThermoFisher) was performed on cervical smear samples (collected in ThinPrep®). Risk scores for CIN2+ and CIN3+ from QG-MPH data were calculated and compared to histological endpoints CIN2+ and CIN3+.
Results: Cross-sectional data of 287 patients and prognostic results of 166 patients with a non-intervention follow-up after >3 months were identified. Comparison of QG-MPH risk scores to diagnosis had a sensitivity/specificity for CIN2+ of 76.1%/56.1% and for CIN3+ of 86.5%/37.9%, respectively. Regarding prospective histologic findings as endpoints, sensitivity and specificity was similar with 77.0% /55.4% for CIN2+, 90.2%/39.2% for CIN3+, respectively. The subanalysis of 31 follow-ups after initial CIN2 diagnosis showed that the QG-MPH risk score from the first visit corresponded with CIN2 lesion development. In progressive/stable/regressive lesions the QG-MPH risk score CIN2+ was positive in 92.9%/70.6%/58.3%, respectively. It was negative in progressive/stable/regressive lesions in 7.1%/29.4%/41.7%, respectively.
Conclusions: QG-MPH risk scores (including quantified HPV oncogene and biomarker expression) detects high-grade dysplasia in a referral population. It may have a prognostic value for dysplasia development warranting further studies.

HIGH FREQUENCY OF HPV GENOTYPES 59, 66, 52, 51, 39 AND 56 IN WOMEN FROM WESTERN MEXICO

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus infection is an important factor associated with cervical cancer (CC) development. The prevalence and genotype distribution vary greatly worldwide. Local epidemiological data constitutes an important step towards the development of vaccines for the prevention of cervical cancer. In this work, we studied the prevalence of HPV genotypes in women from Western Mexico by COBAS 4800 and Linear Array Genotyping Test (LA).
Methods: Cervical samples from open population of women (n=3,000), and samples derived from cervical intraepithelial neoplasia grade 1 (CIN 1, n=77) or with cervical cancer (CC, n=66) of six States of Western Mexico (Aguascalientes, Colima, Jalisco, Michoacán, Nayarit and Guanajuato) were recruited. DNA was extracted, and HPV genotyping was performed by COBAS 4800. HPV-positive samples were additionally genotyped by LA.
Results: The overall HPV prevalence among open population of women was 12.13% (n=364). In the positive samples, single infections (SI) with HPV16 was detected in the 12.36% (n=45/364) of cases, while the positivity rates for SI with HPV18 or the pool of HPV genotypes detected by COBAS 4800 (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) was 1.37% and 74.45% respectively. LA analysis of the samples showed that there is a high prevalence of HPV59, 66, 51, 39 and 56, both in the open population of women, and in samples of women with CIN 1 and CC.
Conclusions: Our data indicate that there is high prevalence of HPV genotypes not included in the vaccines currently available in Mexico. More studies are necessary to determine the impact of HPV59, 66, 51, 39 and 56, on the risk of developing CC and precancerous lesions.

HPV PREVALENCE AND RISK FACTORS AMONG UNVACCINATED HIV-NEGATIVE AND HIV-POSITIVE SOUTH AFRICAN ADOLESCENT GIRLS: BASELINE RESULTS FROM THE HOPE STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The HPV vaccine One and two-dose Population Effectiveness (HOPE) study aims to assess the effectiveness of two different HPV vaccine dose strategies in preventing HPV 16 and 18 infection in sexually active South African adolescent girls.
Methods: From June to December 2019, we surveyed girls aged 17-18 years at 18 sentinel clinics in four South Africa provinces (Gauteng, Mpumalanga, North West and Free State). Eligible participants completed a self-administered demographic and risk factor questionnaire, underwent HIV counselling and rapid testing, and provided a self-collected vaginal swab for HPV testing using SeeGene Anyplex™ II HPV28 assay at a central laboratory. We assessed factors associated with HPV 16/18 infection using logistic regression (p value <0.05).
Results: Of 640 respondents, the median age sexual debut was 16 (IQR 16-17 years), 6% (25) reported sexual debut <15 years, and 75% (480) reported 2+ lifetime sex partners. HIV seropositive participants represented 27% (173) of the sample. Of these, 91% (158) were on anti-retroviral treatment (ART) (median months on ART 24 [IQR 5-85]). Overall HPV 16/18 prevalence was 22% (141), while any high-risk HPV prevalence was 59% (376). HPV 16/18 prevalence was almost two-fold higher in HIV positive (53/171, 31%) compared to HIV negative girls (88/467, 19%) (OR 1.90, 95% CI: 1.28-2.83). Having a non-vaccine type HPV infection (OR 13.43, 95% CI: 6.44-28.0), a history of vaginal sex (OR 4.32, 95% CI: 2.41-7.75), and using hormonal contraception (OR 1.82, 95% CI: 1.25-2.67) were also significantly associated with HPV 16/18 infection.
Conclusions: These data highlight the burden of HPV vaccine-type specific infection in an unvaccinated South African age cohort, especially among those living with HIV. This baseline survey will provide an important comparison for future estimates of vaccine impact among both HIV positive and negative populations. We will present updated final analyses.

UNDERSTANDING LONG TERM SEROLOGICAL PROTECTION FOLLOWING HPV VACCINES – EARLY DATA FROM A SUBSTUDY IN A RANDOMIZED CONTROLLED TRIAL IN THE GAMBIA

BASIC RESEARCH / IMMUNOLOGY

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Introduction: HPV vaccines provide exceptional protection against infection and disease through generating neutralizing antibodies. The antibody titres are sustained – showing no signs of waning over years, even after a single vaccine dose. Such sustained antibody responses are more typical of live-attenuated vaccines than sub-unit vaccines. It is thought that the repetitive structure of the virus-like particles (VLP) may enhance B-cell activation but the immunological mechanisms responsible for sustained titres are poorly understood. This study aims to characterise phenotypically and functionally the plasma cells, memory B-cells and T follicular helper cells (Tfh) – critical T-cell subset responsible for generation of high affinity antibodies generated by one and two doses of Gardasil 9.
Methods: ELISpot and Fluorospot assays have been established to enumerate antigen specific plasma cell and memory B cells. To test for HPV specific Tfh responses, T cells are stimulated with HPV 16 and 18 VLP and a mitogen (SEB) positive control. Activation of the Tfh subset is identified using an activation induced marker (AIM) flow cytometry panel. Flow cytometry is also being used to determine the phenotype of the plasma cells and memory B-cells after vaccination.
Results: HPV type specific IgM and IgG plasma cells (Figure 1) and memory B cells peaked at day 7 following a first vaccine dose and around day 5 following a second dose. Robust HPV 16 and 18 type specific Tfh responses were also demonstrated around the same timepoint (Figure 2).

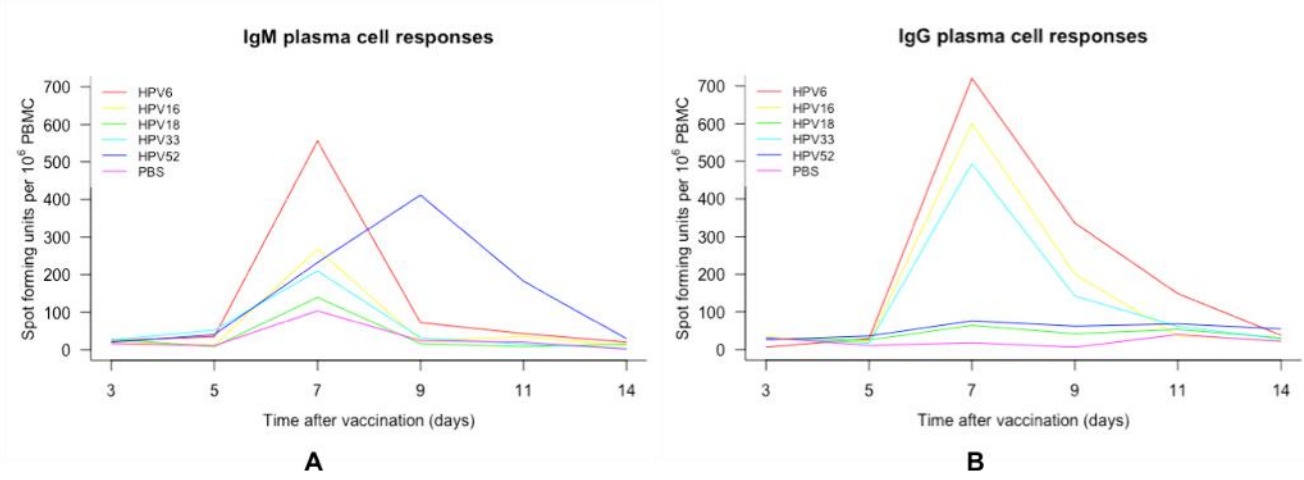

Figure 1: HPV type specific IgM (**A**) and IgG (**B**) plasma cell responses to Gardasil 9 vaccination.

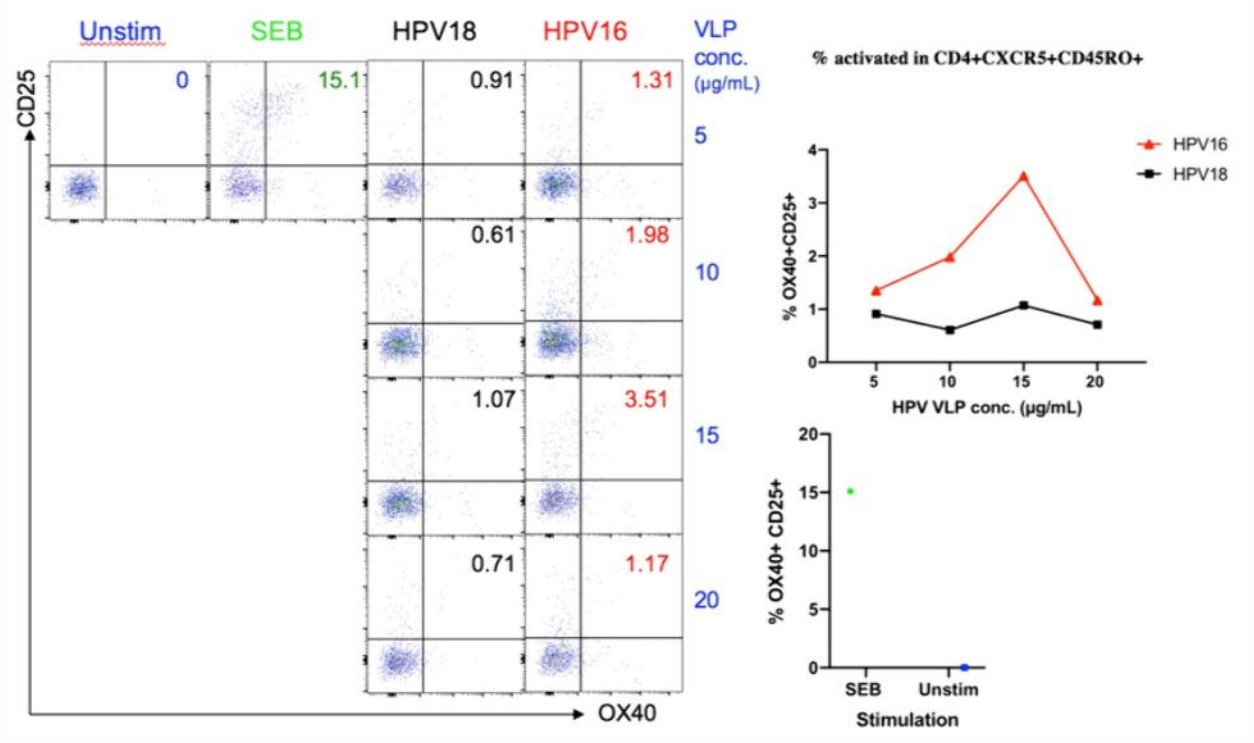

Figure 2: Activation induced HPV type specific Tfh responses following T cell stimulation with HPV 16 and 18 VLP and a mitogen positive control (SEB). The unstimulated population (negative control) is shown.

Conclusions: HPV vaccination induces plasma cell, memory B and Tfh cell responses that are activated robustly by VLP. Through applying these assays in the context of a clinical trial exploring one and two dose HPV vaccination in different age-groups, we hope to gain greater understanding of the key cellular populations responsible for the sustained protection HPV vaccines generate and potential implications for future single dose regimens.

SINGLE DOSE OF QUADRIVALENT HPV VACCINE IS HIGHLY EFFECTIVE AGAINST HPV INFECTION IN YOUNG PREGNANT WOMEN 8 YEARS FOLLOWING VACCINATION IN FIJI: AN OBSERVATIONAL STUDY

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: In 2008/9 Fiji received a donation of quadrivalent Human Papillomavirus (4vHPV) vaccine. All girls aged 9–12 years were eligible for vaccination (n=~30,000) but not all received the full schedule. We calculated the vaccine effectiveness (VE) of 1, 2 and 3 doses of 4vHPV against HPV genotypes 16/18 in young women, 8 years following vaccination.
Methods: A prospective observational study was undertaken (2015-19) in pregnant women ≤22y, who were age-eligible to receive 4vHPV in 2008/9, and vaccination status confirmed by written record. Potential confounders were recorded and a vaginal swab (FLOQSwab, Copan Italy) was taken. HPV L1 gene DNA was detected by PGMY-primer PCR and DNA ELISA. Positives were genotyped using LINEAR ARRAY® HPV Genotyping Assay (ROCHE DIAGNOSTICS) with modification for the detection of 37 genotypes. “Control” genotypes were the 30 non-vaccine and vaccine-unrelated genotypes. VE and 95% CI were calculated using (1- adjusted Poisson regression model)*100, adjusted for age, ethnicity and smoking.
Results: 820 women were enrolled: 0 dose n=370; 1 dose n= 160; 2 doses n=100; 3 doses n=190. The prevalence of genotypes 16/18 in the 0, 1, 2 and 3 dose groups were 13%, 3%, 0%, and 2%, respectively. The prevalence of “control” genotypes in the 0, 1, 2 and 3 dose groups were 49%, 31%, 39% and 52%, respectively. The adjusted VE against genotypes 16/18 for 1, 2 and 3 doses were 81% (95%CI 48% to 93%), 100% and 89% (95%CI 64% to 96%), respectively.
Conclusions: A single dose of 4vHPV provides long-term protection against HPV genotypes 16/18.

THE RATIO OF HPV DNA DETECTION IN URINE SPECIMENS BY TWO DIFFERENT REAL-TIME PCR METHODS; TURKISH POPULATION DATA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: The aim of this study was HPV diagnosis from urine samples of patients with positive HPV results of cervical specimens by two different real-time PCR methods and to compare the results.
Methods: A number of 151 patients, who had a previous HPV DNA-positivity in their cervical samples, were included in this study. Detection and genotyping of HPV in urine and cervical swab specimens was performed by two different real-time PCR tests (Cobas®4800,Roche Molecular Diagnostics, and Digene HPV Genotyping LQ Test,QIAGEN,Germany). The urine samples of 151 patients were evaluated via Roche Test and 91 out of 151 patients were also evaluated via Qiagen Test.
Results: All patients with HSIL have type 16, and patients with other cytology findings have less positivity for type 16. The rates of positive HPV results from urine samples were 57%(Roche-Cobas) and 70.3%(Qiagen), respectively. The distribution of HPV genotypes from cervical and urine samples were given in Table 1.

Table 1: The distribution of HPV types in cervical and urine samples

Genotypes	Cervical Swab(n,%)	Urine(n,%) Roche	Urine(n,%) Qiagen
Type16	44(38.4%)	25(16.6%)	17(18.6%)
Type18	15(9.9%)	6(4%)	1(1.1%)
Type16+OHR-HPV	27(17.9%)	11(7.3%)	25(27.4%)
Type18+OHR-HPV	6(4%)	2(1.3%)	3(3.3%)
Type16+18+OHR-HPV	1(0.7%)	1(0.7%)	-
Type16+18	-	-	2(2.2%)
OHR-HPV	58(38.4%)	41(27.2%)	25(27.4%)
Negative	-	48(31.8%)	20(21.9%)
Invalid	-	17(11.3%)	7(7.7%)
Total	**151**	**151**	**91**

Conclusions: Screening programs should be standardized, practical, sufficient, and effective. In this study, the results of HPV detection from urine samples were evaluated via different real time PCR kits. HPV positivity was not detected in all urine samples; however we observed that when a higher volume of urine specimen is used, the HPV positivity rate increases. These results suggest that urine could be a good non-invasive choice to diagnose HPV infection in women, if kits for urine samples are developed.

THE PROOF-OF-PRINCIPLE OF MARKER DISCOVERY FOR DIFFERENT ANOGENITAL CANCERS BY A NOVEL METHOD FOR GENOME-WIDE DNA METHYLATION PROFILING (MED-SEQ)

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: DNA methylation serves as an important marker for mis-regulation of gene expression in cancer, is applied to classify tumors and can predict disease outcome and treatment options.
Methods: We developed a novel method that facilitates genome-wide methylation marker discovery allowing successful identification of methylation changes associated with pre-cancer and cancer at very low cost. The assay involves isolation and purification of DNA from formalin-fixed paraffine-embedded (FFPE) or fresh biopsies (only 10-50ng DNA is needed). A DNA methylation dependent restriction enzyme digestion releases 32 base pair DNA methylated fragments that are sequenced by next generation sequencing. This Methylated DNA sequencing (MeD-seq) assay is very robust, allowing detection of DNA methylation at more than 50% of the 30 million CpGs present in our genome. With respect to costs and sequencing depth MeD-seq is superior to all available technologies and requires no DNA bisulphite treatment. MeD-seq is compatible low amounts of DNA derived from solid tumor tissue enriched by laser capture microdissection (LCM) and liquid biopsies.
Results: We compared the MeD-seq profiles from cervical Squamous Cell Carcinoma (SCC), cervical Adeno-Carcinoma Usual Type (AdC) and Endometrial Serous and Endometrioid Carcinoma between cancers vs controls and cancers vs other cancers. Identification of Differentially Methylated regions (DMR) comparing MeD-seq profiles visualized through an Integrative GenomicsViewer (IGV) facilitated identification of primer and probe regions for quantitative Methylation-specific PCRs (qMSP) to detect tumor-specific or different general-tumor types.
qMSPs were developed and the methylation status of selected potential markers was determined in different tumor and control tissues. Our diagnostic qMSP are tumor-specific and general-tumor as already determined in IGV beforehand.
Conclusions: MeD-seq is a reliable low-cost technology to establish genome-wide DNA methylation profiles laser microdissected FFPE material of cancer and controls and can be used to call DMRs for development of PCR-based assays.

GENOTYPICAL CHARACTERIZATION OF THE HUMAN PAPILOMA VIRUS VERSUS STUDY CYTOCOLPOSCOPIC IN A PUBLIC HOSPITAL-LIMA PERU

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Introduction: Cervical cancer is one of the neoplasms that cause mortality in women in Peru, currently representing a public health problem. According to report of the World Health Organization, cervical cancer is the fourth most common cancer in women worldwide. **Objective:** To establish the relationship between high-risk human papilloma virus (HR-HPV) genotypes with the degree of cytological lesions and colposcopy findings in women of the Dos de Mayo National Hospital during the years 2016-2018.
Methods: Methodology: A retrospective study was carried out, descriptive type of non-experimental design and cross section. 96 medical records of patients were reviewed with molecular diagnosis positive for HR-HPV that includes cytological and colposcopy analyzes, and only 76 cases met the inclusion criteria. In order to evaluate the correlation between the variables, contingency tables with a significance level of 0.05 are used.
Results: Results: The frequency of HR-HPV in participants was 27.51%, of this group another HR-HPV group had the highest distribution with 80.3%. The most frequent cytological lesion is low-grade squamous intraepithelial lesions (LSIL) with 61.85%. The minor colposcopic findings were the most frequent in 76.32%. The age group of the population with positive HR-HPV belongs to over 36 years of age. The level of significance obtained in the Pearson Chi-square statistic was less than 0.05, establishing a relationship between the variables studied.
Conclusions: Conclusions: There is a significant correlation between the study variables, however, there are no conclusive results regarding the connection between HR-HPV genotypes with the type of cytological and colposcopy lesion, which is the result of an HPV infection. It is not only determined by the type of HPV, but also by other factors.

HPV VACCINATION IMPACT IN HPV INFECTION PREVALENCE IN A PRIVATE OPPORTUNISTIC SCREENING SETTING

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2008 the HPV vaccine (Gardasil®) was introduced in the Portuguese National Immunization Program for girls aged 13 years (born from 1995 on). In 2014 the schedule was changed to 2 doses at 10-13 years old. From 2009-2011 a catch-up program for 17 years old (born 1992-1994) was conducted. Full dose coverage ranged between 83-93%. Most of these women have not reached yet screening age. Nevertheless, some get tested for high-risk (HR) HPV in private opportunistic screening.
Methods: Data stored in LAP LIS from inception until present concerning women who had an HR-HPV test (Roche cobas® 4800 HPV test) <25 years was extracted and pooled according to their birth year (born after 1994 [mostly vaccinated <13 years]; born 1994-92 [vaccinated at 17 years]; born <1992 [not vaccinated/vaccinated after 17 years]); 2138 fulfilled the established criteria.
Results: The following table shows the prevalence of HR-HPV in the different cohorts, as well as the relative risks (RR), using as reference the cohort born <1992:

HPV	Born < 1992 (n=331)	Born 1992-4 (n=901)	Born >1994 (n=951)
HPV16	6.3%	3.3% RR 0.52 (0.305-0.904), *p*=0.02	0.7% RR 0.12 (0.050-0.270), *p*< 0.0001
HPV18	1,5%	0.4% RR 0.29 (0.079-1.09), p=0.07	0.2% RR 0.14 (0.027-0.714), p=0.02
HPV16/18	7.9%	3.6% RR 0.45 (0.274-0.747), *p*= 0.0018	0.9% RR 0.12 (0.057-0.254), *p*< 0.0001
HPV others	31.7%	32.5% RR 1.02 (0.853-1.232), *p*= 0.791	33.2% RR 1.05 (0.873-1.256), **p**= 0.617

Conclusions: Women <25 years who were vaccinated before 13 years old, had a reduction in the rate of HPV16/18 of nearly 90%; in those vaccinated at 17 years old the reduction was of around 50%. There was no impact in the rate of infection by other HR-HPV genotypes. Our data highlights the importance of vaccinating at young age and the potential role for vaccines with additional hr-HPV types."

RETENTION OF HLA-E EXPRESSION ON RESPIRATORY PAPILLOMAS (RPS) LACKING HLA-A,-B: AN HPV6/11 STRATEGY TO EVADE NK CYTOLYSIS IN RRP.

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Previously, we described decreased/absent classical class I MHC (HLA-A, B, C) expression by keratinocytes in HPV-induced respiratory papillomas from patients with recurrent respiratory papillomatosis (RRP). These cells should be cleared by natural killer (NK) cells. Additionally, we reported increased NK cells in papillomas without evidence of inflammation, and a decrease in blood-derived NK cell function in these patients. NK-induced cytolysis of target cells is prevented by NK cell recognition of self through class I MHC expression, and is activated by the loss of HLA-A,-B,-C expression and subsequent ligation of NK activating KIR and other NK receptors. To determine if the T_H2/Treg enriched microenvironment and the restricted KIR haplotypes expressed by RRP patients previously reported are the only cause for NK cell failure to kill HPV6/11-infected keratinocytes in papillomas lacking HLA-A, B, C, we analyzed classical class I MHC HLA-A,-B and non-classical HLA-E expression by papillomas.
Methods: Paraffin block sections from different patients were stained selectively for HLA-A, -B, and non-classical HLA-E by standard immunohistochemistry.
Results: HLA-A was expressed in both the stroma and basal layers of a subset of papillomas, but not the spinous layer. HLA-B was expressed only in the stromal tissue of all papillomas studied. However, non-classical HLA-E was strongly expressed in the spinous and more superficial layers of all papillomas studied, the same layers where viral expression is elevated.
Conclusions: In addition to the skewed immunosuppressive micromilieu in papillomas, and restricted activating KIR haplotypes expression by RRP patients, strong HLA-E expression would further block NK cell cytolysis of HPV-expressing keratinocytes that have lost classical class I MHC expression. This strategy is reminiscent of HIV blockade of T_H1/T_C1 cell recognition of HIV peptide presentation to T-cells in the context of HLA-A and -B, and the retention of HLA-E to inhibit NK cell activation.

THE INTERACTION BETWEEN PUBERTAL TIMING AND CHILDHOOD MALTREATMENT ON THE RISK OF HUMAN PAPILLOMAVIRUS INFECTION IN SEXUALLY-ACTIVE ADOLESCENT FEMALES

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: History of childhood maltreatment and early pubertal timing have been linked to increased sexual behaviors in adolescent females, but little is known about their impact on risk of cervical HPV infection. This study examined the effect of pubertal timing, and its interaction with history of childhood maltreatment, on detection of cervical HPV in a study of urban adolescent females.
Methods: This paper assessed cross-sectional data (baseline) from an HPV vaccine surveillance study at a large adolescent health clinic in New York City. Study participants completed a questionnaire on sexual history and received a gynecological examination with a collection of cervical cells by cytobrush for HPV testing by MY09/11-PCR. Pubertal timing was calculated from self-reported age at menarche, with “early” and “late” menarche defined as one standard deviation below (<11 years) or above (≥14 years) the mean. Childhood exposure to abuse (sexual, physical and emotional) and neglect (physical and emotional) was assessed using the Childhood Trauma Questionnaire.
Results: Participants included 862 sexually-active girls 12-19 years of age, of which 95.5% reported themselves as Hispanic, African-American, or both. The average reported age at menarche was 11.7 years. Early menarche (at <11 years of age) was marginally associated with higher odds of detection for any HPV type (OR=1.40, 95%CI: 0.95-2.05) compared to age at menarche of 12-13 years, independent of family demographics, age at first intercourse and lifetime number of partners. However, the association was moderated by history of childhood maltreatment; whereas early menarche was associated with higher odds of cervical HPV among maltreated girls (OR=3.32, 95%CI:1.61-6.85), it was not among girls with no history of childhood maltreatment (OR=0.96, 95%CI:0.61-1.50; p-interaction<0.01).
Conclusions: Early onset of menarche was associated with higher risk of cervical HPV infection, which was amplified among victims of childhood maltreatment.

COMPARISON OF HPV GENOTYPE SPECIFIC DNA AND E6/E7 MRNA DETECTION AND PREVALENCE OF ANAL HPV INFECTION IN HIV-INFECTED MEN WHO HAVE SEX WITH MEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Human Papiloma Virus (HPV) infection and the development of anal cancer (AC) is increasing in HIV-positive men who have sex with men (MSM). Most subjects who screen positive by HPV-DNA testing or cytology do not have concurrent precancer. The challenge is differentiating the screen-positive subjects with benign, transient HPV infections from those that have precancerous lesions with a high risk to progress to cancer. We aim to estimate the anal HPV prevalence and the performance of three HPV detection tests.
Methods: The ELAVI67 project, a prospective longitudinal study, includes samples from 347 HIV-MSM recruited at baseline in Barcelona. Baseline samples have already been collected and follow-up samples are currently being collected every 6/12 months after the baseline during minimum 24 months. The ELAVI67 cohort underwent anal smear and HRA with biopsy of suspected dysplasia areas. Baseline anal smear samples were tested by anal liquid-based cytology, HPV DNA detection performed by both Linear Array (LA) (37 HPV genotypes) and Hybrid Capture®2 (HC2) (13 high-risk (HR-HPV) genotypes), and E6/E7-mRNA test using Aptima® (14 HR-HPV genotypes).
Results: Prevalence HR-HPV was 40.9% by HC2, 79.3% by LA and 50.1% by Aptima. The overall agreement and ki between LA and HC2 for the common genotypes was poor (66%, 0.325). Whereas, the concordance and ki for shared genotypes between LA and Aptima was higher (74%,0.475) and increasingly better as the genotypes compared were restricted to HPV16/18/45 or to HPV16. For the identification of high-grade lesions (HSIL), the detection of HR-HPV by LA showed the most sensitive values (95%), although the specificity dropped to a 28% (AUC,0.61). The test that displayed a better performance was Aptima, showing a sensitivity of 80% and a specificity of 63% (AUC,0.71).
Conclusions: Preliminary results indicate that E6/7-mRNAtest perform better than HC2 and LA and could be considered for the detection of HSIL.

POST-VACCINE HPV INFECTION RATES IN A LARGE INNER-CITY ADOLESCENT HEALTH CLINIC: RESULTS FROM A VACCINE SURVEILLANCE STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Rates of HPV infection, genital warts and cervical dysplasia have decreased since introduction of the HPV vaccines in many populations, especially where vaccine uptake has been high. However, less is known about high-risk populations where vaccine uptake has been delayed. As part of an ongoing study of sexually-active adolescent females attending a large urban health center in New York City, we assessed HPV detection rates following vaccination with Gardasil®.
Methods: Shortly after the introduction of the quadrivalent (4vHPV) vaccine in the U.S. in 2007, we initiated a longitudinal study of adolescent women presenting for health services and HPV vaccination at Mount Sinai Adolescent Health Center. Participants received a gynecological examination every six months with collection of cervical, anal and oral samples for HPV testing by MY09/11-PCR. We evaluated changes in age-adjusted post-vaccine HPV rates from 2007-2018 by Chow test and multivariate regression for repeated data.
Results: The study cohort included 1375 vaccinated women aged 13-21 years at baseline, with an average follow-up of four years. All study participants were sexually-active with an average reported age at first sexual intercourse of 15.0 years, and age at HPV vaccination of 14.8 years. Whereas age-adjusted detection rates for 4vHPV vaccine-related types (6/11/16/18/31/33/45) have declined each year for cervical (adjusted odds ratio [aOR]=0.84, 95%CI:0.78-0.90) and anal HPV (aOR=0.86, 95%CI:0.79-0.93), detection rates increased for non-vaccine high-risk types (35/39/51/56/59/68) for cervical (aOR=1.05, 95%CI:1.01-1.09) and anal HPV (aOR=1.05, 95%CI:1.01-1.10). The largest increases were seen for non-vaccine *alpha7*-types (e.g., 68 and 39). These changes were independent of age at vaccination, sexual behavior, and other sexually transmitted diseases, including Chlamydia, which did not show a concomitant increase over the same time period.
Conclusions: Whereas HPV vaccination continues to show evidence of effectiveness against vaccine targeted types, rates of infection by non-vaccine related types may be increasing in some populations.

HIV MODIFIES THE EFFECT OF TOBACCO SMOKING ON ORAL HUMAN PAPILLOMAVIRUS INFECTION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: People living with HIV (PLWH) are more likely to smoke and harbor oral human papillomavirus (HPV) infections, putting them at higher risk for head and neck cancer (HNC). We hypothesized that HIV seropositivity may modify the association between smoking and oral HPV.
Methods: Consecutive PLWH (n=169) and HIV-negative individuals (n=126) with and without oral lesions were recruited between 2004 and 2013 from outpatient clinics at two large health centers in New York and New Jersey, United States. Lifetime smoking history and other use habits were collected using questionnaires. Participants underwent oral examination and provided oral rinse samples for HPV genotyping at enrollment, and 6 and 12 months later. Next-Generation Sequencing was used to test for α-, β-, and γ-HPV types. We used multivariable logistic regression models to test for the differential effects of smoking on oral HPV detection by HIV status.
Results: PLWH were more likely to have smoked than HIV-negative individuals (76% vs. 65%), and to present with oral HPV, including α (39% vs. 28%), β (73% vs. 63%), and γ-types (33% vs. 20%). HIV co-infection, however, significantly modified the association between smoking and detection of oral HPV, including high-risk types (p-interaction=0.015). Among PLWH, an average ever-smoker (with 15.4 pack-years of smoking) was significantly more likely to present with an α-HPV (odds ratio [OR]=2.95, 95% confidence interval[CI]:1.1-7.7], β-HPV (OR=3.01, 95%CI:1.1-8.2), or γ-HPV type (OR=2.14, 95%CI:0.8-5.8), compared to PLWH non-smokers. In contrast, no significant associations with smoking were observed among HIV-negative individuals. Associations with smoking were also observed with detection of persistent oral α- and β-HPV of the same type at consecutive visits among PLWH (OR=2.62, 95%CI:1.0-7.1).
Conclusions: Our results show consistently stronger associations between tobacco smoking and oral HPV detection, including of α-, β-, and γ-HPV types, among PLWH compared to at-risk HIV-negative individuals.

ACCEPTABILITY OF SELF SAMPLING FOR CERVICAL CANCER SCREENING AMONG REGULAR ATTENDERS IN SPAIN

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Self-sampling in cervical cancer screening (CC) has been primarily used as a strategy to increase coverage in women with insufficient CC, but has rarely been used as a strategy in regular users. The objective is to evaluate self-sampling acceptability and compare two different training types in women usually attending CC in Spain.
Methods: 1,614 women aged 30-65 years and regularly attending screening from Canary Islands and Catalonia are recruiting and randomized in two groups: G1) women who learn from the clinician how to use the self-sampling device and practice by collecting a self-sample in the health centre. G2) Women who receive the same instructions but without practice. The clinician collects a sample and sociodemographic and clinical data from women in both groups. One month later all women collect a home self-sample, respond an acceptability questionnaire and return them to the health centre. Acceptability is analyzed according to the training group and questionnaire results.
Results: Until September 2019, 310 women have been recruited and randomized. 26% of women had university studies and 17% primary studies. 82% are employed, of which 91% work for others and 72% have full-time jobs. 57% have dependent children. Preliminary results show significant differences (p=0.016) in the monthly return of self-sampling. G1 women return more self-samples (83%, N=118) than G2 women (70%, N=92). 87% of women in G1 and G2 who returned their self-samples considered it was a good or very good experience, 80% trusted in the result and 95% would recommend it. 39% preferred to collect self-samples themselves, compared to 16% who preferred to go the clinician. 78% would like self-sampling to be introduced in the CC.
Conclusions: The self-sampling shows good acceptance. Instructions to use the device given by the clinician and a prior practice seems to increase the confidence on the procedure and the adherence to its use.

ATTRIBUTABLE FRACTION OF HPV RELATED HEAD AND NECK CANCERS IN THE RECURRENT / METASTATIC SETTING. A LITERATURE REVIEW OF PHI-III CLINICAL TRIALS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Head and neck cancers (HNC) represent the 6th most common malignancy worldwide, with HPV being associated, in most of the literature, with ~25% of all cases. Recurrent/metastatic (RM) disease is carrying the poorest prognosis and in many reports appears equally poor for both HPV+/– cancers. Consequently, HPV attributable fraction (AF) in RM setting becomes important for estimating the actual burden of HPV+HNC. This study presents the HPV-AF of RM-HNC as captured in the descriptive data of last decade's PhI-III trials.
Methods: We searched Clinicaltrials.gov for Ph I-III HNC trials in "Completed, Active-Not recruiting, Unknown" Status initiated from 01-Jan-2010 to 04-May-2019. PubMed, CENTRAL & EMBASE databases were searched for related publications and ASCO/ESMO Journals of congresses for related abstracts using the corresponding NCT#. Studies selected had: available results on HPV fraction, RM patients enrolled, oropharynx (OPX) included in the HN sub-sites & investigational products (IPs) intended for treatment.
Results: We identified 809 HNC trials of which 21 fulfilled the criteria (4-PhI;13-PhII;4-PhIII). HPV-AF in RM-HNC had been estimated in these 21 trials (reports ranging from 3.9% to 52.0%) involving 3,461 subjects with 24.9% of them being HPV+. Furthermore, 10 of the 21 trials had Oropharyngeal cancer (OPC) specifically reported (OPC ranging from 25.0 to 68.0% of HNC). HPV-AF in the OPC subset was estimated in these 10 trials (reports ranging from 20.0% to 88.9%) involving 390 subjects with 54.6% of them being HPV+.
Conclusions: HPV-AF in the RM patients was estimated around 25%, corresponding to the HPV-AF of total HNC cases, and raised to~55% for the RM-OPC. The significant proportion of HPV+HNC that recur or give metastases should be taken under consideration when defining the actual burden of disease, while the incremental trend of HPV+HNC, mainly driven by the increase in OPC, highlights the potential of primary prevention through vaccination.

HPV WORLD-THE NEWSLETTER ON HUMAN PAPILLOMAVIRUS

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction:

The HPV field has defined as a target the worldwide intervention to prevent cervical and other HPV-related cancers. Scientific details of the rationale and implementation are being produced and typically reported in the scientific literature. However, there is a communication gap with the hundreds of thousands of health care professionals that remain the critical link interacting with health systems, families and schools, with limited access to conventional scientific data.
Methods: HPV WORLD (HPW) was launched in 2017 aiming at 1) identifying the salient points in HPV natural history and disease elimination strategy that need to be known by the second ring of professionals implicated in the elimination campaign; 2) inviting some of the most relevant authors in the field to synthesize research findings and interventions, by producing extended abstracts (600-800 words) with 2-3 graphs or tables and 5 references prioritizing high-quality recent reviews of the topic; 3) disseminating these contributions in a newsletter twice a month using a reader-friendly digital format, with visually attractive artwork, and adapted to portable electronic devices. Published materials are archived in the website www.hpvworld.com, indexed by self-explanatory keywords and easily resent or circulated through scientific societies and networks of interested professionals. Translations and printed versions of contributions' collections for educational purposes (i.e. on HPV screening) are occasionally produced.
Results: Since 2017 HPW has published and disseminated close to 100 contributions and collaborated with some 150 authors. The number of visitors to the website is approaching 25000 and the number of subscribers is rapidly increasing. Several scientific institutions and societies have endorsed the project, including IPVS, EUROGIN, AOGIN, ESO, e-Oncologia, HPV Information Centre and HPV Prevention Board.
Conclusions: HPW seems to be an appropriate vehicle for HPV communication and dissemination to the second ring of professionals in the HPV field.

NOVEL HIGH THROUGHPUT SCREENING METHOD DETECTS INTEGRATION EVENTS ACROSS LARGE SAMPLE POPULATIONS FROM CIN1 TO CANCER

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: It is unclear when HPV integration occurs during viral persistence. If we could identify early integration events, we could improve our understanding of HPV integration's role in cancer progression. To identify samples with early integration (CIN1, CIN2 and CIN3), we developed a high throughput screening method to identify samples with indications of HPV integration.
Methods: Using our proprietary Ampliseq HPV whole-genome assays, we sequenced 6,732 samples across high-risk types 16 (2756), 18 (1714), 35 (760), and 45 (1149) from our NCI-KPNC PaP cohort and samples collected worldwide by IARC. Using a bioinformatic algorithm, we designed parameters that would evaluate the sequencing reads looking for loss or drop in reads surrounding the E2 gene region, while E6/E7 reads remained high, as a potential indicator of an integration event. Scores were assigned to each sample and binned according to confidence level. In a subset of the integration positive samples we visually confirmed these sequence read patterns and used human whole-genome sequencing (10X Genomics technology) to validate the integration event.
Results: Starting with HPV18, we evaluated integration event rates for cancers, precancers (HSIL, CIN3/CIN2) and controls (<CIN2). We detected evidence of integration events in 80.6% of the HPV18-positive cancer samples. Interestingly, 15.4% of the precancers had evidence of integration, and 8.9% of the controls. In 24 of these samples with HPV18 sequence detected integration events, we confirmed HPV integration using human whole genome sequencing. We are currently evaluating integration rates using this method for HPV16, HPV35, and HPV45.
Conclusions: Our data shows that screening large populations using HPV genome sequencing assays may provide a quick assessment of potential integration events even from samples with early stages of HPV infections. We are extending this approach to other types, and further refining our detection algorithm to improve our percentage of detected integration events through comparisons with other methods.

HPV VACCINATION PROTECTS AGAINST HPV INFECTION AND DISEASE IN SEXUALLY ACTIVE ADULTS: A REVIEW OF QUADRIVALENT HPV VACCINE CLINICAL TRIALS

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: The quadrivalent HPV (qHPV) vaccine clinical program included sexually active females regardless of baseline HPV status. Therefore, per-protocol efficacy analyses for each vaccine HPV type (HPV6/11/16/18) included participants infected by other vaccine or non-vaccine HPV types. The qHPV vaccine demonstrated consistently high clinical efficacy in females aged 16–45 years. The vaccine is prophylactic, without efficacy against disease caused by HPV types present before vaccination.
Methods: We summarize data from the randomized, placebo-controlled, double-blind, international FUTURE I (NCT00092521), II (NCT00092534), and III (NCT00090220) qHPV vaccine studies in females aged 16–26 (N=17,622; FUTURE I and II) and 24–45 years (N=3819; FUTURE III). HPV DNA positivity was a surrogate for current infection; anti-HPV seropositivity and HPV DNA negativity was a surrogate for past infection.
Results: Clinical trial data indicate that infection with all vaccine HPV types is rare: 0.1% of 3578 North American females were positive for all four qHPV vaccine types by serology and/or HPV DNA; none were infected with all 9-valent HPV vaccine types. Most prevalent HPV infections in females aged 16–25 years consist of only one or two high-risk HPV types (Barr, *Am J Obstet Gynecol* 2008). In FUTURE I and II participants infected with 1–3 vaccine HPV types, the qHPV vaccine protected against HPV-related cervical and external genital disease caused by the remaining HPV types (FUTURE II Study Group, *J Infect Dis* 2007). The qHPV vaccine also prevented cervical and external genital disease in females aged 16–26 years and persistent infection in females 27–45 years regardless of previous exposure to vaccine HPV types (Olsson, *Human Vaccines* 2009; Castellsague, *Br J Cancer* 2011).
Conclusions: HPV vaccination can protect against HPV infection and disease in adults previously infected with HPV. Vaccination should not be withheld from sexually active individuals with prior HPV exposure.

THE IMMUNOGENICITY OF PLANT-PRODUCED HUMAN PAPILLOMAVIRUS (HPV) VIRUS-LIKE PARTICLES

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: The HPV L1 capsid protein can self-assemble into virus-like particles (VLPs) that are structurally like native virions. Three commercially available HPV vaccines that are effective at preventing HPV infections, are VLP based. However, these vaccines are expensive, therefore limiting their use in the poorer developing countries. Recently, the use of plants to produce vaccines has begun to be more favourably looked upon as a cost-effective alternative to conventionally used expression systems. The aim of this study was to evaluate the plant-based transient expression system as a tool to produce potentially cost-effective HPV L1 VLP-based vaccines, particularly for developing countries.
Methods: The L1 proteins of eight high-risk HPV types (HPV 16, 18, 31, 33, 35, 45, 52, and 58) and two low risk types (HPV 6 and 34) were transiently expressed in *Nicotiana benthamiana* and the assembly of VLPs assessed by transmission electron microscopy (TEM). HPV 35, 52 and 58 VLPs were selected for immunogenicity studies in mice, as HPV 35 is the fifth most prevalent type in Africa and HPV 52 and 58 are among the most frequently reported high-risk types in Sub-Saharan Africa. The immunogenicity of the vaccines was evaluated by testing for the presence of anti-L1 antibodies in sera from immunised mice using ELISAs and western blots. Sera from immunized mice were also tested for the presence of neutralising antibodies using pseudovirion based neutralization assays (PBNAs).
Results: L1 proteins of all ten HPV types were successfully expressed in N. bethamiana, and TEM analysis showed the presence of fully assembled VLPs and/or capsomeres. The analysis of the immune response showed that type-specific L1-specific antibodies were produced which were able to successfully neutralize homologous pseudovirions in PBNAs.
Conclusions: This study successfully demonstrated the potential for using plant-based transient expression systems to produce affordable and immunogenic HPV vaccines, particularly for developing countries.

HUMAN PAPILLOMAVIRUS (HPV) VIRAL LOAD AS DIAGNOSTIC BIOMARKER FOR CERVICAL LESIONS PROGRESSION

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Despite the widespread of HPV infections, only a small fraction of women with a hrHPV infection will progress to pre-cancer or cancer. This indicates that additional risk factors are important for carcinogenesis. HPV type-specific viral load has been associated to an increased risk of cervical cancer development, with its potential use as a molecular triage tool in self-sampling based screening programmes. This ongoing study aims to determine HPV viral load level among different sample types: cervical, vaginal and urine samples, as well as assessing the correlation between viral load and grade of cervical lesion.
Methods: Presently, clinician-collected cervical, self-collected vaginal (FLOQSwab, Copan), urine samples (Collipee, Novosanis), were obtained from 180 women attending the Colposcopy Clinic, San Gerardo Hospital (Monza, Italy). All samples were extracted using NucliSENS easyMAG (bioMerieux) and HPV detection carried out using AnyplexII HPV28 (Seegene). Viral load was evaluate using “in house” HPV type-specific assays able to detect 7 different HPV types (HPV16, 18, 31, 33, 45, 51, 52).
Results: A very good HPV test concordance was observed between vaginal and urine self-samples as compared to clinician-collected cervical samples (gold standard). Usually, HPV viral load detection resulted higher among cervical samples compared to both self-sample types. Median values are reported in Figure1. Preliminary results have shown a higher viral load median value for HPV16 and HPV 31 types in patients with a high-grade intraepithelial lesion than patients with low-grade dysplasia (HPV16: 7.36E+07 vs 3.94E+06 copies/10^4 cells; HPV 31: 1.98E+05 vs 3.83E+04 copies/10^4 cells).

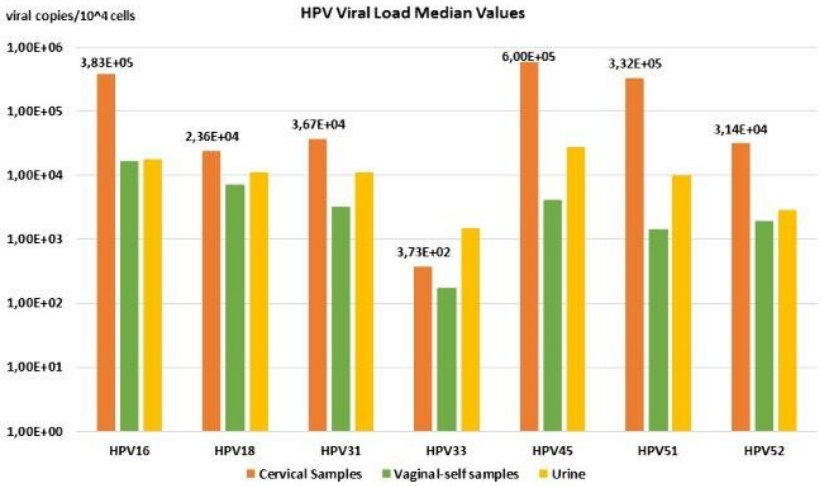

Figure1. HPV genotype-specific viral load. Data were obtained from analysis of sample collected from HPV positive women (n=43 HPV16; n=8 HPV18; n=24 HPV31; n=4 HPV33; n=5 HPV45; n=22 HPV51 and n=17 HPV52). Viral load values were reported as viral copies/10^4 cells)

Conclusions: Higher HPV viral loads may indicate viral persistence, progression to cervical dysplasia, and may even serve as a prognostic biomarker in cervical cancer screening based on self-collection; however, longitudinal studies are needed to confirm these preliminary data.

PREVENTING CERVICAL CANCER IN OLDER VIETNAMESE WOMEN: PILOT STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Our aim is to establish the feasibility and response rate of a population-based screening programme for Vietnamese women aged over 50. Almost all cervical cancers in post-menopausal women are caused by HPV infection acquired before age 50 and about 80% of cervical cancer deaths occur after age 50. A single HPV test after menopause with treatment of HPV positive women either immediately or after retesting a year later to exclude transient infections is therefore a practicable means of achieving a large reduction in lifetime cancer risk.
Methods: Women aged 50-64 resident in 10 small districts in Ho Chi Minh City will be invited. Recruitment will continue until 300 have been screened. A sample of 100 current or former female sex workers will also be invited. Younger women are at substantial risk of acquiring a new HPV infection, so a single test cannot confer high lifelong protection, and radical cervical treatment can predispose to subsequent premature delivery. Participants will attend a district health centre to complete a questionnaire and provide a self-administered vaginal swab followed by a nurse-taken LBC sample. Cytology will be done only on HPV+ samples. HPV+ women with abnormal cytology will be referred for colposcopy and management according to hospital guidelines. Other HPV+ women will retested after a year. Those still HPV+ (with or without cervical abnormality) will be offered colposcopy and LEEP if deemed feasible.
Results: Preliminary results will be presented on recruitment, HPV prevalence, and attitudes and knowledge on HPV and screening. The main outcomes at follow-up will be the proportion of HPV+ women who attend for retesting, the HPV clearance rate within a year and the proportion of those still HPV positive in whom LEEP can be performed.
Conclusions: We hope to demonstrate that national HPV screening of older women is feasible and affordable

PRELIMINARY RESULTS FROM AN ORGANIZED SCREENING PROGRAM OF CERVICAL CANCER, IN LISBON, PORTUGAL

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The implementation of organized screening programs for cervical cancer allows early detection of the disease. Abnormalities found on screening require follow-up, diagnosis and treatment, in order to prevent the development of cancer or to treat cancer at an early stage. We pretend to analyse cytological and histological results from samples that test positive for HPV16/18 and for other HR HPV, that participate in an organized screening program in Lisbon metropolitan area, Portugal.
Methods: Samples were analysed by a HR-HPV test (HPV14, Seegene) and ThinTrep PAP test for cytologic evaluation.
Results: All HPV+ samples with cytological/histological results, collected between February-May 2019, were included in this study: 35/1292 positive for HPV16/18 (G1) and 51/1292 positive for other HR HPV (G2). The median age of women from G1 was 40y (G1) and 43y (G2). The G1 women were referred for colposcopy, however cytological evaluation was performed posteriorly. All samples from G2 were cytologically evaluated for possible referral for colposcopy, if cytological changes were detected.Regarding the results obtained in both groups (table 1), we want to highlight that the initial LSIL and HSIL results in G1 (15.38%/11.54%) and G2 (13.73%/5.88%) were confirmed by colposcopy/biopsy: G1 with 50.00%/33.33% and G2 with 28.57%/33.33%.

		Colposcopy/Histology (HPV16-18/HR)			
Cytology (HPV16-18/HR)		(%)	Negative(%)	LSIL(%)	HSIL(%)
Negative	G1 (n=12)	46.15 (12/26)	66.66 (8/12)	33.33 (4/12)	-
	G2 (n=20)	39.22 (20/51)	-	-	-
ASCUS	G1 (n=6)	23.08 (6/26)	16.66 (1/6)	66.66 (4/6)	16.66 (1/6)
	G2 (n=17)	33.33 (17/51)	70.59 (12/17)	29.41 (5/17)	-
ASC-H	G1 (n=1)	3.85 (1/26)	-	-	100 (1/1)
	G2 (n=2)	3.92 (2/51)	-	50 (1/2)	50 (1/2)
AGC	G1 (n=0)	-	-	-	-
	G2 (n=2)	3.92 (2/51)	50 (1/2)	50 (1/2)	-
LSIL	G1 (n=4)	15.38 (4/26)	50 (2/4)	50 (2/4)	-
	G2 (n=7)	13.73 (7/51)	71.43 (5/7)	28.57 (2/7)	-
HSIL	G1 (n=3)	11.54 (3/26)	33.33 (1/3)	33.33 (1/3)	33.33 (1/3)
	G2 (n=3)	5.88 (3/51)	66.66 (2/3)	-	33.33 (1/3)
Total	G1 (n=26)		46.15 (12)	42.31 (11)	11.54 (3)
	G2 (n=51)		64.52 (20)	29.03 (9)	6,45 (2)

Conclusions: Although the reduced number of samples positive for HPV and that this percentage is in aggreement with other published studies (6.7%), we are detecting more infection than disease. These preliminary results also show an increase trend in the LSIL and HSIL cytology relative results, that is confirmed in the histological evaluation when comparing HPV16/18 and HPV HR groups.

HIGH NEGATIVE PREDICTIVE VALUE OF E6/E7 MRNA HPV AFTER A 3-YEAR FOLLOW-UP OF 1.334 WOMEN FROM A CERVICAL CANCER SCREENING PILOT

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: The negative predictive value of a screening test is important for determining the safety of negative results. Nowdays, numerous HPV screening tests are in use. Our objective was to determine the predictive value of a negative HPV test performed with an E6/E7 mRNA test.
Methods: After cotesting 5,053 women of ages 25-65 y.o. with liquid-based cytology (LBC) and APTIMA® HPV (AHPV), those with a positive AHPV or with LSIL+ cytology were adviced to undergo colposcopic biopsy. Those women without a high grade (CIN2+) cervical lesion were followed-up as per European and national recommendations. From the group of women with a negative cotest, an active recruitment by phone calls was established 3 years after the baseline cotest. Predictive values for CIN2+ of those women with adequate FU were calculated.
Results: The baseline cotest showed a 9% (454) AHPV prevalence. From those women, 265 had a 3 year follow-up (FU) with colposcopy and biopsy, yielding 100 CIN2+ lesions (risk of 37,7%). From those with a negative AHPV result, active 3-year recruitment was performed in 1,023 women and found 44 women with a new HPV infection. In 33 cases, a biopsy was performed, finding 3 new cases of CIN2+ lesions (9,1%). From 71 women with a negative AHPV and abnormal cytology at baseline, adequate FU was available in 45. Only 1 high-grade lesion, an endometrial adenocarcinoma at baseline, was found. Therefore, the NPV for AHPV in our study was 99,6%, while the PPV was 37,7%.
Conclusions: Primary mRNA HPV testing with APTIMA® in a screening population provides a NPV higher than other HPV tests reported in the literature after 3 years of adequate follow-up. Therefore, the safety of this test is reassuring as a screening tool.

EXPERIENCES WITH CERVICAL CANCER SCREENING IN MALAWI: DATA ON KNOWLEDGE, ATTITUDES, AND UPTAKE FROM A HIGH-BURDEN, LOW-RESOURCE SETTING

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Coverage of routine cervical cancer screening in Malawi is very low, even though it has the highest cervical cancer burden in the world. We performed a multi-level assessment of Malawian women's and men's knowledge and perceptions of cervical cancer risk and screening, following recent scale-up of screening and treatment programs.
Methods: Based on the Multi-Level Health Outcomes Framework, we conducted interviews with adult Malawians (men and women) at facilities that offer cervical cancer screening; eligible participants were recruited regardless of HIV status or history of cervical cancer screening. Trained researchers asked respondents about their experiences with and opinions of cervical cancer disease and screening. Interviews were audio recorded with permission, transcripts were translated from Chichewa (the local language) to English, and a theory-informed codebook was developed. Analysis focused on thematic differences across groups by age, HIV status and screening history.
Results: Half of interviewed women had never been screened for cervical cancer or were at the facility for their first-ever screen, despite wide acknowledgment among both men and women that cervical cancer is dangerous and that screening is important and effective. Many women and men knew someone affected by cervical cancer. Risk factors were generally well-understood, and gender issues were highly salient for both men and women -- relating to sexual transmissibility, husbands' support of screening, and modesty if screened by a male clinician. Women had commonly heard rumors about the procedure being painful or dangerous; but screening-experienced women expressed a desire to educate friends about their painless experience. Health system barriers were commonly reported, including stockouts of basic equipment (speculums), poor communication with health workers, and long travel distances to care.
Conclusions: Despite high knowledge and awareness, there remain significant interpersonal and system-level barriers to cervical cancer screening uptake. Future work should strengthen service delivery, target social networks and intimate partners.

STRESS-RELATED DISORDERS AND THE RISK OF HUMAN PAPILLOMAVIRUS-RELATED CANCERS IN DENMARK

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: The incidence of stress-related disorders is increasing. Stress-related disorders are known to have an immunosuppressive effect and, at the same time, immunosuppression increases the risk of Human Papillomavirus (HPV)-related cancers. We examined whether patients with stress-related disorders have an increased risk of HPV-related cancers.
Methods: Using the population-based medical registries in Denmark, we conducted a cohort study to examine the association between stress-related disorders and the risk of HPV-related cancers. Patients with stress-related disorders (acute stress reaction, post-traumatic stress disorder, adjustment disorder, other reactions to severe stress or reactions to severe stress unspecified) were identified in the Danish Psychiatric Central Research Registry or the Danish National Patient Registry covering all Danish hospitals from 1995 to 2011. HPV-related cancers (cervical, anal, vulvar or vaginal, penile, base of tongue, tonsillar or oropharyngeal cancer) were identified in the Danish Cancer Registry from 1995 to 2013. Patients with stress-related disorders were followed until first diagnosis of HPV-related cancer, date of death, emigration, or 30 November 2013, whichever came first. We computed the standardised incidence ratios (SIRs) and 95% confidence intervals (CIs) of HPV-related cancers as the observed number of cancers divided by the expected number based on national cancer incidence rates by age, sex, and calendar year. We excluded the first year of follow-up from the analyses.
Results: We identified 108,147 patients diagnosed with a stress-related disorder (median age at diagnosis=37.1 years; 61.0% female). Median follow-up time was 7.5 years. During follow-up, 226 cases of HPV-related cancers occurred among patients with any stress-related disorder versus 165 expected corresponding to an overall SIR of 1.37 (95% CI: 1.20-1.56). Similarly elevated cancer risks were observed across all stress-related disorders and across the specific HPV-related cancer sites.
Conclusions: Our results suggest that patients with stress-related disorders may have an increased risk of HPV-related cancers.

MODELLING CERVICAL CARCINOGENESIS AND HPV SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: HPV testing protocols should be based on the simplest plausible model of cervical carcinogenesis.
Methods: Model assumptions 1. Each new HPV infection has a fixed probability (averaged over HPV types) of progressing to precancer before it disappears or becomes latent. 2. Precancer persists, conferring a constant lifelong cancer rate. 3. Genetics and neoplasm characteristics determine a woman's probability and rate. 4. From HPV infection to precancer plus from malignancy to cancer diagnosis averages 7.5 years, and is rarely less than 5 years. The age-distribution of HPV acquisition at entry to the ARTISTIC trial was assumed. The reduction in precancer prevalence, and hence cancer incidence, per screening round was modelled in English birth cohorts.
Results: English cervical cancer incidence rates, including the unexpected large increase at age 25-29 since the screening age was raised from 20 to 25, were predicted with remarkable accuracy assuming 40% precancer elimination per test since organised cytology began. The model also explains the dependence on age and age at first intercourse of cancer incidence in unscreened women.
Conclusions: The simplest model that accounts for the evidence defines the best scientific theory. Our age-independent model of the relationship between HPV infection rates and cancer incidence rates contradicts several current assumptions. The 5-year delay between screening at age 20 and detectable cancer prevention reflects the diagnostic lag, not some peculiar natural history of HPV infection in young women. Precancer is often latent after the initiating HPV infection has cleared or become latent, undetectable by cytology and sometimes shedding HPV below the cut-off of standard HPV tests. Cancer incidence is therefore the only useful measure of precancer prevalence. 5-yearly HPV screening from age 20 instead of 25 would reduce cervical cancer risk below age 30 in unvaccinated English women from ~0.1% to 0.02% or less, and would reduce their lifelong risk from ~0.2% to ~0.1% compared to 3.3% without screening.

IMPLEMENTING TECHNOLOGY THAT DISRUPTS HEALTH SYSTEMS, BUT NOT QUALITY OF CARE: THE POCKET COLPOSCOPE IN LIMA, PERU

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Innovative devices are often targeted at increasing access, improving quality, or reducing costs — the three axes of the infamous 'Iron Triangle of Health Care' which are notoriously difficult to simultaneously optimize. The main aim of this study was to demonstrate that disruptive technologies, if high-quality and appropriately implemented, can result in improved access, cost, and quality of care — overcoming the conventional constraints of the Iron Triangle framework.
Methods: Our team conducted a global value chain (GVC) analysis of the Pocket Colposcope in Lima, Peru and developed surveys and in-depth interviews to evaluate Pocket Colposcope stakeholders. All surveys were developed with consultations from the Duke Evidence Lab and had IRB approval.
Results: GVC identified five leverage points: regulatory approval, task-shifting, collaboration, telemedicine, and patient acceptance. We also indentified stakeholders and processes impact the degree to which the Pocket Colposcope is successfully implemented. 39.4% of women surveyed answered that they had previously wanted a cervical cancer screening test, but had been unable to receive one due to some barrier. The most common responses were distance to clinics (31.0%), participants could not leave work (27.6%), and patients were afraid of receiving a cancer diagnosis (20.7%). All four midwives who participated in the focus group identified the portability of the Pocket Colposcope as the device's most appealing feature. Providers identified the quality of the image, cost to patient, and ease of use as the three most important aspects of the Pocket Colposcope.
Conclusions: The Pocket Colposcope provides an opportunity to make high quality diagnostic technology more accessible at a cheaper price for more people. Often, disruptive technology in low-income settings is expected to increase access at the cost of reducing quality. In the case of the Pocket Colposcope, the disruptive technology is significantly cheaper than existing technology, but is still high quality enough to succeed.

CERVICAL CANCER SCREENING IN PREGNANCY: IDENTIFYING CHARACTERISTICS OF POSTPARTUM FOLLOW-UP

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Advances in prevention, detection and treatment of cervical cancer and precancerous lesions have made cervical cancer one of the most preventable cancers in the world. Pregnancy poses an ideal time for cervical cancer screening because it is a time in which women are known to reliably seek medical care. Current guidelines recommend antenatal colposcopy and postpartum follow-up given the potential risk of treatment during pregnancy. The aim of this study was to identify antepartum, intrapartum, and postpartum characteristics of those patients at high risk of being lost to follow-up at a county hospital.
Methods: Between 2009-2018, women with abnormal pap smear performed during pregnancy within a county system were identified. A retrospective cohort review was performed and demographic and clinical characteristics collected, as well as compliance with recommended antenatal and postpartum care. Bivariate association between patient characteristics and completion of postpartum colposcopy were performed using chi-square test.
Results: Of 89 patients identified with abnormal cytology during pregnancy, the majority were Hispanic (79.8%), Spanish-speaking (64.0%) and without insurance (64.0%). Only 23 patients (25.8%) completed postpartum colposcopy. Those who presented to their postpartum visit were more likely to complete postpartum colposcopy ($p<0.05$). Earlier gestational age at first obstetric visit and pap smear and total number of visits were associated with improved follow-up. Patients with HSIL (50%) were more likely to follow up than patients with LSIL (25%) or ASCUS (17.9%). Over 95% of patients who failed to complete antepartum colposcopy also failed to complete postpartum colposcopy. Of patients who completed an antepartum colposcopy, 45.8% also completed postpartum colposcopy. Of those who completed follow-up, CIN II-III was identified in 30.4% of cases.

Characteristics	Follow-up n=23 (%)	Lost to Follow Up n=66 (%)	P Value
Age (yrs)	29.2 ± 4.14	27.9 ± 5.84	
Gravidity	3.8 ± 1.2	3.7 ± 2.2	
Living Children	3.4 ± 1.1	3.2 ± 2.0	0.15
Gestational Age (weeks)			
At Initial Ob Visit	14.0 ± 6.3	16.0 ± 8.2	0.48
At Cytology	13.6 ± 7.0	16.6 ± 8.2	0.08
At Colposcopy	24.5 ± 7.5	24.3 ± 9.0	0.41
Total No. Ob Visits	12.8 ± 4.0	10.0 ± 4.8	**0.03**
Ethnicity			
Hispanic	23 (100)	48 (72)	**0.005**
Non-Hispanic	0 (0)	18 (27)	
Language			
English	4 (17.4)	25 (37.9)	0.09
Spanish	19 (82.6)	38 (57.6)	
Other	0 (0)	3 (4.6)	
Insurance Type			
Self-Pay	13 (22.8)	44 (77.2)	
AHCCCS	9 (31.0)	20 (69.0)	
Indian HI	0 (0)	1 (100)	
Private	1 (50)	1 (50)	
Postpartum Visit			
Missed	3 (13.0)	28 (43.1)	**0.008**
Attended	20 (87.0)	37 (56.9)	
Year Since Last Pap Smear			
0.3 Years	14 (60.9)	18 (27.3)	**0.009**
4-6 Years	8 (34.8)	34 (51.5)	
7-9 Years	1 (4.3)	14 (21.2)	
Psych Diagnosis			
Yes	4 (40)	6 (60)	0.28
No	19 (24.0)	60 (76.0)	

Conclusions: Compliance with postpartum colposcopy was poor. These findings suggest that behavior during pregnancy can also predict postpartum compliance. Emphasizing the importance of antenatal colposcopy and the routine postpartum visit may enhance compliance with postpartum colposcopy.

RISK OF HPV AMONG FEMALE IMMIGRANT URBAN MINORITY YOUTH: THE ROLE OF NATIVITY STATUS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: There is a growing body of literature exploring the differences in risky sexual behaviors and sexually transmitted infections among ethnic minority adolescents and young adults (AYAs) by nativity status (i.e., US-born vs. foreign-born).
Methods: We evaluated the association between nativity status and prevalence of cervical HPV in an ethnically diverse cohort of sexually-active AYA females receiving the HPV vaccine at a large adolescent health center in New York City. Participants completed a self-administered questionnaire in which they answered questions on where they were born, when they moved to the US (if applicable), and where their biological parents were born. Also, details on sexual activity and other socio-demographic factors were asked. HPV-DNA was tested for using the MY09/11-PCR assay in cervical specimens collected by cytobrush. Differences in detection of high-risk HPV by nativity were assessed by multivariate regression.
Results: While most of the participants were born in the US (89.2%), over half (58.3%) had at least one parent born outside the US. Foreign-born AYAs were less likely than US-born participants to test positive for high-risk HPV (22.7% vs. 32.4%; adjusted odds ratio [aOR]=0.67, 95% confidence interval [CI]:0.99-2.39). High-risk HPV types 51 and 58 were more prevalent among US-born compared to foreign-born AYAs. Among first-generation immigrants, those who moved to the US <10 years prior had marginally lower odds of testing positive for high-risk HPV when compared to third-generation AYAs (20.4% vs. 34.6%; aOR=0.5, 95%CI:0.3-1.1), whereas those who had lived in the US ≥10 years were not significantly different from third-generation AYAs (24.4%; aOR=0.7, 95%CI:0.4-1.3). No difference was seen between third-generation AYAs and second-generation AYAs (30.1%; aOR=1.0, 95%CI:0.8-1.2).
Conclusions: Foreign-born immigrant AYAs appear to have a lower risk of HPV compared to their US-born counterparts with US-born parents. However, differences diminish as the number of years spent in the US increases.

FEMALE VETERANS WITH HIV HAVE AN INCREASED RISK OF HPV-ASSOCIATED GENITAL TRACT CANCERS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Women living with HIV (WLWH) are thought to be at higher risk for HPV-associated genital tract cancers (HGTCs) due to their immune status. However, access to cervical cancer screening often confounds the observed difference in cancer incidence. We conducted this study to determine if there have been any changes in risk or survival among WLWH who develop HGTCs during the anti-retroviral era in a single-payer health system.
Methods: Veteran WLWH and age-matched controls receiving care between October 1, 1999 and December 31, 2016 were retrospectively identified using Veterans Health Administration (VHA) electronic medical records (EMR). Potential HGTC (cervical, vaginal, vulvar, anal, and rectal) diagnoses were identified through VHA Cancer Registry review and ICD-9/10 codes. Demographic, lifestyle, and clinical variables were extracted from EMR for analysis. Incidence Rates (IR), Incidence Rate Ratios (IRR), and 95% confidence intervals (CI) for cancer risk were estimated and Kaplan-Meier survival analysis were conducted.
Results: We identified 1,454 WLWH and compared them to 5,816 age-matched female HIV-negative controls. More WLWH developed HGTCs (total n=29 [2.0%]; cervical=23, vaginal=2, vulvar=2, anal=2, and rectal=0) than HIV-negative women (total n = 25 [0.4%]; cervical = 25, vaginal=2, vulvar=3, anal=3, and rectal=2) (log rank p<0.0001). Cervical cancer incidence rate (IR) was >4-fold higher in WLWH (198.3 per 100,000 person years [py] [CI 198.0-198.5]) than HIV-negative women (IR = 46.6 per 100,000 py [CI 46.6-46.7]; incidence rate ratio [IRR] = 4.25 [CI 3.18-5.68]). The IRs for vaginal, vulvar, and anal cancers were also >3-fold higher in WLWH (Table 1). Overall, WLWH were more likely to develop HGTC compared to their HIV-negative counterparts (log rank p values <0.0001).

Table 1. Incidence Rates (IR) and Incidence Rate Ratios (IRR) for HPV-Associated Cancers in Women Veterans Living with HIV and HIV-Uninfected Control Cohorts

	HIV(+) Women			HIV(-) Women			IRR (95% CI)
Cancer Type	**N**	**IR**	**95% CI**	**N**	**IR**	**95% CI**	
Cervical	23	198.30	(198.0-198.5)	25	46.64	(46.58-46.69)	4.25 (3.18-5.68)
Vaginal	2	17.24	(17.17-17.32)	2	3.73	(3.71-3.75)	4.62 (1.70-12.56)
Vulvar	2	17.24	(17.16-17.32)	3	5.60	(5.58-5.62)	3.08 (1.24-7.68)
Anal	2	17.24	(17.16-17.32)	3	5.60	(5.58-5.62)	3.08 (1.24-7.68)
Rectal	0	0.00	N/A	3	5.60	(5.58-5.62)	N/A
All	29	250.00	(249.7-250.3)	33	61.56	(61.49-61.62)	4.06 (3.15-5.24)

Conclusions: Veteran WLWH are more likely to develop HGTCs in spite of equal access to health care. More research is required to determine optimal high-risk HPV screening strategies for HGTC prevention in WLWH.

USING IMPLEMENTATION MAPPING TO DEVELOP AN MHEALTH INTERVENTION TO INCREASE PROVIDER RECOMMENDATION OF HPV VACCINATION

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Studies indicate provider recommendation is one of the strongest predictors of adolescent HPV vaccine uptake, however inconsistent provider recommendations and inadequate response to parent hesitancy contribute to low HPV vaccination rates compared to other adolescent vaccines. We used Implementation Mapping (IM), a framework used to develop or select implementation strategies, to guide the design of a theory- and evidence-based innovative mHealth intervention for healthcare providers to improve recommendation for HPV vaccination and communication with hesitant parents.
Methods: We used Implementation Mapping to guide the design of an mHealth intervention to increase provider recommendation of the vaccine. The six-step process included a needs assessment, careful delineation of provider and medical assistant behaviors and sub-behaviors, identification of determinants and the selection of methods and strategies for intervening. It also helped guide the application of behavioral science and implementation science models for strategy development.
Results: We developed the innovative app with an overall theme of HPV is cancer prevention message demonstrating various parent-provider clinic-based scenarios for informed-decision making. Messages were framed that specifically targeted provider barriers of knowledge, skills & efficacy, outcome expectations and normative beliefs. Guided by literature on provider barriers and motivations, the intervention utilized methods such as tailoring, chunking, framing, modeling, skill building, education and re-evaluation to target modifiable factors that inhibit providers from providing a strong recommendation. Implementation mapping guided development of this mobile-based training resource, going beyond the typical knowledge base, to focus on motivation, skills and self-efficacy to guide the methods and practical applications (strategy) in the development of the app.
Conclusions: Planning and application of implementing strategies using the IM framework can lead to sustained and effective evidence based interventions. Leveraging implementation science principles around parent-provider decision-making has the potential to amplify system-level interventions to increase uptake of HPV vaccine and prevent cancer.

MEASUREMENT OF HPV-SPECIFIC IGG AND IGM RESPONSES USING A PSEUDOVIRION-BASED ELISA METHOD

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: The human papillomavirus (HPV) pseudovirion (PsV)-based neutralisation assay (PBNA) does not discriminate different antibody isotypes. Here, we examined the use of a PsV-based enzyme-linked immunosorbent assay (ELISA) to measure HPV-specific IgG and IgM antibody responses.
Methods: A cohort study was undertaken in 200 Fijian girls (15-19 years old) previously unvaccinated, or vaccinated with 1-3 doses of 4vHPV (Gardasil®, Merck Inc.) 6 years earlier. A booster dose of 2vHPV (Cervarix®, GSK) was given to all girls. Blood was taken pre- and 28 days following the 2vHPV booster dose. Neutralising antibody (NAb) responses were previously measured by a HPV PBNA. We measured the IgG and IgM response to HPV-16/18 using a PsV-based ELISA.
Results: Preliminary analyses to date (N=10/dosage group) showed significantly higher HPV16-IgG levels in girls previously vaccinated with 2 or 3 doses of 4vHPV compared with girls vaccinated with 1 dose or unvaccinated ($p<0.05$ in all cases): no significant differences in IgM antibody levels were found between all dosage groups. Following 2vHPV, HPV-specific IgG levels were significantly increased in all dosage groups, whereas previously unvaccinated girls also had significantly higher HPV-specific IgM levels ($p<0.05$). Girls previously vaccinated with 1 dose of 4vHPV boosted to a similar IgG level as girls previously vaccinated with 2 or 3 doses. Significant correlations were found between IgG, but not IgM and NAb ($r=0.61$, $p<0.0001$).
Conclusions: These results suggest that a PsV-based ELISA method may be used as an alternative to the PBNA for the measurement of HPV-specific antibody responses, including characterisation of antibody isotype and subclasses following vaccination. Further studies are needed in different settings to validate this approach.

ORAL HEALTH SCREENINGS AND HPV EDUCATION FOR FUTURE ORAL HEALTH PROFESSIONALS: TAILORING CURRICULUM TO MAXIMIZE IMPACT

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Oral health professionals are frequently the first to detect oral and oropharyngeal cancer during routine screenings. The connection between HPV and oropharyngeal cancer is increasingly documented in the literature, as is the importance of provider recommendation for immunization decisions. Oral health professionals can become powerful allies in increasing HPV vaccination rates, but misinformation and lack of resources to start conversations with patients stand in the way of including recommendations for HPV vaccination during oral health screenings.
Methods: A collaborative project between The Arizona Partnership for Immunization (tapi) and Project Zero—Women & Infants (PZWI) developed a curriculum on HPV tailored to dental and dental hygiene students. The curriculum uses the principles of backwards design and includes information and resources that oral health professionals can use to increase their knowledge of HPV vaccination and introduce the topic to their patients. The driving force was to present evidence in a way that would incentivize future providers to recommend vaccination; promoting efficient use of public health resources.
Results: The curriculum has three learning objectives: presenting HPV as a cancer risk factor, understanding the HPV vaccine is a safe prevention measure, and sharing the importance of immunization pre exposure. For each objective, the team included research, tools, and educational content from authoritative sources, and shared key messages that can be used by future providers to share with their patients. Next steps for this project include disseminating the curriculum through partnerships in Arizona and testing its efficacy in improving conversations about HPV in oral health settings.
Conclusions: By sharing the process of creating a curriculum, we want to emphasize the importance of partnerships between academic and public health settings as a way to leverage resources and propose data-based strategies to improve health.

PAN-CANADIAN ACTION PLAN FOR ELIMINATION OF CERVICAL CANCER – MODELLING RESULTS USING THE ONCOSIM MICROSIMULATION TOOL

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Cervical cancer is one of the most preventable and treatable forms of cancer. WHO issued a global call to action in May 2018 to eliminate cervical cancer as a global public health problem. As a member of the UICC, The Partnership is now leading the charge to create a 10-year pan-Canadian action plan to eliminate cervical cancer and will host a summit to launch the plan in Feb 2020.
Methods: OncoSim is a microsimulation model, led and supported by the Canadian Partnership Against Cancer, with model development by Statistics Canada, and is made possible through funding by Health Canada. The OncoSim-Cervical and HPV Microsimulation Model (HPVMM) is a specific OncoSim module that focuses on the prevention, screening, diagnosis and treatment of cervical cancer. Taking a health system perspective, using OncoSim, we seek to: (i) project the potential health and economic impact associated with achieving the target of 90/90/90 by 2030: 90% HPV vaccination, 90% catch-up vaccination, and 90% cervical cancer screening participation in an eligible population by 2030 in Canada. (ii) Assess the likelihood of meeting the 2040 goal to eliminate cervical cancer (less than 4/100,000, crude) in Canada with the implementation of coordinated HPV vaccination programs, HPV vaccination catch-up programs, and cervical cancer screening programs using HPV testing.
Results: Costs and health outcomes will be evaluated in a short-term frame (2020-2030), as well as longer-term (2020-2040) to align with the elimination of cervical cancer targets Incidence and mortality rates, resource utilization (screen numbers, colposcopies etc.) and rates of dysplasia will also be reported
Conclusions: The Canadian Partnership Against Cancer is actively works with its partners to lead the way towards elimination. Over the last five years, OncoSim's projections have helped inform cancer control planning decisions across Canada and the results from this analysis will help inform the Pan-Canadian action plan.

MEK/ERK SIGNALING IS A CRITICAL REGULATOR OF HIGH-RISK HUMAN PAPILLOMAVIRUS ONCOGENE EXPRESSION REVEALING THERAPEUTIC TARGETS FOR HPV-INDUCED TUMORS

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: High-risk (Hr) HPV-induced malignancies are driven by deregulated expression of the E6 and E7 oncogenes and the functions of these viral oncoproteins have been widely studied. Yet, the mechanisms that regulate hr-HPV oncogene transcription and suppress their expression in benign lesions remain poorly understood.
Methods: We used five independent human keratinocyte cell lines that maintain episomal hr-HPV genomes and two cancer cell lines with integrated viral genomes to investigate signaling pathways that modulate HPV oncogene expression. Monolayer cell cultures, epithelial organotypic (raft) tissue models, tumor xenografts and neoplastic tissue biopsy materials were subject to cellular, biochemical and genetic analyses for signaling activities, viral oncogene/protein expression and growth potential. Rigorous statistical analyses were performed.
Results: MEK/ERK signaling increased concomitantly with oncogene expression and increasing neoplastic grade in human cervical intraepithelial neoplasia (CIN) tissue biopsies. Epithelial contact inhibition and tissue differentiation cues suppressed MEK/ERK signaling, and thereby, reduced hr-HPV oncogene expression. However, experimental EGFR/MEK/ERK stimulation rescued signaling and oncogene transcription in proliferating and contact inhibited cells/tissues. Pharmacological inhibitors of EGFR, MEK and ERK quash MEK/ERK signaling, HPV oncogene expression and the neoplastic phenotype in HPV-positive cells, raft tissues and tumor xenografts.
Conclusions: We demonstrate that MEK/ERK signaling is a key regulator of hr-HPV oncogene expression at the transcriptional level regardless of HPV integration status. As epidemiologically identified, cancer-promoting cofactors (tobacco smoke, estrogen, nitric oxide, *Chlamydia*) also promote MEK/ERK signaling, we speculate these cofactors share a mechanism by which they promote hr-HPV persistence and/or disease. As pharmacological ERK inhibition suppresses HPV oncogene expression and the neoplastic phenotype, we propose this as a potential clinical strategy to restrain uncontrolled cell proliferation, reduce oncogene expression and treat HPV neoplasia.

IMPLEMENTING PRACTICE FACILITATION TO IMPROVE HPV VACCINATION IN PEDIATRIC CLINICS IN UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Given logistical barriers to school-located immunization in the U.S., optimizing receipt of immunizations in clinical practices is key to increasing HPV vaccination rates. We compared two implementation strategies (in-person and web-based coaching) for a practice facilitation intervention to engage pediatric providers and staff in quality improvement (QI) projects focused on increasing HPV vaccination.
Methods: Private pediatric practices (N=21) in Tennessee, U.S., were randomized to the two implementation strategies. Practices were presented 9 practice change options, then implemented four selected change options over 12 months (two changes per six months). Outcome metrics were receipt of an HPV vaccine dose during well visits for adolescents ages 11-17 and bundling with other recommended vaccines for 11-12 year olds (HPV, meningococcal and Tdap) in the same visit. Interrupted time series analyses compared practices' 12-month baseline to the 12-month implementation period. We hypothesized both arms would improve HPV vaccination over time, and the in-person coaching arm would improve more than the web-based coaching arm. Fidelity and participant perceptions were also compared.
Results: For receipt of an HPV vaccine dose due during well visits, the web-based arm increased 10.5 percentage points (95% CI: 4.8~16.2, p<.01), while the in-person arm had a non-significant increase of 7.9 percentage points (-1.5~17.2, p=.10). For "bundling" of adolescent vaccines in the same visit, the web-based arm increased 11.0 percentage points (1.7~20.3, p=.019), while the in-person arm increased 14.0 percentage points (4.9~23.1, p<.01). The in-person coaching arm demonstrated greater intervention fidelity compared to the web-based arm. Providers and staff in both arms reported overall satisfaction with the intervention and similar perceived benefits, with more challenges to keeping providers and staff engaged in the web-based coaching arm.
Conclusions: Practice facilitation offers a promising strategy for improving HPV vaccination. Web-based coaching can reach more practices, while in-person coaching enhances fidelity and engagement.

WILL HPV DNA SELF-SAMPLING INCREASE UPTAKE RATE OF CERVICAL SCREENING AMONG YOUNG ADULT HPV-VACCINATED FEMALE IN HONG KONG?

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human Papillomavirus (HPV) is an extremely common viral infection that most sexually active women will acquire HPV at some point in life. Thus, a comprehensive cervical cancer control strategy included an effective screening programme combined with HPV vaccination is needed. Currently, several countries have implemented the HPV DNA self-sampling as an alternative primary cervical screening method. This study aimed to explore the impact of introducing HPV DNA self-sampling in HPV-vaccinated female on the uptake rate of cervical screening in Hong Kong.
Methods: Young adult female aged 25-35 years and above who previously received HPV vaccination in the HPV Vaccination Campaign were approached. Respondents' behaviour towards cervical screening, lifestyle and background information were accessed using a structured questionnaire. A laboratory HPV DNA testing was conducted for those provided HPV self-sampling specimens. Feedback on performing the HPV self-sampling and their future screening preference were recorded in post-survey.
Results: There were 117 eligible respondents agreed to join the study. More than half of the respondents (56%) never done the cervical cancer screening (Pap smear) or under-screened (those not had Pap smear in the past 3 years). Only 86 women with a response rate of 74% (86/117) successfully returned the HPV self-sampling specimen together with the completed post-sampling questionnaire. Interestingly, the proportion of preference towards HPV self-sampling as an alternative primary screening for cervical cancer among those have never screened or under-screened women (53%) is higher than those with regular cervical cancer screening (35%).
Conclusions: The findings prove that the acceptability of HPV self-sampling was considerably high as an alternative cervical cancer screening option to tackle the barriers to Pap smear screening. The findings provide important information for policy formulation in cervical cancer prevention programme, especially the introduction of HPV self-sampling as an alternative primary screening in the health system in Hong Kong.

INFLUENCE OF SOCIOECONOMIC FACTORS ON HUMAN PAPILLOMAVIRUS VACCINE UPTAKE IN ADOLESCENT GIRLS IN FRANCE

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Our study aimed to explore the association between human papillomavirus (HPV) vaccination among teenage girls in France and socioeconomic factors including both individual and contextual characteristics.
Methods: We conducted a retrospective study among girls born between 1997 and 1999 and collected reimbursement data for HPV vaccines from the National Health Insurance Database covering virtually the whole French population. Vaccination initiation was defined as having received at least one dose of HPV vaccine before 17 years old. A multilevel model based on Poisson regression was developed to study the association between vaccination and individual variables as well as the characteristics of their environment of residence (at the city level).
Results: Among 1,051,656 girls included in the study, 35% had initiated HPV vaccination before 17 years old. Individual variables associated with HPV vaccination were year of birth, vaccination status for DTP booster, benefiting from free health insurance offered to low income families, and number of medical consultations in the period 2011-2016. At the city level, vaccination was associated with the deprivation index level, urban unit, rate of immigrants, and access to a gynecologist. Overall, the prevalence of HPV vaccination decreased when the local deprivation level increased, although the opposite was seen in few geographical administrative districts.
Conclusions: This study has described social and territorial inequalities in HPV vaccination in France. It calls for actions to promote and facilitate access to HPV vaccination especially in deprived areas as well as considering public health policies aiming at reducing health inequalities.

ETIOLOGICAL FACTORS IN OROPHARYNX AND ORAL CAVITY SQUAMOUS CELL CARCINOMA DIAGNOSED AT YOUNG AGE: A SPANISH COHORT AND AN USA CASE-CONTROL STUDY.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: There is a gap in knowledge in the etiological factors in head and neck cancers diagnosed at young age. The aim of this study is to compare the demographic, toxic habits and HPV status between a Spanish retrospective cohort of oropharyngeal cancer (OPC) patients (≤45 years old vs >45 years). Furthermore, we have analyzed the toxic habits status between young cases and controls from an USA case-control study (including OPC and oral cavity cancers-OC).
Methods: We have reanalyzed data from a retrospective cohort of patients diagnosed with OPC in four Catalonian hospitals from 1990 to 2017 and a case-control study in USA from 2011 to 2014 at The Ohio State University Medical Center. In the OPC cohort unconditional logistic regression was used to compare age groups. Differences in characteristics between cases and controls were compared using the Pearson's Chi2 test.
Results: 49 young and 816 old OPC patients were included from the Spanish cohort and 23 young cases and 46 controls from the USA study. Spanish cohort characteristics comparing young and old OPC patients are described in Table 1. No significant differences were reported in gender, toxic habits or HPV status (positivity: 12.2% vs 7.5% in young and old OPC patients, respectively). There were more non-smokers HPV-related OPC patients than HPV-negative ones (p-value<0.001) in both age groups. A descriptive of the toxic habits of the patients with OC stratified by case or control in the USA study is describe in table 2. There were no statistically significant differences between cases and controls for all toxic habits evaluated; 57.8% of cases (24) were HPV-positive.

Table 1: Characteristics and association of young patients from a Spanish retrospective cohort of OPC

Characteristics	All		Young OPC		OR		Log-likelihood ratio test P-value
	N	%	N	%	OR	[95%CI]	
Medianage (range)	60.3	(28.5-93.9)	42	(28.5-45.0)			
Gender							0.467
Female	95	11.0	7	14.3	1.4	[0.6-3.2]	
Male	768	88.8	42	85.7	Ref.		
Missing	2	0.2	0				
Tobacco status							0.846
No	90	10.4	4	8.2	Ref.		
<20 cig/day	115	13.3	7	14.3	1.4	[0.4-4.9]	
≥20 cig/day	600	69.4	35	71.4	1.3	[0.5-3.8]	
Missing	60	6.9	3				
Alcohol use							0.234
No	161	18.6	9	18.4	Ref.		
<100 gr/day	246	28.4	9	18.4	0.6	[0.3-1.7]	
≥100 gr/day	401	46.4	27	55.1	1.2	[0.6-2.7]	
Missing	57	6.6	4				
HPV/DNA AND (HPV/mRNA OR P16)							0.259
Negative	797	92.1	43	87.8	Ref.		
Positive	67	7.8	6	12.2	1.7	[0.7-4.2]	
Missing	1	0.1	0				
Total	**865**	**100.0**	**49**	**100.0**			

Table 2: Descriptive of the toxic habits and HPV status of young patients with OC/OPC cancer stratified by case or control in the USA study

Characteristic	All		Case/control				Chi2 test P-value
			Control		Case		
	N	%	N	%	N	%	
Tobacco status							0.500
Never used, never regular or former regular	57	82.6	39	84.8	18	78.3	
Current regular	12	17.4	7	15.2	5	21.7	
Alcohol use							0.053
Never drinker	1	1.4	1	2.2	0	0.0	
Never regular or former regular	34	49.3	18	39.1	16	69.6	
Current regular	34	49.3	27	58.7	7	30.4	
Marijuana status							0.162
Never	25	36.2	15	32.6	10	43.5	
Never regular or former regular	37	53.6	28	60.9	9	39.1	
Current regular	7	10.1	3	6.5	4	17.4	
Total	**69**	**100.0**	**46**	**100.0**	**23**	**100.0**	

Conclusions: No significant differences were reported in gender, toxic habits or HPV status between young and old OPC patients; neither between young cases and controls regarding tobacco, alcohol or marijuana use.

LONG-TERM PREDICTORS OF RESIDUAL OR RECURRENT CERVICAL INTRAEPITHELIAL NEOPLASIA 2-3 AFTER TREATMENTWITH A LARGE LOOP EXCISION OF THE TRANSFORMATION ZONE: A RETROSPECTIVE STUDY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Data on the long term prognostic value of High Risk (HR)-HPV when added to the margins involvement in the management of CIN2-3 large loop excision of the transformation zone (LLETZ) are scarce. We assess the predictive value of HR-HPV test on the 20 years risk of CIN2-3 among LLETZ-treated women for CIN2–3.
Methods: Retrospective cohort study of 242 consecutive adult women affected by CIN 2-3 and treated by LLETZ at the Department of Gynecology of the Hospital Universitari de Bellvitge (Barcelona, Spain) recruited between January 1996 and September 2006, followed to June 2016. Clinical information and HR-HPV status was recruited from pathological reports. Accuracy of the first cytological and HR-HPV after LLETZ results and margins involvement, alone and combined, was assessed by estimating the sensitivity, specificity, positive and negative predicted values of residual/recurrent CIN2–3. Unconditional logistic regression and Cox proportional hazard models were used to identify the determinants of residual or recurrent CIN 2-3, and failure rates were estimated by Kaplan-Meier analysis.
Results: CIN 2-3 was associated with HR-HPV (Hazard Ratio (HaR)=30.58; 95% Confidence Interval (CI)=3.80-246.20); Age>35 years (HaR=5.53; 95%CI=1.22-25.13); and margins (HaR=7.31; 95%CI=1.60–33.44). HR-HPV showed a sensitivity of 88.8% and a specificity of 80%. Women with ecto(+)/endocervical(+) margins (16.7%), those with uncertain (19.4%) and those with ecto(-)/endocervical(+) margins (9.1%) had higher risk of recurrence (Odds Ratio (OR)=13.20 (95%CI=1.02-170.96), OR=15.84 (95%CI=3.02-83.01), and OR=6.60 (95%CI=0.88-49.53)), respectively. Women with involved margins and/or HR-HPV positive had more treatment failure than those who were HR-HPV negative irrespective of margins or had clear margins (P-log rank<0.001).
Conclusions: HR-HPV and margins are both essential for stratifying post-LLETZ risk, and enable personalised management. Given that clear margins present a lower risk, a large excision may be indicated in older women in order to reduce the risk.

HPV PROTEIN FUNCTIONS ARE LINKED TO THE DISTINCT HOMEOSTASIS MECHANISMS THAT REGULATE THEIR EPITHELIAL NICHES

BASIC RESEARCH / VIRUS LIFE CYCLE

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Introduction: The sexually transmitted alpha HPV types infect distinct epithelial niches. We have examined the molecular pathways that regulate normal epithelial homeostasis at four genital target sites, including the vulva, the ectocervix, the cervical transformation zone and the endocervix in order to explain the evolution of high and low risk HPV protein functions, and their mode of HPV persistence.
Methods: Patterns of HPV gene expression in clinical biopsy material, have been correlated by multiplex immunofluoresence imaging with markers of epithelial homeostasis within the femalke genital tract. Molecular pathways were validated using *in vitro* tissue culture systems that model the epithelial basal layer and the process of reserve cell metaplasia.
Results: Epithelial differentiation controlled by p53 appears a common target of these viruses, which is mediated through the inhibition of p53 transcription, or through E6AP-binding and direct E6-mediated degradation. For high and low risk HPV types, tthis results in an inhibition of Notch-mediated commitment to differentiation, and the persistence of HPV infected cells in the basal layer because of their selective growth advantage. The specific ability of the high-risk HPV types to persist at the cervical transformation zone, requires interference with the molecular pathways that regulate reserve cell proliferation and metaplasia. The balance between Wnt and Notch signalling controls differentiation, quiescence and cell division at this site, with the Hippo pathway controlling cell density. E6 interferes with all three regulatory pthways to ensure persistence, with high risk E6 /PDZ domain protein interactions contributing additionally to disruption of normal cell-cell recognition.
Conclusions: HPV protein functions have evolved to modulatethe homeosatic pathways that regulate their specific epithelial target sites, which for high-risk HPV types includes the reserve cells of the cervical transformation zone. The deregulation of such 'normal ' HPV functions underlies the development of neoplasia. Regulators of HPV-modulated epithelial homeostasis are prime candidates for therapeutic development.

EVALUATION OF NOVEL HUMAN PAPILLOMAVIRUS (HPV) STANDARDS AS QUALITY CONTROLS (QC) IN THE WORKFLOW ASSESSMENT OF LABORATORIES PERFORMING HPV TESTING.

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Persistent infection with oncogenic human papillomavirus (HPV) has been linked to cervical cancer. European Guidelines advocate the use of HPV testing as primary cervical cancer screening method in organized population-based programs. Furthermore, HPV-genotyping and viral load are able to distinguish persistent infections and to stratify the risk related to cancer development in the infected population, as individual oncogenic genotypes have different carcinogenic potential. Good performance and reproducibility of laboratory results is fundamental for safe HPV-based screening and requires quality assessment to monitor the entire workflow, including nucleic acid extraction, amplification, and detection. The aim of this study was to evaluate a novel panel of HPV type-specific controls (MICROBIX) on testing with AnyplexII HPV28 (Seegene), a clinically validated full-genotyping assay, and with HPV OncoPredict viral load and RNA assays, two full-genotyping IVD prototypes developed as part of an ongoing Horizon 2020 Project (SME Instrument Grant GA 806551).
Methods: MICROBIX controls, available for hrHPV types 16, 18, 31, 33, 39, 45 and HPV 67, contain components found in HPV-infected clinical samples, such as integrated and episomal viral DNA, viral RNA as well as host epithelial cells. All samples were extracted using NucliSENS easyMAG (bioMerieux) and HPV detection carried out using AnyplexII HPV28 (Seegene), HPV OncoPredict viral load (Hiantis) and HPV OncoPredict RNA (GeneFirst) assays, according to manufacturers' instructions. Absolute HPV viral loads were further evaluated by means of "in house" HPV genotype-specific assays using Droplet Digital PCR (BioRad).
Results: MICROBIX controls showed an excellent compatibility with all evaluated HPV genotyping assays. MICROBIX controls tested in combination with HPV OncoPredict viral load were shown to provide accurate quantitative assessment of genotype-specific viral loads, as compared to the absolute values obtained using Droplet Digital PCR.
Conclusions: The novel MICROBIX HPV genotype-specific controls showed promising results for their future application as QC samples in laboratories performing HPV testing.

SPECULUM-FREE CALLASCOPE FOR CERVICAL SELF-VISUALIZATION: ACCEPTABILITY, FEASIBILITY, AND IMPROVED AWARENESS OF THE REPRODUCTIVE SYSTEM

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Invasive cervical cancer is preventable, yet affects 500,000 women worldwide each year, and over half these women die. Barriers to cervical cancer screening include lack of awareness of cervical cancer and the cervix, fear of the speculum and lack of women-centric technologies. We developed a low-cost (~$50), cervix-imaging device called the Callascope, which comprises an imaging component, camera, and inserter which obviates the need for a speculum and enables self-insertion. Studies are lacking regarding women's willingness to independently image their cervix and women's ability to effectively use the Callascope for self-imaging.
Methods: We conducted two studies: (1) in-depth interviews to assess willingness to self-image the cervix, perceptions of the Callascope, and knowledge, attitudes, and practices (KAP) towards cervical cancer screening, and (2) home-based self-cervix imaging with the Callascope where women recorded an audio-reflection on their experience.
Results: Participants of the interviews (n=12) and home study (n=12) all indicated a preference for the Callascope over the speculum. Interview data showed that 53% of participants had little knowledge of basic reproductive anatomy, and only 17% of participants understood that HPV was a direct cause of cervical cancer. Self-exam data showed that 83% of participants were able to visualize their cervix with the Callascope on the first try and 100% by the end of the study. 100% of participants indicated that the home-exam was an empowering and informative experience.
Conclusions: The Callascope is more comfortable than the speculum and women are able to successfully image their cervices from home without the need for a speculum. With improved diagnostic capabilities, the Callascope could be used by medical providers for clinical exams, particularly in low-resource settings, as a low-cost and more comfortable alternative to the SOC. The Callascope enables home self-screening for cervical cancer and a better understanding of one's body, which could make screening more accessible in low-resource settings.

A SINGLE DOSE OF QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE IS IMMUNOGENIC AND REDUCES HPV DETECTION RATES IN YOUNG WOMEN IN MONGOLIA, SIX YEARS AFTER VACCINATION

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Emerging observational evidence suggests a single-dose of human papillomavirus (HPV) vaccine may be protective against vaccine-targeted HPV infection and associated cervical dysplasia. We aimed to demonstrate whether a single dose of quadrivalent HPV (4vHPV) vaccine was immunogenic and reduced HPV detection rates in young women in Mongolia. We also assessed knowledge and attitudes regarding cervical cancer, HPV and the HPV vaccine.
Methods: An observational study was undertaken to evaluate the immunogenicity and impact on HPV detection rates following a single dose of 4vHPV, given at age 11-17 years in 2012, compared with age-matched unvaccinated women. Real time PCR was performed on self-administered vaginal swabs for HPV detection. Neutralising antibodies (NAb) to high-risk HPV (HRHPV) genotypes 16 and 18 was performed on sera from a subset of 58 participants using HPV Pseudovirion-based neutralization assay. Two questionnaires evaluated knowledge, attitudes and self-swab acceptability.
Results: A total of 475 women, mean age 20·4 years (SD+/- 1.6), were recruited; 118 vaccinated and 357 unvaccinated women. Prevalence for any HPV genotypes was 27·1% and 35·3% for the vaccinated and unvaccinated cohorts, respectively. The prevalence of vaccine-targeted HRHPV16 and 18 was reduced by 92% (95%CI 44-99%) in the vaccinated (1·1%) compared with the unvaccinated (15·4%) group. The percentage of non-vaccine HPV genotypes was similar between vaccinated (26·5%) and unvaccinated (26·7%) groups. Approximately 90% and 58% of vaccinated women remained seropositive after six years for HRHPV16 and 18, respectively, with NAb levels five- and two-fold higher than unvaccinated women ($p<0·001$). The knowledge and attitudes questionnaire results showed an overall low level of knowledge on HPV, HPV vaccines and cervical cancer (14% answered >50% questions correctly). Overall self-swab acceptability was high (>80% for ease).
Conclusions: One dose of 4vHPV vaccine reduced vaccine-targeted HPV genotypes, six years following vaccination, with persistent high levels of vaccine-targeted HPV seropositivity among young Mongolian women.

INTERNATIONAL HPV AWARENESS DAY IN RUSSIA ON MARCH 4, 2019 - GLOBAL RUSSIAN ACTION FOR PREVENTION OF CERVICAL CANCER

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: More than 17,587 women a year in 85 Russian Regions are diagnosed with cervical cancer, 40% of these women die. Doctors and women oriented educational programs were developed in order to implement organized screening and vaccination programs against cervical cancer and HPV-associated diseases in Russia. A part of this strategy was Russian Global action for celebration of International HPV Awareness Day on March 4, 2019
Methods: Doctors program consisted of 2 hours webinar broadcasted to 85 Russian Regions with five lectures of top specialists. Regional Governors supported online connections of local gynecologists, pediatricians and oncologists. 10 Live Regional Conferences were performed with the help of local Health Care authorities. Women program was realised by 3 key activities. Russian web site "hpvday" was created and constantly promoted as a top site explaining Russian women about HPV and how it could be prevented. The site offered locations to undergo vaccination and screening. HPV Day banners were shown in Russian social networks. Distribution of flowers and leaflets in Russian malls was done. Free of charge medical consultations were provided.
Results: 20 000 online connections were achieved during the webinar covering 85 Russian Regions, 10 live Regional conferences were organized. HPVDay web site was visited by 4 million people and 5 million shows were achieved in VKONTAKTE, most popular Russian network; 16 279 HPV-related posts published in social media. 50 publications appeared in RuNet. 20 000 leaflets and flowers were distributed in various molls and out-patient departments by volunteers.
Conclusions: Reducing incidence and cervical cancer-related mortality rates is crucial. In Russia we experience difficulties in reaching of women invited for screening or vaccination. To cope with this situation national informational and educational campaign was developed with International HPV Awareness Day as a part of it. As a result Russian programs for HPV screening and vaccination were implemented

HUMAN PAPILLOMA VIRUS (HPV) IN OTORHINOLARYNGOLOGY AND PHONIATRICS– THE ROLE OF IMAGE 1S ENDOSCOPIC DIAGNOSTICS ON EXAMPLE OF CLINICAL CASES

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: HPV is one of the most important pathogenic agents of the XXI century. There are about 200 types of the virus, including highly oncogenic HPV 16 and 18 responsible for cervical cancer development. In otorhinolaryngology and phoniatrics low-oncogenic HPV types are serious problem and are responsible for the development of laryngeal and nasal papilloma. Despite benign character these diseases are dangerous for the organism, due to its recurrent character and the possibility of total obstruction of the respiratory tract.
Methods: Between 2018 and 2019 two patients were admitted the Otolaryngology Department of the University Hospital of Cracow. The first patient reported voice disorders, hoarseness and sore throat. Second patient presented almost total limitation of patency and the feeling of runoff of mucus on the back wall of the pharynx. Except otolaryngological examination the endoscopy IMAGE 1S using special filters was performed in both patients. Moreover the videolaryngostroboscopic examination was done in the first patient. The directoscopy was performed in the first patinet, while the second underwent endoscopic surgery. In both cases histopathological probes were taken during mentioned medical procedures.
Results: In both cases lesion of HPV etiology was confirmed. After 30 days control examinations took place: videolaryngostroboscopy for the first patient, and endoscopy for the second. Control examinations proved the improvment of local state of both larynx and nasal cavity as well as in phoniatric function of larynx and patency of nasal ducts.
Conclusions: Examples of two clinical cases show that upper respiratory tract HPV infections pose a serious problem for otorhinolaryngology and phoniatrics. Endoscopy using IMAGE 1S camera with filters proves effective and non-invasive detection of lesions caused by HPV infection. It is planned in the Otolaryngology Clinic of the University Hospital of Cracow to expand the study with the diagnostics using Near Infrared ICG endoscopy system in the near future.

POLYNUCLOTIDE IMMUNOTHERAPY FOR HPV ASSOCIATED OROPHARYNGEAL CANCER

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: Background: HPV associated oropharyngeal cancers (OPC) are increasing in prevalence worldwide. Treatment of disease recurrence, either locoregionally or distant, after primary chemoradiotherapy or surgery is not uncommon, and poses a difficult management dilemma with limited success. Polynucleotide vaccines encoding HPV16 E6/E7 fusion proteins have demonstrated efficacy in several animal models of HPV associated cancer. **Aim:** Evaluate a polynucleotide immunotherapy targeted at HPV16 E6 and E7 proteins for immunogenicity and safety in patients with apparent cure after primary therapy for HPV associated OPC.
Methods: A 1:1 mixture of 2 codon modified polynucleotide vaccines encoding HPV16 E6 and E7 with or without ubiquitin were administered at three doses (0.25mg, 1mg, 4mg) intracutaneously on 3 occasions to a total of 12 subjects with treated HPV associated OPC. This study was conducted with the approval of the Australian Therapeutic Goods Administration and the Ethics committee of the Princess Alexandra Hospital. Data management was overviewed by a contract research organisation.
Results: Results: A cell mediated response to HPV 16 E6 and E7 was evident at baseline in all participants using ELIspot. Antibodies against HPV 16 E7 was evident at baseline in 11 of 12 participants using ELISA. Of 12 subjects, 10 demonstrated a significant immune response to one or more of the peptide pools at one or more timepoints. One subject has had a confirmed recurrence of disease 12 months after immunisation. Only minor local adverse events attributable to the vaccine at the site of injection were observed.
Conclusions: Conclusion: This polynucleotide vaccine enhanced specific immunity to a virus derived tumour associated antigen in the majority of immunised subjects without significant adverse events, warranting a further study in subjects with recurrent disease after treatment.

A COMPARISON OF THINPREP AGAINST FOUR NON-VOLATILE TRANSPORT MEDIA FOR HPV TESTING AT OR NEAR THE POINT OF CARE.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: The GeneXpert (Xpert) HPV Test (Cepheid, Sunnyvale, CA) has been used at point-of-care for cervical screening in a number of low-and middle-income countries (LMIC). It is validated for use with ThinPrep-PreservCyt (Hologic, Marlborough, MA) transport medium which has a high methanol content and is therefore toxic and classified as a dangerous good for shipping, making its cost, transportation and use challenging within LMIC. Therefore, we compared the performance of ThinPrep against four known non-volatile PCR transport media for HPV point-of-care testing to determine if a suitable alternative for scale-up is available.
Methods: Methods: Ten-fold serial dilutions were prepared using HPV cell lines 16, 18 and 31 with each line suspended in five media types. Purified DNA was added to each dilution step to ensure similar sample adequacy control (SAC) results. All samples were tested by trained laboratory scientists using the GeneXpert HPV assay. The media types consisted of Phosphate Buffered Saline (Thermo Fischer Scientific, Waltham, MA, USA), Sigma Virocult (Medical Wire & Equipment, Wiltshire, England), MSwab (Copan, Brescia BS, Italy) Xpert Transport Media (Cepheid, Sunnyvale, USA) and ThinPrep-PreservCyt (Hologic Inc., Marlborough, MA).
Results: Results: A total of 105 HPV Xpert tests were conducted in an accredited laboratory in Brisbane, Australia with 7 ten-fold dilutions of each of the 3 viruses tested in all 5 media types. The lowest HPV ten-fold dilution detected for any media or cell line was the fifth dilution, and the Mswab was the only medium that provided detection of HPV to the 5th dilution for all cell lines used.
Conclusions: Conclusions: Results suggest the non-volatile Mswab transport media could be a suitable alternative to ThinPrep for Xpert HPV testing at or near the point of care. A field-based, head to head comparison of both media types using the Xpert HPV assay is warranted to confirm these laboratory-based findings.

ANALYSIS ON HPV AND EBV GENE MAPPING IN NASAL INVERTED PAPILLOMA

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: To analyze the correlation between human papilloma virus (HPV) and Epstein-Barr virus (EBV) infected in nasal inverted papilloma (NIP) tissues. To discover the integration gene sites in NIP infected by such virus.
Methods: We use hybridization and gene chip (HybridMax) and real-time fluorescence quantitative PCR to detect EBV and HPV infection in 102 NIP tissues. Four samples both infected by HPV and EBV were analyzed by high-throughput molecular sequencing.
Results: ①The positive rate of HPV and EBV was 64.71% (66/102) and 20.59% (21/102) respectively; ②Six common integration sites of HPV(+) NIP tissue were KDM4A, SRSF4, SNX7, RALYL, GATAD2B and BACH1. ③Four common integration sites in EBV(+) NIP tissues were GDI1, HIVEP1, MEF2A and MYLIP.
Conclusions: In this study we found that the NIP was closely related to HPV rather than EBV infection. We preliminarily found the integration gene sites of virus on human chromosome, which provided a theoretical support for the diagnosis, treatment and targeted therapy of the disease.

RUSSIAN FIRST HPV PRIMARY SCREENING PROGRAM IN IN ACTION.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Russian First HPV Primary Screening Program was initiated in April 2019 according to latest WHO IARC and in Republic of Bashkortostan where 373 women a year develop cervical cancer and about 46% of these women die. 30.000 women of 30-39 years old were enrolled into the screening program. This age group was chosen because of its highest mortality rate. Samples were collected both for HPV and cytology at the same time. High Risk HPV (hrHPV) positive women were triaged by cytology.
Methods: HPV testing was performed using HC2 technique. Triage was performed by cytology. PAP results classified as ASC-US+ were considered abnormal. Of the women referred for colposcopy, suspicious parts cervical biopsies were taken for histological examination.
Results: 30.000 women of 30-39 years old were tested by the end of 2019. Women were invited for a screening by 15 Centres of Female's Health. 90,04% of the women had an adequate hrHPV test while 9,96% appeared to be hrHPV-positive. HrHPV-negative women were excluded from the screening for the next 5 years interval. HrHPV-positive women were triaged by cytology. All hrHPV-and PAP smear positive women were referred for colposcopy. Patients with CIN 2+ were referred for a treatment.
Conclusions: HrHPV-screening should reduce both incidence and cervical cancer–related mortality. Centres of Female's Health experienced difficulties in reaching of women invited for screening. To cope with this regional informational and educational campaign was developed. 50 volunteers distributed 20 000 leaflets with appeal "Give love, not HPV" explaining basics about HPV and how women might be protected against cervical cancer. It was stated that each women in the age from 30-39 might undergo free of charge screening at a Centre of Female's Health close to her home. Two regional TV channels and more than 50 bloggers were involved into the campaign. More than 120 regional gynaecologists were trained additionally by Federal Experts.

OPTIMAL TRIAGE OF HPV-POSITIVE TEST RESULTS

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: An analysis of the body of science published recently about the clinical value of triage options after HPV-positive test results.
Methods: MedLine was searched from 2001 through 2020 for relevant studies, supplemented by hand-searching of retrieved article reference lists. Eligible studies included prospective studies of women and retrospective studies of residual specimens from women that were tested using HPV genotyping tests. Outcomes were CIN2/CIN3 or CIN2+/CIN3+ or invasive cervical cancer. The comparator was cytology as a triage for HPV-positive results.
Results: Reporting genotyping provides profound discrimination of both current and future CIN3+ risks, due to the differential risks. Genotyping combined with cytology improves risk discrimination for Bethesda categories NILM, ASC-US, LSIL. Improvements in referral rates may be achieved. Similar management for similar risk-discrimination is benchmarked. Immunohistochemical staining with p16 and Ki67 has good evidence for triage of HPV-positive screening results. Methylation of viral HPV and host markers has fair evidence for triage of HPV-positive screening results, and may be applicable to self-collected samples.
Conclusions: Based on quality-evaluated studies that met inclusion criteria, genotyping combined with cytology discriminates risk and supports risk-based clinical action steps by the principle of equal management for equal risk. Viral load could be used to augment genotyping risk discrimination. P16/Ki67 staining may be used as an adjunct to cytology or to replace cytology. Methylation tests may be proposed as a screening test, an adjunct triage test with cytology, or to replace cytology as triage. Future research is needed to determine if genotyping could have clinical use without cytology. Inclusion of vaginal swab and/or urine self-collection as initial screening samples will stimulate development of triage tests that do not require direct sampling of the transformation zone. Models for different management paradigms are described.

CONTRACEPTIVES PROMOTE MOUSE PAPILLOMAVIRUS INFECTION VIA INHIBITION OF ANTI-VIRAL INFECTIVITY IN THE LOWER GENITAL TRACT

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Human papillomaviruses (HPVs) are ubiquitous in humans and cause 5% of all cancers. Contraceptives such as Depo-Provera (Depo medroxyprogesterone, DMPA) are used by an estimated 34 million women worldwide. We demonstrated that contraceptives increased viral susceptibility at the lower genital tract of both athymic nude mice and immunocompetent heterozygous mice. Here we report the role of DMPA in modulating the immune control of viral infections and validated some of the effects using gene modified mice.
Methods: The lower genital tract tissues of heterozygous female mice were harvested after DMPA treatment and analyzed for anti-viral activities via cytokine and chemokine profiling. Gene modified mice including Rag1, IFNγ, CD28, Stat1, Sting, Aim2, and IL36R knockout mice were used to validate the impact of some anti-viral molecules in papillomavirus susceptibility and persistence at the lower genital tract. The infections were monitored by collecting lavages/swabs, isolating DNA and RNA, and analysis by qPCR and qRT-PCR. Infections were further confirmed after the termination of the studies by immunohistochemistry, in situ hybridization, and histology.
Results: DMPA treatment significantly increased viral titers when compared with the control treated group ($P<0.01$, unpaired student t test) and stimulated dysregulation in anti-viral molecules including interleukins and chemokines at the lower genital tract. We found different levels of susceptibility of these mice to mouse papillomavirus at the genital tract. 1) Rag1 gene knockout mice exhibited similar disease patterns as observed in the athymic mice; 2) IFNγ and CD28 gene knockout mice displayed weaker but persistent infections; 3) IL36R, Stat1, Sting and Aim2 gene knockout mice showed minimal disease. All animals cleared infection at the lower genital tract around week nine post viral infection.
Conclusions: Contraceptives promote papillomavirus infection by inhibiting anti-viral pathways and both innate and adaptive immune responses play a role in papillomavirus infection and persistence at the lower genital tract.

#PREGNANCY OUTCOME AND HEALTH PROFILE IN HIV-INFECTED PREGNANT WOMEN AT AN OUTPATIENT CARE UNIT IN VITÓRIA, BRAZIL

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human immunodeficiency virus (HIV) infection, as well as Acquired Immunodeficiency Syndrome (AIDS), a worldwide epidemic, can have severe consequences in terms of maternal and fetal morbidity and mortality. This study aims to describe the clinical and epidemiological profile and reproductive outcome in HIV-infected pregnant women.
Methods: A cross-sectional study of 122 HIV-infected pregnant women who had their delivery at the maternity of a university hospital in Vitória, Brazil, between November 2001 and November 2014. Clinical, maternal, and fetal demographic data were extracted from medical and public records.
Results: The main socioeconomic and health profile findings among these patients were that they were, on average, 29 years old, non-Caucasians [73% (89/122)], of only up to 4 years of elementary schooling [71.3% (87/122)], housewives [53.3 % (65/122)] of married/stable union relationship status [69.7% (85/122)]. Primiparous women were 17.2% (21/122), 33.6% (41/122) had a diagnosis of HIV infection during the current pregnancy and 66.4% (81/122) were diagnosed before the current pregnancy. 56.5% (69/122) of the pregnant women had AIDS criteria, 6.5% (8/122) had syphilis during the pregnancy, 6.5% (8/122) had HPV induced lesions which required surgery at the hospital and 14.7% (18/122) had urinary tract infections during the pregnancy. Two cases of genital herpes and two cases of herpes zoster occurred. Cesarean section was performed in 82.8% (101/122) of cases, preterm delivery comprised 15.6% (19/122), low birth weight 22.1% (27/122) and perinatal death 4.1% (5/122) of cases.
Conclusions: It was observed in this study the occurrence of a profile of HIV pregnant women with low socioeconomic status with a high prevalence of Sexually Transmitted Infections. Preterm delivery and perinatal death were more prevalent than in the general population, signaling the need for preventive actions during prenatal care of HIV-infected pregnant women to reduce these events.

CO-INCIDENCE OF HIGH-RISK HUMAN PAPILLOMAVIRUSES AND EPSTEIN–BARR VIRUS IN COLORECTAL CANCERS IN THE MIDDLE EAST REGION

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: It has been reported that oncoviruses can be present in human colorectal cancers. Oncoviruses such as high-risk human papillomaviruses (HPVs) and Epstein–Barr virus (EBV) are well-known to be involved in the onset and/or progression of several types of human carcinomas including colorectal. However, the co-presence of high-risk HPVs and EBV has not been investigated yet in the middle east region.
Methods: PCR and immunohistochemistry analysis as well as tissue microarray methodology were used in our study.
Results: We herein explored the co-presence of these oncoviruses in a cohort of 102 and 94 colorectal cancer cases from Syria and Lebanon, respectively. We found that 54% of colorectal cancer cases in Syria are positive for high-risk HPVs, while 30% of the cases in Lebanon are positive for these viruses; the most frequent high-risk HPV types in the populations of Syria and Lebanon are 16, 18, 31, 33 and 35. Analysis of the LMP1 gene of EBV showed that 36% of Syrian and 31% of Lebanese cancer samples are positive for EBV, respectively. Additionally, we report that high-risk HPVs and EBV are co-present in 16% and 20% of the Syrian and Lebanese samples, correspondingly; and their co-presence is associated with high/intermediate grade invasive carcinomas.
Conclusions: These data indicate that high-risk HPVs and EBV are co-present in human colorectal cancers where they can cooperate in the initiation and/or progression of these cancers. Therefore, further investigations are needed to elucidate the role of these oncoviruses in human colorectal carcinogenesis.

"SHOULD WE BE WORRIED ABOUT HPV 52 AND HPV 35? QUESTIONS ARISING FROM A ZIMBABWEAN STUDY IN HIV INFECTED WOMEN."

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: High-risk human papilloma viruses (HR-HPV) are the etiologic agents of cervical cancer, which is a leading cause of cancer deaths among Zimbabwean women. Recent data from two Zimbabwean studies reported HPV 52 and HPV 35 as the most common types in women reporting for routine cervical cancer screening, especially among the HIV-infected. The aim of this study was to describe HPV 52 and HPV 35 distribution in histologically confirmed cervical lesions from HIV-infected women.
Methods: HIV-infected women from Newlands Clinic in Harare, who provided a written informed-consent were recruited. Only those with a previous diagnosis of low-grade cervical intra-epithelial neoplasia (CIN 1) or worse (CIN 2, CIN 3 and invasive cancer), from January 2016-October 2019, were eligible. Stored formalin-fixed-paraffin-embedded blocks were retrieved and genotyped for HPV using Multiplex Fluorescent High-Risk Human Papilloma Virus (MF-hrHPV) Realtime (Atila Biosystems, California).
Results: Ninety-three women were recruited and 86 (92%) tested positive for HPV DNA, of which 78% were from CIN 3 samples. The most common genotypes were HPV 16 (41%), HPV 52 (19%), HPV 18 (19%) and HPV 35 (14%). Only 3/12 (25%) of the HPV 35 positive and 3/16 (19%) of the HPV 52 cases were mono-infections.
Conclusions: We report unexpectedly high-prevalence of HR-HPV 35 and HPV 52, in addition to HPV 16 and HPV 18. Although 70% of HPV-related-cancers are included in the bivalent vaccine, which is currently used in Zimbabwe, HPV 35 & HPV 52 are not. Fortunately, HPV 52 is already included on the 9-valent-vaccine but HPV 35 remains a cause of concern. We strongly recommend carrying out larger prospective studies to fully understand the carcinogenic potential and vaccine cross coverage of HPV 35, as well as exploring the potential for selective pressure on genotypes not included in available vaccines.

DIMINISHED INTRATUMORAL B-CELL RESPONSE IDENTIFIES EARLY TREATMENT FAILURES IN HPV+ HNSCC

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPV+ HNSCC patients have superior prognoses compared to HPV- HNSCC patients. However, the survival advantage associated with HPV is not universal and, a subset of HPV+ HNSCC patients fail definitive treatment and progress with metastatic/recurrent disease. Currently, no biomarker is available to distinguish aggressive from indolent HPV+ HNSCC. Immune dysfunction facilitates tumorigenesis and is associated with treatment response, therefore, we hypothesized that restricted intratumoral immune cell function may be used as biomarkers to identify treatment failures.
Methods: This is a retrospective analysis of The Cancer Genome Atlas (TCGA) HPV+ HNSCC cohort (n=98).
Results: Log-rank analyses showed that low B-cell or low CD8+ T-cell fraction, inferred using a deconvolution algorithm from bulk tumor RNA-seq, was associated with inferior overall survival (OS) and disease-specific survival (DSS); however, this association was diminished in a multivariate regression model adjusting for co-variates, including T, N, gender, and site. Since immune cell functionality may be compromised in the tumor microenvironment, activation state, rather than fraction, may better represent the intratumoral immunologic landscape. Low B-cell activation signature or low CD8+ T-cell activation signature was associated with poor OS and DSS. Multivariate analyses showed that B-cell activation signature remained an independent biomarker, whereas, the association between CD8+ T-cell activation and survival lost significance. HPV+ patients with low B-cell activation have a 4.5-fold ($p=0.001$) increase in risk of death with a median OS of 13 months, and a 14-fold ($p<0.001$) increase in risk of disease recurrence with a median DSS of 13 months. Results generated using B-cell receptor (BCR) segment diversity, an alternative approach to assess B-cell function, were highly concordant with the B-cell activation signature dataset.
Conclusions: Our work showed that diminished intratumoral B-cell response is an independent biomarker able to identify early treatment failures (~1 year) in HPV+ HNSCC and could serve as an exclusion criterion for treatment de-escalation regimens.

ASSESSING THE EFFICACY OF HUMAN PAPILLOMAVIRUS DISINFECTION AND THE RISK OF TRANSMISSION FROM CLINICAL LESIONS

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Studies have found that nuclease resistant HPV genomes can be detected on transvaginal ultrasound probes following proper hospital disinfectant procedures (1-3). Recent reports have concluded that oncogenic HPVs derived from laboratory tissue-based models are not susceptible to certain high-level disinfection protocols (4-6), further intensifying the concern that medical instruments may provide transmission of nosocomial HPVs infections. Therefore, we aimed to determine the infectious load of HPVs from clinical lesions and to investigate the effectiveness of classical disinfection protocols on HPV virions derived from model systems.
Methods: Infectious HPV virions were isolated from 293T cell transfection, organotypic epithelial tissue cultures, and mouse xenografts. Clinical samples from recurrent respiratory papillomas (RRPs) and anogenital warts were obtained under IRB approval using emery paper to swab apical surfaces. The infectivity of HPV virion stocks was measured by detecting spliced E1^E4 mRNAs in infected keratinocytes. Infections were validated by time dependence, resistance to ribonuclease, and susceptibility to antibody-mediated neutralization. Suspension-based disinfection protocols employed ortho-phthalaldehyde (OPA) and hypochlorite.
Results: In contrast to prior reports, we found that validated HPV virions obtained from a variety of sources were susceptible to a 2.5-4 $\log_{10}$ reduction in infectious titer when exposed as directed to OPA or hypochlorite. Some HPV virion stocks failed to meet the infectivity criteria of time dependent detection of infection, resistance to ribonuclease and susceptibility to antibody-mediated neutralization. Unvalidated virus stocks may give spurious results and lead to confounding conclusions. Preliminary assessment of HPV infectious titers from clinical lesions suggest that compared to common warts, clinical RRP and anogenital warts have low levels of virions present at apical surfaces.
Conclusions: We conclude that HPVs are susceptible to disinfection by OPA and hypochlorite. Studies are underway to carefully assess the infectious titers of virions present HPV-induced lesions to better determine the risk of transmission from HPV-induced warts at mucosal surfaces.

References:
1. Casalegno et al. PLoS One. 2012;7(10):e48137;
2. Ma et al. Emerg. Med. J. 2013;30(6):472.
3. M'Zali et al. PLoS One. 2014;9(4): e93368.
4. Meyers et al. PLoS One. 2017;12(10):e0187377.
5. Meyers et al. J. Antimicrob. Chemother. 2014;69(6):1546.
6. Ryndock et al. J. Med. Virol. 2016;88(6):1076.

PRIMARY SCREENING FOR CERVICAL CANCER IN COMMUNITY WOMEN USING MOLECULAR HPV DNA TEST - FIRST EXPERIENCE FROM INDIA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: India contributes to 20% of the global cervical cancer burden and screening is often plagued with lower coverage of the targeted screening population. The utility of partial genotyping, identifying the high-risk genotypes for risk stratification has not been explored in our country before. In the current study, the implementation of HPV DNA testing with partial genotyping for the first time in an ongoing community based cervical cancer screening program from India is discussed.
Methods: The program aims to offer High-Risk HPV DNA testing using real-time PCR on a fully automated platform (Cobas 4800, Roche) to 30,000 eligible women (30-65 years) for a period of 5 years. We tested community women (n=3185) by qPCR followed by pap and colposcopy.
Results: Results The prevalence of high-risk HPV in Indian community women is 6.6% (209/3185). Genotype distribution showed 22.4% (47/209) HPV 16 positive, 4.78% (10/209) HPV 18 positive, 62.6% (131/209) positive for other high-risk HPV and 10.5% (22/209) positive for mixed infections. There is a predominance of other high-risk HPV with 4.1% (131/3185) women in the Indian community. There was a statistically significant association between age groups and high-risk HPV infection with older women (>50 years) having mixed infections. All the HR HPV positive samples for Pap showed 4 women (1.9%) with abnormal pap. The women with abnormal pap (2 LSIL and 2 HSIL) had other high-risk HPV. Invasive cervical cancer was identified in one woman aged 60 years with HPV 16, interestingly her Pap results were neither LSIL nor HSIL, suggesting a need for an objective test for primary screening for risk stratification, to aid in detection of cervical cancer.
Conclusions: The primary DNA screening using molecular HR HPV test is feasible in a low resource setting like India identifying women with a propensity to develop >CIN2 lesions needing immediate clinical intervention.

RESULTS OF HPV-TESTING FOR ANAL SCREENING IN MEN WITH DIFFERENT HIV STATUS AND SEXUAL BEHAVIOR

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: The cancer of the anal canal is usually associated with the human papillomavirus (HPV). HIV infection increases the risk of persistence and malignancy. Objectives: to study the prevalence of HPV high carcinogenic risk (HPV HCR) among men with different HIV status and sexual behavior.
Methods: The study was conducted during the period from February to October 2019. The study included 256 men: 73 MSM/HIVpos, 66 MSM/HIVneg, 58 HT/HIVpos и 59 HT/HIVneg. All men underwent the HPV-test with the determination of 14 HPV types of HCR (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68). We used real-time PCR assay.
Results: Among the 256 examined men predominated young men aged 35.9 ± 7.34 (min-18, max-65) and 116 of them (45.3%) were diagnosed HPV of HCR by the HPV-test: MSM/HIVpos – 79.5% (58/73), MSM/HIVneg – 50% (33/66), HT/HIVpos – 22.4% (13/58), HT/HIVneg – 3.4% (2/59). The calculation of the odds ratio revealed: the chance of HPV-infection in the MSM/HIVpos group is higher than in the MSM/HIVneg group (OR=3.867; 95%DI: 1.835-8.146), the chance of HPV-infection in the HT/HIVpos group is higher than in the HT/HIVneg group (OR=8.233; 95%DI: 1.767-38.374), the chance of HPV infection in the group of MSM is higher than in the group of heterosexual men (OR=12.892; 95%DI: 6.764-24.571) ($p < 0.05$).
Conclusions: Conclusion: The results indicate the need for anal screening in all HIV-infected men, regardless of their sexual orientation.

QUALITY CONTROL (QC) METRICS FOR HIGH RESOLUTION ANOSCOPY (HRA) IN AN ANAL NEOPLASIA CLINIC

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: Effective detection and treatment of anal high-grade squamous intraepithelial lesions (HSIL) are dependent on the quality of high resolution anoscopy (HRA). Guidelines for HRA competency were proposed in 2016 by IANS and similar guidelines have been used for quality control (QC) in the ANCHOR study (Table 1). This retrospective study analyzed QC metrics in new patient exams performed in an established anal neoplasia clinic to determine their clinical utility.
Methods: Charts of new patients seen over 6 months by 6 providers in the UCSF Anal Neoplasia Clinic were reviewed for the following metrics: number of exams, satisfactory cytology, histology and HRA; % biopsied, histologic (h)HSIL, discordant cytology/histology (e.g. ASC-H or HSIL cytology without hHSIL), perianal biopsies and hHSIL. Metrics including length of exams, problematic pain or bleeding were not assessed.
Results: All providers met recommended standards for annual number of exams, cytology and histology, satisfactory exams and sufficient specimens. Three clinicians did not meet standards for %hHSIL, only two were deficient for %hHSIL in patients considered at-risk for HSIL. The same clinicians had a higher proportion of discordant cytology/histology results, and an overall lower percentage of biopsied patients. ANCHOR criteria of $\geq$2 biopsies/new exam was not met by 2 clinicians. Few perianal biopsies were done, only one clinician had >10% perianal HSIL.

Table 1: UCSF Anal Neoplasia Clinic quality metric results

IANS Metrics	50-100 per year			≥5%		≥1	≥90% hHSIL within 3 months	<5% (15% in Low Risk) *
ANCHOR Metrics	50 logged exams w/biopsies		≥35%	≥5%	≥10%	≥2	≤5% repeat required	Rare
Provider	**No.Exams (High Risk*) n= 272**	**No. pts biopsied**	**hHSIL**	**Exams perianal biopsies**	**HSIL perianal biopsies**	**Average no. of biopsies**	**Discord. Cyt/Hist**	**Insuff. Cyt or biopsies**
1	27(20)	18 (66%)	12(44%)	2 (7%)	0	>2	4	2
2	27(24)	22 (81%)	18 (67%)	5 (19%)	0	>3	1	0
3	26(13)	12 (46 %)	5 (19%)	0	0	>1	1	0
4	44(33)	34 (77%)	29(66%)	7 (16%)	2 (29%)	>2	0	0
5	89(55)	29 (33%)	19(21%)	1 (%)	0	3	9	2
6	56(42)	20 (36%)	14 (25%)	1 (2%)	0	1-2	11	0

*Considered High-risk for HSIL included: HIV positive all ages/genders, MSM>45, referrals w/HSIL diagnosis

Conclusions: QC metrics indicated most providers require some changes in clinical practice to meet suggested practice standards including Increased biopsies in high-risk patients and increased perianal biopsies in general. Ongoing measurement of performance metrics may be important to ensure the highest possible quality of patient care.

CERVICAL CANCER PROGNOSIS IS INFLUENCED BY THE TUMOR MICROENVIRONMENT AND MICROBIOME

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: While nearly all cervical tumors are infected with HPV, infection alone is not sufficient for tumor development. Although most cervical HPV infections are cleared by cell-mediated immunity, progression to malignancy is linked to an immunosuppressive tumor microenvironment, and recent evidence has linked dysbiosis of the vaginal microbiome with the extensive reprogramming and remodeling of the cervical stroma. In this study, we sought to identify host and microbial prognostic biomarkers in the cervical tumor microenvironment.
Methods: Using expression-based cell-deconvolution methods on RNAseq from 372 cervical carcinomas, we performed hierarchical clustering on principle components to identify three patient clusters, which were identified as either immune-rich, stromal-rich, or an intermediate immune/stromal type. Furthermore, we used microbial transcriptomics to identify microbes significantly associated for both patients with or without tumor recurrence.
Results: Patients with immune cell-enriched tumors exhibited a favorable prognosis. However, both the intermediate and stromal enriched tumors had significantly worse overall and disease-free survival (p = 0.038 and 0.0021), with the stromal type having the worst prognosis. Gene set enrichment analysis (GSEA) revealed that genes associated with epithelial-mesenchymal transition were more strongly associated with the stromal subtype, while the immune type was strongly associated with genes involved in p53 pathways and networks. Furthermore, tumor recurrence was associated with higher abundance of proinflammatory microbes.
Conclusions: We have identified, for the first time to our knowledge, microbes associated with cervical cancer prognosis while confirming that tumors with higher stromal invasion and marked immunosuppression exhibit the worst prognosis.

ANAL CYTOLOGY AND HR-HPV GENOTYPING CONTROL IN HIGH-RISK HIV-MSM PATIENTS AT ANAL SCREENING PROGRAM.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: INTRODUCTION: Diagnostic and therapeutic anal screening of HSIL (AIN-2/3) through high resolution anoscopy (HRA) could become a tedious procedure in demanding patients. Here we evaluate the evolution of anal histological, cytological and virological basal findings in high risk HIV men who have sex with men (HIV-MSM) included in our anal screening program.
Methods: METHODS: A cohort of 209 HIV-MSM with HR-HPV infection or altered anal cytology were selected for HRA between June 2013-June 2016 (table 1). Patients with basal HSIL (AIN-2/3) were classified as HRP-Risk Patients (HRP). Basal and incidental HSIL (AIN-2/3) were systematically treated and controlled.
Results: RESULTS: Virological, cytologycal and histologycal findings in HRP are summarized on tables 2 and 3. HRP (n=35): HSIL (AIN-2): 24. HSIL (AIN-3): 11. Cytology findings in HRP: Basal HSIL (8/35; 23%); ASCUS (12/35; 34,3%). These findings resulted significantly reduced at final control: HSIL (4/35; 11.4%) and ASCUS (7/35; 20%). Conversely, basal NAMC cytology (2/35; 5,7%) was significantly increased at final citology control (12/35; 34,3%). Basal HR-HPV infection in HRP: HPV 16 or HPV 18: 29; HR-HPV not 16 not 18: 32; Negative: 1. Final HR-HPV infection in HRP: HPV 16 or HPV 18: 14 (decreased); HR-HPV not 16 not 18: 24 (decreased); Negative: 5 (incremented); Not performed: 5. At final control HR-HPV persistence was 24 (total: 14; partial: 10); clearence: 5; not performed: 6. HSIL (AIN-2/3) free HRP after treatment were 83%, slightly lower in HSIL (AIN-3) patients (63,6%) Clinical HIV stage C was significantly related with no HSIL (AIN-2/3) treatment response, p=0.02.
Conclusions: CONCLUSIONS Basal anal cytology change after diagnosis and treatment of HSIL (AIN-2/3). Basically, HSIL and ASCUS decreased and NAMC increased in 3 years follow-up. This suggests that cytological control could play a rol in selecting patients for HRA screening. HR-HPV clearence could behave in a similar manner, mainly HPV 16.

THE POTENTIAL COST-EFFECTIVENESS OF HPV VACCINATION AMONG GIRLS AND YOUNG WOMEN IN MONGOLIA

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: Cervical cancer is a leading cause of cancer among women in Mongolia with an age-standardized incidence rate of 23.5 per 100,000. HPV vaccination has not been introduced nationally and Gavi co-financing support is not available in this country. To inform local decision-making regarding introduction, we evaluated the potential cost-effectiveness of HPV vaccination among girls and young women in Mongolia.
Methods: We used UNIVAC (version 1.4), a static decision model, to evaluate the health and economic outcomes of single-cohort vaccination among females from the government perspective compared to no vaccination. We modeled vaccine introduction over 10 birth cohorts starting in 2022 comparing the following strategies: 1) Age of delivery at 9, 11, or 20-years-old; 2) Quadrivalent or bivalent vaccine selection; 3) Vaccine pricing variations. We used locally-specific data for cancer incidence, mortality, treatment and costs. Model outcomes included the number of cancer cases, hospitalizations, deaths, disability-adjusted life years (DALY), and costs with and without vaccination. Incremental costs and health outcomes were discounted at 3% and aggregated into an Incremental Cost-Effectiveness Ratio (ICER).
Results: The base-case scenario of HPV vaccination among 9 year-old girls was projected to avert 5,692 cervical cancer cases, 3,240 deaths, and 11,886 DALYs and incur $2.4-3.1M more costs compared to no vaccination, depending on vaccine selection. At current Gavi pricing ($4.50-$4.60/dose), we estimated an ICER of $166-$265/DALY averted among 9-year-olds and $128-220/DALY averted among 11-year olds. When price per dose was increased to the WHO V3P mean price for non-Gavi LMICs ($14.17/dose), the ICER ranged from $556-820/DALY averted. Targeting females at age 20 resulted in an ICER of $1,768-$2,769 per DALY averted.
Conclusions: Depending on the willingness-to-pay threshold, HPV vaccination among girls is likely a cost-effective investment in Mongolia compared to no vaccination with projected ICERs ranging from 3-22% of the GDP per capita of $3,735.

ROLE OF CYTOLOGY AND HPV ANALYSIS IN COTESTING IN ROUTINE CERVICAL CANCER SCREENING: A LONGITUDINAL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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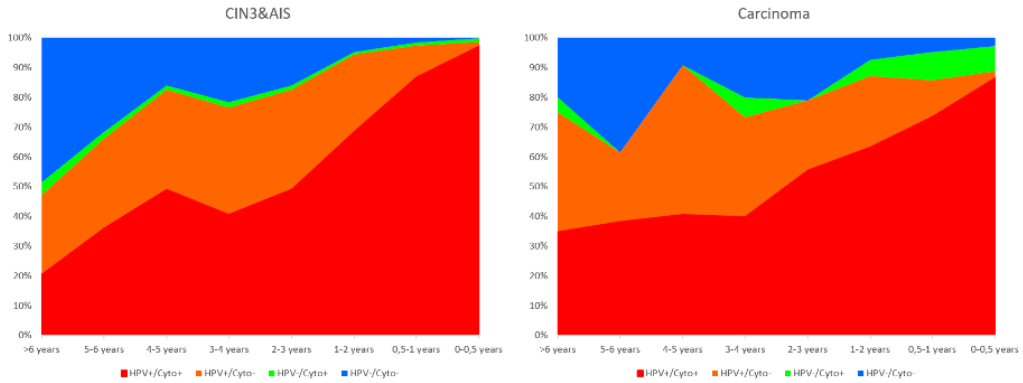
Introduction: Recent international research has questioned the value of cotesting, consisting of Human Papillomavirus (HPV) and cytology testing, in the cervical cancer screening program. They suggest that primary HPV screening is sufficient since the added sensitivity of cotesting is only beneficial in a very small group. This study aims to translate these findings in a population of Belgian women and to re-evaluate the current guidelines.
Methods: Data in this research consisted of liquid based cytology samples that were cotested and taken between June 2006 and December 2014 from the AML database from Sonic Healthcare, Antwerp, Belgium. Women with the diagnosis of cervical precancer (n=3778) or invasive cervical cancer (n=376) who had samples taken before were included. Samples were divided in groups determined by the year they had been taken before diagnosis. Performances of both tests were compared using contingency tables.
Results: Cytology testing showed a sensitivity percentage of 50,5% at the 3-year point in the precancer group, 55,8% in the cancer population. Meanwhile, the HPV test had a positive detection rate of 82,7% in the precancer and 79,1% in the cancer group. The overall detection of cytology/HPV cotesting consisted of 84% in the precancer and 79,1% in the cancer database, resulting in respectively 16% and 20,9% of the samples where diagnosis was not made at the 3-year point interval. 5-year point interval missed respectively 31,7% and 9,1% of the cases. During the last 6 and 12 months, cytology diagnosed respectively 8,4% and 9,5% of the cancer cases when samples were HPV negative.



Conclusions: The findings of this study support the idea that a 3-year interval screening would detect

double as much cases as the 5-year screening, however it still shows a considerate amount of missed cases. Additional cytology analysis increased sensitivity in the last year of the cancer population.

GENOMIC LANDSCAPE OF HPV16 IN OROPHARYNGEAL CANCERS COMPARED TO CERVICAL INFECTIONS IN 4,668 HPV16-POSITIVE INDIVIDUALS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: HPV-driven oropharynx cancer (OPC) has increased over the past decades in developed countries and is predominantly related to HPV16 infection. Little is known about HPV16 genetic variation in OPC. **Objective**: To relate HPV16 genetic variation and OPC for each sublineage and SNP observed in whole-genome sequencing of HPV16, compared to HPV16 in cervical infections, from a total of 4,668 individuals from the U.S. or European regions (primarily White).
Methods: We whole-genome sequenced viral DNA from 253 HPV16-positive OPC from the U.S. University of Pittsburgh or Vanderbilt University Medical Centers and compared viral genomes to 4,415 women with cervical precancer (CIN2/CIN3/AIS; n=2,515), cancer (n=113), or benign (<CIN2; n=1,455) infections from two U.S. NCI studies (KPNC PaP, SUCCEED) and cancers collected by IARC (n=332). We assessed HPV16 sublineages, SNPs and rare variant distributions in OPC compared to HPV16 at the cervix.
Results: The HPV16 sublineage distribution was significantly different in OPC compared to cervical benign infections ($P=1.0x10^{-8}$), precancers ($P=5x10^{-6}$) and cancers (P=0.016), particularly compared to cervical adenocarcinoma ($P=6.3x10^{-16}$). The OPC sublineage distribution was most similar to cervical squamous cell carcinomas (SCC;P=0.18); with a similar enrichment of sublineages A4 ($P=5.6x10^{-6}$) and D2/3 (P=0.002) compared to benign infections. Interestingly, A2 was uniquely more frequent in OPC compared to all cervical infections ($P=3.1x10^{-5}$). Several individual SNPs, independent of sublineage-defining sites, were enriched in OPC compared to cervical cancers (P<0.05). Comparing OPC to cervical cancer, the strongest difference observed was a SNP within the A2 sublineage (URR snp, OR=5.2, 95%CI=3.1-8.6, $P=2.8x10^{-10}$). Combined rare variant analyses determined that OPC had similar hypovariation in E7 to cervical cancers, with higher variation within E6.
Conclusions: OPC HPV16 genetic variation is most similar to cervical SCC. There are some unique differences in OPC that may influence oropharyngeal carcinogenicity; HPV16 variants may help explain its unique ability to cause cancer at multiple anatomic sites.

COMPARISON OF A NOVEL QUANTITATIVE COMPREHENSIVE NEXT-GENERATION SEQUENCING HPV-STI ASSAY WITH ROCHE COBAS HPV ASSAY AND A REVERSE LINE BLOT HYBRIDIZATION ASSAY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Sexually transmitted infections (STIs) impose a major global health and economic burden. Globally, there are 1.1 billion existing infections and each year, there are over 376 million new cases. Many of these STIs are hidden and silent infections that can have serious impact on physical and psychological health. We have developed a comprehensive assay that detects 27 HPVs and 13 STIs uniformly in one single reaction with a simple workflow using next-generation sequencing (NGS) technology.
Methods: A set of 300 samples that were previously tested with Roche Cobas HPV assay and Reverse Line Blot Hybridization (RBL) assay were analyzed by our comprehensive NGS-based method. A panel of multiplex type/species-specific primers were designed to detect 27 HPVs and 13 STIs and two internal human gene controls. Amplification and barcoding/indexing of each sample is performed in a single tube reaction and all the amplicons are pooled and sequenced by NGS.
Results: Our results show that the STI-NGS assay has an excellent agreement with Roche Cobas HPV assay and RBL assay. We could detect HPV and STI types/species with high sensitivity, specificity and uniformity. The comprehensive STI NGS assay has a very simple workflow and the process consists of DNA extraction, single-tube amplification, sample pooling/library preparation and sequencing. The assay can be completed within 24 hours. Our results show that many samples have multiple HPV and STI infections that go undetected in routine clinical and diagnostic testing.
Conclusions: We have developed a highly multiplex and comprehensive STI assay that uses low amount of DNA, detects and quantifies 27 HPVs and 13 STIs in a single-tube and single-step amplification reaction. The assay is quantitative and generates viral load/copy number for all the types/species detected in a sample. The comprehensive STI assay has a simple workflow, easy to automate and is very low-cost.

REPRODUCIBILITY OF THE NEW CLASSIFICATION OF CERVICAL ADENOCARCINOMAS

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: HPV is identified in almost all squamous invasive cervical carcinomas and a high proportion of adenocarcinomas. HPV involvement in cervical adenocarcinoma is between 8.3% - 71.8% depending on the histological subtype. A new morphological classification of adenocarcinomas has been proposed where ADC are classified based on the presence or absence of HPV infection-related features (IECC, International Endocervical Adenocarcinoma Criteria and Classification, 2017). Two adenocarcinoma groups were established: HPV-associated (HPVA) and non-HPV associated (NHPVA). The objective is to evaluate the reproducibility of IECC morphological criteria with a highly sensitive HPV testing in our own series of cervical adenocarcinomas.
Methods: We identified sixty-nine incident cases of endocervical adenocarcinoma identified through Tarragona and Girona cancer registries (Catalonia) between 1998-2007. All adenocarcinoma hematoxylin and eosin (HE) slides were reviewed by two expert pathologists and classified in accordance with the IECC system. HPV DNA was done using SPF-10 PCR/DEIA/LiPA25. Demographic and clinical information was retrieved from the cancer registry databases.
Results: The morphological diagnostic distribution was; HPVA (n=51): usual -type (56.5%), mucinous,

not otherwise specified (10.1%); villoglandular (4.3%), mucinous, intestinal type (2.9%); NHPVA (n=18): clear cell adenocarcinoma (8.7%), gastric-type adenocarcinoma (7.2%), endometroid adenocarcinoma (5.8%), serous adenocarcinoma (2.9%) and mesonephric carcinoma (1.4%). The mean patient's age in HPVA was 50.4, compared to 55.4 in NHPVA ($p>0.05$). HPV was identified in 68.6% of HPVA tumors and in 5.6% of NHPVA tumors ($p<0.05$). Tumor stage IV at diagnosis was 7.8% in HPVA and 16.7% in NHPVA ($p>0.05$). Finally, 27.5% of HPVA patients dead by cervical cancer compared to 33.3% of NHPVA ($p>0.05$).

Conclusions: Our results using IECC criteria with HE are supported by HPV detection results. The use of a specific immuno-marker p16, and HPV detection would help in complex diagnosis.

THE PROJECTED COST-EFFECTIVENESS AND BUDGET IMPACT OF HPV VACCINE INTRODUCTION IN GHANA

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: In Ghana, the age-standardized incidence rate of cervical cancer is 31.5/100,000 and mortality rate is 21.5/100,000. Ghana conducted an HPV vaccination demonstration project in 2014 and has yet to decide on national introduction. We projected the cost-effectiveness and budget impact of adding HPV vaccination into Ghana's national immunization program to contribute to decision-making regarding national introduction from the government perspective.
Methods: We used an established static cohort model (UNIVAC, version 1.4) to evaluate the cost-effectiveness of bivalent or quadrivalent HPV vaccination, incorporating direct vaccine efficacy and cross-protection against non-vaccine targeted HPV types. Vaccine introduction was modeled starting in 2022 and continuing over 10 birth cohorts using a combined delivery strategy of school (80%) and outreach (20%). We modeled vaccination in a single age cohort of 9-year-old girls vs. a multi-age cohort of 9-year-old girls and 10-14-year-old girls (one-time campaign). Outcomes included cervical cancer cases, hospitalizations, deaths, disability-adjusted life years (DALYs) and costs in 2018 USD. We applied a discount rate of 3% to costs and health outcomes. One-way sensitivity analysis identified model drivers.
Results: Compared to no vaccination, quadrivalent HPV vaccination among 9-year-old girls resulted in an ICER of $248/DALY averted (range: cost-saving to $570/DALY averted). Use of the bivalent vaccine among 9-year-olds yielded a lower ICER of $33/DALY averted (range: cost-saving to $333/DALY averted). When a one-time campaign among 10-14 year-old girls was included, the ICER ranged from cost-saving to $736/DALY averted. This represents up to 33% of Ghana's GDP per capita of $2,202 USD. Projected average costs to the government were $10.7-$15.1M annually. Vaccine efficacy (including cross-protection) and cancer treatment costs were key model drivers.
Conclusions: National HPV vaccine introduction in Ghana is likely to be cost-effective, however, budget implications need to be considered. Inclusion of a one-time campaign is expected to create greater value for money than routine immunization alone.

REPRODUCIBILITY AND ACCURACY OF ASSISTED AND AUTOMATED EVALUATION OF P16/KI-67 DUAL STAIN CYTOLOGY USING CYTOREADER IN CERVICAL CANCER SCREENING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Automated evaluation of p16/Ki-67 dual stain (DS) with CYTOREADER, a cloud-based deep-learning application, leads to greater accuracy, efficiency, and substantially improved specificity compared to Pap cytology for triage of HPV-positive women. Here we conducted an evaluation of interobserver reproducibility and accuracy of assisted clinical evaluation of DS slides using CYTOREADER.
Methods: CYTOREADER comprises a fully-automated workflow combining whole-slide scanning with automated evaluation using a deep-neural network for the detection of DS-positive cells. In addition, it provides a computer-assisted mode that presents all DS-positive cells on a slide ranked by the likelihood that a cell is DS-positive. For this pilot study, a total of 160 DS-slides from HPV-positive women were evaluated by 6 readers (4 Cytotechnologists, 2 Pathologists), 40 slides each. Slides were evaluated manually and using both the CYTOREADER assisted- and fully-automated modes. The time to evaluate slides was recorded for both the manual and assisted approach. We assessed the reproducibility of assisted DS evaluation using the percent agreement and evaluated the sensitivity and specificity for detection of cervical intraepithelial neoplasia grade 3 or greater (CIN3+).
Results: The average time to evaluate 10 DS slides was 44 (±18) minutes for manual and 29 (±9.9) minutes for computer-assisted evaluation. The percent agreement was 74.2% between assisted and manual, 71.3% between fully-automated and manual, and 80.4% between assisted- and fully-automated evaluation. The interobserver agreement between two readers was 76.3% for manual and 77.5% for assisted DS evaluation. The sensitivity and specificity for detection of CIN3+ was 83.3% and 52.5% for manual, 94.4% and 52.0% for assisted, and 100% and 61.8% for fully-automated, respectively.
Conclusions: Computer-assisted evaluation is reproducible and achieves greater sensitivity at comparable specificity for CIN3+ compared to manual reading. Using CYTOREADER for either assisted or fully-automated evaluation of DS increases the efficiency and accuracy of slide interpretation for triage of HPV-positive women.

PAN-CANADIAN ACTION PLAN FOR ELIMINATION OF CERVICAL CANCER – USING ONCOSIM MODELING RESULTS TO INFLUENCE POLICY.

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Cervical cancer is one of the most preventable and treatable forms of cancer. WHO issued a global call to action in May 2018 to eliminate cervical cancer as a global public health problem. As a member of the UICC, The Partnership is now leading the charge to create a 10-year pan-Canadian action plan to eliminate cervical cancer and will host a summit to launch the plan in Feb 2020.
Methods: OncoSim is a microsimulation model, led and supported by the Canadian Partnership Against Cancer (CPAC), with model development by Statistics Canada, and is made possible through funding by Health Canada. The OncoSim-Cervical and HPV Microsimulation Model (HPVMM) is a specific OncoSim module that focuses on the prevention, screening, diagnosis and treatment of cervical cancer. OncoSIm has been used to influence cervical cancer screening and prevention policy in Canada since 2014. Taking a health system perspective, the model is now being used to assess achieving the WHO targets of 90/90/90 by 2030: 90% HPV vaccination, 90% catch-up vaccination, and 90% cervical cancer screening participation in an eligible population by 2030 in Canada; and the likelihood of meeting the 2040 goal to eliminate cervical cancer (less than 4/100,000, crude) in Canada with the implementation of coordinated HPV vaccination programs, HPV vaccination catch-up programs, and cervical cancer screening programs using HPV testing.
Results: Costs and health outcomes will be evaluated in a short-term frame (2020-2030), as well as longer-term (2020-2040) to align with the elimination of cervical cancer targets Strategies for influencing policy makers to implement the WHO targets in Canada discussed building on past
Conclusions: CPAC actively works with its partners to lead the way towards Cervical Cancer elimination. OncoSim's projections have helped inform cancer control planning decisions across Canada and the results from this analysis will help inform the Pan-Canadian action plan and beyond.

HPV6 AND HPV11 WHOLE-GENOME SEQUENCES REVEAL SUBLINEAGE AND GENETIC VARIANTS ASSOCIATED WITH THE CLINICAL COURSE OF 436 RECURRENT RESPIRATORY PAPILLOMATOSIS PATIENTS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: HPV6 and HPV11 cause Recurrent Respiratory Papillomatosis (RRP), a rare disease characterized by the growth of papillomas in the airway. The clinical course of RRP is highly variable, and the factors that drive an aggressive versus an indolent course are largely unknown. **Objective**: To determine if HPV6 and HPV11 genome variation is related to the clinical course of RRP patients, and if specific HPV6/11 variants are associated with RRP compared to 351 anogenital infections, using a large multicenter international collection of 436 RRP patients.
Methods: We whole-genome sequenced HPV6 (N=267) and/or HPV11 (N=170) DNA from RRP patients from 35 international centers. 351 anogenital HPV6/11 genomes for comparison were from our NCI-SUCCEED study and also retrieved from GenBank. We evaluated if HPV6/11 sublineages and SNPs were associated with RRP compared to anogenital infections restricted to White individuals, and if they were associated with RRP clinical course (e.g., aggressive vs. indolent) or age at diagnosis.
Results: The RRP HPV6/11 sublineage distribution was significantly different than that in anogenital infections (P=0.004). Compared to anogenital infections, HPV11 A2 was disproportionally more frequent in RRP (OR=1.8, 95%CI=1.2-2.6, P=0.002). Importantly, there were significant differences in the lineages present in aggressive vs. indolent RRP (P=0.046), severe pulmonary vs. not pulmonary RRP (P=0.001), and by age at RRP diagnosis ($P=3.7x10^{-6}$). In particular, the HPV11 A2 sublineage was strongly associated with pulmonary RRP (OR=10.8, 95%CI=3.0-38.3, $P= 2.3x10^{-4}$). Three individual SNPs within HPV11, two in the E1 gene and one in the E2 gene, were associated with aggressive vs. indolent disease course (e.g., E1 SNP, OR=2.4, 95%CI=1-5.9, P=0.029).
Conclusions: HPV6 and HPV11 genetic variation influences the occurrence and clinical course of RRP. The HPV11 A2 sublineage was most associated with severe pulmonary RRP.

AGE PATTERNS IN HPV-POSITIVE AND NEGATIVE ANOGENITAL AND HEAD AND NECK CANCERS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Understanding the age patterns of HPV-related and unrelated cancers is important for elucidating natural history of these cancers and guiding cancer prevention interventions.The aim of this re-analyses was to describe the age at diagnosis by the available information of anogenital and head and neck cancers from the RIS HPV TT/VVAP/Head and Neck ICO international surveys.
Methods: Approximately 18,000 formalin-fixed paraffin embedded blocks preserving anogenital and head and neck cancers were included in the analyses. From those patients country, age, gender, histology, anatomicalsite, and HPV results were available. HPV results included: HPV DNA, mRNA and $p16^{INK4a}$ assessment. Age at diagnosis presented missing data. This missingness was approached through a sensitivity analysis technique by implementing a two-step iterative algorithm, in order to model different scenarios of non response under a non ignorable missing pattern assumption. In the case of head and neck and anal cancers the partial observed information was in the outcome of interest (age at diagnosis) and in a binary covariate (gender). For the rest of the cancers present in the anatomical locations cervix, vulva, vagina and penis,the missingness was only present in the age at diagnosis.
Results: Cervical cancer patients were in average 10 years younger at diagnosis than the rest of locations (Table 1). In cancers of the cervix, vulva, and anus, HPV-positive cases where younger than HPV-negative ($p<0.05$). In cervical cancers, cases with HPVs 16, 18 and 45 where diagnosed at younger ages compared with cases with other types, particularly HPVs 18 and 45 (Table 2). This was not observed in the other anatomical sites.

Table 1. Mean and 95% confidence interval of the age at diagnosis, by cancer site and HPV positivity.

	N with age information N	Mean	[95% CI]	P-value
Cervix*	10,575	50.91	[50.56-51.26]	<0.001
HPV Negative	1,598	53.76	[53.01-54.50]	
HPV Positive[1]	8,977	50.78	[50.48-51.08]	
Vulva*	1,709	61.28	[59.68-62.88]	<0.001
HPV Negative	1,258	70.64	[69.83-71.45]	
HPV Positive[2]	419	62.24	[60.77-63.71]	
Vagina*	407	60.42	[58.74-62.10]	0.074
HPV Negative	113	63.35	[60.66-66.05]	
HPV Positive[2]	288	60.45	[58.76-62.13]	
Anus**	497	62.86	[61.35-64.36]	0.040
HPV Negative	68	66.96	[63.16-70.76]	
HPV Positive[2]	375	62.64	[61.03-64.24]	
Penis*	1,009	64.18	[62.08-66.28]	0.934
HPV Negative	703	64.19	[62.99-65.40]	
HPV Positive[2]	279	64.10	[62.13-66.07]	
OC***	1,178	61.38	[60.58-62.18]	0.493
HPV Negative	1,115	61.51	[60.69-62.33]	
HPV Positive[2]	52	58.13	[53.95-62.32]	
Oropharynx***	1,056	61.03	[60.35-61.70]	0.815
HPV Negative	804	61.93	[61.17-62.68]	
HPV Positive[2]	243	58.11	[56.65-59.58]	
Larynx***	1,004	61.85	[61.18-62.52]	0.900
HPV Negative	963	62.10	[61.43-62.77]	
HPV Positive[2]	36	55.25	[49.90-60.60]	

1: Only HPV-DNA+; 2: HPV-DNA+ AND (mRNA+ OR P16+); *imputation made only for age; **imputation made for age and gender; ***no imputation made (complete data reported).

Table 2. Mean and 95% confidence interval of the age at diagnosis, by cancer site and type-specific HPV positivity.

	N with age information	Mean	[95% CI]	P-value <0.001[1]
Cervix*				
HPV16 single	5,115	50.02	[49.62-50.41]	
HPV18 single	857	48.21	[47.28-49.15]	
HPV45 single	474	46.81	[45.54-48.07]	
Multiples HPVs16/18/45 only	77	49.51	[45.75-53.27]	
Other single	1,892	55.46	[54.80-56.12]	
Other multiple	510	51.61	[50.32-52.89]	
HPV Undetermined	52	50.47	[46.39-54.54]	
Vulva*				0.546
HPV16 single	302	61.59	[59.97-63.20]	
Other HR HPVs	86	62.64	[59.66-65.63]	
Vagina*				0.297
HPV16 single	168	61.04	[59.21-62.87]	
Other HR HPVs	107	59.47	[57.12-61.81]	
Anus**				0.128
HPV16 single	299	63.92	[62.48-65.37]	
Other HR HPVs	52	61.03	[57.74-64.32]	
Penis*				0.390
HPV16 single	193	64.47	[62.51-66.43]	
Other HR HPVs	54	66.32	[62.59-70.04]	
Oral cavity***				0.883
HPV16	47	58.68	[54.58-62.79]	
Other HPVs	5	53.00	[22.50-83.50]	
Oropharynx***				0.454
HPV16	215	58.22	[56.63-59.82]	
Other HPVs	28	57.25	[53.54-60.96]	
Larynx***				0.179
HPV16	16	57.00	[47.76-66.24]	
Other HPVs	20	53.85	[46.93-60.77]	

1: HPV16/18/45 (singles and multiple infections including only these 3 types) vs Other HPVs (single, multiple and Undetermined HPV infections); HR: High Risk; *imputation made only for age; **imputation made for age and gender; ***no imputation made (complete data reported).

Conclusions: We have observed different patterns of age at diagnosis by anatomical sites, HPV positivity and HPV types. These differences will help us to understand the natural history of the infection to cancer and may have implications in prevention strategies.

SELF-TESTING FOR CERVICAL HPV USING MINIMALLY INVASIVE DDPCR-BASED SWABS IN KENYA: A FEASIBILITY AND PROOF OF CONCEPT STUDY

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Background: Kenya has among the highest incidence of cervical cancer (CC) in the world, however only 3% of women are screened. Self-testing methods have the potential to decrease CC prevalence. .
Methods: Prospective validation study at a tertiary carecentre in Nairobi, Kenya. Feasibility of a self-testing model was assessed via surveys of at-risk women, and women with known CC. A subset of women from each group underwent self-administered and physician-administered analyzed by ddPCR to detect HPV 16 and 18 mRNA for oncoproteins E6 and E7. Financial feasibility was assessed via cost analysis.
Results: 100 at-risk women and 25 with CC were recruited. While 76% of women knew about cervical cancer, only 44% believed themselves to be at risk, while less than 30% had ever had screening. The most common barriers werelack of awareness and access. 72% would be more willing to undergo screening if a self-test were available. Four women from each group underwent a self-swab and physician-administered swab. All swabs had sufficient DNA for ddPCR analysis. All women with CC tested positive for oncogenic HPV mRNA, whereas none of the controls were positive.
Conclusions: Effective cervical cancer screening programs are needed in Kenya. Self-screening using ddPCR-based swabs is culturally and socially acceptable, as well as feasible. This method provides a viable alternative to traditional screening, and should be further validated prospectively.

INCREASED RISK OF CERVICAL CANCER IN WOMEN WITH HPV RELATED OROPHARYNGEAL CANCER

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Objectives: To investigate the association between HPV related cancers of the oropharynx and cervix using both retrospective and prospective study designs.
Methods: A provincial cancer registry was used to retrospectively identify all patients diagnosed with OPSCC from 1997-2015. The standardized incidence ratio (SIR) of cervical cancer history in women with p16+/- oropharyngeal squamous cell carcinoma (OPSCC) was measured. Prospectively enrolled patients from 2015 to 2018 were recruited for cervical and oropharyngeal swabs for high-risk HPV testing.
Results: From 373 women with OPSCC included retrospectively, the SIR of cervical cancer was significantly higher in p16+OPSCC (>20, SIR=160/100,000) compared to the general population (SIR=7.4-9.0/100,000). In the prospective cohort, 58 women were recruited for cervical and oropharyngeal oncogenic HPV swabs. Double positive HPV type 16 was identified in 16.7% of women with recent history of cervical cancer.
Conclusions: Women with HPV/p16+ OPSCC have a significantly higher risk of cervical cancer compared to the general population.

POOR TREATMENT OUTCOME OF PRECANCEROUS CERVICAL LESIONS IN HIV POSITIVE WOMEN IS ASSOCIATED WITH T HELPER CELL TYPE 2 CYTOKINE SKEWING.

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Persistent infection with the human papilloma virus (HPV) leads to precancerous lesions and increased risk of cervical cancer if untreated. Surgical excision treatment failure and recurrence is high in HIV positive women.This study aims to investigate the behavioral, virological and immunological factors associated with treatment outcomes of lesions in HIV positive women.
Methods: A prospective cohort study based in Durban, South Africa recruited 200 women with precancerous cervical lesions between October 2016 and August 2018. The endpoint is outcomes of precancerous lesions at 12 months post-excision. Twenty cases (treatment failure) and controls (clearance) of patients matched for HPV 16/18 subtypes, CD4 count and age were selected. Concentrations of 27 pro-inflammatory, anti-inflammatory and regulatory cytokines were measured in cervicovaginal lavage (CVL) and plasma.
Results: There was no significant difference in any CVL cytokine between treatment responders and non-responders. Plasma concentrations of IL-4, IL-5, IL-7, IL- 10 and IL-17 were significantly higher in treatment failures compared to those with good outcomes (all $p < 0.05$). In multivariate linear regression analysis, the number of sexual partners as well as plasma IL-10 and IL-4 remained significantly associated with treatment failure?
Conclusions: A T helper (Th) 2 skewing at surgical treatment is associated with poor treatment response and possibly represents a diversion from the desired Th1 responses. IL-10 is a potential predictive biomarker of treatment outcome and increased cancer risk. The impact of HPV viral load requires further exploration to inform adjunct immunotherapies.

A HIGH PREVALENCE OF ANOGENITAL WARTS AND ANAL HPV INFECTIONS IN WOMEN WITH PRE-MALIGNANT CERVICAL LESIONS AT KING EDWARD HOSPITAL VII, DURBAN.

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: The Human papillomavirus (HPV) is an established cause of anogenital warts, cervical precursor lesions, anal and cervical cancer. Women with cervical intraepithelial neoplasia (CIN) have an increased risk of anogenital warts and subclinical HPV infection in the anogenital compartment; however the prevalence of anal HPV infection in women with CIN remains unclear.
Methods: This was a prospective observational study of 148 women with high grade cervical intraepithelial neoplasia (HSIL) at King Edward VIII Hospital, Durban between October 2016 and March 2017. Clinical, behavioural and demographic data were collected with a structured questionnaire. A sub-set of 30 women over 30 years with no clinical evidence of anogenital warts were selected anal HPV testing. Dry anal mucosal swabs were collected to test for 37 HPV genotypes using the Roche Linear Array.
Results: The mean age of the study participants was 38 years, 97 % (n=145) were African black women, 94.6% (n=140) were HIV positive with a mean CD4 count of 481. The prevalence of anogenital warts was 16% (n=23); anogenital warts was associated with younger age (35 vs 38; p=0.0332), lower CD4 count (357 vs 477; p=0.0156) and presence of vaginal discharge (21.7% vs 9.6%; p=0.0467) respectively. Anal intercourse was not associated with anogenital warts 8.7% vs 9, 6% (p=0.4458). Anal HPV infection was 93.3% (n=28) with HPV 16 and 18 present in 64.3% (n=18). The average number of HPV sub-types per person was four [1; 10]; 25% (n=7) of women had three sub-types per person.
Conclusions: Anogenital warts and sub-clinical anal HPV infection are highly prevalent in women with high grade cervical intraepithelial neoplasia. Anal cytology or anoscopy should be considered in all women with cervical HSIL particularly in HIV positive women.

DEMETHYLATING TREATMENT REPRESENTS A CAUSAL TREATMENT APPROACH AGAINST HPV-TRANSFORMED LESIONS

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: Numerous studies have demonstrated alterations of the host and viral methylation patterns during HPV-induced carcinogenesis. Specifically, DNA methylation tends to increase during lesion progression and also appears to have functional relevance for HPV cancer development. We could show previously that methylation of distinct CpG sites in the HPV upstream regulatory region (URR) interferes with the binding of the regulatory HPV E2 protein in this region, thereby allowing uncontrolled expression of the HPV E6/E7 oncogenes. HPV E6 and E7 themselves promote methylation in the host cell DNA, e.g. in tumor suppressor genes, which may be consequently silenced. Based on those observations we hypothesized that the reversal of aberrant methylation using demethylating agents could represent a causal therapeutic approach for HPV-transformed lesions.
Methods: A panel of eight HPV-transformed cell lines both from the uterine cervix as well as from the head and neck region was treated with the demethylating agent 5-aza-2'-deoxycytidine (DAC), a DNA methyltransferase inhibitor, in different concentrations over one and two weeks. Further, we generated and treated three-dimensional cultures (tumor spheroids and co-cultures of HPV-transformed cells and normal keratinocytes) to assess treatment effects of DAC in a more complex disease model. Proliferative activity, methylation of target genes, mechanisms of growth arrest and epithelial differentiation were analyzed in the treated cells by various methods.
Results: We observed a time- and dose-dependent treatment effect in all cell lines and three-dimensional tumor models comprising demethylation, inhibition of cellular growth and the induction of cellular senescence and apoptosis. Further, analysis of the co-culture models revealed that HPV-transformed cells were apparently preferentially affected by the treatment with DAC over normal keratinocytes.
Conclusions: Treatment with the demethylating agent DAC holds the potential of a truly targeted therapeutic approach against HPV-induced (pre-)malignant lesions by reversing the malignant phenotype of HPV-transformed cells.

UTILIZATION OF MACHINE LEARNING CLASSIFIERS IN A CERVICAL CANCER SCREENING CAMP IN RURAL CHINA

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Methods based on artificial intelligence (AI) have enormous potential for cervical cancer management in low resource settings (LRS), by reducing operator bias at the point of care. However, few implementations of AI in medicine have been successfully deployed in LRS to date. This study aimed to examine an AI point of care tool for clinical management.
Methods: In this study, a clinical decision support (CDS) AI classifier was tested in a screening camp in Inner Mongolia, China. The CDS classifier was built from an existing image set from 1473 colposcopy patients labeled by three colposcopy experts, with an area under the (ROC) curve of 0.93, and runtime <1 sec. CDS was implemented as a function called from the web once images were synced from an Android application. Using a local 3G network, images were uploaded from the colposcope into a secure image portal, from which CDS was accessed. CDS processed all images of sufficient quality from the same patient session, and aggregated the scores using a weighted average. Using this implementation, classifier results were available in minutes. Altogether, images were collected from N=147 patients. Upon patient enrollment, cervical images were captured using a mobile colposcope for classification analysis. Patients flagged by CDS or those with visible lesions after the application of acetic acid, were biopsied.
Results: CDS was able to make a prediction for 145 of 147 imaged patients. Colposcopic impressions were available for 130patients and of the 128 patients with both colposcopic impressions and CDS results, disagreements were found in 16 patients, demonstrating high agreement rates between CDS and colposcopic impressions. Biopsy results are pending.
Conclusions: The first utilization of real-time AI for patient management at the point-of-care in LRS, these results suggest that AI can provide an immediate answer consistent with colposcopic impressions, at the point-of-care in screening programs in LRS.

A CONJOINT ANALYSIS STUDY OF PREFERRED CHARACTERISTICS FOR HOME-BASED SELF-SAMPLING FOR HPV

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Home-based self-sampling for HPV can overcome barriers to clinic-based screening among African American (AA) women, who are under-screened for cervical cancer. The purpose of this study was to assess preferred characteristics for delivery of self-sampling kits (Delivery), return of kits (Return), and communication of results (Results).
Methods: Survey data were gathered at an Indiana AA health fair. Women evaluated scenarios that varied in terms of 3 dimensions: Delivery (mail, pharmacy pickup, or clinic pickup), Return (mail, pharmacy drop-off, or clinic drop-off), and Results (phone call, text message, or mail). A fractional factorial design produced 9 representative scenarios, each of which was rated on a 0 to 100 scale. Ratings-based conjoint analysis (RBCA) determined how each dimension influenced ratings. RBCA importance scores (IS) show how much each dimension contributes to ratings and part-worth utilities (PWU) indicate relative preferences for characteristics within each dimension.
Results: The 118 participants ranged in age from 21-65 (M=45). Across the 9 scenarios, overall willingness to self-sample had a mean of 60.9 (SD=31.3). The most important dimension (IS=40.6) was Return, with preferences for pharmacy drop-off (PWU=1.5) or mailed return (PWU=1.1) over clinic drop-off (PWU=-2.5). The next most important decisional factor (IS=31.9) was Delivery, with a preference for mailed delivery (PWU=1.5) over pharmacy pick-up (PWU=0.04) or clinic pick-up (PWU=-1.6). The least important decisional factor was Results (importance score=27.4), with participants preferring a phone call (PWU=1.0) over a text message (PWU=0.6) or mailed delivery of results (PWU=-1.6).
Conclusions: HPV self-sampling was generally acceptable to these AA women, but respondents indicated clear preferences regarding Delivery, Return, and Results. Clinic pick-up and drop-off were viewed relatively negatively, and women preferred a more personalized delivery of results via phone call. If confirmed, these preliminary findings could inform future home-based self-sampling for HPV interventions.

TRENDS IN CERVICAL CANCER INCIDENCE IN DINDIGUL DISTRICT, TAMIL NADU, INDIA, FOLLOWING LOW-INTENSITY SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical Cancer is the most common cancers among woman in India and other low-and middlie-income contries (LMICs), particularly in rural populations. As part of a trial to evaluate the impact of a single life time screening, 81,269 women aged 30-59 years were offered visual inspection with 4% acetic acid (VIA) during 2000-2003 in Dindigul District, India. Evidence from this study led to the state government to implement VIA screening through the public health services in 2009. The long term impact of this screening initiative on cervical cancer incidencce in the whole district was assessed.
Methods: Trends in cervical cancer incidence during 2000-2015 in the population of Dindigul district were obtained from the Dindigul Ambilikkai Cancer Registry.
Results: The crude and age-standardised incidence rates (ASR) of cervical cancer in the district during 2000-2005 were 24.1 and 23.1 respectively. The corresponding rates for the period 2006-2010 were 23.0 and 21.5 and for 2011-2015 were 21.1 and 18.8 respectively. The ASR for the age-group 30-59 were decreasing from 50.3 in 2000-2005 to 36.0 in 2011-2015 indicating a declining trend in this truncated population which received screeing services. The trends specific to the cohort of population aged 30-59 during 2000-2003 will also be presented.
Conclusions: The decreasing trend in cervical cancer incidence rates in Dindigul district may be partially due to screening received by women in the trial and in the public health serivces beginning 2009 and due to the emerging socio-economic trends.

HUMAN PAPILLOMAVIRUS (HPV) AWARENESS AND HPV PREVALENCE AMONG HIGH SCHOOL LEARNERS IN SOUTH AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: There is paucity of literature on learner's awareness and knowledge of HPV and its associated diseases in South Africa. The study determined pre and post HPV education intervention knowledge and HPV prevalence amongst high school learners.
Methods: Grade 8-12 learners of five high schools in the Eastern Cape Province of South Africa were exposed to HPV education intervention. Self-administered questionnaires were used to assess knowledge before and after the HPV education intervention. Self-collected cervical-vaginal specimen was provided by 213 sexual active female learners for HPV detection (Roche HPV genotyping assay).
Results: 2652 learners were exposed to the HPV education intervention. The learners median age was 18 years (IQR: 16-19). Only 4.1% of participants (107/2563) had heard about HPV, 3.3% (87/2626) about HPV vaccination and 9.3% (246/2634) knew that HPV infection is associated with cervical cancer development. The knowledge about HPV among high school learners was significantly increased after education intervention ($p<0.001$). In the post-education test; grade-12s learners were more likely to have better knowledge than grade-8s (OR: 4.14, 95% CI: 3.13-5.48; $p=0.046$), grade-9s (OR: 1.67, 95% CI: 1.20-2.33; $p=0.003$) and grade-10s (OR: 2.77, 95% CI: 2.12-3.61; $p<0.0001$) but not with grade-11s (OR: 1.13, 95% CI: 0.82-1.54; $p=0.459$). HPV infection was detected in 76.1% (162/213) of female learners (median age 18 years, range: 15-25 years). HPV types targeted by the Cervarix® HPV vaccine (HPV-16/18), currently used in the South African school-based HPV vaccination program, were detected in 14.6% (31/213) and those targeted by the Gardasil®9 (HPV-6/11/16/18/31/33/45/52/58) were detected in 37.1% (79/213).
Conclusions: HPV knowledge was found lacking among learners despite the introduction of a school-based HPV vaccination program more than 5 years ago in South Africa. High HPV prevalence encourages the introduction of Gardasil®9 vaccine and catch-up HPV vaccination in South Africa. Increasing HPV awareness and knowledge could promote uptake of HPV vaccination.

HUMAN PAPILLOMAVIRUS VACCINE NATIONAL INTRODUCTION DECISION-MAKING IN TANZANIA

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The World Health Organization (WHO) recommends human papillomavirus (HPV) vaccination of 9-14 year-old girls for primary prevention of cervical cancer. An HPV vaccine demonstration program was conducted in 2014 targeting 9-year-old girls in one region of Tanzania, and then HPV vaccine was introduced into the national immunization schedule for 14-year-old girls in 2018. We sought to understand the key decision-makers and drivers behind decision-making for national introduction and implementation.
Methods: We interviewed key informants (immunization program manager and partners) and decision makers (National Immunization Technical Advisory Group and National Inter-Agency Coordinating Committee members) in Tanzania from May-September 2019 using a semi-structured tool to obtain information on factors driving the national HPV vaccine introduction and implementation decisions including target age and delivery strategy.
Results: We interviewed 10 key informants and decision makers. National HPV vaccine introduction was motivated by a successful demonstration program, financial support from Gavi, The Vaccine Alliance, government commitment, and high cervical cancer burden. Despite initial plans to vaccinate 9–14 year-old girls, a single age cohort (14-year-old girls) was selected due to global vaccine supply constraints. This age cohort was selected to ensure equity and not miss any eligible age cohorts; high school enrollment gave confidence in the ability to reach this older cohort. Tanzania piloted both campaign and routine delivery strategies during their demonstration program, and subsequently selected routine delivery for national introduction.
Conclusions: The drivers behind decision-making in Tanzania included both country-context and global factors. Vaccine supply constraints will likely remain a limitation for several years. Weighing programmatic feasibility and equity will allow decision makers to determine optimal target age and delivery strategies for their country-context. Further evaluation of Tanzania's national introduction, coverage, and sustainability will be critical to assess the impact of HPV vaccinate introduction decisions.

TRENDS IN RECEIPT OF PAPANICOLAOU (PAP) TESTS AMONG INSURED AND UNINSURED WOMEN AGED 21–39 YEARS, BEHAVIORAL RISK FACTOR SURVEILLANCE SYSTEM, UNITED STATES, 2008–2016

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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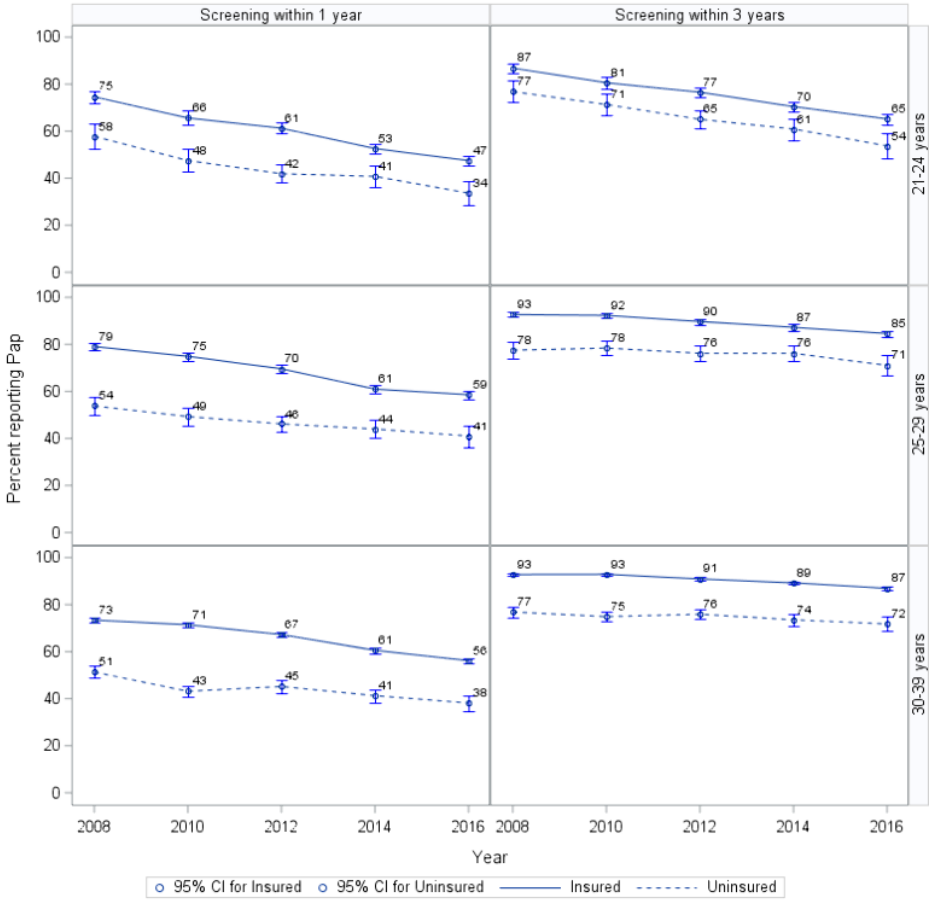
Introduction: In the United States, changes in cervical cancer screening recommendations in the past decade have evolved toward longer intervals between Papanicolaou (Pap) screenings (3 years vs. 1 year). This has resulted in a lower proportion of women screened annually. Through 2016, most U.S. screening included a Pap test. Here, we describe trends in self-reported Pap testing among insured and uninsured women.
Methods: We estimated proportions who reported receiving a Pap test (defined as receiving a Pap test within 1, and 3 years of interview) and 95% confidence intervals (CI) by insurance status and age group among women aged 21–39 years, using even year data from the Behavioral Risk Factor Surveillance System (BRFSS), 2008-2016. We assessed trends in screening by insurance status using logistic regression models, and used odds ratios and proportions screened in 2008 to estimate the yearly percent decrease in screening.
Results: From 2008 to 2016, each even year survey included 42,000–50,000 women aged 21–39 years; the proportion uninsured declined from 20% in 2008 to 15% in 2016. Insured women were screened within 1 year at higher proportions than uninsured women (Figure). Screening within 1 year declined the most among 21–24 year-olds (4%/year among insured, 5% among uninsured), and among the older age groups, declined 3%/year for both insured and uninsured (Figure). Similarly, screening within 3 years declined the most among 21–24 year-olds (2%/year among insured, 3%/year among uninsured), and <1%/year among older age groups.



Conclusions: In the United States between 2008 and 2016, fewer women lacked health insurance; women were less likely to be screened if uninsured, regardless of age group, year, or screening interval. Higher proportions screened and smaller declines in screening within 3 years vs. 1 year is consistent with adoption of longer screening intervals.

PROTOCOL FOR THE PREVENT ANAL CANCER (PAC) PALPATION STUDY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Men who have sex with men (MSM), especially MSM with HIV, have increased risk for anal cancer; however, screening for either anal precancers or anal cancers is not widely recommended. The Prevent Anal Cancer (PAC) Palpation Study will recruit MSM and transwomen, aged ≥25 years in two cities in the United States (Chicago and Houston) to test anal self-exams (ASE) and anal companion exams (ACE) that seek to reduce morbidity and mortality from anal cancer.
Methods: The PAC Palpation Study (1R01CA232892) will recruit 800 HIV+ and HIV- persons through 2021 with oversampling of Black MSM given their underrepresentation in HPV research and high risk for HIV. Participants will be taught about anal anatomy, pathology, and the procedure for an ASE or ACE, and then conduct the exam in private and record a result of either abnormal or normal. The primary objective is to compare the participant's ASE or ACE result at baseline with the clinician's gold-standard Digital Anal Rectal Exam (DARE) to determine concordance, sensitivity and specificity. The secondary objectives are to test the effect of practice on concordance after one year, and, using mathematical modeling, estimate the cost-effectiveness of ASE, ACE, and DARE and their impact on survival and health-related quality of life.
Results: Enrollment has not begun. Implementation lessons learned include harmonization of human protections, community engagement, and web-based/app-based recruitment and eligibility screening across multiple sites. Quality of life and other questions related to cost-effectiveness have been included in computer-assisted self-interviews.
Conclusions: The PAC Palpation Study will test the ability of ASE and ACE to detect early anal cancer tumors when they are much more treatable. Results could propel the development of a low-resource screening for rapid dissemination to populations with high anal cancer risk and no currently proven screening options.

NUCLEAR PKM2 IS REQUIRED FOR THE ONCOGENIC POTENTIAL OF E7 IN CERVICAL CANCER

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: HPV E7 is a major driver of cervical cancer. E7 stimulates the cell cycle by inhibiting pRb and its family members. However, their inactivation is not sufficient for cervical cancer in a mouse model, indicating that other E7-interacting proteins are necessary. Pyruvate kinase M2 (PKM2) interacts with HPV16 E7 (16E7), but the functional significance of this interaction has not been explored. Homotetrameric PKM2 is an active glycolytic enzyme generating ATP and pyruvate in the cytoplasm. However, accumulating evidence supports that nuclear PKM2 functions are crucial for cancers. In addition, several oncoproteins such as 16E7 and EGFR prevents PKM2 tetramerization and promotes its nuclear translocation in mouse fibroblasts. Furthermore, PKM2 expression is upregulated in several cancers including breast and lung cancer.
Methods: We knocked down PKM2 using shRNA and used ML265, a small molecule, to block nuclear translocation of PKM2. We performed cell counting, focus-forming assay, and colony-forming assay.
Results: PKM2 interacted with 16E7 in SiHa and CaSki cervical cancer cells and with 18E7 and 45E7 in vitro. 16E7 promoted the nuclear localization of PKM2 in C33A cells. 16E7 increased expression of PKM2 in cervical cancer cells. PKM2 knockdown decreased the proliferation of SiHa cells. Overexpression of 16E7 in C33A cells increased cell proliferation, which was abrogated by PKM2 knockdown. To interrogate whether nuclear PKM2 is crucial, we used ML265, a small molecule that activates the pyruvate kinase function of PKM2 by promoting its tetramerization. We reasoned that it would inhibit nuclear functions because PKM2 tetramers remain in the cytoplasm. ML265 inhibited cell proliferation, colony formation, and focus formation in SiHa cells.
Conclusions: Our results support that E7's ability to upregulate and prompt nuclear translocation of PKM2 is necessary for cervical cancer growth. We propose that blockade of PKM2 nuclear translocation or its nuclear function will be effective at preventing and treating cervical cancer.

HEALTH PROFESSIONALS' VIEWS AND EXPERIENCES OF THE RENEWED AUSTRALIAN CERVICAL SCREENING PROGRAM: 12 MONTHS INTO THE RENEWAL

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Recent research has shown that women have concerns about the changes to the National Cervical Screening Program and health professionals are influential when changes to recommendations are required. Attitudes of health professionals practising in Australia since its implementation in December 2017 are unknown. This study explored the attitudes and experiences of health professionals practising in Australia towards the introduction of primary HPV screening.
Methods: Interviews were conducted with 31 health professionals involved in cervical screening during December 2018. This included general practitioners, obstetricians & gynaecologists, gynaecological oncologists, pathologists and nurses. The interviews were analysed using thematic analysis.
Results: Overall, health professionals had positive attitudes towards the renewed cervical screening program and introduction of primary HPV screening. These were focused around the availability for vaccination for all girls and boys and viewing the changes as a 'real step forward' with belief that the cervical screening test is a better test. Four main themes emerged from the data: practical system challenges, communication and education, finding ways around the guidelines and other 'collateral'. Practical system challenges included increased colposcopy referrals, complex screening pathways and issues with self-collection. In terms of communication and education, the limited public education was recognised, in addition to challenges with particular age groups of women. Finding ways around the guidelines was exampled by over-referral of symptomatic tests and misinformed self-collection. Other 'collateral' was demonstrated through reduced opportunistic screening opportunities due to less frequent primary care presentations.
Conclusions: Women's understanding and experience of the renewed National Cervical Screening Program will likely depend upon clinicians' ability and willingness to explain the rationale behind the changes, and to respond confidently to patient concerns regarding these changes. It is essential that concerns and challenges identified in this study are addressed with clinicians to improve implementation of primary HPV screening programs.

WOMEN EXPERIENCES OF THE RENEWED NATIONAL CERVICAL SCREENING PROGRAM IN AUSTRALIA 12 MONTHS FOLLOWING IMPLEMENTATION

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Most research to date exploring women's views and experiences of the Renewal of the Australian National Cervical Screening Program (NCSP) was conducted prior to their implementation. This study aimed to explore women's experiences of the renewed NCSP, from the perspective of women who have received different HPV test results.
Methods: Qualitative interviews were conducted with a sample of women in Australia aged 25 – 74 years who received cervical screening since December 2017.
Results: 26 women were interviewed. Four main themes emerged: 1) knowledge and attitudes about the changes: some lack of awareness of the changes was still evident, but others that understood that HPV is detected earlier than abnormal cells and HPV is common, expressed positive attitudes towards the test and felt less anxious due to less frequent screening; 2) information dissemination: almost all women wanted more information about both the changes and the possible results from the new cervical screening test; 3) screening behaviour and experiences: some women trusted the reasons behind the changes and had postponed their cervical screen until the changes had been implemented following their doctor's advice. Most women envisaged the NCSP changes would have minimal impact on their screening behaviour and; 4) focus on meaning of results and the new test: overall women were able to recall their HPV results and understand the implications for future cervical screening. Women with no previous history of abnormal smears were somewhat anxious if they received HPV+ results, whereas those with previous history were less fazed.
Conclusions: Women show some understanding of HPV and the new cervical screening test, but more written information and public communication about the changes and possible results are warranted. In particular, efforts are needed to improve information for women who are HPV+ with no history of abnormal results receive the information they need to alleviate anxiety.

NATIONAL INTRODUCTION OF HPV VACCINATION IN SENEGAL — SUCCESSES AND CHALLENGES

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The World Health Organization recommends human papillomavirus (HPV) vaccination for girls aged 9–14 years to prevent cervical cancer. Following successful demonstration programs in 2014–2016 using school-based campaigns, HPV vaccination was introduced nationwide in Senegal for 9-year-old girls in 2018 through a continuous routine service delivery strategy at health facilities, schools and other outreach sites. We assessed vaccine introduction in Senegal to understand factors driving immunization program decision-making, perceived successes and challenges.
Methods: We conducted semi-structured interviews with purposively selected national-level stakeholders and comprehensive desk reviews of country documents regarding HPV vaccine introduction, including decision-making, planning, training, communication, service delivery, monitoring and supervision.
Results: We interviewed ten stakeholders. Due to global vaccine shortage, introduction was limited to a single age cohort; 9-year-old girls were chosen to reach more girls during primary education as school enrolment rates decline thereafter. Vaccination through routine delivery platforms was perceived to be more cost-effective than a campaign approach. High-level political commitment and collaboration between immunization and education partners were frequently cited reasons for achieving HPV vaccine introduction. All interviewees reported that a health care worker (HCW) strike, negative rumours and vaccine hesitancy negatively impacted introduction. Other challenges, specifically related to caregiver communication, included insufficient data on attitudes towards HPV vaccination among HCWs, teachers and community members.
Conclusions: Strong leadership and a multi-sectorial approach likely contributed to successful HPV vaccine introduction in Senegal. Looking forward, to build sustainability of HPV vaccination, it is important to improve understanding and engagement among all stakeholders, including HCWs and community members, and to strengthen and innovate communication and crisis management strategies. Further assessment of operational costs and achieved coverage is critical to understand efficiency and effectiveness of Senegal's vaccination strategy. In the context of HPV vaccine shortages; affected countries will need to evaluate feasibility and equity to determine best target age group for vaccination.

IMMUNOCYTOCHEMISTRY NEGATIVITY OF HPV L1 CAPSID AS A BIOMARKER OF POOR PROGNOSIS IN PATIENTS WITH ASCUS OR LSIL

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Efficient and highly predictive biomarkers reflecting the prognosis of persistent atypical squamous cells of unknown significance(ASCUS) and low grade squamous intraepithelial lesion(LSIL)s are unavailable and need to be developed urgently. We aimed to develop a predictive model for diagnosis of cervical intraepithelial neoplasia(CIN)2+ by analyzing the immunocytochemical expression of the HPV L1 capsid protein in patients with persistent ASCUS and LSIL with a high risk of HPV infection.
Methods: Cervical cytology samples comprising (70 ASCUS and 215 LSIL Pap smears) were analyzed. Immunocytochemical identification of the HPV L1 capsid protein in cervical cytology samples was performed. Expression levels of HPV L1 capsid protein in cervical cytology samples were measured, and the correlation between HPV L1 expression and cervical pathologic diagnosis was evaluated. The risk for CIN2+ was calculated using the results of immunocytochemistry and the HPV DNA test.
Results: Negative results for HPV L1 immunochemistry test were more frequently observed in CIN2+, and expression of the HPV L1 capsid protein was higher in CIN1 or cervicitis (Fisher's exact test, $p<0.05$). Diagnosis rates for CIN2+ were highest for the combination of HPV L1 capsid protein immunocytochemistry, cytology and HPV test when compared with other combinations (Akaike information criterion (AIC): 191.7, Schwarz criterion(SC): 206.3, $p<0.001$).
Conclusions: Absence of HPV L1 capsid expression and presence of HPV type 16 or 18 infection are reliable predictors of progression to CIN2+ in patients showing persistent ASCUS and LSIL.

HPV VIRAL LOAD AS PREDICTOR FOR PRESENCE OF CERVICAL INTRAEPITHELIAL NEOPLASIA IN SELF-COLLECTED VAGINAL FLUID SAMPLES

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Due to the low sensitivity of cervical cytology the primary screening test has been replaced by HPV testing which have a higher sensitivity but does not provide as high specificity. In order to increase the specificity several methods have been explored as triage such as analysis of HPV viral load. A number of studies have evaluated the use of HPV viral load but results have been conflicting with respect to its clinical utility. This study was performed to evaluate the use of high-risk HPV (hrHPV) viral load in the screening test to predict persistent infection and presence of cervical CIN2+.
Methods: We followed women between 30-60 years of age in a population screening cohort who performed self-sampling of vaginal fluid followed by a hrHPV test. Women who were hrHPV positive in their screening test repeated the hrHPV test 3-6 months later and these were included in the present study.
Results: show that women with persistent infection had higher HPV viral load in the primary screening test than women with transient infections, both for HPV16 (p=5.33e-03) and the total viral load of all hrHPV (p=3.88e-07). In women with persistent HPV16 infection and histologically confirmed CIN2+ had 48% an increase in HPV16 titer in the follow-up test as compared to 20% of women with persistent infection without CIN2+ lesions. When analysing all hrHPV types together, 41% of women with persistent infection and CIN2+ had an increase in titer as compared to 26% of women without CIN2+.
Conclusions: Viral load of hrHPV in the primary screening test is associated with presence of CIN2+. Serial testing of HPV viral load has the potential to distinguish women with CIN2+ lesions from women with persistent infection without CIN2+ lesions.

HPV INFORMATION CENTRE AS A PLATFORM TO MONITOR CERVICAL CANCER ELIMINATION

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: The HPV Information Centre, www.hpvcentre.net, is a web-based resource that has been online since 2007. It was first launched in collaboration with WHO and afterwards with the International Agency for Research on Cancer (IARC). The Centre routinely monitors, captures, processes, analyses, and disseminates key data for the prevention of HPV-related cancers.
Methods: HPV infection statistics are produced through systematic reviews of biomedical literature and meta-analysis. HPV-related cancer statistics are compiled from IARC's global estimations (GLOBOCAN) and the registry data of high quality available in successive volumes of Cancer Incidence in Five Continents. Cervical cancer screening and HPV vaccination programmes characteristics are identified through systematic searches. Sexual behaviour: systematic reviews and complementary data on cofactors, sociodemographics and other immunization statistics: selected international databases. The Centre produces standardized summaries of HPV-related disease burden and associated risk factors, prevention strategies, screening activities, and immunization programs for each of the 194 WHO member states. Fact sheets include concise self-explanatory graphs and tables to offer a quick overview of the situation in the designated population. More elaborated supplementary tables and comments can also be found in country-specific, regional and worldwide Full Reports. The system also allows queries to generate statistics summaries.
Results: To date more than 2,000 references have been included among more than 20,000 candidate publications identified in PubMed and other search engines. Since its launch the Centre has received more than 400,000 visits. In all these years, the Centre has received visits from all world countries and all their dedicated reports have been downloaded. The Centre is now working on updating statistics and developing new indicators for the elimination campaign (see communications on cervical cancer screening worldwide #1202 and HPV vaccine coverage statistics).
Conclusions: The Centre will continue its work monitoring progress and producing statistics to help global cervical cancer elimination campaign.

ASSOCIATION OF THE VAGINAL MICROBIOTA IN SELF-COLLECTED SAMPLES WITH PERSISTENT HPV16 INFECTION

BASIC RESEARCH / MICROBIOME

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Introduction: A vaginal flora dominant by non-*Lactobacillus* may be a risk factor for HPV infection. This study was performed to compare the vaginal microbiota in women with a persistent HPV infection and CIN2+ histology, with those that cleared the HPV infection in 5-6 months after the screening test.
Methods: Women aged 30-49 were selected from a previous randomized study that compared detection rate of CIN2+ lesions in women performing repeated self-sampling for hrHPV testing with screening based on Pap smear cytology. 96 women were selected for analysis with 16S rRNA Ion Torrent Amplicon Sequencing. Of these, 32 women were negative for hrHPV in their baseline test, 26 were infected only with HPV16 in baseline test and subsequently HPV negative in the follow-up test, and 38 were single positive with HPV16 in both baseline and follow-up test and diagnosed with CIN2+ histology during follow-up.
Results: The mean time between baseline and follow-up sample was 5.7 months. In total, 131 bacteria were identified on species level, and an additional 87 on genus or family level. Cluster analysis grouped samples into those dominated by *Lactobacillus spp*, *Atopobium*/*Gardnerella* or *Streptococcus*/*Prevotella*. In the baseline test, women with transient (42%, p = 0.018) or persistent HPV infection (37%, p=0.047) had higher proportion of the non-*Lactobacillus* dominant groups as compared to HPV negative women (22%). In the follow-up sample, there was no difference in the frequency of non-*Lactobacillus* dominant flora between women with transient (35%) and persistent HPV16 infection (26%) (p=0.18). In the baseline test, 8% of women with transient infection had a flora dominant by *Atopobium*/*Gardnerella*, as compared to 16% of women with persistent HPV16 infection (p = 0.007).
Conclusions: Non-*Lactobacillus spp* dominant flora is more prevalent in women with transient and persistent HPV16 infection. An *Atopobium*/*Gardnerella* dominant flora is associated with persistence of HPV16 infection and presence of CIN2+.

STAGE IA1 OF MICROINVASIVE CERVICAL CANCER. IS HYSTERECTOMY NECESSARY AS A DEFINITIVE TREATMENT?

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: FIGO stage IA1 microinvasive cervical cancer (MIC) was traditionally treated with a hysterectomy. The aim of this study is to compare the results of patients who were followed up after the MIC diagnosis and those patients who underwent a second treatment directly after the diagnosis without prior control.
Methods: Retrospective study including 144 cases of stage IA1 MIC diagnosed after conization, between 1987 and June 2019.
Results: HPV 16 was the most common genotype. In the group which received a second treatment directly –without any follow-up visits after conization– 75% underwent hysterectomy and the rest underwent a second conization. Regarding the histological results obtained in those patients, who had a hysterectomy as a second direct treatment, 65% were negative for intraepithelial lesions, 9% were low-grade lesions, 16% high-grade and only 10.5% confirmed invasive carcinoma. The histological results obtained in those patients who had a re-conization as a second direct treatment were negative in 32%, low grade in 37%, 5% of CIN 2 and malignancy was confirmed in 26%. There were no negatives cases in the group followed-up prior after the diagnosis. 100% were high-grade lesions in the hysterectomized patients, and 25% of those who were re-conizated. There were not any cases of unnecessary hysterectomy in this group.
Conclusions: The best approach to treat stage IA1 MIC is conization and always scheduling surgical treatment depending, not only on the histological grade obtained after the first treatment, but also taking into account the follow-up visit results. Our results demonstrated that the hysterectomies performed without a previous visit to study the residual cervix result in histopathology-negative outcomes in 65% of cases. Therefore, confirmation of the residual disease by evaluating the margin status is essential to make the proper decision regarding the second treatment, because is possible to perform a conservative management in many cases.

INCIDENCE AND CLEARANCE OF GENITAL AND ORAL HUMAN PAPILLOMAVIRUS INFECTION IN MALE PATIENTS WITH SEXUALLY-TRANSMITTED INFECTIONS IN VIETNAM

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: We recently reported the low concordance of oral and genital human papillomavirus (HPV)infection among male patients with sexually transmitted infections (STIs) in Vietnam, and the lower prevalence of HPV infection in the oral cavity than in the genitals. This study aimed to investigate the incidence and clearance of HPV infection and the concordance of newly acquired HPV infection in the genitals and oral cavity of the male patients with STIs in Vietnam.
Methods: This longitudinal study included 164 male patients with STI, with median age of 32.5 years. Patients were examined for HPV-DNA in the oral cavity and the genitals twice annually, with the median follow-up period of 14.6 months. Kaplan-Meier analysis was done for the incidence and clearance of HPV infection.
Results: In the oral cavity and genitals, the prevalence of high-risk HPV (hrHPV) infections was 10.1% and 21.3%, the incidence was 15.6 and 9.5 per 1000 person-months ($P = 0.001$), and the median time to the clearance was 6.2 and 9.0 months ($P = 0.004$), respectively.Among the genitals (penis, urethra, and urine), the incidence of hrHPV infection was highest in the penis (8.1, 3.1, and 0.8 per 1000 person-months, respectively; $P < 0.001$), whereas the median time to clearance did not significantly differ (8.0, 14.3, and 10.4 months, respectively; $P = 0.671$). The timing and HPV genotypes of newly acquired HPV infection showed discordance between the genitals and the oral cavity.
Conclusions: The lower prevalence of HPV infection in the oral cavity than in the genitals may be due to the faster clearance of HPV infection in the oral cavity than in the genitals. Oral HPV infection may occur independently from genital HPV infection among the male patients with STIs in Vietnam.

CHANGES IN HPV SEROPREVALENCE FROM AN UNVACCINATED TOWARDS A GIRLS-ONLY HPV VACCINATED POPULATION IN THE NETHERLANDS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In the Netherlands, HPV vaccination was included in the National Immunisation Programme for 12-year old girls in 2010 with the bivalent vaccine. Vaccine uptake initially increased from 56% to 61%, but declined to 45%. To assess its impact on the population level, we examined the changes in HPV seroprevalence in the Dutch population comparing pre-and post-vaccination data.
Methods: Serum samples were used of men and women (0-89 years of age) from two nationwide cross-sectional population based serosurveillance studies performed before (2006-07 survey, n=6384) and after (2016-17 survey, n=6612) implementation of HPV-vaccination in the Netherlands. The last survey included an oversampling of the migrant population. Seven high-risk HPV-specific antibodies; HPV16, 18, 31, 33, 45, 52 and 58, were tested in a VLP-based multiplex-immunoassay. Vaccinated individuals were excluded from seroprevalence and riskfactor analyses.
Results: Preliminary results show us that overall HPV-prevalence is higher in the 2016-17 survey compared to the 2006-07 survey, 25.8% and 23.6%, respectively. Prevalence for HPV16 was highest (13% and 11.4%) and males have a lower seroprevalence than females. The step up in HPV-seroprevalence occurred around 15-19 years of age in both study periods, especially in women. HPV seropositivity for any type was significantly associated with sex, ethnicity, number of sexual partners and history of reported STD. Interestingly, seroprevalence for HPV16 in men was lower in the post-vaccination survey. Although in the male age group 15-39 this effect was not significant(Table 2).

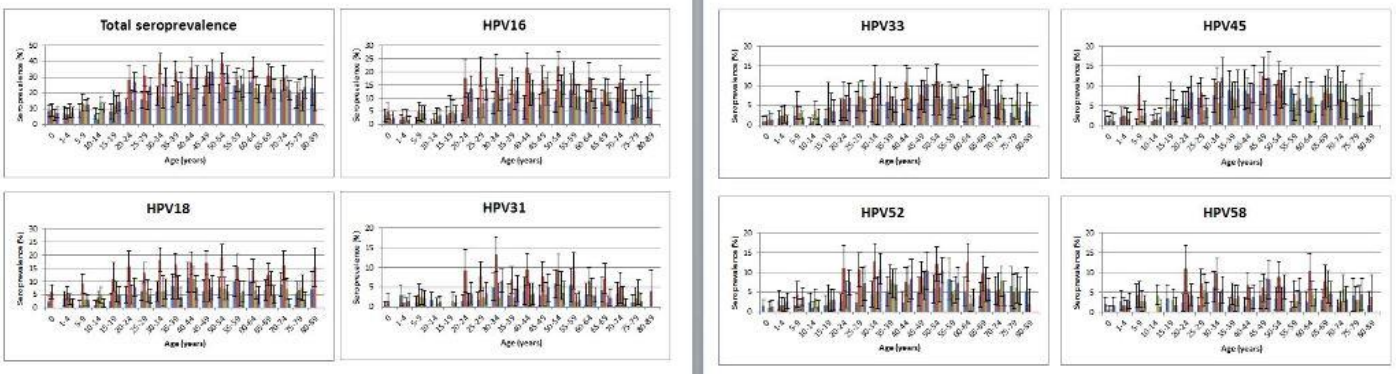

Figure 1: Total HPV seroprevalence and seroprevalence of seven high-risk HPV types in The Netherlands in the 2016-2017 survey males (blue) and women (red) and in the 2006-2007survey males (green) and women (purple). Error bars indicate 95% confidence intervals.

Table 1 Risk factor analysis for any high-risk type HPV IgG seronegativity among unvaccinated, sexually active participants older than 14 years of age, in the 2016-17 serosurveillance study in the Netherlands (N=3827)

Potential risk factor for any high-risk type HPV seronegativity	% HPV seropositive N/n(%)	Univariate Crude OR (95% CI)	Model after backward selection aOR (95% CI)
Age			
15-19	9/52 (17.3)	**Ref**	Ref
20-29	127/586 (21.7)	1.2 (0.5-2.9)	
30-39	208/714 (23.1)	1.6 (0.7-3.8)	
40-49	177/646 (27.4)	1.6 (0.7-3.7)	
50-59	184/630 (29.2)	1.7 (0.7-3.9)	
60-69	186/648 (28.7)	1.3 (0.6-3.2)	
70-79	103/448 (23.0)	1.0 (0.4-2.5)	
80-89	22/103 (22.2)	0.8 (0.3-2.1)	
Sex			
Men	333/1752 ((19.0)	**Ref**	**Ref**
Women	683/2075 (32.9)	**1.9 (1.6 - 2.3)**	2.2 (1.8-2.6)
Urbanization			
1= very strong urban	257/850 (30.2)	**Ref**	**NS**
2= strong urban	358/1253 (28.6)	**0.9 (0.8 - 1.1)**	
3= moderate urban	179/705 (25.4)	**0.8 (0.6 - 1.0)**	
4= mediocre urban	150/694 (21.6)	**0.7 (0.5 - 0.8)**	
5= non-urban	72/325 (22.2)	**0.7 (0.5 - 0.9)**	
Education			
High	365/1456 (25.1)	**Ref**	**NS**
Middle	290/1113 (26.1)	**1.2 (1.0 - 1.4)**	1.2 (1.0 – 1.4)
Low	301/1029 (29.3)	**1.2 (1.0 - 1.4)**	1.2 (1.0 – 1.5)
Missing (included in var)	640229 (26.2)	**1.1 (0.8 - 1.5)**	1.0 (0.7 – 1.4)
Net monthly income			
<<970	51/172 (29.7)	**Ref**	NS
971-1.355	104/303 (34.3)	**1.1 (0.7 – 1.6)**	
1.356-1.969	167/521 (32.1)	**1.1 (0.8 - 1.6)**	
1.970-3.314	273/1126(24.3)	**0.8 (0.6 - 1.1)**	
3.315-3.500	66/280 (23.6)	**0.7 (0.5 - 1.1)**	
>3.501	218/924 (23.6)	**0.8 (0.6 - 1.0)**	
missing	137/501 (27.4)	**0.8 (0.6 - 1.2)**	
Ethnicity (country of birth)			
Dutch	744/3043 (24.5)	**Ref**	Ref
First generation migrant	210/561 (37.4)	**1.8 (1.5 - 2.2)**	1.8 (1.4-2.1)
Second generation migrant	62/222 (27.9)	**1.3 (0.9 - 1.8)**	1.2 (0.8-1.6)
Smoking ever			
No	412/1661 (24.8)	**Ref**	**NS**
Yes	502/1817 (27.6)	**1.1 (0.9 - 1.2)**	
Missing	102/349 (29.2)	**1.3 (1.0 - 1.8)**	
Alcohol			
Yes	723/2714 (26.6)	**Ref**	Ref
No	182/736 (24.7)	**0.9 (0.8 - 1.1)**	0.8 (0.6-1.0)
Missing	111/377 (29.4)	**1.2 (1.0 - 1.6)**	1.0 (0.8-1.3)
BMI			
<18.5	15/55 (27.3)	Ref	NS
18.5-25	409/1626 (25.2)	1.1 (0.6 - 2.1)	
25-30	305/1170 (26.1)	1.1 (0.6 - 2.2)	
≥30	146/507 (28.8)	1.2 (0.6 - 2.4)	
Missing	141/469 (30.1)	1.3 (0.7 - 2.6)	
Current steady partner			
Yes	801/3111 (25.8)	**Ref**	**NS**
No	169/562 (30.1)	**1.3 (1.1 – 1.6)**	
Missing	46/154 (29.9)	**1.4 (0.9 – 2.0)**	
First time			
<17 years	287/883 (32.5)	**Ref**	**NS**
17-19 years	354/1348 (26.3)	**0.8 (0.7 – 1.0)**	
≥20 years	228/1085 (21.0)	**0.5 (0.4 - 0.7)**	
Missing	147/511 (28.8)	**0.9 (0.7 – 1.1)**	
Number of partners last 6 months			
0	163/567 (28.8)	Ref	NS
1-2 partners	715/2762 (25.9)	0.6 (0.7 - 1.1)	
>2 partners	24/62 (38.7)	1.4 (0.8 - 2.3)	
Missing	114/436 (26.2)	2.0 (0.7 - 1.3)	
Ever been diagnosed with STD			
Yes	136/278 (48.9)	**Ref**	Ref
No	762/3112 (24.5)	**0.4 (0.3 - 0.5)**	0.6 (0.5-0.7)
Missing	118/437 (27.0)	**0.4 (0.3 - 0.6)**	0.6 (0.4-0.9)
Condom last time sexual intercourse			
Yes	126/552 (22.8)	Ref	Ref
No	808/2935 (27.5)	1.1 (0.9- 1.4)	1.1 (0.9-1.4)
Missing	84/340 (24.7)	1.0 (0.7 - 1.4)	0.6 (0.4-1.0)
Number of partners lifetime			
1-2 partners	331/1773 (18.7)	**Ref**	Ref
3-5 partners	244/905 (27.0)	**1.5 (1.3 - 1.9)**	1.5 (1.2-1.8)
6-9 partners	139/380 (36.6)	**2.2 (1.7 – 2.8)**	2.2 (1.7-2.9)
≥10 partners	196/438 (44.8)	**3.4 (2.8 - 4.2)**	3.3 (2.6-4.1)
Missing	106/331 (32.0)	**2.2 (1.7 – 2.9)**	2.7 (1.8-3.9)

Table 2: Prevalence difference between the 2016-17 and 2006-07 survey (a) and Prevalence difference between the male population from 15-39 years of age of the 2016-17 and 2006-07 survey (b) after pooling both surveys : adjustment of

a	All N= 5194 HPV seropositive n (%)	aPR (95% CI)	Men N= 2308 HPV seropositive n (%)	aPR (95% CI)	Women N= 2886 HPV seropositive n (%)	aPR (95% CI)
Any HPV type						
2006-2007	546 (24.1)	Ref	208 (21.2)	Ref	338 (26.3)	**Ref**
2016-2017	778 (26.6)	1.0 (0.9-1.2)	245 (18.5)	0.9 (0.7-1.1)	533 (33.3)	**1.2 (1.0-1.3)**
HPV16						
2006-2007	276 (12.2)	Ref	111 (11.3)	**Ref**	165 (12.8)	**Ref**
2016-2017	394 (13.5)	1.0 (0.9-1.2)	102 (7.7)	**0.7 (0.5-0.9)**	292 (18.2)	**1.3 (1.0-1.6)**
HPV18						
2006-2007	151 (6.7)	**Ref**	73 (7.4)	Ref	78 (6.1)	**Ref**
2016-2017	280 (9.6)	**1.4 (1.1-1.7)**	99 (7.5)	1.0 (0.7-1.4)	181 (11.3)	**1.8 (1.3-2.3)**

demographic characteristics and sexual risk factors.

b	Men 15-39 years of age N= 904	
	HPV seropositive n (%)	aPR (95% CI)
Any HPV type		
2006-07	60 (15.8)	Ref
2016-17	76 (14.5)	0.98 (0.7-1.4)
HPV16		
2006-07	34 (8.9)	Ref
2016-17	38 (7.3)	0.87 (0.5-1.4)
HPV18		
2006-07	22 (5.8)	Ref
2016-17	27 (5.2)	0.90 (0.5-1.6)

Conclusions: We showed that HPV-seroprevalence has risen in the Netherlands in a decade, especially in women. Interestingly, a decrease in HPV16 seroprevalence among the male population was observed. This effect seems to be unlikely to be attributed to herd immunity from the girls-only HPV-vaccination program since the seroprevalence among men in age 15-39 years, likely to benefit from vaccination effect in women, between the surveys was not statistically significant different.

PHYSICIAN REPORTED COMMUNICATION STRATEGIES FOR HPV VACCINE RECOMMENDATION: A QUALITATIVE STUDY WITHIN A LARGE ACADEMIC HOSPITAL SYSTEM IN THE UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Although HPV vaccination rates have improved, they remain suboptimal in the United States (US). Several states, including New Jersey, have lower uptake compared to the national average. Strong physician recommendation is associated with increased uptake; however, specific strategies used by physicians to recommend the vaccine are underexplored.
Methods: We conducted a qualitative study using in-depth interviews with family medicine, pediatrics, and adolescent medicine physicians (n=12) within a large academic-hospital system in New Jersey. We recruited physicians from four primary care settings. Interviews aimed to understand factors influencing physician recommendations and differences in recommendation strategies across settings (e.g., federally qualified health centers (FQHCs), hospital-affiliated practices) and between specialties.
Results: All physicians reported strong support for HPV vaccination, intention to recommend at the target 11-12 age groups, and providing factsheets to parents. Many physicians used electronic medical records and/or the state immunization registry for monitoring rates, but few were able to report clinic level rates. The majority needed to overcome hesitancy for at least 10-30% of parents and misinformation from the internet. Physicians in hospital-affiliated practices reported more vaccine refusals compared to physicians at FQHCs. Most physicians used the example of having their own children vaccinated for HPV as a first line strategy for addressing parental hesitancy. Other strategies included using data or professional authority to address safety concerns, linking HPV to cervical cancer, highlighting only needing two doses if vaccinated younger, and normalizing the vaccine rather than providing too much information.
Conclusions: While our findings indicate physicians are knowledgeable about HPV vaccination and recommend it to parents, they find it necessary to use varying strategies to overcome parental hesitancy. Future research should examine how physician communication strategies relate to uptake and the effectiveness/implementation of alternate physician communication strategies within real-world contexts.

IMMUNOPROFILING OF ORAL AND OROPHARYNGEAL TUMORS OF DIFFERENT ETIOLOGY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Head and neck carcinomas (HNC) are the world's sixth most common cancer. Most of HNC are associated with tobacco and other environmental factors but a growing part of oropharyngeal tumors are caused by persistent infection of human papillomavirus (HPV). Patients with HPV positive cancers have a better prognosis with fewer recurrences. This may be caused by different anti-tumor immune response and immune profile of patients. Multispectral fluorescent immunohistochemistry (fIHC) is a powerful tool for a detailed analysis of the tumor microenvironment. This method allows to access the phenotype and calculate cells in different compartments of the tumor since in comparison to flow cytometry, an architecture of the tissue remains preserved. fIHC is uniquely suited to study interaction of immune and cancer cells in situ.
Methods: In this study four different panels consisting of five antibodies each were optimized and tested on formalin-fixed paraffin-embedded (FFPE) slides of the human tissue using Opal™ 7-Color Fluorescent IHC Kit (PerkinElmer). These panels include antibodies against markers for phenotyping of immune cells (CD3, CD4, CD8, FOXP3) as well as for the description of their function (PD1, CTLA4, ICOS, CCR4). The presence and quantity of immune cells with different phenotypes were evaluated in stroma and tumor compartment using InForm™ software (PerkinElmer) in retrospective samples with known etiology. For all patients the demographic and clinical data were available and these patients were followed for up to 18 years.
Results: Preliminary analyses have shown statistically significant differences in number of cells of different phenotypes in tumors of different etiology. Besides HPV etiology some population of immune cells in the tumor microenvironment predict independently better survival of patients. More detailed survival analyses with inclusion of other clinical and demographic data will be presented.
Conclusions: Detailed analyses of the tumor infiltrating lymphocytes allows for selection of prognostic markers in HNC of different etiology.

PREVALENCE OF HPV DNA POSITIVITY AND ABNORMAL CERVICAL CYTOLOGY AMONG HIV POSITIVE WOMEN

CLINICAL RESEARCH / MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

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Introduction: Introduction : HIV infection causes impaired cell mediated immunity which in turn is responsible for persistent HPV infection & increase risk for abnormal PAP Test .The relationship among Human Immunodeficiency Virus , Human papilloma virus, and development of Cervical Intraepithelial Neoplasia are undoubtedly complex and incompletely understood. Present study was an attempt to find out the prevalence and relationship of abnormal cervical cytology and HPV infection in HIV positive women.
Methods: Material and Methods : This was a cross-sectional study conducted on 95 HIV seropositive and equal number of seronegative women attending Gynaecology OPD . After thorough history and examination specimen was collected from the cervix using cytobrush for HPV DNA testing , subtyping and cytology.
Results: Results : Most common symptom in both the groups was discharge per vaginum. HPV DNA positivity was significantly higher in seropositive group [18.6% vs 7.4%] . HPV 16 and 18 co-infection was found only in seropositive group. Premalignant condition like AGC, ASCUS, LSIL , HSIL and cell suspicious of malignancy were found only in Seropositive group (3% ,1% ,5% ,1% ,1% respectively). Higher CD4 counts in HIV positive women was associated with lower HPV DNA positivity(CD4 counts between less than 249 the percentage of HPV DNA positivity were 53% , between 250-499 it was 31% and for CD4 count >500 HPV DNA positivity was 19%). There was no significant association found between Antiretroviral treatment and HPV DNA positivity in HIV Seropositive woman . **Figure : Correration CD4 Count and Human Papilloma Virus .**
Pearson correlation(-0.982)
Conclusions: Conclusion: It is inferred that the prevalence of abnormal cytology and HPV DNA positivity is higher amongst HIV positive women and there was an association between HPV DNA positivity with lower CD4 counts but not with Anti Retroviral therapy.

ANTITUMOR ACTIVITY OF A "DANDELION" EXTRACT ON CELLS INFECTED WITH HUMAN PAPILLOMAVIRUS

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Chemo-therapeutic limited variety for lesions caused by human papillomavirus (HPV), from warts to cervical cancer (CC) makes it necessary to search new compounds to treatment. *Taraxacum (T.) officinale (dandelion)*, showed bioactivities, in leukemia and melanoma cells. We evaluate effects of a *T.officinale* root extract on proliferation, survival, migration and viral oncogenes expression, in CC cell lines.
Methods: Ethanolic extract (R-EtOH) was obtained from roots of *T. officinale* and CC cell lines HPV-infected (CaSki and HeLa), CC cells HPV-negative (C33A) and keratinocytes (HaCaT), were used. Inhibitory concentrations IC_{20} and IC_{50} were obtained, evaluating cytotoxicity by MTT reduction for 48h, which were used for subsequent tests. Clonogenic assay, allowed evaluate survival after exposure to R-EtOH for 48h. Apoptotic response was observed: using TUNEL test by microscopy after 48h of exposure, and through measurement of Annexin-V/7-AAD at 24h and 48h by flow cytometry (FC). Effect on cell migration was evaluated by a wound healing test. Autophagy induction was evaluated at 48h, for inmunoflouresces, with anti-LC3. qPCR was performed for evaluate relative expression of E6 and E7 (HPV 16; 18) oncogenes.
Results: R-EtOH extract showed a dose-dependent cytotoxic effect in all cell lines, mainly in CC cells. R-EtOH decreased the number and size of colonies in all cell lines, chiefly CC cells. Increase concentration of R-EtOH, as well as the exposure time, resulted in a higher percentage of cells in apoptosis, for CC cells. R-EtOH effectively decreased cell migration. R-EtOH induced significant increase of autophagosomes while E6 and E7 genes expression was reduced dose-dependent of R-EtOH.
Conclusions: Conclusions: Our results suggest that R-EtOH contains bioactive components that decrease the expression of HPV oncogenes and affect the proliferation, survival and migration of CC cells. Thus, R-EtOH is a promising extract for future studies, in the treatment of CC, as in other cancer types.

ACCEPTABILITY OF SELF-SAMPLING POINT OF CARE HPV-BASED CERVICAL SCREENING: A THEMATIC SYNTHESIS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Over the past few years, the global health community has pushed for the use of high-risk HPV (hrHPV) testing for primary cervical screening for women 30 years of age and older globally. HPV testing has high sensitivity and specificity compared with conventional cervical cytology, allows for less frequent screening, and when used at the point-of-care (POC), bypasses the need for sophisticated laboratories. Additionally, evidence shows that the introduction of self-sampling has helped increase the uptake of cervical screening in LMICs. Such new technologies can, however, place additional stress on women and health care workers (HCW). It is critical to better understand the impact on different end-users to develop better communication messages that will make this user-friendly technology more acceptable. This qualitative systematic review explores women's and HCW's experiences and perceptions of screening and the socio-cultural factors influencing the acceptability of self-sampling HPV-based cervical screening in all settings.
Methods: We systematically searched ten online databases (including Medline and Google Scholars) for qualitative studies in any setting published in English between 1986 and May 2019. The studies were analyzed using the thematic synthesis approach and coded using the Nvivo 12.0 software. The quality of the included studies was assessed using the Critical Appraisal Skills Programme tool (CASP).
Results: Of an initial search yielding 5319, a final list of 25 articles were included. The studies represented interventions conducted in the following settings: 48% in US and Canada, 12% in Latin America, 16% in Sub-Saharan Africa and Europe (each), and 8% in Australia. The qualitative findings (themes) will be presented during the conference.
Conclusions: Qualitative research is important to provide contextual information about how to prepare women and health facilities for HPV-based testing. The findings of this thematic synthesis will provide guidance for action and inform future implementation programs to increase the uptake of HPV-based cervical screening globally.

URINARY HPV DNA TESTING AS A TOOL FOR CERVICAL CANCER SCREENING IN FRANCE: THE CAPU3 STUDY

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: In France, since July 2019, cervical cancer screening is based on HPV testing on Pap smear for women aged 30 to 65, and cytological examination of a Pap smear for women aged 25 to 29. Previous studies in our lab have shown that urinary HPV testing for high-risk HPV (HR-HPV) testing increases rates of compliance. In collaboration with the Cancer screening coordination center of the Pays de la Loire region, we conducted a study to offer urinary HPV testing for 13000 women aged 35 to 65 who don't have regular cervical smear.
Methods: 500 to 700 letters proposing an at-home urinary HPV testing are sent monthly. Women accepting to participate send their first-stream urine samples by mail to the Virology Laboratory. HR-HPV detection is performed using Anyplex II HPV28 Detection (Seegene®) that detects 19 HR-HPV genotypes. Patients with HR-HPV positive results are encouraged to perform a cervical smear as soon as possible to detect the presence of cervical lesions.
Results: Between November 2016 and November 2018, 13535 letters were sent to women. After exclusion (past hysterectomy, recent smear or refusal), the participation rate is 15.4%. Out of the 1915 analyzed specimens, 1711 and 190 were negative and positive for at least 1 HR-HPV respectively. HR-HPV others than HPV16 or HPV18 were mostly detected as HPV53 (23.7%) and HPV68 (14.2%). Among the smears, 23 abnormal smears were observed and 6 high-grade cytological lesions after colposcopy and biopsy have been detected.
Conclusions: Because home HPV urinary testing is non-invasive and does not require medical attention, it may be an alternative to the usual screening for women who are reluctant to use Pap smear, thus extending screening coverage in our department.. Furthermore, 89.5% of the HPV-positive women benefited from a Pap smear collected by a clinician during follow-up.

HPV VACCINATION UPTAKE IN BOYS AFTER INTRODUCTION OF GENDER-NEUTRAL HPV VACCINATION IN GERMANY - A RETROSPECTIVE DATABASE ANALYSIS (IMS VACCINE ANALYZER)

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In June 2018 the German Standing Committee on Vaccination (STIKO) published a gender-neutral recommendation for HPV vaccination for girls and boys 9-14 years old (with catch up to 17). Since January 2019 it is part of mandatory funding by health insurances. Vaccination is provided by office-based physicians and no invitation system exists. The aim of this study was to monitor the monthly uptake of HPV vaccination in boys in Germany.
Methods: The study design consisted of a retrospective database analysis between January 2018 and April 2019. The used IMS Vaccine Analyzer contains anonymized digital vaccination records from a panel of approximately 350 office-based physicians (pediatricians, GP, gynecologists). Numbers documented in this database were projected to national level by using a separate database, IMS Pharmascope Vaccines, which contains 100% of vaccinations distributed in Germany. The primary outcome of the study was the monthly number of boys receiving the first dose of HPV vaccination. Secondary outcomes included the monthly number of vaccinated girls. No data on population size existed for the presented analyses.
Results: While the monthly number of boys 9 to 17 years old receiving HPV vaccination in Germany before the gender-neutral ecommendation was low (first doses 98 to 950 per month January 2018 to May 2018), it started to steadily increase from a low level in June 2018 (832) to December 2018 (9,670) and further increased sharply with fully implemented reimbursement in January 2019 (28,691). A further steady increase was observed until April 2019 (51,934). The monthly number of girls 9 to 17 years old receiving first dose of HPV vaccination fluctuated between 27,287 and 50,788.
Conclusions: The results demonstrate a strong increase in the number of boys that received HPV vaccination in Germany after gender-neutral recommendation and funding. Further analyses will link the results to population size to estimate HPV vaccination coverage.

METHODOLOGIES USED FOR ASSESSING IMPACT AND EFFECTIVENESS OF THE QUADRIVALENT HUMAN PAPILLOMAVIRUS VACCINE (4VHPV) ON HPV-RELATED OUTCOMES: A SYSTEMATIC LITERATURE REVIEW

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Finding data and appropriate methods for measuring impact[#]and vaccine effectiveness (VE)[#] of the human papillomavirus (HPV) vaccine is not trivial. We revieweddata sources and methods used in vaccine impact and VE studies regarding anogenital warts (AGW), cervical lesions and HPV infection.
Methods: A systematic literature review of Medline and Embase was conducted for studies (2016-2019) evaluating the impact or VE of the 4-valent HPV vaccine. Data sources and methods used were categorized by study outcome.
Results: Of 2,428 publications screened, 59 papers (28 impact, 22 VE, 9 both) were included (**Table 1)**. Data sources varied by outcome: electronic health records/claims databases for AGW (10/14, 71.4%); cancer screening registries for cervical lesions (15/20, 75.0%); surveys for HPV infection (23/25, 92.0%). The 42 studies collecting vaccination history relied primarily on self-reporting (21/42, 50.0%) or vaccine registries (13/42, 33.3%). Self-reported vaccination was validated in 5/21 studies (23.8%) using vaccine registries mostly. Coded outcomes were validated through medical chart review in 5/14 (35.7%) studies.

Table1. Characteristics of 4vHPV vaccine impact and effectiveness studies (N= 59).

Variable	Outcome		
	AGW (N=14)	Cervical lesions (N=20)	Infections (N=25)
Measurement	Impact (9), Vaccine Effectiveness (5)	Impact (9), Vaccine Effectiveness (9), Both (2)	Impact (10), Vaccine Effectiveness (8), Both (7)
Outcome data source	Claims database (7), EHR (3), Register (2) Hospital discharge DB (1), Survey (1)	Claims database (1), EHR (2), Register (15), Prospective study (1), Survey (1)	Register (2), Survey (23)
Exposure data source	Claims database (3), EHR (1), Register (2), Self-reported (1)	Register (4), Self-reported (4), EHR (2), Clinical trial (1)	Register (7), Self-reported (16)
Study design	Cohort (13), Cross-sectional survey (1)	Cohort (16), Case-control (3), Cross-sectional survey (1)	Cohort (5), Cross-sectional survey (20)
Years after vaccination	W: 3-8 years M: 0-3 years	W: 4-10 years	W: 3-11 years M: 2-3 years

*Impact is defined as population prevented fraction of infections/abnormalities by comparing population before and after vaccination program or trends over time; VE is defined as proportion of prevented infections/abnormalities comparing vaccinated and unvaccinated individuals.
AGW: anogenital warts, EHR: electronic health records, DB: database, W: women, M: men

Conclusions: A large variety of data sources and methods are being used to assess the impact and VE of 4vHPV, with a heavy reliance on registries and ecological designs.The use of appropriate negative controls, adjustment for confounders, and validation of vaccination status and outcome can be important tools to mitigate potential biases.

PERFORMANCE OF A DNA METHYLATION MARKER PANEL USING LIQUID-BASED CERVICAL SCRAPES TO DETECT CERVICAL CANCER AND ITS PRECANCEROUS STAGES

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: A change of the current screening algorithms to a HPV-based screening setting is discussed in several countries due to higher sensitivity of HPV testing compared to cytology. Reliable triage methods are, however, an essential prerequisite in such a setting to avoid overtreatment and higher screening costs.
Methods: A series of cervical scrapes collected in PreservCyt liquid-based cytology (LBC) medium from women with cervical cancer (n = 5), cervical intraepithelial neoplasia grade 1–3 (n = 74), and normal cytology (n = 201; further n = 352 collected in SureThin) were assessed for methylation of the marker regions ASTN1, DLX1, ITGA4, RXFP3, SOX17, and ZNF671 using the GynTect assay and compared to cobas HPV and CINtec Plus biomarker results.
Results: All samples from women with cervical cancer, 61.2% of CIN3, 44.4% of CIN2 and 20.0% of CIN1 cases were scored positive for the GynTect methylation assay. In contrast, all CIN, irrespective of severity grade, and carcinomas were positive by both, CINtec Plus and cobas HPV. The specificity of GynTect for CIN3+ was 94.6% compared to 69.9% for CINtec Plus and 82.6% for cobas HPV (all HPV types) and 90.6% for cobas HPV 16/18. DNA methylation analysis of this methylation marker panel (GynTect assay) in cervical scrapes consistently detects cervical cancer and the majority of CIN3 as well as a subset of CIN1/2 lesions. The detection rate among cytologically normal samples is extraordinarily low (1.5%).
Conclusions: GynTect shows excellent performance when using cervical scrape material collected in liquid-based cytology media, a prerequisite for employing such a test as a triage in screening programs. Compared to the other test systems used in this work, GynTect showed higher specificity while still detecting all cancer cases.

THE ASSOCIATIONS BETWEEN SERUM CONCENTRATIONS OF FOLATE AND VITAMIN B12 AND CERVICAL INTRAEPITHELIAL NEOPLASIA OF COLOMBIAN WOMEN INFECTED WITH HIGH RISK HUMAN PAPILLOMAVIRUSES.

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Only a proportion of women infected with high-risk (HR) Human Papillomaviruses (HPVs) develop higher-grades of cervical intraepithelial neoplasia (CIN2+) and invasive cervical cancer (ICC). Since lower folate and vitamin B12 status was documented to alter the risk of HR-HPV associated CIN2+ in several populations, weevaluated these associations in a cohort of Colombian women infected with HR-HPVs (HR-HPV+).
Methods: Cases (CIN2+) and controls (<CIN2) were selected from 2,661 women followed-up for 2 years in a randomized pragmatic trial. Cases (n=169) and controls (n=169) were HR-HPV+ women with histologically confirmed diagnoses of CIN. Controls were matched by age-and follow up time similar to that of cases.The concentrations of serum folate and vitamin B12 were determined by the radioimmunoassay SimulTRAC-SNB-Vitamin B12/Folate-RIAKit. Median of micronutrients were compared by Mann-Whitney test. Folate and vitamin B12 concentrations were categorized as normal, probably deficient or deficient following World Health Organization recommendations. The risk of CIN2+ associated with deficient/probably deficient concentrations of micronutrients was estimated by logistic regression models adjusted for age and other confounding factors.
Results: 16% of cases and 15.3% of controls had deficient concentrations of folate (<3ng/ml). 8.3% of cases and 10.6% of controls had deficient values of B12 (<150pg/ml). There was no difference in the median concentration of folate (5.6 vs. 6.1ng/ml p=0.5) or vitamin B12 (342.1 vs. 337.5pg/ml p=0.25) between cases and controls. Deficiency of folate [OR for normal vs. deficient/probably deficient values: (1.16; 95%CI: 0.57-2.39) or vitamin B12 [OR for normal vs deficient-probably deficient values (0.79; 95%CI: 0.33-1.93] were not associated with increased risk of CIN2+.
Conclusions: Lack of significant associations between folate/vitamin B12 and CIN2+ in this population could be due to sufficient exposure to these micronutrients from natural food sources and/or fortified food.

"PREVALENCE OF HUMAN PAPILLOMAVIRUS IN MALE PARTNERS OF INFERTILE COUPLES. SEMEN QUALITY AND COINFECTION ANALYSIS"

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Previous studies revealed that HPV was more prevalent in infertile subjects compared to fertile ones. Some studies associate HPV infection with reduced mobility and sperm viability, while others do not report these alterations. Most of these studies do not analyze the concomitant presence of other STI associated with infertility.
Methods: 143 male partners of infertile couples were analyze to evaluate genital tract HPV infection prevalence and its correlation with sperm parameters. Samples consisted of a mixture of semen and urethral swab. HPV was analyzed by PCR method and genotyped by RFLP analysis. The presence of Chlamydia trachomatis, Ureaplasma urealiticum, Mycoplasma hominis, HSV1 and HSV2 was also analyzed. Seminal quality was evaluated according to WHO 2010 standard.
Results: We found that 26,3 % of the samples were positive for HPV. The most prevalent genotype found was genotype 6. Others low risk genotypes found were 11 and 72. Oncogenic and possibly oncogenic HPV (31, 16, 18, 82 and 53) were detected in 31.25% of positive samples. 62.5% of the patients HPV positive had co-infection with at least one of the other pathogens analyzed. The HPV+ patients did not show specific alterations in the seminal parameters with respect to the HPV- group. We do not found presence of leukocyspermia associated with HPV infection.
Conclusions: This study provide the first national estimate of genital HPV prevalence in male population of infertile individuals in Argentina. The distribution of genotypes found was different from that of other geographical areas, highlighting the importance of local studies of HPV infection. The absence of leukocytospermia in HPV positive patients would indicate that the virus promotes a local anti-inflammatory environment. Evaluate other STI associated with infertility such as those studied in the present work could contribute to understand the real effect of HPV in seminal quality.

CUTANEOUS INFECTIONS WITH BETA AND GAMMA HUMAN PAPILLOMAVIRUSES: A SCOPING REVIEW

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Beta (β) and gamma (γ) HPV types have been implicated in cutaneous disease and are potential risk factors for skin cancer; however, the evidence is inconsistent. We performed a scoping review focused on cutaneous β and γ HPVs to identify the extent of the available epidemiologic evidence, provide an overview of studies, and identify gaps in the literature.
Methods: We systematically searched (Embase and MEDLINE), reviewed and selected relevant studies – published in English after 1979 – that tested for β and γ HPVs on the skin of ≥ 20 participants.
Results: After screening 2118 abstracts, 214 studies were included; 115 case-control, 61 case series, 24 cohort, and 14 other study designs. The majority (79%) of these studies were published in 2000 or later. Most studies included participants from Europe (56%) North America (14%) or Australia (13%). Studies tested samples for β and/or γ HPVs in normal skin from healthy individuals (39%); from organ transplant recipients with warts (7%), actinic keratosis (4%), squamous cell (16%) or basal cell carcinoma (10%); from immunocompetent individuals with warts (14%), actinic keratosis (15%), squamous cell (36%) or basal cell carcinoma (23%). Approximately one-third (35%) of studies collected data on participants' past ultraviolet exposure. Most studies (94%) reported on prevalent β or γ HPV infections. Fifty-two percent tested participants exclusively for β-HPVs, 5% for γ-HPVs only, and 43% for both types. Studies tested for HPV in sera (28%), biopsies of diseased (49%) or normal tissues (17%), skin cells (28%), or hairs (15%), with PCR being the most frequently used detection method (66%), followed by ELISA (13%).
Conclusions: This scoping review will advance the knowledge on the available evidence on β and γ HPV types in skin cancer and other cutaneous diseases and will identify important gaps in our knowledge to be addressed by further research.

A GERMAN ONLINE SURVEY OF PATIENTS WITH CIN, HIGHLIGHTING THE PSYCHOLOGICAL DISTRESS DURING REPETITIVE DIAGNOSTICS CYCLES

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: Cervical cancer screening using Pap smear or HPV testing is associated with repetitive retesting cycles, often several month or even years. This procedure of follow-ups creates a burden to women as they will have to stand the ongoing uncertainty whether cancer is already in progress or not. We designed a survey to address the question of psychological burden due to abnormal Pap smear results and/or positive HPV tests.
Methods: The online-survey had a semi-structured design, combining explorative questions with validated elements and participants went through a 37-item survey including the IES-R („Impact of Event Scale-Revised“) and parts of the CDDQ (Cervical Dysplasia Distress) questionnaires. Participants were recruited using online marketing (Facebook and Google) and the community from “Myriam von M” on Facebook (posts with link to survey).
Results: We received 3753 questionnaires within 9 weeks. 53.1% of the women (mean age 31.8y) had already been affected with suspicious Pap smears for more than 1y and 69.3% stated to be afraid of developing or being diagnosed with cervical cancer, whereas 49.4% expressed the fact they were even anxious about dying. More than two third of the participants reported that their worries about the Pap (69.9%) and HPV (76.4%) findings are at least “quite a bit” (Scores 3,4 & 5 on a 5-point scale) and 48.1% stated that the risk of conizations and preterm birth is important to them and “clearly” to “severely” impacting their life (Scores 4 & 5).
Conclusions: This survey is the first of its kind to investigate the psychological distress during repetitive diagnostics cycles from patients with abnormal Pap/HPV findings and highlights important findings in relation to the unmet clinical needs of the participants. Better awareness of the psychological burden of disease and of available diagnostic or treatment options are needed which may help to improve patients quality of life.

COMPARISON OF TWO METHYLATION BASED DIAGNOSTIC ASSAYS ON A COHORT OF 210 CERVICAL SCRAPES: GYNTECT AND QIASURE

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPV DNA testing as a primary screening marker is being implemented in several countries. Due to the high HPV prevalence in the screening population, effective triage strategies for HPV-positive cases are required. Methylation markers are presently discussed as a suitable tool for triaging HPV positive women. We compared the two assays GynTect and QIAsure.
Methods: In a retrospective setting 210 samples from the colposcopy clinic of the university hospital in Jena were tested with GynTect, comprising 6 (ASTN1, DLX1, ITGA4, RXFP3, SOX17, ZNF671) different methylation and QIAsure, comprising 2 (FAM19A4, mir124) methylation markers. The cohort comprises 2 cervical cancer scrapes, 5 CIS, 38 CIN3, 18 CIN2 and 15 CIN1 and 92 no CIN samples, all tested HPV positive. In addition, 40 HPV negative Pap I samples were tested.
Results: A subset of 2 cervical cancer scrapes, 43 CIN3 and CIS, 8 CIN2 and 5 CIN1 and 82 no CIN, all HPV positive, have already been tested with both assays. Detection rates of cancer and CIN3 cases were similar with 100% detection of cancer and CIS with both assays and 68.4 vs 60.5% CIN3 detection for QIAsure and GynTect, respectively. Regarding ≤CIN2 samples, detection rates are more different with 37.5 vs 25.0% for CIN2, 40.0 vs 20.0% for CIN1 and 37.5 vs 13.4% for no CIN samples.
Conclusions: Analyses for more ≤ CIN2 samples are still ongoing and will be completed for the meeting. This subset already indicates a difference between both assays regarding the detection rates of mild lesions and HPV positive, but unsuspicious samples. Both assays intend to detect HPV-positive women with clinically relevant disease, thus being a suitable tool for the use in triage screening settings. So both, sensitivity for relevant lesions and adequate specificity is required for such a triage assay.

HPV VACCINATION:KNOWLEDGE,AWARENESS AND ATTITUDE AMONG MIDDLE EASTERN AND LEBANESE HEALTHCARE PROVIDERS

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Most developing countries lack organized HPV vaccination and Cervical cancer (CC) screening programs. To improve knowledge,awareness and attitude(KAA) among Middle Eastern and Lebanese (MEL) HCPs toward HPV-vaccination (HPVV) the Lebanese Society of Obstetrics and Gynecology (LSOG) has regularly organized educational sessions. The aim of our longitudinal study was to assess change in the KAA among MEL-HCPs attending LSOG meetings in 2009 and 2018 and to identify knowledge gaps and factors that affect the attitude toward offering HPV-V.
Methods: HCPs attending the 2009 and 2018 were voluntarily invited to participate in an IRB approved standardized questionnaire. Chi-square and logistic regression analysis was conducted.
Results: 362 (around 30% of all attendees) agreed to participate and which were equally divided between 2009 and 2018 LSOG meetings. The majority were Obstetricians and Gynecologists(OBGYN) (87.8% and 80% respectively in 2009 and 2018). There was a trend for more female HCPs (66%vs.52%), married HCPs (66%Vs.52%), and private practitioners (54%Vs.44.2%) in 2018 than in 2009. Table 1 shows knowledge of HCPs on HPV, its relation to CIN2+ and CC and available HPV-vaccines, and tHCPs' attitude toward opening the subject with their patients.Table 2 summarizes the degree to which various factors influence HCPs' decision to recommend vaccination.

	Survey Items	2009	2018	Total	P-value
Knowledge	1.knowledge on lifetime risk of acquiring a genital HPV infection	9.6% (17/177)	8.5% (15/177)	9% (32/354)	0.56
	2.knowledge of the Composition of Available HPV vaccines	77.3% (140/181)	34% (51/151)	57.5% (191/332)	<0.001
	3.knowledge on Proper sexual stage of life to prescribe HPV vaccine	X	70% (124/177)	x	x
	4.Knowledge that Vaccine Booster not a necessity.	27.8% (49/176)	22% (39/177)	25% (88/353)	0.32
	5.knowledge on HPV-V 's efficacy in preventing cervical cancer.	78.2% (136/174)	80% (99/124)	78.8% (235/298)	0.614
	6.knowledge on the present vaccines' efficacy in preventing CIN2+ .	53.6% (98/183)	47% (65/138)	49.8% (160/321)	0.33
	7.knowledge on longevity of vaccines' efficacy in preventing future CIN2+	32.4% (58/179)	70.7% (104/147)	48.8% (159/326)	<0.001
	8.knowledge on HPV-Vaccine's Mechanism of action (neutralizing antibodies).	32.4% (58/179)	71% (104/147)	49.7% (162/326)	0.012
Attitude	1.HCP attitude in recommending HPV vaccination	76.8% (142/185)	65% (115/177)	71% (257/362)	0.015
	2.HCP's confidence in convincing patients with HPV-V.	56.8% (96/169)	59% (63/107)	57.6% (159/276)	0.57
	3.HCP always addressing Questions related to sexuality with their patients	27% (48/177)	26% (34/131)	26.7% (82/308)	0.95
	4.Few Patients interested in HPV-V per HCP's assumption	46.9% (83/177)	49.6% (68/137)	48% (151/314)	0.75

R-square(Sig)	Total-Predictive Accuracy(Sig)
30-41%(<0.001)	79%(<0.001)

Predictors of HPV-V's recommendation by HCP's knowledge(LSOG-2018)	AOR(95%CI,P-value)
1.Right age to vaccinate	3.16(1.29-7.73;<0.001)
2.Vaccine's mechanism of action	4.93(1.88-14.18;<0.001)
3.Vaccines' efficacy in preventing CIN2+	5.16(1.98-12.29;<0.001)
4.Vaccines' longevity in preventing future CIN2+	1.511(0.65-3.52;0.339)

Conclusions: Being knowledgeable about HPV, its relation to CIN2+ and CC, about the available vaccines and their efficacy and how long this efficacy lasts have a strong impact on the HCPs' attitude and their predisposition to recommend HPV vaccination to their patients. KAA-HPVV among HCP attending the LSOG annual meeting remains suboptimal since 2009 despite repeated exposure to various HPV-V educational sessions. This is reflected in a very low HPV-V uptake in the country and requires more concerted efforts form all stakeholders.

GENOTYPE DISTRIBUTION AND RISK FACTORS FOR HUMAN PAPILLOMA VIRUS INFECTIONS AMONG FEMALE SEX WORKERS IN BENIN, WEST AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: There is scarcity of data about human papillomavirus (HPV) in female sex workers (FSWs) in Sub Sahara Africa. This study aimed to: (1) assess the prevalence and genotype distribution of HPV among FSWs; (2) evaluate factors associated with low-risk (LR) and high risk (HR) HPV types.
Methods: This is a Baseline data from 312 FSW recruited during a longitudinal study in Cotonou from 2017 to 2018. The Linear Array HPV genotyping test (LA-HPV) (Roche Molecular Systems) was used to identify the HPV genotypes. The cross-reactivity between HPV52 and HPV-33, 35 or 58 was further tested with a real-time PCR assay specific for HPV52. Descriptive statistics and logistic regression were used. Adjusted Odd ratios (aOR) with 95% confidence intervals (95%CI) were estimated.
Results: HPV data were available for 309 FSWs. The mean age was 34.97 years (± 10.66) and the first sexual debut was 17.53 years (± 2.66). HIV, gonorrhea and chlamydia prevalence rates were 25.8%, 13.8% and 7.4%, respectively. At least one HR-HPV was found in 269 women (87.1%). The five most prevalent HR-HPV were: HPV58 (37.5%), HPV16 (36.6%), HPV52 (28.8%), HPV35 (23.3%), HPV45 (15.2%). At least 239 women (77.4%) had one LR-HPV and the five most prevalent were: HPV62 (35.6%), HPV81 (23.6%), HPV61 (23.0%), HPV84 (16.2%) and HPV72 (15.2%). The main factors associated with HR-HPV infections were age 20 to 30 years (aOR = 4.62; 95%CI: 1.13 – 18.9), separated/widow (aOR = 4.17; 95%CI: 1.36 – 12.82) and single women (aOR = 5.00; 95%CI: 1.16 – 21.51). Factors associated with LR-HPV were HIV infection (aOR = 2.91; 95%CI: 1.20 – 7.06), single women (aOR = 3.60; 95%CI: 1.35 – 9.60) and vaginal washing (aOR = 2.27; 95%CI: 1.10 – 4.71).
Conclusions: These data confirmed the necessity to emphasize on cervical cancer prevention in FSWs in Sub Sahara Africa.

HUMAN SUBJECTS CONSIDERATIONS IN HPV VACCINE RESEARCH IN ADOLESCENTS IN THE UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: US state privacy laws can present unique human subjects considerations when conducting HPV vaccine research in minor adolescents. Washington State privacy laws permit 13-17 year-olds to consent to their own mental health, substance use, and reproductive health care. For care related to sexually transmitted infections (STIs), the minimum age for consent is 14 years. At Kaiser Permanente Washington (KPWA), an integrated healthcare system, HPV vaccination is considered an STI service and is confidential between 14-17 year-olds and their healthcare provider. Information about this type of care cannot be disclosed to parents without the adolescent's consent.
Methods: In 2018 we sought to conduct a study to understand barriers to HPV vaccine series completion among KPWA members. Human subjects review and approval for this research was more complex than anticipated due to issues of parental consent and assent for minors aged 14-17 years since HPV vaccination raises privacy concerns. We had originally planned to interview parents of 9-13 year-olds and individuals aged 14-19 years, but we learned we could not approach 14-17 year-olds for their assent to participate in the study without risking disclosure of their HPV vaccination information to their parents without their consent.
Results: After numerous discussions with the KPWA Institutional Review Office and consultations with KPWA legal and privacy departments, we modified our approach strategy and interview plans. We were ultimately approved to interview parents of 11-17 year-olds and young adults aged 18-19 years.
Conclusions: Conducting HPV vaccine research in minor adolescents in the US necessitates allocating additional resources and allowing sufficient time to understand state privacy laws regarding adolescent healthcare and to engage key stakeholders including institutional review offices, healthcare providers who specialize in care of adolescent populations, and if applicable, legal and privacy departments. Researchers should also be prepared to modify their study to comply with privacy requirements.

EFFECTIVENESS OF HUMAN PAPILLOMAVIRUS VACCINE: A CASE-CONTROL STUDY WITH BAYESIAN MODEL AVERAGING

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: The full benefit of human papillomavirus (HPV) vaccines may not be realized in real-world settings due to delays in immunization. At older ages, many women will have already been exposed to HPV rendering this prophylactic vaccine less effective.This study aimed to determine the extent to which age at the time of immunization influences the vaccine's effectiveness (VE) against HPV-attributable high-grade cervical lesions (HGCL).
Methods: We conducted a matched case-control study of women in New Haven County, Connecticut, where there is population-based surveillance for HGCL and genotyping of HPV from cervical specimens. Cases were vaccine-eligible women with a HGCL attributable to HPV 16 or 18. Controls were women with normal Pap smear results, matched to cases by age, medical practice, and date of Pap smear. Participants were interviewed and records were reviewed for immunization history and potential confounders. Matched odds ratios (mOR) from conditional logistic regression were estimated by age at time of immunization ($\leq$18 years, $\geq$19 years). The VE was estimated as 1-mOR. Multivariable models were used to adjust for potential confounding. Consensus estimates of the adjusted VE were calculated using Bayesian Model Averaging (BMA).
Results: A total of 312 women (108 cases and 204 controls) were included. Cases and controls were similar in age, race/ethnicity, marital status, level of education, income, use of contraception, and history of sexually transmitted diseases (Table 1). The adjusted effectiveness of $\geq$1 dose of the vaccine was 43%. When the first dose was given at $\leq$18 years of age, the VE was 77% (Figure 1).

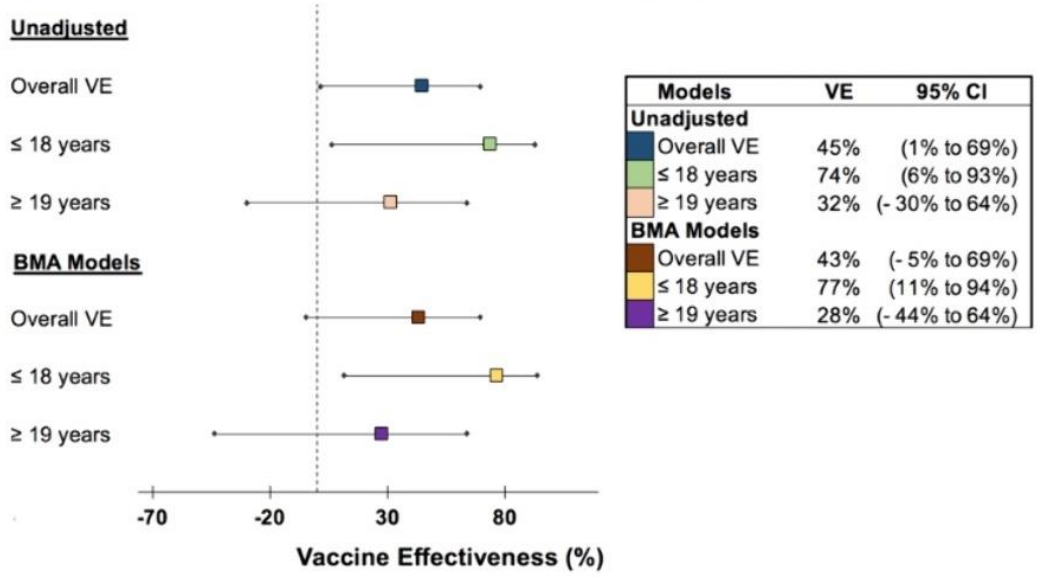
Table 1. Characteristics of Enrolled Participants by Case Status, N=312

	Cases	Matched Controls	p-value*
Total	108 (35%)	204 (65%)	-
Age (yrs.), median (range)	27 21-36	27 21-36	0.51
Race/ethnicity			
White (non-Hispanic)	68 (63%)	109 (53%)	ref.
Black (non-Hispanic)	12 (11%)	42 (21%)	0.31
Hispanic	23 (21%)	35 (17%)	0.86
Other/Multi-race	5 (5%)	18 (9%)	0.13
Publicly insured	35 (32%)	44 (22%)	0.04
Never married	79 (73%)	142 (70%)	0.51
Some college education	82 (76%)	169 (83%)	0.14
Annual income of < $50,000	75 (69%)	134 (66%)	0.50
Smoker	49 (45%)	52 (25%)	<0.01
Sexually active	104 (96%)	191 (94%)	0.32
First sexual encounter <16 years of age	21 (20%)	17 (9%)	<0.01
Four or more sexual partners	65 (63%)	93 (49%)	<0.01
Condom use every time	42 (40%)	92 (48%)	0.29
Prior OCP user	72 (69%)	148 (77%)	0.28
History of STDs	30 (29%)	39 (20%)	0.08

* Estimated using univariate unconditional logistic regression

^ Missing observations imputed: Education=3, Income=24, Smoker=3, Age of first encounter=6, Condom use=4, OCP use=48, History of STD's=24

Figure 1. Effectiveness of HPV Vaccine by Age at the Time of Immunization



Conclusions: These data quantify the clinical effectiveness of HPV vaccine and use real-world data to highlight the fact that the vaccine's protective effect is greater when given ≤18 years of age. These empirical estimates provide evidence that can be used to promote timely immunization for adolescents.

COMMUNICATING WITH WOMEN ABOUT EXTENDED SCREENING INTERVALS: A RANDOMISED ONLINE EXPERIMENT

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: The introduction of primary HPV screening means screening intervals are likely to increase for HPV-negative women. The UK National Screening Committee recommends increasing screening intervals from 3 to 5 years for women aged 25-49 years. As part of the implementation, it is important to ensure the longer interval is acceptable to women and is not seen as cost-cutting or risky. We compared three ways of explaining the change.
Methods: Women aged 18-45 recruited from an online survey panel were randomised to view one of three versions of information about HPV-based screening and extended intervals: 1) Basic information; 2) Extended information including details of the long timeline from HPV acquisition to cancer; 3) Extended information plus a diagram. The primary outcome was acceptability of the longer interval. Explanatory variables included beliefs about the time from HPV infection to cancer (timeline beliefs) and demographic factors. ANOVA and multiple linear regression analyses were used to compare outcomes between groups.
Results: Overall, 597 participants completed the study with 189, 199 and 209 randomised to Exposures 1, 2 and 3 respectively. Mean age was 34.5 years (SD=9.9). Significant between-group differences were found for acceptability and timeline beliefs. Compared with women in Group 1, those in Group 3 had significantly greater trust in the extended interval (p=.009), confidence it was safe (p=.015), relief at a longer interval (p=.009), understanding of the reason for change (p<.001) and belief that the HPV test was better than cytology at detecting abnormalities (p<.001). They also had more accurate timeline beliefs. In multivariable analyses, exposure (3 vs. 1) and timeline beliefs were significant predictors of acceptability.
Conclusions: Providing women with a clear rationale for extended screening intervals, including information on the long timeline from HPV acquisition to cancer development, could help ensure the changes are acceptable and well-understood. Inclusion of a diagram facilitates understanding.

DEVELOPMENT OF A TOOL TO ASSESS THE DETERMINANTS OF HPV VACCINE HESITANCY IN FRANCE: RESULTS OF A DELPHI STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: This study aimed to develop and undertake a preliminary validation of a French Survey Questionnaire for the Determinants of HPV Vaccine Hesitancy (FSQD-HPVH), using the WHO Strategic Advisory Group of Experts (SAGE) Vaccine Hesitancy Model of Determinants as a framework.
Methods: We undertook an electronic-based Delphi consultation among a panel of Francophone experts in two rounds. Round 1 consisted of the assessment of a structured questionnaire comprising of three parts ((i) Contextual influences, (ii) Individual and group influences, and (iii) Vaccine/vaccination-specific issues), in line with the SAGE model. Items included in this questionnaire were based on a literature review. Definitions of the factors included in the SAGE model were provided in the questionnaire. The panel of experts was asked to score each item using a 3-point Likert scale, in which 1 meant "Essential", 2 "Useful but not essential", and 3 "Not necessary". The panel was also invited to comment on the clarity/comprehension of the questions and to suggest reformulations and additional items. Lawshe's Content Validity Ratio (CVR) was computed to assess the level of consensus for each statement. Only items upon which agreement was not reached in Round 1 (CVR<0.6) and newly proposed items were submitted for evaluation in Round 2, using the same procedure.
Results: Fifteen experts completed Round 1 and 2. Of 83 items evaluated in Round 1, 35 (42%) had a CVR > or = 0.6 and were retained for the final questionnaire. In Round 2, 66 items were submitted to the same panel and consensus was reached for 22 (33%) items. The final FSQD-HPVH version includes 57 items.
Conclusions: In conclusion, 57 items of FSQD-HPVH with good content validity were developed in this study. Adequate assessment of the determinants of HPV VH is the first step towards an evidence-based approach to improving HPV vaccination rates in France.

THE ROLE OF SUPEROXIDE DISMUTASE 2 (SOD2) IN HPV-MEDIATED CARCINOGENESIS

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Persistent infection with high-risk HPV types may alter the balance between the production of oxidant species and the activity of the antioxidant system contributing to cervical carcinogenesis. Superoxide dismutase 2 (SOD2), one of the most important antioxidant enzymes, is responsible for catalyzing the dismutation of superoxide anions radicals in hydrogen peroxide and molecular oxygen. In a previous study of the group, we observed the correlation between increased expression of SOD2 protein and cervical disease severity. However, the role of SOD2 in cervical carcinogenesis is, at present, unknown. In this study, we analyzed the role of SOD2 in the tumorigenic potential of cervical cancer derived cell lines.
Methods: The expression of SOD2 in cervical cancer derived cells lines (HeLa and SiHa) was knocked down using specific shRNAs. These cells were used to perform proliferation, viability, migration, invasion and colony formation assays. Similar experiments are being performed with cells overexpressing SOD2.
Results: We observed that SOD2 silencing was associated with decreased cell proliferation, viability, migration, invasion and colony formation capacity of HPV-transformed cells.
Conclusions: These results shown that SOD2 could be involved HPV-mediated cell transformation. Additionally, the analysis of the present study could contribute to the understanding of SOD2 function in HPV-mediated carcinogenesis.

SCREENING OF PREMALIGNANT CERVICAL LESIONS INDUCED BY HPV: A MOLECULAR AND CYTOLOGICAL COMBINED APPROACH IN THE DOMINICAN REPUBLIC.

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: Cervical Cytology have been a key strategy to reduce late diagnosis of cervical cancer. However, there are limitations to the sensitivity and specificity of this test. Cervical cancer is caused by infection with high-risk human papillomavirus, mainly 16 and 18 (HPV), representing 55-60% and 10-15 %, respectively. HPV RNA detection not only enhanced screening sensitivity to almost 100%, but also made the test very specific. Therefore, current recommendations screening includes the combination of cytology with HPV molecular detection as the most accurate diagnostic tool. Cervical cancer is still a frequent in Latin America and the Caribbean. The objective of this study was to analyse the impact of the use of two diagnostic interventions to access cervical cancer in Dominican women.
Methods: *We retrospectively analysed a 12-month period of patients with prescribed cervical cytology and HPV molecular detection during primary consultation. Samples were collected using Thin Prep® vials, automatically processed,* and examined by the pathology department using the Bethesda system*. DNA molecular detection was also obtained from the same samples statistical analysis was performed using EpiInfo™.*
Results: *A total of 100 samples were included in the analysis. Mean age was 31 years-old (SD:7). HPV detection was positive in 30%, and cytological assessment was 55% (n=55) normal, and the remaining abnormal (44%, n= 44). Correlation of HPV detection and normal cytological results was 48.21% (Fisher Exact Test 0.0000035875). The total abnormal results were 45% negative, 42% ASC-US, and 12% LSIL.Serotype 16 was the most frequent (75%), followed by 18 and 45 (25%).*

Table.1. HPV genotypes and cytology results.

Variable	Results
Age	Median of 31, Q25=28 and Q75=36
HPV	
Positive	30% (HPV 16 75% HPV 18-45 25%)
Negative	70%
Pap	
Normal	55%
Abnormal	44% (58.57 VPH negative)

Conclusions: Combination of HPV detection along with cervical cytology is a good screening strategy. However, in resource limited settings molecular identification is a barrier of access due to cost and technical equipment. Moreover,HPV molecular test cannot replace cytological evaluation, being still cheaper, and easy to perform.

CERVICAL METHANOGENS ASSOCIATED TO HUMAN PAPILLOMA VIRUS INFECTIONS

BASIC RESEARCH / MICROBIOME

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Introduction: The microbiota of the female genital tract has an important role in protecting the body from disease. HPV infection susceptibility is associated to changes in the microbial composition of this area. Dysbiosis may be due to bacterial or fungal infections, nonetheless. there are other members of the human microbiome that may play a role in the susceptibility to infections. We aimed at characterizing the cervical archaeal community by sequencing shotgun metagenomes.
Methods: Women coming for gynecology and colposcopy evaluation at the UPR and San Juan City clinics (San Juan Metropolitan area), and who did not meet several excluding criteria including having taken antibiotics for the last month, were recruited for the study. Selected cervical swab samples from 5 HPV positive and 5 HPV low-risk samples, underwent genomic DNA extractions and sequencing. Library construction and shotgun sequencing was done with the Illumina HiSeq2000 platform (insert size 350 bp; 100 bp of PE reads). Approximately 90% of the contigs had more than 1,000bp and ~10% had sizes ranging from 1,000-5,000bp. We used Shogun to produce taxonomic profiles from shotgun metagenomic reads.
Results: We were able to detect methanogenic archaea in these cervical samples. Archaeal diversity was dominated by *Methanosarcina* with other less dominant taxa such as *Methanolobus, Methanococcus, Natrococcus* and *Methanobrevibacter. Methanosarcina barkeri* and *Methanosarcina vacuolata* were more prevalent in high-risk HPV samples compared to low-risk samples.
Conclusions: Beyond Bacteria and Fungi, Archaea colonize the human cervical microenvironment. The implications of these interactions require further studies. Archaea, although mostly beneficial may in some case be correlated to disease, such as inflammatory bowel disease, or paravertebral abscesses, which may indicate an induction of pro-inflammatory signals that can trigger dysbiosis. We believe Archaeal diversity should be further explored in association to HPV and dysplasia to better develop new approaches to increase cervicovaginal homeostatis and develop better probiotic products.

THE EXPERIENCES AND PERSPECTIVES OF ABORIGINAL AND TORRES STRAIT ISLANDER WOMEN WHO NEVER/RARELY PARTICIPATE IN CERVICAL SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: In Australia, stark differences persist in cervical cancer outcomes for Aboriginal and Torres Strait Islander women, who experience two-fold higher incidence and four-fold higher mortality than other Australian women. Estimates suggest that two-thirds of Aboriginal and Torres Strait Islander women do not participate in cervical screening, despite a national program. We aimed to describe the perceptions of cervical screening among Aboriginal and Torres Strait Islander women who have not participated in cervical cancer screening.
Methods: We conducted semi-structured interviews with 30 Aboriginal and Torres Strait Islander women aged from 25–70 years who had not participated in cervical screening in the past 5 years. Participants were purposively sampled from Primary Health Care Centres from three jurisdictions. Transcripts are being analysed thematically.
Results: Preliminary results showed loss of control and shame caused women to avoid or refuse screening. The experience of screening and a potential diagnosis of cancer evoked fear, shame, embarrassment, feelings of stupidity, and of being violated. These emotions were amplified for women with experiences of trauma. Some women described unwelcome pressure from health professionals/family to screen. For many women, doctor's gender, lack of trust and privacy, and fear of pain were mentioned as obstacles to screening. Some women felt self-collection was a good strategy to overcome barriers to screening, while others noted concerns about doing the self-collection properly. Women suggested strategies to overcome barriers, including group screening days and greater availability of information.
Conclusions: Our findings suggest that cervical screening elicits a range of negative emotions as well as an unwelcome surrendering of control. Overcoming these barriers requires a range of strategies, including explicitly addressing women's fears and negative emotions, providing emotional support and appropriate information, ensuring that clinical care and screening are trauma-informed, and promoting and supporting self-collection to reclaim control.

CYTOLOGIC FINDINGS THROUGH LIQUID BASED IN ANAL CANCER SCREENING AMONG HIV+ AND HIV- MEN WHO HAVE SEX WITH MEN IN THE DOMINICAN REPUBLIC.

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Anal cytology is a cost-effective tool for the early diagnosis of anal cancer and anal intraepithelial lesions induced by HPV infection, especially in high-risk populations as HIV+ and - Men who have Sex with Men (MSM). HIV has been related to the highest prevalence of anal HPV infection and incidence of anal cancer worldwide. Unfortunately, there are no guidelines nor standardized screening for anal cytology at the Dominican Republic' MoH and the region. Moreover, statistics for malignant and premalignant lesions among HIV- MSM are scant or inexistent. The aim of this study was to report cytology findings of anal samples collected from self-identified HIV+ and - MSM through liquid based cytology.
Methods: All self-identified MSM attending primary care units for HIV Care and Pre-Exposure Prophylaxis (PrEP) program were offered an anal swab. Samples were collected using ThinPrep®, stained with PAP and evaluated through the Bethesda system. Data was analyzed by JASP(Version 0.10.2).
Results: A total of 275 samples were collected, HIV+ (n=162), and HIV- on PrEP (n=113). Mean age was 30 years old (SD: ±10). Abnormal results We found a total of 52 Low-grade squamous intraepithelial lesion (LSIL), In HIV +, found 6 Atypical squamous cells of undetermined significance (ASC-US) and 6 in PrEP. Only among the HIV+ group, 2 cases reported High-grade squamous intraepithelial lesion (HSIL).

Table 1. Group comparison among HIV+ and HIV- cytological findings

		HIV Serostatus					
Cytologic Results		**HIV+**		**HIV-**		**Total**	
Normal		106		103		209	
Abnormal		56		10		66	
Total		**162**		**113**		**275**	
X^2 12.659 p< .001							

Conclusions: HPV-induced premalignant lesions are not limited to people living with HIV/AIDS. However, it is among HIV+ MSM were we found the majority of published data on HPV and HSIL. In contrast, we found similar findings in HIV- in LSIL, this latter reinforce the importance of anal screening and HPV detection as an integrated approach. In primary care setting where the test might be available.

PERSPECTIVES OF ABORIGINAL AND TORRES STRAIT ISLANDER WOMEN WHO PARTICIPATE IN CERVICAL SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: In Australia, Aboriginal and Torres Strait Islander women experience a higher burden of cervical cancer than other Australian women. Cervical cancer is largely preventable through cervical screening, but many Aboriginal and Torres Strait Islander women do not screen. However, approximately one third of Aboriginal and Torres Strait Islander women do participate in cervical screening and screen regularly but the factors involved in commencing and continuing to screen remain less known. We aimed to describe Aboriginal and Torres Strait Islander women's experiences of and views about participation in cervical screening.
Methods: We conducted semi-structured yarns with 50 Aboriginal and Torres Strait Islander women aged 25 – 70 years who had completed cervical screening in the past 5 years, purposively sampled via Primary Health Care Centres (PHCCs) from three jurisdictions. All interviews were conducted by an Aboriginal or Torres Strait Islander woman.
Results: Two authors conducted iterative thematic analysis using a grounded theory approach. Major themes included women's desire for control over their health, including the responsibility to be healthy for themselves and their families, importance of passing on knowledge, and overcoming emotional obstacles to screening; knowledge about cancer and cervical screening; access to appropriate services; and impact of past experiences, including having children and early experiences of cervical screening, on screening attitudes.
Conclusions: This study centred the views and experiences of Aboriginal and Torres Strait Islander women. Through this approach, the findings offer insights into factors that support Aboriginal and Torres Strait Islander women to take part in screening and highlight ways in which women feel empowered and in control of their health through participation in the cervical screening program. Understanding these factors will ensure screening services continue to support women to screen regularly and may inform strategies to better facilitate under or never screened women to start screening and increase screening rates overall

CANCER BURDEN ATTRIBUTABLE TO HPV INFECTION BY CANCER SITE, SEX, GEOGRAPHICAL AREA AND AGE IN CHINA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: HPV causes cervical cancer plus a fraction of other anogenital and head and neck cancers. Understanding HPV-attributable cancer burden at a population level is essential to evaluate the potential benefit of existing HPV vaccines, and to inform cancer control policy. HPV-attributable cancer burden is currently unknown in China.
Methods: We extracted data of cancer incidence and mortality in 2014 from Chinese cancer registry annual report and of national population from National Bureau of Statistics. Cancer burden was estimated by incorporating cancer rates and population forecasts by site, sex, geographical area and age, and then combined to corresponding population attributable fractions (PAFs).
Results: The results indicated that an estimated 110,894 HPV-attributable new cancer cases occurred in China in 2018, including 99,253 cervical cancer (89.5%), 4,449 non-cervical cancers in females (4.0%) and 7,192 cancers (6.5%) in males, with penile cancer being the most common incident cancer in males. The age-standardized incidence of HPV-attributable cancers in China was 5.69 per 100,000 persons, being slightly higher in rural (5.94) than urban (5.52) areas. More than half of cervical cancer cases occurred within the age group 40-54. 76% of non-cervical cancers occurred in females aged 45-79, while 42% of cancers among males were diagnosed at age 55–69 years. 35,683 HPV-attributable cancer deaths were estimated, including 29,683 due to cervical cancer (83.2%), 2,307 (6.5%) and 3,693 (10.3%) due to non-cervical cancer in females and males respectively.
Conclusions: The cancer burden attributable to HPV in China is substantial. HPV vaccination and cervical screening should be prioritized.

ANAL HPV INFECTION DIAGNOSIS IN SPECIALIZED SERVICE: GENDER DIVERSITY AMBULATORY IN VITÓRIA, BRAZIL

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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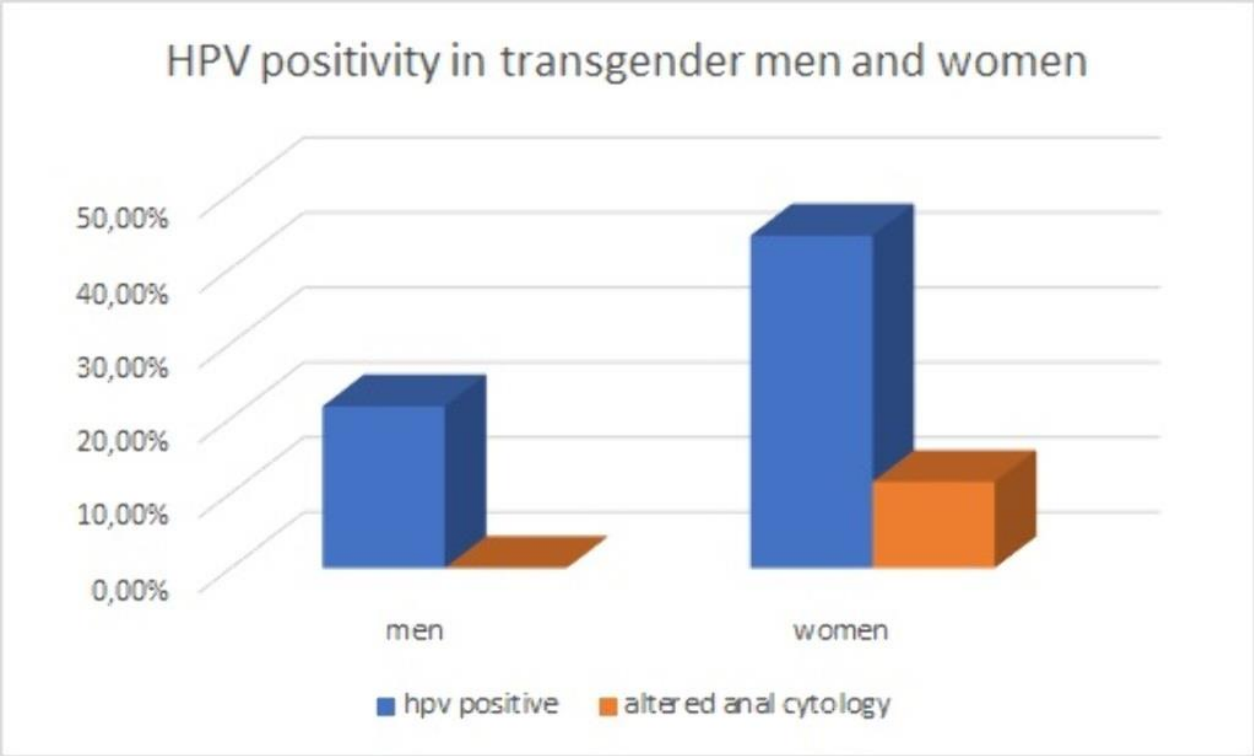
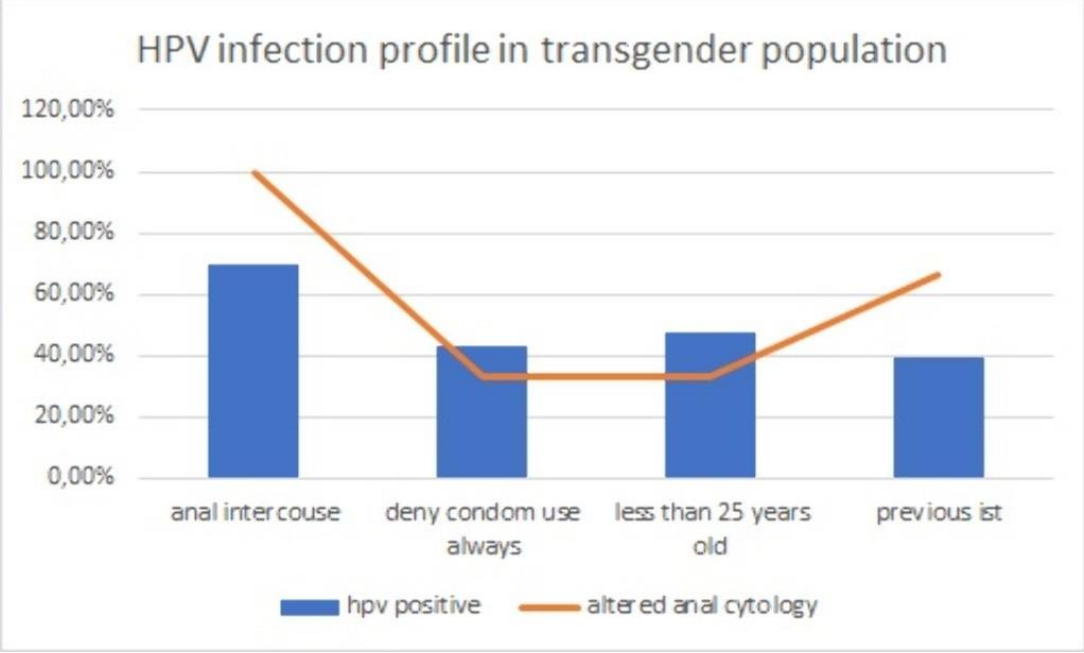
Introduction: Transgender individuals define their gender identity and express their gender in a variety of ways. The term gender identity refers to their own experience of being different from the term sexual orientation. HPV infections are mainly transmitted through sexual contact and may be associated with biological, social, and cultural parameters and are responsible for the onset of anal cancer.
Methods: Cross-sectional study on HPV infection in the anal region diagnosed with PCR in outpatients of gender diversity, university hospital, in Vitoria, Brazil, from August/2018 to September/2019, based on information collected from attendance cards and medical records, and through a previously structured questionnaire. A database was prepared using the statistical program SPSS – data entry (Statistical Package for the Social Sciences) 20.0.
Results: The medical records of 83 users treated at the outpatient clinic were analyzed. The average age was 27 years old, 51.8% are under 25 years old. There was a higher prevalence of brown (43.4%), only 19.3% self-declared black. Transgender men represented 62.7% of users and had a higher level of education compared to transgender women, with 75% having completed high school, and 13,5% have completed higher education. Positivity for anal HPV was found in 21,6% of transgender men, and 44.4% of transgender women, of this 11.5 % had a low-grade intraepithelial lesion on anal cytology. Of the patients with anal HPV positivity, 30.4% denied anal intercourse, and only 39.1% always reported condom use. Only transgender women were HIV positive (4.8%).





Conclusions: The study shows an increased prevalence of anal HPV infection in this population, mostly in transgender women, demonstrating vulnerability and the reflection of this infection on the health of these users. Specialized services that act to ensure the prevention, guidance and monitoring of these patients equitably and integrally are very important to prevent HPV infection and anal cancer.

RAPID E6/E7 MRNA QUANTITATIVE DETECTION OF HIGH-RISK HPV INFECTION BASED ON FLOWCYTOMETRY

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Persistent infection with high-risk human papillomavirus (HR-HPV) is the necessary cause of cervical carcinoma. HPV DNA testing is used for primary screening and co-testing. A primary focus to identify HPV infection at stage of integration of HPV viral genome to cervical epithelial cell. The activity of E6/E7 mRNA needs to be quantified within infected cervical epithelial cell.
Methods: Women presenting with intermenstrual bleeding, postcoital bleeding, prolonged vaginal discharge or an unhealthy cervix underwent VIA and collection of cervical samples in ThinPrep® PreservCyt® Solution (Hologic MA, USA) for HR-HPV DNA testing (HC2, Qiagen), cytology HPV mRNA (HPV OncoTect 3Dx (IncellDx, CA, USA), colposcopy and biopsy.
Results: 302 women underwent screening. Lesions detected were: CIN1 (n=39), CIN2 (n=3), CIN3 (n=3) and invasive cancer (n=3). VIA and HC2 showed the best sensitivity. HPV OncoTect 3Dx test standardization was done. Samples were hybridized with oligonucleotide probes for E6/E7 mRNA and counterstained with a nuclear dye for cell cycle analysis. Cells were analyzed on a CytoFLEX (Beckman Coulter, Inc. CA). Ectocervical cells were differentiated from endocervical cells, inflammatory cells and debris using forward and side light scatter properties, depending on the size of cell and cytoplasmic complexity. It quantitatively detected both E6/E7 mRNA overexpression and cell proliferation in intact cervical cells
Conclusions: E6/E7 mRNA detection allows identification of a transcriptionally active virus genome. A larger study is needed for standardisation of the morphological cut-off to differentiate between transient and persistent HPV infections, recognize high-grade CIN and establish its role in the screening strategy

HIGH-RISK AND LOW-RISK HPV TYPES INDUCE DIFFERENT LESIONS IN THE CERVICO-VAGINA OF THE PATIENTS WITH VULVAR AND ANAL CONDYLOMA ACUMINATUM

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF GENITAL AND SKIN WARTS

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Introduction: It is reported that not only HPV-6 or HPV-11 but also some high-risk HPV types are identified in samples of condyloma acuminatum. We have often detected high-risk HPV types in the cervix of the patients with vulvar condyloma. We try to determine HPV types in various lesions of the cervico-vagina in order to discriminate responsible HPV type for condyloma and other lesions including squamous intraepithelial lesions (SILs).
Methods: Cervico-vaginal cell samples were obtained from the women with vulvar condyloma acuminatum and vaginal/cervical papillary lesion (may be condyloma) as a liquid-based cytology samples to identify the HPV type by Genosearch-31. The cases with multiple HPV infections have been analyzed by microdissection of each lesion. HPV type was determined with uniplex E6/E7 PCR method, which is able to detect 39 HPV types.
Results: The mean age of the patients with condyloma acuminatum of the vulva was 26.1 years and with vaginal/cervical papilloma (condyloma) was 33.4 years, suggesting cervicovaginal lesions are due to persistent infection. Eighty-nine % of vulvo-anal condyloma acuminatum were positive with HPV-6, and 11% were positive with HPV-11. Among such condyloma patients, 34% had the vaginal/cervical papillary lesions, and 53% had SIL. Almost all vaginal/cervical papillary lesions were positive with HPV-6 or -11. Sixty-five % of the patients with cervico-vaginal papilloma had multiple HPV infections including high-risk HPV types. High-risk HPV types were only identified in aceto-white flat lesions (SILs) which were composed with abnormal squamous epithelium as seen in typical CIN or VAIN. In contrast, low-risk HPV types like HPV-42, 44, 62, 71, 81, 89, and 90 induced aceto-white lesions similar to the SIL, but it was composed with normal squamous cells sometimes with small spikes.
Conclusions: Cervico-vagina of condyloma patients appears to be a reservoir for many high-risk and low-risk HPV types. Only high-risk HPV types induce the SILs (CIN, VAIN).

MICROINVASIVE CERVICAL CARCINOMA IN A WOMAN WITH FERTILITY DESIRE: CONSERVATIVE TREATMENT

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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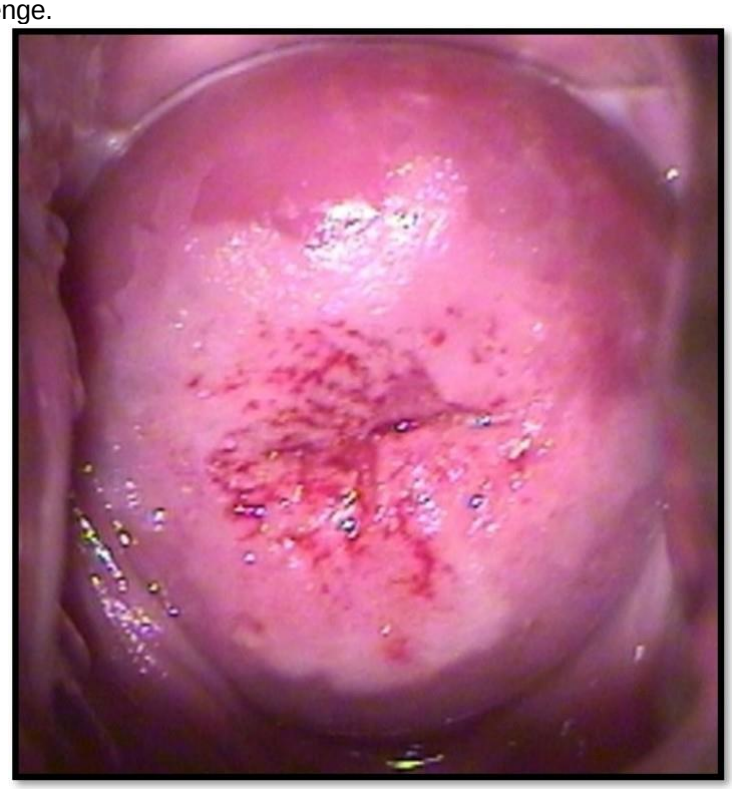
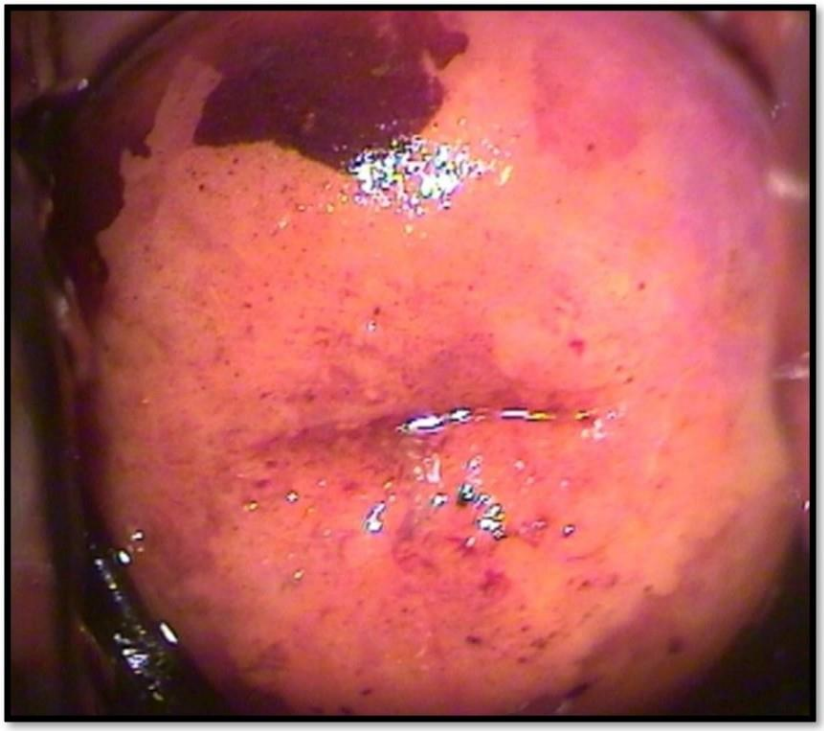
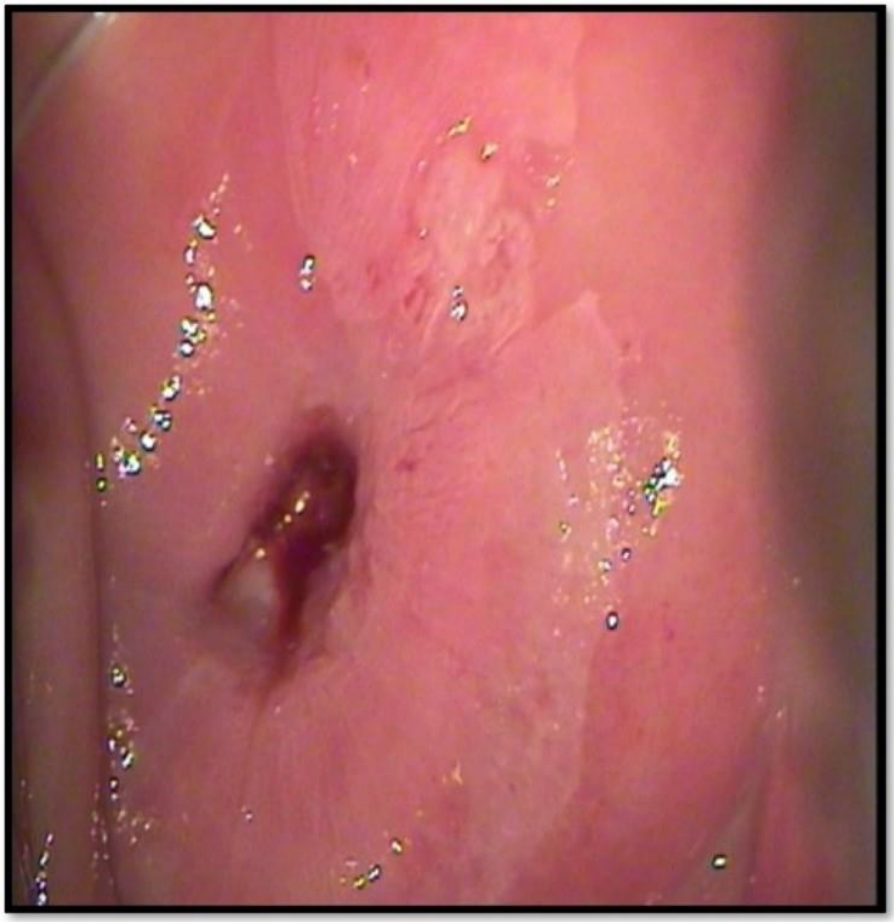
Introduction: Cervical carcinoma is the most common malignancy associated with pregnancy. FIGO stage IA1 microinvasive squamous cell carcinoma is usually diagnosed after conization, when maximum depth of 3 mm of invasion and maximum horizontal spread of 7 mm is observed. A treatment with radical surgery was proposed decades ago, however when pregnancy is desired, optimal less invasive treatment is a challenge.



Methods: The case of 33-year-old nulliparous woman referred to Lower Genital Tract Pathology Unit of the Mother-and-Child University Hospital Complex of the Canary Islands with diagnosis of high grade squamous intraepithelial lesion (HSIL) and positive for HPV 16 and others high risk HPV types. A conization was performed and the pathohistological diagnosis was well differentiated squamous cell carcinoma with stromal invasion of 1 mm in depth and positive canal and resection margins. No signs of cancer spreading were present (FIGO



IA1).



Results: The first control postconization at 6 months, was low-grade SIL and positive for HPV 16 and others HPV with p16-expression. Five months later, a new test was performed obtaining a negative PAP smear and biopsy but nevertheless persistent HPV-16 infection. The patient became pregnant from assisted reproduction techniques and delivered a newborn weighing 3450 g at 40+2 weeks. The follow-up continued in the unit until 2019 when the results of a PAP smears was still negative but HPV-16 infection persisted, then a second conization was indicated. Histological evaluation of the conization specimen showed CIN 3 and negative endocervical canal and margins.

Conclusions: More conservative surgical approaches (conization) to early stages in cervical cancer for young women have been suggested as an appropriated management. Fertility-conserving surgery is safe for nulliparous young women with stage IA1 cervical carcinoma.

CHARACTERIZATION OF HPV TYPES IN ACTINIC KERATOSIS AND IN THE CORRESPONDING HEALTHY SKIN SAMPLES BY NEXT-GENERATION SEQUENCING

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: Cutaneous squamous cell carcinoma (cSCC) arises from malignant progression of the precursor lesion, actinic keratosis (AK), which develops on photo-damaged skin. Ultraviolet (UV) radiation exposure is the main risk factor in the development of AK and cSCC. Many findings also support the involvement of β human papillomaviruses (HPVs) in AK and cSCC development, while very little is known on γ HPV types. The objective of this study was to have global view on the PV type distribution in AK and healthy skin (HS) samples using different PCR protocols combined with next-generation sequencing assay.
Methods: We evaluated the presence of HPV types in AK (n=244) and in the corresponding HS (n=242) samples from immunocompetent individual. PCR amplifications were performed using two different set of primers (FAP59/64 and FAPM1). Purified amplicons were pooled and sequenced using the NGS platform MiSeq Illumina and subsequently analyzed following a specific bioinformatics workflow.
Results: The NGS analysis revealed the presence of a large number of known β and γ HPV types. Regarding γ types, reads for the different species were in some cases higher in AK versus HS (e.g. γ-1, γ-3, γ-7, γ-8, γ-9, γ-11, γ-15, γ-17). Interestingly, γ-1 HPV types appear to be more enriched in AK than in HS. The majority of γ-1 reads corresponded to HPV4. In addition, 27 putative novel β, 16 γ and 4 unclassified PVs were also isolated.
Conclusions: This study describes the distribution of large number of PV types in HS and AK of the same individuals. It also allowed the detection of putative novel PVs. The evidence that species γ-1 HPV types (e.g., HPV4) appear to be enriched in AK in comparison to HS deserves further biological and epidemiological studies to evaluate their role in skin (pre)cancerous lesions, and deserve further *in vivo* and *in vitro* studies.

EVALUATION OF DRY BRUSH SPECIMEN TRANSPORT VS. A LIQUID TRANSPORT MEDIA FOR HPV TESTING WITH THE NEWLY VALIDATED AMPFIRE HR-HPV ASSAY.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Sensitive, molecular high-risk HPV (HR-HPV) tests for early detection of cervical precancerous lesions are now in wide-spread use in many high-income countries. However, screening and prevention programs in low- and middle-income countries (LMICs) suffer from major cost and infrastructure constraints, poor participation, loss to follow-up, and concerns about sustainability. If an accurate, inexpensive, and simple technology of HR-HPV testing can be used with self collected vaginal samples, screening and prevention programs in LMICs may be greatly improved. **Objective:** To demonstrate transporting a dry brush vaginal sample is an accurate transport method to detect HR-HPV.
Methods: 500 women are currently being recruited between the ages of 30-55 from outpatient and colposcopy clinic. Three samples are being collected by doctor from each patient. The first sample was "pseudo self –collected sample" from the vagina before placing vaginal speculum. The brush was placed in an empty collection bottle. Two other brush samples were obtained directly from the endocervix after placement of speculum. One brush was placed into an empty collection bottle and the other placed in 2ml liquid Ampfire transport media. All samples are being analyzed by Ampfire HR-HPV assay which has the ability to accept raw sample. McNemar Chi-square statistic was used for analysis.
Results: The first 197 patient samples have been analyzed. Percent HPV positives for vaginal dry, cervix dry, and cervix liquid, were 44.7%, 47.2%, 43% respectively. There was no significant difference in detection rate for HR-HPV of the dry vaginal sample compared to the direct endocervical liquid sample (P=0.664), or the direct dry brush sample (P=0.302).
Conclusions: The full data set will be reported. However, if the above trend continues the dry brush transport could markedly simplify and reduce costs for specimen transport. Used with self-collected vaginal samples, it may become an important addition to population based cervical cancer screening programs.

HE TAPU TE WHARE TANGATA (THE SACRED HOUSE OF HUMANITY): EXPLORATION OF THE CERVICAL SCREENING CLINICAL PATHWAY FOLLOWING OFFER OF HPV SELF-TEST

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Māori (Indigenous New Zealand) women experience inequities in cervical cancer morbidity and mortality. Human Papilloma Virus (HPV) causes the majority of cervical cancers and new technology means women can self-test for HPV using a vaginal swab. As part of a community RCT in rural New Zealand looking at the offer of a self-taken HPV swab for under-screened (no screen in 4+ years) Māori women, we are undertaking a qualitative sub-study to explore the journeys of these women. This study is ongoing with data collection finishing mid-2020.
Methods: A qualitative Kaupapa Māori (by Māori, for Māori) methodology is applied. Participants are interviewed by a female Māori researcher, who is experienced in appropriate rituals of encounter. Three groups of women are interviewed: swab declined, swab accepted negative result, and swab accepted positive hrHPV result with referral to colposcopy. Data are analysed using thematic analysis.
Results: Preliminary analysis (interviews with 20 participants) indicates several key themes. Women who declined were steeped in their beliefs that interventions are dangerous and were often scared of receiving a positive result. Women who accepted the swab all reported positive feedback citing privacy, quickness/ease, and convenience of the test. These women said that they will be more likely to re-screen using a self-test and encourage their female family members to screen too. Women referred to colposcopy were often scared and confused, and reported that they had been told their HPV result in an insensitive manner.
Conclusions: The lived realities for these women varied with the HPV self-test being accepted and valued as an option for screening by most. However, there is urgent need to upskill clinicians in their knowledge of HPV and the cervical screening pathway, and to implement a national public health campaign. This study has translational implications for upcoming changes to the New Zealand National Cervical Screening Programme.

BASELINE DETECTION OF EPSTEIN-BARR VIRUS AND HPV IN ANAL SECRETIONS PREDICTS FUTURE HPV PERSISTENCE AND ANAL DYSPLASIA

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: In a number of recent studies, detection of Epstein-Barr virus (EBV) in anal or cervical secretions along with high-risk HPV (hr-HPV) predicts concurrent anal or cervical dysplasia in HIV+ individuals. To further examine the role of EBV in dysplasia, HIV+ men and women were followed prospectively. The goal of this study is to examine the future development of HPV-related lesions and HPV persistence in those with detectable anal EBV.
Methods: Participants were men and women with stable HIV infection (mean CD4 T-cell count, 523 cells/ml; median HIV viral load, 39 copies/ml) who completed a sociodemographic survey and provided anal swabs for cytology, HPV and Epstein-Barr virus (EBV) testing. Anal biopsies were taken if clinically indicated. These individuals were followed at 6-month intervals for an average of 2 years.
Results: The population (n=188) was 88% male, 54% black, with a mean age of 49.1 years. High risk HPV (hrHPV) was detected in 68%, and EBV in 29%. Persistent high-risk HPV was seen in 32%, 48% had dysplastic anal Pap smear and 15% had high-grade anal biopsies. Those individuals who were shedding EBV were more likely to have high-risk HPV persistence (p=.04), a dysplastic Pap smear (p=.03), and an abnormal anal biopsy. There was no association with development of a high-grade anal biopsy.
Conclusions: High rates of hr-HPV infection and anal dysplasia were found in this HIV infected population. The presence of EBV in anal samples may assist in determining those with persistent hr-HPV infection and the development of a dysplastic anal Pap smear. Ongoing studies are investigating the role of EBV in the pathogenesis of dysplasia, particularly in view of the lack of association with high grade lesions.

HPV INFECTION AND CITOLOGY DIAGNOSIS USING A SELF-SAMPLING METHODOLOGY IN STUDENTS OF UNIVERSITY OF NORTHERN PORTUGAL REGION

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide. Our goal was to test self-sampling methodology to characterize the prevalence of High-Risk HPV genotypes and correspondent cytological diagnosis in university students from the North-East region of Portugal.
Methods: A total of 81 university students were given self-sampling systems for cervical-vaginal samples collection. High-Risk HPV genotyping was performed using the Anyplex™ II HPV HR Detection (Seegene®). A smear of the sample was then done using Hologic equipment and the diagnosis was made by a Senior Cytoscrenner using the Bethesda System of classification.
Results: The median age of women was 21.0 years and mean age of first sexual intercourse was 17±1.9 years.High-Risk HPVs were detected in 31 women (38.3%), with single and multiple infections to be responsible for 16.0% and 22.3%, respectively. HPV-68 (9.9%) was the most frequent genotype, followed by HPV-31, -51, -58, -59 and -66. We also observed that three women had HPV-16 and one HPV-18. We observed that women reporting more than two lifetime sexual partners, first sexual intercourse under 17 years old, non-Portuguese nationality (mainly African origin) and non-vaccinated status were associated with higher prevalence of High-Risk HPVs (p=0.001, p= 0.014, p=0.005 and p=0.016, respectively). Within the HPV positive samples, we found 12 ASC-US, 6 NILM and 3 LSIL. In these samples we found HPV 9-valent vaccine genotypes in 9, 1 and 2 cases, respectively.
Conclusions: Our study revealed that 1) self-collecting samples are useful for the detection of High-Risk HPVs and for the cytological diagnosis; 2) the prevalence of High-Risk HPV infection in university students of North-East region of Portugal is high, particularly in those with over 21 years of age of non-Portuguese nationality.These results highlight the importance of continuing to develop prevention strategies and that self-collected samples may be a useful sample in the context of HPV-detection.

SEROLOGY 36 MONTHS AFTER VACCINATION WITH A MIXED FORMULATION TWO-DOSE SCHEDULE OF NONAVALENT AND BIVALENT HUMAN PAPILLOMAVIRUS (HPV) VACCINE

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Several clinical trials have shown that HPV vaccine dosing schedules that use different HPV vaccine formulations are safe. The mixed schedules induce seropositivity for HPV types included in the vaccines, however, no data are available regarding antibody persistence. Here we present the results at 36 months follow-up of subjects participating in a clinical trial with one dose of nonavalent (9vHPV) and one dose of bivalent vaccine (2vHPV) administered 6 months apart (NCT02567955).
Methods: Of the 172 boys and girls enrolled (9-11 years-old), 169 (98.3%) were tested at month 7 and 36 of the study. The sera were tested with a 9-plex VLP-based IgG ELISA (M9ELISA).
Results: At month 7, 99.4-100% of subjects were positive for all 9 HPV types included in 9vHPV. Seropositivity remained high at month 36 but varied by HPV type (range 92.4% to 100%). All subjects were seropositive for HPV types 16 and 52, and all but one (99.4%) for HPV 6, 11 and 18. The seropositivity for HPV31, 33, 45 and 58 was 96.4%, 95.9%, 92.3% and 98.2%, respectively. Between month 7 and 36 GMTs decreased 1.4-19-fold, depending on HPV type. The decrease in GMTs was greatest for HPV16 and 18 (14-19-fold), followed by HPV31, 33, 45, 52 and 58 (2.4-8.4-fold). The decrease was smallest for HPV6 and 11 (1.4-1.7-fold).
Conclusions: The results show persistence for at least 36 months of antibodies to HPV types included in the 9vHPV vaccine in nearly all subjects vaccinated with a dose of 9vHPV and a dose of 2vHPV. In the absence of a protective post-vaccination antibody threshold, the clinical significance of different antibody titers and their decrease with time since vaccination remain unknown.

TAP1/2 GEN POLYMORPHISMS ARE ASSOCIATED IN THE OUTCOME OF RECURRENT RESPIRATORY PAPILOMATOSIS IN POPULATION OF THE WEST OF MEXICO

CLINICAL RESEARCH /RECURRENT RESPIRATORY PAPILLOMATOSIS

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Introduction: Recurrent respiratory papillomatosis (RRP) is a chronic disease associated with human papilloma virus (HPV) and characterized by exophytic lesions in the respiratory tract. Effective T-cell-mediated clearance of HPV-infected cells may be defective in patients with RRP, leading to recurrent disease. This work describes the principal HPV genotypes, the viral load, and the presence of SNPs in the transporter associated with antigen presentation (TAP1/2) via the major histocompatibility complex (MHC) class I in population from the west of Mexico.
Methods: Patients from a public hospital with RRP. Analysis of severity according Derkay scale, screening by PCR using primers MY09/MY11, L1C1/L1C2 and GP5/GP6 then HPV genotyping and the measurement of viral load with Aniplex II kit from Seegene. SNPs was performance employing Applied Byosistems TaqMan probes.
Results: Samples were collected from 55 patients from 2014 to 2018; with an age range 2-73 years. Regarding the HPV were found HPV6, 11, 31, 56, and 58; HPV6 & 11 were the most common genotypes. 15 patients presented co-infections. In terms of severity, a range of 1-56 surgical interventions, with average of 10.1 per patient. SNPs TAP1/2 were associated with increased risk of RRP. The OR for TAP1 SNP was 3 in average, while for TAP2 was more signficatively, some SNP, reaching 6 in average.
Conclusions: SNPs TAP 1/2 are factors of risk associated with RRP. There is significant correlation between the severity of the disease with TAP 2 mainly.

COMPREHENSIVE EVALUATION OF THE ANTIGENIC IMPACT OF INTRA-GENOTYPIC VARIANT DIVERSITY ON RECOGNITION BY NEUTRALIZING MONOCLONAL ANTIBODIES RAISED AGAINST LINEAGE A L1 VIRUS LIKE PARTICLES

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Naturally-occurring variants of Human papillomavirus (HPV) genotypes have been defined as lineages and sub-lineages, but little is known about the impact of this diversity on protein function. We have previously demonstrated that variation within the major (L1) and minor (L2) capsid proteins impact the susceptibility of HPV to serum antibodies elicited by vaccination and natural infection. Higher resolution mapping of variant residues, however, requires the availability of appropriate tools, such as type-specific monoclonal antibodies (MAbs). These empirical data will improve our understanding of the consequences of natural variation on capsid antigenicity.
Methods: We investigated the susceptibility of 37 representative pseudovirus variants of HPV16, HPV18, HPV31, HPV33, HPV45, HPV52 and HPV58 to neutralization by type-specific murine MAbs raised against the A lineage of their respective genotypes. Homology models derived from available HPV L1 crystal structures were generated to permit mapping of variant residues onto the surface-exposed L1 protein for relevant variants.
Results: Type-specific lineage A-specific MAbs demonstrated differential reactivity against some, but not all, variants within its respective genotype. Some of these differences were minor (<4 fold) while some variants displayed orders of magnitude reduced sensitivity. These differences in antigenicity were mapped to a limited number of variant residues on the capsid surface.
Conclusions: These data contribute to our understanding of HPV L1 variant antigenicity and may have implications for seroprevalence or vaccine immunity studies based upon L1 antigens.

SERUM CONCENTRATIONS OF EMERGING VITAMIN D BIOMARKERS AND DETECTION OF PREVALENT HIGH-RISK HPV INFECTION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Vitamin D has potential immunomodulating benefits in infection. One prior population-based cross-sectional study showed a protective association between serum concentrations of 25(OH)D and high-risk human papillomavirus (hrHPV) detection. Additional biomarkers relevant to different aspects of the vitamin D metabolic pathway may more completely characterize vitamin D status, but have not been evaluated in relation to hrHPV infection.
Methods: Stored sera from women aged 30-50 years (N=404) enrolled into an HPV natural history study from 2011-2012 in Seattle, Washington were tested for 25(OH)D and 4 novel vitamin D biomarkers: 1,25(OH)D, 24,24(OH)D, free vitamin D, and vitamin D binding protein. 25(OH)D was modeled as both a continuous and categorical measure (sufficiency cut-points: ≥20ng/mL or ≥30ng/mL). Other vitamin D biomarkers were modeled as continuous variables. Cross-sectional associations between vitamin D serum concentrations and cervicovaginal hrHPV detection were estimated using logistic regression models. Analyses were adjusted for age, race, season, education, oral contraceptive use, smoking status, body mass index, and serum concentrations of calcium and phosphate. Post hoc analyses examined the association between likely vitamin D supplementation (25(OH)D ≥50ng/mL) and hrHPV.
Results: 25(OH)D serum concentrations were not significantly associated with hrHPV when modeled as either a continuous (adjusted odds ratio [aOR] per 1ng/mL increase=1.01,95%CI:0.98-1.03) or categorical (aOR for ≥20ng/mL cut-off=0.82,95%CI:0.36-1.87; aOR for ≥30ng/mL=0.83,95%CI:0.49-1.42) variable. Each 1ng/mL increase in 24,25(OH)D was borderline statistically significantly associated with higher likelihood of hrHPV detection (aOR=1.20,95%CI:0.95-1.51). No significant associations were observed for other biomarkers. Women with serum concentrations of 25(OH)D ≥50ng/mL had a higher likelihood of prevalent hrHPV compared to women with levels <50ng/mL (aOR=2.53,95%CI:1.01-6.34).
Conclusions: 25(OH)D serum concentrations were unassociated with hrHPV detection. Higher levels of one novel biomarker, 24,25(OH)D, were positively associated with hrHPV, an unexpected finding. Post hoc analyses warrant further exploration into the relationship between vitamin D supplementation and hrHPV infection.

CERVICAL PRE-CANCER VS INVASIVE CANCER: MOLECULAR DIFFERENTIATION HAS POTENTIAL FOR IMPROVING CERVICAL CANCER SCREENING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Persistent infection with high-risk human papillomavirus (hr-HPV) is an important co-factor in cervical cancer development and is associated with DNA methylation on both human and viral genes. The S5 DNA-methylation classifier, based on target CpG sites of the human gene *EPB41L3*, and viral late gene regions of HPV-16,18,31 and 33 has demonstrated better performance for detection of cervical intraepithelial neoplasia grade 2/3 (CIN2/3) women than either HPV16/18 genotyping, cytology or combination. We tested the performance of S5 in detecting invasive cancers versus pre-cancers and quantified the degree of separation between normal, CIN3 and invasive cancer S5 scores.
Methods: Methylation status of the S5 selected CpG sites was tested in DNA extracted from exfoliated cervical cells from the UK (n=138), Spain (n=100), Colombia (n=96), Philippines (n=50), Georgia (n=42), Ethiopia (n=79), India (n=60), South Africa (49), Bhutan (n=60) and USA – New Mexico (n=200). Samples were histologically defined as normal (healthy patients), CIN3 and invasive cancer. DNA bisulfite conversion was carried out and followed by pyrosequencing for the 6 components of the classifier.
Results: Methylation at all sites increased proportionally with disease severity (Cuzick trend of z=9.2933, p,0.0001). The separation of normal from CIN3 and from invasive cancer was highly significant (Mann Whitney tests, all p<0.0001). ROC curves were used to assess the diagnostic potential of S5 in differentiating CIN3 and cancers from normal patients. The AUC was 0.94 (CI 95%: 0.92 to 0.96, p<0.0001) with a sensitivity of 93% and a specificity of 75%, based on a cut-off at highest Youden J-index. We found a strong correlation between S5 scores and disease lesion r = 0.64 (95% CI 0.59 - 0.68, p<0.0001).
Conclusions: The S5 methylation classifier may be useful in cervical screening programs for differentiating normal and pre-cancers from invasive cervical cancers in women across different countries..

MICROBIOTA ASSOCIATION WITH ANAL PRECANCEROUS LESIONS IN MEN WHO HAVE SEX WITH MEN (MSM) LIVING WITH HIV

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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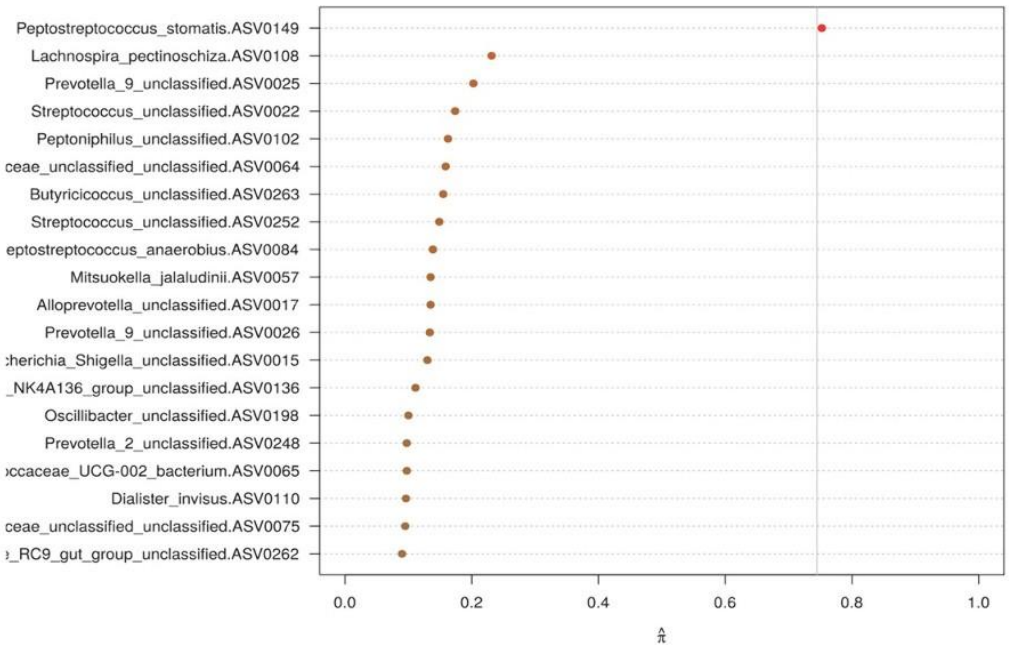
Introduction: Persons living with HIV are at a 30-fold increased lifetime risk of anal cancer in the US. Current treatment methods for pre-malignant anal lesions are not sufficient due to the high likelihood of recurrence. We need to explore other biomarkers associated with the detection of those lesions and lesion progression.
Methods: MSM living with HIV undergoing high resolution anoscopy (HRA) were enrolled in the ALTO Study at the Vanderbilt Comprehensive Care Clinic. Participants completed a detailed questionnaire assessing sexual history, anal douching and antibiotic usage. Prior to anal cytology and the HRA exam, a fecal specimen was collected from the anal canal and placed onto a fecal occult blood test card. The outcome of interest based on anal cytology was negative (negative and ASCUS combined) or positive (LSIL and HSIL combined) for lesions. DNA was extracted from the FOBT cards and 16S rRNA deep sequencing was used to characterize the stool microbiome.
Results: The most abundant genus overall was *Prevotella*, which on average represented 28% of the reads per sample; all other genera were at <10% relative abundance. Microbiome alpha-diversity increased with increasing frequency of anal douching, but anal douching did not correlate with any other microbiome associations. One amplicon sequence variant (ASV), identified as *Peptostreptococcus stomatis*, was highly ranked with the stability selection test when anal lesions were set as the outcome variable (selection probability 0.75, above the probability cutoff of 0.745 based on a per family error rate of 0.0499), suggesting it was the most predictive ASV of whether the patients had no lesions or abnormal lesions (Figure). This *P. stomatis* ASV was more abundant in patients with abnormal lesions.
Conclusions: *Peptostreptococcus stomatis* was more abundant in patients with abnormal lesions. While *Peptostreptococcus* is often a commensal organism, it can become pathogenic in immunosuppressed patients.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CERVICAL SCREENING WITH LIQUID BASED CITOLOGY AND HPV DETECTION AND GENOTYPING IN SOLID ORGAN TRANSPLANT WOMEN IN SAO PAULO, BRAZIL

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Solid organ transplant individuals have high risk of HPV persistent infection and HPV-related cancers due to life-long immunosuppressive therapy. This study aimed to evaluate the prevalence of HPV infection and precancerous cells changes in solid-organ transplant women using immunosuppressive drugs in comparison to healthy women.
Methods: This is a cross sectional study that enrolled solid organ (kidney, liver, lung and heart) transplant women aged 18 to 45 years, who were transplanted more than 6 months before, and have started their sexual life. A comparison group constituted of healthy women of the same age was also included. Cervical samples were collected by cervicovaginal smear and put in preservative fluid – BD SurePath™ for oncotic colpocytology and HPV detection. Cytological results were classified according to the Bethesda 2016 system terminology. HPV detection and genotyping was performed using a microarray-based test kit (PapilloCheck®) that allow simultaneous detection and identification of 24 HPV types, including 18 high-risk and 6 low-risk types.
Results: Among the solid organ transplant women (n=110): 82 (74.5%) were negative for intraepithelial lesion or malignancy, 11 (10.0%) had atypical squamous cells, 12 (10.1%) had low-grade squamous intraepithelial lesion (LSIL) and 5 (4.5%) had high-grade squamous intraepithelial lesion (HSIL). Among healthy women (n=126): 104 (82.5%) were negative for intraepithelial lesion or malignancy, 20 (15.9%) had atypical squamous cells, 1 (0.8%) had LSIL, 1 (0.8%) had HSIL. Pre-cancerous cell changes were significantly more frequent in transplant recipients (p=0.0001). HPV were detected in 18 of 69 (26.1%) transplant women and in 17 of 84 (20.2%) healthy women. Among transplant women, 4/18 and 10/18 had HPV types included in HPV4 and HPV9 vaccines, respectively, whereas among healthy women these number were 2/17 and 4/17, respectively.
Conclusions: Pre-cancerous cell changes were significantly more frequent in transplant recipients as compared to healthy women of the same age.

PD-1 BLOCKADE SYNERGIZES WITH INTRATUMORAL VACCINATION OF A THERAPEUTIC HPV PROTEIN VACCINE AND ELICITS REGRESSION OF TUMOR IN A PRECLINICAL MODEL

BASIC RESEARCH / IMMUNOLOGY

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Introduction: HPV viral oncoproteins E6 and E7 are ideal targets for therapeutic vaccine development since they are consistently expressed in HPV-associated tumors. Recently, immune checkpoint blockades have shown great promise for cancer treatment. It has been demonstrated that the efficacies of these immunotherapies correlate with the level of tumor-infiltrating CD8+ T cells. Most patients with cancer do not have significant tumor infiltration of immune cells, especially CD8+ T cells. Therefore, the antitumor responses of immune checkpoint blockade may be suboptimal in these tumors. In the current study, we hypothesize that intratumoral vaccination with a therapeutic HPV protein vaccine (TA-CIN) could significantly increase the number of tumor-infiltrating CD8+ T cells in a preclinical model and thereby synergize with PD-1 blockade, resulting in better control of tumors compared with either PD-1 blockade or vaccination alone.
Methods: We examined the immunogenicity and antitumor effects of intratumoral vaccination with TA-CIN in combination with or without PD-1 blockade in TC-1 tumor model.
Results: We observed that intratumoral vaccination with TA-CIN generated the strongest antigen-specific CD8+ T cell response and antitumor effects compared to intramuscular vaccination or intratumoral vaccination with either E7-specific short or long peptides. Intratumoral TA-CIN vaccination also generated systemic immune response that can control TC-1 tumors in different locations. Furthermore, intratumoral TA-CIN vaccination induced significantly more tumor infiltration of antigen-specific CD8+ T cells. The potent immunogenicity and antitumor effects of intratumoral TA-CIN vaccination depends on the *Batf3* pathway, since knock-out of *Batf3* abolished antigen-specific CD8+ T cell responses and antitumor effects. Finally, PD-1 blockade synergizes with intratumoral TA-CIN vaccination resulting in significantly enhanced antigen-specific CD8+ T cell responses and complete regression of tumors compared to PD-1 or vaccination alone.
Conclusions: Our results provide rationale for future clinical testing of intratumoral TA-CIN vaccination in combination with PD-1 blockade for the control of HPV-associated tumors.

HLA-G POLYMORPHISM IN MEN'S ORAL AND GENITAL HPV INFECTION OUTCOMES

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: The host factors that influence the natural history of HPV infection are not well known. Human Leukocyte Antigen (HLA)-G has shown to play a role in women's reproductive life as well as in development of cervical cancer. Our aim was to evaluate the role of HLA-G in men's oral and genital human papilloma virus (HPV) infection outcomes.
Methods: Altogether 133 fathers, who were followed-up for six years in the Finnish Family HPV-study, were included in the analyses. HLA-G alleles were tested by direct DNA-sequencing. Oral, urethral and semen samples were collected and analyzed for 24 different HPV genotypes with Multiplex HPV genotyping. The following oral and genital HPV infection outcomes where considered: prevalence, incidence, clearance and persistence. Unconditional logistic regression was used to determine associations between HLA-G alleles and genotypes with HPV infection outcomes.
Results: Overall, eight different HLA-G alleles were identified with 14 different HLA-G genotype combinations. The most common HLA-G allele among the fathers was G*01:01:01; 86.5 % (n=115) followed by G*01:01:02; 29.9 % (n=53). The most common genotype was G*01:01:01/01:01:01; 37.6 % (n=50) followed by G*01:01:01/01:01:02; 23.3% (n=31). Our preliminary results show that none of the HLA-G alleles or genotypes among these fathers play a role in the HPV infection outcomes.
Conclusions: Among the 133 men investigated we could not distinguish HLA-G polymorphism to have a role in the natural history of oral or genital HPV infections.

ANAL AND ORAL HUMAN PAPILLOMAVIRUS INFECTION AMONG MEN WHO HAVE SEX WITH MEN AND TRANSGENDER WOMEN FROM ARGENTINA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

V. Fink[1], L. Svidler Lopez[1], G. Presencia[1], J. Basiletti[2], M. Tejo[1], E. Lacunza[3], A. Gun[1], O. Sued[1], M.E. Salas[3], M.A. Picconi[2], M. Abba[3], O. Coso[4], P. Cahn[1], E. Mesri[5]
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Introduction: Men who have sex with men (MSM) and transgender women (TGW) have a high incidence of HIV in Argentina and are at high risk for HPV infection and its associated cancers. The quadrivalent HPV vaccine has been available for free for 11 years-old children since 2017 and for immunocompromised hosts (11-26 years) since 2014. A cohort was set up to study oral and anal HPV epidemiology.
Methods: Individuals were recruited between April 2018-July 2019. Oral and anal samples were collected and conventional anal cytology performed. DNA was purified using Qiagen DNA purification kits. HPV genotyping was done by BSGp5+6+ PCR-reverse line blot hybridization, which allow to identify 13 high risk (HR) and 24 low risk (LR) HPVs.
Results: Seventy-four individuals were recruited. Baseline characteristics of participants are shown in table 1.

Table 1: Baseline characteristics of participants

Characteristics	TGW (n=12)	MSM (n=62)
Age (years) (median)	29 (26-37)	35 (30-43)
Lifetime tobacco use	58%	55%
Lifetime sexual partners (median- IQR)	500	100
Lifetime sexual work	100%	23%
Condom use for anal sex with stable partner occasional partners	 29% 55%	 50% 60%
Condom use for oral sex with stable partner occasional partners	 14 % 13%	 4% 18%
HIV positive	58%	87%
CD4 cell count (cell/ml) (median- IQR)	684 (524-952)	737 (453-948)
Antiretroviral therapy/ VL<50	86% 80%	87% 85%

IQR= interquartile range

Anal cytology results were: negative (36%), LGSIL (53%), HGSIL (8%) and ASCUS (3%). HPV was detected in 92% of the anal (70% HR-HPV) and 32% of the oral samples. Smoking was associated to

anal HR-HPV and oral HPV (p=0.015 and p=0.032). Lifetime sexual partners >100 was associated to oral HPV (p=0.021). Anal cytological lesion was related to HPV and HR-HPV (p=0.024 and p=0.008). Coinfections were common (2-10 genotypes) (67% of anal and 14% of oral samples). Table 2 shows the most frequent HPV genotypes diagnosed.

Table 2: Most frequent HPV genotypes

	TGW	MSM
Anal samples	n= 12	n=61*
HPV positive	11/12	56/61
HR-HPV genotypes	HPV-16= 4 HPV-18=3 HPV-58=3	HPV-16=13 HPV-18=9
LR-HPV genotypes	HPV-44=3 HPV-81=3	HPV-6=16 HPV-44= 13 HPV-42=10 HPV-81=9
Oral samples	n=11*	n=60*
HPV positive	4/11	20/61
HR-HPV genotypes	HPV-16/35/45/52=1	HPV-16=4 HPV-18=4 HPV-39=3
LR-HPV genotypes	HPV- 11/43/44/70/72/81= 1	HPV-44=5 HPV-72=3

***DNA was not possible to obtain in one anal and two oral samples.**

HPV-16 and HPV-18 were the most frequent HR-HPV. However, among the studied subjects, 77% did not have HPV-16 and 84% did not have HPV-18, both vaccine preventable, and could theoretically benefit from vaccination.

Conclusions: Considering the high HPV infection rate with predominance of HR-types and associated premalignant lesions, preventive strategies, including screening and vaccination, need to be reinforced. While there is an expansion of the HPV vaccine indications worldwide, there is a need to consider a broader HPV vaccination coverage in Argentina. Funding: NIH2P30AI073961-06/ U54CA221208

CERVICO-VAGINAL MICROBIOME SIGNATURE AS A POTENTIAL BIOMARKER FOR HPV16 INFECTION

BASIC RESEARCH / MICROBIOME

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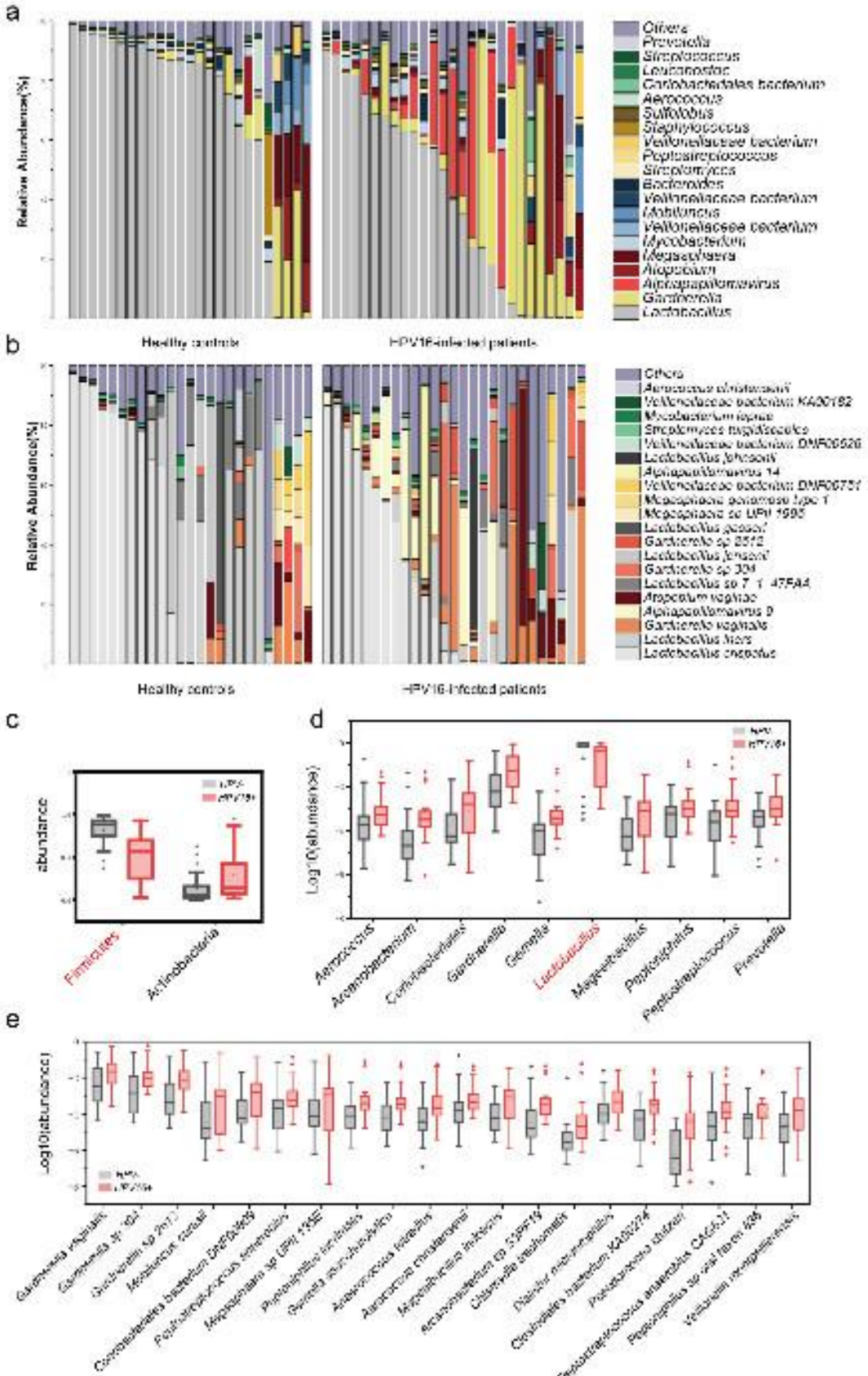
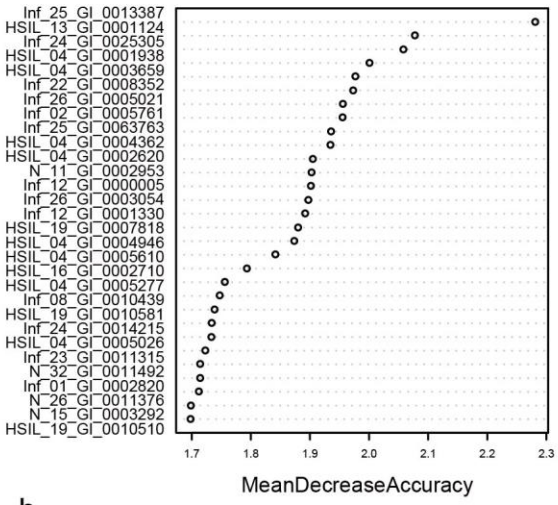
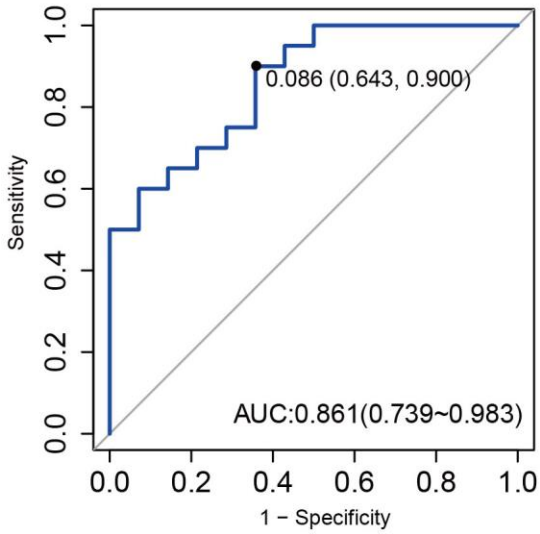
Introduction: The association of microbiome imbalance with cancer development is being one of the research hotspots. The persistent HPV infection is a causal event in cervical cancer initiation, but, in which the role of vaginal microbiome is unknown. The aim of this study was to provide a comprehensive investigation describing the relationship between high-risk HPV16 infection and vaginal ecosystem.
Methods: We performed metagenome-wide association studies on vaginal samples from 27 women with HPV16 positive and 25 age-matched healthy controls in this cross-sectional study. Microbial DNA was extracted for shot-gun metagenomic sequencing and bioinformatics analysis. We further employed quantitative polymerase chain reaction (qPCR) assays to evaluate two selected gene markers of HPV16 infection in an independent validation cohort of 88 women and 81 controls, and six selected species markers in a subset of validation cohort of 45 women and 53 controls.
Results: *Gardnerella vaginalis* was significantly enriched in HPV16-positive women compared to controls. Abundances of 17 genera, 7 species and 12 genes biomarkers distinguished HPV16-positive individuals from controls with an area under the receiver-operating characteristic curve (AUC) of 0.819, 0.918 and 0.861, respectively. Quantitative PCR measurements of two gene markers and three of six differential species were validated significantly enriched in HPV16-positive women in an independent validation cohort.

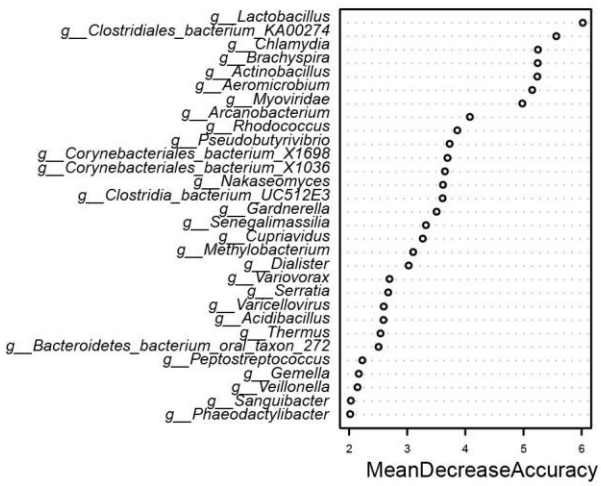

a
Relative Abundance(%)
Others
Prevotella
Streptococcus
Leuconostoc
Corynebacteriales bacterium
Aerococcus
Sulfolobus
Staphylococcus
Veillonellaceae bacterium
Peptostreptococcus
Streptomyces
Bacteroides
Veillonellaceae bacterium
Mobiluncus
Veillonellaceae bacterium
Mycobacterium
Megasphaera
Atopobium
Alphapapillomavirus
Gardnerella
Lactobacillus
Healthy controls
HPV16-infected patients
b
Relative Abundance(%)
Others
Aerococcus christensenii
Veillonellaceae bacterium KA00182
Mycobacterium lepraemurium
Streptomyces hygroscopicus
Veillonellaceae bacterium DNR00528
Lactobacillus johnsonii
Alphapapillomavirus 14
Veillonellaceae bacterium DNR00751
Megasphaera genomosp type 1
Megasphaera sp UPII 199 6
Lactobacillus gasseri
Gardnerella sp 2512
Lactobacillus jensenii
Gardnerella sp 394
Lactobacillus sp 7_1_47FAA
Atopobium vaginae
Alphapapillomavirus 9
Gardnerella vaginalis
Lactobacillus iners
Lactobacillus crispatus
Healthy controls
HPV16-infected patients
c
abundance
Firmicutes
Actinobacteria
d
Log10(abundance)
Aerococcus
Aerophagabacterium
Corynebacteriales
Gardnerella
Gemella
Lactobacillus
Megasphaera
Peptoniphilus
Peptostreptococcus
Prevotella
e
Log10(abundance)
Gardnerella vaginalis
Campylobacter sp 10_1_50
Dialister pneumosintes
Mobiluncus curtisii
Corynebacterium bovis DSM20582
Peptostreptococcus stomatis
Megasphaera sp UPII 135E
Peptoniphilus lacrimalis
Gemella asaccharolytica
Aerococcus viridans
Aerococcus christensenii
Mycobacterium indicus pranii
ectosymbiont sp 3 SPR19
Citrobacter freundii
Dialister micronesiensis
Corynebacterium bovis DSM20582
Peptostreptococcus stomatis
Peptostreptococcus anaerobius CAG:31
Peptoniphilus sp oral taxon 386
Veillonella montpellierensis

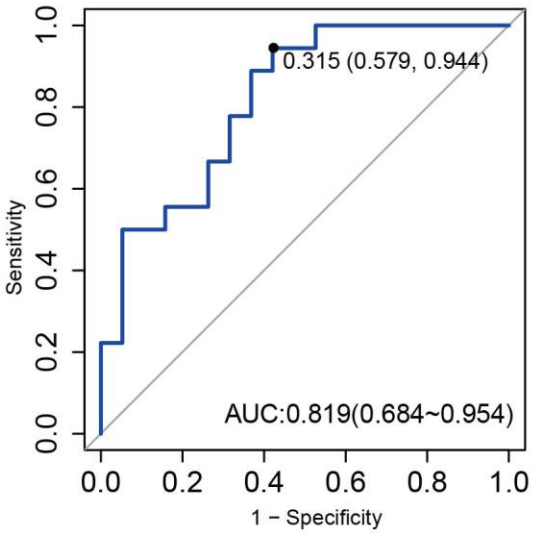
a


Inf_25_GI_0013387
HSIL_13_GI_0001124
Inf_24_GI_0025305
HSIL_04_GI_0001938
HSIL_04_GI_0003659
Inf_22_GI_0008352
Inf_26_GI_0005021
Inf_02_GI_0005761
Inf_25_GI_0063763
HSIL_04_GI_0004362
HSIL_04_GI_0002620
N_11_GI_0002953
Inf_12_GI_0000005
Inf_26_GI_0003054
Inf_12_GI_0001330
HSIL_19_GI_0007818
HSIL_04_GI_0004946
HSIL_04_GI_0005610
HSIL_16_GI_0002710
HSIL_04_GI_0005277
Inf_08_GI_0010439
HSIL_19_GI_0010581
Inf_24_GI_0014215
HSIL_04_GI_0005026
Inf_23_GI_0011315
N_32_GI_0011492
Inf_01_GI_0002820
N_26_GI_0011376
N_15_GI_0003292
HSIL_19_GI_0010510
1.7
1.8
1.9
2.0
2.1
2.2
2.3
MeanDecreaseAccuracy

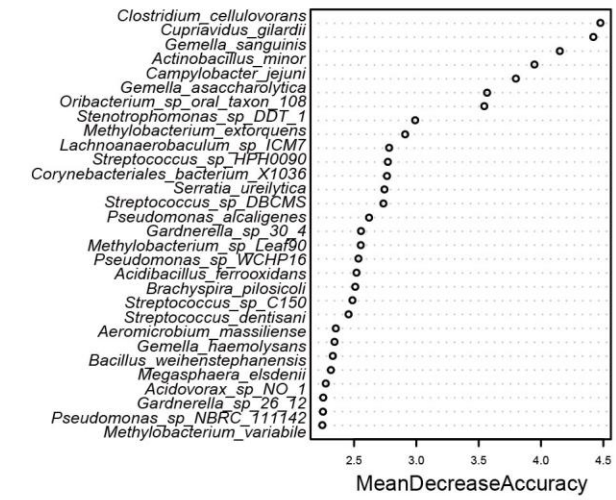

0.086 (0.643, 0.900)
AUC:0.861(0.739~0.983)
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0

b


g__Lactobacillus
g__Clostridiales_bacterium_KA00274
g__Chlamydia
g__Brachyspira
g__Actinobacillus
g__Aeromicrobium
g__Myoviridae
g__Arcanobacterium
g__Rhodococcus
g__Pseudobutyrivibrio
g__Corynebacteriales_bacterium_X1698
g__Corynebacteriales_bacterium_X1036
g__Nakaseomyces
g__Clostridia_bacterium_UC512E3
g__Gardnerella
g__Senegalimassilia
g__Cupriavidus
g__Methylobacterium
g__Dialister
g__Variovorax
g__Serratia
g__Varicellovirus
g__Acidibacillus
g__Thermus
g__Bacteroidetes_bacterium_oral_taxon_272
g__Peptostreptococcus
g__Gemella
g__Veillonella
g__Sanguibacter
g__Phaeodactylibacter
2
3
4
5
6
MeanDecreaseAccuracy


0.315 (0.579, 0.944)
AUC:0.819(0.684~0.954)
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0

c


Clostridium_cellulovorans
Cupriavidus_gilardii
Gemella_sanguinis
Actinobacillus_minor
Campylobacter_jejuni
Gemella_asaccharolytica
Oribacterium_sp_oral_taxon_108
Stenotrophomonas_sp_DDT_1
Methylobacterium_extorquens
Lachnoanaerobaculum_sp_ICM7
Streptococcus_sp_HPH0090
Corynebacteriales_bacterium_X1036
Serratia_ureilytica
Streptococcus_sp_DBCMS
Pseudomonas_alcaligenes
Gardnerella_sp_30_4
Methylobacterium_sp_Leaf90
Pseudomonas_sp_WCHP16
Acidibacillus_ferrooxidans
Brachyspira_pilosicoli
Streptococcus_sp_C150
Streptococcus_dentisani
Aeromicrobium_massiliense
Gemella_haemolysans
Bacillus_weihenstephanensis
Megasphaera_elsdenii
Acidovorax_sp_NO_1
Gardnerella_sp_26_12
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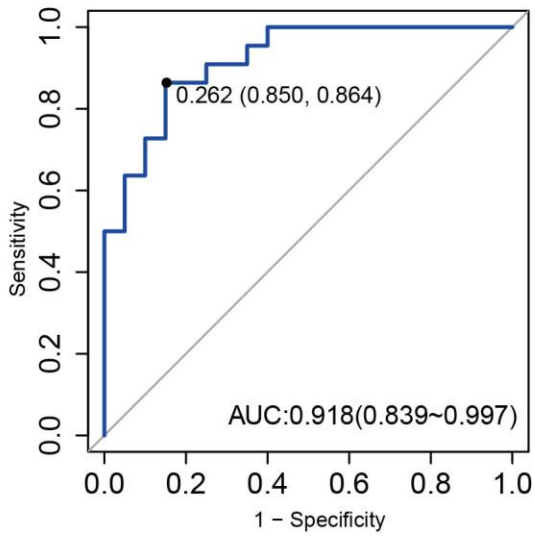
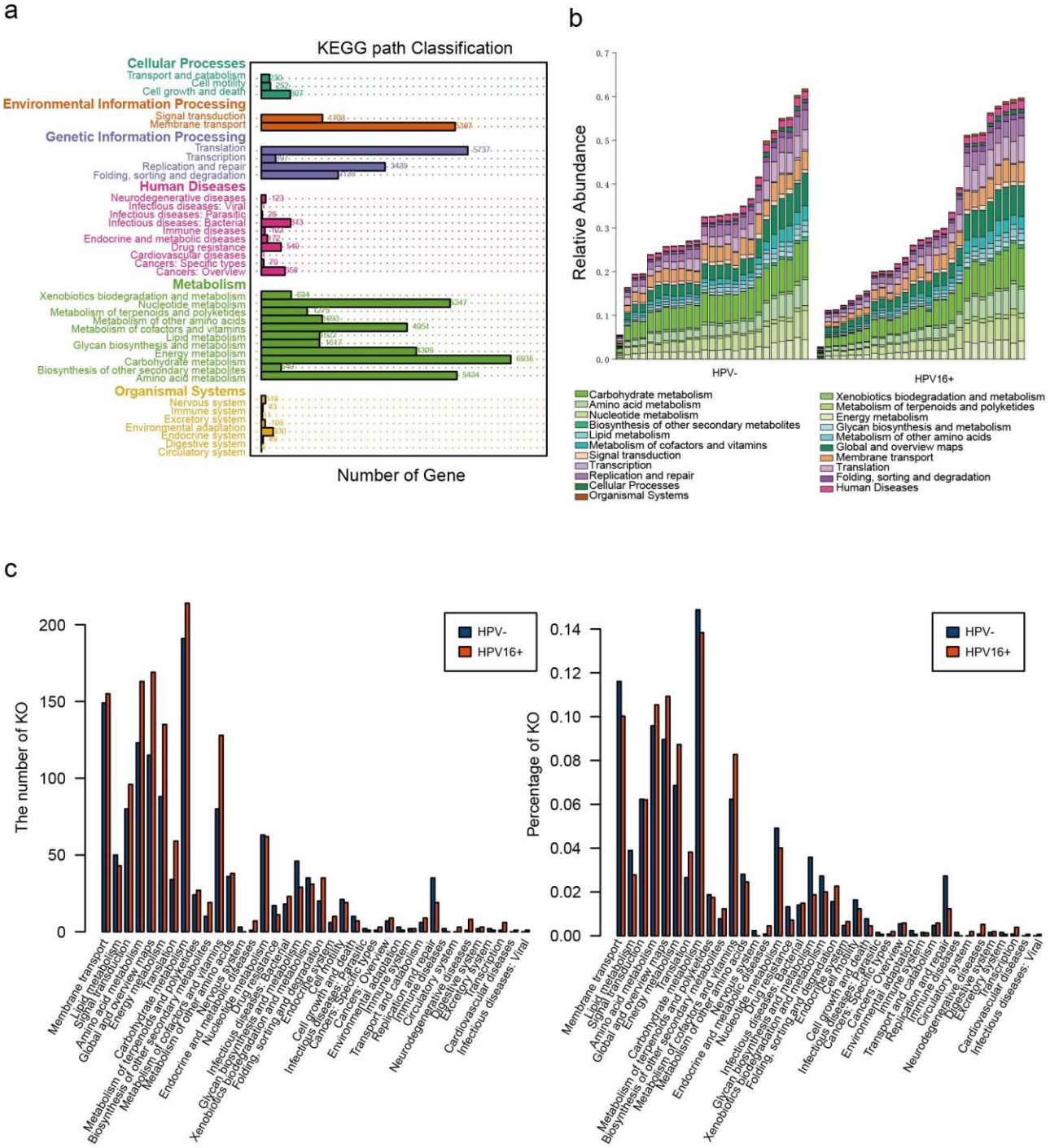
Methylobacterium_variabile
2.5
3.0
3.5
4.0
4.5
MeanDecreaseAccuracy


0.262 (0.850, 0.864)
AUC:0.918(0.839~0.997)
Sensitivity
1 − Specificity
0.0
0.2
0.4
0.6
0.8
1.0



Conclusions: We present the first metagenomic profiling study of HPV16-positive vaginal microbiomes to our knowledge. Women with HPV16 infection present with different vaginal microbiome signature. The potential biological markers for high-risk HPV infection may provide new insights into the preventative and therapeutic procedure of high-risk HPV persistent infection.

IDENTIFYING ACTIVE COMPONENTS OF CANDIDA SKIN TEST REAGENT USED AS AN ADJUVANT IN AN HPV THERAPEUTIC VACCINE, PEPCAN

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: *Candida* skin test reagent has been used as an adjuvant for an HPV therapeutic vaccine due to its immunostimulatory effects. The goal of this project was to identify its active components and mechanisms.
Methods: Dialyzed *Candida* was fractionated in to 20 one minute parts using liquid chromatography tandem mass spectrometry. Each fraction was tested for induction of IL-12 transcription with quantative reverse transcriptase-polymerase chain reaction by monocyte-derived Langerhans cells from healthy donors (n=5) prescreened for IL-12 production with *Candida*. Five fractions induced IL-12 secretions in 4 of 5 donors. A total of 10 discrete small molecules (100-600 g/mole), disignated A-J, were identified. The fractions containing 3 of these molecules (A, F, and I) were consistently present in another lot of Candin, and were not present in PBS (dialysis fluid). Whole transcriptome profiling and multiplex cytokine analysis of supernatants [IL-1beta, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12 (p70), IL-13, IL-15, IL-17, eotaxin, basic FGF, G-CSF, GM-CSF, IFN-gamma, IP-10, MCP-1 (MCAF), MIP-1alpha, MIP-1beta, PDGFBB, RANTES, TNF-alpha, VEGF] were performed in 10 screen-positive donors. RNA-seq data were demultiplexed, trimmed for adaptors, cleaned, mapped, annotated, and normalized. Principal component analysis (PCA), differential expression (DE) analysis, and over-representation analysis (ORA) were performed.
Results: The PCA did not reveal clustering; however, DE analyses revealed increased expression of 9 genes with the fraction containing A in comparison to PBS. Six these 9 genes significantly over-expressed were metallothineins. ORA revealed involvement of multiple pathways utilizing ions, such as copper, zinc, and cadmium, as well as those involved in cellular responses. Cytokine analysis revealed that the most number of significant increases (6 cytokines) occurred in the same fraction containing A.
Conclusions: The fraction containing A appears to be most biologically active. Future study would involve identification of this molecule, and a confirmation of its immunostimlulatory activities.

ANAL HPV INFECTION RATES IN HIGH-RISK MEN ATTENDING A SEXUALLY TRANSMITTED INFECTION CLINIC IN BRAZIL.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

N. Tosato Boldrini, H. Dos Reis, L. Volpini, P. De Vargas, L. Spano, L. De Freitas, A. Miranda
UFES, Gynecology And Obstetrics, VITÓRIA, Brazil

Introduction: Anal cancer rates in human immunodeficiency virus (HIV)-infected individuals have continued to increase over the past decades despite the use of antiretroviral therapy. The objective of this study was to determine the prevalence, genotype distribution, and risk factors associated with anal HPV infection among men attending an STI clinic in Brazil.
Methods: We conducted an observational study of 80 men. A survey was administered that includes demographic, behavioral, and clinic assessment. Anal specimens were collected for HPV testing by PCR followed by reverse line blot analysis for genotyping during a regular visit.
Results: The mean age of the study sample was 40,0 (±12.6). The most common HR types were 16, 55, and 52. HR anal HPV infection was found in 71.4% of the participants. Multiples HPV types in the anal canal were found in 46,8% of the sample. 73.8% of participants reporting being men who had sex with men (MSM). MSM had a significantly higher prevalence of any HPV (81,4%), HR (62,4%) and multiples HPV infection (67,4%) (p-value=0.003). In addition, 34.2% of the MSM had positivity in the high-resolution anoscopy for anal intraepithelial lesions (p-value=0.05).

variable	Total sample(%)	MSM	non MSM	p-value
Age	40.0±12.6	37.2±13.52	42.0±13.97	0.001
Education level				<0.0001
Less than 5 years	05(07.0)	01(02.1)	04(19.0)	
Primary education	13(18.3)	06(12.5)	07(33.3)	
Secondary education	29(40.8)	19(39.6)	09(42.9)	
Higher education	24(33.8)	22(45.8)	01(04.8)	
Employed				0.001
no	06(8.1)	06(12.5)	00(0.0)	
yes	61(82.4)	41(85.4)	16(76.2)	
retired	07(09.5)	01(02.1)	05(23.8)	
Self-reported STI				0.0015
yes	57(78.1)	39(81.3)	14(66.7)	
no	16(21.9)	09(18.8)	07(33.3)	
Body mass index				0.060
Under weight	05(06.5)	03(06.3)	02(09.5)	
Eutrophic	38(49.4)	24(50.0)	08(38.1)	
Over weight	30(39.0)	19(39.6)	09(42.9)	
obese	04(05.2)	02(04.2)	02(09.5)	

Conclusions: Anal HPV is common among sexually active men attending an STI clinic with a higher likelihood of anal HPV infection among MSM. Anal cancer screening in patients at risk is of fundamental importance.

FUNGAL BIOMES AND THEIR RELATIONSHIP WITH HPV INFECTION IN ANOGENITAL MUCOSA OF WOMEN IN PUERTO RICO: A POPULATION-BASED APPROACH

BASIC RESEARCH / MICROBIOME

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Introduction: The characterization of bacterial biomes has revealed bacterial populations associated to HPV infection and dysplasia, however, there are several unanswered questions. Fungi are a major neglected part of the human microbiome, which can form biofilms in the host's mucosa, and likely modify the epithelial microenvironment. We performed an unprecedented assessment of anogenital fungal diversity and its association with anal and cervical HPV infections in order to shed light on the complex interkingdom microepithelial interactions.
Methods: We used ITS-2 gene sequencing from anogenital samples from a cross-sectional population-based study of women aged 16-64 from the San Juan metropolitan area of Puerto Rico (253 women). Women self-collected cervical and anal samples, and anthropometric measurements were taken to determine body mass index (BMI). HPV typing was done with MY09/MY11 consensus HPV L1 primers. Positive specimens were typed by dot-blot hybridization. Yeast were characterized taxonomically using the UNITE database, and analyzed according to HPV and BMI status of the patients with QIIME and R.
Results: The prevalence of cervical and anal HPV infections (low-risk [LR] and high-risk [HR] combined) was 19.8% and 24.5%, respectively. We found no significant changes in the community structure according to HPV infection status. *Candida* was the most dominant yeast in both the cervix and anus, decreasing its relative abundance in obese and HPV-positive women. A significant abundance of *Malassezia (p<0.05) was* also found in HR-HPV+ women, in those obese and in postmenopausal women.
Conclusions: Findings reveal a polymicrobial colonization of yeast in all women, regardless of HPV positivity and BMI, especially *Candida*. *Malassezia*, a lipophilic yeast, were mostly found in obese patients and those HPV-positive, indicating a likely pathogenic role. The revealed mycoses may represent a major therapeutic challenge. This study represents a tremendous potential of mycobiome-related processes to be used in anogenital cancer prevention and diagnostics.

EVALUATION OF MULTIPLE BIOMARKERS ON BALANCING OVERTREATMENT AND UNDERTREATMENT FOR SELF-SAMPLING HPV POSITIVE WOMEN IN AN HPV-AND-TREAT APPROACH

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: HPV-and-Treat approach incorporating self-sampling HPV test and thermal ablation seems to be pragmatic in low-resource areas. However, overtreatment and undertreatment remain problems to be resolved. We aimed to identify promising biomarkers that could be incorporated into HPV-and-Treat approach to achieve a balance between overtreatment and undertreatment.
Methods: 9,526 women were recruited in China in 2017. Participants received self-sampling hrHPV tests at baseline. HrHPV-positive women underwent colposcopy, biopsy and thermal ablation within a single visit at baseline and have been followed up one year later. HPV genotyping, HPV16/18 E6 oncoprotein and targeted human genes (ASTN1/DLX1/ITGA4/RXFP3/SOX17/ZNF671) methylation assays were performed among hrHPV-positive women. We evaluated overtreatment and undertreatment of the HPV-and-Treat approach with HPV primary screening and HPV screening followed by colposcopy or biomarker triage classifiers among hrHPV-positive women at baseline. Overtreatment was defined as treatment in patients with no CIN. Undertreatment was defined as no treatment in patients with CIN.
Results: 1,711 hrHPV-positive women were included in the final analysis. The overall overtreatment rate in women with abnormal colposcopy was 42.1%(95%CI35.3-49.1%), which could be minimized to 8.5%(95%CI3.4-19.9%) after triaging HPV positives with HPV16/18 E6 oncoprotein, with undertreatment rates of 7.1%(95%CI5.9-8.5%) and 10.6%(95%CI9.2-12.2%), respectively. The overtreatment rate was 16.7% in women with HPV16/18 infection and abnormal colposcopy, and 27.4% in women with positive human gene methylation and abnormal colposcopy, with similar undertreatment rates (9.5% vs 9.3%). For an assumptive approach with self-HPV test followed by treatment directly, the overtreatment rate reached up to 82.1%(95%CI80.3-83.9%), which were still up to 77.2% and 64.1% after triaging by human gene methylation and HPV16/18 genotyping. A significant decline was observed by triaging with colposcopy (42.1%,95%CI35.3-49.1%) and HPV16/18 E6 oncoprotein (27.9%,95%CI20.2-37.2%), with the undertreatment rates of 7.1% and 9.1%.
Conclusions: HPV16/18 E6 oncoprotein was a promising biomarker that could be incorporated into the HPV-and-Treat approach to balance overtreatment and undertreatment.

PREDICTED IMPACT OF SCALING UP PRIMARY HPV TESTING VERSUS CYTOLOGY-BASED CERVICAL SCREENING IN JAPAN

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The draft strategic plan for the WHO call to action for the elimination of cervical cancer recommends women undergo HPV testing a minimum of twice in their lifetime. While Japan is one of the 70 executive member countries supporting the draft strategic plan, it does not currently recommend HPV testing as a primary screening tool and coverage is low at 30-40%. We aimed to assess the impact of a range of alternative screening technologies and the impact of increasing coverage from current rates to 80%.
Methods: We calibrated an existing well validated platform (Policy1-Cervix) to data from Japan on HPV prevalence rates, cervical cancer incidence rates, cervical cancer mortality, survival by stage and HPV types in cancer. When modelling alternative screening options, we considered primary HPV testing with cytology triage, primary HPV testing with partial genotyping (16/18 directly to colposcopy) and HPV/cytology co-testing.
Results: Increasing coverage from 30-40% to 80% will reduce the age-standardised rate of cervical cancer and mortality from 17.8 per 100,000 to 12.1 per 100,000 (32% reduction) and 3.85 to 2.51 per 100,000 (35% reduction), respectively, even if cytology is retained. Switching to primary HPV screening (with or without cytology co-testing) would further reduce incidence rates to 8.0-8.1 per 100,000 (55% reduction) and mortality rates to 1.63-1.65 per 100,000 (57% reduction). Primary HPV testing with partial genotyping had similar effectiveness to HPV and cytology co-testing but required significantly fewer colposcopies and precancer treatments.
Conclusions: Increasing coverage rates will substantially reduce cervical cancer incidence and mortality rates in Japan. Switching to primary HPV testing with partial genotyping is one of the most effective strategies, and required fewer additional treatments and colposcopies compared to HPV and cytology co-testing. HPV testing will also allow for self-sampling which may help to increase coverage.

PROTOCOL FOR THE PREVENT ANAL CANCER (PAC) SELF-SWAB STUDY

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Men who have sex with men (MSM), especially MSM with HIV, have increased risk for anal cancer; however, screening for either anal precancers or anal cancers is not widely recommended. The Prevent Anal Cancer (PAC) Self-Swab Study will recruit 400 MSM and transwomen, aged ≥25 years in Milwaukee, Wisconsin into a clinical trial to assess screening modalities that seek to reduce morbidity and mortality from anal cancer.
Methods: The PAC Self-Swab Study (7R01CA215403), is a randomized clinical trial (NCT03489707) to evaluate compliance with annual home-based (self) vs clinic-based HPV DNA specimen collection among HIV+ and HIV- MSM and transwomen. Secondary objectives of the trial will determine factors associated with annual screening compliance; estimate the influence that home-based vs clinic-based screening has on the uptake of high-resolution anoscopy (HRA); estimate the association between high-risk HPV persistence and anal high-grade squamous intraepithelial lesions (HSIL); and estimate the association between HPV-16/host DNA methylation and anal HSIL.
Results: Enrollment of the study has not begun. To date, the design for the home-based self-swabbing kit has been optimized in two pilots; surveys in English and Spanish have been created; five community-based clinics in Milwaukee have contracted to do anal swab screening and Digital Anal Rectal Exams (DARE) for study participants (9 clinicians have been trained in swabbing and DARE); and the community advisory board has advised on kit design, recruiting, and survey instruments.
Conclusions: The outcomes will establish the level of screening compliance and factors associated with annual DNA testing; how home-based vs. clinic-based screening, in addition to other characteristics like perceived susceptibility (e.g., HIV status), influences uptake of HRA; and the utility of anal HPV DNA persistence and viral/host DNA methylation testing. These outcomes will inform the delivery of future screening programs.

RELATIONSHIPS OF P16 IMMUNOHISTOCHEMISTRY AND OTHER BIOMARKERS WITH DIAGNOSES OF CERVICAL ABNORMALITIES: IMPLICATIONS FOR LAST TERMINOLOGY

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Lower Anogenital Squamous Terminology (LAST) standardization recommended $p16^{INK4a}$ immunohistochemistry (p16) on biopsies diagnosed as cervical intraepithelial neoplasia (CIN) grade 2 (CIN2) to classify them as low-grade or high-grade squamous intraepithelial lesions (HSIL). The aim of this investigation was to assess whether p16-positive CIN2 biopsies were similar enough to CIN3 such that making a distinction between the two would be unnecessary.
Methods: The New Mexico HPV Pap Registry selected a state-wide, stratified sample of 4,100 cervical biopsies diagnosed by local community pathologists (CP), including 1,512 CIN2. Biopsies underwent a consensus, expert panel (EP) review (without p16), p16 interpreted by a third pathology group, and HPV genotyping, results of which were grouped hierarchically according to cancer risk. Antecedent cytology diagnoses were also available. Trends in p16 positivity by biopsy diagnosis or HPV risk groups were calculated.
Results: Biopsies more often tested p16 positive with increasing severity of CP diagnoses, overall (P_{trend}<.001) and within each HPV risk group (P_{trend}≤.001). All abnormal grades of CP-diagnosed biopsies were more likely to test p16 positive with a higher HPV risk group (P_{trend}<.001), and testing p16 positive was associated with higher HPV risk group than testing p16 negative for each grade of CP-diagnosed biopsies (P<.001). p16-positive, CP-diagnosed CIN2 biopsies were less likely than CP-diagnosed CIN3 biopsies to test HPV16 positive, have an antecedent HSIL+ cytology, or to be diagnosed as CIN3+ by the EP (P<.001 for all). p16-positive, CP-diagnosed CIN1 biopsies had lower HPV risk groups than p16-negative, CP-diagnosed CIN2 biopsies (P<.001).
Conclusions: p16-positive, CP-diagnosed CIN2 have lower cancer risk than CP-diagnosed CIN3. LAST classification of "HSIL" diagnosis, which includes p16-positive CIN2, should annotate the morphologic diagnosis (CIN2 or CIN3) to inform all management decisions. This is especially true for young women diagnosed with CIN2 for whom surveillance rather than treatment is recommended.

COLPOSCOPIC IMPRESSION IN A BIRTH COHORT PREVIOUSLY ELIGIBLE FOR HPV-VACCINATION

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: Subsidized human papilloma virus (HPV) vaccination has been offered on-demand and as catch-up for girls aged 13-18 in Sweden since 2006 with a coverage of 55-60%. Since the first women in Sweden eligible for vaccination entered the cervical screening program in 1993, questions on how to evaluate colposcopic have arisen. Evidence is inconsistent as to whether colposcopic features for the detection of HSIL are influenced by specific HPV genotypes and there are no previous studies to our knowledge evaluating colposcopy in vaccinated and unvaccinated women from the same birth cohort entering the organized cervical screening program. As colposcopic impression may be different due to a reduction in the prevalence of vaccine-types HPV 16/18, the aim of the study was to compare the colposcopic impression between the groups.
Methods: Women in the 1994 and 1995 birth cohorts who entered in the screening program at age 23 in one region of Sweden and had a positive screening result were identified and underwent colposcopy. Colposcopic impression was evaluated according to the Swedescore. Colposcopic opinion was assessed as benign, low grade, high grade or invasive. Punch biospsies were taken and histopathologic findings were used as golden standard.
Results: In 2018, 59 women from the 1994 birth cohort attended colposcopy, of which 19 (32%) reported being vaccinated. There were a total of 22 HSILs identified in the 1994 cohort. In the vaccinated group 25% (2/8) of women with HSIL had a Swedescore of 8-10 (indicating HSIL); 40% (4/10) in the unvaccinated group. Colposcopic opinion was evaluated as high grade in 75% (6/8) of women with HSIL in the vaccinated group; 70% (7/10) in the unvaccinated group.
Conclusions: Preliminary results indicate that colposcopic examination including the Swedescore and colposcopic opinion may be useful tools also in the evaluation of vaccinated women entering the cervical screening program in Sweden.

CURRENT EXPERIENCE OF CERVICAL CANCER SCREENING AND TREATMENT IN FIJI

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Fiji, along with other Asia Pacific regions, are classified as low and middle income (LIMC) region. There is a lack of effective cervical cancer screening in remote areas resulting in high disease burden. Recent data shows cervical cancer ranks as the second most common cancer among women in Fiji.
Methods: The Pacific Island Cervical Cancer Screening Initiaitve (PICCSI) has been recently established by Australian medical volunteers in conjunction with the local community targeting cervical cancer screening and treatment in remote areas. The pilot project commenced in August 2018 where approximately 350 women aged between 30 to 50 years old from remote areas, which include rural clinics in western Fiji (Nadi, Sigatoko, Rakiraki, Tavua , Ba, etc) underwent HPV testing and those positive for 14 high-risk HPV strains ((16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68) were treated on the same day with colposcopy assessment. The study is still ongoing and more Fijian women are currently being screened and treated.
Results: In 2018, 30 women were tested positive for HPV infection and 13 women underwent a loop excision of the transformation zone (LLETZ). The PICCSI is still ongoing and more women are currently being screened and treated till the end of 2019. All of the liquid base cytology (LBC), cervical biopsies and LLETZ specimens are sent to the VCS Foundation in Melbourne due to lack of on site pathology services in remote areas in Fiji. The data on the prevalence of HPV and cervical dysplasia in remote areas in Fiji will be availabe by the end of the pilot study.
Conclusions: The aim of the PICCSI would be to expand in other areas in the Pacific if the pilot study successfully shows significant impact in screening and treating cervical dysplasis in poorly remote areas in Fiji.

RISK OF VULVAR, VAGINAL AND ANAL HIGH-GRADE INTRAEPITHELIAL NEOPLASIA AND CANCER ACCORDING TO CERVICAL HUMAN PAPILLOMAVIRUS (HPV) STATUS: A POPULATION-BASED PROSPECTIVE COHORT STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Virtually all cervical cancers and some vulvar, vaginal and anal cancers are caused by high-risk human papillomavirus (hrHPV). Our aim in this population-based, prospective cohort study was to assess the subsequent risk of vulvar, vaginal and anal intraepithelial neoplasia grade 2/3 or cancer (VIN2+, VaIN2+ and AIN2+) according to cervical hrHPV status.
Methods: Liquid-based cervical cytology samples were collected from 40,399 women screened against cervical cancer in Copenhagen, Denmark, during 2002–2005. Samples were tested for hrHPV using Hybrid Capture 2 (HC2) and genotyped using INNO-LiPA. We linked the cohort with nationwide registries to identify cases of VIN2+, VaIN2+ and AIN2+ during up to 15 years of follow-up. We estimated cumulative incidences and age-adjusted hazard ratios (HRs) according to cervical hrHPV status at baseline.
Results: Women with cervical HPV16 infection at baseline had increased hazard of VIN2+ (HR=2.6; 95% confidence interval [CI], 1.2–5.5), VaIN2+ (HR=23.5; 95% CI, 6.8–81.6) and AIN2+ (HR=3.7; 95% CI, 1.1–12.2) compared with HC2 negative women. Women with other hrHPV types than HPV16 also had increased hazard of VaIN2+ (HR=7.1, 95% CI, 2.3–22.3) and AIN2+ (HR=2.2; 95% CI, 0.9–4.9), but not of VIN2+ (HR=1.0; 95% CI, 0.5–1.9) compared with HC2 negative women. The 10-year cumulative incidences of VIN2+, VaIN2+ and AIN2+ in women with cervical HPV16 were 0.3% (95% CI, 0.2%–0.7%), 0.2% (95% CI, 0.1%–0.5%) and 0.1% (95% CI, 0.0%–0.4%), respectively.
Conclusions: Cervical HPV16 infection is associated with an increased risk of subsequent vulvar, vaginal and anal high-grade intraepithelial neoplasia and cancer.

ACCEPTABILITY AND UPTAKE OF HPV SELF-SAMPLING AS AN ALTERNATIVE METHOD FOR CERVICAL CANCER SCREENING IN TORONTO, CANADA

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Introduction:Cervical cancer remains a global public health concern even though scientific advancements have made the disease virtually preventable. The link between human papillomavirus(HPV) and cervical cancer and the subsequent improvement in screening technology have led to improved access and coverage of cervical screening via self-sampling. In Ontario, Canadian women who identify as South Asian, West Asian, Middle Eastern and North African have the lowest rates of screening and research suggests they have a higher burden of cervical cancer. In this study, we aimed to understand screening decisions and understand acceptability of HPV self sampling among under-screened women.

Methods: Methods: Working with community champions, we recruited women who identify as South Asian, West Asian, Middle Eastern and North African, and are under- or never screened for cervical cancer, in Toronto, Ontario and surrounding areas. Women self-selected whether or not they tried the self-sampling kit, and all participants provided feedback on the feasibility, acceptability, and preferences through surveys. Women who tried self-sampling were followed up with to understand their experience using the device, while those that did not, were contacted to see if they went on to have a Pap test.
Results: Results: To date, we have recruited over 70 women. The majority of the women have chosen to try the self-sampling kit and have provided feedback on the device and the acceptability of self-sampling. We will present data on the knowledge, attitudes and practices of the surveyed women, to better understand their experience with cervical cancer screening.
Conclusions: Conclusions: Self-sampling is appealing to some women who are under- or never-screened for cervical cancer. This screening method addresses some of the barriers that prevent women from seeking Pap tests.

PERFORMANCE OF THREE HPV SELF-SAMPLING DEVICES: A RANDOMISED STUDY AMONG NON-ATTENDERS IN SLOVENIAN CERVICAL CANCER SCREENING PROGRAMME

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) self-sampling can significantly increase attendance in cervical screening compared to mailing a reminder letter. However it is not clear whether the type of the self-sampling device is an important predictor of the response.
Methods: Women aged 30-64 years in the opt-out arm of the Slovenian randomised self-sampling study were randomised to three devices: Qvintip (n=3,284), HerSwab (n=3,284) or DelphiScreener (n=2,988). In the opt-in arm Qvintip was used (n=9,556). Women were invited to return the self-sample but could also obtain cytological sample from their gynaecologist. All HPV-positive women were referred to colposcopy. We investigated the impact of the device on the women's response, HPV positivity and sample inadequacy, biopsy rate and histology results as well as on the positive predictive value (PPV) for CIN2+.
Results: Among the 23,956 enrolled women with mean age of 49.8 years, the overall response was significantly higher (P<0.001) in HerSwab (40%) and Qvintip (39%) opt-out scenarios than in the DelphiScreener opt-out (33%) scenario. In the opt-in scenario, Qvintip had a 34% response. HPV self-sampling response was significantly higher in all opt-out arms compared to opt-in (18%), however in the opt-out scenario it was again higher (P<0.001) for HerSwab (30%) and Qvintip (29%) compared to Delphi Screener (24%). HPV positivity was higher on Delphi Screener (12%) compared to HerSwab (7%, P<0.001) and Qvintip (8%, P<0.003). About 1% of women had a CIN2+ and this did not differ significantly between the devices. The PPV ranged from 10% (DelphiScreener) to 15% (other devices).
Conclusions: The type of self-sampling device should be carefully considered when designing a screening strategy for non-responders. As demonstrated in our study, the differences in the response and HPV positivity can be observed that are not necessarily related to the underlying high-grade disease risk, potentially influencing the cost-effectiveness of the programme.

DETECTION OF HIGH RISK HUMAN PAPILLOMAVIRUS (HR-HPV) IN PRECANCEROUS LESIONS OF CERVICAL CANCER

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: The High risk Human Papillomavirus (HR-HPV) is the etiologic agent of cervical cancer, second female cancer in Algeria. The objective of this work is to carry out a preliminary prospective study for the detection of HR-HPV infections in Tlemcen, where screening is based solely on cytology.
Methods: One hundred and thirty (130) cervical specimens were used in this study. HPV detection was performed by the Cobas® 4800 HPV test in a laboratory of medical analysis “Ibn Sina” (Constantine) using a real-time PCR. This test identifies specifically HPV16 and/or HPV18 types, and detects simultaneously the remaining HR-HPV types.
Results: A percentage of 21.5% represents positive HPV specimens (28/130) with 5 multiple infections (HPV16 associated) and 23 single infections. The rate of infection by HPV16 (alone or combined) was 28.6% (8/28). Risk factors that appear to be related to HPV infection were, in addition to HIV infection, the lack of early and regular screening; where the majority of patients performed their smears for the first time at an advanced age whose principal reason of gynecological consultations was hemorrhage on contact. In addition to abusive use of oral contraception, and early age of marriage.
Conclusions: These preliminary results encourage us to develop a study on a larger sample of patients, including the HPV test. This test will optimize the performance of early screening of this cancer in our population; to define the prevalence of HPV infection and the distribution of different genotypes, which is necessary in the introduction of vaccination.

CHADOX1 AND MVA HETEROLOGOUS PRIME BOOST VACCINATION IN LOW-GRADE HPV-RELATED CERVICAL LESIONS

CLINICAL RESEARCH / THERAPEUTIC VACCINES – CLINICAL ASPECTS

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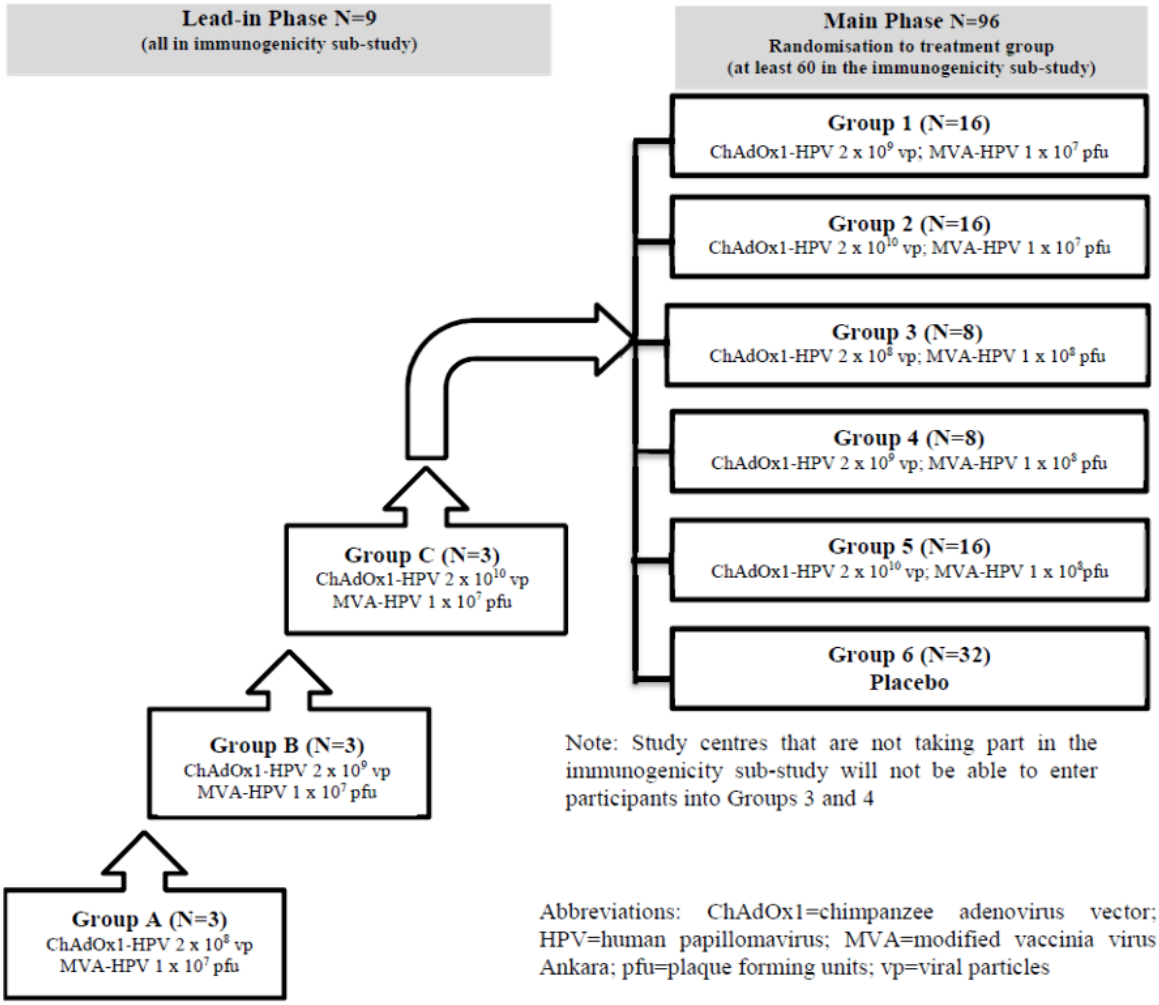
Introduction: Clearance of HPV and related cervical lesions is associated with the development of a robust T cell response. Therapeutic vaccination is a promising approach to restore T cell immunity, treat infections and malignancies. A two-dose heterologous vaccination strategy using non-replicating viral vectors, Chimpanzee Adenovirus Oxford 1 (ChAdOx1) and Modified Vaccinia virus Ankara (MVA), has been safe and immunogenic in clinical studies across various indications. This is the first study to evaluate the safety, tolerability, immunogenicity and efficacy of ChAdOx1 and MVA in participants with persistent cervical high-risk HPV (hrHPV) infection and low-grade cervical lesions.
Methods: MVA boosts and prolongs the T cells induced by ChAdOx1. Doses of ChAdOx1 up to 5×10^{10} vp and MVA doses up to 2.5×10^{8} pfu have been evaluated in various indications. We will investigate different doses of ChAdOx1 and MVA to deliver sequences from high risk HPV strains (16, 18, 31, 52, 53 and 58). The study will be conducted sequentially under an umbrella protocol design (Fig 1): - An open label dose escalation study investigating 3 varying doses of ChAdOx1 (baseline) and a fixed dose of MVA (Day 28) with a 3-months follow-up period (n=9). - A blinded, randomised (2:1), placebo-controlled study investigating 3 varying doses of ChAdOx1 (baseline) and 2 doses of MVA (Day 28) with a 12-month follow-up period (n=96).



Results: 105 participants will be enrolled. The primary objective is to evaluate safety of both vaccines. The secondary objectives will include dose determination for further development, clearance of hrHPV infection and resolution of associated cervical lesions.
Conclusions: The success of therapeutic vaccination depends on an appropriate prime-boost vaccination strategy. This study evaluates the impact of a heterologous prime boost therapeutic vaccination strategy to clear persistent cervical hrHPV infection and revert low-grade cervical lesions. Available study results will be presented at the meeting.

PRACTICE-, PROVIDER-, AND PATIENT-LEVEL FACILITATORS OF AND BARRIERS TO HPV VACCINE PROMOTION AND UPTAKE IN THE STATE OF GEORGIA

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: The state of Georgia (U.S.) experiences higher HPV-associated cancer burden and lower HPV vaccine uptake compared to national estimates. There has been little research utilizing multilevel frameworks to study facilitators of and barriers to HPV vaccine promotion and uptake in Georgia. Guided by the P3 model that concomitantly assesses practice-, provider-, and patient-level factors influencing preventive health behaviors, we examined this question, using the perspectives of diverse healthcare providers recruited from five geographic regions in Georgia.
Methods: Between April and July 2018, we conducted six focus group discussions with a total of 55 healthcare providers. Questions focused on multilevel facilitators of and barriers to HPV vaccine promotion and uptake that healthcare providers observed in their practices. Data analysis was guided by the P3 model and a deductive coding approach based in grounded theory.
Results: At the practice level, providers discussed organizational priorities of HPV vaccinations, ability to schedule future HPV vaccine doses, use of informatics for immunization medical records, availability of HPV vaccine, and ability to coordinate with community resources. At the provider level, influential themes included time constraints, role, knowledge, self-efficacy to discuss HPV vaccine, and HPV vaccine confidence. At the patient level, providers noted issues related to patients' trust, experiences with HPV vaccine-preventable diseases, perceived high costs, perceived side effects, and concerns with sexual activity.
Conclusions: Effective interventions should incorporate elements addressing each of the levels of the P3 model. Interventions may include incentives to boost vaccine rates and incorporating technology for vaccination appointment scheduling. Additional emphasis should be placed on improving across-practice information exchange and providing additional education for providers on HPV vaccine knowledge. Patient-provider communication and trust emerges as an important intervention target. Providers should be trained in addressing concerns about HPV vaccine, such as those related to costs, side effects, and sexual activity.

TRIAGE OF PRIMARY HPV TESTING COMBINED WITH SELF-SAMPLING USING HPV 16/18 GENOTYPING AND/OR CYTOLOGY. A SUB-ANALYSIS OF THE GRECOSELF STUDY

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Triage of HPV positive women to colposcopy is necessary in the framework of HPV-based primary cervical cancer screening combined with self-sampling. Within the GRECOSELF study, a nationwide cross-sectional study on HPV-DNA testing with self-sampling, we evaluated HPV 16/18 genotyping and cytology for the triage of women tested HPV positive on self-collected cervicovaginal samples.
Methods: Women between 25-60 years old, who resided in rural Greece were provided with a dry swab for cervicovaginal sampling. Each sample was tested for high-risk (hr) HPV with the cobas® HPV test, which detects HPVs 16 and 18 separately, and HPVs 31,33,35,39,45,51,52,56,58,59,66 and 68 as a pooled result. HrHPV positive women were referred to colposcopy/biopsy. A sample collected prior to colposcopy was used for Liquid-based cytology (LBC).
Results: Between May 2016 and November 2018, 13,111 women were recruited. Of these 1070 (8.3%) were hrHPV positive. Amongst those women there were 297 (2.3%) tested positive for HPV 16 and/or 18. Of the 1070 hrHPV positive women, 773 (72.2%) accepted to undergo colposcopy. A cervical sample was collected, prior to colposcopy, in 317 women out of the 773 who underwent colposcopy. Cervical Intraepithelial Neoplasia grade 2 or worse (CIN2+) was detected in 75 cases (0.6%). The optimal trade-off between sensitivity and positive predictive value (PPV) was presented by the combination of partial genotyping (HPVs 16/18) and cytology (for the non-16/18 hrHPV positive cases), i.e. sensitivity 96.55% [confidence interval (CI): 91.86-100.0%)], and PPV 23.33% (CI: 17.98-28.68).
Conclusions: For women residing in rural Greece, who were tested positive for hrHPV DNA with the cobas HPV test on self-collected cervicovaginal samples, the optimal triage strategy was HPV 16/18 genotyping combined with cytology for the non-16/18 hrHPV positive cases.

ASSESSMENT OF ISOTHERMAL AMPLIFICATION AMPFIRE ASSAY FOR DETECTION AND GENOTYPING OF HPV IN FORMALIN-FIXED PARAFFIN-EMBEDDED HEAD AND NECK CANCER SAMPLES

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF OROPHARYNGEAL, HEAD AND NECK CANCER

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Introduction: Infection with high risk HPV is etiologically linked to a group of oropharyngeal squamous cell carcinomas (OPSCCs) that show better clinical outcome and response to treatment. The combination of $p16^{INK4A}$ overexpression and HPV-DNA testing increases diagnostic accuracy and have a better prognostic value. The aim of this study was to assess the AmpFire HPV Multiplex and Genotyping Tests, for formalin-fixed paraffin-embedded (FFPE) samples.
Methods: Extracted DNA of the entire collection of OPSCC FFPE specimens collected between 2014-2019 at Hospital de Bellvitge summing a total of 160, plus 23 samples of other head and neck (HN) localizations were routinely tested using the Linear Array HPV Genotyping Test (LA). Additionally, viral DNA was detected and 15 HR- HPV types genotyped using the AmpFire HPV Multiplex and Genotyping Tests (Atila Biosystems). The DNA was amplified and real-time fluorescent detected using a 60ºC isothermal reaction for 74 min.
Results: LA and AmpFire HPV Multiplex tests showed, for total samples and OPSCC, a positive agreement of 98.89% and a 99.36% and a kappa index of 0.972 and 0.984, respectively. An overall concordance of 100% for the presence of HPV16 and 18 was observed. Amongst the samples where the test detected “Other HR-HPV genotypes”, the AmpFire Genotyping test was performed. The main disagreement was found for genotypes HPV45 and HPV52. It is worth mentioning that LA is unable to identify HPV52 alone in samples containing HPV33, HPV35, and/or HPV58 as a cross-reactive probe for all these genotypes is used. Moreover, 145 OPSCC samples had the $p16^{INK4A}$ IHC test done. The agreement observed between positives and negatives for HPV-DNA and $p16^{INK4A}$ was 93.8% and a ki of 0.848.
Conclusions: The AmpFire HPV Tests are simple sample-to-answer and low cost assays for detection and genotyping of HPV in HN FFPE samples.

'SCREEN AND TREAT' PROGRAMME FOR CERVICAL CANCER PREVENTION IN PUNE, INDIA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The World Health Organization estimates that there will be about 154 259 new cases of cervical cancer in India by 2040. We are implementing a 'screen and treat' programme in Pune, India with an objective to expand access to cervical cancer screening to indigent women.
Methods: The programme was initiated in November 2016. Cervical cancer screening and ablative treatment (when indicated) were provided in our 'mobile clinic van' to women living in and around Pune city. The screening was provided using visual inspection of the cervix with 5% acetic acid (VIA) by trained personnel followed by immediate treatment of screen-positive women with thermocoagulation (Wisap or Liger's thermocoagulation), if eligible. Screen positive women not eligible for ablative treatment were referred for colposcopy/biopsy/excisional treatment.
Results: A total of 10 979 women aged between 30 and 60 were screened with VIA in 281 outreach screening clinics. The overall VIA positivity was 6.8% (95% CI 6.3-7.3) and there was a declining trend from 7.6% (95% CI 6.8-8.5) in the year I, 7.1% (95% CI 6.4-7.9) in year II and 5.4% (95% CI 4.6-6.3) in year III. Of the screen-positive women, 305/697 (43.8%) received treatment with thermocoagulation. Two women diagnosed with cervical cancer (2/ 10979, 0.018 %) were referred appropriately for anti-cancer treatment. There were no serious adverse events following treatment with thermocoagulation. 14/311 (4.5%) women complained of some side effect (pain/cramps in abdomen, mild bleeding, fever, discharge, severe bleeding, menorrhagia, PID) following thermocoagulation which subsided after treatment.
Conclusions: It is feasible, acceptable and safe to implement a community based cervical cancer screening programme using the 'screen and treat' strategy. Ablative treatment with thermocoagulation is safe and well-tolerated.

PRIMARY CERVICAL CANCER SCREENING USING SELF-SAMPLING FOR HPV DNA TESTING: EVIDENCE OF ACCEPTANCE FROM A NATIONWIDE CROSS-SECTIONAL STUDY IN GREECE

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: The aim of this analysis is to assess the acceptance of cervicovaginal self-sampling for HPV-DNA testing amongst Greek women, residing in rural areas, within the framework of the GRECOSELF study.
Methods: Women recruited within GRECOSELF, a nationwide cross-sectional study on HPV-DNA testing combined with self-sampling, were between 25-60 years old and resided in rural areas of Greece. Women were recruited by midwifes, collected a cervicovaginal sample using a dry cotton swab, and filled out a questionnaire. Questions regarding self-sampling acceptance were as follows: 1)“Did you understand the instructions given?”, 2)“Did you experience difficulties during self-sampling?”, 3)“Did you feel uncomfortable?” 4)“Did you feel pain?”, 5)“Are you certain that you followed the instructions correctly?” 6)“Where would you prefer to perform self-sampling?”, 7)“Have you ever felt uncomfortable during physician-sampling?” 8)“If physician and self-sampling were equally effective which one would you prefer?”, 9)“If physician and self-sampling were equally effective, would you check yourself more often?”
Results: Between May 2016 and June 2018, the study recruited 13,111 participants. Of these 8,401 (64.1%) reported that they would prefer self-sampling to physician-sampling. No or little pain or discomfort during self-sampling was experienced by the majority of the women [n=12,627, (96.3%), and n=12,403 (94.6%) respectively]. Also, most of the women (92.5%) stated that self-sampling instructions were very clear or clear and 89.1% reported having very few or a few difficulties during self-sampling. Moreover, 61.8% reported that they would prefer to self-sample at home instead of a primary care facility. Pain and discomfort during the procedure, although rare, were significant factors against acceptance. Most of the women reporting a negative impression, had a negative experience in their history.
Conclusions: Self-sampling is the preferred sampling method for cervical cancer screening, compared to physician-sampling, amongst Greek women residing in rural areas. It is easy to perform and causes minimal discomfort.

ARTIFICIAL INTELLIGENCE AND ORAL BRUSH SAMPLING FOR MICROBIOLOGIC DIAGNOSIS IN GENERAL DENTAL PRACTICE, A NEW ENTITY TOWARDS EFFICIENT EXPLAINABLE CYTOLOGY.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The incidence of oral cancer (OC) exceeds cervical cancer and has a poor prognosis due to late diagnosis. When patients are reviewed by their general dentist (GDP) screening can easily be done. Our aim is to compare the outcome of oral brush sampling between performers in GDP to specialists in oral medicine (OM).
Methods: OC screening will include 10 GDP in Sweden to compare results between GDP to specialists in oral medicine (OM) and develop our AI software for the automated cytology diagnosis. Brush biopsies will be obtained (n=200) of potentially malignant lesions (PML, lichen, leukoplakia) and healthy oral mucosa as controls (n=200). We use a brush method proven to be safe and accurate according to our previous study (n=160) of documented OC, PML or anogenital hrHPV lesions. Brush samples are collected and an automated analysis of hrHPV with FTA elute micro card and automated cytology with Thin Prep liquid base will be performed. Patients with PML are referred to OM for repetitive sampling and routine histological investigation. Results of both cytology and hrHPV DNA from GDP and the OM will be compared.
Results: The inclusion of patients is ongoing. Results from an earlier study of the automated cytology screening show that the system is reliable for classifying oral cells with our AI based, deep learning, deep convolutional neural networks. Evaluation from a previous study show hrHPV is detected with the same accuracy with the FTA microcard as with the liquid base method.
Conclusions: Our aim is to reduce the prevalence of OC by introducing screening of high risk patients by GDP including intervention against tobacco habits and alcohol abuse. Screening for OC and PML in GDP will track patients at risk for developing OC and detect cell changes at an early stage, to reduce the treatment burden and mortality rate.

HPV GENOTYPING OF ANAL SPECIMENS FROM HIV+MSM PARTICIPANTS: VALIDATING AMPFIRE HPV GENOTYPING ASSAY (ATILA BIOSYSTEM) AGAINST LINEAR ARRAY HPV GENOTYPING TEST (ROCHE).

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HIV+MSM are at highest risk of developing squamous cell carcinoma of the anus. Over 80% of these cases are caused by high-risk Human Papillomaviruses (HR-HPV) types 16 or 18. Linear Array HPV Genotyping test (Roche), the gold standard for decades, is no longer available. An alternative was needed. We evaluated AmpFire HPV Genotyping Assay (Atila BioSystem) and compared results to Roche's test.
Methods: 150 anal swab-based specimens collected in PreservCyt media from consented HIV+MSM participants with ≥ASCUS grade cytology results, being referred for High Resolution Anoscopy, were tested for HPV by both assays according to each manufacturers' protocol. Atila uses crude cell lysate, isothermal multiplex amplification, fluorescent detection of HPV16/18/31/33/35/39/45/51/52/53/56/58/59/66/68 in 96 well plate format; results available in 90 min. Roche requires DNA extraction, multiplex PCR amplification, probe hybridization, colorimetric detection with visual readout; results are available within 1-2 days.
Results: Comparisons were made for all 15 HR-HPV types, and for HPV16/18 only; the two HR-HPV types most highly associated with anal cancer. Agreement in the former comparison was 89.5% (95%CI; 0.8248-0.9326) (Kappa=0.6392); agreement in the latter was 90% (95%CI; 0.8404-0.9429) (Kappa=0.796). Analytical sensitivity, specificity, PPV and NPV for all 15 HR-HPV types were 62.2%, 96.3%, 80.6% and 91.1%, while those for HPV16/18 were 89.1%, 90.7%, 87.7% and 91.8%. HPV16 was most prevalent; detected in 32% (Atila) or 30.7% (Roche) of HIV+MSM participants. HPV16/18 were detected in 47.3% (Atila) or 46.7% (Roche) of participants. Detecting multiple HR-HPV types from anal specimens was common. Average [median] numbers of HR-HPV types detected per specimen was 3 [3] (Atila) and 2.2 [2] (Roche).
Conclusions: We validated anal specimens from HIV+MSM participants on Atila's assay. Agreement between the two assays was good, especially for HPV16/18. Atila's protocol takes less time to obtain results, is more economical and uses fewer specialized equipment to run.

PREVALENCE AND PREDICTORS OF LOSS TO FOLLOW-UP OF GAY AND BISEXUAL MEN (GBM) IN THE LONGITUDINAL STUDY FOR THE PREVENTION OF ANAL CANCER (SPANC)

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Loss-to-follow-up (LTFU) in cohort studies may result in biased estimates of outcomes, due to differences between those retained and those LFTU. To our knowledge, LTFU has never been investigated in studies of anal human papillomavirus and/or anal high-grade squamous intraepithelial lesions (HSIL).
Methods: SPANC was a prospective, 3-year, cohort study of the natural history of anal HPV and HSIL conducted from 2010-2018. GBM aged ≥ 35 years were recruited from community-based settings. Characteristics of participants LTFU after their baseline visit were compared with those who attended at least one further visit using logistic regression.
Results: Among 617 men enrolled, 220 (35.7%) were HIV-positive, median age 49 years. Overall, 85 participants (13.8%) were LTFU (including 30 (13.8%) HIV-positive participants). Independent predictors of LTFU were: lower level of education (p-trend=0.020), younger age (p-trend=0.004), never having smoked cigarettes (p-trend=0.066), and at 2-week interview, reporting feeling more tense during the initial examination (p-trend=0.020) and higher levels of psychological distress (p-trend=0.012). HIV status, HSIL diagnosis, pain and/or bleeding following study procedures were not independently associated with LTFU. In a subanalysis of LTFU among HIV-positive participants, independent predictors of LTFU were reporting a more unpleasant experience with digital-anorectal examination (p=0.048), never having smoked cigarettes (p-trend=0.012) and higher nadir T-cell count (p-trend=0.018).
Conclusions: In addition to a poorer experience of study procedures and subsequent distress, there were some characteristics of participants LTFU in SPANC which are known to be associated with a lower risk of anal cancer including younger age, never smoking, and higher nadir T-cell count. Given that participants were solely informed that GBM (especially HIV-positive) are at elevated risk of anal cancer, it is possible that following an unpleasant examination experience, some men sought further risk factor information online which may have, partly, influenced their decision to discontinue in the study.

CANADA'S ROLE IN ACCELERATING GLOBAL ELIMINATION OF CERVICAL CANCER

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Elimination of cervical cancer by 2030 is a key global objective proposed by WHO. Canadian experts have determined that, to achieve this goal, the Montreal Global HPV prevention objectives need to be met in the targeted population; · 90% of girls fully vaccinated with the HPV vaccine by 15 years old; · 90% of women screened with an HPV test; and · 90% of women identified with cervical disease receive treatment and care.
Methods: A group of 20 prominent international HPV/cervical cancer experts attended a planning workshop and created a report on Canada's role in accelerating global elimination of cervical cancer. National/international recommendations have been made to the Canadian Government that would enable Canadians to become major contributors in efforts to attain the goals set by WHO.
Results: Canadian experts have the scientific expertise and the tools to reach the WHO 2030 objective of decreasing cervical cancer incidence to fewer than 4 per 100,000. The main challenge in the planning of cervical cancer elimination is to secure funding and political support. In order to reach this ambitious objective, innovative approaches must be developed with community leaders to bring the reality of cervical cancer elimination to all communities but especially to communities that experience higher rates of cervical cancer.
Conclusions: Canada should assume international leadership for cervical cancer elimination. Over 100 recommendations for action have been proposed within this important document. Two powerful tools exist for this drive to cervical cancer elimination by 2030: HPV prophylactic vaccines and cervical cancer screening. To take the greatest advantage of these tools, knowledgeable experts must be involved and efforts expedited to implement at least some of these recommendations. If there are delays, the international cervical cancer elimination objective will not be met, with the possible exception of a few rich countries that are already approaching the goal.

POPULATION-BASED HUMAN PAPILLOMAVIRUS INFECTION AND GENOTYPE DISTRIBUTION AMONG WOMEN IN RURAL AREAS OF SOUTH CENTRAL ETHIOPIA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Introduction: In Ethiopia, cervical cancer is the second leading cause of morbidity and mortality from all cancers in women. Persistent infection with Human Papillomaviruses (HPV) plays a key role in the development of cervical intraepithelial neoplasia and invasive cervical cancer. To establish baseline data on the population-based prevalence of HPV infection and genotype distribution, we investigated cervical HPV epidemiology among rural women who attended a trial for HPV-based screening of cervical cancer.
Methods: A population-based study was conducted among rural women aged 30-49 years old in Butajira, south-central Ethiopia. A total of 893 samples were tested for HPV DNA from 1020 screened women. A self-sampling device (Evalyn Brush®, Rovers, The Netherlands) was used to collect a cervico-vaginal sample and HPV presence and genotype was determined using the BSGP5+/6+ PCR with MPG-Luminex read out.
Results: The positivity rate for HPV was 23.2% (177/764). Among the evaluated women in this study, 20.5% and 10.3% were high risk and low risk HPV positive, respectively. Fifty five (7.2%) of the women showed multiple high risk HPV infections. Age-specific prevalence of high- risk HPV infection among the studied women showed that the peak frequency of infection was in the age-group 30-34 years old [58.6% (92/157)] and went down to the 45-49 years old [3.8% (6/157)]. The top five prevalent high- risk HPV genotypes in this study population were HPV16 (57.1%), 35 (20.3%), 52 (15.8%), 31 (14.1%), and 45 (9.6%).
Conclusions: The overall HPV prevalence, high-risk HPV infection and multiple HPV infections were high among the investigated population and HPV16, HPV35, HPV 52, HPV 31, and HPV 45 were the most prevalent genotypes in Butajira district. As a first population-based study in the country, our results can serve as valuable reference to guide nationwide cervical cancer screening and HPV vaccination programs in Ethiopia.

EVOLUTIONARY DYNAMICS OF TEN NOVEL GAMMAPAPILLOMAVIRUSES: INSIGHTS FROM PHYLOGENETIC INCONGRUENCE, RECOMBINATION AND PHYLODYNAMIC ANALYSES.

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: INTRODUCTION: Human papillomaviruses (HPVs) are genetically diverse, belonging to five distinct genera: Alpha, Beta, Gamma, Mu and Nu. All papillomaviruses have double stranded DNA genomes that are thought to evolve slowly because they co-opt high-fidelity host cellular DNA polymerases for their replication. Despite extensive efforts to catalogue all the HPV species that infect humans, it is likely that many still remain undiscovered.
Methods: METHODS: Here we use the sequences of ten novel *Gammapapillomaviruses* (Gamma-PVs) and 214 related HPV sequences to analyse the evolutionary dynamics of these viruses at the whole genome and individual gene scales. Specifically, we use phylogenetic tree incongruence tests to identify incongruence and direct recombination tests to determine whether observed phylogenetic incongruences might be linked to recombination. We further use the novel sequences to estimate the likely times of the most recent common ancestor (MRCA) of the *Gamma-PVs*.
Results: RESULTS: We found statistically significant incongruences between the phylogenetic trees of different genes which imply gene-to-gene variation in the evolutionary processes underlying the diversification of Gamma-PVs. We were, however, only able to detect convincing evidence of a single recombination event which, on its own, cannot explain the observed incongruences between gene phylogenies. The divergence times of the last common ancestor (LCA) of the Alpha, Beta, Mu, Nu and Gamma genera was predicted to have existed between 49.7-58.5 million years ago, before splitting into the five main lineages. The LCA of the Gamma-PVs at this time was predicted to have existed between 45.3 and 67.5 million years ago: approximately at the time when the simian and tarsier lineages of the primates diverged.
Conclusions: CONCLUSION: Consequently, we report here phylogenetic tree incongruence without strong evidence of recombination.

SWAB IT! A VALUABLE SCREENING TO HPV DETECTION AND GENOTYPING AMONG DIFFERENT BODY DISTRICTS. AN UPDATE ON HPV-MRNA DETECTION

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Among HPV infections (HPVI), there is a plentiful literature about cervical swabs, but a poor epidemiology about different body districts. Nowadays, anal cancers are screened for the presence of HPV and the pathological role of this virus is well known. We use mRNA test to distinguish transient HPVIs from persistent or progressive ones even in male population
Methods: From May 2015 to January 2019 we analyzed our database comprehensive of a consecutive pool of 4100 patients (401 male, M) who routinely came to our attention for a HPVI screening. We offered swab tests to look for HPVI at cervical, oral, anal and seminal/urethral area
Results: Cervical: 3649 patients, 2524 HPVI detections, 1336 co-infections, 1256 High risk HPV types detected. Anal: 148 patients (56M), 94 infections (35M), 54 co-infections, 38 High risk HPV types. Oral: 52 patients (20M) 1 infection. Seminal/Urethral: 399 patients, 209 infections (92 co-infections, 86 High risk HPVI). 998 tests patients were followed by E6/E7-mRNA qualitative expression analysis. 206 were positive (15M) with 18 co-infections.
Anal cytology listed 62 patients with a swab test. Among them, 12 patients had a high risk HPVI, and 2 of them had anal carcinoma
Conclusions: Since the male population have a poor compliance in term of awareness about HPVI, we hope to improve screening for general population. Our HPV DNA/mRNA data are not satisfying, but the mRNA analysis is effective to assess the aggressiveness of the infection. Genotyping analysis remains the main screening tool for the evaluation of HPV infection

PROGNOSTIC IMPACT OF HUMAN PAPILLOMAVIRUS INFECTION ON CERVICAL DYSPLASIA, CANCER, AND PATIENT SURVIVAL: A 10-YEAR RETROSPECTIVE ANALYSIS IN SAUDI ARABIA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Cervical cancer is caused by persistent human papillomavirus (HPV) infection. However, HPV prevalence data and survival rates among HPV-infected women are scare in Saudi Arabia. This study assessed the prevalence of HPV genotypes between 2006 and 2016 and determined whether HPV presence predicted cervical dysplasia classification, cervical cancer, or survival among women attending a Saudi referral hospital.
Methods: Cervical biopsy specimens underwent HPV detection using PCR, HPV viral load quantification using quantitative real-time PCR, HPV genotyping using GenoFlow array testing, and tumor suppressor protein $p16^{INK4a}$ expression measurement using immunohistochemistry. Kaplan-Meier plots were constructed to analyze overall survival rates and to assess survival based on age, HPV presence, cervical dysplasia, and cervical cancer.
Results: Of the 316 cervical specimens examined, HPV was detected in 96 (30.4%); 37% had cervical cancer; 14% cervical intraepithelial neoplasia (CIN) III, 5% CIN II, and 17% CIN I. The two most common types detected were HPV-16 (56.2%) and HPV-18 (8.3%). A significant association was found between HPV-16 viral load and disease progression ($P < .001$, Mann-Whitney *U*) and between HPV presence and cervical cancer ($\chi 2$, 56.78; $P < .001$). HPV status was a significant predictor of survival: HPV-negative women had poorer survival rates than HPV-positive women (multivariate Cox regression, hazard ratio, 7.04; 95% CI, 2.03-24.45). In addition, overexpression of $p16^{INK4a}$ was correlated with the severity of histologic abnormality (log-rank test, $P = .049$).
Conclusions: These findings suggest that implementing cervical cancer and HPV screening programs will decrease cervical cancer rates and improve survival rates of women in Saudi Arabia.

SHOULD HUMAN PAPILLOMAVIRUS VACCINATION TARGET WOMEN OVER AGE 26, HETEROSEXUAL MEN AND MEN WHO HAVE SEX WITH MEN? TARGETED LITERATURE REVIEW OF COST-EFFECTIVENESS

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: Human papillomavirus (HPV) vaccination for young women up to age 26 is highly costeffective and has been implemented in 65 countries globally. We investigate the cost-effectiveness for HPV vaccination program in older women (age > 26 years), heterosexual men and men who have sex with men (MSM).
Methods: targeted literature review was conducted on PubMed for publications between January 2000 and January 2017 according to the PRISMA guidelines. We included English-language articles that reported the incremental cost-effectiveness ratio (ICER) of HPV vaccination programs for women over age 26, heterosexual men, and MSM and identified the underlying factors for its cost-effectiveness.
Results: We included 36 relevant articles (six, 26 and four in older women, heterosexual men and MSM, respectively) from 17 countries (12 high-income (HICs) and five low- and middle-income (LMICs) countries). Most (4/6) studies in women over age 26 did not show cost-effectiveness ($65,000–192,000/QALY gained). Two showed cost-effectiveness, but only when the vaccine cost was largely subsidised and protection to non-naïve women was also considered. Sixteen of 26 studies in heterosexual men were cost-effective (ICER = $19,600–52,800/QALY gained in HICs; $49–5,860/QALY gained in LMICs). Nonavalent vaccines, a low vaccine price, fewer required doses, and a long vaccine protection period were key drivers for cost-effectiveness. In contrast, all four studies on MSM consistently reported cost-effectiveness (ICER = $15,000-$43,000/QALY gained), particularly in MSM age < 40 years and those who were HIV-positive. Countries' vaccination coverage did not significantly correlate with its per-capita Gross National Income.
Conclusions: Targeted HPV vaccination for MSM should be next priority in HPV prevention after having established a solid girls vaccination programme. Vaccination for heterosexual men should be considered when 2-dose 4vHPV/9vHPV vaccines become available with a reduced price, whereas targeted vaccination for women over age 26 is unlikely to be cost-effective.

IMPLEMENTATION OF SECONDARY CERVICAL CANCER PREVENTION IN THE REGIONAL CENTER OF CERVICAL PATHOLOGY.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF HPV-ASSOCIATED SKIN LESIONS OTHER THAN WARTS

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Introduction: Objective. To analyse the application of the methods of cervical cancer (CC) prevention in the Regional center cervical pathology (RCCP) Rostov-on-don.
Methods: In 2008, the Regional center of cervical pathology (RCCP) was organized on the basis of the clinical and laboratory complex of the Regional consultative diagnostic center (OCDC) in Rostov-on-don, where the office of human papillomavirus (HPV) vaccination began its work. In 2012 the program of CC screening with the method of liquid-based cytology was introduced for the first time in Russia. It covered 54 medical organizations of the Rostov region (RR). HPV positive patients with abnormal PAP smears are invited to RCCP for making a diagnosis and treatmenLiquid base cytology, the HPV test PCR RealTime, video colposcopy, cervical biopsy by the method of loop excision or conization.
Results: During 2008 - 2018 released 23 newsletters and the booklet were put out, 5 round tables were held for the female population of RO on the etiology and treatment of cervical cancer, the possibilities of vaccination in RCCP. From 2014 to 2017, 188 641 cytological studies were performed, CC being revealed in 189 women - 0.1 % , H-SIL and ASCH in 566 (0.3 %), ASCUS in 377 (0.2%), L-SIL in 23014 (12.2%), absence of intracellular lesion or malignancy (NILM) in 164495 (87.2%). 2162 HPV – positive women aged 19 to 69 years were invited to see a gynecologist in the RCCP. Treatment with conization (622) and cervical excision (830) was performed in 1452 patients. H-SIL and CIS in 1162 women (78%).
Conclusions: Regional screening program with an active call of patients, using such diagnostic method as liquid base cytology and HPV testing, allow timely detection and treatment of precancerous lesions of the cervix, i.e. to carry out secondary prevention of cervical cancer.

DOMINICAN PROVIDER PRACTICES FOR CERVICAL CANCER SCREENING IN SANTO DOMINGO AND MONTE PLATA PROVINCES

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Cervical cancer is the second leading cause of cancer death for women in the Dominican Republic. Pap smear screening in the Dominican Republic has not achieved adequate reduction in cervical cancer mortality. The purpose of this study was to examine Dominican provider practices for cervical cancer screening and the use of national or international screening guidelines.
Methods: We surveyed 101 gynecology specialists, 50 non-specialists, and 51 obstetrics-gynecology residents in the Santo Domingo and Monte Plata provinces of the Dominican Republic regarding their cervical cancer screening practices and use of guidelines. Bivariate (chi-square) analyses were conducted to compare screening practices by demographic and practice characteristics.
Results: The majority of providers followed WHO guidelines (62.9%) and/or Dominican national norms (59.4%). The majority (87%) of providers use time since first sexual activity as the basis for screening initiation; 96% advise screening every 6-12 months. The most commonly used screening test is the conventional Pap smear. Colposcopy was recommended most often for all abnormal Pap results.
Conclusions: Dominican providers report they follow national and/or international cervical cancer screening guidelines. They do not follow age-based screening guidelines, nor have they adopted an extended interval for screening and continue to recommend screening at least annually. A culture of early and frequent screening has consequences in terms of cost, high demand for follow up services, and reduced capacity to reach the populations at highest risk. Early screening also may challenge the acceptability of adopting alternative screening technologies such as HPV testing.

IMPROVING CERVICAL CANCER PREVENTION SCREENING AMONG MEDICALLY-UNDERSERVED WOMEN. A COMMUNITY BASE PROGRAM. A PILOT STUDY.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Our community is comprised of over 6 million people that is very diverse economically, culturally, ethnically and educationally. Twenty-nine percent are foreign born, 22% have not completed high school, 21% live in poverty, 22-26% do not have health insurance and another 400,000 are undocumented immigrants. The purpose of this study was to optimize the cost efficacy of cervical cancer screening in this population through incorporating HPV DNA (DNA) Testing (Cobas) and mRNA (RNA) testing (APTIMA) by reducing the need for diagnostic and therapeutic interventions and increasing the screening interval.
Methods: We partnered with clinics in communities of greatest need to provide cervical cancer screening. Screening consisted of a pelvic exam and pap test. Subsequently HPV mRNA testing was added in April 2019 and DNA testing in August 2019. We evaluated the frequency of diagnostic and therapeutic interventions as a result of the incorporation of HPV testing.
Results: Between 2012 and April 2019, 1606 screening exams with pap were performed with 10.2% abnormal, all of which underwent colposcopy, 50% were treated with LEEP, and 50% required repeat pap. In June 2019, 85 screening exams were performed with pap and RNA. 10.6% of paps were abnormal, 2 of 6 ASCUS paps had RNA, 4 cytologically negative paps had RNA and 2 of 7 unsatisfactory paps had RNA. 3 patients underwent colposcopy with 1 LEEP. In August 2019, 154 screening exams were performed with 12 (7.8%) abnormal paps, 3 had both DNA and RNA, one had RNA only. Twelve had normal paps with DNA of which 8 had RNA. Only 4 (33%) underwent colposcopy and none required LEEP.
Conclusions: The incorporation of HPV mRNA and DNA testing has decreased the frequency of therapeutic interventions in our patient population and allowed for an increase in screening interval to 5 years in 81.6% of our patients.

DOMINICAN PROVIDER ATTITUDES TOWARDS HPV TESTING FOR CERVICAL CANCER SCREENING AND CURRENT CHALLENGES TO CERVICAL CANCER PREVENTION IN THE DOMINICAN REPUBLIC: A MIXED METHODS STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Creating effective programs for cervical cancer prevention is essential to avoid premature deaths from cervical cancer. The Dominican Republic has persistently high rates of cervical cancer, despite the availability of Pap smear screening. This study explored Dominican provider attitudes towards HPV testing and current challenges to effective cervical cancer prevention.
Methods: In this CFIR-driven mixed methods study, we conducted in-depth interviews (N=21) and surveys (N=202) with Dominican providers in Santo Domingo and Monte Plata provinces regarding their perspectives on barriers to cervical cancer prevention and their knowledge and attitudes towards HPV testing as an alternative to Pap smear.
Results: Providers believed the main barrier to cervical cancer prevention was lack of cervical cancer awareness and resulting inadequate population screening coverage. Providers felt Pap smear was widely available to women in the Dominican Republic and were unsure how a change to HPV testing for screening would address gaps in current cervical cancer screening programs. A subset of providers felt HPV testing offered important advantages for early detection of cervical cancer and were in favor of more widespread use. Cost of the HPV test and target age for screening with HPV testing were the main barriers to acceptability.
Conclusions: Providers had limited knowledge of HPV testing as a screening test. The group was divided in terms of the potential impact of a change in screening test in addressing barriers to cervical cancer prevention in the Dominican Republic. Findings may inform interventions to disseminate global evidence-based recommendations for cervical cancer screening.

AGE-STANDARDIZED HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN2+) INCIDENCE RATES BY AREA-BASED SOCIOECONOMIC MEASURES, ALAMEDA COUNTY, CALIFORNIA, UNITED STATES, 2008-2017

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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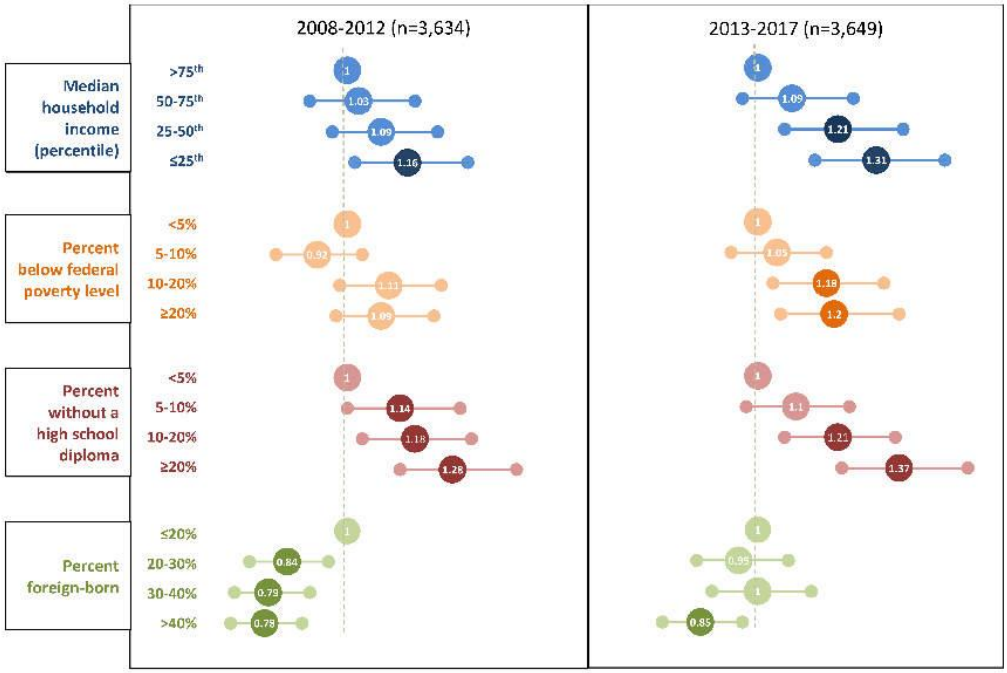
Introduction: Little is known about variations in CIN2+ incidence by socioeconomic status. Evaluating cervical disease by area-based socioeconomic measures may facilitate a broader understanding of CIN2+ incidence, particularly when individual-level data are not available. We analyzed age-standardized CIN2+ incidence rates by area-based measures of income, education, and nativity during two 5-year periods (2008-2012, 2013-2017) following introduction of HPV vaccine, in Alameda County (population 1.7 million), a diverse urban area in California with large Asian and Latina foreign-born populations.
Methods: Geocoded data for census tracts in Alameda County were analyzed from population-based surveillance of CIN2+ (HPV-IMPACT), 2008-2017. We obtained denominators and data on median household income, percent without a high school diploma, percent living under federal poverty level, and percent foreign-born from American Community Surveys. Case counts within census tracts were aggregated across area-based measure strata and age groups (18-24, 25-29, 30-34, 35-39, 40+). Strata were compared using age-standardized incidence rate ratios.
Results: In 2008-2012, CIN2+ incidence was significantly higher for census tracts in the lowest income tier compared to those in the highest tier (Figure 1). In 2013-2017, CIN2+ incidence was significantly higher for tracts in the two lowest income tiers compared to the highest, and the two highest poverty tiers compared with the lowest. In both time periods, tracts with the lowest percentages of high school graduates had the highest CIN2+ incidence, and tracts with the highest percentage of foreign-born residents had the lowest CIN2+ incidence.
Conclusions: We found a persistent inverse association between level of education and income with CIN2+ incidence during the HPV vaccination era, similar to the associations observed in studies of HPV prevalence. The unexpected finding of lower incidence in areas with more foreign-born residents merits further evaluation of possible barriers in accessing cervical cancer screening, risk or protective cultural factors, race/ethnicity and country of origin.

Figure 1: Age-standardized incidence rate ratios of high-grade cervical intraepithelial neoplasia (CIN2+) for four different area-based socioeconomic measures in Alameda County, 2008-2012 and 2013-2017



*statistically significant incidence rate ratios (alpha<0.05) are represented with darker markers

PERCEPTION OF SINGAPORE WOMEN ON CERVICAL CANCER, CERVICAL CANCER SCREENING AND HPV PRIMARY SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Singapore's national cervical cancer screening programme started in 2004 with conventional Pap smear as its screening modality and garnered approximately 30,000 screens per year. In May 2019, the programme adopted human papillomavirus (HPV) primary screening for women 30 years and older. Alongside the change in modality, to improve uptake of cervical cancer screening, HPB conducted perception studies to put the word on HPV screening and to encourage women to go for cervical cancer screening. This presentation focuses on the findings and efforts undertaken as a result of the perception studies.

Methods: Focus group discussions (FGD) were conducted among 74 women between 21 and 70 years old in January 2019. The exclusion criteria were women who have had cervical cancer and/or a full hysterectomy. They were divided into eight groups under three categories: young (21 to 29 years old), mid-age (30 to 49 years old) and older (50 years and above). Questions in the FGD included perception of cervical cancer, cervical cancer screening and HPV-DNA test.
Results: There was a high awareness of cervical cancer as a female health issue. However, their understanding cervical cancer and its screening were limited and perceptions were mostly inaccurate across all age groups. Misconceptions such as bad hygiene as a cause for cervical cancer were particularly pertinent amongst the older age groups. While aware of Pap smear, most women did not know what they were screened for. They cited following-up with a gynaecologist after pregnancy as a reason for undergoing Pap smear. After being informed about the HPV-DNA test, most women chose HPV-DNA test over Pap smear.

Conclusions: The campaign incorporated the findings and focused on raising awareness of HPV, benefits and cost of a HPV-DNA test. Interim findings showed 2.5% increase in cervical cancer screens during the campaign's first month.

ANTI-HPV ACTIVITY IN CERVICOVAGINAL LAVAGES FROM WOMEN USING A GRIFFITHSIN/CARRAGEENAN VAGINAL FORMULATION.

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: More than 290 million women are infected with a human papillomavirus (HPV). Although HPV vaccines are undoubtedly important tools to prevent new infections, vaccination uptake has not been optimal. Carrageenan has been identified as a potential anti-HPV agent that could be used in topical formulations to prevent new infections and possibly accelerate clearance of existing infections. We evaluated the anti-HPV activity of cervico-vaginal lavages (CVLs) from women using a griffithsin (GRFT)/carrageenan multipurpose prevention vaginal gel.
Methods: We tested CVLs from 13 healthy HIV-negative, non-pregnant women who volunteered for a Phase 1 safety trial. Participants were instructed to insert one dose of gel (0.1 % GRFT in 3% carrageenan gel or 3% carrageenan only) vaginally once daily x 14 days. CVLs were collected before gel application and 4h, 8h or 24h after single or multiple gel applications. Anti-HPV activity was evaluated using the HPV16 PsV luciferase assay.
Results: CVLs recovered 4, 8 or 24h after gel application had EC_{50} values between 0.066 and 0.000032 (based on sample dilution). EC_{50} values from CVLs collected at all three timepoints post gel application were significantly lower from baseline EC_{50} values ($p<0.0001$).
Conclusions: Our results support the further development of GRFT/carrageenan multipurpose topical formulation to prevent sexually transmitted infections, including HPV.

HUMAN PAPILLOMAVIRUS (HPV) TYPES ASSOCIATED WITH ORAL FOCAL EPITHELIAL HYPERPLASIA AMONG INDIGENOUS AUSTRALIANS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Focal Epithelial Hyperplasia (FEH) or Heck's disease is caused by HPV types 13 or 32. The study aim was to estimate the prevalence of HPV13 and HPV32 among Indigenous Australians.
Methods: Data was obtained from a large convenience sample of Indigenous South Australians aged 18+ years. Data was collected from Feb 2018 to Jan 2019. Face to face interviews and saliva sample collections were undertaken by experienced Indigenous research officers. The interview included participants' demographic characteristic (age, sex, residential location), social economic status (education level, household income), sexual health behaviours (have received/given oral sex), and health status (general/oral health and quality of life-'EuroQol'). HPV DNA was tested using nested MY/GP+ PCR. All HPV DNA positive samples were sequenced to HPV type viral DNA sequences.
Results: A total 1,011 Australian Indigenous adults aged 18+ years took part. The overall prevalence of HPV13 and/or HPV32 infection was 20.6% (95% CI: 18.1%-23.1%). The prevalence of HPV13/32 infection was highest among those aged 30-39 years (28.2%, 95% CI: 22.1%-34.3%), residing in non-metropolitan locations (26.0%, 95% CI: 22.6%-29.4%), not owning their own car (25.4%, 95% CI: 21.3%-29.4%), chewing tobacco (44.4%, 95% CI: 25.7%-63.2%) and knowing little bit/not much about white fella ways (30.6%, 95% CI: 23.7%-37.5%). A higher prevalence of HPV 13/32 infection was additionally found among those reporting their general health as excellent/very good/good (22.3%, 95% CI: 19.1%-25.5%) and with no reported quality of life problems (as assessed by EuroQoL) (26.9%, 95% CI: 21.5%-32.3%).
Conclusions: The prevalence of HPV13 and HPV32 infections among Indigenous South Australians was associated with age, residential location, socio-economic factors, chewing tobacco status and self-rated health. There appeared to be no association with sexual behaviours.

AWARENESS AND KNOWLEDGE OF HPV AND HPV VACCINE AMONG A NATIONALLY REPRESENTATIVE SAMPLE OF ADULTS IN THE UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Background: HPV vaccine is a safe and effective method for protecting against different types of HPV-related cancers. HPV vaccine is recommended for both sexes and approved by the Food and Drug Administration in the United States (U.S.) for adults aged 27-45 (in addition to being already approved for those aged 11-26). This study examines current population-level knowledge of HPV and predictors of awareness of HPV vaccine among U.S. adults.
Methods: Methods: We analyzed cross-sectional data from the 2018 Health Information Trends Survey (HINTS) (unweighted N=3,504), which collects nationally representative data about the U.S. public's perceptions of cancer. We calculated weighted prevalence estimates for HPV knowledge. We used a weighted multivariable logistic regression to examine associations between awareness of HPV vaccine and predictors (gender, race/ethnicity, nativity, education, household income, and residential area).
Results: Results: Of the sample, 61% reported having heard of HPV; of those who had heard of HPV, 75% knew HPV causes cervical cancer, 29% knew HPV causes penile cancer, and 24% knew HPV causes anal cancer. Around 61% reported HPV vaccine awareness. HPV vaccine awareness was significantly associated with being female (aOR=3.89), being born in the U.S. (aOR=2.08), higher education (aOR=2.53), and higher income (aOR=1.94). Lack of HPV vaccine awareness was associated with being Black compared to White (aOR=0.54).
Conclusions: Conclusion: Compared to data from previous HINTS cycles, our findings show a decline in population-level HPV and HPV vaccine knowledge among adults in the U.S., which necessitates more research, policy, and actions to promote knowledge. We also found evidence of current sociodemographic disparities in HPV awareness. Future research can consider targeting those who are male, Black, not born in the U.S, and have lower education and household income (e.g., subgroups with lower awareness) for health education messages around HPV vaccine.

PRE-VACCINE POPULATION-BASED ASSESSMENT OF HPV GENOTYPES IN CERVICAL CARCINOMA IN SITU AND INVASIVE CERVICAL CANCER IN CATALONIA, SPAIN

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Catalonia, a region of 7.5 million inhabitants in northeast Spain, started in 2008 a school-based, single-cohort HPV vaccination programme targeting 11-year-old girls. We aimed to assess the pre-vaccine HPV-genotype distribution in cervical carcinoma in situ and adenocarcinoma in situ (CIS/AIS) and in invasive cervical cancer (ICC), to determine the potential impact of current HPV vaccines and establish the baseline for future impact evaluation.
Methods: In this population-based study, we identified through cancer registry databases all CIS/AIS and ICC cases diagnosed during 2003-2007 and 1998-2007, respectively, in Tarragona and Girona provinces. Pathology laboratories provided archival formalin-fixed paraffin-embedded specimens. SPF-10PCR/DEIA/LiPA25 system was used for HPV detection and genotyping. Negative cases were assessed for DNA quality. We estimated the HPV prevalence and relative contribution (RC) of the genotypes included in the current HPV vaccines.
Results: During the study period, 837 histologically-confirmed CIS/AIS and 556 ICC cases were identified. A total of 664 CIS/AIS cases and 380 ICC cases with valid HPV DNA results were obtained.

HPV DNA was detected in 95.5% of CIS/AIS and 76.8% of ICC. Invasive adenocarcinoma and older ages were more prone to be HPV negative. RC of HPV16/18 was 61.1% and 75.6% in CIS/AIS and ICC, respectively, and RC of HPV 6/11/16/18/31/33/45/52/58 was 90.9% and 92.8%, respectively. Estimates will be presented by age, histology and cancer stage.
Conclusions: We obtained the baseline data for monitoring future trends.The HPV vaccination programme in Catalonia will substantially reduce the incidence of CIS/AIS and ICC. Surveillance through population-based cancer-registry genotyping of cancer/CIS cases is challenging and costly but will provide with the highest level of evidence on the impact of HPV vaccination on invasive cancer. Catalonia may be used as HPV surveillance site in a potential international network of selected cancer registries to monitor type-specific trends by age, histology and stage.

ASSESSING GAMMAPAPILLOMAVIRUS INFECTIONS OF MUCOSAL EPITHELIA WITH TWO BROAD-SPECTRUM PCR PROTOCOLS

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Human papillomaviruses (HPVs) have been divided into mucosal and cutaneous types according to their primary epithelial tissue tropism. However, recent studies have shown the presence of several cutaneous HPV types in mucosal lesions and healthy mucosa from different anatomical sites.
Methods: In the present study the HPV prevalence and type-specific distribution were assessed in a variety of mucosal samples obtained from 435 individuals, using a combination of two established broad-spectrum PCR primer systems: *Gamma*-PV PCR and CUT PCR, designed and developed by our research group.
Results: Overall HPV prevalence in anal canal swabs, genital warts, cervical cancer biopsies and oral swabs was 85%, 62%, 47% and 4%, respectively. In anal canal swab samples, *Alpha*-PVs were the most frequently detected (59%), followed by *Gamma*- (37%) and *Beta*-PVs (4%). The prevalence and persistence of HPV infection in the anal canal of 226 individuals were further explored. Overall HPV, *Gamma*-PVs and multiple HPV infections were significantly higher in men vs. women (p=0.034, p=0.027 and p=0.003, respectively), multiple HPV infections were more common in individuals ≤ 40 years of age (p=0.05), and significantly higher prevalence of *Gamma*-PVs and multiple HPV infections was observed in HIV-1-positive vs. HIV-1-negative individuals (p=0.003 and p=0.04, respectively). Out of 21 patients with follow-up anal canal swabs, only one persistent infection with the same HPV type (HPV58) was detected.
Conclusions: Our findings suggest that *Gamma*-PVs (except *Gamma*-6-PVs) are ubiquitous viruses with dual muco-cutaneous tissue tropism. Anal canal *Gamma*-PV infections may be associated with sexual behavior and the host immune status. This study expands the current knowledge on *Gamma*-PVs' tissue tropism, providing valuable data on the characteristics of HPV infection in the anal canal and its transmission dynamics.

E-LEARNING ON HPV CANCER EPIDEMIOLOGY AND PREVENTION: AN ICO-UOC PROGRAM

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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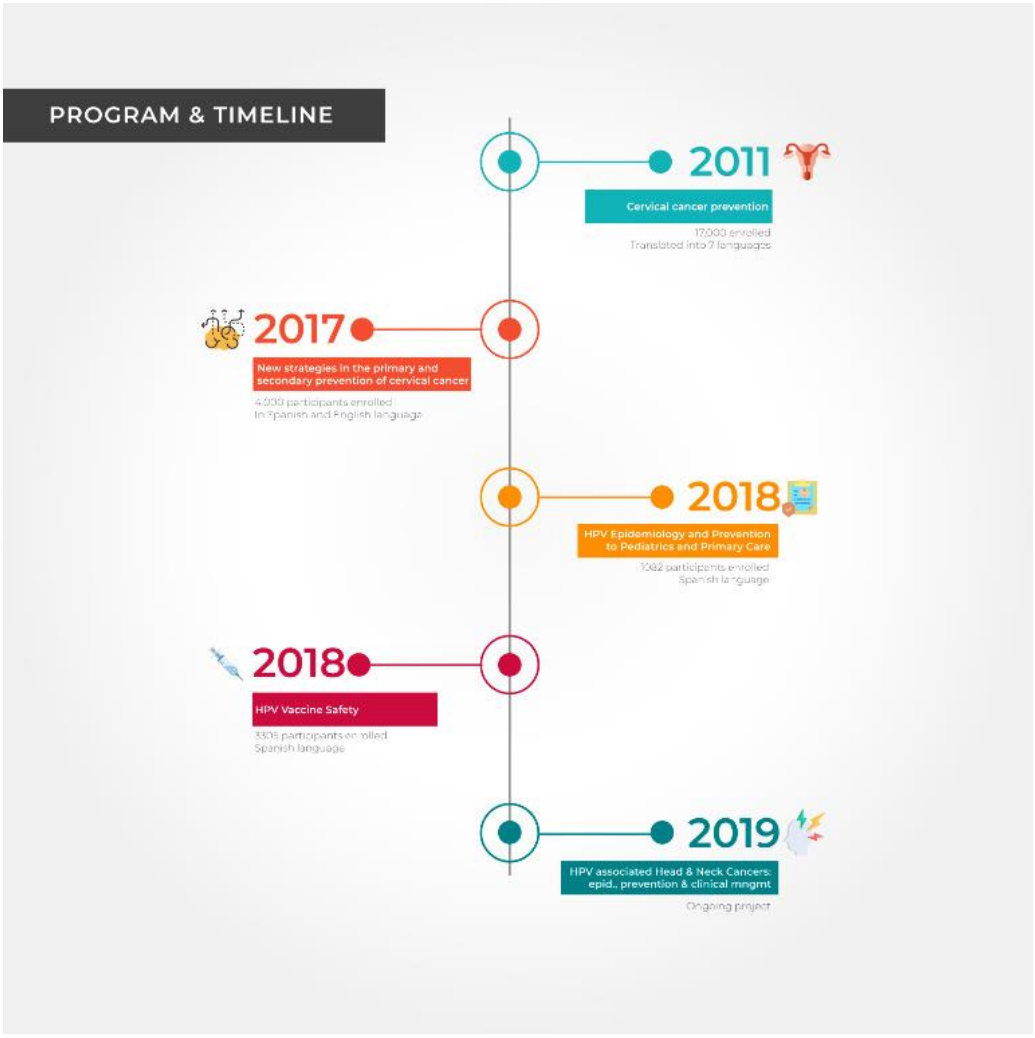
Introduction: Health education is a major step in the fight against preventable diseases such as cervical cancer. The Cancer Epidemiology Research Programme at the Catalan Institute of Oncology (ICO) along with the e-learning program e-oncología have been developing an extensive virtual training program on HPV and associated diseases for over 8 years.
Methods: Since the launching of the first generic course on Cervical Cancer Prevention in 2011, three more courses have been developed to target specific professional profiles and topics. Furthermore, the generic course has been translated to 7 languages, including Japanese and Chinese.



The digital content of all the courses has been developed using interactive elements and multimedia to facilitate learning. The modular structure of the courses allows for the addition of specific modules including the prevention and screening protocols for the country of interest. In evaluating the program the model developed by Moore, Green and Gallis (2009) has been used.

Results: There are two modes of access to the courses: classrooms that are permanently open with free access to any participant and closed classes for specific groups of students with similar interests. The open classroom model is similar to the Massive Open Online Course (MOOC) platforms, i.e. it is accessible to a large number of participants without cost. Students can consult tutors who are permanently available. This methodology results in a completion rate usually over the 60%.

Online Courses	Enrolled	Passed
Cervical Cancer Prevention	18,502	12,849
New strategies in the primary and secondary prevention of cervical cancer	3,982	2,330
HPV Epidemiology and Prevention to Paediatrics and Primary Care	1,084	716
HPV Vaccine Safety	4,949	1,861
TOTAL	**28,517***	**17,756**

***** Of all students, over 10,000 from Latin America.

Conclusions: The use of e-learning has proven to be very useful to provide in short time a large number of health professionals with evidence-based information on cervical cancer prevention. The analysis of the results indicates that: Even with a MOOC type model of delivery it is important to monitor and tutor students to ensure high success rates. Course content should be adapted and adjusted to different professional profiles.

ANAL HPV INFECTION IN GAY AND BISEXUAL MEN IN TWO CITIES IN TANZANIA

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: There are few data on anal HPV infection in men who have sex with men in Sub-Saharan Africa. Such data are important to estimate trends in anal cancer, and to develop prevention, early detection and policy recommendations for this key population. We report on a study of gay and bisexual men in a large and a smaller city in Tanzania in which anal swabs for HPV were obtained.
Methods: As part of a larger study of gay and bisexual men, HIV and STIs in Tanzania in 2012, we obtained anal swabs from 234 gay and bisexual men in Dar es Salaam and Tanga, Tanzania. Swabs were frozen and subsequently tested using COBAS PCR for HPV-16, 18, and any additional high-risk HPV type (31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68). N=157 samples had sufficient material for analysis, while 45 had insufficient material. Data were then analyzed for demographic and behavioral variables associated with high risk HPV types
Results: Of the total sample, median age was 23, and preference for sexual positioning was no anal sex, 25%, receptive only 33%, insertive only 33%, and anal versatile, 10%. Of 157 samples analyzed, 52.2% were positive for a high risk type, including 15.9% for HPV-16 and 9.6% HPV-18. Data on behavioral and demographic risk factors associated with high risk type infection, and then HPV-16 infection are being analyzed at the time of writing this abstract (9/9/2019) and will be completed withing two months.
Conclusions: Data indicate a high level of high risk HPV and HPV-16 in Tanzanian gay and bisexual men, although somewhat lower than for MSM in Western countries. The data are comparable to reports from a Nigerian sample. Data on demographic and behavioral risk factors are currently under analysis.

INHIBITION OF WEE1 KINASE ENHANCES THE EFFECT OF CHEMO(RADIO)THERAPY IN HUMAN PAPILLOMA VIRUS (HPV)-ASSOCIATED CERVICAL CANCER

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: Wee1 regulates G2–M checkpoint of cell-cycle. Inhibition of Wee1 promotes cell mitosis without DNA repair in cases with TP53 deficiency. Since human papillomavirus (HPV) E6 involves the inactivation of p53, cervical cancer is likely to be an appropriate target for Wee1 inhibitor. We herein aimed to evaluate the additional effect of Wee1 inhibitor to the chemo(radio)therapeutics in cervical cancer.
Methods: Cervical cancer cell lines such as Caski (HPV16+), SiHa (HPV16+) and C33A (HPV-, P53 mut), and prostate cancer cell line, LNCap (HPV-, P53 wt), were used to evaluate the effect of Wee1 inhibitor (AZD1775). Cell surviving rate and expression level of related proteins were evaluated by MTT assay and western blotting, respectively. Cell cycle status was evaluated by flow cytometry. A clonogenic assay was performed to evaluate cell reproductive death. All the experiments were evaluated under the treatment condition with cisplatin alone or with radiation.
Results: Stepwise exposure of AZD1775 with cisplatin showed the synergistic effect to HPV positive cell lines (CasKi and SiHa), however, not in HPV-negative cells (C33A and LnCap). The expression level of pCDC2 was reduced after exposure to AZD1775.On the other hand, the expression level of γH2AX was increased, suggesting the cytotoxic effect of AZD1775 by direct DNA damage. Cell cycle analysis showed increased Sub-G0 / G1 population, indicating the induction of apoptosis by AZD1775 exposure. In addition, concurrent chemo-radiotherapeutics condition by irradiation (0 to 10 Gy) with cisplatin treatment showed obvious cell colony reduction with AZD1775 treatment.
Conclusions: Our result indicated the potential of Wee1 inhibition with standard therapeutics such as cisplatin and chemoradiotherapy. Wee1 inhibition can be a novel strategy to improve the prognosis in cervical cancer.

CERVICAL SAMPLES APPLIED TO FTA CARD ANALYSED WITH HPVIR TEST COMPLIES WITH THE INTERNATIONAL GUIDELINES FOR HPV TEST TO BE USED IN CERVICAL CANCER SCREENING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: The collection of the cervix is mainly based on cells suspended in liquid-based media (LBC). In several studies, it has been proven that LBC analysed with Cobas® HPV test meets the criteria of the international guidelines for clinical validation. The indicating FTA card is a dry medium in which applied cervical cells are kept stable at room temperature. HPVIR is a multiplex real-time PCR test that detects and quantifies 12 high-risk HPV. The purpose of this study was to evaluate whether a strategy with cervical specimens collected on the FTA card and subsequently analysed with HPVIR test meets the criteria of the international guidelines for a clinically validated method of cervical cancer screening.
Methods: A non-inferiority test was used to compare the clinical sensitivity and specificity of the candidate test (FTA card and HPVIR) with a reference test (Cobas® HPV test) based on LBC samples. Two clinical samples (LBC and FTA) were collected from 896 participants in population-based screening. We evaluated the clinical specificity in 799 women without ≥ CIN2, and the clinical sensitivity in 67 women with histologically confirmed ≥ CIN2. The reproducibility was studied by performing inter- and intra-laboratory tests of 558 additional clinical samples of which 51% previously tested HPV positive.
Results: The clinical sensitivity and specificity for samples collected on the FTA card and analysed with HPVIR test were non-inferior to the reference test (non-inferiority test score, $p = 1.0 \times 10^{-2}$ and $p = 1.89 \times 10^{-9}$, respectively). Adequate agreement of > 87 % was seen in both the intra- and inter-laboratory comparisons.
Conclusions: Samples collected on the indicating FTA card and analysed with HPVIR test fulfil the requirements of the international guidelines and can therefore be used in primary cervical cancer screening.

SYSTEMATIC HPV SELF-SAMPLING FOR NON-RESPONDERS TO THE GERMAN CERVICAL CANCER SCREENING PROGRAM: PROTOCOL OF THE HASCO-STUDY

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: In 2020, Germany will switch from opportunistic cytology screening to an organized system with co-testing in 3-yearly intervals. In the past, the participation rate was around 70% in a time frame of three years. The non-participators are at higher risk to develop cervical carcinoma. Previous studies have shown an improving number of patients participating when being re-invited. The willingness to participate in self sampling programs is even higher. Based on this information, the ***Ha****nnover* ***S****elf-****Co****llection* study was designed to evaluate a systematic approach towards human papillomavirus (HPV) self-sampling for non-responders to the German cervical cancer screening program.
Methods: 20.000 women aged 30 to 65 years living in the city and region of Hannover, Lower Saxony are randomly included. 10.000 women directly receive a self-sampling kit, the other 10.000 a letter of information and option to participate in the study (opt-out vs. opt-in strategy). Stratifications will be made by age (7 cohorts) and area of living (city vs rural). Women tested positive for high-risk HPV (PCR-based HPV assay) are prompted to get a cytological smear by their gynecologist. Women with normal cytology will be re-checked after 6 months. Suspicious cytology results lead to an immediate colposcopy. Further treatment will be performed according to the German S3-guideline prevention of cervical cancer.
Results: We designed a prospective randomized study to primarily examine: I) the participation rate (opt-out vs. opt-in model), II) the compliance after a positive HPV test, III) the comparison between two self-sampling gadgets, IV) triaging the samples by new DNA-methylation tests.
Conclusions: To get hold of non-responders to cervical cancer screening programs, self-sampling for HPV is a promising option. Aim of this study is to generate an overall recommendation to improve cervical cancer screening in Germany, especially for non-responders. This study is supported by Deutsche Krebshilfe.

VALIDATION OF SELF-REPORTED RECEIPT OF ANAL CANCER SCREENING BY CYTOLOGY OR ANOSCOPY AMONG MEN ATTENDING HIV SPECIALTY CARE IN ONTARIO, CANADA

CLINICAL RESEARCH / MANAGEMENT OF HPV DISEASE IN HIV-INFECTED PEOPLE

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Introduction: Research continues to evaluate the benefits of anal cancer screening among men living with HIV. Validation of self-reported measures of anal cancer screening is important for survey of screening history. It may also inform clinical decision-making regarding offer of screening. Within a multisite clinical HIV cohort, we used medical chart data to validate self-reported receipt of anal cancer screening by anal cytology and/or anoscopy.
Methods: We analysed data from the Ontario HIV Treatment Network Cohort Study, a multi-site clinical cohort in Ontario, Canada. Male participants who were interviewed in 2016-2017 were asked if they had ever had anal cancer screening by anal cytology and anoscopy. Medical chart data regarding anal cancer screening were available for a subset of men. These linked data were used to assess the validity of self-reported receipt of cytology/anoscopy (composite outcome) as evaluated by concordance, sensitivity, specificity and report-to-record ratio.
Results: 416 men had both medical chart data regarding anal cancer screening and self-reported measures of anal cancer screening. A total of 35% and 29% reported anal cytology and anoscopy, respectively; in all, 41% reported either or both. In medical charts, 16% had a record of anal cancer screening via either modality. Concordance between self-report and medical chart abstracted data was 72% (95% CI: 68%, 76%). Sensitivity of the self-reported measure was 91% (95% CI: 84%, 98%) and specificity was 68% (95% CI: 63%, 73%). The report-to-record ratio was 2.57.
Conclusions: Self-reported measures of anal cancer screening have reasonable concordance with medical chart data, with high sensitivity and moderate specificity. The high report-to-record ratio suggests that either men may over-report anal cancer screening, or that they were screened with another procedure or by another provider, which we were unable to ascertain. Nevertheless, these findings suggest a high negative predictive value for men who deny being screened for anal cancer.

INTERVAL CERVICAL CARCINOMA, IS IT MORE COMMON THAN WE THINK?

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Interval cervical cancer is an invasive carcinoma following a normal Papanicolaou smear, in patients with a negative history of cervical-cancer screening. It is a rare entity with no specific risk factors, however it is associated with a persistence of HPV infection.
The purpose of this study was to analyse those cases of invasive cervical cancer diagnosed during an opportunistic screening of women with at least one normal cytology in the previous 3 years.
Methods: A retrospective descriptive study which included data of women diagnosed of rapid-onset cervical cancer in the Lower Genital Tract Pathology Unit of the Mother-and-Child University Hospital Complex of the Canary Islands, in a 10-year period.
Results: Interval cervical cancer was detected in 57 patients with negative cervical cancer screening. The most common histological result was squamous cell carcinoma (56%), and the rest had a glandular component (adenocarcinoma or adenosquamous carcinoma). The clinical stage at the moment of the diagnosis was IB1 in 61%. The main cause of referral was high grade squamous intraepithelial lesion (HSIL), in 44%. 56% were HPV 16 DNA-positive. The most common symptom was vaginal bleeding. The mean age was 47 years, 18% of women were nulliparous, 23% reported long-term oral contraceptive use, 33% were active smokers. Approximately half of the patients had more than ten cytologies throughout their life and most of them had normal cytologies in the last two years.
Conclusions: Interval cervical cancer is a not-so-rare entity, especially in the context of opportunistic screening. These data prove the inefficacy of cytology in the detection of glandular lesions. In order to solve this problem, it would be advisable to act on two levels of prevention: on the one hand, to improve vaccine coverage rates and on the other, to establish a population-based screening with HPV test in women over 35 years.

FIVE-YEAR STUDY OF TWO LEVELS OF PRACTICE-BASED INTERVENTIONS TO ENHANCE PROVIDER RECOMMENDATIONS FOR THE HUMAN PAPILLOMAVIRUS VACCINATION: A PROGRESS REPORT

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Human papillomavirus (HPV) vaccine's uptake in United States (US) lags behind that of other vaccines due at age 11-12 years. Nearly 90% of US teens aged 13-17 years received Tetanus-diphtheria-acellular pertussis vaccine and the first dose of meningococcal conjugate vaccine. Only 51% completed the 2-or-3 dose HPV vaccine series. While HPV vaccination occurs at clinic visits in the US, one-third of US teens aged 13-17 had no preventive visits in the previous 4 years, and 40% had only one such visit. Furthermore, though provider recommendations significantly impact vaccine uptake, parents often report receiving no provider-recommendation for HPV. We sought to refine and test multilevel interventions to address parent, provider, and system-level barriers to HPV vaccine uptake.
Methods: We used parent and provider interviews and focus groups to refine two interventions: reminder-recall communications for parents of 11-12 year-old children due for HPV vaccination and audit-and-feedback reports and resources for providers. We are now evaluating the impact of these strategies on HPV vaccination rates in a stepped-wedge, cluster-randomized pragmatic trial with process evaluation. We are conducting this trial over four years with six similar practices randomized at each year-long step to none, one, or both interventions.
Results: Stakeholder engagement during year 1 resulted in a revised strategy for parent reminder-recall communication and provider audit-and-feedback reports as well as development of new resources to support providers' ability to make evidence-based recommendations. During year 1 we measured baseline HPV vaccination uptake in the 3,322 eligible 11-12 year-olds in the six practices. We launched year 2 in April 2019 with one intervention implemented in two practices, the other in two practices, and none in the remaining two.
Conclusions: Engagement of users optimized interventions before their deployment and evaluation in a pragmatic trial. The ongoing randomized trial will provide evidence of the effectiveness of each intervention alone and together.

ORAL ADMINISTRATION OF POLY-GAMMA-GLUTAMIC ACID SIGNIFICANTLY ENHANCES THE ANTITUMOR EFFECT OF HPV16 E7-EXPRESSING LACTOBACILLUS CASEI IN A TC-1 MOUSE MODEL

CLINICAL RESEARCH / THERAPEUTIC VACCINES – CLINICAL ASPECTS

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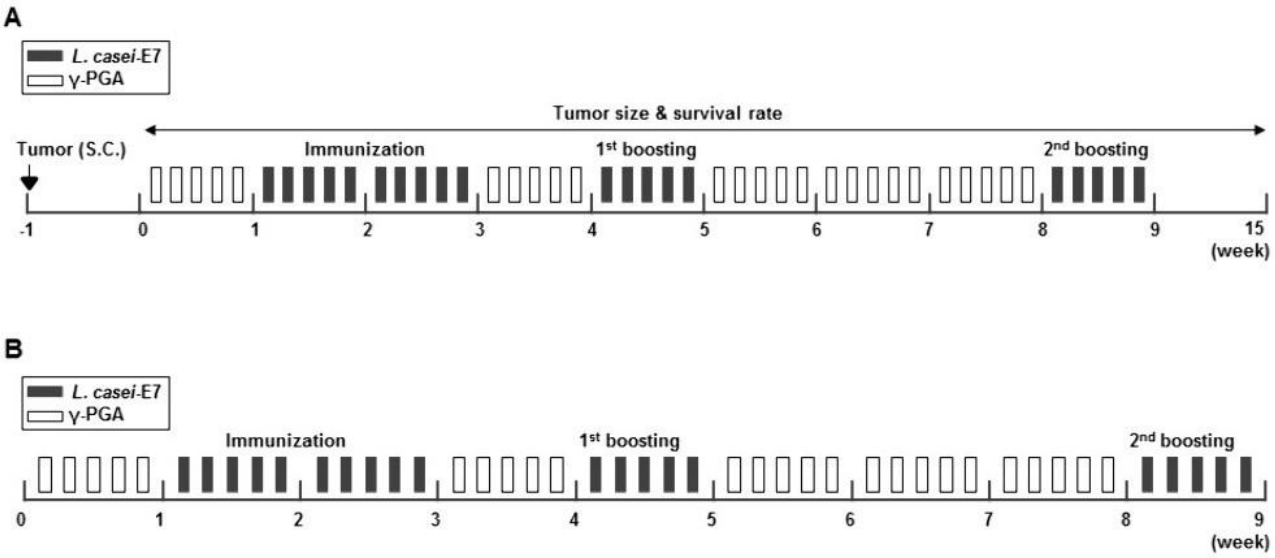
Introduction: The conventional prophylactic vaccines for human papillomavirus (HPV) efficiently prevent infection with high-risk HPV types, but they do not promote therapeutic effects against cervical cancer. Previously, we developed HPV16 E7-expressing *Lactobacillus casei* (*L. casei*-E7) as a therapeutic vaccine candidate for cervical cancer, which induces antitumor therapeutic effects in a TC-1 murine cancer model. To improve the therapeutic effect of *L. casei*-E7, we performed co-treatment with poly-gamma-glutamic acid (γ-PGA), a safe and edible biomaterial naturally secreted by *Bacillus subtilis*. We investigated their synergistic effect to improve antitumor efficacy in a murine cancer model. The treatment with γ-PGA did not show *in vitro* cytotoxicity against TC-1 tumor cells; however, an enhanced innate immune response including activation of dendritic cells was observed. Mice co-administered with γ-PGA and *L. casei*-E7 showed significantly suppressed growth of TC-1 tumor cells and an increased survival rate in TC-1 mouse models compared to those of mice vaccinated with *L. casei*-E7 alone. The administration of γ-PGA markedly enhanced the activation of natural killer (NK) cells but did not increase the E7-specific cytolytic activity of $CD8^+$ T lymphocytes in mice vaccinated with *L. casei*-E7. Overall, our results suggest that oral administration of γ-PGA induces a synergistic antitumor effect in combination with *L. casei*-E7.
Methods:



We did experiments as above figures.
Results:

Figure 1

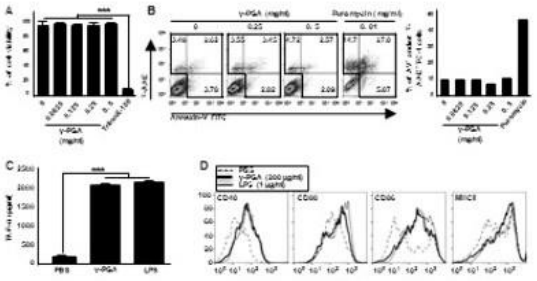


Figure 2

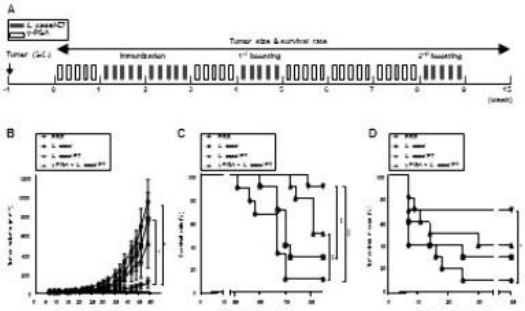


Figure 3

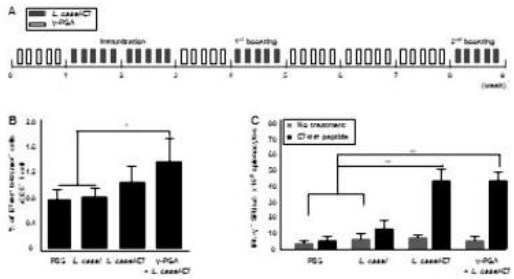


Figure 4

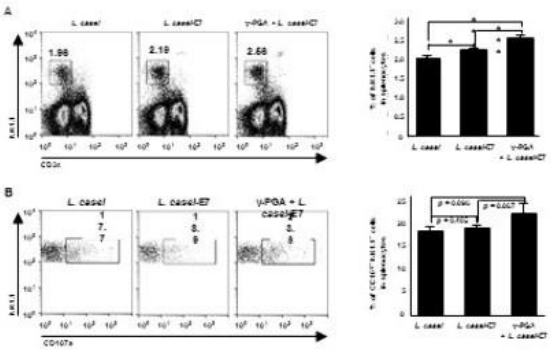
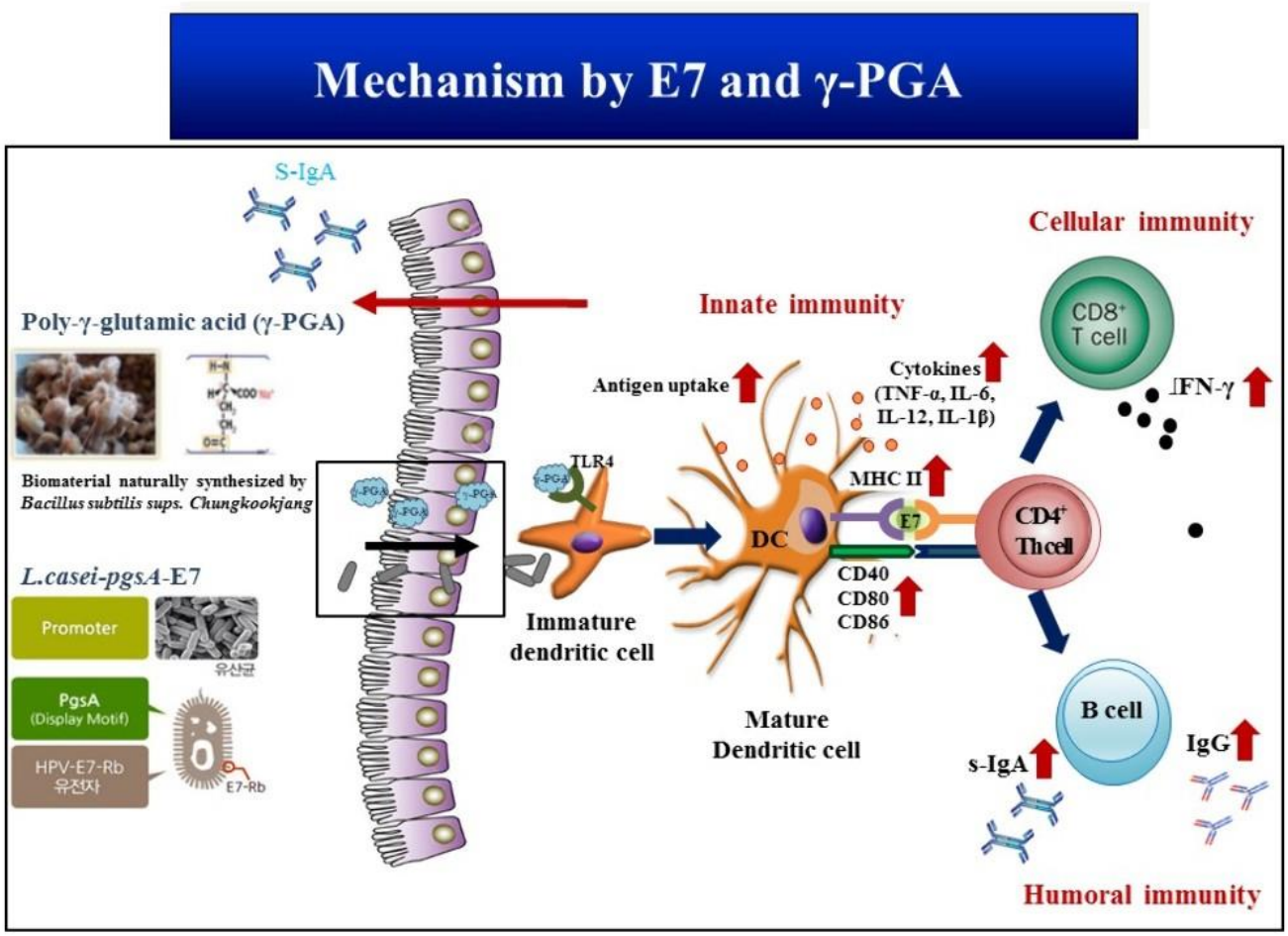


Fig. 1. The effect of γ-PGA on the viability of tumor cells and the activation of immune cells in vitro. Fig. 2. The antitumor efficacy of oral administration with L. casei-E7 and γ-PGA. Fig. 3. Antigen-specific CTL responses to oral administration of L. casei-E7 and γ-PGA. Fig. 4. The increases in NK cells and CD107a-expressing NK cells in response to oral administration of L. casei-E7 and γ-PGA.

Conclusions:



Taken together, γ-PGA may be a potential adjuvant for a *L. casei-E7* therapeutic vaccine to improve the antitumor effect in TC-1 tumor mouse model.

DETECTION OF HPV IN TEENAGE FEMALE SCHOOL STUDENTS FROM TWO PROVINCES IN THAILAND – BASELINE PREVALENCE FOR VACCINE MONITORING

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: There is currently no evidence-based data on prevalence of HPV among teenage female students in Thailand. This baseline information is important for the design of HPV vaccine effectiveness studies and the monitoring of vaccination impact. To detect HPV in female school students, urine collection is an easy and culturally acceptable alternative to cervical samples.
Methods: Female school students of 15-18 years of age from two socio-demographically comparable provinces of Buriram (n=4,205) and Udon Thani (n=4,389) provided self-collected first-void urine samples using Colli-Pee device (Novosanis, Belgium). Samples were refrigerated and processed (concentrating cells from 10 mL to 1 mL) within 96 hrs of collection. HPV was detected with the high-throughput Roche Cobas 4800 system, detecting HPV16, HPV18, and 12 pooled high-risk (HR: 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68) HPV genotypes.
Results: Overall, 12.5% (1,077/8,594) of the students tested positive for HPV (Buriram: 13.2%, 554/4,205; Udon Thani: 11.9%, 523/4,389). The HPV prevalence by genotype and province is presented in the table below. Vaccine types HPV 16 and/or 18 were detected in 4.93% (424) of students tested in both provinces (5.7% Buriram, 4.19% Udon Thani).

Province	Any HPV genotype	Any HPV16	Any HPV18	Any HPV16 and/or 18	HR Non-HPV16/18
Buriram (N=4205)	13.17% (554)	3.9% (165)	2.44% (103)	5.70% (240)	7.47% (314)
Udon Thani (N=4389)	11.92% (523)	3.0% (132)	1.61% (71)	4.19% (184)	7.72% (339)
Overall (N=8594)	12.53% (1077)	3.46% (297)	2.0% (174)	4.93% (424)	7.60% (653)

Conclusions: The prevalence of HPV was similar in both provinces, indicating exposure in approximately 12% of teenage female students in these regions of Thailand. The prevalence of vaccine-targeted HPV16 and/or HPV18 types was 4.93%. Vaccination at the recommended school grade in Thailand (~ 9-12 yrs) should prevent most of these infections.

COMPARISON OF HPV DETECTION IN CERVICAL SWABS AND URINE SAMPLES USING THE COBAS 4800 SYSTEM IN THAILAND

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: HPV detection and genotyping methods used in clinical trials have relied on clinician-collected cervical specimens. Self-collected cervico-vaginal swabs or urine have potential use in screening and epidemiologic studies and may be more acceptable to some populations. We evaluated the feasibility of using urine as a sample for HPV detection and genotyping in a planned study of HPV vaccine effectiveness in Thailand.
Methods: Women (22-70 years) presenting for health check at the gynecology clinic at two hospitals in Bangkok were enrolled. First-void urine was collected with Colli-Pee device (Novosanis, Belgium), followed by clinician-collected cervical smear (liquid-based Pap, Roche, Switzerland) at the time of pelvic exam on the same day. Cells from 10 mL of urine were pelleted, 9 mL supernatant discarded, and cell pellet resuspended in the remaining 1 mL urine. The automated Cobas 4800 system adjusted for each sample type was used for HPV detection. The assay identifies HPV 16 and 18, grouped detection of 12 additional high-risk genotypes, and evaluates sample adequacy.
Results: Paired specimens from 240 women (mean age 46 years) were available for testing. All women found urine sampling with the Colli-Pee device to be acceptable. All samples were adequate for evaluation. Nearly all sample pairs (96.7%) gave concordant results: 198 concordant negative, 34 concordant positive (10 HPV16, 1 HPV18 and 27 other high-risk HPV). Of the 8 sample-pairs with discordant results, failure to detect HPV was evenly split between cervical and urine samples. Detection sensitivity and specificity for HPV16/18 were both 100%. Sensitivity and specificity for other high-risk HPV were 86.2% and 97.6%, respectively.
Conclusions: Urine collection was well accepted to women in this study. HPV detection in urine showed good sensitivity and specific when compared to clinician-collected cervical swabs. These results support the feasibility of using urine for HPV detection for vaccine effectiveness assessment.

THE EFFICACY OF CONVENTIONAL AND LIQUID-BASED CYTOLOGY IN WOMEN INFECTED WITH HPV TYPE 16

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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"Garmonia" Medical Center, Laboratory Department, Yekaterinburg, Russian Federation

Introduction: It is still debated which test should be performed first during cervical screening: the cytology or HPV test. Conventional cytology (CC) and liquid-based cytology (LBC) have different sensitivity which could be dependent upon HPV viral load. We compared the efficacy of CC and LBC (BD SurePath) in detecting koilocytic changes (KC) in HPV-positive women.
Methods: 3370 women aged 18-65 (mean age 30±23 years) undergone cervical co-testing in “Garmonia” Medical Center (Yekaterinburg, Russia) in 2016-2018. HPV test was performed using real-time PCR “HPV-Quant-21” kit (DNA-Technology, Russia), which allows genotyping of HPV for 21 types and evaluation of the absolute viral load (DNA copies/sample) and relative viral load (RVL, DNA copies/10^5 epitheliocytes). Depending on the cytology type, patients were divided into two groups: those who undergone CC (N=1591) and LBC (N=1779). Statistical analysis was carried out using the IBM SPSS Statistics version 21.0 software package.
Results: HPV type 16 was the most prevalent. It was detected in 395 (11.7%) of 3370 women. Among them, 219 women were co-tested with CC (Group 1) and 176 — with LBC (Group 2). KC were detected in 103 (48.0%) patients from Group 1 and 130 (73.9%) patients from Group 2 ($p<0,01$). The KC rate in HPV-16-positive women depended on RVL and the cytology type. When RVL was $<10^3$ DNA copies/10^5epitheliocytes, KC were detected in 37.5% samples using CC and in 56.3% using LBC. When RVL was $10^3< 10^5$DNA copies/10^5epitheliocytes, KC were determined in 40.7% with CC and in 75.4% with LBC ($p<0.01$). When RVL was $>10^5$ DNA copies/10^5epitheliocytes, KC were detected in 57.8% of samples using CC and in 75.8% using LBC ($p<0.01$).
Conclusions: Both CC and LBC failed to detect koilocytes in every forth HPV-16-positive woman with high RVL. HPV test using HPV-Quant-21” kit is more effective for primary screening from this point of view.

MANAGEMENT OF BULKY CERVICAL CANCER: MODIFICATION, INTENSIFICATION, INDIVIDUALIZATION

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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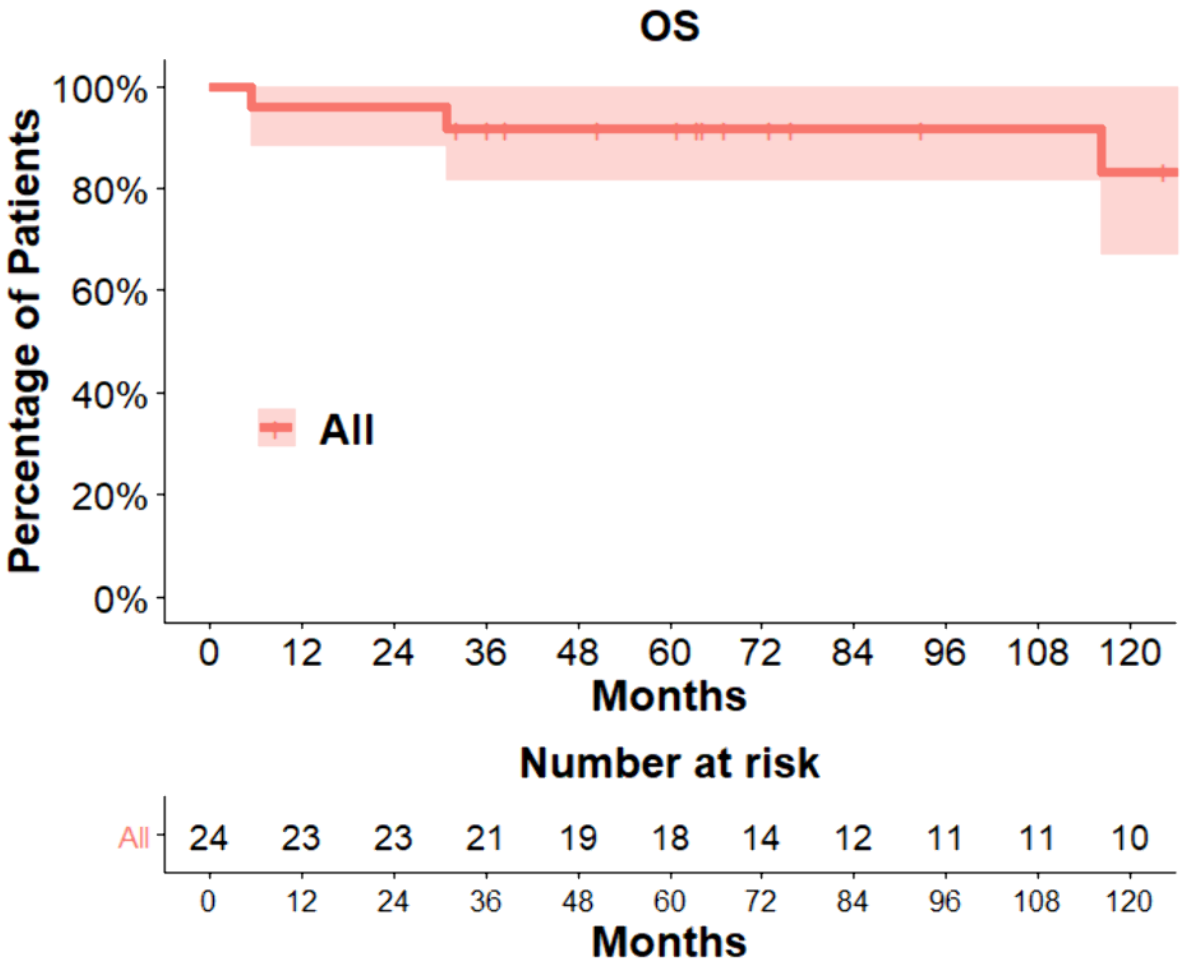
Sun Yat-Sen Cancer Center, Department Of Gynecology, Taipei, Taiwan

Introduction: Definitive chemoradiation and radical hysterectomy with pelvic lymph node dissection both are treatment options for FIGO 2018 stage IB3 and IIA2 bulky cervical carcinoma. However, significant acute and late treatment-related toxicities were observed. Induction chemoradiation with simple extrafascial hysterectomy may potentially reduce this toxicity. This study aims to retrospectively assess the outcomes of this multimodality therapy. Besides, residual tumor pattern and morphological change was presented to guide further optimization of brachytherapy.
Methods: Twenty-four patients with FIGO IB3 and 2A2 bulky carcinoma of cervix received planned induction chemoradiation with weekly cisplatin followed by simple extrafascial hysterectomy during 2000-2017 in our institution were identified. Most patients were squamous cell carcinoma (N=19, 79.2%), followed by adenocarcinoma (N=3, 12.5%), adenosquamous carcinoma (N=1) and poorly differentiated neuroendocrine tumor(N=1).There median age was 51.9 years (range, 40.5-68.7 years) and the median tumor size was 50.3mm (range, 40-95mm). The EQD2 for high risk clinical target volume defined by GEC-ESTRO guideline was between 50 to 60 Gray(a/b=10) in 93.3% of patients. Surgery was performed 47 days (range, 27-70 days) after completion of chemoradiation.
Results: With a median follow-up of 7.03 years (range, 0.4-15.6 years), 5-year overall survival, local recurrence free survival, and distant metastasis free survival were 91.7%, 91.3%, and 95.8%. 11 of 24 (45.8%) experience pathological complete response (pCR). Two late grade 3 urinary toxicity was observed, one patient experienced local recurrence and one had ureteral injury during operation. Although not statistically significance, patients with pCR and squamous cell carcinoma had better outcome.Treatment effect include cytologic alteration such as cytoplasmic vacuolation and nuclear pleomorphism, as well as stromal changes such as fibrosis with mucin pools at the site of previous tumor.
Conclusions: Induction chemoradiation combined with simple extrafascial hysterectomy in FIGO 1B3 and 2A2 bulky cervical squamous cell cancer is feasible with minimal toxicity and good oncological outcome.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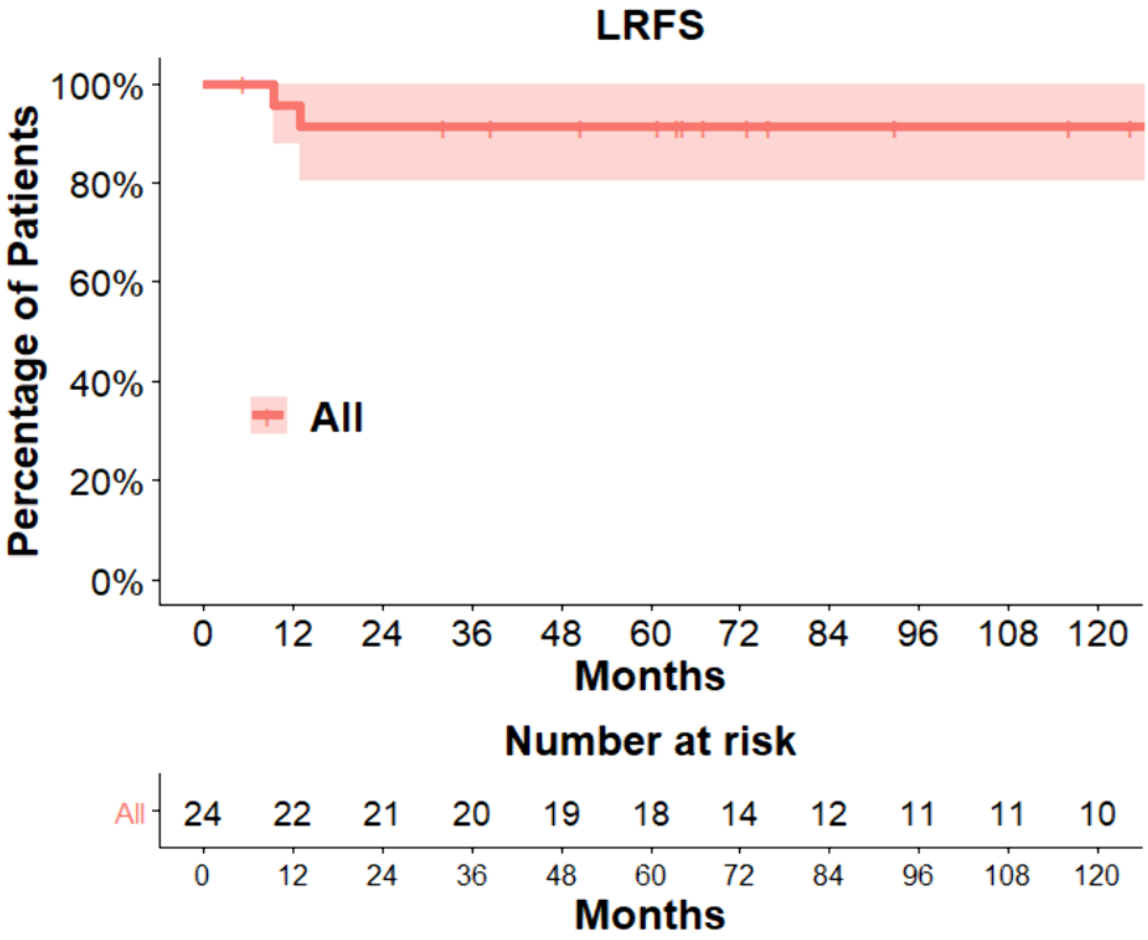
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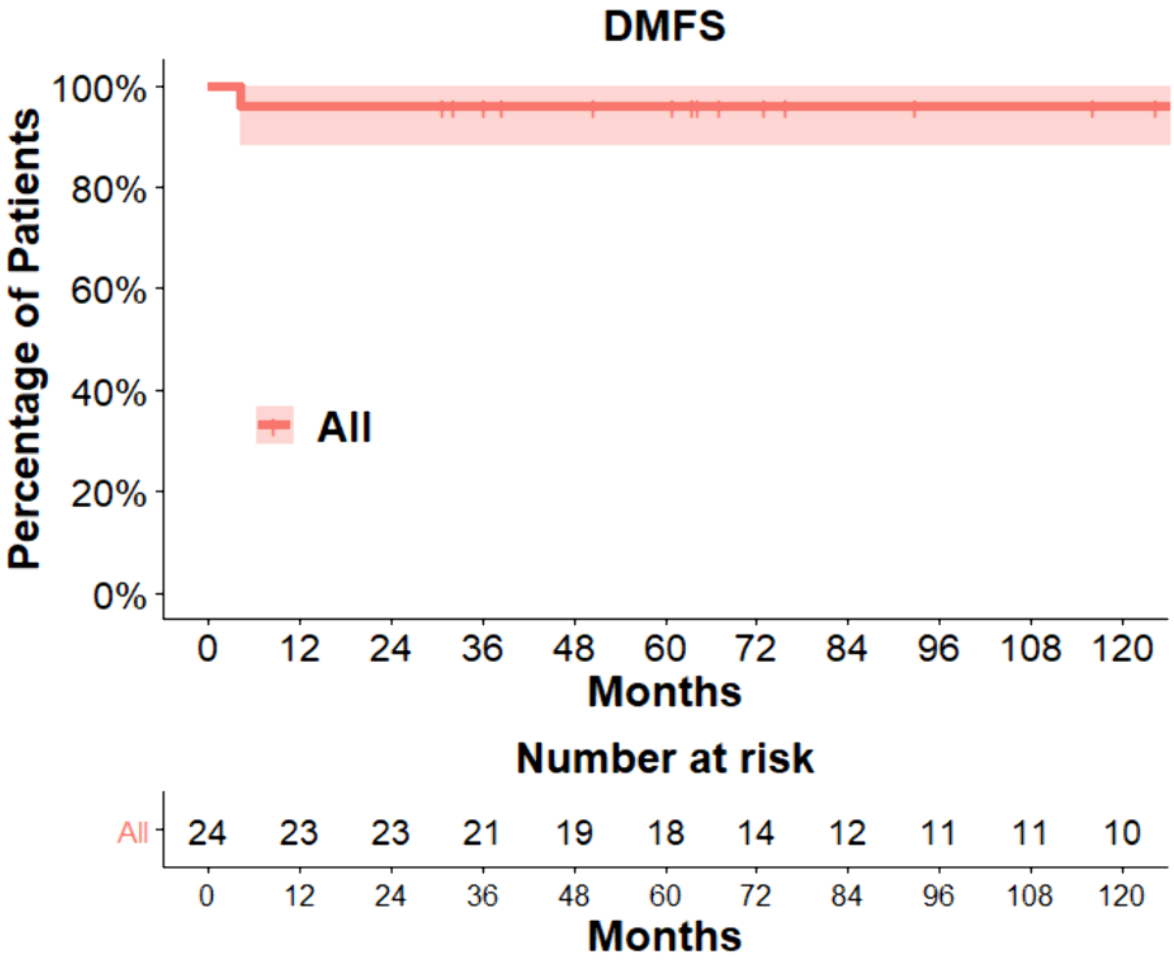
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BURDEN OF HPV RELATED ANOGENITAL DISEASES IN YOUNG WOMEN IN GERMANY – AN ANALYSIS OF GERMAN STATUTORY HEALTH INSURANCE CLAIMS DATA FROM 2012 – 2017

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2007 the German Standing Committee on Vaccination (STIKO) released the first HPV vaccination recommendation for girls. In 2015, HPV vaccination rate was reported with 31% in 15 years old and 45% in 17 years old girls (3 doses). The aim of this study was to evaluate the burden of potentially HPV-related anogenital diseases in young women in years following introduction of HPV vaccination.
Methods: We conducted a retrospective claims data analysis using the Institute for Applied Health Research Berlin (InGef) research database. In the period from 2012-2017, all women from birth cohorts 1989-1992 were identified if they were continuously insured at the age of 23-25. Women were included who were too old (birth cohort 1989) for HPV vaccination as well as women who were eligible for HPV vaccination according to STIKO recommendation (birth cohorts 1990-1992). Using ICD-10-GM codes, the administrative prevalence (95% confidence interval) of genital warts, anogenital dysplasia grade I, grade II and grade III was calculated. Most records of cervical dysplasia most likely resulted from routine screening and further work-up. No information on HPV vaccination status was available.
Results: From 2012-2017 a total of 15,358 (birth cohort 1989), 16,027 (birth cohort 1990), 14,748 (birth cohort 1991) and 14,862 (birth cohort 1992) women at the age of 23-25 were continuously insured. A decrease in the administrative prevalence was observed for genital warts (1.30% (1.12-1.49) birth cohort 1989 vs. 0.94% (0.79-1.10) birth cohort 1992) and dysplasia grade III (1.09% (0.93-1.26) birth cohort 1989 vs. 0.71% (0.58-0.86) birth cohort 1992).
Conclusions: A decrease of the burden of genital warts and anogenital diseases grade III was observed in the younger birth cohorts that were eligible for HPV vaccination according to STIKO. Further research is necessary to confirm the observed trend, including analyses linked to vaccination status.

PREVALENCE OF THE QUADRIVALENT VACCINE HPV TYPES IN THE 5 REGIONS OF BRAZIL: DATA FROM POP-BRAZIL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The quadrivalent HPV vaccine (types 6, 11, 16 and 18) was introduced in the Public Health System of Brazil in 2014. This vaccine prevent infections against the most concerning high-risk (HR) and low-risk (LR) HPV types. Despite the high frequency of this types worldwide, variations in frequency were observed among countries or regions. To analyse the prevalence of quadrivalent vaccine HPV types in the five regions of Brazil.
Methods: We evaluate 7,694 unvaccinated participants aged 16 to 25 years. Individuals were submitted to an interview with sociodemographic and behavioural characteristics, and they provide biological samples from cervical/penile region. Linear Array® Test (Roche) was used for HPV detection and genotyping. We weighted the measures by population size in each capital and by sex.
Results: The distribution of HPV 11 ($p < 0.0003$) and 16 ($p < 0.003$) types varied significantly between regions. The Midwest has the higher prevalence (HPV 11: 4.48%; HPV 16: 10.83%) while the lowest frequencies were found in Southeast (HPV 11: 0.56%; HPV 16: 5.65%). When HPV was grouped in LR-HPV and HR-HPV or vaccine types, the Midwest maintains the highest frequencies, 10.36%, 13.94% and 22.92% respectively. Significant variation between sexes were observed only in the Southeast region with women showing a higher frequency of HR-HPV (11.5% *vs*. 4.03%, $p < 0.021$) and vaccine HPV types (14.38% *vs*. 5.72%, $p < 0.015$) than men. HPV 11 was more frequent in men than in women in Southeast (1.23%. *vs*. 0.17%; $p < 0.042$), in Midwest (8.05% *vs*. 1.84%; $p < 0.019$), and in North (3.19% *vs*. 0.72%; $p < 0.012$).
Conclusions: Brazil has a continental territory with a multicultural population and socioeconomic diversities. These factors may contributed to the differences in HPV vaccine types distribution between the regions and can lead to differences in effectiveness of vaccination across each region.

PREFERENTIAL EXPRESSION OF A SINGLE HPV GENOTYPE IN INVASIVE CERVICAL CARCINOMAS INFECTED BY MULTIPLE HPV GENOTYPES

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: Infection by multiple HPV genotypes is frequently detected in cervical lesions and is considered a risk factor to carcinogenesis. Although evidences indicate that each HPV genotype infection occurs independently, with limited interaction between different genotypes, the carcinogenic process associated with HPV coinfections is not well established. Here we characterized the HPV genome expression and integration in patients with invasive cervical carcinomas associated with infections by multiple HPV genotypes.
Methods: DNA and RNA extracted from the same biopsy fragment of 19 invasive cervical carcinomas were used, respectively, for: (i) hybridization assay to identify the presence of multiple HPV genotypes, and (ii) for RNA-seq analysis to characterize the expression and integration of the different HPV genotypes.
Results: DNA hybridization assay identified the presence of two to six different HPV genotypes in each biopsy. No preferential coinfection between genotypes belonging to the same HPV species was observed, however, HPV16 infection was detected in 18 of the 19 samples. Simultaneously low-risk and high-risk HPVs infection was observed in four samples. The RNA-seq analysis showed that in 16 samples a single HPV genotype was preferentially expressed, with mean coverage per base >20x in 14 samples and >3x in 2 samples, while the renaming genotypes were low (coverage <0.5x) or not expressed. Additional 3 samples showed low number of HPVs reads (<200), indicating low or no expression of the genotypes (coverage per base <0.3x). Finally, the search for HPV/human chimeric transcripts identified the HPV integration site in 12 samples, which a single sample with two different HPV genotypes simultaneously integrated. The integrated HPV genotype was the one preferentially expressed.
Conclusions: The present study indicates that in invasive cervical carcinomas with multiple HPVs infection a single virus type has its genome preferentially expressed, suggesting that this genotype is responsible for the tumor progression and maintenance.

A NATIONWIDE SURVEY ON THE KNOWLEDGE, ATTITUDES, AND PRACTICES REGARDING HPV AND HPV VACCINATION IN THE GENERAL POPULATION OF CHINA

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

F. Zhao[1], S. Hu[1], X. Xu[1], Y. Zhang[2], Y. Liu[3], C. Yang[4], Y. Wang[5], Y. Wang[6], Y. Yu[7], Y. Hong[8], X. Zhang[9], X. Cao[9], L. Xu[9]
[1]National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Department Of Cancer Epidemiology, Beijing, China, [2]Henan Provincial Center for Disease Control and Prevention, Institute For Expanded Program On Immunization, Henan, China, [3]Jilin University, Department Of Epidemiology And Statistics, Changchun, China, [4]Sichuan University, Department Of Epidemiology And Biostatistics/west China School Of Public Health/west China Forth University Hospital, Chengdu, China, [5]Southern Medical University, Department Of Healthcare, Affiliated Shenzhen Maternity And Child Healthcare Hospital, Shenzhen, China, [6]Affiliated Tumor Hospital of Xinjiang Medical University, Department Of Cancer Institute, Urumqi, China, [7]Baotou Medical College, School Of Public Health, Baotou, China, [8]Affiliated Drum Tower Hospital of Nanjing University Medical School, Affiliated Drum Tower Hospital Of Nanjing University Medical School, Nanjing, China, [9]MSD China Holding Co., Ltd, Medical Affairs Department, Shanghai, China

Introduction: Nearly all cervical cancers are caused by HPV. High incidence of HPV-related diseases in China remains a major threat to the nation's public health. HPV vaccines were introduced to mainland China since 2017, which provide promising solutions to relieve cervical cancer disease burden. This knowledge, attitude, and practice (KAP) survey was the first nationwide study to assess the public's awareness and behavior towards HPV and HPV vaccines in the post-vaccine era in China.
Methods: This cross-sectional KAP survey examined the general population (age 18 to 45 years) from 30 provinces in China. The surveys were administered online and offline (ratio 1:1; Figure 1).

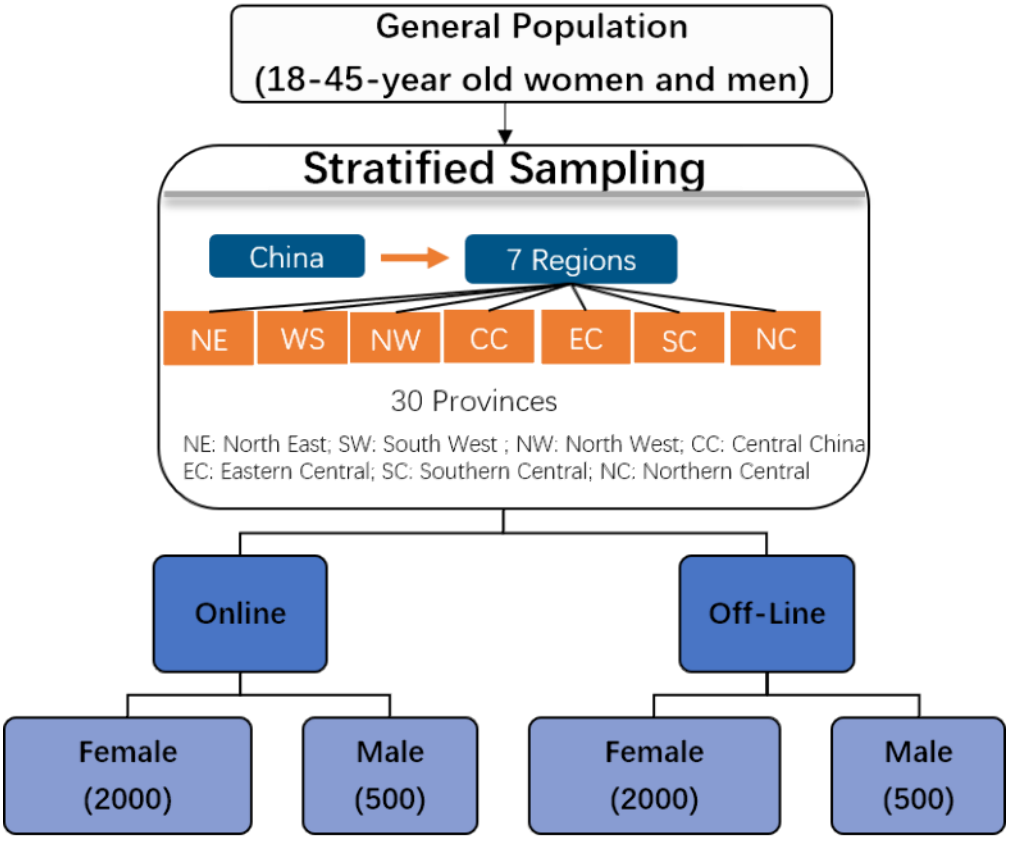

Figure 1. Flowchart of the present study.

Results: 4000 females (32.1±7.81y) and 1000 males (31.8±7.96y) participated in this survey. 31.4% (n=1254) of females and 21.7% (n=217) of males have heard of HPV. 33.7% (n=1347) of females and 22.9% (n=229) of males have heard of HPV vaccines. Among those who have heard of HPV vaccination, 84.8% of females and 69.4% of males agreed that they could benefit from HPV vaccination (Figure 2). The HPV knowledge score (KS) was 5.36±4.71 of 21 for females and 3.93±4.19 of 20 for males; HPV vaccine KS was 3.19±1.46 of 6 for females and 2.41±1.55 of 5 for males. The willingness of vaccination for participants themselves, their sons and their daughters were 49.2%, 43.5% and 66.5% in females; while 34.6%, 30.9% and 41.6% in males(Figure 3).

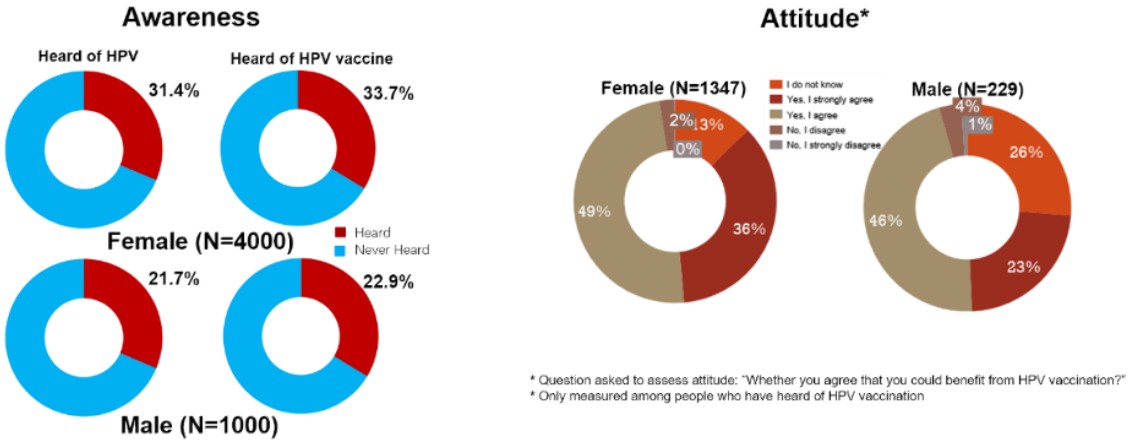

Figure 2. Awareness and Attitudes of HPV and HPV vaccine in females and males.

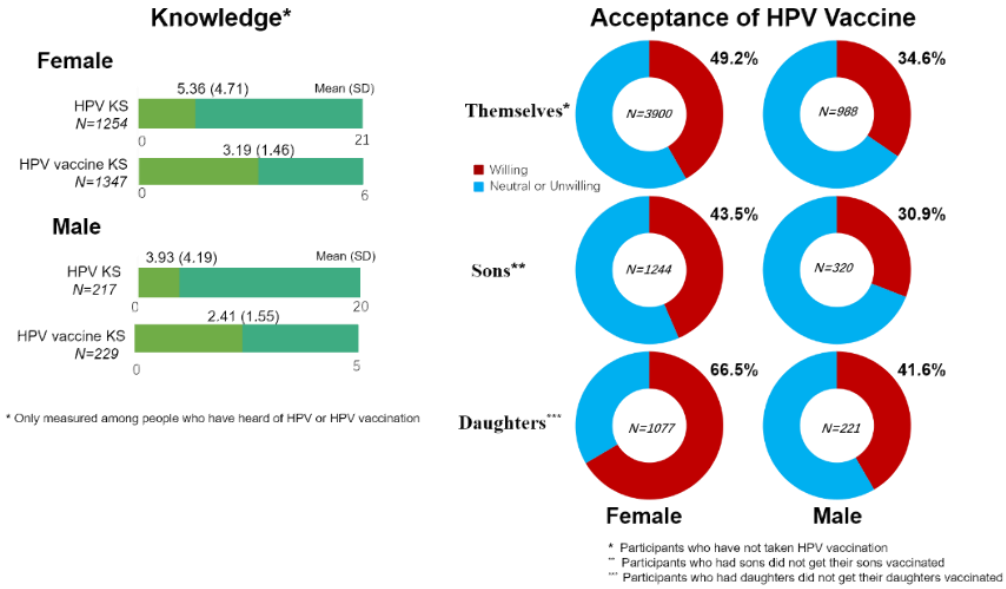

Figure 3. Knowledge of HPV and HPV vaccine and acceptance of HPV vaccine in females and males.

Conclusions: A large proportion of Chinese females and males showed willingness for vaccination, but their knowledge about HPV and HPV vaccines remain limited, indicating that public education needs further improvement to ensure optimal vaccine uptake in China.

EFFECTIVENESS OF SINGLE DOSE OR TWO DOSES OF BIVALENT HPV VACCINE (CERVARIX) IN FEMALE SCHOOL STUDENTS IN THAILAND – STUDY DESIGN AND VACCINATION COVERAGE

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

S. Jiamsiri[1], S. Rerks-Ngarm[1], Y. Chon[2], H.S. Ahn[2], H.-W. Seo[2], N. Premsri[1], S. Park[2], S. Chinaworapong[2], C. Namwat[1], Y. Poovorawan[3], E. Unger[4], N. Poudyal[5], L. Markowitz[6], J.-L. Excler[7], J. Lynch[7]
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Introduction: Thailand introduced a two-dose (2D) HPV vaccination regimen nationwide in grade 5 female school students in 2017. We are conducting an HPV vaccine effectiveness study comparing single dose (SD) and 2D regimens of Cervarix in grade 8 students. The study design and baseline implementation are presented.
Methods: The study is being conducted in Udon Thani (SD) and Buriram (2D) provinces and includes: vaccination of grade 8 students, baseline cross-sectional (CS) surveys for HPV prevalence in unvaccinated grade 10/12 students, and CS surveys for HPV prevalence at Year 2 and Year 4 post-vaccination when grade 8 students reach grade 10/12. Blood is collected from a subset prior to vaccination and at Year 2 and Year 4 for assessment of vaccine immunogenicity. A sexual behavioral questionnaire is collected in a subset of students. For each component, parent or guardian consent and/or female student assent are obtained. The primary endpoint is HPV16 and HPV18 DNA prevalence measured by urine DNA PCR (Cobas 4800) at Year 2 and Year 4 post-vaccination, Effectiveness will be determined by comparing prevalence from Year 2 and Year 4 in vaccinated students with baseline prevalence in unvaccinated students.
Results: In 2018, 15,981 grade 8 female students were vaccinated; coverage was 91.5% (7355/8034) in Udon Thani (SD) and 95.5% (8626/9033) in Buriram (2D). All 8594 randomly selected grade 10/12 students provided a urine specimen for HPV testing. More than 91% of students responded to the sexual behavioral questionnaire. Blood collections were completed from all of the 200-student subset in each province.
Conclusions: The first year of the HPV vaccination effectiveness study was successfully implemented in two provinces of Thailand. The complete baseline assessments and high vaccine coverage will allow future analysis of Year 2 and Year 4 data to evaluate effectiveness of SD and 2D regimens.

HUMAN PAPILLOMAVIRUS PREVALENCE IN URINE SAMPLES FROM TEENAGE FEMALE STUDENTS BY SCHOOL TYPE AND GRADE IN THAILAND

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

S. Jiamsiri[1], P. Nilyanimit[2], J. Chansaenroj[2], S.A. Hyeon[3], H.-W. Seo[3], S. Rerks-Ngarm[1], N. Premsri[1], C. Namwat[1], S. Park[3], S. Chinaworapong[3], E. Unger[4], N. Poudyal[5], L. Markowitz[6], J.-L. Excler[7], J. Lynch[7], S. Vongpunsawad[8], Y. Poovorawan[8]
[1]Ministry of Public Health, Department Of Disease Control, Nonthaburi, Thailand, [2]Faculty of Medical, Chulalongkorn University, Pediatric, Bangkok, Thailand, [3]International Vaccine Institute, Biostatistics And Data Management, seoul, Korea, Republic of, [4]Centers for Disease Control and Prevention, National Center For Emerging And Zoonotic Infectious Diseases, Atanta, United States of America, [5]International Vaccine Institute, Infectious Disease, Seoul, Korea, Republic of, [6]Centers for Disease Control and Prevention, National Center For Immunization And Respiratory Diseases, Atlanta, United States of America, [7]International Vaccine Institute, Pediatric, Seoul, Korea, Republic of, [8]Faculty of Medicine, Chulalongkorn University, Pediatric, Bangkok, Thailand

Introduction: Thailand introduced a two-dose (2D) human papillomavirus (HPV) vaccination regimen nationwide in grade 5 female school students in 2017. We are conducting a vaccine effectiveness study to explore whether single dose (SD) and 2D Cervarix vaccination (grade 8, 13-15 years of age) result in similar reductions in vaccine-type HPV prevalence. The primary endpoint is HPV16 or 18 prevalence assessed by urine DNA at Year 2 and Year 4 post-vaccination compared to unvaccinated students assessed in baseline surveys. Little is known about HPV prevalence among teenage female students in Thailand.
Methods: Study was approved by IRBs/Ethics Committee. Consent and assent were obtained for all participants. Baseline cross-sectional surveys (CS) for HPV prevalence were conducted among unvaccinated female students from high school grade 10 (G10) and vocational school year 1 (VS1) and G12, VS3. In baseline surveys, 8,594 self-collected first-void urine samples were obtained from Buriram (n=4,205) and Udon Thani (n=4,389) provinces. Urine samples were analyzed with Cobas 4800, which detects HPV16 and 18 and 12 pooled high-risk types.
Results: Results: Overall, HPV prevalence was 12.5% (1,077/8,594); Buriram: 13.2% (554/4,205); Udon Thani: 11.9% (523/4,389). Vaccine-type prevalence ranged from 1.3% to 11.2% (Table).

Province	School - Grade	HPV16	HPV18	HPV16/18	Non-HPV16/18	Any HPV
Buriram	G10	1.2%	0.9%	2.1%	4.2%	6.2%
	VS 1	5.8%	3.2%	8.2%	9.0%	17.1%
	G12	2.5%	1.4%	3.4%	6.1%	9.5%
	VS 3	7.6%	5.3%	11.2%	12.6%	23.8%
Udon Thani	G10	0.9%	0.5%	1.3%	2.8%	4.2%
	VS 1	4.8%	2.7%	6.6%	9.27%	15.9%
	G12	1.4%	1.0%	2.2%	6.2%	8.4%
	VS 3	5.3%	2.5%	7.4%	14.5%	21.9%

Conclusions: HPV prevalence among teenage female school students varied by grade and type of school. These data will be used to adjust study design, if needed, for CS surveys at Year 2 and Year 4

post-vaccination among students from the same schools and grades.

PREVALENCE OF DISEASE-ASSOCIATED HPV TYPES AMONG 15-59 YEAR-OLDS IN THE UNITED STATES, 2013-2014

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human papillomavirus (HPV) causes genital warts, cervical precancers, and several types of cancer. Most genital warts are caused by HPV types 6 and 11. Commercial HPV tests used during cervical cancer screening target 14 high-risk (HR) HPV types. Of these, International Agency for Research on Cancer (IARC) has classified 12 as Group 1 (carcinogenic), one as Group 2A (probably carcinogenic), and one as Group 2B (possibly carcinogenic). We estimated the prevalence of and number of people infected with several HPV type categories in the United States.
Methods: The 2013-2014 National Health and Nutrition Examination Survey was used to estimate the prevalence of any HPV (any of 37 types detected using Linear Array), HPV 6/11, 12HR types (HPV 16/18/31/33/35/39/45/51/52/56/58/59, Group 1), 14HR types (Group 1 plus HPV 66/68), and combinations of disease-associated types (12HR+6/11, 14HR+6/11) among 15-59 and 15-24 year-olds, overall and by sex. The number of infected persons was estimated by applying weighted prevalences to U.S. population estimates.
Results: Overall, prevalence of any HPV was 40.6% among 15-59 year-olds (Table 1) corresponding to approximately 76.6 million infected persons (Table 2). In this age group, any HPV prevalence was 42.9% in males and 38.5% in females. 14HR+6/11 prevalence among 15-59 year-olds was 25.4% in males and 20.5% in females corresponding to 23.6 million infected males and 19.6 million females. Among 15-24 year-olds, 14HR+6/11 prevalence was 17.8% among males and 27.2% among females, corresponding to an estimated 3.9 million infected males and 5.8 million females. Estimates for 12HR+6/11 were 2-3 percentage points lower than estimates for 14HR+6/11 in all groups.

Table 1: Prevalence of any HPV and disease-associated HPV type categories, NHANES

	Weighted Prevalence (95% CI)		
Age and HPV type group	**Males**	**Females**	**Total**
Age 15-59 years	N = 1969	N = 2179	N = 4148
Any HPV	42.9 (39.0-46.9)	38.5 (35.2-42.0)	40.6 (37.5-43.9)
6/11	2.7 (2.1-3.6)	1.1 (0.6-2.1)	1.9 (1.5-2.5)
12HR	21.1 (19.0-23.3)	17.4 (14.9-20.2)	19.1 (17.2-21.2)
14HR	23.8 (21.8-26.0)	19.8 (17.4-22.5)	21.8 (19.8-23.8)
12HR+6/11	22.7 (20.3-25.4)	18.1 (15.5-21.0)	20.3 (18.2-22.7)
14HR+6/11	25.4 (23.1-27.8)	20.5 (18.0-23.3)	22.9 (20.8-25.1)
Age 15-24 years	N = 570	N = 575	N = 1145
Any HPV	26.7 (22.1-32.0)	43.0 (36.6-49.7)	34.9 (29.9-40.2)
6/11	1.1 (0.4-3.1)‡	0.8 (0.3-1.9)†	0.9 (0.5-1.9)†
12HR	15.5 (12.1-19.7)	24.1 (18.5-30.9)	19.8 (16.2-24.0)
14HR	17.2 (14.0-21.1)	26.9 (20.9-33.8)	22.0 (18.1-26.5)
12HR+6/11	16.0 (12.6-20.2)	24.5 (19.0-31.0)	20.2 (16.7-24.4)
14HR+6/11	17.8 (14.5-21.6)	27.2 (21.4-34.0)	22.5 (18.6-26.9)

NHANES, National Health and Nutrition Examination Survey; HR, high risk HPV types; 12HR, International Agency for Research on Cancer (IARC) Group 1: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; 14HR, IARC Group 1 and HPV 66 and 68.
†Relative standard error between 30% and 50%; ‡Relative standard error >50%.

Table 2: Number of persons infected with any HPV and disease-associated HPV type categories, NHANES

	Number of infected persons, in millions (95% CI)		
Age and HPV type group	**Males**	**Females**	**Total**
Age 15-59 years			
Any HPV	39.9 (36.3-43.6)	36.8 (33.7-40.2)	76.6 (70.8-82.8)
6/11	2.5 (2.0-3.4)	1.1 (0.6-2.0)	3.6 (2.8-4.7)
12HR	19.7 (17.7-21.7)	16.6 (14.3-19.3)	36.0 (32.5-40.0)
14HR	22.1 (20.3-24.2)	18.9 (16.6-21.5)	41.1 (37.4-44.9)
12HR+6/11	21.1 (18.9-23.6)	17.3 (14.8-20.1)	38.3 (34.3-42.8)
14HR+6/11	23.6 (21.5-25.9)	19.6 (17.2-22.3)	43.2 (39.2-47.4)
Age 15-24 years			
Any HPV	5.8 (4.8-7.0)	9.2 (7.8-10.6)	15.1 (12.9-17.4)
6/11	0.2 (0.1-0.7)	0.2 (0.1-0.4)	0.4 (0.2-0.8)
12HR	3.4 (2.6-4.3)	5.1 (3.9-6.6)	8.6 (7.0-10.4)
14HR	3.8 (3.1-4.6)	5.7 (4.5-7.2)	9.5 (7.8-11.4)
12HR+6/11	3.5 (2.8-4.4)	5.2 (4.1-6.6)	8.7 (7.2-10.5)
14HR+6/11	3.9 (3.2-4.7)	5.8 (4.6-7.3)	9.7 (8.0-11.6)

NHANES, National Health and Nutrition Examination Survey; HR, high risk HPV types; 12HR, International Agency for Research on Cancer (IARC) Group 1: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59; 14HR, IARC Group 1 and HPV 66 and 68.

Conclusions: In the United States, millions of people are infected with a disease-associated HPV type. While most infections will clear, a portion of these will progress to disease. This burden highlights the need for continued cervical cancer screening and HPV vaccination to prevent disease.

INTERVENTIONAL STUDY EVALUATING CERVICAL CANCER SCREENING STRATEGIES FOR WOMEN IN PRECARIOUS CONDITIONS IN FRANCE

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Médecins du Monde (MdM) beneficiaries live in extremely precarious conditions, have limited access to cervical cancer screening (CCS) and are particularly exposed to papillomavirus (HPV) infection. The study aimed to evaluate two CCS strategies: Pap Smear test (PST) versus self-sampling HPV-test+PST in case of positivity).
Methods: Interventional, multicenter, comparative and randomized study. Implementation period: Mars 2017- December 2018. Inclusion criteria: women from 25 to 65 years old in four MdM programs (Healthcare Clinics, mobile clinics in informal settlements and sex workers programs) and four locations (Lyon, Bordeaux, Rouen and Paris). Exclusion criteria: “screening up to date”, “total hysterectomy” or “no sexual intercourses”. Evaluation criteria: proportion of women with complete screening tests (negative HPV test or PST done) and proportion of cytological abnormalities detected (≥ASCUS). Statistical analysis: logistic and Cox regression.
Results: From 799 participants, 112 were excluded (14.0%). Mean age was 41.0 years. Women were mainly from sub-Saharan countries (62.7%), in irregular situation (73.4%) and without health coverage (59.3%). 22.4% have never visited a gynecologist and 53.4% had never done a PST. 23.8% were sex workers. 304 women were assigned to the control arm (CA-PST) and 383 to the intervention arm (IA-HPV+PST). The proportion of screening completeness was 39.5% in the CA and 71.3% in the IA (RR = 1.80 (1.55-2.10)). The CCS was completed in 18.6 days in the CA and 9.5 days in the IA (HR = 2.48, (1.99-3.08)). The proportion of cytological abnormalities detected was 2.0% in the CA and 2.3% in the IA (OR=1.20 (0.42-2.40). There was a high proportion of lost to follow-up after PST referral (60.7% in CA and 63.0% in CI).
Conclusions: Self-sampling HPV test approaches precarious population to CCS, improve its completeness and optimizes PST performance. It is essential to reduce the number of lost to follow-up, especially after a positive HPV-test.

EPIDEMIOLOGICAL PROFILE STUDY OF GENITAL CANCERS IN IN A REGION OF WESTERN ALGERIA BETWEEN 2012 AND 2016

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: A highly probable relationship between several sexually transmitted diseases and the occurrence of genital cancers has been demonstrated by several studies, this has been particularly well documented about cervical cancer and other genital cancers, whose relationship with papillomavirus infections is highly likely. Cervical cancer is the main genital cancer. It represents a real public health problem in Algeria.
Methods: A descriptive retrospective analysis to determine the epidemiological profile of génital cancers over a period of five years between 2012 and 2016 was carried out at epidemiology service of Tlemcen hospital (western Algeria).
Results: A total of 476 cases of genital cancers have been recorded over the last five years, with a peak in 2014 (30%). Cervical cancer was the largest with 233 cases (48.94%). The most represented age group in this study was 51-60 with 31.30%. The average age of genital cancers appearance was 56.5 years, with age extremes ranging from 21 to 92.
Conclusions: Prevention strategies mainly target cervical cancer. The screening program and the vaccine against HPV offer optimism that genital cancers can be prevented.

HPV CIRCULATING TUMOURAL DNA AS A POTENTIAL BIOMARKER TO MONITOR ANAL LESIONS IN HIV-INFECTED MEN WHO HAVE SEX WITH MEN (MSM)

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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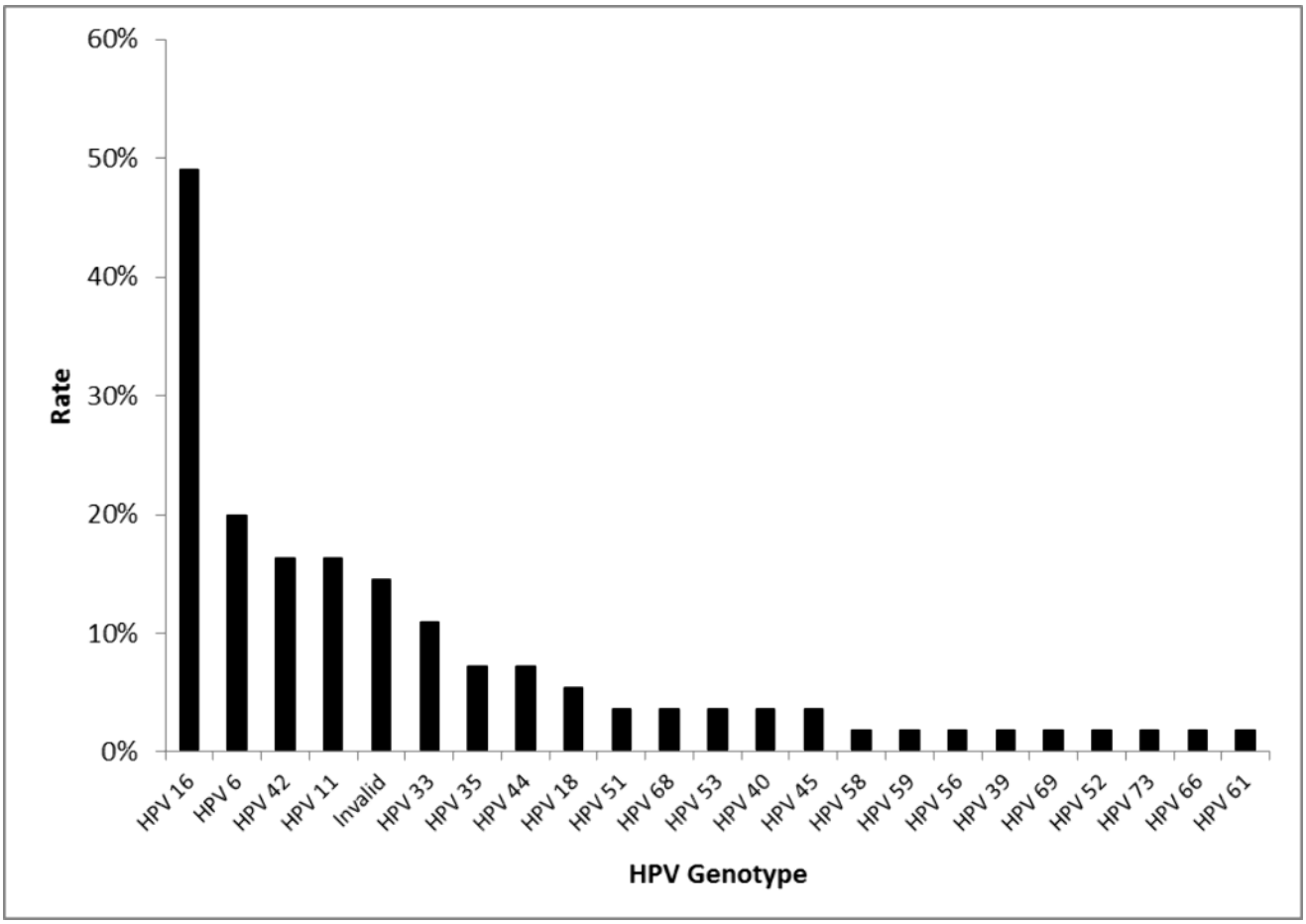
Introduction: Human papillomavirus (HPV) is the principal cause of anal squamous cell carcinomas (ASCC) (>90%). Recently, our team reported the potential interest of HPVctDNA to monitor post-treatment high grade anal intraepithelial neoplasia. No study evaluates HPVctDNA to monitor patients with low grade/high grade anal intraepithelial neoplasia (LGAIN/HGAIN) potentially at risk to develop ASCC.We evaluated HPVctDNA as a predictive and prognostic biomarker in HIV MSM patients particularly affected by LGAIN/HGAIN or ASCC.
Methods: 55 HIV MSM with anal lesion followed at Hôpital Européen George Pompidou (Paris) for HIV infection have been enrolled. We characterized oncogenic HPV genotype in anal biopsies. According to it, HPVctDNA detection by droplet-based digital PCR (ddPCR) was performed on plasma samples collected at the time of anal lesion diagnosis. So far, we have developed ddPCR to detect the most prevalent oncogenic HPV namely HPV16, -18, -31 and -33.
Results: In all biopsies, we reported 22 different HPV genotypes and as expected, HPV16 was the most prevalent (49%). Finally, regarding HPV16, -18, -31 or -33 genotype detected in anal lesion biopsy, corresponding HPVctDNA by ddPCR could have been performed on 30 plasmas. No HPVctDNA was detected in plasma of LGAIN/HGAIN patients. For 7 ASCC patients , 5 have undetectable HPVctDNA. For the 2 positive patients, a longitudinal analysis of HPVctDNA from plasma collected one year before and after diagnosis has been performed. In one case, HPVctDNA was already detected in anterior plasma and in both HPVctDNA became negative following treatment, correlating with a clinical cure.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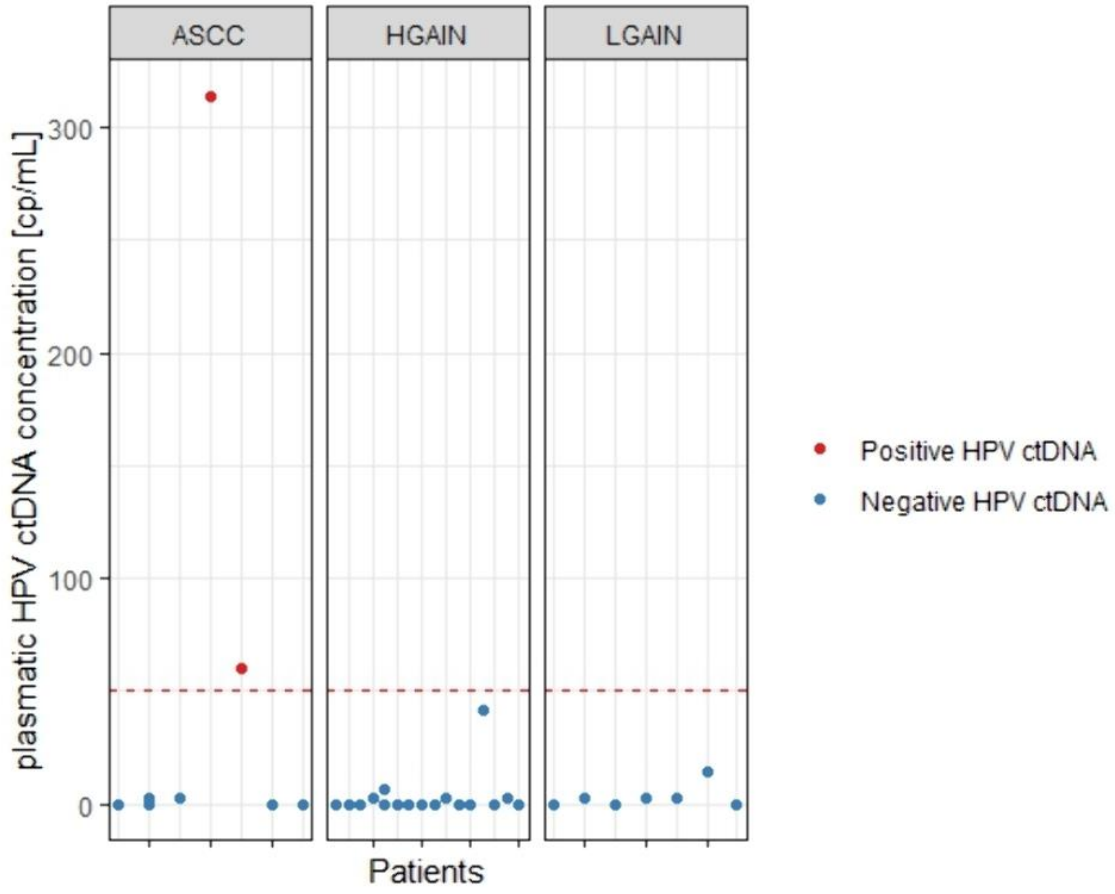
HPV Genotype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100
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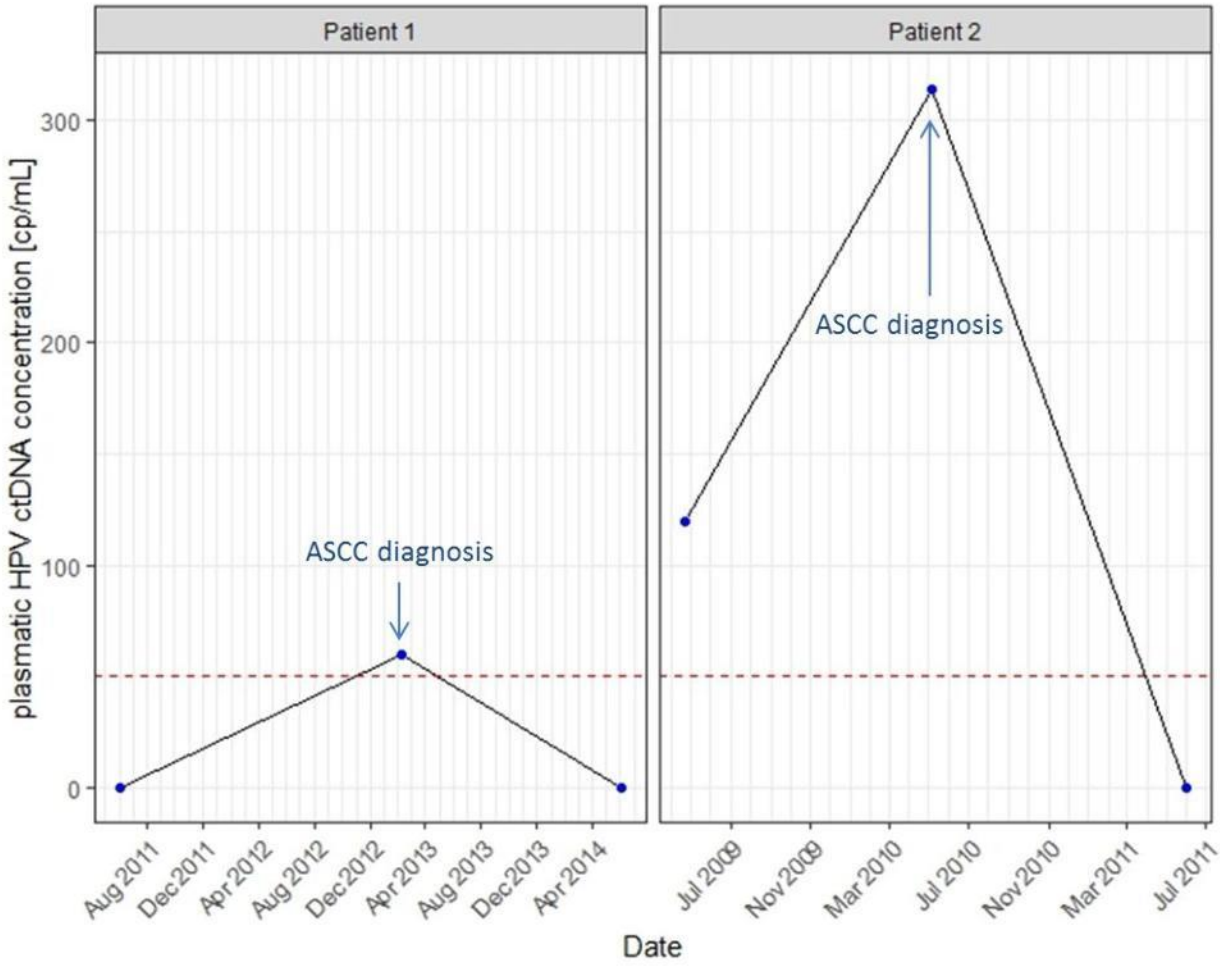
Patients
Positive HPV ctDNA
Negative HPV ctDNA



Conclusions: Our result confirmed the capacity of HPVctDNA as a non-invasive biomarker to detect ASCC and its specificity regarding anal lesion stages. Moreover, the possibility to early detect HPVctDNA before anal cancer diagnosis leads the way for a wider evaluation of HPVctDNA as a complementary tool to monitor ASCC development in at risk HIV MSM population.

PROGRESS IN THE PRE-CLINICAL CHARACTERIZATION OF A BROADLY PROTECTIVE VACCINE AGAINST CUTANEOUS HUMAN PAPILLOMAVIRUSES

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: Building on our previous developments of a modular, thermo-stable vaccine platform based on L2 polytopes (PANHPVAX), we have designed new prototype vaccines targeting multiple cutaneous human papillomaviruses (cHPVs) with the ultimate goal of establishing a broadly protective vaccine for immune compromised individuals, particularly organ transplant recipients (OTRs), who are at risk of HPV-related, chronic and recurrent skin disorders.
Methods: Eight *Escherichia coli*-expressible antigens were designed by fusing different L2 polytopes derived from several different cHPVs to the *Pyrococcus furiosus* thioredoxin scaffold. The immunogenicity of genetic fusion derivatives of the above antigens with the immunogenicity-enhancing, heptamerization domain OVX313 was also investigated. Twenty novel, cHPV targeting Pseudovirion-based Neutralization Assays (PBNAs) were established and deployed for assessing the levels of neutralizing antibodies (Ab) elicited by vaccination of mice and guinea pigs.
Results: All candidate vaccines featured a high (>70°C) thermostability. In the murine, but not in the guinea pig model, we observed an immunogenicity enhancement induced by the OVX313, which resulted in the production of higher neutralizing Ab titers. The tested vaccine prototypes induced robust *in vitro* neutralization of at least 8 different cHPV types in mice. We observed two leading vaccines, which enable neutralization of 17 different cHPVs in guinea pigs, and 11 of the 13 tested cHPV types in mice. Importantly, we also obtained evidence of cross-neutralization of 13 high-risk HPV types, including HPV16 and HPV18.
Conclusions: The broad cross-neutralizing responses induced by the L2 polytope vaccines will be further investigated by passive transfer of immune sera in a murine challenge model. The experience being acquired with the clinical development of PANHPVAX, a GMP pipeline will be established for this newly developed cHPV vaccine. The availability of a cHPV vaccine is important not only to bridge an existing clinical gap, but also to elucidating the causal role of HPV in skin carcinogenesis.

HIGH APOBEC3B MRNA EXPRESSION IS ASSOCIATED WITH HUMAN PAPILLOMAVIRUS TYPE 18 INFECTION IN CERVICAL CANCER

BASIC RESEARCH / VIRUS – HOST INTERACTIONS"

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Introduction: The APOBEC3 (A3) proteins belong to a family of cytidine deaminases and exhibit the ability to insert mutations in DNA and/or RNA sequences. APOBEC3B (A3B) has been associated with increased risk of breast cancer and is also described as an important risk factor for cervical cancer development. Recent reports demonstrate the possible role of A3B as a DNA mutagen with a consistent high expression in several cancer types. Nevertheless, the data concerning A3B influence on HPV infection and cervical cancer seem limited and show discrepancies. The aim of this study was to investigate the role of A3B expression level on cervical cancer in affected women positive for different HPV types.
Methods: Tumor samples from uterine cervix biopsies were collected from 216 women registered at Hospital do Câncer II of Instituto Nacional de Câncer José de Alencar Gomes da Silva (INCA, Brazil, Rio de janeiro). A3B expression levels were quantified from RNA samples extracted from cervical biopsies using real-time quantitative PCR and differences in A3B expression levels were compared among samples according to viral type and clinical variables were analyzed.
Results: Median A3B expression levels were higher among HPV18+ samples when compared to HPV16+ counterparts, and were also increased compared to samples positive for other HPV types. In squamous cell carcinoma, HPV18+ samples also showed increased median A3B expression when compared to Alpha-9 species or only to HPV16+ samples.
Conclusions: In conclusion, our findings suggest that A3B expression is differentially upregulated in human cervical cancer samples infected with HPV18 and indicate that A3B could be potentially used as a biomarker for cervical cancer and HPV infection.

HUMAN PAPILLOMAVIRUS INFECTION AMONG WOMEN ATTENDING FAMILY PLANNING CLINIC IN NIGERIA: PREVALENCE, CORRELATES AND CO-INFECTION WITH CHLAMYDIA TRACHOMATIS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Infection with high-risk genotypes of human papillomavirus (HPV) is considered the main cause of invasive cervical cancer. A number of epidemiologic studies have suggested that HPV and *Chlamydia trachomatis* (CT) play a synergistic role in the etiology of cervical intraepithelial neoplasia and subsequent cervical cancer. The current study aimed to evaluate the HPV prevalence and the risk factors for co-infection with CT among women attending family planning clinic in Nigeria.
Methods: Following enrolment, 90 patients were screened for IgG antibodies to virus-like proteins of HPV types 6, 8, 16, and 18. CT seropositivity was tested by enzyme-linked immunosorbent assay for the detection of IgG and IgM antibodies.
Results: The prevalence of HPV IgG was 20%. Seropositivity for CT IgM was 77.8% while the IgG was 0%. A total of 10 women (11.1%) were seropositive for both CT IgM and HPV IgG antibodies. Seropositivity for HPV IgG was significantly associated with age at marriage ($P < 0.001$), current Chlamydia infection ($P < 0.011$), and number of children ($P < 0.025$), while seropositivty for HPV IgG and Chlamydia trahomatis IgM was significantly associated with age at coitarche ($P < 0.028$), number of life sex partners ($P < 0.033$), and history of multiple sexual partners ($P< 0.002$).
Conclusions: This study highlights a high seroprevalence for *Chlamydia trachomatis* and HPV co-infection among female family planning attendees in Nigeria. Risk factors associated with *Chlamydia trachomatis* and HPV co-infection are age at first sexual intercourse, number of life sex partners and history of multiple sexul partners.

DETECTION OF HIGH-RISK HPV GENOTYPES IN CLINICIAN-COLLECTED AND SELF-COLLECTED SAMPLES STORED ON FTA CARDS FROM WOMEN IN RURAL EASTERN CAPE, SOUTH AFRICA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Infection with persistence human papillomavirus (HPV) has been associated with cervical cancer. The burden of HPV is high among South African women. There is limited data on the prevalence of high-risk (HR)-HPV genotypes in the rural Eastern Cape Province. Therefore, we aimed to investigate and compare HR-HPV prevalence in clinician-collected and self-collected genital specimens.
Methods: Cervical clinician-collected and vaginal self-collected specimens were collected using Viba-brush and smeared onto FTA cards. A total of 417 women aged 30 to 98 years were recruited from community-based clinic in the rural Eastern Cape, South Africa. HR-HPV genotypes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, and 59) were determined using the *hpVIR* real-time PCR assay.
Results: HR-HPV prevalence was 26.4% (109/413) in clinician-collected and 27.9% (115/413) in self-collected specimens. The overall concordance was 86.9% (95% CI:83.3-90.0) and kappa value of 0.67 (95%CI:0.588 to 0.750), showing a good agreement. HPV33/52/58, HPV16 and HPV35 were the most commonly detected genotypes in both clinician-collected and self-collected specimens. Most participants (77.2%) reported that they would be willing to perform self-sampling at home and return for testing. However, 95.7% of participants preferred clinician-collection to self-collection. The study participants gave a positive response about self-collection, with 89.4% reporting to have had self-confidence, 94.9% reporting to be very Intrigued and 71.4% reported experiencing slightly discomfort when taking the specimen.
Conclusions: High HR-HPV prevalence was observed. There was good agreement between the self-collected and clinician-collected specimens. Self-collection can have a positive impact in cervical screening programme in South Africa by increasing coverage of women in rural areas, those who are unable to visit the clinics and women attending clinics where cytology based-programme are not functioning effectively. The data of HR-HPV genotypes will assist in identifying ways to prevent and monitor HR-HPV genotypes that are not covered by the vaccines currently in use.

REASONS FOR NOT ATTENDING CERVICAL CANCER SCREENING AND ASSOCIATED FACTORS IN RURAL ETHIOPIA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Attaining high coverage of Cervical Cancer(CC) screening is a key to effectively combat the high burden of cervical cancer globally. Social, economic, and cultural factors have been associated with participation of women in CC screening programs elsewhere. This study aimed to identify factors associated with the non-participation in cervical cancer screening and reasons for non attending.
Methods: A community-based randomized cluster trial was conducted at the Butajira Health and Demographic Surveillance Site (HDSS) in Ethiopia. A total of 2356 women aged 30-49 in 22 clusters were invited to receive one of the two screening approaches (self-collected HPV tests or VIA). The differences between those who participated and who did not were analyzed according to the socio-demographic and economic characteristics.
Results: Out of sensitized women (2356) in both arms, 15.9% and 49.5% and did not attend cervical cancer screening using self-sampling for HPV and VIA, respectively. In both arms, compared with women who attended screening, women who did not were more often in the VIA arm, living in rural area, engaged in informal occupations, and were not married. The majority of non-attendants in both HPV (89%) and VIA (77.3%) arms perceived themselves to be at no risk of CC. The main reasons given for refusal of screening were lack of time to attend screening (73%), physical wellbeing (14%), and fear of screening (6%).
Conclusions: We found that perceived time constraint was the most important barrier to screening. Perceived no risk of getting the disease, living in rural settings, and women occupations have also played a key role for women to withhold screening. To increase the uptake of cervical cancer screening at community level, a swift and convenient screening-service has to be offered to allow participation in a short time and at the doorstep. Also, awareness creation activities should address misconceptions related with screening.

PREVALENCE OF GENITAL HUMAN PAPILLOMAVIRUS (HPV) INFECTION BEFORE IMPLEMENTATION OF THE VACCINATION PROGRAM IN BOTSWANA

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Improved life-expectancy among people living with HIV in Botswana has led to a concomitant increase in HPV-associated cervical cancer in this population. A prophylactic HPV vaccination program began in February 2015 for 9 to 13-year old girls in Botswana. However, limited data is available on HPV prevalence prior to implementation of the program. Therefore, this study aimed to determine the baseline prevalence of high-risk HPV, specifically HPV 16 and/or 18, in young unvaccinated women in Botswana.
Methods: We enrolled 719 unvaccinated female students at the University of Botswana. High vaginal swabs were collected at enrollment and every six months thereafter. DNA was extracted using easyMag® and nested polymerase chain reaction (PCR) was performed to determine HPV status. HPV-positive samples were genotyped by restriction fragment length polymorphism PCR.
Results: Average age was 19.3 years (range=18-26; SD=1.14 years). HPV prevalence at baseline was 58.3% (419/719); HPV 16 and/or 18 (with or without other genotypes) was detected in 33.9% (142/419) of these cases. At baseline, 9 (1.3%) of the 719 participants were HIV-infected. 144 participants had 6-month follow-up collections and the results showed that 69 (47.9%) were HPV-positive and 75 (52.1%) were HPV-negative. 84.1% (58/69) of the HPV-positive cases remained positive at 6-month follow-up visit, and 31% (18/58) of the persistently infected cases had HPV 16 and/or 18. At 12-month and 18-month follow-up visits, HPV 16 and/or 18 was detected in 34.2% (27/79) and 31.7% (13/41) of the HPV positive cases, respectively.
Conclusions: Among 18 to 26-year old unvaccinated women in Botswana, overall prevalence of genital HPV was 58.3%. HPV 16 and/or 18 were more likely to be associated with persistent infection at the 6-month follow-up visit, suggesting a significant infection rate in the pre-immunization period. However, more studies are needed to determine prevalence of other HPV genotypes against which the vaccine might not confer immunity.

DETECTION OF CERVICAL LESIONS IN AIR-DRIED SMEARS BY LINEAR CLASSIFIERS BASED ON REAL-TIME PCR ANALYSIS OF MRNA AND MIRNA EXPRESSION LEVELS

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Modern cervical screening for high-grade precancerous lesions and cancer is based on cytology and high-risk human papillomavirus (HR-HPV) DNA detection. However, the sensitivity of cervical cytology is limited and strongly influenced by human factors. HPV testing, despite its higher sensitivity, offers a much lower specificity, and, moreover, is misses HPV-negative lesions. Therefore, the search for new biomarker-based cervical screening methods is actual. Here, we evaluated the diagnostic performance of miRNA and mRNA-based molecular classifiers in >600 air-dried smears of patients with underlying cervical lesions of different grade, cancer, or without the disease.
Methods: The air-dried Pap stained cervical smears were collected at four clinical settings. Total nucleic acid extraction, identification, genotyping and viral load assessments of HR-HPV DNA were performed using commercial kits (AO Vector-Best, Russia). The levels of 26 candidate microRNAs and 12 mRNAs were assessed by real-time qPCR. Levels of miR-124 and MAL2 promoter methylation were analyzed by methyl-sensitive PCR.
Results: The concentrations of selected miRNAs and mRNAs changed gradually with the increase of lesion severity. CDKN2A was the best mRNA marker of cervical lesions whereas miR-375 was the best miRNA marker. In general, miRNA-based classifiers were better at discriminating HSIL from LSIL, but mRNA-based classifiers better discriminated HSIL from NILM. The miRNA classifiers generated false-positive results in patients with atrophy and after surgical interventions. The best classifier, based on combined analysis of 3 miRNAs and 3 mRNAs, was more predictive for HSIL than HPV testing at the similar sensitivity. The degree of HSIL risk estimated by combined classifier correlated to MAL2 and miR-124 methylation, but not to the HPV viral load or genotype.
Conclusions: Our results support the feasibility of using cellular biomarker-based methods in cervical screening. This approach could provide advantages over HPV-based triage tests, as it skips the cases of transient HPV infection, and can detect HPV-negative lesions.

PREVALENCE OF HIGH-RISK AND LOW-RISK HPV AND COMMON GENOTYPES IN TIGRAY, ETHIOPIA

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: In Ethiopia, cervical cancer (CC) is the second leading cause of cancer-related mortality, only surpassed by breast cancer. An estimated 7,095 women are diagnosed with CC annually in Ethiopia, translating into an age standardized rate (ASR) of 26.4 compared to 6.6 for the USA and 7.1 for the UK Data on low-risk (LR) and high-risk (HR) HPV prevalence and genotypes is lacking. Our study aims to determine the prevalence of LR and HR HPV and genotypes in one region of Ethiopia.
Methods: We conducted HPV DNA testing on 290 women in Tigray, Ethiopia, to determine the prevalence of LR and HR HPV as well as common genotypes. Trained resident physicians collected cervical swabs at two hospitals following a regional mobilization. DNA extraction was conducted in Addis Ababa using the QIAamp DNA Mini Kit (Qiagen). HPV DNA testing was conducted at the Charité - Universitätsmedizin Berlin using Luminex multiple HPV genotyping (MPG). Ethical and IRB approval were obtained prior to beginning the study.
Results: Out of 290 samples collected, 222 were tested for HPV. One-fourth (25.2%) tested positive for HR or LR HPV or both. Prevalence of HR HPV and LR HPV was 17.1% (95% CI, 12.0% - 22.0%) and 10.4% (95% CI, 6.4% - 14.4%), respectively. Concurrent HR and LR HPV was found in 2.3% of samples. Among HR HPV (n = 38), the most common genotype was HPV 16 (21.1%) followed by 31 (13.2%), and 52 (7.9%). HPV 16 was present in 31.6% of all HR HPV cases. More than one HPV genotype was present in 31.6% of HR HPV cases.
Conclusions: Our study is among the first to explore LR and HR HPV and genotypes among women in Ethiopia. Testing from other sites in Ethiopia along with our data will help in designing vaccination campaigns, including selecting the most appropriate genotypes to target.

THERMOSTABILIZATION OF A BROAD-SPECTRUM HPV VACCINE CANDIDATE

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: Licensed HPV vaccines are comprised of L1 protein assembled into virus-like particles (VLPs), and provide protection limited to the 2-7 vaccine-types of the 13 hr mucosal HPV types. Hence, current vaccines do not eliminate the need for costly routine cervical screening. CxCa burden is particularly high in resource-poor countries that can afford neither expensive HPV vaccines nor screenings, and in which vaccine distribution is hindered in part due to vaccine cold-chain requirements. To increase the clinical spectrum of vaccine protection, chimeric RG1-VLPs have been generated that repetitively present the conserved HPV16 cross-neutralization epitope 'RG1' (aa17-36) of the minor protein L2 within an immunodominant surface loop of HPV16 L1-VLPs. In animal immunizations, RG1-VLPs induced robust (cross-)protection against 13 mucosal hr, additional low-risk and cutaneous HPV. RG1-VLPs are currently being produced under cGMP conditions for first-in-human clinical studies.
Methods: To facilitate worldwide vaccine distribution, RG1-VLPs were lyophilized formulated with aluminum hydroxide (alum) as dry powder vaccine and thermostability to elevated temperatures (4 vs. 37/50/70°C over 1 month) was examined by immunizing mice.
Results: Antisera from lyophilized RG1-VLP-immunized groups showed robust anti-HPV16-L1-VLP and anti-RG1-peptide ELISA titers, while antibody responses were markedly decreased in groups immunized with non-lyophilized RG1-VLPs (+alum) incubated at 50°C and 70°C. (Cross-)neutralization against HPV16/18/31/39 and beta-HPV8 was generated by lyophilized RG1-VLP stored at 50°C and 70°C, but was undetectable following immunization with stored non-lyophilized RG1-VLPs. Thus following incubation at higher temperatures lyophilized RG1-VLPs maintain the ability to induce (cross-)neutralization, although a trend towards reduced cross-neutralization was seen in the highest temperature group (70°C). A T cell response, as measured by IFN-g ELISPOT, was induced in splenocytes from mice immunized with lyophilized and non-lyophilized RG1 VLP independent of the incubation temperature.
Conclusions: In conclusion, lyophilization affords thermostability to this RG1-VLP vaccine candidate, and may eliminate cold-chain requirements that would facilitate its global distribution.

CHARACTERIZATION OF THE EARLY CELLULAR IMMUNE RESPONSES INDUCED BY HPV VACCINES AND THE RELATION TO LONG-TERM IMMUNITY

BASIC RESEARCH / IMMUNOLOGY

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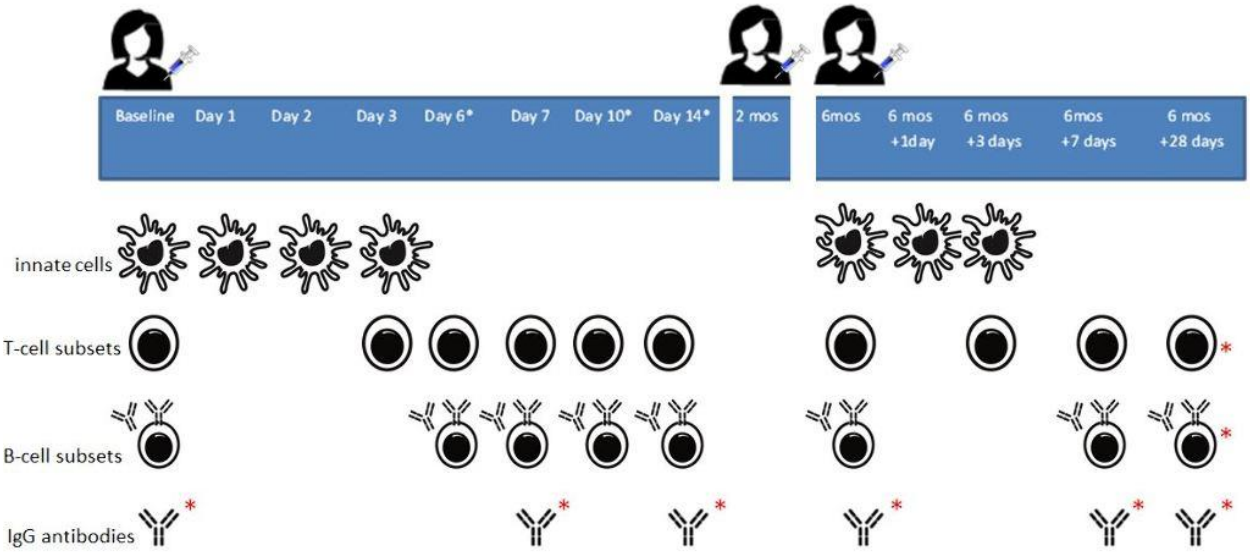
Introduction: Vaccination triggers a broad array of immune cells. Early reactions, almost immediate after vaccination, include induction of innate cells followed by recruitment and activation of antigen-specific B- and T-cells. Here we analyzed a broad set of cellular immune responses induced by two HPV vaccines to get a better understanding of the early immune responses. Moreover, we aim to correlate these to long-term antibody and cellular responses.
Methods: We studied innate, plasma-cell, antibody, memory B-cell and T-cell responses in 20 healthy HPV-seronegative women following a three-dose schedule with either the bivalent or nonavalent HPV vaccine. Peripheral blood samples were collected at eight predefined time-points after primary vaccination and four time-points post booster. These samples were subjected to in-depth analysis of up to 250 innate and adaptive immune cell subsets by the means of high-throughput flow cytometry (Blanco et al., JACI, 2018), specific antibody levels analyzed by VLP-based MIA and specific memory B and T-cell responses determined by ELISPOT assays.



*= HPV serotype-specific
Participants are either vaccinated with the 2vHPV or 9vHPV vaccine according a three-dose schedule.
*Day 2, 6, 10 and 14 were only included in the time-finding part of this study and only sampled from the first five donors.

Results: Preliminary results revealed early expansion of several innate cell subsets already at day 1 after the first vaccination. This expansion was followed by a T-cell response at day 3, showing a difference in

Thelper (Th) cell skewing between the two vaccinated groups. All donors showed a clear expansion of plasma cells at day-7 post vaccination, which were mostly of the IgG1 isotype. This study is ongoing and the cellular dynamics of all participants at all time points will be analysed.

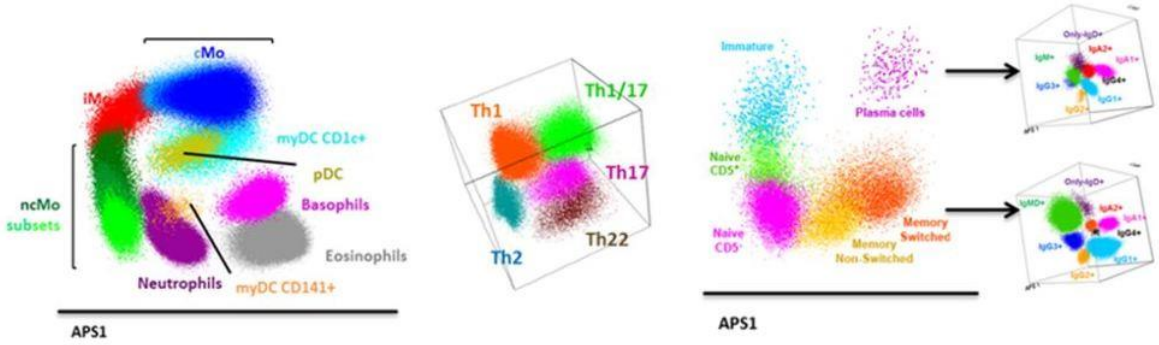


Figure 2: Automatic population separator (APS) overview of all studied cellular populations.

Conclusions: For the first time we show an in depth analysis of immune cellular dynamics after HPV vaccinations. Based on the preliminary analysis of the results after the first HPV vaccination we conclude that the kinetics of multiple innate and adaptive immune cell subsets post vaccination are intriguing. All results will be further discussed at the IPVC.

GENES REGULATED BY HPV 16 E6 AND HIGH EXPRESSION OF NFX1-123 IN CERVICAL AND HEAD AND NECK CANCERS

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: High-risk (HR) HPV E6 partners with cellular proteins to dysregulate genes and pathways, driving cancer development. The protein partnership between HPV type 16 E6 (16E6) and NFX1-123 is multifunctional — NFX1-123 modulates activation of telomerase by 16E6, leading to cellular immortalization. NFX1-123 also regulates keratinocyte differentiation. 16E6 augments this, leading to greater HPV L1 expression while also protecting against typical concomitant cell cycle arrest. We previously found genes upregulated in a microarray of keratinocytes with 16E6 and overexpressed NFX1-123 and wanted to determine if expression of NFX1-123 and these genes were increased in cervical and head and neck cancers.
Methods: The Cancer Genome Atlas (TCGA) and The Human Protein Atlas were searched for NFX1 expression (all isoforms) in cervical and head and neck cancers. 19 previously identified 16E6/NFX1-123 upregulated genes were analyzed for expression in cervical and head and neck cancers in these databases. Immunohistochemical staining for NFX1-123, Notch1, Keratin 1, and Ki67 was performed in normal, HPV 16+ preneoplastic, and HPV 16+ cancer cervical samples.
Results: There was high expression of NFX1 in both cancers compared to normal tissue. In primary cervical samples, NFX1-123, Notch1, and Ki67 expression were also increased in HPV 16+ cervical cancers. Furthermore, we found that 89% (17 out of 19) and 100% (19 out of 19) of 16E6/NFX1-123 upregulated genes in keratinocytes were significantly overexpressed in cervical and head and neck cancers, respectively, in both mRNA and protein.
Conclusions: NFX1-123 is highly expressed in cervical cancers, and cervical and head and neck cancers have high expression of genes previously identified as altered by NFX1-123 and 16E6. This association highlights that NFX1-123 may significantly participate in HPV cancer initiation and progression.

ESTIMATED NUMBER OF CASES OF HIGH-GRADE CERVICAL LESIONS DIAGNOSED IN THE UNITED STATES BY HISTOLOGICAL GRADE, 2008 AND 2016

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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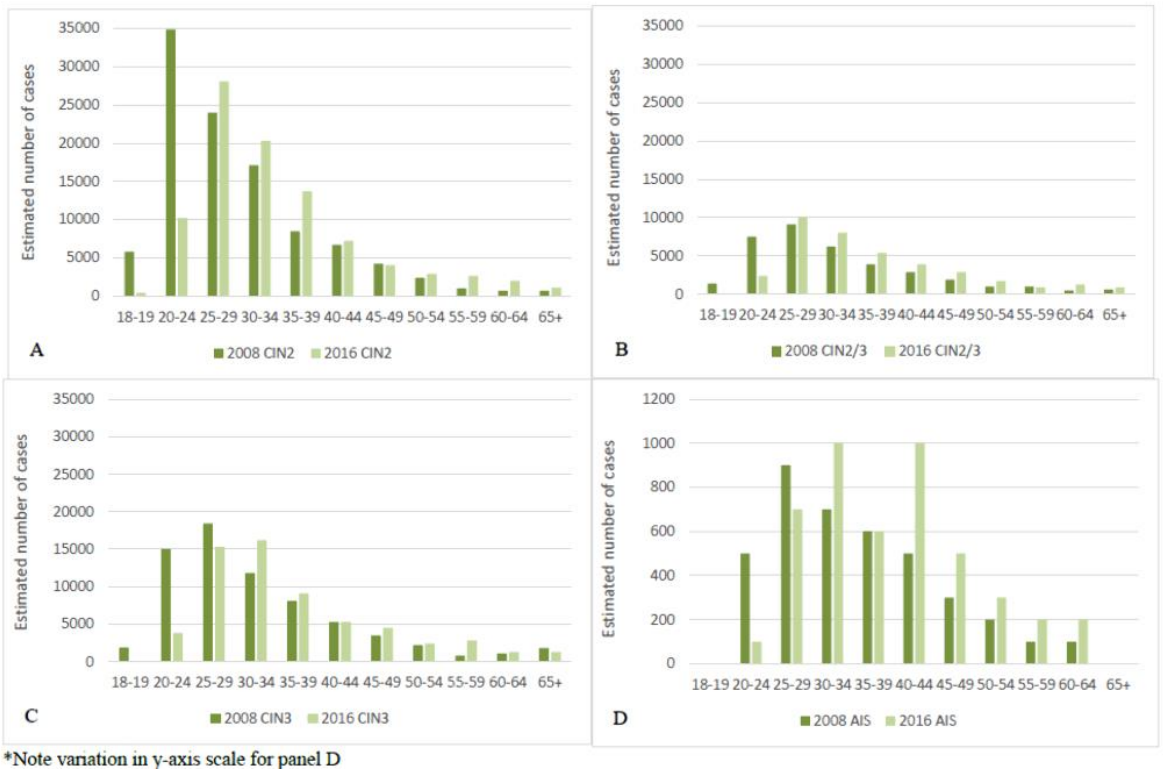
Introduction: In 2008 and 2016, an estimated 216,000 and 196,000 cervical intraepithelial neoplasia (CIN)2+ cases were diagnosed in the United States. A decline in the proportion of CIN2+ attributable to HPV types targeted by quadrivalent vaccine (52% to 43%), the primary vaccine used from 2006–2016, has already been observed. To further characterize CIN2+ burden and vaccine impact, we estimated the number of CIN2, CIN2/3, CIN3, and adenocarcinoma in situ (AIS)±CIN cases among women ≥ 18 years in 2008 and 2016, and the proportion attributable to vaccine types.
Methods: To estimate U.S. case numbers, age-specific rates for each diagnosis were calculated from a 5-site, population-based surveillance system and applied to the age-specific, annual U.S. population. In cases 18–39 years, archived diagnostic specimens were tested for HPV DNA. The proportion high-risk quadrivalent-type-positive (HPV16/18) was estimated by diagnosis and age group, and applied to age groups ≥40 years.
Results: In 2008, an estimated 106,000 CIN2, 36,000 CIN2/3, 69,900 CIN3, and 3,900 AIS cases were diagnosed in women ≥ 18 years; in 2016, an estimated 92,500 CIN2, 37,500 CIN2/3, 62,000 CIN3, and 4,600 AIS cases were diagnosed. The largest decrease in all diagnoses was in 20-24 year-olds (Figure). The highest burden of CIN2 was in 20–24 year-olds in 2008 and 25–29 year-olds in 2016; the highest burden of CIN3 was in 25–29 year-olds in 2008 and 30–34 year-olds in 2016. The proportion of quadrivalent-type-positive CIN2, CIN2/3, CIN3, and AIS was 40%, 61%, 63%, and 89%, respectively, in 2008, and 27%, 50%, 59%, and 83% in 2016.

Figure. Estimated number of CIN2+ cases diagnosed in the United States among women ≥ 18 years by age group and histological grade, 2008 and 2016, A) CIN2, B) CIN2/3, C) CIN3, D) AIS.



*Note variation in y-axis scale for panel D

Conclusions: The CIN2+ declines among 20–24 year-olds and shift in age distribution of disease likely reflects vaccine impact and updated cervical cancer screening recommendations (older age of initiation and longer screening intervals). The decline in proportion quadrivalent-type-positive CIN2 is evidence of vaccine impact.

ALTERNATIVE DOSING SCHEDULES FOR HPV VACCINES AMONG GIRLS AND YOUNG WOMEN: A SYSTEMATIC REVIEW AND META-ANALYSIS

CLINICAL RESEARCH / PROPHYLACTIC VACCINES – CLINICAL ASPECTS

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Introduction: Three licensed HPV vaccines are approved for 2- or 3-dose schedules: 0, 6 months or 0, 1-2, 6 months. Alternative dosing schedules, particularly single dose and extended intervals between doses (>=12 months), are being considered to address vaccine shortages or operationalize flexibility.
Methods: We searched PUBMED/MEDLINE for publications reporting anti-HPV-16 and -18 ELISA data as geometric mean titers (GMT) following administration of one of the licensed HPV vaccines (2vHPV, 4vHPV, and 9vHPV) to females ages 9-26 years. GMT ratios and confidence intervals (CIs) comparing alternative to standard schedules were calculated using mixed effects meta-regression controlling for baseline HPV status and disaggregated by vaccine, subtype, time point, and age group (9-14 and 15-26 years). Non-inferiority was defined as the lower bound of the 95% CI for the GMT ratio being greater than 0.5.
Results: Our search returned 2,464 studies, of which 24 were included in data analyses. Comparing extended interval to standard schedules (Table 1), at one month post last dose and 36 months post first dose the 2vHPV vaccine showed non-inferiority for HPV-18 but not HPV-16. The 4vHPV vaccine showed non-inferiority for both subtypes at all time points, except for one month post last dose for HPV-16. The 9vHPV vaccine demonstrated non-inferiority for both subtypes at one month post last dose. For single dose (Table 2), data was only available for 2vHPV and 4vHPV, which did not meet criteria for non-inferiority for either subtype at all time points and age groups compared.

Table 1. Non-inferiority of extended interval compared to standard schedules

Vaccine	HPV type	Time point*	Age group	Standard dose n	Extended dose n	Ratio (95% CI)
2VHPV	16	1 mo.	9-14	2626	355	0.80 (0.34 – 1.88)
2VHPV	**18**	**1 mo.**	**9-14**	**2634**	**369**	**0.94 (0.53 – 1.67)**
2VHPV	16	36 mo.	9-14	1579	339	0.88 (0.33 – 2.35)
2VHPV	**18**	**36 mo.**	**9-14**	**1589**	**355**	**1.19 (0.53 – 2.65)**
4VHPV	16	1 mo.	9-14	1747	155	0.88 (0.44 – 1.74)
4VHPV	**18**	**1 mo.**	**9-14**	**1763**	**155**	**0.99 (0.62 – 1.61)**
4VHPV	**16**	**36 mo.**	**9-14**	**1071**	**212**	**2.17 (0.53 – 8.94)**
4VHPV	**18**	**36 mo.**	**9-14**	**1087**	**213**	**1.45 (0.66 – 3.17)**
4VHPV	**16**	**72 mo.**	**9-14**	**101**	**124**	**1.48 (0.70 – 3.17)**
4VHPV	**18**	**72 mo.**	**9-14**	**101**	**124**	**1.87 (0.79 – 4.42)**
9VHPV	**16**	**1 mo.**	**9-14**	**409**	**160**	**1.72 (0.98 – 3.03)**
9VHPV	**18**	**1 mo.**	**9-14**	**409**	**160**	**1.28 (0.70 – 2.35)**

* 1 mo. = 1 month post last dose; 36 mo. = 36 months post first dose; 72 mo. = 72 months post first dose
** non-inferior comparisons bolded

Table 2. Non-inferiority of single dose compared to standard schedules

Vaccine	HPV type	Time point*	Age group	Standard dose n	Single dose n	Ratio (95% CI)
2VHPV	16	36 mo.	9-14	1579	36	0.14 (0.03 – 0.69)
2VHPV	18	36 mo.	9-14	1589	36	0.22 (0.06 – 0.87)
2VHPV	16	36 mo.	15-26	3334	104	0.28 (0.13 – 0.59)
2VHPV	18	36 mo.	15-26	3366	104	0.32 (0.16 – 0.66)
2VHPV	16	72 mo.	15-26	442	104	0.36 (0.18 – 0.73)
2VHPV	18	72 mo.	15-26	442	104	0.47 (0.24 – 0.91)
4vHPV	16	36 mo.	9-14	1071	11	0.05 (0.01 – 0.47)
4vHPV	18	36 mo.	9-14	1087	11	0.15 (0.03 – 0.72)
4vHPV	16	72 mo.	9-14	101	11	0.13 (0.03 – 0.58)
4vHPV	18	72 mo.	9-14	101	11	0.51 (0.11 – 2.40)

* 36 mo. = 36 months post first dose; 72 mo. = 72 months post first dose

Conclusions: When evaluated against standard schedules, although robust immunogenicity was demonstrated across all multi-dose groups, non-inferiority of extended interval dosing was mixed across vaccines, subtypes, and time points. Single dose did not meet criteria for non-inferiority in any comparisons. Sparse data limited the number of possible comparisons, and further research is warranted.

SCALING UP CERVICAL CANCER PREVENTION IN WESTERN KENYA: TREATMENT ACCESS FOLLOWING A COMMUNITY-BASED HPV TESTING APPROACH

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Human papillomavirus (HPV) testing within a screen-and-treat program has the potential to lower mortality from cervical cancer in low-resource settings. We evaluate access to treatment following community-based HPV-testing.
Methods: Women age 25-65 years underwent HPV self-testing at a community health campaign in Western Kenya. HPV-positive women were invited for treatment at neighboring health facilities. We determined the proportion of women successfully accessing treatment and variables associated with successful treatment acquisition.
Results: Among 750 women in the study, 140 (18.6%) tested positive for HPV. One hundred and thirty women were notified of their HPV results, of whom 77 (59.2%) sought treatment, and 73 (52.1%) received cryotherapy. Women who received treatment had a significantly shorter time from screening to result notification [91 days (SD ± 23)] compared to those who did not receive treatment during study follow-up [99 days (SD ± 18), p=0.03]. There was no difference between women who accessed treatment compared to those who did not in respect to age, HIV status, marital status, education level, or history of cervical cancer screening.
Conclusions: Effective cervical cancer prevention programs must link screening to timely and appropriate treatment. In this study evaluating access to treatment among HPV-positive women following a multi-disease community-based campaign in Western Kenya, we found that while treatment with cryotherapy was highly acceptable to women, linkage to treatment was suboptimal, at only 52%, six months after screening. This highlights an urgent need for strategies aimed at strengthening linkage to treatment in similar settings. To support the cost-effectiveness of HPV-based screening, strategies to decrease loss-to-follow-up such as point-of-care diagnostics with same-day treatment, and/or faster time to result notification, and use of patient navigators to promote adherence to follow-up need further investigation.

VALIDATION OF HPV16 E2BS3&4 METHYLATION AS INDEPENDENT FROM GLOBAL HOST-GENOME METHYLATION AND ITS RELATION TO CLINICAL ENDPOINTS IN A COHORT OF OPSCC PATIENTS

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: The key regulator of viral oncogene expression in HPV-driven squamous cell carcinoma including the oropharynx (OPSCC) is the HPV E2 protein which binds to specific binding sites (E2BS) in the HPV upstream regulatory region (URR). CpGs present in the E2BS can be epigenetically modified by methylation which affects E2's affinity to the sites and thereby provides a mechanism for promoting carcinogenesis by E6/E7 oncogene overexpression through functional inactivation of E2. Previously we observed a bimodal pattern of methylation levels in E2BS3 and 4 in OPSCC which additionally was independent from global host genome methylation during formation of metastasis as assessed in the LINE-1 retrotransposon. Furthermore, E2BS methylation was related to clinical data such as survival. We are employing the current, independent cohort of OPSCC patients from Cologne, Germany in order to validate our earlier results.
Methods: We analyzed methylation levels in 4 CpGs in E2BS3 and 4 by pyrosequencing bisulfite-converted DNA from 28 $p16^{INK4a}$+/HPV16-DNA+ FFPE samples of primary tumors and 17 metastases from a cohort of OPSCC patients from Cologne, Germany. We will test for association with clinical data and compare the results to our earlier cohort from Berlin, Germany.
Results: The distribution of methylation levels in the validation cohort from Cologne as well as the previous cohort from Berlin suggests the existence of two groups of low and high methylation in primary tumors. Median methylation in primary tumor samples was 6 percent (range 1 to 87) with most samples below 20 percent and a smaller group at around 80 percent. Analysis of LINE-1 methylation and correlation of E2BS methylation to clinical parameters is currently ongoing.
Conclusions: The occurrence of groups of low versus highly methylated OPSCC samples in our cohort suggests a directed effect and might be indicative of E2BS methylation working in a switch-like manner to modulate E2's regulator function.

THE EFFECT OF FREE HPV-TESTING IN NORTH-WEST CROATIA AS A PART OF PUBLIC HEALTH PREVENTIVE ACTION

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Compared to cytology, hrHPV testing has been shown to reduce the risk of developing cervical cancer through increased sensitivity for underlying disease. In 2020, Croatian pilot study of primary hrHPV screening in one of Croatian counties is anticipated to begin. The aim of this public health action conducted in 2019 was to offer free hrHPV test to women in north-west Croatia during one week in order to promote cervical cancer prevention and implementation of primary hrHPV screening.
Methods: Out of 476 collected and tested cervical samples during the “Lila week” in Zagreb, 107 cervical samples from younger women (20-34 years) and 321 samples from older women (>34 years) were collected, while for 48 samples no age data were available. Liquid based cytology (LBC) were performed only from hrHPV-positive cervical samples collected from older women. The cytology was reported using Bethesda system, and Cobas HPV test was used for hrHPV detection.
Results: A total of 77 (16.3%) hrHPV-positive samples were detected. HPV16 was detected in 18 samples and HPV18 in five samples. The hrHPV test was positive in 10.28% tested women from older group, and in 33.6% women from younger age group. Analyzing the population of hrHPV positive women, the highest prevalence of non-16/18 hrHPV genotypes was observed in younger women ($p<0.01$). Among older hrHPV-positive women LBC detected three ASCUS, 24 LSIL, and one HSIL (28/33).
Conclusions: The unexpected high frequency of ASCUS+ detected in hrHPV-positive older women could be explained with bigger interest of that group of women for this public health action.

EPIDEMIOLOGY OF ANAL CANCER IN NEW HAVEN COUNTY, CONNECTICUT: 2006–2013

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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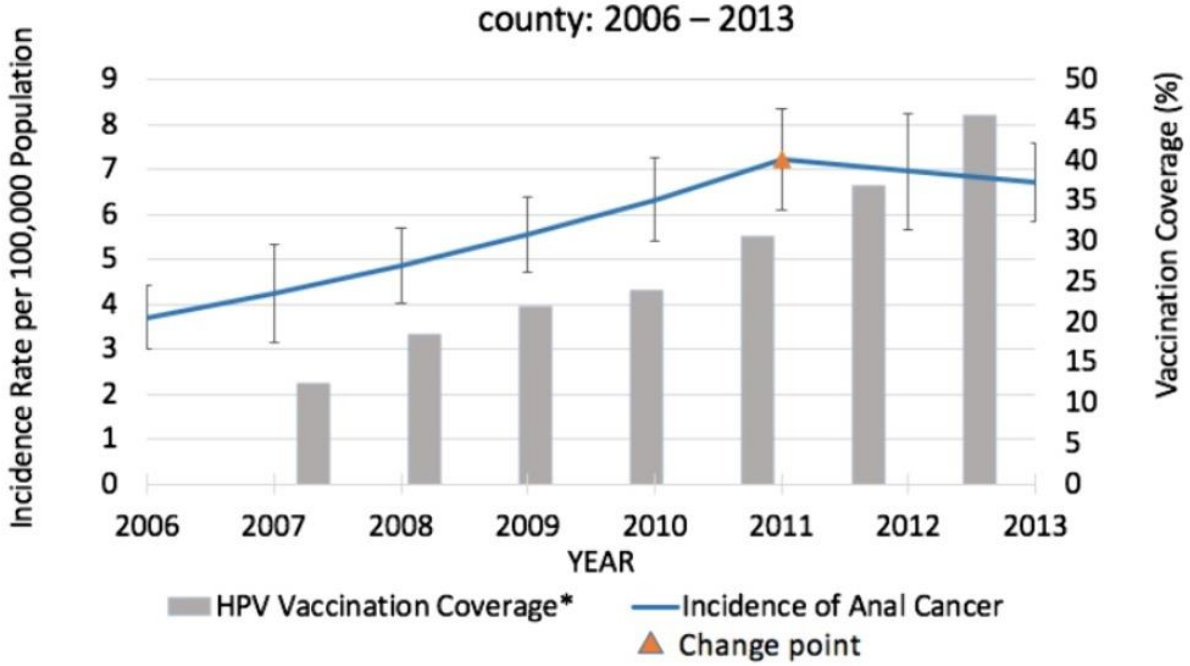
Introduction: HPV vaccine was introduced in the United States in 2006. Over 90% of anal cancers are potentially preventable with HPV vaccine. The objective of this study was to explore the potential impact of HPV vaccine on the epidemiology of anal cancer in the post-vaccine era.
Methods: Incident cases of anal cancer among residents of New Haven County (NHC) were identified from 2006–2013 using discharge diagnosis codes from the Yale-New Haven Health System, the largest healthcare provider in Connecticut and home to the only comprehensive cancer center in the state. The annual incidence rate (IR) was estimated by sex and age-groups (30-49, 50-64, and ≥65-years)using data from the US Census. Trends in the IR of anal cancer were characterized by the annual percentage change (APC) using Join-point regression.
Results: From 2006–2013 there were 246 newly diagnosed cases of anal cancer in NHC (median age= 58 years, IQR= 52-69 years). Most were women (58%) and were publicly insured (52%). During the 8-years, the age-adjusted annual IR increased from 3.7 to 6.7 per 100,000 population (average APC= 8.8, $p<0.01$). Changes in the IR of anal cancer were statistically significant only in women 50-64 and ≥65 years of age. Join-point analyses identified 2011 as a significant point of change (Figure 1), when the slope changed from an increasing trend (APC = 14.3; 95%CI = 12.4 to 14.3) to a decreasing trend (APC = -3.8; 95%CI: -3.6 to -3.9). The APC was significantly lower in the younger age-group (IRR=0.27, $p<0.01$).

Figure 1. Age-Adjusted Incidence of Anal Cancer in New Haven county: 2006 – 2013



*Estimated ≥1 HPV vaccination coverage among adolescent boys and girls 13-17 years: National Immunization Survey-Teen, United States, 2007-2013

Conclusions: The overall incidence of anal cancer continues to rise in the post-vaccine era, though most of the burden remains in older men and women who were least likely to have received HPV vaccine. Continued surveillance is needed to determine whether the IR will continue to decrease as vaccine uptake increases.

HIGH SEROPREVALENCE OF MULTIPLE HIGH-RISK HUMAN PAPILLOMAVIRUS TYPES AMONG THE GENERAL POPULATION OF BONAIRE, ST. EUSTATIUS AND SABA, CARIBBEAN NETHERLANDS

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Incidence of cervical cancer and mortality rates differs geographically, being highest in African and Caribbean countries. Seroepidemiological data is an important tool to provide information on lifetime cumulative human papillomavirus (HPV) exposure and past infection, but has not been available yet for Caribbean Netherlands (CN) – comprising the islands Bonaire, St. Eustatius and Saba. Hence, a cross-sectional population-based serosurveillance study was performed in 2017, and here we report on seven high-risk (hr-)HPV types (HPV16, 18, 31, 33, 45, 52 and 58).
Methods: Participants (n=1,823, aged 3 months-90 years, randomly selected from the population registry) donated a blood sample and completed a health-related questionnaire. Hr-HPV-specific IgG-antibodies were tested in a VLP-based multiplex-immunoassay. Vaccinated individuals (n=102) (quadrivalent vaccine was introduced on St. Eustatius and Saba in 2013, and bivalent vaccine on all islands in 2015) were excluded from seroprevalence estimations. Risk factors for HPV seropositivity were analysed using GEE and restricted to those unvaccinated, >14 years of age and ever had sex (n=1,080).
Results: Overall HPV seroprevalence was 29.7% (95% CI 26.9-32.4). From 15 years of age, overall seroprevalence was 34.0% (95% CI 30.8-37.3), with over half of them being seropositive for ≥ 2 hr-HPV types. HPV16 and HPV52 were most prevalent (both 13.1%) and HPV33 (8.9%) least. Seroprevalence was highest on St. Eustatius (38.4%), followed by Bonaire (33.4%) and Saba (33.1%), and substantially higher in women (51.4%) than men (18.1%, p=<0.0001). In multivariate analyses, age group 25-34 years, women, increasing lifetime sexual partners and history of reported STI were significantly associated with HPV seropositivity.

Table 1 Weighted seroprevalence for seven high-risk HPV types and combinations in the total population of Caribbean Netherlands among those from 15 years of age without vaccination, by sex

	Seroprevalence (95% CI)					
	Overall *n*=1,180		Men *n*=505 (42.8%)		Women *n*=675 (57.2%)	
High-risk HPV types						
HPV16	13.1	(11.0-15.2)	6.8	(4.4-9.3)	19.9	(16.5-23.3)
HPV18	11.8	(9.7-13.8)	5.6	(3.3-7.9)	18.5	(15.1-21.9)
HPV31	10.9	(9.0-12.8)	5.6	(3.4-7.9)	16.6	(13.5-19.7)
HPV33	8.9	(7.1-10.8)	6.0	(3.5-8.5)	12.2	(9.4-14.9)
HPV45	9.4	(7.6-11.3)	5.3	(3.1-7.5)	13.9	(11.0-16.9)
HPV52	13.1	(10.8-15.4)	7.1	(4.3-9.9)	19.7	(16.2-23.2)
HPV58	12.7	(10.5-14.9)	7.5	(4.7-10.3)	18.4	(14.9-21.8)
HPV combinations						
HPV16 and 18	5.5	(4.1-7.0)	3.9	(2.1-5.7)	7.4	(5.2-9.5)
HPV16 or 18	19.3	(16.8-21.9)	8.5	(5.8-11.3)	31.1	(27.1-35.1)
Positive for 1 or more high-risk HPV types	34.0	(30.8-37.3)	18.1	(14.0-22.2)	51.4	(47.1-55.7)
Positive for 2 or more high-risk HPV types	18.1	(15.5-20.6)	8.8	(5.8-11.8)	28.1	(24.3-32.0)
Positive for 7 high-risk HPV types	2.0	(1.1-3.0)	2.3	(0.8-3.8)	1.8	(0.6-2.9)

Table 2 Weighted seroprevalence for seven high-risk HPV types and combinations in the total population of Caribbean Netherlands among those from 15 years of age without vaccination, by island

	Seroprevalence (95% CI)					
	Bonaire *n*=744 (63.0%)		St. Eustatius *n*=278 (23.6%)		Saba *n*=158 (13.4%)	
High-risk HPV types						
HPV16	11.4	(9.0-13.8)	20.7	(15.0-26.4)	18.3	(11.5-25.2)
HPV18	11.3	(8.9-13.7)	15.2	(10.3-20.2)	11.0	(5.7-16.3)
HPV31	9.6	(7.4-11.8)	16.4	(11.2-21.5)	14.9	(9.0-20.8)
HPV33	8.3	(6.2-10.5)	12.5	(7.8-17.2)	9.2	(4.5-14.0)
HPV45	8.9	(6.7-11.0)	12.6	(7.9-17.3)	9.9	(5.0-14.8)
HPV52	13.7	(11.0-16.4)	10.6	(6.3-15.0)	11.3	(6.1-16.4)
HPV58	12.3	(9.7-14.9)	16.6	(11.3-21.8)	10.0	(5.1-15.1)
HPV combinations						
HPV16 and 18	4.9	(3.4-6.5)	8.2	(4.2-12.2)	7.4	(3.0-11.9)
HPV16 or 18	17.7	(14.8-20.6)	27.7	(21.5-33.9)	21.9	(14.6-29.2)
Positive for 1 or more high-risk HPV types	33.4	(29.6-37.3)	38.4	(31.7-45.1)	33.1	(24.8-41.3)
Positive for 2 or more high-risk HPV types	17.7	(14.7-20.7)	20.8	(15.4-26.3)	17.0	(10.7-23.3)
Positive for 7 high-risk HPV types	1.5	(0.5-2.6)	4.4	(0.8-7.9)	3.4	(0.3-6.6)

Conclusions: In accordance with the Caribbean region, seroprevalence of multiple hr-HPV types is high in CN, especially among women. In addition to the recently introduced vaccination, introduction of HPV screening in women in CN could therefore have great impact.

ASSOCIATION OF MYCOPLASMA HOMINIS IN THE VAGINAL MICROBIOTA AND HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION IN ASYMPTOMATIC AFRICA WOMEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: The vaginal microenvironment plays a role in persistence of high-risk HPV (HR-HPV) and cervical carcinogenesis. The genital carriage of HR-HPV, common curable sexually transmitted infections (STIs), *Mycoplasma spp*., *Lactobacillus spp*., and bacterial vaginosis (BV)-associated pathogens was evaluated in asymptomatic African women.
Methods: Women were consecutively recruited at the outpatient clinic for women's sexual health "La Renaissance Plus", N'Djamena, Chad. Genital secretions were self-collected using veil (V-Veil-Up Gyn Collection Device, V-Veil-Up Pharma Ltd., Nicosia, Cyprus), and were tested by multiplex real-time PCR for HR-HPV by Anyplex™ II HPV28 genotyping test (Seegene, Seoul, South Korea), STIs (*Chlamydia trachomatis*, *Neisseria gonorrhoeae*, *Mycoplasma genitalium*, *Trichomonas vaginalis*) and *Mycoplasma spp*. (*M. hominis*, *Ureaplasma parvum*, *U. urealyticum*) by Allplex™ STI Essential Assay (Seegene), *Lactobacillus spp*., *Gardnerella vaginalis*, *Atopobium vaginae*, *Mobiluncus spp*., *Candida albicans*, other *Candida spp*. and BV by Allplex™ Vaginitis Screening Assay (Seegene).
Results: A total of 253 women (mean age, 35.0 years) was enrolled. The prevalence of HPV infection was 37.9%, including 62.5% of HR-HPV. Common STIs were infrequent (2.8%) [*C. trachomatis* (1.2%), *N. gonorrhoeae* (0.4%), *M. genitalium* (1.6%), *T. vaginalis* (0.4%)]. Prevalences of genital *Mycoplasmas spp*. were high (54.2%) [*U. parvum* (42.6%), *U. urealyticum* (19.8%), *M. hominis* (19.1%)]. Carriage of *G. vaginalis* (83.4%), *A. vaginae* (37.9%), *Mobilincus spp*. (89.7%), *C. albicans* (17.4%) and other *Candida spp*. (22.9%), were high. The *Lactobacillus spp*. flora was generally normal (62.8%). BV was diagnosed in 32.4%. By bivariate analysis, HR-HPV infection was associated with *A. vaginae* (P=0.050), *M. hominis* (P=0.01) and BV (P=0.04). By multivariate analysis, strong association between HR-HPV and *M. hominis* persisted (adjusted odd ratio: 2.5; 95%IC: 1.3-5.1; P<0.01).
Conclusions: Multiplex PCR testing allows easy diagnostic approach of female genital microbiota. HR-HPV infection was associated with *M. hominis*, which may play a role in HR-HPV induced cervical carcinogenesis in African women.

POPULATION-BASED HPV SEROSURVEY AMONG UNVACCINATED FEMALES REVEALS HPV16 HERD EFFECT POST- GENDER-NEUTRAL VACCINATION WITH MODERATE VACCINATION COVERAGE: FOLLOW-UP OF A COMMUNITY RANDOMISED TRIAL

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The elimination of cervical cancer through means of human papillomavirus (HPV) vaccination programs requires the attainment of herd effect. For HPV16, which has a high basic reproduction number, the vaccination coverage required to achieve herd effect has been suggested to exceed that realistically achieved in average populations. We evaluated which vaccination strategy provides the best herd effect when vaccination coverage is moderate.
Methods: A population-based community randomised HPV vaccination trial was launched between 2007-10. 33 communities were randomised to receive moderate vaccination coverage gender-neutral, girls only, or no HPV vaccination of 1992-95 born early adolescents. We retrieved samples biobanked during 2005-16 (from the era preceding completion of vaccination, 2005-10, and the post-vaccination era, 2011-16) from all 8022 unvaccinated pregnant women ≤23 years old were resident in the 33 communities. The retrieved serum samples were analysed for antibodies to 17 HPV types and herpes simplex virus type 2 (HSV-2) using Luminex assays. To measure herd effects, pre-vaccination era HPV seroprevalence was compared to that post-vaccination, by trial arm, applying stratification of core-group membership (using HSV-2 seropositivity as a proxy).
Results: A slight post-vaccination reduction in HPV18 seroprevalence occurred in both the girls only and gender-neutral intervention arms. However, significant reduction in HPV16 seropositivity was only observed in the gender-neutral arm (PR=0.79, 0.72-0.87) and amplified further among the HSV-2 seropositives (PR_{HSV2+}=0.64, 0.50-0.81).
Conclusions: The implementation of gender-neutral vaccination when vaccination coverage is only moderate enables herd effect against HPV16, the most difficult HPV type to eliminate.

HEALTH WORKER AND STAKEHOLDER PERSPECTIVES OF POINT-OF-CARE HPV-DNA TESTING AND SAME-DAY TREATMENT FOR CERVICAL SCREENING IN PAPUA NEW GUINEA

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Papua New Guinea (PNG) has among the highest estimated burden of cervical cancer globally yet has no organized national HPV vaccination or cervical screening programs. As part of a field trial among 3400 women to evaluate an innovative point-of-care (POC) HPV 'test and treat' cervical screening strategy (ISRCTN13476702), we conducted interviews with key informants, including health care workers (HCW) and other key stakeholders to capture their insights into the intervention.
Methods: In-depth interviews were conducted with 25 key informants (15 HCWs, 10 stakeholders) selected purposively from Well Woman Clinics in Madang (Madang Province) and Mt. Hagen (Western Highlands Province). Interviews were conducted in English, transcribed, and then analyzed using Nvivo 12.0 qualitative data management software.
Results: In light of the burden of cervical cancer in the country, all participants agreed that a national cervical screening program, explicitly same day test-and-treat services addressed an immense unmet need. Using an innovative POC diagnostic technology enabled a continuum of care that was not possible in earlier cervical screening models (Pap smears or VIA). The 'test-and-treat' intervention enabled women to be treated by thermal ablation the same day, thus mitigating the significant losses to follow-up seen in earlier programs. Self-collection of vaginal swabs was identified as a key driver for the high uptake of the new service, principally because it overcame barriers associated with pelvic examination. On arrival at the clinic, health education was provided in Tok Pisin and utilized culturally appropriate language (i.e. 'sowa lo billum blo pikinini') to explain cervical cancer, its risks, testing, and treatment process. This helped create an environment where women felt better informed about cervical cancer testing and prevention, promoting trust in the service.
Conclusions: Successful uptake of a point-of-care test-and-treat cervical screening program included enabling a continuum of care, allowing for self-collection, and ensuring culturally appropriate health education.

CERVICAL HIGH-RISK HUMAN PAPILLOMAVIRUS INFECTION AMONG NORTHERN UAE POPULATION WITH ABNORMAL CYTOLOGY: PREVALENCE AND TYPE-SPECIFIC DISTRIBUTION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Even though there are some data published on human papillomavirus (HPV) epidemiology in United Arab Emirates (UAE) or Gulf Cooperation Council (GCC) countries, the distribution of genotypes in abnormal cervical cytology has not been previously determined. The present study aimed to determine the distribution of HPV genotypes in cervical samples from women living in northern UAE and analyzed the correlation between high risk (HR)-HPV infection types and cytology results.
Methods: Between 2016 and 2018, 142 women showing abnormal cervical cytology residing in northern UAE were enrolled in this study. The data were collected retrospectively from the single tertiary hospital in northern UAE. Cervical specimens were analyzed by using AnyplexII HPV28 Detection kit (Seegene, IVD in Europe).
Results: The mean age was 43.0 years old ranged 25 to 73 years. Most of the women showed ASCUS or LSIL (77.5%). Of 142 women with abnormal cytology, 65 (45.8%), 24 (16.9%), and 53 (37.3%) presented positive for HR-HPV, low risk-HPV, and negative HPV, respectively. Multiple infections with two or more HR-HPVs were detected in 18 (27.7%) of HR-HPV women. Amongst HR-HPV positive women, HPV-16 (16.9%), HPV-53 (15.4%), HPV-51 (10.8%), HPV-68 (10.8%), HPV-18 (9.2%) and HPV-39 (9.2%) were the most common genotypes in northern UAE population. The relative risk for CIN 2+ among women with HPV-16 or HPV-18 was significantly higher compared with that of the patients with infection of any of the other HR-HPVs.
Conclusions: The current study provides data on HR-HPV prevalence in northern UAE and delivers an evidence base for supporting the introduction of regional and screening and vaccine programs in this area.

THE CHEMICAL PEELING THERAPY USING A LIQUID PHENOL OR TRI-CHLOROACETIC ACID (TCA) FOR PREMALIGNANT LESIONS INDUCED BY HIGH-RISK HPV INFECTION

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: High-risk HPV types induce the precursor lesions like cervical and vaginal intraepithelial neoplasia (CIN, VAIN). Conservative therapies are needed for young patients with these lesions, since there are some complications in pregnancy after the cervical conization. We try to establish a new ablation therapy for these lesions.
Methods: After obtaining the informed consent, 319 eligible women with CIN or VAIN participated this study. Liquid phenol (89%) or 70% trichloroacetic acid (TCA) was applied on whole the cervix or the vagina at 2-4 weeks intervals, and this was repeated until Pap test became negative in subsequent two tests for 4 weeks.
Results: Finally 107 CIN1, 112 CIN2, 71 CIN3, 16 VAIN1, 9 VAIN2/3 and 4 cervical cancer were diagnosed. Twenty-six high-grade CIN patients undertook cervical loop-electronic excisional procedure (LEEP), 4 cancer patients had hysterectomy, and 4 immune-suppressed patients resisted to the treatment. Among remaining 285 patients, 198 were successfully treated with phenol therapy or TCA alone, and 92 had this therapy with oral intake of traditional medicine, Yokuinin (Adlay, Ma-Yuen) every day. Mild abdominal pain or discomfort were common adverse effects, but tolerable. Average periods until clearance was 4.1, 7.6 and 11 months for CIN1, CIN2, CIN3, respectively. No difference in the clearance periods between CIN and VAIN, but combinations of CIN and VAIN needed longer treatment periods than single disease. The recurrence rate was 8.5%, but all were cleared by the second treatment. Higher grade lesions and HPV16 or 18 infection were significantly, and lesion size and smoking were marginally associated with longer treatment periods. Yokuinin shortened treatment periods in CIN3 cases. Ten patients had their babies without any troubles in pregnancy.
Conclusions: The chemical peeling with phenol or TCA appears to be a safe and effective therapy for CIN and VAIN, although patients have to withstand long treatment periods.

MONITORING HPV VACCINE IMPACT IN AUSTRALIA: RESULTS BASED ON COBAS 4800 AND LINEAR ARRAY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Australia introduced HPV vaccination in 2007 and the cervical screening program transitioned to primary HPV testing with genotyping for HPV 16/18 in 2017, opening up the possibility of using routine screening data to monitor the impact of HPV vaccination. Compass is a major RCT of HPV vs cytology screening acting as a sentinel experience for the new screening program. We investigated the impact of HPV vaccination in women ≥25 years and compared pre- and-post-vaccination HPV prevalence estimates using different technologies for HPV testing.
Methods: We used Australian pre-vaccination (2005-7) HPV prevalence Linear Array (LA) data from WHINURS (1933 samples) and post-vaccination (2014) LA data from Compass pilot (2,991 samples) to estimated vaccine impact on oncogenic HPV prevalence. We also compared post-vaccination HPV prevalence estimates with LA vs cobas 4800 (i.e. clinical HPV testing) from Compass.
Results: Using the LA data, the ratio between other high risk (OHR) types and HPV 16/18 prevalence (OHR-HPV:HPV16/18) at ages 25-34/35-44/45-55/56-64 years was 1.65; 3.47; 2.29; 3.50, respectively, for WHINURS (pre-vaccination) and 7.46; 2.52; 2.55;1.83, respectively, for Compass (post-vaccination). In the 25-34 age group absolute prevalence dropped from 10.3% to 1.8% for HPV 16/18 ($p<0.001$). Comparable prevalence ratios (OHR-HPV:HPV 16/18) were also observed between cobas and LA for Compass except for the 55-64 year group; [cobas (OHR-HPV:HPV 16/18): 7.92; 2.81; 2.33; 9.00 for 25-34/35-44/45-54/55-64 year groups, respectively; LA (see above)]. [Absolute HPV (16/18) prevalence, cobas:1.7%/1.6%/1.1%/0.2% for 25-34/35-44/45-54/55-64 year groups, respectively, vs. LA:1.8%/2.2%/1.4%/1.1%, respectively; and OHR-HPV, cobas:13.3%/4.6%/2.6%/1.7% for 25-34/35-44/45-54/55-64 year groups, respectively vs. LA:13.3%/5.7%/3.5%/2.1% respectively].
Conclusions: The marked reduction in vaccine-targeted HPV 16/18 infections in women aged 25-34 years indicates the substantial impact of HPV vaccination. Similar prevalence estimates between cobas and LA support the potential use of data from HPV screening programs for long-term monitoring of infection prevalence in screened women.

DEVELOPMENT OF AN HR-HPV PROFICIENCY TEST BY THE BELGIAN NATIONAL REFERENCE CENTRE FOR HPV: A CONCEPT.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: It is essential for accredited laboratories to participate regularly in EQA-schemes. Commercially available HPV EQC-schemes are often limited to HPV16/18 only, whilst there is a growing need to equally include other HR-HPV genotypes. Furthermore, laboratories are more frequently opting to introduce a (partial) genotyping assay. To this end, the Belgian National Reference Centre (NRC) for HPV has developed an EQA-concept fulfilling the current needs.
Methods: A non-plasmid based EQA-scheme was developed from anonymized leftover cervical LBC samples between December 2018 and May 2019. Strong positive samples, covering all hrHPV types, were diluted to generate sufficient material for 44 laboratories and extensive testing. The panel was extensively validated for presence of HR-HPV genotypes repeatability, reproducibility, robustness, and uniformity of aliquot preparation before sending to the participating laboratories. The EQA will be analyzed with an according penalization scheme at different levels, i.e. clinical, genotyping, and analytical level. Distribution of the panel and result analysis will be facilitated by the Quality of Laboratories service (Sciensano) with two weeks reporting time. Extended sample evaluation was done on 3 different HPV assays, including the WHO IARC assay considered as gold standard. Only samples with 100% concordant results between the different assays were selected. Stability was confirmed weekly for 5 weeks. To simulate robustness, transport to Sciensano and back was organized prior to testing.
Results: Out of 23 samples who fulfill the robustness criteria, 12 samples were selected hereby generating a well-defined balanced panel. The final panel consisted of 2 negative samples (1 sample only comprising lrHPV types), 1 pure Thinprep sample, 4 HPV16/18 samples, and 5 other hrHPV genotype samples.
Conclusions: It can be concluded that the Belgian NRC is able to produce a robust EQA-panel for hrHPV genotyping. Further improvements need to be introduced, including reporting and diluent (confirmed negative samples instead of Thinprep Medium).

DETECTION OF HIGH-RISK HUMAN PAPILLOMAVIRUS BY A NOVEL ISOTHERMAL HPV ASSAY AMONG PREGNANT WOMEN IN PEMBA ISLAND, TANZANIA

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Human papillomavirus (HPV) is globally the most common sexually transmitted virus. Prevalence of infection differs, with highest rates reported in South America and sub-Saharan African, including Tanzania. In pregnancy, hormonal and immune changes facilitate HPV persistence, increasing cancer and placental infection risks. HPV infection during pregnancy has been associated with adverse outcomes, such as preterm prelabor rupture of membranes. This study aims to contribute evidence on the prevalence of HPV infection and persistence across two timepoints among pregnant women in Pemba Island, Tanzania. Testing was performed using Atila AmpFire HPV detection kit, a novel isothermal amplification based assay.
Methods: Vaginal swabs collected at two timepoints using FLOQSwabs and eNAT buffer (COPAN Italia) were tested by nucleic acid isothermal amplification with real time fluorescence detection assay for HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68 (AmpFire HPV Detection kit, Atila BioSystems, US).
Results: Samples from 439 individual pregnant women were tested. Of those, 385 samples were collected at the first, and 187 samples at the following, timepoint. Overall HPV prevalence was 11% and 6%, at the two time points respectively. Among the 133 women whose samples were tested at both timepoints, the persistence rate of HPV was 64%.

	number of infections at first timepoint (%)	number of infections at second timepoint (%)
HPV 16	4 (1.04)	1 (0.53)
HPV 18	0 (0)	0 (0)
HPV others[a]	41 (10.6)	10 (5.4)

Table 1: Prevalence of high-risk HPV strains at two timepoints during pregnancy. [a] Genotypes were 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68.
Conclusions: High risk HPV genotypes were detected during pregnancy with a high persistence rate. Additional testing of samples from the same cohort of women is ongoing. Further analysis with the cohort characteristics and adverse pregnancy outcomes will follow.

RECOMBINANT LIVE-ATTENUATED INFLUENZA VIRUSES CO-EXPRESSING BOVINE PAPILLOMAVIRUS 1 (BPV1) E6 AND E7 INDUCE TUMOUR REGRESSION IN EQUINE SARCOID PATIENTS

CLINICAL RESEARCH / THERAPEUTIC VACCINES – CLINICAL ASPECTS

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Introduction: Bovine papillomaviruses types 1 and 2 (BPV1, BPV2) induce semi-malignant skin tumours termed sarcoids in horses. Sarcoids seriously compromise the health and welfare of affected individuals due to their high propensity to progress upon accidental or iatrogenic trauma, and to reoccur in a more severe, multiple form following ineffective treatment.
Methods: We have developed live-attenuated influenza (Flu) A and B viruses co-expressing shuffled BPV1 E6 and E7 antigens as potential sarcoid immunotherapeutic.
Results: In a phase I trial involving 12 sarcoid- and BPV1/2-free horses, intradermal administration of vaccine candidates was well tolerated with the only transient side effect being mild fever in four horses for < 8 hours following first administration of the Flu A BPV1-E6E7 virus. Importantly, vaccine candidates also proved biologically safe: repeated screening of secretions and faeces by RT-PCR and focus forming assay in the course of the trial demonstrated the absence of virus shedding. In an ongoing patient trial involving 30 horses bearing multiple, partly recurrent sarcoids, one lesion per horse was injected three times (days 1, 3, 5) with the influenza A virus, and then boosted three times with the influenza B virus (days 8, 10 and 12). Treatment led to significant tumour regression in five, and stable disease in three patients subjected to this therapeutic regimen thus far. In two patients, tumours recurred 5 months post treatment, indicating that the viral vaccines and/or treatment schedule need to be further optimized as to induce a long-lasting therapeutic effect in all the patients. Immunotherapy is currently repeated in these horses. Intriguingly, treatment also had a systemic effect in all individuals as revealed by synchronous regression or growth arrest of non-injected lesions located at different sites of the horses' integument
Conclusions: To our knowledge, this is the first immunotherapeutic approach showing significant reduction of tumour burden in equine sarcoid patients.

Table 1: Follow-up on the horses treated so far.

Horse #	Month 1	Month 2	Month 3	Month 4	Month 5
1	↘	↘	↘	↗	↗
2	↘	↘	↘	↗	↗
3	→	→	→	→	→
*5	→	→	→	→	
6	→	→	→	→	
7	↘	↘	↘	↘	
8	→	→	↘	↘	
9	↘	↘	↘	↘	

↘: tumour regression; →: tumour growth arrest; ↗: tumour progression
*Horse #4 lost to follow-up

Figure 1: Selected sarcoids from two horse patients before the first treatment (left; d1) and at 4 months follow-up (right):

Sarcoids were injected intralesionally with the vaccines. Only the lesion indicated by the white arrow (see top left) was treated in the patient with axillary sarcoids.

PREVALENCE AND INCIDENCE OF EXTERNAL GENITAL WARTS AMONG PREGNANT QATARI WOMEN IN STATE OF QATAR 2010-2019

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Introduction: Human papilloma virus (HPV) is the most common sexually transmitted virus worldwide. However, the information related to prevalence and incidence of HPV infection is limited in the Arab and GCC countries.
Methods: Methods:A cross-sectional observational study was conducted among 17years and older Qatari and Non-Qatari pregnant and non-pregnant women. The data was collected at the Sexually-transmitted infection (STI) clinic in the Dermatology Department at Hamad Medical Corporation (HMC), Qatar, for the period between 2010 and 2019. Type of data collected direct observation.
Results: Results: Total number of external genital warts that were documented between 2010 to 2019 was 876 cases. The allover prevalence was 3.3/10000 while the incidence was 2.6/100000 August 2019. The incidence and prevalence was highest among the age group 32 for males and 30 for females. Notably, the number of cases increased significantly since 2013 while the lowest incidence and prevalence was among age group of 45 and older.
Conclusions: Conclusion: The data demonstrate the prevalence and incidence of HPV infection in a university hospital setting in Qatar, and shows the highest prevalence and incidence of HPV-induced warts among the age of 32 for males and 30 for females, and the lowest in the 45 years and older group. Together, the data raises the importance of administering the HPV vaccination programs among young adults in Qatar.

DECREASED IFN EPSILON EXPRESSION DURING HPV ANAL INFECTION IN HIV+ MEN

BASIC RESEARCH / REGULATION OF GENE EXPRESSION

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Introduction: Interferon (IFN)-epsilon is an emerging component of innate immune defence at the mucosal surface. HPV infection has been strongly associated with squamous cell carcinoma of the anal canal; its incidence is relatively low in the general population but substantially elevated in HIV-infected (HIV+) individuals. It remains to be understood whether anal HPV infection modulates the expression of IFN-epsilon. This study aims to characterize the mucosal expression of IFN-epsilon during anal HPV infection through an integrative analysis with common type I IFN components and virological parameters.
Methods: Anal brushings were collected from HIV+ men, attending Proctology and Infectious Disease Units at Policlinic Umberto I Hospital in Rome. Detection of HPV DNA and genotyping were performed by PCR and sequencing. The mRNA copy content of type I IFN-genes (alfa2, beta and epsilon) and their heterodimeric receptor IFNAR1-IFNAR2 was measured by TaqMan RT–PCR, relatively to a cellular invariant gene.
Results: This study included 50 Caucasian HIV+ patients on long-term antiretroviral therapy. HPV DNA was detected in 74% of anal samples and high-risk (HR) genotypes were more than half. Despite individual variability in expression levels, there was a strong positive correlation among IFN-epsilon, all type I IFN genes and IFNAR1 subunit. The expression levels of the type I IFN-genes were all lower in men positive to HR HPV-positive than in those positive to low-risk, consistently with what is known about cervical infections; interestingly, IFN-epsilon appeared more down-regulated than IFNs alfa2 and beta in the HR group.
Conclusions: In this first study on the type I IFNs response to HPV infection in the anal mucosa, IFN-epsilon expression appeared to be targeted by HR-HPVs. Follow-up studies will be performed to clarify the role of type I IFNs in anal HPV clearance and to ascertain local dysfunctions of mucosal immune response in HIV+ patients.

COMPASS-PLUS: EVALUATING THE PSYCHOLOGICAL IMPACT OF PRIMARY HPV SCREENING WITHIN THE AUSTRALIAN CERVICAL SCREENING PROGRAM

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: In December 2017 Australia's screening program transitioned to 5-yearly primary HPV screening with partial genotyping for women aged 25-74 years. HPV testing has a higher sensitivity for the detection of precancerous lesions. However, there is little evidence regarding the psychological effects of HPV screening. Compass-PLUS, a sub-study of Compass (randomised trial of primary HPV screening vs cytology) has been established to evaluate the psychological aspects of primary HPV screening in the context of the renewed program.
Methods: Compass-PLUS has a repeat cross-sectional survey design. Participants in the Compass trial are invited by email or text message to participate in the sub-study, shortly after receiving their screening result. Following consent, participants complete on-line questionnaires at baseline, 6 months, and 3 months after their one year, 2.5 years (cytology arm only) and 5 year Compass visit. The primary outcome is to evaluate anxiety and distress in women with different HPV and cytology results. Factors related to cervical screening outcomes and adherence, utility scores and other outcomes will also be investigated.
Results: Recruitment to Compass-PLUS commenced in June 2019. Within the first 3 months, a total of 525 women aged 25-39 years were invited, of whom 165 have consented (response rate of 31%). Based on data from the first 102 participants, 67% are in the HPV arm of Compass and 33% in the cytology arm (consistent with the 2:1 trial randomisation) which will enable comparisons between low, intermediate and high risk groups based on test results, in-line with the program. The majority of women were Australian-born (76%), married/registered partnership (56%), have a university degree/higher certificate (59%), live in a city (75%) and in the highest two quintiles of socioeconomic status (68%).
Conclusions: Compass-PLUS will inform the support of women who have high risk HPV test results and the successful long-term implementation of Australia's screening program.

NEXT GENERATION SEQUENCING FOR HPV DETECTION AND CHARACTERISATION IN LUXEMBOURG.

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: We compared untargeted next generation sequencing (NGS) and a PCR test to assess the diversity of human papillomaviruses (HPV) in young women in Luxembourg.
Methods: Cervical samples of 739 women (mean age 22.4 y.) were tested by the commercial test Anyplex II HPV28 (Seegene) able to detect 28 HPV genotypes. After enrichment by rolling circle amplification, DNA extracts were sequenced on Illumina Miniseq. Quality checked reads were filtered by alignment to the human reference genome (GRCh38) and mapped against 319 HPV reference genomes from PaVE (and NCBI) using Bowtie2 in paired-end mode. Samples have been considered as positive if paired reads mapped in a concordant manner and covered at least 100bp (determined by minimum read length passing QC) of the respective HPV reference genome. Complete genome assemblies were obtained by using SPAdes 3.13.0 followed by phylogenetic analysis in MEGA 7.
Results: Overall, HPV positivity was 50% by Anyplex and 46% by NGS. Agreement between the two methods was 80.8% (kappa=0.616, McNemar $P<0.05$). HPV42, 53 and 51 were the most frequently detected genotypes by either method. Detection of HPV types and recovery of complete genomes by NGS was strongly correlated with the viral load of Anyplex. NGS detected a total of 26 additional genotypes in 118 samples, HPV67 (3.5%), HPV90 (3.1%), HPV62 (2.8%) being most frequently observed. We assembled 159 complete (1 scaffold) and 53 almost complete genomes (>97% coverage, >1 scaffold). We identified two novel lineages for genotypes 42, 74 and 101 and one novel lineage for genotypes 54, 66, 73, 83, 90 and 108, as well as 11 novel sub-lineages.
Conclusions: Next-generation sequencing is a powerful method for unbiased HPV detection enabling the identification of novel lineages and sub-lineages. The recovery of complete genomes will be important information for assessing HPV evolution as a potential impact of widespread vaccination programmes.

INFECTION- AND VACCINE-INDUCED HPV-SPECIFIC ANTIBODIES IN CERVICOVAGINAL SECRETIONS. A REVIEW OF THE LITERATURE.

BASIC RESEARCH / IMMUNOLOGY

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Introduction: Human papillomavirus (HPV) infects and propagates in the cervical mucosal epithelium. Hence, in addition to assessing systemic immunity, the accurate measurement of cervical immunity is important to evaluate local immune responses to HPV infection and vaccination. This review discusses studies that investigated the presence of infection and vaccine-induced HPV-specific antibodies in cervicovaginal secretions (CVS).
Methods: We searched the two main health sciences databases, PubMed and the ISI Web of Science, from the earliest dates available to March 2019. From the eligible publications, information was extracted regarding (i) study design, (ii) the reported HPV-specific antibody concentrations in CVS (and the associated serum levels, when provided), (iii) the CVS collection method, and (iv) the immunoassays used.
Results: The systematic search and selection process yielded 44 articles. The evidence of HPV-specific antibodies in CVS after natural infection (26/44) and HPV vaccination (18/44) is discussed. Many studies indicate that HPV-specific antibody detection in CVS is variable but feasible with a variety of collection methods and immunoassays. Most CVS samples were collected by cervicovaginal washing or wicks, and antibody presence was mostly determined by VLP-based ELISAs. The moderate to strong correlation between vaccine-induced antibody levels in serum and in CVS indicates that HPV vaccines generate antibodies that transudate through the cervical mucosal epithelium.
Conclusions: Although HPV-specific antibodies have lower titres in CVS than in serum samples, studies have shown that their detection in CVS is feasible. Nevertheless, the high variability of published observations and the lack of a strictly uniform, well-validated method for the collection, isolation and quantification of antibodies indicates a need for specific methods to improve and standardize the detection of HPV-specific antibodies in CVS.

VAGINAL MICROBIOTA COMPOSITION ACCORDING TO REAL-TIME PCR IN PATIENTS WITH HPV-ASSOCIATED CERVICAL INTRAEPITHELIAL NEOPLASIAS

BASIC RESEARCH / MICROBIOME

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Introduction: Vaginal dysbiosis is one of co-factors for the development of cervical neoplasias. The aim of this study was to analyze qualitative and quantitative composition of vaginal microbiota in patients with cervical intraepithelial neoplasias (CIN).
Methods: Vaginal microbiota of 312 patients was evaluated by means of RT-PCR (“Femoflor-16” kit, DNA-Technology, Russia). Patients were divided into 3 groups: Group 1 included 109 HPV-positive patients with LSIL, Group 2 - 102 HPV-positive patients with HSIL, Group 3 - 102 HPV-negative women with NILM (control group). The kit allows detecting the quantity (expressed in genome equivalents per 1 ml (GE/ml)) of lactobacilli and 15 groups of opportunistic microorganisms (OM). The special software was used to automatically calculate the total bacterial load (TBL) and the proportion of OM and lactobacilli in relation to the TBL. Depending on the proportion of lactobacilli and OM in theTBL, three types of vaginal microbiota were identified: normocenosis —the proportion of lactobacilli > 80 % of the TBL; apparent dysbiosis (AD) —the proportion of lactobacilli < 20 % and OM > 80 % of the TBL; moderate dysbiosis — the proportion of lactobacilli and OM 20% < 80%of the TBL. HPV test was performed using real-time PCR “HPV-Quant-21” kit (DNA-Technology, Russia). Statistical data processing was performed using SPSS Statistics v. 20.0.
Results: Normocenosis was detected in 75(68.8%), 26(25.5%) and 100(98%) of patients of Group 1, 2 and 3 respectively ($p<0.01$). MD was detected in 12(11.1%), 16(15.7%) and 1(1.0%) cases respectively. AD in 22(20.1%), 60(58,8%) and 1(1.0%) of patients of Group 1, 2 and 3 respectively($p<0.01$). In the structure of AD, anaerobic dysbiosis was prevalent in women of Group 1 and 2 (68.2%, 75% respectively).
Conclusions: HPV-associated CIN are accompanied by the development of apparent dysbiosis with the prevalence of obligate anaerobes.

PREVALENCE OF HPV INFECTION IN MSM ATTENDING SPECIALIST SEXUAL HEALTH SERVICES IN ENGLAND PRIOR TO WIDESPREAD HPV VACCINATION FOR MSM

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccination for gay, bisexual and other men who have sex with men (MSM) aged up to 45 years attending specialised sexual health services (SSHS) and HIV clinics began in England as a pilot in June 2016, with national roll-out from April 2018. We are conducting multi-site surveillance of type-specific HPV DNA prevalence in MSM attending SSHS in England, starting with a baseline survey prior to and during early stages of the pilot.
Methods: Anonymised residual rectal swab specimens from MSM aged up to and including 45 years undergoing chlamydia and/or gonorrhoea screening at 8 SSHS were collected. Specimens were linked to data reported to the GUMCAD STI Surveillance System (demographics, prior STI and HIV diagnosis, and HPV vaccination). Specimens were tested for type-specific HPV DNA using an in-house multiplex PCR and Luminex-based genotyping test.
Results: Of 1733 samples tested (of 3800 collected), 1641 (95%) had an adequate result. The prevalence of any HPV type was 66.9% (95% CI 64.6-69.2; n=1098). Prevalence of any quadrivalent vaccine types HPV16/18/6/11 was 38.8% (95% CI 36.5-41.2; n=637) and HPV16/18 was 21.9% (95% CI 19.9-24.0; n=359). HPV 16/18 prevalence was higher (30%; 95% CI 27.5-33.5) MSM with prior STI or HIV diagnoses. Note: Results are preliminary at abstract submission – full results will be presented at IPV
Conclusions: Preliminary results of our baseline surveillance of HPV prevalence in MSM attending SSHS are consistent with previously published data from a single, large London clinic: most MSM eligible for HPV vaccination were not currently infected with an HPV vaccine type. Prevalence by uptake of vaccination and other factors, and the findings of subsequent collections, will be used to assess the success of HPV vaccination of MSM in England.

DISTRIBUTION OF HUMAN PAPILLOMAVIRUS GENOTYPES AND HOST EPIGENETIC CHANGES ASSOCIATED WITH CERVICAL CANCER PROGRESSION IN WOMEN WITH AND WITHOUT HUMAN IMMUNODEFICIENCY VIRUS INFECTION IN BOTSWANA

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Cervical cancer remains a significant cause of morbidity and mortality in women worldwide and is the leading cause of cancer-related death in Botswana. Persistent HPV infection leads to cervical cancer. Host epigenetic changes have also been recognized as important players in carcinogenesis.
Methods: We assessed hr-HPV prevalence and genotype distribution in tissue specimens from confirmed invasive cervical cancer cases and non-cancers using Real-Time PCR. We also assessed the methylation status in invasive cancer vs. non-cancers in bisulfite-treated DNA by Methylation-Specific PCR using primers designed to distinguish methylated from un-methylated DNA in order to evaluate *DAPK1* promoter methylation as an epigenetic marker.
Results: 126 cervical cancer cases and 86 non-cancers were analyzed. 88 (69.8%) women with cervical cancer were HIV-infected. Fifty-seven (64.8%) of the HIV-infected women had a baseline $CD4^+$ count ≥ 350 cells/µl, and 82 (93.2%) were on ART at the time of cervical cancer diagnosis. The median age of HIV-infected patients was significantly younger than that of HIV-uninfected patients ($p < 0.001$). Hr-HPV genotypes identified included the HPV-16 (75.4%), HPV-18 (28.6%), and *other* hr-HPV genotypes (16.7%). HIV infection was positively associated with the presence of the HPV-16 genotype ($p = 0.036$), but not with HPV-18 or with *other* hr-HPV genotypes. Overall methylation analysis was assessed in 85 cervical cancer cases and 86 non-cancer tissue blocks. DNA methylation status in cervical cancer patients was 64.7% compared to the non-cancer patients (25.6%). A significant strong association between *DAPK1* promoter methylation and cervical was shown compared to non-cancer ($p<0.001$). HIV status was not associated with *DAPK1* promoter methylation ($p=0.87$) in cervical cancer group.
Conclusions: These results highlight the importance and potential impact of large-scale HPV vaccination programs covering HPV-16 and HPV-18 genotypes in countries like Botswana with high burden of HIV infection. Furthermore methylation markers may have valuable role in early detection of invasive cervical cancer.

CORRELATION BETWEEN HUMAN PAPILLOMAVIRUS GENOTYPES AND CITOLOGY IN THE NORTH REGION OF PORTUGAL: DATA FROM REGIONAL CERVICAL CANCER SCREENING

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: Data from more than 100,000 women revealed that the prevalence of High-Risk Human papillomavirus (HR-HPV) in the North region of Portugal is of 10.2% with distinct age and geographical distribution. Here we explore the correlation between HR-HPV genotypes distribution and cytology to improve the knowledge on cervical disease in Portugal.
Methods: We have combined the information from HR-HPV genotypes and cytology of a total of 9517 HR-HPV positive women that had been enrolled in the Regional Cervical Cancer Screening Program from the Northern Region of Portugal between August 2016 and December 2017.
Results: Regarding cytology, 5148 (54.1%) cases were negative for intraepithelial lesion or malignancy (NILM), 2733 (28.7%) with atypical squamous cells of undetermined significance (ASC-US) and 271 (2.8%) atypical squamous cells that cannot exclude an HSIL(ASC-H), 1079 (11.3%) low-grade (LSIL) and 252 (2.6%) high-grade (HSIL) squamous intraepithelial lesions, 4 (0.04%) Adenocarcinomas In Situ (AIS) and 2 (0.02%) Invasive Cervical Cancer (ICC) **– Table I**. Single infections (n=7224 cases, 75.9%) by any of HPV-16/18/31/33/45/52/58 were present in 30.1% of NILM, 37.5% of ASC-US, 70.6% of ASC-H, 35.7% of LSIL, 75.0% of HSIL, 50% of AIS and 100% of ICC– **Table II**. Regarding HR-HPV multiple infections (n=2259 cases, 23.7%) we found that HPV-16/18/31/33/45/52/58 were present in 59.1% of NILM, 67.5% of ASC-US, 80.5% of ASC-H, 66.2% of LSIL, 91.7% of HSIL and 100% of AIS – **Table III**.

TABLE I

CYTOLOGY	Total	HPV16	HPV18	HPV31	HPV33	HPV35	HPV39	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV66	HPV68
NILM	5148	298	117	702	183	227	1045	214	467	550	439	412	322	454	776
AGC	**28**	3	3	4	1	0	6	1	2	2	1	1	2	3	3
ASC-US	**2733**	369	99	448	148	156	444	106	336	320	271	261	198	252	379
ASC-H	**271**	99	16	56	20	18	19	10	21	35	11	24	8	13	27
LSIL	**1079**	150	45	205	56	76	132	42	209	126	201	113	97	163	128
HSIL	**252**	133	12	49	22	19	19	6	18	32	10	24	9	8	12
ICC	**2**	2	0	0	0	0	0	0	0	0	0	0	0	0	0
AIS	**4**	2	1	2	1	0	0	0	0	0	1	0	0	0	0
Total	**9517**	**1056**	**293**	**1466**	**431**	**496**	**1665**	**379**	**1053**	**1065**	**934**	**835**	**636**	**893**	**1325**

NILM, negative for intraepithelial lesion or malignancy; AGC, Atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells that cannot exclude an HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; AIS, Adenocarcinoma In Situ; ICC, Invasive Cervical Cancer.

TABLE II

CYTOLOGY	Total	Single	4-VAL	9-VAL	HPV16	HPV18	HPV31	HPV33	HPV35	HPV39	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV66	HPV68
NILM	**5148**	4252	266	1279	202	65	468	121	125	854	142	316	351	292	281	194	281	560
AGC	**28**	24	4	9	2	2	3	1	0	6	0	0	2	1	1	1	2	3
ASC-US	**2733**	1955	259	733	216	43	232	73	61	266	52	178	165	135	117	88	119	210
ASC-H	**271**	194	76	137	68	8	40	11	7	3	3	11	19	3	7	4	1	9
LSIL	**1079**	627	84	224	68	16	66	22	23	46	11	87	40	75	41	24	73	35
HSIL	**252**	168	87	126	84	3	21	7	8	4	3	9	16	0	8	1	1	3
ICC	**2**	2	2	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0
AIS	**4**	2	1	1	1	0	0	0	0	0	0	0	0	1	0	0	0	0
Total	**9517**	**7224**	**779**	**2511**	**643**	**137**	**830**	**235**	**224**	**1179**	**211**	**601**	**593**	**507**	**455**	**312**	**477**	**820**

NILM, negative for intraepithelial lesion or malignancy; AGC, Atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells that cannot exclude an HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; AIS, Adenocarcinoma In Situ; ICC, Invasive Cervical Cancer; 4-val, High-Risk HPV genotypes presente in 4-valent HPV vaccine; 9-val, High-Risk HPV genotypes presente in 9-valent HPV vaccine.

TABLE III

CYTOLOGY	Total	Multi	4-VAL	9-VAL	HPV16	HPV18	HPV31	HPV33	HPV35	HPV39	HPV45	HPV51	HPV52	HPV56	HPV58	HPV59	HPV66	HPV68
NILM	5148	869	138	514	96	52	234	62	102	191	72	151	199	147	131	128	172	216
AGC	**28**	4	2	3	1	1	1	0	0	0	1	2	0	0	0	1	1	0
ASC-US	**2733**	771	195	521	153	56	216	75	95	178	54	158	155	136	144	110	133	169
ASC-H	**271**	77	37	62	31	8	16	9	11	16	7	10	16	8	17	4	12	18
LSIL	**1079**	452	108	299	82	29	139	34	53	86	31	122	86	126	72	73	90	93
HSIL	**252**	84	55	77	49	9	28	15	11	15	3	9	16	10	16	8	7	9
AIS	**4**	2	2	2	1	1	2	1	0	0	0	0	0	0	0	0	0	0
Total	**9517**	**2259**	**537**	**1478**	**413**	**156**	**636**	**196**	**272**	**486**	**168**	**452**	**472**	**427**	**380**	**324**	**415**	**505**

NILM, negative for intraepithelial lesion or malignancy; AGC, Atypical glandular cells; ASC-US, atypical squamous cells of undetermined significance; ASC-H, atypical squamous cells that cannot exclude an HSIL; LSIL, low-grade squamous intraepithelial lesions; HSIL, high-grade squamous intraepithelial lesions; AIS, Adenocarcinoma In Situ; ICC, Invasive Cervical Cancer.

Conclusions: This study shows that HR-HPV genotypes present in the 9-valent vaccine are responsible for a significant part of cytological abnormalities >= ASC-US, nevertheless there still exist significant cases of other HR-HPV genotypes which supports the utility of synergy strategies for cervical cancer prevention using vaccines and cervical cancer screening.

THE IMPACT OF HPV VACCINATION IN THE UNITED STATES (U.S.): A STATE-WIDE POPULATION-BASED EVALUATION IN NEW MEXICO

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: While ecological studies have demonstrated the impact of the 4-valent HPV vaccine in various settings, here we report the largest population-based investigation in the U.S. prior to mass introduction of the 9-valent HPV vaccine.
Methods: Two state-wide random stratified samples from women undergoing routine cervical screening were selected. Liquid-based cytology collected in two periods, 2007-2009 and 2013-2016, each representing approximately 100,000 women, were genotyped by Roche Linear Array. Weighted relative prevalence (RP) and 95% confidence intervals (95%CI) for HPV genotypes and various groupings were estimated for women aged 15-19y, 20-24y and 25-29y. Weighted logistic regression models were fit to estimate positivity for HPV16 and 4-valent types (HPV6/11/16/18), adjusting for birth cohort and age.
Results: A significant reduction in prevalence for HPV16, HPV18, HPV31 and HPV33 was observed. Among the 15-19y, RP=-76.22 (95%CI=-84.12, -68.32) for HPV16, RP=-82.93 (95%CI=-94.95, -70.91) for HPV18, RP=-51.25 (95%CI=-69.35, -33.16) for HPV31, and RP=-41.50 (95%CI=-78.29, -4.70) for HPV33. However a significant relative increase for HPV39 and HPV59 among women 15-19y and for HPV52 and HPV59 among women 20-24y was observed. Whilst a significant reduction in RP for all carcinogenic HPV types combined was observed among women 20-24y, when excluding HPV16/18 there was no difference. There was also a significant increase in RP for all non-carcinogenic HPV types combined, although prevalence significantly decreased for HPV6 and HPV11. The odds of positivity for HPV16 and 4-valent HPV types combined decreased with later birth cohorts (HPV16: 0.81 in 1990, 0.11 in 1996; 4-valent types: 0.73 in 1990, 0.09 in 1996) compared to the 1989 birth cohort.
Conclusions: Large reductions in prevalence of HPV-6,-11,-16,-18,-31 and -33 were observed across the study period, however increases in carcinogenic and non-carcinogenic HPV types may have unanticipated consequences and therefore warrants further investigation. Ongoing public health efforts in New Mexico continue to inform HPV-based prevention strategies over time.

FURTHERING QUALITY AND ORDER IN HPV RESEARCH

BASIC RESEARCH / TAXONOMY

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Introduction: The International HPV Reference Center continues its efforts in advancing towards quality and order in human papillomavirus research and diagnostics.
Methods: The International HPV Reference Center is responsible for assigning HPV type numbers to novel HPV types, maintaining a reference clone repository, distributing samples of the reference material for research use, issuing international proficiency panels for HPV genotyping and supporting the International HPV Animal Reference Center. All services are described in detail in the corresponding webpage: https://www.hpvcenter.se.
Results: The established HPV types, currently up to HPV220, belong to 5 different genera: alpha (65 types), beta (53 types), gamma (98 types), mu (3 types) and nu (1 type). In the last 5 years, 86% (24/28) of all novel HPV types belong to the gamma genus. Since the Center was transferred to KI in 2012, reference clones (611 plasmids) have been provided to 78 different research laboratories, and the global proficiency program for HPV genotyping has seen an increasing participation (currently >145 laboratories) and complete proficiency has increased over time (from <50% to 80% of datasets). The International HPV Reference Center has achieved open access to all genotypes sequences and data and, provides up to date e-learning lectures and webinars to the scientific community.
Conclusions: In summary, an increasing complexity of the HPVs requires international efforts to support a recognized quality and order among HPV types.

COMPARATIVE ANALYSIS OF URINE FRACTIONS FOR OPTIMAL CIN3 AND CERVICAL CANCER DETECTION USING METHYLATION MARKERS

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Urine sampling is an interesting solution to increase the uptake of cervical screening. Previous studies pointed out good accuracy for HPV detection and the feasibility of cervical cancer detection by urinary DNA methylation analysis. Urine can be separated in different fractions: full void urine, urine sediment and urine supernatant. This study aims to determine which urine fraction is most competent to distinguish between healthy controls, high grade cervical intraepithelial neoplasia (CIN3) and cervical cancer by DNA methylation analysis.
Methods: Urine samples were collected from 17 women with cervical cancer, 30 women with CIN3 and 30 healthy female controls. Each urine sample was processed into 3 fractions and tested for 5 methylation markers (*ASCL1, GHSR, LHX8, SST, ZIC1)* by quantitative methylation specific PCR. Spearman correlation coefficients between paired urine fractions were determined and methylation levels between disease categories were compared. Receiver operating characteristic curves were made and area under the curve (AUC) was calculated for CIN3 and cervical cancer detection.
Results: In general strong correlations (r>0.60) were found between the different urine fractions for all markers. Significant difference between CIN3 patients and controls was found for 2 out of 5 markers in full void urine, 4 out of 5 markers in urine sediment and 2 out of 5 markers in urine supernatant (AUC 0.55- 0.79). All markers demonstrated a significant increase in DNA methylation levels and an excellent performance (AUC 0.87- 0.99) in all urine fractions to discriminate between cervical cancer and controls.
Conclusions: This study shows a good performance of all urine fractions for cervical cancer detection. Our results also indicate the potential of CIN3 detection by urinary methylation analysis and demonstrate best performance of urine sediment to detect CIN3.

GENITAL HPV PREVALENCE AMONG TWO-DOSE BIVALENT HPV VACCINE ELIGIBLE GIRLS IN THE NETHERLANDS AFTER THREE YEARS OF FOLLOW-UP: THE HAVANA2 COHORT

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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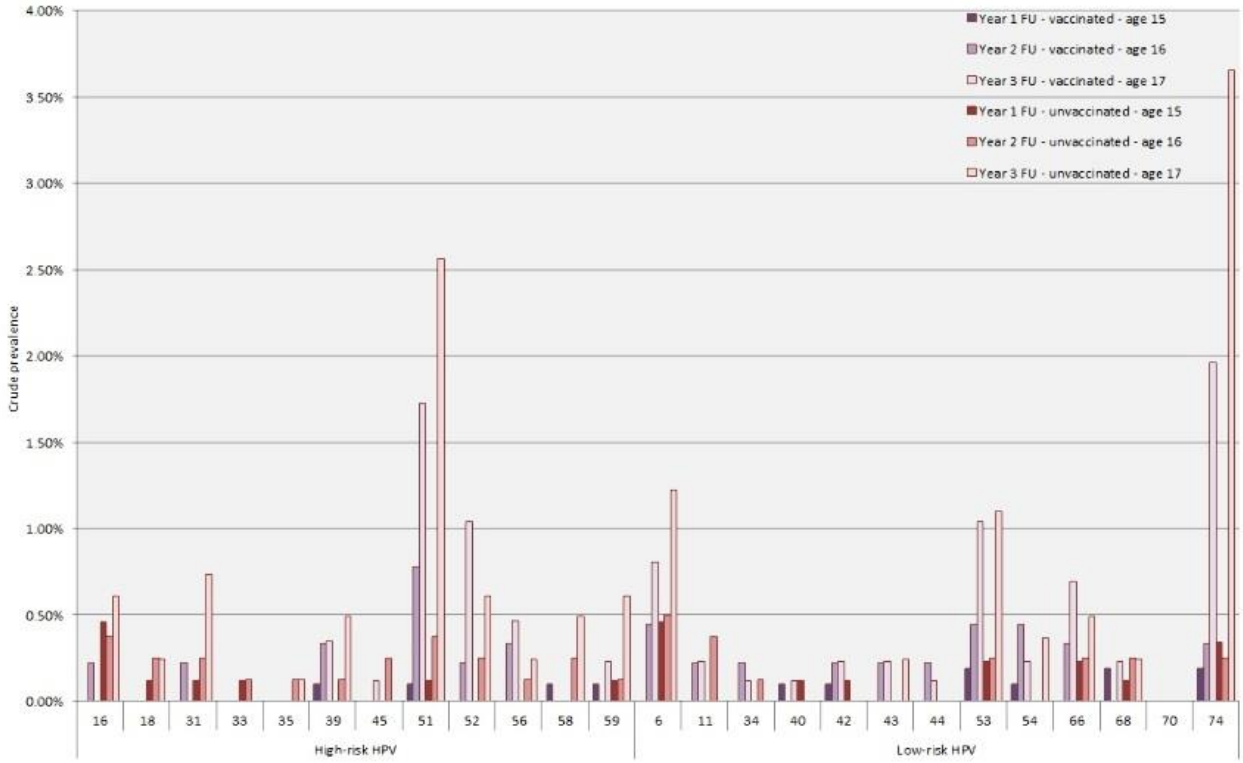
Introduction: The Netherlands introduced the bivalent HPV vaccine into the National Immunization Program as a girls only vaccine in a three-dose schedule in 2009. Following the EMA advice in 2014, the Netherlands was one of the first countries that switched towards a two-dose schedule. Alongside this implementation, a population-based longitudinal cohort was established: HAVANA2. Here, we describe participant characteristics and compare HPV prevalence among vaccinated and unvaccinated girls over three years of follow-up (3y-FU).
Methods: In 2016, we invited 39261 girls who were eligible for the two-dose schedule in 2014 (birth cohort 2001) for participation in HAVANA2. Of these, 2571 girls provided informed consent. Yearly, participants provided a vaginal self-swab and a questionnaire on demographics and sexual behavior. Using the HPV-DEIA-LiPA25 platform, genital swabs were genotyped to study prevalence of high-risk (including HPV16/18) and low-risk HPV types.
Results: In total, 2121 girls provided a vaginal self-sample and a questionnaire at least once in the first three years of study (52.9% vaccinated). 1378 participants provided materials for all 3y-FU. The majority of the study population was Dutch (88.9%) and 84.3% reported to be sexually naive at study entry. Preliminary results show that the high-risk HPV type with the highest prevalence was HPV51 both for vaccinated (1.7%) and unvaccinated participants (2.6%) at 3y-FU. The cumulative prevalence over three years of HPV16/18 infections was low: 0.2% among vaccinated and 1.5% among unvaccinated, respectively.



Conclusions: After 3y-FU, the total number of infections was low. Nevertheless, the decreased high-risk and vaccine type HPV prevalence among vaccinated compared to unvaccinated girls indicate the first effect of the two-dose schedule providing protection in a population setting. Follow-up of this cohort is planned for at least two more years aiming to estimate vaccine effectiveness estimates against (persistent) high-risk HPV infections for a two-dose schedule.

DEVELOPMENT OF A CERVICAL CANCER SCREENING APPROACH BASED ON FIRST-VOID URINE: VERIFICATION OF STANDARDIZED AND VOLUMETRIC COLLECTION.

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: The development of a first-void (FV) urine-based cervical cancer (CC) screening approach will lower the barriers to testing since CC screening currently depends on physician-taken cervical scrapes. Urine has been suggested as an easily accessible and non-invasive source of biomarkers to test for the presence of high-risk HPV (hrHPV), the main etiologic agent of CC. The first step towards developing a self-sampling screening approach is to identify the optimal FV volume to detect hrHPV and to verify the sampled volume. This study aimed to evaluate the accuracy of the FV urine volume collected with the Colli-Pee, a user-friendly device developed by Novosanis.
Methods: Volumetric tests are performed in the lab where 250mL water was poured into the Colli-Pee to represent the urine flow. Additionally, 30 hrHPV-positive women were included in the study. Each participant is asked to collect three consecutive FV urine samples at home using the Colli-Pee able to capture either 4mL, 10mL or 20mL (commercially available), with a minimum time interval of 2h. The volume of each sample is verified by pipetting the collected urine from the tube. The tubes were prefilled with Novosanis' UCM preservative (ratio1:3) to allow for preservation of the urine content at ambient temperatures.
Results: Lab results show an average collected volume of 3.98mL (SD=0.04), 9.38mL (SD=0.11) and 20.31mL (SD=0.75) with respectively the 4mL (n=5), 10mL (n=5) and 20mL (n=144) Colli-Pee variant. Preliminary data from 16 women confirm the results for Colli-Pee 10mL (9.94±0.65mL) and Colli-Pee 20mL (20.46±2.39mL).
Conclusions: Previous studies have shown that the Colli-Pee is a well-accepted solution for home-based FV urine collection. New generation Colli-Pee devices for the collection of 10mL and 4mL, enable integration with commercially available high-throughput machines. Hence, verification of the collected volume is an important step towards commercializing the first fully molecular integrated CC screening approach based on FV urine.

DETECTION OF A SINGLE HPV TYPE IN INVASIVE CERVICAL CANCER (IVCC) USING THE LASER CAPTURED MICRODISSECTION AND THE UNIPLEX E6/E7 PCR METHOD

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: About 10% of IVCC cases were positive with multiple HPV types, and about 5% of cancer were not detected any HPV types in our previous study. To determine a single HPV type responsible for cancer development, we used a new procedure.
Methods: Nine IVCC cases having multiple HPV types and 8 IVCC cases which not detected any HPV types by the previous assay were investigated. Formalin fixed and paraffin embedded were cut out by laser captured microdissection. HPV genotyping were determined using the uniplex E6/E7 PCR method able to detect E6 or E7 DNA of 39 HPV types.
Results: Among 9 cases of multiple HPV type infection, 4 cases were positive with HPV-16, 3 cases with HPV-18, and each one case was HPV-67 and -59. Among 8 cases not detected HPV, HPV-16 was found in 2 cases, HPV-18 and -67 were in each one case, and 2 cases were negative. The negative cases were 2 adenocarcinoma (ADC) and one minimal deviation adenocarcinoma and large cell neuroendocrine carcinoma. One adenosquamous carcinoma (ADSQC) with HPV-52 and one SCC with HPV-51 were examined, and HPV-18 and HPV-16 were identified. HPV-52 was positive in squamous cell area covering ADSQC tumor in the first case, and HPV-51 was detected in the vagina of the second case. In 17 cases, HPV-16 was in 6 cases (4 SCC, one ADC, one small cell neuroendocrine carcinoma), HPV-18 in 4 cases (one SCC, 2 ADC, one ADSQC), HPV-67 in 2 SCC, and HPV-59 in one ADC were identified.
Conclusions: HPV genotyping using tissue microdissection procedure with the uniplex E6/E7 PCR is the most powerful tool to identify HPV genotype in cancer specimen. HPV-67 is likely to be high-risk type, since it was identified in 2 SCC cases who have died for the cancer.

HR-HPV/CYTOLOGY-BASED ORGANIZED CERVICAL CANCER SCREENING PROGRAMME IN 30-64 YEARS OLD PARAGUAYAN WOMEN. A POPULATION COHORT STUDY (ESTAMPA STUDY).

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Objetive. To assess the feasibility of implementing organized cervical cancer screening programs based on HR-HPV/cytology.
Methods: In 2014-2017, 10082 eligible women aged 30-64 from two well-established catchment areas of Central Department, were invited to be screened with HR-HPV (Hybrid Capture 2) and cytology. Those with any positive screening test were referred to colposcopy with biopsy collection if needed. Women with CIN2+ were offered treated and those with <CIN2 were invited to a control visit at 18 months with HR-HPV test. Colposcopy was offered to women if HR-HPV infection persisted followed by treatment for CIN2+. The main strategies used in the follow-up were telephone calls/messages and home visits offering self and clinical HPV sampling.
Results: 4984/10082 (49.4%) women were enrolled in the screening program. In addition, 693 women aged 30-64 from other areas were also screened. A total of 5314 women were included in the present analysis. HR-HPV was positive for 13.8% and cytology was abnormal (ASC-US+) for 2.9%. In total, 88.6% of 770 with HR-HPV-positive/abnormal cytology had colposcopy, and 71 CIN2+ cases were detected. HR-HPV had 97.2% sensitivity (95%CI:90.3-99.2) and 87.3% specificity (95%CI:86.4-88.2). Cytology had 60.6% sensitivity (95%CI:48.9-71.1) and 97.9% specificity (95%CI:97.5-98.3). Furthermore, 12 women with high-grade on cytology and colposcopy were also treated with LLETZ with a final diagnosis of <CIN2+. Finally, 687 women met the criteria for being invited to the 18 months visit. 90% of them attended this visit in an average time of 1.9 years (standard deviation 0.7). The persistence of HR-HPV was 41.5% and 89% had colposcopy. Additionally, 17 CIN2+ cases were detected.
Conclusions: It was possible to carry out an organized cervical cancer screening model, implementing steps that favored the performance of HR-HPV test as well as the execution of strategies that strengthen the follow-up of women at risk of developing cervical lesions.

GYNTECT® DNA METHYLATION ASSAY MAY BE AN OPTION FOR TRIAGE OF HPV-SCREENING POSITIVE WOMEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Screening for cervical cancer using an HPV-based assay is currently being implemented in many countries worldwide. The advantage of HPV-based screening is increased sensitivity compared to cytology, but the specificity is inferior. To avoid overtreatment reliable triage of HPV-positive women is required. DNA methylation could be a feasible method for this triage.
Methods: This study is based on a cohort of 305 women from a referred population. From each woman a physician-taken cytology sample, a self-collected vaginal sample, a urine sample and a histology sample was collected. The first 44 HPV-positive physician-taken cytology samples have been tested with a DNA methylation assay, GynTect®. Two-three ml of ThinPrep material was used for the analysis following the manufactures instructions. QPCR was performed on the QuantStudio 12K Flex instrument. A Gyntect score is calculated, and the sample considered positive if the score is equal to or higher than 6. The test result was compared to the histology diagnoses.
Results: In this pilot study 20 samples were tested GynTect positive and 24 were test negative.

	CIN2+ pos	CIN2+ neg	CIN3+ pos	CIN3+ neg
GynTecyt pos	18	2	16	4
GynTecyt neg	10	14	1	23

The sensitivity and specificity for CIN2+ and CIN3+ were calculated, and for CIN2+ the sensitivity was 64% and the specificity was 88%, while for CIN3+ it was 94% and 85%, respectively.
Conclusions: These preliminary results indicate that the GynTect® assay could be an option for triage of HPV positive samples. Accordingly, the remaining physician-taken samples will be tested to strengthen these initial results, and updated results will be presented. In addition, the self-collected vaginal samples are also expected to be tested with this methylation assay, as these samples cannot be triaged with cytology.

PRESENCE OF INFECTIONS AS A RISK FACTOR OF A FALSE NEGATIVE CYTOLOGY RESULT IN THE POLISH CERVICAL CANCER SCREENING PROGRAMME

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: False negative (FN) Pap test results arise from lack of abnormal cells in the smear related to sampling errors or lesions developing deep in the endocervical canal, and interpretation errors associated with many factors such as distortion of the microscopic image by infectious factors and inflammatory changes. We have attempted to verify whether presence of specific microorganisms in cervical smear increases the risk of FN cytological diagnosis.
Methods: Results of 1.6million screening cytologies collected in 2010-2011 were linked with National Cancer Registry database to search for invasive cervical cancer (CC) cases. Histologically confirmed cases diagnosed in 3 years after cytological result were considered as interval (if preceded by normal result; ICC) or screen detected (if preceded by abnormal result; SDC). Logistic regression was applied to calculate odds ratios of FN result depending on specific type of infection. Level of <0.05 was established as statistically significant.
Results: We identified 309 ICC and 738 SDC (Table 1). Infection with *Candida* contributed the highest risk of incorrect diagnosis (OR=5.68, 95%CI 1.46–22.11); also *Bacterial vaginosis* and other changes in bacterial flora raised odds significantly (OR=3.61, 95%CI 1.66 – 7.87 and OR=3.56, 95%CI 2.14 – 5.91, respectively). Presence of *Chlamydia trachomatis*, *Trichomonas vaginalis* or unspecified bacterial infection were non-significant risk factors (OR=1.44, 95%CI 0.34–6.05, OR=1.33, 95%CI 0.44–4.01 and OR=1.10, 95%CI 0.74–1.64, respectively). Combined infections doubled the odds of FN diagnosis (OR=2.11, 95%CI 1.56–2.85).

Microorganism	Cervical cancer cases, n (%)		OR	95% confidence interval	p-value
	SDC (738 cases)	ICC (309 cases)			
Candida	9 (1.2%)	5 (1.6%)	5.68	1.46 - 22.11	0.012
Bacterial vaginosis	3 (0.4%)	7 (2.3%)	3.61	1.66 - 7.87	0.001
Changes in bacterial flora	28 (3.8%)	38 (12.3%)	3.56	2.14 - 5.91	<0.001
Chalmydia trachomatis	5 (0.7%)	3 (1.0%)	1.44	0.34 - 6.05	0.621
Trichomonas vaginalis	9 (1.2%)	5 (1.6%)	1.33	0.44 - 4.01	0.610
Unspecified bacterial infection	88 (11.9%)	40 (12.9%)	1.10	0.74 - 1.64	0.646
Any of mentioned above	**138 (18.7%)**	**101 (32.7%)**	**2.11**	**1.56 - 2.85**	**<0.001**

Conclusions: Presence of any microorganism on the cytological slide elevated the risk of FN diagnosis; *Candida, Bacterial vaginosis* and changes in bacterial flora were associated with the highest risk. It should be determined if treatment of women with features of infections decreases the risk of a FN result. Further studies are required to verify if co-infections (apart from HPV) with *Candida*, *Bacterial vaginosis* and changes in bacterial flora facilitate development of CC.

EFFECTIVENESS OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN REPAIRING CERVICAL MUCOSA WITH HPV LESIONS. INTERIM ANALYSIS RESULTS OF AN OBSERVATIONAL STUDY

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: Real-life studies are mandatory for complementation of RCT. They inform on the "effectiveness" of a treatment what is intended to do in routine circumstances. Objective: to evaluate the effectiveness of Papilocare® -a *Coriolus versicolor*-based vaginal gel- on repairing HPV-dependent low-degree cervical lesions and HPV clearance.
Methods: Observational, multicenter, prospective, one-cohort study (PAPILOBS study). Currently recruiting 300 vaccinated or not vaccinated HPV-positive women aged > 25y with pap result of ASC-US or LSIL and concordant colposcopy image during routine clinical visits in Spain. Patients are treated with Papilocare® 1 cannula/day for 21 days the first month + 1 cannula/alternate days for 5 months. After this 6-month period, patients with altered cytology and HPV persistency are treated for a 6-month extension period with the same dosage. Interim analysis of patients with normal pap smear and concordant colposcopy image (primary endpoint) and patients with HPV clearance at 6/12 months is presented. The study was approved by the ethical committee of Public University Hospital of Puerta de Hierro (Madrid). Informed consent was signed by all patients.
Results: At 6 months, data of 72 and 71 patients for pap smear/colposcopy and HPV presence, respectively, are available. 65% of patients (47/72) had negative pap smear and concordant colposcopy. HPV clearance was observed in 54% of patients (38/71). Data of 18 patients included in the 6-month extension treatment period, are available. At 12 months, 94% of patients (17/18) had negative pap and colposcopy and HPV clearance was observed in 83% of patients (15/18).
Conclusions: In this preliminary analysis, Papilocare® has shown a notable effect in both repairing HPV-dependent low-degree cervical lesions and clearing HPV, in real life conditions. Objectives can be obtained after a 6-month treatment period in most of the patients, achieving 94% extending the treatment to 12 months. These findings need to be confirmed upon study completion.

HUMAN PAPILLOMAVIRUS TYPES IN CERVICAL DYSPLASIA AMONG YOUNG HPV-VACCINATED WOMEN: POPULATION-BASED NESTED CASE-CONTROL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccines protect against infections with the most oncogenic HPV types, cervical intraepithelial neoplasia (CIN) and cervical cancer. We investigated whether development of cervical intraepithelial neoplasia (CIN) lesions in HPV-vaccinated women is associated with vaccine-targeted HPV types or not.
Methods: Linkage of the Swedish vaccination and cervical screening registries identified all females born 1980-2000 who had been HPV vaccinated before 2014-12-31 (n=305,320) and had attended cervical screening in 2006-2018 (N=79,491). We further selected women HPV vaccinated below 17 years of age and screened in the capital region (N=5,874). Among those, 125 developed CIN and had a cervical cryopreserved sample available (42.5 % of all eligible CIN cases). After 1:2 matching to disease-free controls (N=242), samples were analyzed for HPV DNA and associations between HPV type and CIN diagnosis were estimated with conditional logistic regression.
Results: Vaccine-targeted HPV types were rare among both CIN cases (2.4 % HPV16, 0.8 % HPV18) and their matched controls (0.4 % HPV16 and 18). No woman had HPV6 or 11. The CIN lesions were associated with the non-vaccine HPV types 31, 33, 42, 45, 51, 52, 56, 59 and 66.
Conclusions: CIN lesions among young HPV vaccinated women are mostly attributable to infection with non-vaccine HPV types. The phenomenon may be important for surveillance and design of cervical cancer control strategies.

TRENDS IN HPV INFECTION PREVALENCE UP TO 8 YEARS AFTER GIRLS-ONLY HPV16/18 VACCINATION IMPLEMENTATION IN THE NETHERLANDS: A REPEATED CROSS-SECTIONAL STUDY IN STI-CLINIC VISITORS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The population effects of HPV vaccination extend beyond direct protection among vaccinated individuals; evidence for herd effects unfolds as follow-up time after vaccination increases and infection dynamics change. Here, we provide an overview of observed trends for 25 HPV types up to eight years post vaccination implementation in the Netherlands, where the bivalent HPV16/18 vaccine has been offered to (pre)adolescent girls since 2009 with moderate vaccination coverage (between 49-61%).
Methods: In this updated analysis, we used data from the PASSYON study, conducted in STI clinics throughout the country. The study was initiated in 2009 (pre-vaccination) and repeated in 2011, 2013, 2015, and 2017 among clinic visitors aged 16-24 years. We studied genital HPV prevalence over time among heterosexual men, all women, and unvaccinated women using Poisson GEE models, adjusted for known confounders. Type-specific trends were studied for all high and low-risk genotypes detected by the SPF10-LiPA25 platform.
Results: In this analysis, we included 2,414 heterosexual men and 6,354 women (of whom 64.7% reported to be unvaccinated). Significant declines in HPV16 and 18 were observed for all women as well as heterosexual men and unvaccinated women (crude prevalences in Figure 1). Declines in cross-protective HPV types were observed among women (for HPV31 and 45) and heterosexual men (for HPV31). Focusing on the high-risk HPV types, we observed significant increases in HPV56 among all women and in HPV52 among unvaccinated women (Table 1).

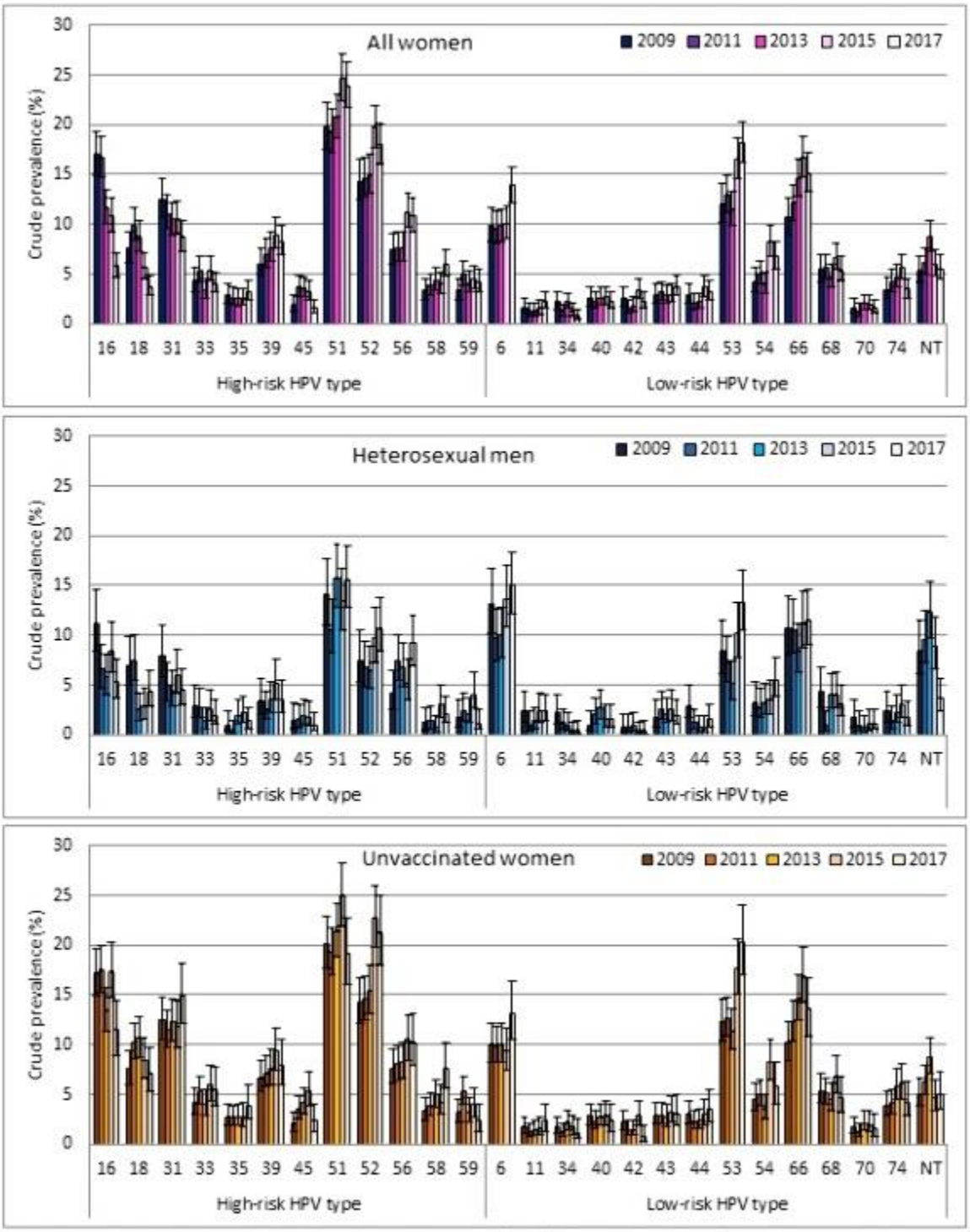

Figure 1: Crude HPV prevalence of 25 HPV types among all women (pink), heterosexual men (blue), and unvaccinated women (orange)

Table 1: Linear trends in prevalence over time (adjusted) among all women, heterosexual men and unvaccinated women.

		All women			Heterosexual men			Unvaccinated women		
		Beta[1]	95% C.I.	p-value	Beta[2]	95% C.I.	p-value	Beta[3]	95% C.I.	p-value
High-risk HPV types	HPV-16	-0.15	-0.17 - -0.12	<.0001	-0.12	-0.18 - -0.06	<.0001	-0.06	-0.09 - -0.03	<.0001
	HPV-18	-0.12	-0.15 - -0.09	<.0001	-0.17	-0.24 - -0.09	<.0001	-0.04	-0.08 - -0.01	0.02
	HPV-31	-0.07	-0.01 - -0.04	<.0001	-0.10	-0.17 - -0.03	0.005	-0.02	-0.06 - 0.01	0.22
	HPV-33	-0.04	-0.08 - 0.01	0.08	-0.09	-0.19 - 0.02	0.10	-0.01	-0.06 - 0.05	0.80
	HPV-35	-0.01	-0.07 - 0.05	0.68	0.03	-0.09 - 0.15	0.61	0.01	-0.07 - 0.08	0.90
	HPV-39	0.01	-0.02 - 0.05	0.51	-0.02	-0.11 - 0.06	0.57	0.01	-0.04 - 0.05	0.83
	HPV-45	-0.05	-0.20 - -0.01	0.04	-0.11	-0.22 - 0.01	0.07	0.02	-0.03 - 0.08	0.44
	HPV-51	0.01	-0.02 - 0.03	0.69	-0.03	-0.08 - 0.02	0.19	-0.02	-0.05 - 0.01	0.19
	HPV-52	0.01	-0.02 - 0.03	0.43	0.01	-0.06 - 0.07	0.88	0.03	0.01 - 0.06	0.03
	HPV-56	0.03	0.01 - 0.07	0.04	-0.01	-0.07 - 0.06	0.83	0.01	-0.03 - 0.05	0.61
	HPV-58	0.04	-0.01 - 0.08	0.13	0.03	-0.09 - 0.15	0.61	0.05	-0.01 - 0.11	0.06
	HPV-59	-0.02	-0.06 - 0.02	0.39	-0.05	-0.14 - 0.04	0.27	-0.07	-0.12 - -0.01	0.02
Low-risk HPV types	HPV-6	0.02	-0.02 - 0.05	0.32	-0.02	-0.08 - 0.03	0.39	-0.01	-0.05 - 0.03	0.70
	HPV-11	0.02	-0.06 - 0.09	0.68	-0.05	-0.17 - 0.08	0.46	0.01	-0.08 - 0.11	0.78
	HPV-34	-0.13	-0.20 - -0.05	0.0006	-0.30	-0.47 - -0.14	0.0004	-0.05	-0.14 - 0.04	0.26
	HPV-40	-0.03	-0.09 - 0.02	0.24	-0.05	-0.15 - 0.05	0.34	-0.03	-0.11 - 0.04	0.37
	HPV-42	-0.01	-0.07 - 0.05	0.76	-0.15	-0.33 - 0.03	0.09	-0.07	-0.16 - 0.02	0.13
	HPV-43	0.01	-0.05 - 0.06	0.96	-0.06	-0.16 - 0.03	0.19	-0.02	-0.09 - 0.05	0.60
	HPV-44	0.03	-0.03 - 0.09	0.31	-0.16	-0.32 - -0.01	0.04	-0.01	-0.08 - 0.07	0.89
	HPV-53	0.03	0.00 - 0.05	0.05	0.01	-0.05 - 0.07	0.81	0.03	-0.1 - 0.06	0.07
	HPV-54	0.06	0.02 - 0.09	0.01	0.01	-0.07 - 0.10	0.80	0.03	-0.02 - 0.08	0.25
	HPV-66	0.02	-0.01 - 0.04	0.24	-0.04	-0.10 - 0.01	0.12	0.01	-0.02 - 0.05	0.38
	HPV-68/73/97	-0.03	-0.06 - 0.01	0.21	-0.04	-0.13 - 0.05	0.39	-0.03	-0.08 - 0.02	0.28
	HPV-70	0.01	-0.07 - 0.07	0.90	-0.13	-0.28 - 0.02	0.10	-0.01	-0.09 - 0.07	0.80
	HPV-74	-0.02	-0.06 - 0.02	0.37	-0.06	-0.16 - 0.04	0.26	0.01	-0.05 - 0.05	0.93

[1]: Adjusted for age, STI clinic policy change, lifetime sex partners, history of any sexually transmitted infection, duration relationship with steady partner, notified for STI, sex partners past 6 months, condom use with casual partner
[2]: Adjusted for age, STI clinic policy change, lifetime sex partners, history of any sexually transmitted infection
[3]: Adjusted for age, STI clinic policy change, lifetime sex partners, history of any sexually transmitted infection, notified for STI, sex partners past 6 months, condom use with casual partner

Conclusions: Our results provide compelling evidence for herd effects against vaccine and cross-protective HPV types among men (first-order effect) as well as herd effects against vaccine types among unvaccinated women (second-order effect). These results are promising regarding the eventual impact of

girls-only HPV vaccination as they demonstrate that herd effects become noticeable throughout the population even with moderate vaccination coverage. Increases in other high-risk HPV types require continued monitoring of infection dynamics.

EFFECT OF A MULTI-INGREDIENT CORIOLUS VERSICOLOR-BASED VAGINAL GEL IN HPV INFECTED WOMEN: NORMALIZING DIFFERENT RISK HPV-DEPENDENT CERVICAL LESIONS (ASCUS/LSIL)

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: The aim of this study was to evaluate the effect of the Papilocare®, a multi-ingredient *Coriolus versicolor*-based vaginal gel, on the normalization of cervical HPV-dependent atypia (ASCUS and LSIL) and associated colposcopy alterations in three groups of patients according to the oncogenic potential of HPV strains.
Methods: Multicenter, randomized, open-label, parallel-group, usual practice-controlled clinical trial (Paloma RCT). Unvaccinated HPV+ women aged between 30 and 65 with cytology of ASCUS or LSIL and concordant colposcopy image were randomized into 3 groups: A) Papilocare® 1 cannula/day for 1 month + 1 cannula/alternate days for 5 months; B) Papilocare® 1 cannula/day for 3 months + 1 cannula/alternate days for 3 months; C) Control group: no treatment (usual clinical practice). patients with normal cytology and concordant colposcopy image (primary endpoint) were evaluated at 6 months in total, high-risk HPV (16,18,31,33,35,39,45,51,52,56,58,59,68) and very high-risk HPV (patients infected by any combination of 16, 18 and 31) populations. Pap smear evaluation and HPV identification (Clart® HPV4) were blind and centrally conducted by an independent researcher at the IECM laboratory (Lugo, Spain). Papilocare® arms (A+B) were combined as treatment group.
Results: A total of 84, 66 and 29 patients corresponding to total population, and high-risk and 16-18-31 subpopulations were evaluated, respectively. At 6 months, normal cytology and concordant colposcopy image was observed in 85% (45/53), 88% (36/41) and 73% (11/15) of patients treated with Papilocare® vs 65% (20/31), 56% (14/25) and 43% (6 /14) of patients in control group, in the total population, and high-risk and 16-18-31 subpopulations (p=0.0311; p=0.0034; p=0.0959, chi-square test) respectively.
Conclusions: While spontaneous normalizations of HPV-dependent cervical lesions decreases as the risk of HPV strains increases, the robust efficacy of Papilocare® in normalizing cervical lesions has been maintained in the 3 groups, with a statistically significant difference vs control group in the total and high-risk populations.

COST-EFFECTIVENESS OF CERVICAL CANCER ELIMINATION IN CHINA

PUBLIC HEALTH / EPIDEMIOLOGY / ECONOMICS AND MATHEMATICAL MODELLING

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Introduction: The WHO has announced an initiative to eliminate cervical cancer, which involves scaling up vaccination (to 90%), twice-lifetime HPV screening (to 70%) and cancer/precancer treatment (to 90%) by 2030. China has the largest burden of cervical cancer in the world, with an estimated 98,900 diagnosed and 30,500 dying from the disease in 2015. Furthermore, cervical cancer rates have recently been increasing. Despite a recently introduced screening program for rural residents, both screening and vaccination coverage remains low, with no national program. We aimed to assess the long-term cost-effectiveness of achieving the 2030 scale-up coverage targets for vaccination and screening in China.
Methods: We use an extensively validated platform (*'Policy1-Cervix'*) to evaluate the coordinated scaleup of twice lifetime HPV-based screening and broad-spectrum vaccination. The model was calibrated to local data; screening costs were derived from an original study that applied scaling methods to micro-costing data. A strategy was considered cost-effective if its cost-effectiveness ratio was less than the willingness-to-pay threshold (1xGDP = $US 9770.80 per capita).
Results: Twice-lifetime screening with vaccination was a very cost-effective method of achieving elimination, with a cost-effectiveness ratio of $714/QALYS. This method can potentially achieve elimination (<4/100,000 cancer incidence) by 2064, with a resulting mortality rate of 1.7 by this year. Rapid scale-up of screening and vaccination will result in 1.72 million cases averted and 736,000 lives saved over the 50 year period 2020-2069.
Conclusions: Screening twice per lifetime with high-coverage female vaccination in China would be very cost-effective and could result in elimination of cervical cancer by 2064.

SOCIO-DEMOGRAPHICAL CORRELATES OF HUMAN PAPILLOMAVIRUS (HPV) VACCINE UPTAKE: OPPORTUNISTIC AND CATCH-UP VACCINATION IN NORWAY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Many women who are not eligible for routine HPV vaccination may access catch-up or opportunistic vaccination. However, the social profile of catch-up and opportunistic vaccination has rarely been investigated. In Norway, catch-up vaccination has recently been offered free of charge to women born 1991 or later, while out-of-pocket opportunistic vaccination has been available since the HPV vaccines were licensed for use.
Methods: By use of nationwide registries, we obtained the HPV vaccination status as well as sociodemographic data for all Norwegian girls born 1975-1996 who were living in Norway during 2006-2018 (N = 821 244). We compared the sociodemographic characteristics of unvaccinated women to women who initiated HPV vaccination by unadjusted and multiply adjusted logistic regression.
Results: The overall uptake for opportunistic and catch-up HPV vaccination was 2.7% and 44.0%, respectively. The likelihood of opportunistic HPV vaccination increased by own education status, maternal education status, maternal occupational status, household income and birth cohort. Moreover, girls with immigrant parents were far less likely to be opportunistically vaccinated than girls with Norwegian-born parents. There were also some regional differences in opportunistic vaccination uptake. Similar patterns and effect sizes were observed for catch-up vaccination as for opportunistic vaccination.
Conclusions: There are strong inequalities in opportunistic and catch-up vaccination in Norway. Compared to a previous study of free-of-charge routine HPV vaccination, the inequalities are stronger for opportunistic and catch-up vaccination. The similar results for catch-up and opportunistic vaccinationin in our study indicate that factors additional to individual out-of-pocket cost are strongly associated with vaccine uptake. Tailored catch-up campaigns with intensive support for vulnerable groups might increase the vaccination uptake and mitigate emerging health disparities.

EVALUATING THE IMPLEMENTATION OF THE SELF-COLLECTION CERVICAL SCREENING PATHWAY FOR SCREENING IN VICTORIA: PARTICIPANT PERSPECTIVES

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: There has been a plateau in the reduction of cervical cancer in Australia without significant change since 2002 due to a decline in screening participation. The renewal of the Australian National Cervical Screening Program (rNSCP) enabled HPV self-collection to be available to women over 30 years who were at least 2 years overdue or never-screened. The aim of this study is to evaluate the implementation of the self-collection cervical screening pathway in Victoria from the participant perspective.
Methods: VCS Pathology was the only laboratory in Australia accredited to conduct testing for self-collected screening samples at the time of the study. VCS held contact details for all screening participants involved in the self-collection pathway. Screening participants were recruited for semi-structured interviews through a two-stage opt-out process which involved both screening participants and their practitioners. Interviews with screening participants (n=23) were audio-recorded and coded in N-Vivo using template analysis.
Results: There were diverse reasons that participants were overdue or never screened. They included logistic barriers (e.g rurality), sexuality and gender identity, history of sexual violence and previous experience with clinical examination. There was a diversity in the implementation of self-collection due to differences in adoption practices between clinical settings. Despite this, all participants expressed a high degree of satisfaction with self-collection and identified that the availability of self-collection, as well as their practitioner's engagement, as being critical to their decision to participate in screening. Empowerment was a key theme of the interviews.
Conclusions: Overall self-collection is an effective and acceptable way to improve the uptake of screening in never and under-screened women. The success of the program is due to providing flexibility without compromising clinical confidence. Ongoing availability and expanded self-collection will be critical to reaching under and never screened women to ensure equity in cervical cancer prevention in Australia.

DEVELOPMENT OF SEQUENCING METHODS FOR HPV16 AND 12 OTHER HR-HPV

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: HPVs are responsible for 5% of all cancers, mostly at the cervical and anal canal sites. HPV16 is the most frequently genotype associated with (pre)-cancer development following a persistent infection. Since recent next generation sequencing (NGS) analyses revealed that HPVs are highly polymorphic, it can be hypothesized that within genotypes, HPV variants may present different carcinogenic properties. The aim of our study was to develop NGS methods for High Risk (HR)-HPVs in order to analyse HPV genome variations during natural history of cervical lesions.
Methods: First, we took advantage of the Hybrid Capture II screening test to capture DNA of 13 HR HPV genomes (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68) and prepare libraries. An amplicon strategy was also developed to specifically sequence HPV16 using primers amplifying HPV16 whole genome. In-house NGS pipe-lines were developed and used for sequencing data analysis. DNA extracted from HPV infected cells and from previously genotyped cervical specimens were used to validate NGS protocols.
Results: The capture method permitted to retrieve concordant HPV genotypes in 90% (n=17/19) of cases. One sample (5%) presented partially concordant genotypes as one HPV51 was missed by NGS. One sample (5%) was discordant. Concerning the amplicon method, HPV16 was correctly identified from 47 samples allowing a 100% concordance with the INNO-LiPA genotyping. HPV16 variant identification is still ongoing.
Conclusions: Two standardised and affordable NGS methods to sequence the whole genome of HR-HPV and HPV16 from clinical samples will be presented. By implementing these techniques on cervical samples representative of the natural history of cervical cancer, we show how our methods will help to identify HR-HPV variants and study their potential role in carcinogenesis.

EVALUATION OF DNA EXTRACTION PROTOCOLS FOR STUDYING CERVICAL MICROBIOTA FROM LIQUID BASED CYTOLOGY USING 16S RRNA-BASED SEQUENCING

BASIC RESEARCH / MICROBIOME

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Introduction: Cervical microbiota is associated with cervical intraepithelial neoplasia (CIN). Although bacterial composition analyzed 16S rRNA gene sequencing is known to be affected by cell lysis prior to DNA extraction, protocols from the cervix are not standardized. We aimed to compare DNA extraction procedures for the evaluation of cervical microbiota.
Methods:

Table 1. DNA extraction methods and characteristics.

Method	Kit (Item No.)	Manufacturer	Sample volume	Selections made within protocols	Beading	Carrier RNA	Addition
1	ZymoBIOMICS (D4300)	Zymo Research	300 µl	None	Yes	No	None
2	Power Fecal Pro (51804)	Qiagen	300 µl	None	Yes	No	None
3	QIAamp DNA Mini Kit (51304)	Qiagen	200 µl	DNA Purification from Blood or Body Fluids; Protocols for Bacteria: Isolation of genomic DNA from Gram-positive bacteria	No	No	Mutanolysin
4	IndiSpin Pathogen Kit (SPS4104)	Indical Bioscience	300 µl	Pretreatment B2, small beads	Yes	Yes	None

Liquid-based cytology (LBC) samples of cervix were obtained from 20 patients with CIN 2 or higher (19/20 HPV positive, 95%) in a Phase II Clinical Trial of HPV treatment vaccine (NCT02481414). We evaluated 80 extractions from 4 different commonly used procedures (Methods 1-4). 16S rRNA gene sequencing of the V4 region was performed, and α diversities determined using phylogenetic diversity, observed OTUs, Shannon index, and evenness were compared. Linear discriminant analysis Effect Size (LEfSe) for specific bacteria among the procedures was also examined.
Results: A total of 11,149,582 reads (mean 139,370 reads per sample) were analyzed, and 90% of the reads were assigned to Gram-positive bacteria mainly from the phyla *Actinobacteria* and *Firmicutes*. Method 1 returned significantly higher phylogenetic diversity than Method 2 ($p = 0.005$, $q = 0.030$), but not the other two procedures. Other measures of α diversity were not significantly different. However, LEfSe identified significantly enriched microbiota in Method 1, i.e. *Bacteroidetes*, *Deinococcus-Thermus*, *Firmicutes*, and *Proteobacteria*, compared to the other Methods.
Conclusions: Method 1 showed the broadest diversity based on taxonomic distance, although there were no differences in other index of α diversity. These findings suggested that α diversity index based on taxonomic distance may be more sensitive than the index based on the number of species in high clonal community such as cervical microbiota mainly composed of *Lactobacillus* species. These results may be helpful towards standardizing microbiome research utilizing LBC of cervix.

FRQUENCY OF HIGH-RISK HPV FROM FORMALIN FIXED PARAFIN EMBEDED BIOPSY SAMPLES OF INVASIVE CERVICAL CANCER LEISONS

BASIC RESEARCH / GENOMICS OF HPV-ASSOCIATED DISEASE

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Introduction: In Nigeria, cervical cancer is associated with death of about 8000 women annually. HPV type 16 and 18 have been reported to be the most common genotypes associated with cervical cancer. This study assessed the distribution HPV genotypes in FFPE cervical cancer biopsy samples stored in the Dept of Pathology, UCH Ibadan.
Methods: Fifty histologically confirmed cervical cancer FFPE biopsy samples spanning a period of three years were analysed for HPV infection. The FFPE samples were dewaxed, DNA extracted from them and tested for the presence of HPV. The HPV DNA was detected and genotyped using multiplex PCR protocol with primers that targets E6/7 gene region of the virus.
Results: A total 49 of the 50 FFPE cervical biopsy tested positive for High-Risk HPV DNA. Thirty nine of the 49 HPV positive samples were successfully genotyped by PCR. The most prevalent HPV types detected were 16 (35.1%), 35 (19.3%), 18 (16.1%), 43 (4.2%), and 52 (2.7). Multiple HPV genotypes were also detected in 5 (12.8%) of the samples.
Conclusions: This study confirms the role of HPV infection in cervical cancer and supporting WHO recommendation of including HPV DNA in cervical cancer screening programme. There are multiple HPV genotypes associated with cervical cancer in Nigeria and not only HPV 16 and 18. There is need for introduction multivalent vaccine and not just for HPV 16 and 18 for the prevention of HPV infection in the country.

DOES THE ASSOCIATION BETWEEN HPV 16 AND OTHER HIGH-RISK HPV TYPES INFLUENCE PERSISTENCE/RECURRENCE OF HPV INFECTION AFTER CONIZATION?

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: HPV 16 is the most prevalent HPV type found in the genesis of cervical cancer and other anogenital and oropharyngeal malignant tumors and this is because of its enormous capacity of persistence, among other causes. The aim of this study was to assess the association of HPV 16 with other high-risk HPV (HRV) types and HPV 16 with no other HPV has more risk of persistence/recurrence after conization.
Methods: For the study, 283 women with just HPV 16 infection were compared with 164 infected with HPV 16 and other HRV before conization, in the Lower Genital Tract Pathology Unit of the Mother-and-Child University Hospital Complex of the Canary Islands between 2014 and 2018. The following variable records were analysed: age at conization, age at first intercourse, parity, smoking status, number of sexual partners, HPV vaccination, histological results, excision margin status, type of positive margin and endocervical biopsy result. HPV persistence/recurrence was considered when HPV DNA is still positive in postconization control at 6 or 18 months. HPV Genotyping was performed using the COBAS 4800 HPV Test. Patients with associated HPV 18 infection and only HRV types were excluded.
Results: No statistical significance has been found in the epidemiological variables, neither in histological result or margin status. HPV 16 co-infection with other HRV has more risk of persistence than HPV 16 alone (OR 2,3 IC 95% (1,48-3-3,45)) in first control at 6 months, as well as in the second follow-up at 18 months (OR 3,24 IC 95% (1,5-6,6)).
Conclusions: The association of other high-risk HPV types and HPV 16 behaves as a risk factor for HPV persistence after conization, independently of margin status of the specimen.

SYSTEMATIC REVIEW AND META-ANALYSIS: HPV VACCINE IMMUNOGENICITY AND SAFETY IN SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Women with Systemic Lupus Erythematosus (SLE) is more likely to acquire persistent HPV infection, cervical dysplasia and cervical cancer. HPV vaccination is the most effective prevention, however SLE patients may have reduced immune responses to vaccination. We conducted a systematic review and meta-analysis to evaluate HPV vaccines safety and immunogenicity in SLE population.
Methods: This systematic review and a meta-analysis are in accordance with PRISMA Statement and was registered at PROSPERO (CRD42017055139). Were included cohort studies and clinical trials that met the following inclusion criteria: a) population: immunocompromised patients, except HIV/AIDS; b) intervention: have taken any HPV vaccine; c) comparison group: none or healthy subjects; d) outcome: immunogenicity or safety. We performed an extensive search on nine electronic databases; the last updated on August 8th, 2019. Two independent reviewers extract data from the included studies, after duplicate withdraw.
Results: 3,923 references were retrieved from all database. After duplicates withdrawal, 2,720 studies remained. After reading the title, summary and the entire full text, six articles were selected.

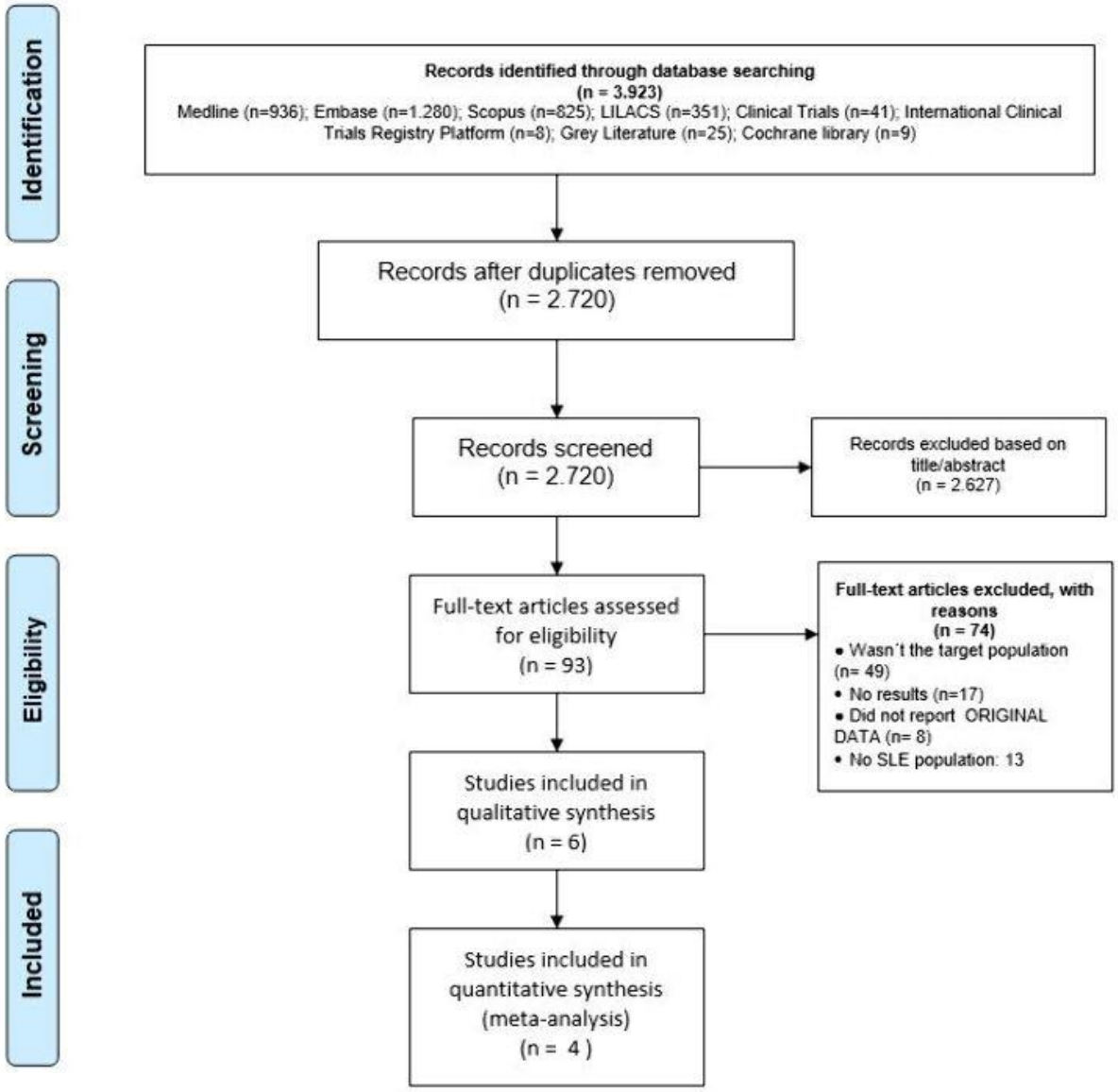
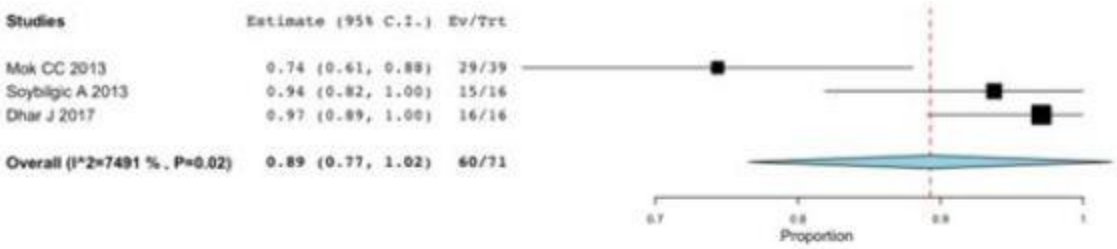


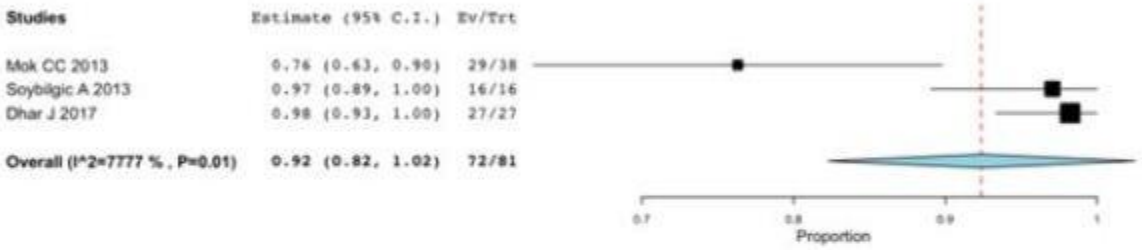
Figure 1: Study selection flowsheet

Overall seroconversion a month after complete vaccination was 89% (95%CI 0.77–1.02) for HPV6; 92% (95%CI 0.82–1.02) for HPV11; 96% (95%CI 0.91-1.00) for HPV16 and 91% (95%CI 0.81–1.01) for HPV18. The heterogeneity among studies range from 0% for HPV16 to 77% for HPV11.

HPV 6 Seroconvertion

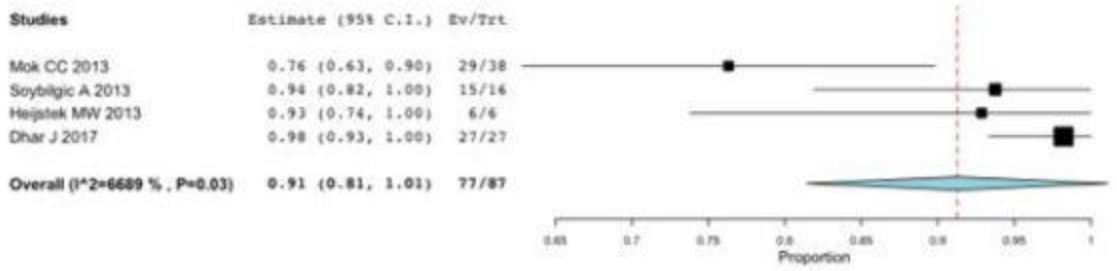


HPV 11 Seroconvertion

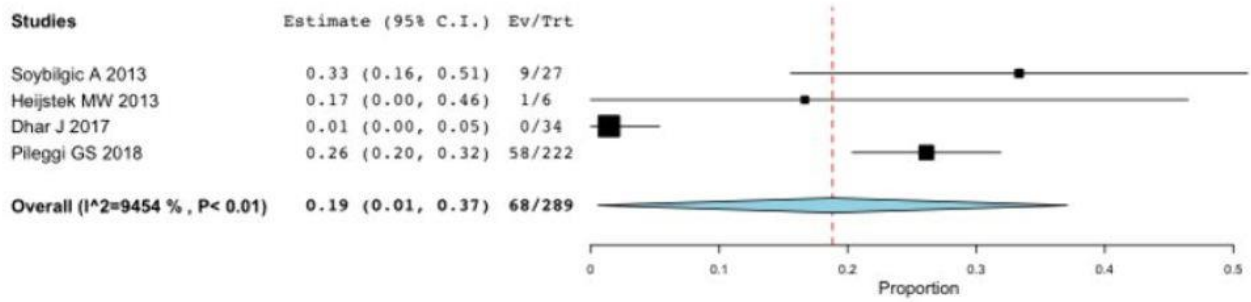


HPV 16 Seroconvertion

HPV 18 Seroconvertion



A second meta-analysis was conducted to analyze SLE flair following vaccination, including four studies. Overall SLE flair was 19% (95%CI 0.01–0.37).



Conclusions: HPV vaccine is safety and immunogenic in SLE population. It seems like that the rate of SLE flair who had took HPV vaccine is similar to no vaccinated subjects. Vaccination could be a very important preventive approach for this population leading to better quality of life and high survival.

HUMAN PAPILLOMA VIRUS ASSOCIATED ANOGENITAL PATHOLOGY IN FEMALES WITH HPV POSITIVE OROPHARYNGEAL SQUAMOUS CELL CARCINOMA

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Human papilloma virus (HPV) is a sexually transmitted infection with nearly universal lifetime exposure.[1-3] The point prevalence in genital samples ranges between 39.7-46.7%, resulting in 0.27% annual incidence of cervical intraepithelial neoplasia.[4-5] Lifetime oral exposure in sexually active adults ranges from 65-100%, with 3-11% resulting in persistent oral cavity HPV infection.[2,4] Patients with HPV related oropharyngeal squamous cell carcinoma (OPSCC) may be at elevated risk for HPV associated anogential infection[4]; however the prevalence of related anogenital pathology and procedures in this population remains unknown.
Methods: 90 cases of HPV-OPSCC in female Mayo Clinic patients were identified from 2011 to June 2019. Data was abstracted from the otolaryngology OPSCC RedCap Database and the electronic medical record. Patients were contacted via telephone, consented for participation, and completed a phone questionnaire. Responses and pathology were verified when possible via applicable internal and external medical records.
Results: 60 of 90 patients had accessible gynecologic or colorectal records. Among these 60 patients, 27 (45%) had a history of any anogenital HPV associated diseases. 17 (28.8%) required procedures to treat HPV associated genital diseases. The cervix was the most common genital site of infection. 17 (28.3%) patients had abnormal pap spears, with 11 patients (18.3%) requiring procedures (hysterectomy, excision, cryotherapy) to treat cervical disease. One case of invasive cervical carcinoma was noted. HPV related vulvar and/or vaginal disease was noted in 3 (5%) patients. Anal disease was noted in four (6.6%) patients, with high grade neoplasia in two and invasive anal carcinoma in two. All patients with anal disease had a history of cervical disease.
Conclusions: Patients with a history of HPV-OPSCC are at an elevated risk compared to the general public for developing anogenital HPV associated pathology. A multidisciplinary approach between otolaryngology, gynecology and colorectal surgery should be utilized to optimize screening and early detection for these patients.

THE CAUSES FOR FALSE POSITIVE RESULTS IN DUAL P16/KI-67 EVALUATION ON CONVENTIONAL SMEARS

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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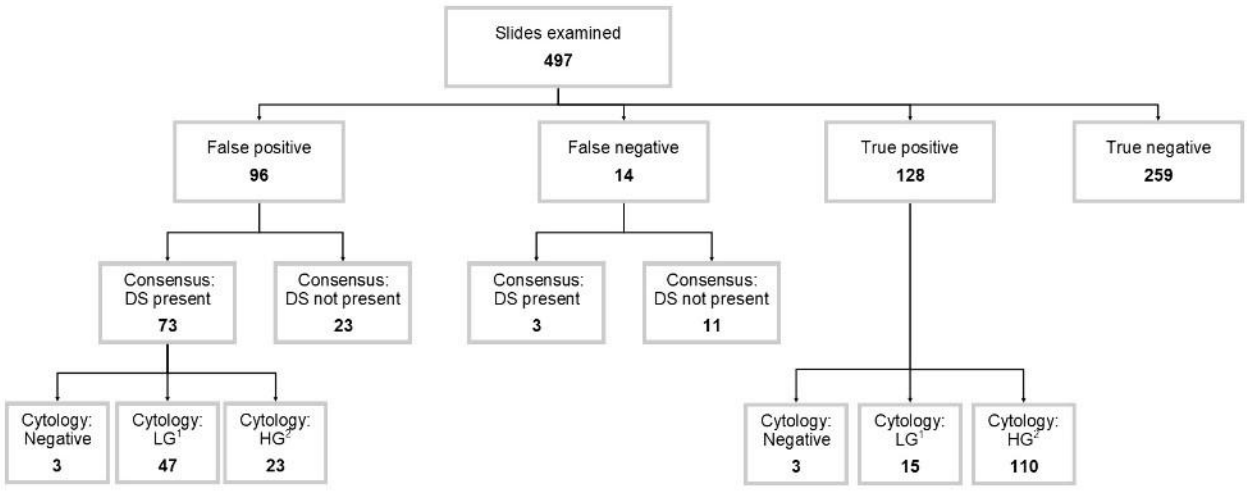
Introduction: After the training program for the evaluation of dual p16/Ki-67 immunocytochemical staining (DS) on conventional smears, four evaluators had 111 of false positive (FP) and false negative (FN) results according to CIN2+ histopathological diagnosis. We aimed to identify the causes behind the false results.
Methods: Three evaluators (a student, senior cytotechnologist and cytopathologist) evaluated 497 DS slides with known CIN2+ result and reported 96 FP and 14 FN results. The consensus of five cytopathologists made the final decision about whether DS is present. An experienced cytopatologist examined FP cases in which the consensus found DS and evaluated morphological features of DS cells according to the Bethesda 2014. The cases were categorized into the group with low-grade (LG) morphology and the group with high-grade (HG) morphology (Figure 1). 128 true positive (TP) cases served as a control. Fisher's exact test was used to compare morphology between groups of FP with DS and TP cases (significance level $\alpha = 0.050$).
Results: Consensus of five cytopatologists concluded that among the 96 FP results, DS was present in 73 (76.0%), while DS was misinterpreted as positive in 23 (24.0%). Among the 14 FN results, DS was not present in 11 (78.6%), while it was overlooked in 3 cases (21.4%). Among the 73 FP results with DS present, LG morphology was observed in 47 cases (64.4%) and HG in in 23 cases (31.5%), while 3 cases (4.1%) were morphologically negative. Among the 128 TP controls, LG morphology was less common (15 cases; 11.7%) while HG was more common (110 cases; 85.9%). Three cases (2.3%) were morphologically negative. The difference in distribution of morphology was statistically significant ($p < 0.001$).



[1]Low grade cytology: atypical squamous cells of undetermined significance (ACSUS), low-grade squamous intraepithelial lesion (LSIL).
[2]High grade cytology: atypical squamous cells – cannot exclude HSIL (ASC-H), high-grade squamous intraepithelial lesion (HSIL).

Figure 1. Morphological characterization of p16/Ki-67 dual stained cells.

Conclusions: DS with LG morphology was more common in FP cases while DS with HG morphology predominated in TP cases.

THE VALUE OF DIAGNOSTIC CONISATION PROCEDURE FOR DETECTION OF HIGH GRADE LESIONS IN THE WOMEN WITH LONGTERM CYTOLOGY FINDINGS AND UNSATISFACTORY COLPOSCOPY.

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: The risk of development high-grade lesions and invasive cervical cancer increases with age. Unsatisfactory colposcopy, where the area of interest is not visible in women with a positive cervical screening test , is a common area of clinical uncertainly due to the lack of clear evidence and guidance. In cases of apparent long-term discordance between cytology and unsatisfactory colposcopy (transformation zone type III) a biopsy adequate to make the diagnosis is essential. Endocervical curettage can not be implemented due to cervix stenosis. ECC is further unreliable as a diagnostic procedure when used for the initial assessment of women with ASCUS suggested on cytology. In cause of unclear findings and append request the patients the cone excision were indicated.
Methods: We analyzed retrospectively 776 patients after the cone procedure in group of women between 22 and 80 years old in our clinic.
Results: The main cause for undertaking this medical procedure was pathologically pap smear Pap III D2 (66%) and HPV persistence over 5 Years (15,01%). Colposcopy was due to type III transformation zone in over of 99 % unsatisfactory. In our group after the conisation procedure showed in 21 % of cases (N=26) any pathologically abnormalities, in 6 % of the woman were detected CIN 2+ lesions. We didn't detect any carcinoma whatsever. Simoultanously 4 cases of VaIN II-III were identify
Conclusions: There is insufficient evidence to support the use of cone biopsy in the triage of high grade intraepithelial lesions in the patients with discrepancy between cytology findings and unsatisfactory colposcopy. However adequate triage methods are releaded to identify those women. The consequent indication for the diagnostic cone procedure must be taken in order to prevent the over-treatment. Anxiety of missing a cancer deters long-term cytological follow-up and resulting in higher than anticipated excisions rate in women with unsatisfactory colposcopy.

HPV TESTING ON SELF-SAMPLES: AN ALTERNATIVE STRATEGY TO DETECT PERSISTENT INFECTIONS IN WOMEN WITH CERVICAL DYSPLASIA

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: The use of self-sampling for high-risk human papillomavirus (hrHPV) detection has been proved to be a valid and more acceptable alternative to increase coverage to screening attendance. Moreover, self-sampling instead of physician-sampling has demonstrated to be equally accurate, in particular for assays that use nucleic acid amplification. HPV-testing on self-samples may also be applicable in predicting recurrent infections in women with cervical dysplasia, reducing useless treatments and patient's lost-to-follow-up. This ongoing study aims to study the accuracy of HPV testing on vaginal and urine self-samples as compared to physician-collected cervical samples (gold standard) in women referred to colposcopy for an abnormal Pap smear and followed-up to monitor the possible lesion progression.
Methods: Presently, clinician-collected cervical, self-collected vaginal (FLOQSwab, Copan), and urine samples (Colli-pee, Novosanis), were obtained from 180 women attending the Colposcopy Clinic, San Gerardo Hospital (Monza, Italy). 25 (13.8%) women were followed-up after 6/12 months depending on their clinical outcome. All samples were extracted using NucliSENS easyMAG (bioMerieux) and HPV detection was carried out using AnyplexII HPV28 (Seegene).
Results: Preliminary results have shown a 64% (115/180) hrHPV positivity at baseline, with HPV16 (39.1%; 45/115) and HPV31 (22.6%; 26/115) being the most frequent types detected. At follow-up, all women reported the same or lower grade cytology results, as expected. 40% of women (10/25) have shown a persistent HPV infection. However, 7 of them (7/10) showed a negative Pap-smear result. A very good HPV test concordance was observed between vaginal and urine self-samples as compared to clinician-collected cervical samples, both at colposcopy and at follow-up.
Conclusions: Preliminary data have shown that HPV infection continue to persist even if cytological lesion regressed. Promising results was demonstrated in the use self-sampling during follow-up visits of women with cervical dysplasia.

TRENDS IN PRECANCEROUS CERVICAL LESIONS AFTER HPV VACCINE INTRODUCTION BY LEVELS OF POVERTY, CONNECTICUT, USA, 2008-2017

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Monitoring precancerous cervical lesions is useful for evaluating HPV vaccine impact especially where vaccination coverage is sub-optimal, as it is in the United States. Area-based poverty, the percent of population in a census tract living below the poverty level, has been demonstrated to be a useful method to evaluate socioeconomic disparities in health outcomes. Previous studies in Connecticut have found significant declines in precancerous cervical lesions in young women. The objective of this study was to determine if these declines occurred across levels of area-based poverty.
Methods: Ten years of incidence data, 2008-2017, from a state-wide active surveillance system of precancerous cervical lesions in Connecticut women were analyzed. Levels of area-based poverty were divided into four groups (<5%, 5-9.9%, 10-19.9%, ≥20%) using recommended cut points from the Public Health Geocoding Project. Incidence rates and average annual percent changes (AAPC), stratified by age and poverty groups were estimated using Joinpoint Regression software.
Results: The total number of women diagnosed with precancerous cervical lesions reported from 2008-2017 was 17,605 (range 1,320-2,128 per year). The largest declines were demonstrated in women aged 21-24 years (AACP=-20.9; CI -26.4.9, -15.0). Significant declines were seen across all poverty levels. The AAPCs ranged from -14.7 to -16.9 and were not significantly different from one other (Figure 1, Table 1). The inflection point (year) for each poverty level ranged from 2011-2014. A smaller but significant decline was observed in women aged 25-29 years (AACP=-3.4; CI -6.5, -0.3).
Conclusions: This analysis adds to the growing body of evidence that demonstrates population level HPV vaccine impact in young women. Analysis by area-based poverty demonstrated similar declines across areas with different levels of poverty in young women. This indication of equitable impact is encouraging. This analysis supports ongoing efforts to promote optimal HPV vaccine coverage across communities.

HPV VACCINATION AMONG YOUNG ADULT WOMEN: COVERAGE, KNOWLEDGE, AND BARRIERS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccines have been available in the United States (US) for women since 2006, but only moderate uptake has been achieved. Routine vaccination is recommended at ages 11–12, and catch-up vaccination is recommended through age 26 years. The purpose of this analysis was to describe coverage and patterns of immunization among a diverse urban sample of young adult women.
Methods: Women born after 1980 (age-eligible for HPV vaccination) with normal cervical cancer screening results enrolled in a case-control study of HPV vaccine effectiveness during 2016–2019 were included in this analysis (n=285). Data were obtained from medical record reviews for HPV vaccination and self-administered interviews.
Results: The sample was diverse with respect to race/ethnicity (53% white, 19% black, 17% Hispanic) and socioeconomic status (60% college degree, 73% private insurance). A total of 103 women (36.1%) had received HPV vaccine. Women who had not received HPV vaccine had lower knowledge that HPV is a common infection (81% vs. 90%, p=.05) and that HPV causes genital warts (60% vs. 86%, p<.001). Among unvaccinated women, the most common reasons were not being offered vaccine (42%) and believing they were too old (42%).
Conclusions: HPV vaccination coverage continues to be suboptimal in young adult women in the US. Poor HPV knowledge is associated with not being vaccinated; efforts to raise awareness of the frequency and sequelae of HPV infection could promote uptake. Many women also believed they were too old for vaccination, though all women were age-eligible for vaccination. Lack of recommendation continues to persist as a common reason for not being vaccinated. Raising awareness of catch-up recommendations to age 26 years (and new recommendations for shared decision making to age 45) among both women and health care providers could further promote uptake in young adult women.

DEVELOPMENT OF A HR-HPV PROFICIENCY TEST BY THE BELGIAN NATIONAL REFERENCE CENTRE FOR HPV: A PILOT STUDY.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: It is essential for accredited laboratories to participate regularly in EQA-schemes. Commercially available HPV EQA-schemes are often limited to HPV16/18 only, whilst there is a growing need to equally include other HR-HPV genotypes. To this end, the Belgian National Reference Centre (NRC) for HPV has developed an EQA-concept fulfilling the current needs.
Methods: A non-plasmid EQA scheme from anonymized leftover cervical samples covering a wide range of viral load of all HR-HPV types were distributed to 44 accredited laboratories. The panel was extensively validated for presence of HR-HPV genotypes (WHO IARC laboratory as gold standard). Distribution of the panel and result analysis was facilitated by the Quality of Laboratories service (Sciensano, former Belgian Institute of Public Health) with a two weeks reporting time. The EQA was analyzed at 1) overall qualitative reporting level, 2) genotyping level, and 3) analytical level. According penalization schemes were defined upfront. In this pilot experiment, erroneous answers remained without consequences, and laboratories were given the opportunity to provide feedback to the organizers.
Results: Replies from 44/44 accredited Belgian laboratories were received, covering 9 different HPV assays. All laboratories answered timely. Table 1 presents a summary of first results of this pilot study.

Sample Code	Sample Content[1,2]		Matrix	Expected Result	Percentage Correct (%)	
	Genotype	Comment			Clinical level[3]	Genotyping level[4]
H19_1	HPV16	low positive	Thinprep® (Hologic)	positive	100	100
H19_2	HPV18, 45, 56		Thinprep® (Hologic)	positive	100	77
H19_3	HPV45, 68		Thinprep® (Hologic)	positive	97	84
H19_4	no DNA	only LBC medium	Thinprep® (Hologic)	non evaluable	89	89
H19_5	HPV31, 35, 39		Thinprep® (Hologic)	positive	100	98
H19_6	HPV6, 11, 53, 67	no hrHPV types	Thinprep® (Hologic)	negative	98	98
H19_7	HPV18	low cell control	Thinprep® (Hologic)	positive	93	82
H19_8	HPV16, 66		Thinprep® (Hologic)	positive	100	86
H19_9	HPV51, 52, 53, 56	low positive	Thinprep® (Hologic)	positive	100	95
H19_10	HPV52	low positive	Thinprep® (Hologic)	positive	70	68
H19_11	no HPV		Thinprep® (Hologic)	negative	100	100
H19_12	HPV39		Thinprep® (Hologic)	positive	98	95

[1] Confirmed by NRC HPV (Riatol qPCR, Abbott HPV Realtime, Seegene Anyplex)

[2] Confirmed by WHO IARC (Lyon, France)

[3] HPV detected or not detected within clinical defined threshold

[4] HPV16, 18 and/or other detected

Conclusions: Although we consider this pilot experiment as successful, some limitations were identified. Further development of the reporting form (e.g. electronic reporting, reduction of ambiguity). Introduction of a clinical case for patient management would be of added value. Response time (2 weeks) was considered too limited by some laboratories. A 100% national participation rate was achieved with this pilot project. Overall, Belgian laboratories performed well during this pilot study, and are proficient to perform HPV analysis. Some lower scores can be related to assay-specific limitations rather than laboratory-related factors. Further in-depth analysis is planned to gain insight in test/laboratory performance.

DESIGN OPTIMIZATION OF THE COLLI-PEE FIRST-VOID URINE SAMPLE DEVICE TO ENABLE HPV SCREENING USING COMPUTATIONAL FLUID DYNAMICS.

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: First-void (FV) urine collection has the potential to be a useful, non-invasive sample method in testing the presence of hrHPV DNA related to cervical cancer screening. The objective of this study was to determine the flow behavior of the FV urine in the novel generation small volumes (10mL, 4mL) Colli-Pee sampling devices. Hereby it was critical to verify: (1) The collected fraction FV vs pass-through spillage (volumetric validation). (2) Identify device architectural design aspects that ensure a minimal wash-out, resulting in a higher concentration FV urine sample.
Methods: 3D CAD models (Mentor Graphics Siemens FloEFD) were built to enable a Computational Fluid Dynamics (CFD) study. These simulations enabled evaluation of the different stages of floater movement under different flow conditions (flow rates 25mL/s to 40mL/s, variable time 15s to 30s and device tilt +/-15°). In-house rapid prototyping manufacturing (3D printing) allowed the verification of the most suited design to evolve into injection molded parts.
Results: showed that for the 10mL variant, all captured volumes were 10mL+/-1mL (average of 10.7mL). With an average time of 1.26sec until floater activation to cut off collection in the tube, a total volume of average 15mL (FV) had passed. For the 4mL variant all captured volumes were 4mL+/-1mL (average of 4.0mL). With an average time of 0.9sec before floater activation, a total volume of average 6.5mL (FV) had passed.
Conclusions: CFD simulation has proven to be an essential tool to predict the different flow dynamics and higher accuracy of the captured volumes in smaller design variants. Failing a design fast is essential to keep the costs low and speed up development. Introducing complex floater geometry proved key to counterbalance the higher stream force on the smaller scale novel devices.

UNDERSTANDING HESITANT PARENTS' VIEW TOWARD THE NEWLY ENACTED HPV VACCINE SCHOOL ENTRY POLICY IN PUERTO RICO

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Human papillomavirus (HPV) vaccine is an important tool for the prevention of HPV-related cancers. In the United States of America, the Advisory Committee on Immunization Practices recommends a routine HPV vaccination for boys and girls aged 11 and 12 years old. In Puerto Rico (PR), the Secretary of Health established a school entry requirement of at least 1 dose of HPV vaccination in girls and boys aged 11 and 12 years taking effect in August 2018. The proposed study aims to examine hesitant parents' views and opinions of the process of implementing the new HPV vaccination policy in PR and understand barriers and facilitators related to HPV immunization among parents hesitant to vaccinate their children.
Methods: Three focus groups (n=12) and two in-depth, semi-structured interviews were conducted among parents or guardians of boys and/or girls aged 11 and 12 years old, who were not vaccinated against HPV on time (did not comply with the recent HPV school entry requirement). The interviews were recorded and transcribed verbatim. By applying thematic analysis, emergent themes were identified.
Results: All the participants were women, and 64% reported having an education higher than high school. Qualitative analysis revealed 4 main topics: (1) concern about the vaccine's side effects, (2) lack of information of the new school entry policy and of the HPV vaccine, (3) lack of communication between the school and parents regarding the policy; and (4) claims of parental autonomy in decisions concerning their children's health.
Conclusions: The main barriers to HPV vaccination among parents interviewed were the low understanding of the HPV vaccine and of the mandate's implementation, and the concern of the vaccine's side effects. Active involvement of the schools and the government is required to improve the dissemination of information about HPV vaccination in order to clarify doubts, concerns and misinformation among hesitant parents.

DIBENZO[A,L]PYRENE (DB[A,L]P), A TOBACCO ORAL CARCINOGEN, IS A CO-FACTOR FOR MALIGNANT PROGRESSION OF MOUSE ORAL PAPILLOMAVIRUS INFECTIONS.

BASIC RESEARCH / ANIMAL MODELS

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Introduction: We have established a mouse papillomavirus (MmuPV1) model to test the role of various co-factors in oral HPV-associated disease progression. Select tobacco carcinogens were applied orally and daily for 10 weeks starting 4 weeks after oral MmuPV-1 infection of athymic mice. The purpose of the study was to ascertain whether the co-presence of oral tobacco carcinogens could accelerate oral PV disease progression.
Methods: Groups of athymic mice of both genders were infected with MmuPV1 in the oral cavity using our delayed-wounding infection model. The experiment included 4 cohorts of mice that were treated orally: (1) infected with MmuPV1 and treated with DMSO-saline; (2) infected with MmuPV1 and treated with the tobacco carcinogen dibenzo[a,l]pyrene (DB[a,l]P) (DBP); (3) uninfected and treated with DMSO-saline, and (4) uninfected and treated with DBP. At 4 weeks after virus infection, oral treatments began and continued for 10 additional weeks. At monthly intervals, oral lavages were collected for subsequent assessment of viral load via qPCR. At 14 weeks post viral infection, the experiment was terminated, and mouse oral tissues were collected for histology (H&E), in situ hybridization for viral DNA, immunohistochemistry for viral capsid protein, and pathological assessment for papillomatous morphology and appearance of squamous cell carcinoma in situ.
Results: We observed increased rates of squamous cell carcinoma (SCC) in situ in oral tissue infected with MmuPV1 and treated orally with DBP. Mice treated with DBP alone showed minimal disease. Virally-infected epithelium showed strong levels of viral DNA and capsid protein staining whereas areas of SCC showed reduced viral DNA staining indicative of lower viral copy per nucleus that correlates with HPV cancers.
Conclusions: We have confirmed that the mouse oral PV infection model is an excellent platform to assess the impact of co-factors such as tobacco carcinogens for oral PV cancerous progression.

MIR-9-5P EXERTS A DUAL ROLE IN HIGH-RISK HPV-INDUCED CERVICAL CARCINOGENESIS AND TARGETS TRANSCRIPTION FACTOR TWIST1

BASIC RESEARCH / TRANSFORMATION AND CARCINOGENESIS

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Introduction: Both cervical squamous cell carcinoma (SCC) and adenocarcinoma (AC) display deregulated expression of microRNAs, and biological relevance has been proven for some of them. Interestingly, for miR-9-5p, which is encoded by three precursor genes, a histotype dependent pattern has been observed. Increased expression linked to a chromosomal gain of 1q is seen SCC, whereas expression is low in AC. This study aimed to comprehensively analyse the regulation and functionality of miR-9-5p in cervical SCC and AC.
Methods: Tissue specimens and HPV-containing cell lines were analysed for miR-9 expression and/or DNA methylation. Cervical cancer cells were transfected with a miR-9-5p mimic and an miR-9-5p inhibitor and assessed for altered gene expression, cell viability and colony formation. miR-9-5p target genes were tested by luciferase dual-reporter assays.
Results: Analysis of cervical tissue samples showed that low levels of miR-9-5p in ACs are caused by methylation of its precursor genes, in particular miR-9-1. Stratification of tissue samples and cell lines by hrHPV type indicated that differential expression of miR-9-5p in SCC and AC is both histotype and hrHPV dependent, with highest expression seen in HPV-16 positive SCC and HPV16-positive cells. miR-9-5p exerted an oncogenic function by promoting cell viability and anchorage-independent cell growth in cervical cancer cell lines SiHa (SCC, HPV16) and CaSki (metastasis, HPV16), while it assumed a tumor suppressive role in HeLa (AC, HPV18). TWIST1, a transcription factor involved in epithelial-to-mesenchymal transition (EMT), was confirmed as novel direct target of miR-9-5p.
Conclusions: Our results show that miR-9-5p plays a dual role in cervical cancer in an histotype and hrHPV type dependent manner. The mesenchymal protein TWIST1 is identified as a novel miR-9-5p target. miR-9-5p and/or TWIST1 might provide new options for cancer prevention and treatment.

ADVANCES ON A HIGH-THROUGHPUT PSEUDOVIRION-BASED NEUTRALIZATION ASSAY FOR DETECTION OF VACCINE-INDUCED NEUTRALIZING ANTIBODIES TO THE MINOR CAPSID PROTEIN L2 OF HUMAN PAPILLOMAVIRUSES

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: Among different methods to detect vaccine-induced antibody (Ab) levels to structural proteins of human papillomaviruses (HPVs), the Pseudovirion-based Neutralization Assay (PBNA) distinguish itself as the one able to measure functionally relevant, neutralizing Ab titers. Since novel HPV vaccines based on the L2 protein are now approaching phase-I clinical trials, we have assessed a high-throughput oriented approach allowing the detection of neutralizing Abs to the L2 protein.
Methods: An automated, purely add-on, high-throughput PBNA (HT-PBNA) setting was used to assess the neutralizing Ab levels to the L2 protein in animal polyclonal sera and monoclonal antibody (mAb) preparations. Fifteen HPV Pseudovirions (PsV) – including 8 furin-cleaved intermediates (fc-PsV) - formed of L1 and L2 capsid proteins encapsidating a gaussia-luciferase reporter plasmid were produced in HEK293 cells and used as surrogates for measuring *in vitro* neutralization of 8 HPV types. Two reporter cell lines – HeLaT and LoVoT - were investigated for characterization of Ab titers.
Results: While testing a pool of vaccinated animal sera, we observed 24- to 120-fold higher neutralizing Ab titers to the L2 protein of HPV6, HPV16, HPV18 and HPV31 by using fcPsV in the HT-PBNA settings, compared to the standard HT-PBNA. A further 5- to 140-fold increase in sensitivity was observed upon combining fcPsV and LoVoT in the HT-PBNA settings for the same L2 pooled sera. The use of LoVoT cells, however, provided weaker and highly variable report signal compared to HeLaT. Nevertheless, the use of fc-PsV associated to a HT-PBNA settings consistently showed increased sensitivity for detection of L2 neutralizing Abs to 8 HPV types in the sera of vaccinated rabbits, compared to the standard HT-PBNA.
Conclusions: A high-throughput, automated, highly sensitive PBNA, with great reproducibility represents a key approach to determine the efficacy of HPV L2 vaccines that are currently being tested.

COMPARISON OF HPV PREVALENCE IN SOUTH AFRICAN ADOLESCENTS RANDOMIZED TO RECEIVE INJECTABLE, ORAL OR VAGINAL HORMONAL CONTRACEPTIVES

CLINICAL RESEARCH / OTHER CLINICAL RESEARCH

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Introduction: Human papillomavirus (HPV) is one of the most prevalent sexually transmitted infections (STIs) in South Africa, particularly in adolescents. Factors contributing to this increased HPV risk in adolescents are not yet fully understood. While some observational studies have suggested that hormonal contraceptives (HC) influence HPV risk, others found no effect. In a randomized cross-over study, the impact of commonly used HCs including the injectable norethisterone enanthate [NET-EN], combined oral contraceptive pills [COCP] were compared with the combined contraceptive vaginal ring [CCVR]; NuvaRing with respect to HPV prevalence in adolescents from Cape Town, South Africa.
Methods: Eighty-nine healthy HIV-uninfected adolescent females (15-19 years), naïve to Cervarix HPV vaccine (part of national roll-out), were randomized (1:1:1) to receive NET-EN, CCVR NuvaRing, or COCP for 16 weeks. HPV genotyping was performed from cervical swabs using the HPV Direct Flow CHIP assay.
Results: HPV prevalence was high, with 91% of young women (81/89) having at least one HPV type detected. Overall HPV prevalence did not differ significantly by HC arm: 96.7% (29/30) using CCVR were HPV+, 96.4% (27/28) of those using COCP, and 80.6% (25/31) of those randomized to NET-EN were HPV+. Furthermore, the majority of adolescents were infected with high-risk (HR) HPV types, with HPV-51 and HPV-52 being the most common (each 17.3%). Adolescents on CCVR had significantly higher numbers of HR-HPV types than those randomized to using either COCP (n=67; n = 46, respectively; p=0.04) or NET-EN (n = 42; p=0.03).
Conclusions: The overall and HR-HPV prevalence was high in this cohort, with non-vaccine types HPV-51 and -52 being the most common. While HC arm did not appear to impact overall HPV prevalence, the prevalence of HR-HPV types in particular were significantly higher in young women randomized to the CCVR arm compared to either COCPs or Net-EN.

HPVPRO STUDY: HPV PREVALENCE IN CZECH WOMEN IN CERVICAL AND CERVICOVAGINAL SWABS

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The cervical screening program in the Czech Republic is based on cytology with HPV triage. The implementation of primary HPV screening and increasing cervical screening attendance are a major challenge. The objective of the HPVPro study was to find out the HPV prevalence in the screening population of Czech women since there are no data for the Czech Republic. The second objective was to compare HPV DNA detection in paired self-sampled cervicovaginal swabs and physician-obtained cervical swabs.
Methods: Cervical swabs were taken by a gynaecologist from 1044 Czech women (age 30-64 years) during the regular screening examination. Cervicovaginal swabs were obtained by self-sampling using digene HC2 collection device, Qiagen (HPVPro1, 544 women) and EvalynBrush, Rovers Medical Devices (HPVPro2, 500 women). All samples were analysed using Hybrid Capture 2 (HC2, Qiagen), 500 paired samples from the HPVPro2 study were analysed also using Qiascreen HPV PCR Test (Qiagen).
Results: Hybrid Capture 2 detected hrHPV positivity in 11.2% (117/1044) of cervical swabs and 14.0% (76/544) of swabs sampled by HC2 collection device and 10.4% (52/500) of swabs sampled by EvalynBrush. HC2 detected hrHPV positivity in at least one sample in 15.2% (159/1044). Qiascreen detected hrHPV in 9.7% (47/486) of cervical swabs and 10.5% (51/486) of cervicovaginal swabs. Qiascreen detected hrHPV positivity in at least one sample in 11.5% (56/486). Concordance of cervical and cervicovaginal hrHPV positivity was 93% for HC2 and 97.1% for Qiascreen.
Conclusions: HPV prevalence in the screening population of Czech women is between 11% and 15% depending on the used HPV detection method. HPV detection in cervical and cervicovaginal swabs was highly concordant. The offering of self-sampling could significantly increase the attendance of Czech women in the cervical screening program. This work was supported by grants: IGA LF UP 2019_003, CZ.02.1.01/0.0/0.0/16_019/0000868, LM2015064 and charity Cancer Research Czech Republic.

HPVPRO STUDY: COMPARISON OF HYBRID CAPTURE 2, QIASCREEN AND COBAS 4800 HPV FOR DETECTION OF HPV DNA IN CERVICAL SWABS

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Cervical cancer is caused by persistent infection by at least one high-risk human papillomavirus (hrHPV) genotype. Cytology-based cervical cancer screening is switched to HPV screening in the majority of European countries. Cervical cancer screening program in the Czech Republic is still based on cytology with HPV triage. The objectives of the study were to compare the detection of hrHPV using three HPV screening methods and to investigate HPV prevalence in Czech screening population.
Methods: Five hundred cervical swabs were sampled from Czech women (age 30-64years) during regular gynecological examination. All samples were analyzed using digene HC2 HPV DNA Test (HC2, Qiagen), QIAscreen HPV PCR test (Qiagen) and cobas® 4800 HPV (Roche) HPV DNA detection methods.
Results: All samples were suitable for analysis using HC2, Qiascreen failed in 0.4% samples and cobas failed in 0.8% sample. HrHPV DNA was detected in 11.4% (57/500) samples using HC2, in 9.4% (47/500) samples using QIAscreen and in 10.8% (54/500) samples using cobas. All three methods gave concordant result in 94% (470/500) of samples. All three methods gave concordant result in 94% (16/17) samples from women with abnormal cytology findings (ASC-US +).
Conclusions: HrHPV prevalence in the screening population of Czech women is between 9.4% and 11.4% depending on the used HPV detection method. All three compared method gave concordant result in 94% of the analyzed samples. This work was supported by grants: IGA LF UP 2019_003, CZ.02.1.01/0.0/0.0/16_019/0000868, LM2015064, and charity Cancer Research Czech Republic.

TOPICAL IMIQUIMOD TREATMENT OF HIGH-GRADE CERVICAL INTRAEPITHELIAL NEOPLASIA (HSIL): CHANGING PARADIGMS.

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: -**Background and objectives:**HSIL treatment reduces the incidence and mortality from cervix cancer. The potential complications of surgical excision and the stability of intraepithelial lesions over time justify conservative management.Imiquimod represents one of the most promising agents in the conservative treatment of HSIL. The aim is to analyze the results of HSIL treatment with imiquimod in young women who still want to conceive.
Methods: - Methods:A retrospective observational study was conducted from January 2010 - April 2019. Eligible patients were young women who still want to conceive,cytological and / or histological diagnosis of HSIL, adequate and satisfactory colposcopy and limited peripheral lesions without endocervical involvement and possibility of follow-up. Written informed consent was obtained.
Results: - Results:78 patientswith CIN 2–3 were analyzed. 70% were referred due to HSIL, 18% LSIL and 12% ASCUS. Mean age at HSIL diagnosis was 26.9 years, first sexual contact around 16.2 years. 84.6% of were nulliparous. 26,9% were smokers. 52.4% of the patients were hormonal contraceptive users, 39.7% used barrier methods and 7.9% intrauterine device. Only 35% of the patients were vaccinated against HPV. HSIL diagnosis was mainly histological (90%). 90% presented pathological colposcopic findings and 75% were positive for HPV 16/18 and 25% to other high risk genotypes. The average number of doses received was 4.9 with an interval from the first to last dose of 3.8 months. Treatment response was achieved when decrease in lesion grade by cytology and/or histology, without taking HPV status into consideration. 51% responded to the treatment. In the group of women who responded to treatment, 68.6% have a persistence of HPV vs 31.4% that clear up HPV. Only 16 patients had mild side effects.
Conclusions: - Conclusions: Imiquimod is an effective and tolerable HSIL therapeutic option in young patients without a fulfilled motherhood desire that allows to reduce the lesion degree.

HPV INFECTIONS IN PARAGUAYAN FEMALE SEX WORKERS IN CERVICAL AND ANUS SAMPLES, AND PRESENCE OF OTHERS CERVICAL SEXUAL TRANSMITED INFECTIONS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Introduction: Oncogenic high-risk human papillomavirus (HR-HPV) is the main causative agent of almost 100% of cervical cancer, and 88% of anal cancer. Female sex workers (FSW) have twice the risk of genital HPV infection than women in the general population. **Objective:**To detect types of HPV and determine the presence of cervical sexual transmitted infections associated with the development of lesions in the cervix and anus.
Methods: Methods: 224 female sex workers were included. HPV types detection was carried out using the PGMY09 / 11 PCR technique and BSGP5 + / 6 + PCR followed by reverse hybridization. Genital PCR co-infections of *Chlamydia trachomatis*-CT, Herpes simplex virus-HSV, *Mycoplasma genitalium*-MG, *Ureaplasma urealyticum*-UU,*Neisseria gonorrhoeae*-NG, and conventional cytology to detect anogenital lesions.
Results: Results: The frequency of HPV and HR-HPV detected in the cervix was 53.1% and 47.8% and 60.7% and 50% in the anus, respectively. 34.4% had HR-HPV infection in both locations. HPV positive women in the cervix had a higher frequency of infection in the anus (p<0,0001). HPV 16 was the most frequent. 3.5% and 6.3% of the women presented abnormal cytology in the cervix and anus respectively. In cervix frequencies of 20%, 9.8%, 5.4%, 16.5% of CT, HSV, NG and UU were detected respectively. In both sites, a higher frequency of HPV was observed in younger women. No association was observed between HPV and other cervical infections.
Conclusions: Conclusion: The results of this first study in FSW in Paraguay, showed a high frequency of HR-HPV and other infections suggest the need to implement strategies to strengthen the detection of sexual transmitted infections in both genital sites in order to prevent the development of anogenital lesions.

COMPARISON OF A VLP-BASED AND GST-L1-BASED MULTIPLEX IMMUNOASSAY TO DETECT VACCINE-INDUCED HPV-SPECIFIC ANTIBODIES IN FIRST-VOID URINE.

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Vaccine-induced human papillomavirus (HPV) antibodies originating from cervicovaginal secretions were recently shown to be detectable in first-void (FV) urine. This presents a novel opportunity for non-invasive sampling to monitor HPV antibody status in women participating in large epidemiological studies and HPV vaccine trials. With a view towards method optimization, this study compared measurement of HPV antibodies in FV urine using a multiplex L1/L2 virus-like particles (VLP)-based ELISA (M4ELISA) with previously reported results using a glutathione S-transferase (GST)-L1-based immunoassay (GST-L1-MIA).
Methods: We tested 53 paired FV urine and serum samples from 19- to 26-year-old healthy women, unvaccinated (n = 17) or vaccinated with either the bi- or quadrivalent HPV-vaccine during adolescence (n = 36). HPV6/11/16/18 antibodies were measured using M4ELISA and compared with GST-L1-MIA results. Inter-assay and inter-specimen correlations were examined using the Spearman's rank test (rs).
Results: As expected, lower HPV antibody concentrations were found in FV urine than in serum. Vaccinated women had significantly higher HPV6/11/16/18 antibody levels in both FV urine and serum compared with those unvaccinated (M4ELISA; FV urine $p = 0.0003$; serum $p \leq 0.0001$). HPV antibody levels in FV urine and serum showed a significant positive correlation (M4ELISA anti-HPV6/11/16/18, rs = 0.85/0.86/0.91/0.79, $p \leq 0.001$). Despite assay differences, there was good correlation between M4ELISA and GST-L1-MIA (FV urine anti-HPV6/11/16/18, rs = 0.86/0.83/0.89/0.53, $p \leq 0.0001$; serum anti-HPV6/11/16/18, rs = 0.93/0.89/0.94/0.75, $p \leq 0.0001$).
Conclusions: FV urine HPV antibody detection is comparable with both assays, further supporting this non-invasive sampling method as an option for HPV vaccine assessment. Approaches to improve the sensitivity of HPV antibody detection in FV urine include sample concentration and options for data normalization.

IMPACT ADOPTING WHO COVERAGE RECOMMENDATIONS ON CERVICAL CANCER ELIMINATION IN THE UNITED STATES

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: The World Health Organization (WHO) global call for action towards the elimination of cervical cancer (CC) as a public health problem involves setting ambitious screening and vaccination coverage targets. The draft WHO strategic plan for elimination proposes a CC incidence target of 4/100,000 women per year. We performed a comparative modeling analysis using two models from the Cancer Intervention and Surveillance Modeling Network (CISNET) consortium to explore the impact of reaching vaccination and screening coverage levels outlined by the WHO, as well as other potential strategies.
Methods: We performed a comparative modeling analysis that used two independently-developed CISNET models (Harvard and Policy1-Cervix) to project CC incidence rates per 100,000 women over time associated with alternative HPV vaccination and screening scale-up scenarios. Both models involved a dynamic multicohort-modeling platform to capture changes in human papillomavirus (HPV)-induced CC over time, including herd effects from vaccination. We explored the impact of alternative standard population structures, inter alia.
Results: Under status quo assumptions, both models projected that CC incidence would fall below 4/100,000 women by year 2038-2046. Scaling-up screening coverage to 90% by 2020 was the most impactful intervention in terms of elimination timing and relative cancer reductions, averting an average of 1,350-2,230 additional cases per year over 2020-2100. Sensitivity analysis using different population structures generated a range around these predictions. Increasing HPV vaccination coverage to 90% or vaccinating adults aged 26-45 years had nominal impacts on cancer incidence.
Conclusions: These validated CISNET-cervical models, which reflect uncertainty in the natural history of CC, found that national CC incidence rates may fall below 4/100,000 women by 2046, but this could be expedited if screening coverage is improved. These national estimates do not apply to all subgroups of women; therefore, reaching under-screened and under-vaccinated women remain key to achieving CC elimination for all women.

INVESTIGATION OF THE RELATIONSHIP BETWEEN HR-HPV-SPECIFIC T-CELL RESPONSES AND HR-HPV DNA IN HEALTHY WOMEN AND WOMEN WITH CERVICAL ABNORMALITIES IN A LONGITUDINAL STUDY

CLINICAL RESEARCH / THERAPEUTIC VACCINES – CLINICAL ASPECTS

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Introduction: Cell-mediated immune responses play a crucial role in regression of HPV lesions and clearance of infections. However, studies evaluating the role of T cell responses to specific proteins have produced conflicting results, likely reflecting the diverse methods used and predominance of cross-sectional analyses.
Methods: We established a prospective longitudinal cohort of women aged 16-55 years to study the relationship between detection of T-cell responses to early proteins and detection of hrHPV DNA. Cohort 1 comprises asymptomatic sexually active women aged 16-24. Cohort 2 comprises women aged 25-55 undergoing colposcopy, with mild, moderate or severe dyskaryosis. Women are followed for 12 months and provide a blood sample and self-taken vaginal swab at 4-monthly (Cohort 1) or 6-monthly (Cohort 2) intervals. T cell responses to all hrHPV early proteins are quantified by IFNγ Elispot and flow cytometry using overlapping 15-mer peptides based on HPV16, HPV52 and selected conserved sequences across 5 hrHPV genotypes.
Results: 144 women were enrolled in the study: 107 in Cohort, mean age 21y; 37 in Cohort 2, mean age 32y. Baseline data are reported. Prior prophylactic vaccination was reported in 88% Cohort 1 and 21% Cohort 2. HPV DNA was detected in 27 (25%) Cohort 1 and 31 (91%) Cohort 2. hrHPV isolates were non-16/18 types in 100% Cohort 1 and 82% Cohort 2. HPV16/18 were also detected in 21% Cohort 2. T-cell responses to E1/E2 or E6/E7 peptides (HPV52 > HPV16) were detected in 22/103 (21%) Cohort 1 and 15/31 (48%) Cohort 2. Overall, E1/E2 was most frequently targeted.
Conclusions: There was no consistent relationship between baseline hrHPV DNA prevalence and T-cell reactivity. Our data suggest that transient infections infrequently elicit T-cell responses. Longitudinal analysis is directed at determining the phenotype and duration of T-cell responses that are associated with hrHPV clearance or persistence.

EVALUATING THE IMPLEMENTATION OF THE SELF-COLLECTION CERVICAL SCREENING PATHWAY FOR SCREENING IN VICTORIA: PROVIDER PERSPECTIVES

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: The renewal of the Australian National Cervical Screening Program (rNSCP) enabled HPV self-collection to be made available to women over 30 years who were at least 2 years overdue or never-screened women. The introduction of self-collection was one of the aspects of the rNCSP that practitioners felt less confident with. The aim of this study is to interview practitioners using self-collection to understand how the program is working and develop recommendations to improve uptake.
Methods: VCS Pathology held contact details for all practitioners who sent self-collect samples for testing between the period of December 1, 2017 and March 2019. Practitioners were recruited from VCS data based on their use of and experiences with self-collection. Interviews with practitioners (n=17) were audio-recorded and coded in N-Vivo.
Results: Practitioners were highly positive about the self-collection pathway because of its' acceptability to women. Self-collection addressed barriers due to gender of the provider, logistic barriers (e.g rurality) and barriers due to the experience of women (eg. sexuality and gender identity, history of sexual violence and attitudes to clinical examination). Restrictions to women's eligibility for self-collection was cited as a key barrier to expanded implementation. The implementation of self-collection varied significantly between practices with some practices taking a proactive approach to incorporating self-collection into regular practice. Practitioners' motivation and engagement both significantly reduced barriers to implementation and increased uptake. This was particularly true of practices where the barriers to uptake were around the characteristics of the practice (eg. rurality and availability of female practitioners).
Conclusions: Overall participating providers found that self-collection was an effective and acceptable way to improve the uptake in never and under-screened women. The success of the program is increased by incorporating self-collection into regular practice management and tailoring the processes to the specific needs of the practice.

DEVELOPMENT OF THE FIRST TRANSGENIC MOUSE MODEL FOR HPV16-RELATED PENILE CANCER.

BASIC RESEARCH / ANIMAL MODELS

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Introduction: Penile cancer is an uncommon and under-studied disease whose incidence is higher in developing countries. Approximately half of the cases are associated with infection by high-risk human papillomavirus (HPV). Metastatic disease is associated with poor survival and therapeutic advances are slow, partly because the absence of animal models for basic and translational research.
Methods: Here, we report the development of a mouse model for HPV-related penile cancer, using transgenic mice where the expression of all the HPV16 early genes is targeted to keratinizing squamous epithelia by the cytokeratin 14 (CK14) gene promoter.
Results: These animals spontaneously developed condylomatous lesions and penile intraepithelial neoplasia (PeIN) at 30 weeks-old. The lesions retained expression of CK14 and of the HPV16 oncogenes *E6* and *E7* and showed deregulated cell proliferation, demonstrated by Ki67 labeling of suprabasal cells. We then treated these mice topically with the chemical carcinogen dimethylbenz(o)anthracene (DMBA) for 16 weeks. DMBA increased the incidence of PeIN lesions and induced squamous cell carcinoma in 7 out of 30 animals. Malignant lesions were located in the prepuce and glans and showed histological features closely resembling those of HPV-associated penile cancers.
Conclusions: These observations provide experimental evidence for the etiological role of HPV16 in penile cancer. This is the first model to recapitulate key steps of HPV-related penile carcinogenesis and reproduce the morphological and molecular features of penile cancer, providing a unique *in vivo* tool for studying its biology and advancing translational research.

THE PREVALENCE OF ANAL HIGH-RISK HPV INFECTION AND ANAL SQUAMOUS INTRAEPITHELIAL LESIONS AMONG RWANDAN WOMEN LIVING WITH HIV

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: Women living with human immunodeficiency virus (WLWH) are at increased risk of high-risk human papillomavirus (hrHPV) infection. WLWH are up to 15 times more likely to develop anal cancer compared with HIV-uninfected women and WLWH with cervical HPV infection or cervical high-grade SIL are at particularly high risk. There are few data on anal hrHPV and anal high-grade SIL among WLWH in low and middle income countries (LMIC). This study described the prevalence of anal hrHPV types and anal squamous intraepithelial lesions (SIL) in high risk Rwandan WLWH.
Methods: We recruited **55** WLWH participating in a cervical cancer screening study at Rwanda Military Hospital (RMH) to assess the prevalence of anal hrHPV and anal ASIL. Thirty women had cervical intraepithelial neoplasia grade 2 or more severe disease (CIN2+) on cervical biopsy and 25 women had cervical hrHPV infection as detected by the Xpert HPV platform but with pathology less than CIN2. An anal swab was collected in PreservCyt for cytology and hrHPV testing followed by high resolution anoscopy (HRA) with HRA-guided anal biopsies taken. HPV testing was performed using the Ampfire HPV genotyping assay.
Results: Twenty-two (40%) were positive for anal hrHPV with 10 (45.5%) being HPV16+ among the anal hrHPV+. Six (60%) of the 10 women positive for anal HPV16 also had HPV16 in the cervix. Biopsies were obtained from 24 (42%) women. Preliminary pathology results indicated that 12 (50%) of the biopsies taken were low-grade SIL, 1 (4.2%) was high-grade SIL and the remainder was normal. There was no difference in anal hrHPV and in severity of clinical lesions by recruitment status (cervical hrHPV Vs cervical CIN2+).
Conclusions: Preliminary results from our pilot study indicate a high prevalence of anal hrHPV (40%). This highlights the importance of screening for anal HPV and anal SIL among high risk WLWH.

THE IMPACT OF VACCINATION ON THE CLARIFICATION OF THE HUMAN PAPILOMA VIRUS (HPV) IN PATIENTS TREATED FOR SQUAMOUS INTRAEPITELIAL LESIONS (SIL)

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: BACKGROUND: The HPV vaccine is effective in primary prevention against cervical cancer and other lesions of the genital tract. In addition, the recurrence of high-grade squamous intraepithelial lesions (HSIL) decreases in adult women, who were treated with conization and vaccination. The aim was determine the HPV clearance in patients who receive escisional cervical treatment and HPV vaccination.
Methods: METHODS: A retrospective descriptive study was conducted from January 2015 to December 2017. The case group included 340 patients vaccinated against HPV after LLETZ cone and control group included 531 unvaccinated. Patients with an invasive cancer, older than 45 years or not HSIL indication Lletz were excluded. Post-treatment control was performed with cytology and HPV test at 6 months and annually in case of HPV persistence.
Results: RESULTS: The average age was 35.37 years. There were no differences in parity (p=0.97), first sexual contact (p=0.1), number of sexual partners (p=0.1) and tobacco (p=0.27). There were no differences in margin involvement (33% vaccinated vs 32% unvaccinated) (p=0.08), endocervical biopsy (10% vaccinated vs. 14% unvaccinated) (p=0.22). There were differences in histological outcome of CIN 2-3 (vaccinated 80% vs 72% unvaccinated) (p = 0.004) that is associated with a higher risk of persistence (OR 2.1 95% CI (1.27-3.52)). There were no differences in HPV clearance (81% not vaccinated vs 76% vaccinated) or HPV persistence (18% vs. 24% respectively) (OR 1.4 95% CI (1-1, 97)) in the first control at 6 months. A higher HPV clearance was observed in the vaccinated group (40% vs. 23%) and a higher HPV persistence in the unvaccinated group (77% vs. 60%) (OR = 0.59 IC 85% (0.35-0.99)) in the annual control (18 months after conization).
Conclusions: CONCLUSIONS: Vaccination in conized women contributes significantly to HPV clearance despite the higher frequency of HSIL. Therefore, we recommend systematic vaccination in patients undergoing excisional treatment.

CORRELATIONS BETWEEN BIOLOGICAL MARKERS OF CUTANEOUS HUMAN PAPILLOMAVIRUS AND THEIR ASSOCIATIONS WITH ULTRAVIOLET RADIATION EXPOSURE

BASIC RESEARCH / BETA AND GAMMA CUTANEOUS HPV INFECTION, BIOLOGY, AND NATURAL HISTORY

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Introduction: Previous epidemiologic studies of cutaneous human papillomavirus (cuHPV) infection and keratinocyte carcinomas (KC) have reported inconsistent results, perhaps due in part to their use of different cuHPV infection biomarkers. Furthermore, few studies have incorporated objective measures of ultraviolet radiation (UVR) exposure to examine UVR and cuHPV as potential cofactors in association with KC. A better understanding of the relationship between cuHPV infection biomarkers and UVR is needed to advance future research on the interplay of cuHPV infection and UVR exposure in KC development so that novel KC prevention strategies may be developed.
Methods: A cross-sectional analysis of baseline cuHPV seropositivity and cuHPV DNA positivity in skin swabs (SSW) and eyebrow hairs (EBH) corresponding to 17 beta-HPV types was conducted among 981 participants of the VIRUSCAN Study, a prospective cohort study of patients undergoing routine skin cancer screening examinations and followed for KC development. Recent UVR exposure was measured at baseline using a spectrophotometer, and associations with three markers of cutaneous beta-HPV infection were assessed, adjusting for age and sex.
Results: Beta-HPV seropositivity was associated with viral DNA positivity in EBH (OR=1.40; 95% CI=1.05-1.88) and SSW (OR=1.86; 95% CI=1.25-2.74). Participants in the highest tertile of UVR exposure were more likely to be beta-HPV seropositive (OR=1.81, 95% CI=1.16-2.85), and have beta-HPV DNA in EBH (OR=1.57, 95% CI=1.06-2.33) and SSW (OR=2.22, 95% CI=1.25-3.96), compared to participants with lowest UVR exposure. Similar associations were observed for two specific types previously shown to induce KC in laboratory animals under conditions of UV exposure, HPV types 8 and 38.
Conclusions: Recent UVR exposure was positively associated with three different markers of cutaneous beta-HPV infection. Future studies of cuHPV and KC should incorporate objective measures of UVR in order to advance our understanding of the role of UVR exposure in cuHPV-associated KC development.

HPV IDENTIFICATION IN LATIN AMERICAN INDIGENOUS POPULATION

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Prevalence and mortality of Cervical Cancer (CC) is high in developing countries, varying by region and by human population. The onset is related to an active infection with HPV-AR in the context of multiple risk factors: SES, age of first sexual intercourse, multiple sexual partners, multiparity, smoking, etc. Different studies confirm a high prevalence of HPV infection among indigenous populations in Latin America. This work aims to consolidate the existing information for the identification of HPV in this region.
Methods: A systematic review of the literature was performed applying the Matrix Method and PRISMA statement guidelines. Pubmed; Web of Science; Embase Indexing; Cochrane; SCOPUS; SciELO; BVS; OVID; and Google Scholar were used as electronic databases. Keywords/MESH terms used: HPV; Cervix; Women; Indigenous; Tribal; Natives; Aboriginal; Ethnic Groups with their equivalencies in Spanish and Portuguese. References were reviewed using pre-defined criteria. Discrepancies were solved by consensus.
Results: A total of 13 articles were selected. By countries, Brazil had 4 articles, Argentina, Venezuela, and Guatemala 2 each. Ecuador, Peru and Suriname 1. The majority (84%; n= 11) were written in English the others in Spanish and Portuguese respectively. HPV-16 was the viral type most frequently identified; however, among indigenous populations, viral types other than HPV-16 were more prevalent. Regarding socio-demographic factors, the studies did not perform an exhaustive analysis of them.
Conclusions: There is a dearth of evidence regarding typology and characteristics of HPV infections among indigenous populations in Latin America. The existing studies do not elaborate on moderating/mediating variables. This region is diverse, indigenous populations still represent an important share of the demographics. Understanding the reasons for the ecological diversity of HPV infections becomes an important challenge. Culturally appropriate lifestyle transformations should become important drivers for public health interventions to prevent CC in these populations.

HOST CELL DNA METHYLATION ANALYSIS IN SELF-SAMPLES FOR DETECTION OF CERVICAL PRECANCER AND CANCER IN HPV-POSITIVE WOMEN ATTENDING ROUTINE SCREENING

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: The IMPROVE study shows that HPV testing with a clinically validated PCR-based assay has similar accuracy on self-collected and clinician-collected samples in terms of the detection of cervical precancer and cancer (CIN3+). These findings support the use of HPV self-sampling as a primary screening method in routine screening. However, an additional triage test is necessary for HPV-positive women to identify those with clinically meaningful disease. Given that cytology cannot be reliably performed on self-samples, alternative triage markers are required that are directly applicable to self-samples. By genome-wide DNA methylation profiling we have identified methylated host cell genes associated with CIN3+. These methylation markers showed a good performance as triage markers on HPV-positive self-samples from screening non-attendees. This study was set out to evaluate their performance among regular screening responders.
Methods: Archived specimens from a randomised, non-inferiority trial evaluating self-sampling in cervical screening (IMPROVE study) were used. We assessed DNA methylation status of methylation markers *ASCL1, LHX8* and *ST6GALNAC5* using quantitative methylation-specific PCR (qMSP).
Results: Methylation levels in HPV-positive self-samples increased significantly with severity of underlying cervical disease (CIN0/1 vs CIN3 vs cervical cancer, $p < 0.01$). All cervical carcinoma cases were detected by the 3-gene classifier.
Conclusions: DNA methylation markers, such as *ASCL1, LHX8* and *ST6GALNAC5*, provide an intriguing new molecular triage tool in cervical screening, as they can be objectively tested directly on HPV-positive self-samples. Our findings warrant further exploration of these methylation markers for the management of women with HPV-positive self-samples in cervical screening.

KNOWLEDGE AND BELIEFS ABOUT CERVICAL CANCER PREVENTION AMONG WOMEN LIVING WITH HIV IN BOTSWANA

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: The cervical cancer burden is significant in low- and middle-income countries (LMIC), with HIV co-infection a significant risk factor. Despite scaling up of screening programmes, uptake varies across LMIC and is sub-optimal in Botswana. We explored cervical cancer and screening knowledge and beliefs of women living with HIV (WLWH) to identify strategies to improve screening participation.
Methods: A mixed-methods approach was used, including a cross-sectional survey of womem aged 25-55 years from an HIV clinic and in-depth interviews among a sub-group of participants. Survey data were analysed descriptively. Qualitative data were analysed thematically using the Health Beliefs Model (HBM) as a theoretical framework.
Results: 312 WLWH completed the survey. 84 (27%) reported knowing the cause of cervical cancer; however, only 20 (6%) identified HPV as a cause. 100 women correctly identified a sexual behaviour as a risk factor for cervical cancer. Common reasons for previous screening included attending on the advice of a healthcare worker (HCW) (n=108) and participants' desire to know their health status (n=108). 15 women had never been screened, mainly due to time limitations (n=7) and fear of the results (n=3). Qualitative analysis of 8 interviews revealed a high essential awareness of cervical cancer; however, misconceptions regarding causes and prevention, such as good hygiene or sexual behaviours, affected women's perceived susceptibility. Cervical cancer was sometimes viewed as a 'death sentence', which influenced perceived severity and benefits of screening. Accordingly, fear of abnormal screening results was a common barrier. Women trusted information from HCW and were interested in education delivered by HCW through the media, workshops and clinic-based programmes.

Table 1: Using the HBM model to understand women's knowledge and attitudes to cervical cancer and guide educational material to promote engagement in screening

HBM variable	Knowledge or beliefs to reinforce	Opportunities to improve knowledge or beliefs
Perceived susceptibility	*'Anyone who is sexually active can get HPV'*	*'You shouldn't put your fingers in your private parts because…It may lead to a wound and this wound can change to cervical cancer'*
Perceived severity	*'I think if it has just started, with those small signs or symptoms, I believe it can be treated.'*	*'Just the word "cancer," if you're talking about cancer, they say, "Huh, death sentence"'*
Perceived benefits	*'I normally come and do that [Pap smear]. Maybe after every two years I come in. I want to prevent cervical cancer.'*	*'After he heard that the results are okay, and he was dancing and saying, "Yeah, I guess we will have another baby now."'*
Perceived barriers	*'I am still in the dark, I need extensive education'*	*'They're ignorant because they lack…I think they lack education.'*
Cues to action	*'If a medical person comes to you and you discuss these things… they will be doing it from knowledge. They have the skills of that. So, you have to hear what they're saying and then accept the advice.'*	*'I once tested myself because I noticed some bruises'*
Self-efficacy	*'I was even booked to do the cervical cancer screening today. I did that 2016, I was supposed to do it in 3 years' time, which was 2019'*	*'People come to work but I never even sit and listen to it [Health education].'*

Conclusions: Misconceptions about cervical cancer and screening persist in Botswana. Interventions targeting local knowledge gaps and barriers are needed to change beliefs and screening behaviours. HCW are trusted information sources, highlighting opportunities to improve knowledge and promote screening through multiple channels.

TRENDS IN CERVICAL ADENOCARCINOMA IN NORWAY – A REGISTERY BASED STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Before the introduction of cytology, screening in the 1970s Cervical Cancer (CC) was the 4th most common female cancer in Norway. After half a century, in 2016 CC is the 11th most common cancer among women overall. Adenocarcinoma (AC) is rare compared to Squamous cell carcinoma (SCC). Although cytology screening is effective in preventing the more common SCC, current studies suggests that it is far less effective against AC than against SCC. We aimed to describe the epidemiology of AC in the screening era using national registry data.
Methods: For the period of 1953-2017, we extracted data on all incident cases of cervical cancer from Cancer Registry of Norway, population data by age and calendar year was obtained from the National Registry. The age standardized incidence rate (ASIR), mortality rates and 5-year relative survival was assessed.
Results: *During the period of 1953 to 1974, the annual ASIR of CC increased from 18.5/10^5 to 24.8/10^5, and decreased significantly thereafter to 12.5/10^5 in 2017, while the rate for AC increased from 1.11/10^5 to 2.72/10^5 in 2017 with a peak of 3.78/10^5 in 2015. The overall mortality rate of CC decreased from 5.24/10^5 in 1961 to 1.54/10^5 in 2017, while AC mortality was relatively stable at around 0.5/10^5 in the same period. AC 5-year relative survival increased from 44% in 1953 to 79% in 2012*.
Conclusions: In the screening era, the overall incidence of CC is decreasing, while the incidence of AC is increasing. AC mortality was unchanged by screening, while relative survival increased. The traditional cytology screening has less effect on AC. Norway has gradually implemented HPV primary screening since 2015, with possible impact the epidemiology of AC.

PERFORMANCE OF COMBINATIONS OF BIOMARKERS AS TRIAGE FOR HPV-DNA POSITIVE WOMEN IN CERVICAL CANCER SCREENING

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: On behalf of the NTCC2 Working Group The New Technologies for Cervical Cancer 2 (NTCC2) trial aimed at evaluating E6/E7 mRNA overexpression and p16/ki67 dual staining for their performance in triaging HPV-DNA-positive women within organized cervical cancer screening.
Methods: Women were recruited in four centres and tested with HPV-DNA Cobas 4800 or Hybrid Capture 2 assays. HPV-DNA-positive women were triaged with cytology and tested for E6/E7 mRNA and p16/ki67; abnormal cytology referred to colposcopy; negative cytology randomised to immediate colposcopy or 1-year HPV re-testing. We present immediate colposcopy referral and CIN2+ sensitivity (lesions found within 24 months), with 95% Confidence Interval (95%CI), of cytology [ASCUS+ and high grade (HG) thresholds], E6/E7 mRNA, p16/ki67, and HPV 16-18 typing for women tested with Cobas 4800, alone or in combination. Combinations positivity criteria: "AND" = positivity of both tests, "OR" = positivity for one of the two.
Results: 3147/40509 (7.8%) women were HPV-DNA positive (1446 tested with Cobas). Cumulatively, 174 CIN2+ were found (52 among women tested with Cobas). **Table 1**. Performance of single and combinations of tests for triage of HPV-DNA positive women

Single tests	Tested Women	Immediate referral	Sensitivity	Sensitivity 95%CI
cyto ASCUS+	3139	26.5%	66.1%	(58.5-73.1)
cyto HG	3139	5.9%	47.1%	(39.5-54.8)
mRNA	3131	66.8%	96.1%	(91.9-98.4)
p16	3069	32.1%	78.7%	(71.9-84.6)
HPV16-18	1446	27.0%	61.5%	(47.0-74.7)
Combined tests	**Tested Women**	**Immediate referral**	**Sensitivity**	**Sensitivity 95%CI**
cyto AND mRNA	3124	22.3%	64.9%	(57.4-72.0)
cyto AND p16	3063	14.6%	59.8%	(52.1-67.1)
cyto OR p16	3141	43.6%	85.1%	(78.9-90.0)
cyto HG OR p16	3141	32.7%	82.8%	(79.0-96.8)
p16 AND mRNA	3065	27.8%	78.2%	(71.3-84.1)
cyto OR HPV16-18	1446	45.0%	92.3%	(81.5-97.9)
p16 OR HPV16-18	1446	47.0%	90.4%	(79.0-96.8)

Conclusions: The combination of HPV 16/18 typing with cytology or p16/ki67 resulted in high sensitivity, but with a substantial increase in colposcopy referral compared to single test strategies.

CONCURRENT HUMAN PAPILLOMAVIRUS INFECTIONS BEFORE AND AFTER INTRODUCTION OF THE HPV VACCINE IN NORWAY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Infection with multiple human papillomavirus (HPV) types is common, but whether infection with certain HPV types has an effect on risk of infection with other types is not known. We studied concurrent HPV infections among both vaccinated and unvaccinated 17-year-old Norwegian girls.
Methods: Urine samples from girls in the first birth cohort offered HPV vaccine through the Norwegian Immunization Program (born in 1997) and from girls not offered free-of-charge vaccination (born in 1994) were collected and tested for 37 HPV genotypes. Individual records of HPV vaccination were obtained through linkage with the Norwegian Immunization Registry. Unvaccinated girls born in 1994 (n = 5245) and vaccinated girls born in 1997 (n = 5039) were included in the analyses. Risk of HPV infection was modelled using mixed-effect logistic regression with an individual-level random intercept in order to account for dependencies between infections due to subject-specific factors. Expected frequencies of concurrent infection with each pairwise combination of the vaccine types and high-risk types (6/11/16/18/31/33/35/39/45/51/52/56/58/59) were compared to observed frequencies.
Results: Infection with multiple HPV types was observed in 9.2% of girls in the 1994-cohort and 3.7% of girls in the 1997-cohort. Of HPV-infected girls, 50.3% and 35.4%, respectively, had multiple infections. The following pairwise combinations of HPV types were observed significantly more often than expected: 16+52 ($p=0.049$), 18+51 ($p=0.02$), 31+52 ($p=0.005$), 33+51 ($p=0.002$), 39+45 ($p=0.04$), 39+52 ($p=0.02$), 39+58 ($p=0.03$), 45+59 ($p=0.02$) in the 1994-cohort, and 6+18 ($p=0.04$), 11+16 ($p=0.049$), 33+51 ($p< 0.001$), 33+58 ($p=0.01$), 39+56 ($p=0.03$) in the 1997-cohort. No pairs were observed significantly less often than expected in either cohort.
Conclusions: In both the unvaccinated and the vaccinated cohort, more girls than expected had concurrent infection with HPV33 and HPV51. Other findings were not consistent across birth cohorts. Thus, no clear evidence of interactions between any other types was found.

REDUCING FALSE POSITIVE REFERRALS IN HRHPV POSITIVE WOMEN WITHIN THE DUTCH CERVICAL CANCER SCREENING PROGRAMME: A MODELLING STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: After implementing primary high-risk human papillomavirus (hrHPV) screening in the Netherlands, an increase was observed in the number of unnecessary referrals compared to the old cytology-based screening. Evaluating the optimal triage strategy for the Dutch setting is necessary prior to any change to the current programme.
Methods: The microsimulation model MISCAN was used to calculate the number of screening tests, referrals, cervical intraepithelial neoplasia (CIN)/cancer diagnoses, cancer deaths, life-years and quality-adjusted life-years (QALYs) gained and costs for ten different triage strategies, each with either 6, 12 or 18 months until repeat testing. Costs and effects were discounted annually by 4% and 1.5% respectively.
Results: Extending the time to repeat testing from 6 to 12 months reduced unnecessary referrals (<=CIN 1) by 7%, with no impact on cervical cancer incidence, mortality or QALYs. In addition to 12 month time to repeat testing, increasing the cytology threshold for direct referral from ASC-US to LSIL and implementing hrHPV16/18 genotyping both resulted in further reductions in unnecessary referrals (LSIL referral: -32%; genotyping: -34%) and increased the positive predictive value for CIN2+ (LSIL referral: 26%; genotyping: 27%). Increasing the cytology referral threshold resulted in a small increase in incidence and mortality (2% and 3% respectively), whereas genotyping resulted in little to no increase in incidence and mortality (1% and -1% respectively). Consequently, increasing the cytology referral threshold and adding genotyping resulted in a loss of QALYs (7% and 4% respectively).
Conclusions: Results indicate that extending time to repeat cytology testing from six to 12 months reduces the number of false positive referrals with little to no effect on incidence of, or mortality from, cervical cancer. Further reductions can be achieved by tightening the referral cytology classification from ASC-US to LSIL and by implementing genotyping.

USING NOVEL WAYS TO IMPROVE HPV KNOWLEDGE: A STEP AWAY FROM TEXT

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: HPV vaccination and screening are now being used in many counties. Information about HPV (usually in leaflet form) is provided alongside these prevention strategies, yet knowledge of HPV remains sub-optimal in many women. We designed two independent studies to explore whether providing HPV information in non-textual formats led to better HPV knowledge and improved retention over-time.
Methods: Two independent samples of women were recruited from an online survey panel (sample 1: 18-24 years, sample 2: 25-49 years). In both studies women were randomised to one of three groups: a) read text about recycling (control group), b) read text about HPV, c) received non-textual HPV information. In study 1, the non-text information consisted of an interactive quiz, with built-in feedback. In study 2, the non-text intervention was an animated video about HPV with voiceover and subtitles. Women completed a validated HPV knowledge measure (possible score 0-16) immediately after information exposure and 3-weeks later.
Results: In both studies there were significant differences in HPV knowledge scores immediately after information exposure ($F(2,584)=48.32$ and $F(2,344)=10.97$, both $p<.001$). In study 1, women who completed the interactive quiz had higher knowledge scores (M=9.9) than the control and HPV text groups (M=6.7 and M=8.4 respectively). In study 2, women who watched the video had higher knowledge scores (M=10.6) than the control group (M=8.9) but not the HPV text group (M=10.3). Between-group knowledge differences remained significant at 3-week follow-up in study 1 ($F(2, 137)=159.877$, $p=.002$), but not study 2.
Conclusions: Presenting HPV information in non-text ways seems promising for knowledge acquisition and retention, in the short-term at least. In particular, younger women, among whom knowledge is lower, may benefit from an interactive quiz. Given the use of smartphones in this population, this would be a feasible intervention to improve HPV knowledge, facilitating informed participation in screening.

SURGICAL TREATMENT OF EXTENSIVE CONDYLOMATA LESIONS AND THE USE OF 5% LOCAL IMMUNOMODULATOR TO PREVENT LESION RECURRENCE.

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: Extensive Genital condylomata is a warty lesion induced by Human papillomavirus infection (HPV). There is no standard treatment and chemotherapy drugs can be used locally or systemically, in addition to immunotherapy, radiotherapy and extensive surgical resections alone or combination with other therapies due to 25 % recurrence with severe morbidity in extensive genital condyloma. The objective of this study is to describe the efficacy of imiquimod in preventing recurrence after surgical treatment of multiples genital condyloma.
Methods: A Retrospective study of a series of fifteen patients with extensive genital condylomata identified among 444 women treated at a sexually transmitted infection outpatient clinic at a University Hospital in Vitoria - Brazil, from January 2017 to August 2019.
Results: Fifteen female patients underwent extensive genital condylomata surgery and 5% imiquimod for eight to twelve consecutive weeks after surgical lesion healing. The mean age was 27 years old being 46.6% nulliparous, six housewives, six cases of HIV- infected woman and one patient with systemic lupus erythematosus. The patients were followed by quarterly follow up for two consecutive years, with no recurrence.
Conclusions: Surgical excision of extensive genital condylomata lesions is the method of choice for treatment. Local immunotherapy is an adjuvant treatment in relapse prevention. Imiquimod is a efficient treatment option for recurrence prevention after surgical treatment of extensive condyloma, despite the high costs and side effects frequency.

EPIDEMIOLOGY OF JUVENILE ONSET RECURRENT RESPIRATORY PAPILLOMATOSIS IN THE UNITED STATES, 2015-2019

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Juvenile-onset recurrent respiratory papillomatosis (JORRP) is a rare disease characterized by repeated growth of wart-like lesions in the respiratory tract of children. JORRP is most often caused by human papillomavirus (HPV) types 6 or 11, usually acquired through vertical transmission. HPV vaccination is routinely recommended for U.S. adolescents; quadrivalent and 9-valent HPV vaccines protect against new infections with HPV 6, 11, and other types. We describe JORRP epidemiology in the United States to understand the potential impact of HPV vaccination.
Methods: Patients with JORRP aged <18 years were prospectively enrolled from 25 U.S. pediatric otolaryngology centers. Patient demographics and maternal characteristics were reported by mothers, and clinical history was abstracted from medical records. Tissue and brush biopsies from papillomas were collected and tested for 37 types of HPV DNA. We calculated descriptive statistics including interquartile ranges (IQRs) and reported maternal vaccination status.
Results: From January 2015 through August 2019, 200 prevalent patients with JORRP were enrolled. Median age at diagnosis was 4.5 years (IQR: 2.3—6.4), 129 were first-born (64.5%), 108 are male (54.6%), and 179 were delivered vaginally (89.5%). Median maternal age at time of delivery was 22 years (IQR: 19—26). No mothers reported receiving HPV vaccine before delivery. Among 150 patients with specimens tested, HPV was detected in 143, including 119 (79.3%) with HPV 6, 23 (15.3%) with HPV 11, and one with HPV 16. Multiple types were detected in 3 (2.0%); none had only non-vaccine-preventable types.
Conclusions: JORRP patients were commonly first-born children delivered vaginally to mothers in their late teens or early 20s. None of their mothers had been vaccinated against HPV before delivery, and a vaccine-preventable HPV type was identified in all specimens with detectable HPV. Prospective monitoring is ongoing. HPV vaccination, which is routinely recommended for U.S. adolescents, can reduce JORRP in the United States.

IARC HANDBOOK VOLUME 18 - CERVICAL CANCER SCREENING AND PREVENTION

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: At the World Health Assembly in May 2018, WHO Director-General Dr. Tedros Adhanom Ghebreyesus made a global call for action towards the elimination of cervical cancer. The *IARC Handbooks* programme will respond to this call through a collaboration with WHO on this project, by evaluating the effectiveness of current and emerging modalities of cervical cancer screening, and by establishing a comparison of the effectiveness of the methods.
Methods: The *IARC Handbooks of Cancer Prevention* series produce **comprehensive reviews** and **consensus evaluations** of the evidence on the effectiveness of preventive interventions that may reduce cancer incidence or mortality. IARC's process for developing *Handbooks* engages independent, interdisciplinary Working Groups of international scientific experts who perform a transparent synthesis of different streams of evidence, which is then translated into an overall evaluation according to set criteria.
Results: The IARC Handbooks programme will re-evaluate the effectiveness of cervical cancer screening (previous volume published in 2005), with consideration of new screening technologies, including human papillomavirus (HPV) testing, as well as implementation of screening in the context of HPV vaccination.
Conclusions: This Handbook will have a major impact for cervical cancer control in low- and middle-income countries, and will also help high-income countries to reduce social inequalities.The outcome of the Handbook will directly feed into the process for making recommendations by WHO,

A NOVEL LINK BETWEEN INFLAMMATORY SIGNALLING AND EXPANSION OF THE STEM CELL COMPARTMENT IN HPV-DRIVEN CARCINOGENESIS

BASIC RESEARCH / VIRUS – HOST INTERACTIONS"

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Introduction: Cervical cancer is a consequence of high-risk human papillomavirus (HR-HPV) infection and develops through a multistage process. We have previously shown that STAT3, a major factor for epithelial carcinogenesis, is strongly tyrosine-activated in cervical pre-cancerous high-grade lesions (Schröer et al., Cancer Res 2011; Walch-Rückheim et al., Cancer Res 2016). The mechanism underlying this potent STAT3 activation, however, was unclear.
Methods: We generated 3D-organotypic cultures with HR-HPV transformed keratinocytes and primary cervical fibroblasts, conducted retroviral infections to express HR-HPV oncogenes, analyzed 2D and 3D co-cultures in neutralization and siRNA knock-down experiments, by qRT-PCR Western blot, immunohistochemistry or -fluorescence.
Results: In this study we demonstrate that neither HR-HPV E6/E7 oncogene expression in host keratinocytes nor their transformation with HR-HPV were sufficient to directly activate STAT3. In organotypic 3D-cultures, however, STAT3 was strongly pTyr705-activated in the HPV-transformed epithelium. This was almost entirely dependent on the presence of stromal fibroblasts. Neutralization and knock-down experiments in 2D- and 3D-co-cultures identified IL-6 as the crucial fibroblast-derived paracrine mediator of STAT3-activation. In fibroblasts NF-κB p65-activation was found to be necessary for both IL-6 production and epithelial STAT3-activation. Our data further provide evidence that the epithelial stemness maintaining factor p63 was induced upon this paracrine IL-6/STAT3-loop in 3D-cultures, and that p63 expression in HPV-transformed epithelia was largely lost, when NF-κB p65 was knocked-down in stromal fibroblasts.
Conclusions: Our study implies that STAT3 activation in HPV-transformed precancerous cervical lesions is not cell-autonomous. Rather, a NF-κB-activated IL-6-producing stroma is required for paracrine epithelial STAT3-activation to support expansion of the p63-positive stem cell compartment conducive for carcinogenesis. Our study provides novel insight in the regulatory epithelial-mesenchymal circuits of cervical precancer, which might help to better understand how pre-cancerous lesions develop and to define novel strategies for diagnosis and intervention.

DETECTION OF BOTH HIGH-RISK HPV & EPSTEIN-BARR VIRUS PREDICTS FUTURE ABNORMAL CERVICAL CYTOLOGY IN HIV+ PATIENTS

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: Human Papillomavirus (HPV) plays a defining role in the development of cervical cancer. High-risk types of HPV are necessary but not sufficient to develop cervical disease. Previous data has shown a potential role of Epstein-Barr Virus (EBV) as a co-factor to HPV in the development of cervical disease. This study focuses on the predictive ability of detection of both hr-HPV and EBV in the development of disease in a cohort of HIV+ women
Methods: Cervical samples were collected from a cohort of 125 HIV+ women and tested for the presence of high-risk HPV, EBV and Pap smear testing. Cervical biopsies were collected as per clinical guidelines. Demographic characteristics, laboratory data including CD4 cell counts and HIV viral load, and social/behavioral risk factor questionnaires were collected. These women were followed prospectively via electronic medical record
Results: The cohort's average age was 42.3, mostly (88%) African-American with a mean CD4 cell count of 476 cells/ml and median HIV viral load of 124 copies/ml. High risk HPV was detected in 84% and EBV in 54%. Abnormal Pap smears developed in 46% and 48% had a subsequent cervical biopsy. The presence of EBV and hr-HPV increased the development of future abnormal Pap smears (46% vs 30%, p=.03) as compared to those with hr-HPV only. However, there was no difference in the development of an abnormal cervical biopsy in those shedding both EBV and HPV (59% vs 61%).
Conclusions: The presence of EBV in conjunction with hr-HPV does increase the risk of development of abnormal cervical cytology but not histological lesions. EBV may still be useful as a biomarker for those who will develop early cervical disease prior to histological changes. Future studies will focus on better defining the role of EBV utilizing cervical biopsy tissue.

HUMAN PAPILLOMAVIRUS GENDER-NEUTRAL VACCINATION RECOMMENDATIONS: DO HEALTH TECHNOLOGY ASSESSMENT AGENCIES OR NATIONAL IMMUNIZATION TECHNICAL ADVISORY GROUPS INCLUDE HEAD AND NECK CANCER BURDEN IN THEIR APPRAISAL?

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human Papillomavrus (HPV) vaccination has been recommended in over 90 countries (WHO 2019). Although originally recommended to only girls, several countries have extended their HPV vaccination program to include boys to reduce the burden of HPV-related diseases. Recent data demonstrated that HPV vaccination could reduce HPV oral infection (Herrero et al. 2013; Castillo et al. 2019). In this study we assessed if Health Technology Assessment (HTA) agencies and National Immunization Technical Advisory Groups (NITAGs) have included HPV-related head and neck cancers (HNC) when evaluating a HPV gender-neutral vaccination (GNV) program.
Methods: A systematic review was performed to identify country specific reports on HPV GNV programs to collate data focusing on HNC. The search conducted in August 2019 included HTA agencies and NITAGs from 32 countries that recommended GNV. In addition, HTA and NITAG reports were searched in MEDLINE® and EMBASE® using Ovid SP®. The data extraction covered HNC anatomic sites, oral HPV infection, epidemiology data (incidence, prevalence, genotype distribution), economic data and appraisal of the presented data. Using PRISMA guidelines, reports were double-screened for inclusion in the assessment.
Results: In total, 15 reports were included, of which 69% were published in Europe. Different HNC anatomic locations were included, however, 53% of the reports included oropharyngeal cancers only. HNC epidemiological data were published in 73% of the reports. HNC burden data varied widely and six reports acknowledged that HNC could be prevented if included in the regular HPV vaccination program. When HNC data were included in the cost-effectiveness analyses, the incremental cost-effectiveness ratio results were more favorable versus without HNC.
Conclusions: Burden of HPV-related HNC has been recognized by several HTA agencies and NITAGs when evaluating HPV GNV programs. Nevertheless, the data might be limited in some countries and underestimating HNC burden. Further research on HPV-related HNC burden should be conducted.

HPV VACCINATION ACROSS A CASCADE OF KNOWLEDGE, UPTAKE, AND WILLINGNESS IN GAY, BISEXUAL, AND OTHER MEN WHO HAVE SEX WITH MEN (GBMSM): A CIRN STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2015-2016, Canada began offering publicly-funded HPV vaccination to gbMSM aged ≤26 years in some jurisdictions. We developed a novel cascade approach to characterize uptake of HPV vaccine among gbMSM in three Canadian cities soon after the implementation of the public programs.
Methods: Engage is a sexual health study among gbMSM aged 16+ in Vancouver, Toronto, and Montreal recruited via respondent driven sampling (RDS) starting in 02/2017. Our 4-stage HPV vaccination cascade was: (1) unaware of HPV vaccine; (2) aware and undecided/unwilling to get vaccinated; (3) aware and willing to get vaccinated; and (4) aware and vaccinated (referent group). We used multinomial logistic regression adjusted for city to identify correlates of the vaccination cascade stage. Our results are RDS unadjusted and stratified by age of eligibility for free vaccine (eligible: ≤26; ineligible: >26).
Results:

Table 1a: Characteristics associated with being aware of the vaccine and vaccinated compared to the first three stages of the HPV vaccination cascade among men aged ≤26 years (eligible for free vaccination) in the Engage study (N=494).

Characteristics of Interest	Stage 1: Unaware of HPV vaccine (N=90)		Stage 2: Aware of vaccine + unvaccinated + undecided/unwilling to get vaccinated (N=68)		Stage 3: Aware of vaccine + unvaccinated + willing to get vaccinated (N=113)		REFERENT Stage 4: Aware of vaccine + vaccinated (N=223)
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%
Received information on sexual health in past 6 months							
No	20.0	Ref	25.0	Ref	4.4	Ref	4.9
Yes	80.0	*0.27 (0.11, 0.67)*	75.0	*0.22 (0.09, 0.53)*	95.6	1.23 (0.41, 3.71)	95.1
Routine vaccination history (Hep A, Hep B, Flu, or Meningococcal vaccine)							
No	38.9	Ref	30.9	Ref	17.7	Ref	5.4
Yes	61.1	*0.11 (0.05, 0.23)*	69.1	*0.15 (0.07, 0.34)*	82.3	*0.24 (0.11, 0.52)*	94.6
Any healthcare access							
No	28.9	Ref	23.5	Ref	12.4	Ref	7.6
Yes	68.9	*0.24 (0.12, 0.51)*	75.0	*0.37 (0.17, 0.85)*	87.6	0.57 (0.27, 1.22)	91.5

Other model covariates include: age, education, sexual orientation, and city.

Table 1b: Characteristics associated with being aware of the vaccine and vaccinated compared to the first three stages of the HPV vaccination cascade among men aged >26 years (ineligible for free vaccination) in the Engage study (N=1691).

Characteristics of Interest	Stage 1: Unaware of HPV vaccine (N=460)		Stage 2: Aware of vaccine + unvaccinated + undecided/unwilling to get vaccinated (N=178)		Stage 3: Aware of vaccine + unvaccinated + willing to get vaccinated (N=771)		REFERENT Stage 4: Aware of vaccine + vaccinated (N=282)
	%	aOR (95% CI)	%	aOR (95% CI)	%	aOR (95% CI)	%
Received information on sexual health in past 6 months							
No	28.7	Ref	21.9	Ref	12.6	Ref	5.3
Yes	71.3	*0.31 (0.17, 0.56)*	78.1	*0.41 (0.21, 0.81)*	87.4	0.59 (0.32, 1.07)	94.7
Routine vaccination history (Hep A, Hep B, Flu, or Meningococcal vaccine)							
No	22.8	Ref	15.7	Ref	9.1	Ref	4.6
Yes	77.2	*0.27 (0.13, 0.54)*	84.3	*0.35 (0.16, 0.77)*	90.9	0.56 (0.28, 1.12)	95.4
Disclosed sexual orientation to provider*							
No	13.3	Ref	11.4	Ref	6.5	Ref	4.1
Yes	86.7	*0.25 (0.11, 0.57)*	88.6	*0.25 (0.10, 0.64)*	93.5	0.49 (0.22, 1.08)	95.9

Other model covariates include: age, education, income, ethnicity, insurance coverage, and city. *% among those with a provider.

Results are based on 2185 men enrolled as of 02/2019. Among 494 men aged ≤26, 18.2% were unaware of the HPV vaccine; 13.8% were aware/undecided/unwilling to get vaccinated; 22.9% were aware/willing to get vaccinated; and 45.1% were aware/vaccinated. Corresponding proportions among 1691 men aged >26 were 27.2%, 10.5%, 45.6%, and 16.7%. Men in stage 1/2 were less likely to have received sexual health information in the past 6 months, accessed healthcare (if ≤26), disclosed their sexual orientation to a provider or have a history of routine vaccination (if >26) (Table 1a&b). Men ≤26 years in stage 1/2/3 were less likely to have a history of routine vaccination (Table 1a). We also found that vaccinated men (stage 4) were more likely to identify as gay versus bisexual/queer/other (if ≤26), and, if >26, to have a higher income and education, and have insurance coverage.

Conclusions: Characterizing vaccination cascades may help target new interventions such as increased awareness of sexual health/HPV and determine target sub-populations for vaccine promotion to increase vaccine uptake.

A PHAGE-DISPLAY SELECTED PEPTIDE WITH POTENTIAL TO CONTROL HPV-RELATED TUMORS

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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Introduction: High-risk Human Papillomavirus is the etiologic agent of cervical cancer and other tumors in humans. Despite the existence of prophylactic vaccines against infections by the most common types of HPV, therapeutic alternatives are limited to control HPV-associated tumors.
Methods: We found some homologous motifs for high-risk HPV proteins using immune-panning of a peptide phage display library with sera from HPV-16-seropositive female patients. The recombinant bacteriophages (PEP1) were purified and amplified for use as immunogens. We vaccinated immunocompetent mice prophylactically with one of our recombinant bacteriophages, using the insertless M13 bacteriophage as a control. These mice were then challenged with TC-1 tumor cells (HPV-16 positive), and the immune responses triggered during tumor progression were evaluated. We also used a therapeutic approach, injecting tumor cells before immunization with the bacteriophage. Tumor growth was monitored and tumors, spleens and lymph nodes were evaluated for the level and type of the immune responses
Results: Tumor growth was significantly reduced in prophylactic and therapeutic immunizations, although tumor reduction was minimal when mice were treated 9 days after TC-1 cells grafting. The reduction in tumor growth also translated into a significantly greater survival for the immunized mice. Cell infiltration studies did not reveal changes in several immune subpopulations, but an upward trend in cytotoxic T lymphocytes was observed in mice immunized with PEP1. We further confirmed this finding by grafting TC-1 cells in CD8-knockout mice, where the previously observed reduction of tumor growth was abolished. An increase in CD8:CD4 rate was observed in the immunized mice and this is an indication of a cytotoxic tumor environment. Further studies are warranted.
Conclusions: Phage display is a veritable tool in the discovery of new molecules that could offer a wide range of uses including immunogens. This could be a path towards new vaccines development

ACCURACY OF HUMAN PAPILLOMAVIRUS VIRAL LOAD QUANTIFICATION FOR TRIAGING HIGH RISK (HR)-HPV-POSITIVE WOMEN

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: INTRODUCTION :Primary high risk human papillomavirus (HR-HPV) screening is being widely adopted in national programs for cervical cancer screening. However since majority of the HPV infections are transient, most suitable triage strategies for the HR-HPVpositive women are still being explored. This study evaluated the association between HR-HPV viral load and cervical intraepithelial neoplasia (CIN) lesions and its potential for triage after primary HPV screening.
Methods: METHODS: We conducted a retrospective review of 229 HPV positive women in the age group of 30-60, who underwent primary screening for HR HPV DNA testbetween January 2017 to December 2018 at the tertiary cancer centre. HR HPVwas detected by Hybrid Capture 2 assay and viral load was measured by the ratio of relative light units to standard positive control (RLU/CO).Histopathology established the pathological grades of CIN.The clinical performance to detect CIN 2 and above lesions (CIN2+) at different viral load cut-off values was calculated.
Results: RESULTS :The prevalence ofCIN2+ among HPV positive women was 30.6 % (70/229).The mean RLU/CO values for histopathology grades ofnegative CIN, CIN 1, CIN 2, CIN 3, and invasive cancer were 330.65, 610.72, 694.35, 910.85 and 778.39 respectively. The severity of cervical lesions increased with the increasing viral load($P < 0.001$).The algorithm using RLU/CO value cut offs at >=10, >=100, and>= 1000 for detecting CIN 2+ lesions had sensitivity of 0.91 (0.82 - 0.97), 0.73(0.61 - 0.83) and 0.33 (0.22 - 0.45)and specificity of 0.26 (0.19 - 0.33), 0.56 (0.48 - 0.64) and 0.86 (0.79 - 0.91) respectively. Increasing the cut-point of the HC2 viral load assay improved the specificity and decreased the false positive ratesat the cost of loss in sensitivity.
Conclusions: CONCLUSIONS: Increase in the HR-HPV viral load increases the risk of cervical cancer and precancerous lesions. Quantifying viral load can be effectively utilised for strengthening cervical screening programs.

UPTAKE AND CORRELATES OF CERVICAL CANCER SCREENING AMONG WOMEN ATTENDING INTEGRATED MULTI-DISEASE COMMUNITY OUTREACH CAMPAIGN

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Despite the increased risk of cervical cancer among HIV-positive women, many HIV-care programs do not offer integrated cervical cancer screening. Incorporating self-collected Human Papillomavirus (HPV) testing into HIV programs is a potential strategy to identify women at higher risk for cervical cancer while leveraging the staffing, infrastructure and referral systems for existing services. Community-based HIV and HPV testing has been effective and efficient when offered in single-disease settings.
Methods: This cross-sectional study was conducted within a community outreach and multi-disease screening campaigns organized by Family AIDS Care & Education Services in Kisumu County, Kenya. In addition to HIV testing, the campaigns provided screening for TB, malaria, hypertension, diabetes, and referrals for voluntary medical male circumcision. After these services, women aged 25-65 were offered self-collected HPV testing. A subset of all women attending the campaigns completed a survey on their attitudes and knowledge on HPV and cervical cancer. Rates and predictors of cervical cancer screening uptake and of HPV positivity were analyzed using tabular analysis and Fisher's Exact Test.
Results: Between April and June, 2018, 2,016 women of screening age attended the outreach campaigns. Of those, 721 women (35.8%) screened, and 134 women (18.6%) were HPV-positive. Seventy-four HPV-positive women (55.2%) accessed treatment within six months. Older women (28.1% vs. 39.9%; p=0.047) or women with more children (36.8% vs. 51.7%; p=0.001) were less likely to screen whereas women who were encouraged by a family member other than their spouse (p=0.001) were more likely to screen. Relationship status, education, and HIV status were not associated with HPV screening uptake.
Conclusions: The low screening uptake may be attributed to implementation challenges at the campaign. However, given the potential benefits of integrating HPV testing into HIV outreach campaigns, these challenges should be examined to develop more effective multi-disease outreach interventions and optimize the single-visit approach to health services.

COMMUNITY PHARMACISTS VACCINATE AGAINST CANCER (CPVAC): PRELIMINARY FINDINGS FROM A PILOT RANDOMIZED CONTROLLED TRIAL

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: In 2016 only 37.5% of boys and 49.5% of girls completed the HPV vaccine series, with racial/ethnic minority youth populations lagging in vaccine completion. Barriers to vaccine completion: caregivers' lack of awareness to receive additional vaccine doses, lack of time to attend an additional vaccine-only primary care clinic appointment, and other structural barriers that prohibit caregivers and their children from returning to primary care clinics for additional vaccine doses. Pharmacists are licensed to vaccinate against the HPV virus, and a healthcare model which incorporates these professionals into the immunization neighborhood may increase HPV vaccine completion rates. The aims of this study are to 1) determine the preliminary efficacy of CPVAC to increase HPV vaccine series completion with the community pharmacist vs. with the primary care provider; and 2) assess perceived intervention feasibility and acceptability of CPVAC among intervention participants and primary care clinic staff.
Methods: Driven by the Diffusion of Innovation, Community Pharmacists Vaccinate Against Cancer (CPVAC) is pilot randomized controlled intervention which test a healthcare delivery model in which children receive dose 1 of the HPV vaccine with their primary care providers (PCP). They are then randomized to intervention or control group. Intervention participants will receive the additional doses with their preferred pharmacy, and control group participants receive standard care.
Results: To date, 26 participants have been enrolled in the study (11 Intervention, 15 Control). Preliminary data for the first 26 participants will be collected beginning in November 2019. The research team will also have a better understanding of study feasibility at this time.
Conclusions: If this study demonstrates preliminary efficacy, feasibility, and acceptability, study findings from can be used to inform a larger randomized controlled trial to examine intervention effectiveness and analyze the cost-benefit of working with community pharmacies to enhance HPV vaccine completion among adolescents.

ARIZONA PHARMACY PROFESSIONALS' BEHAVIORS, SUBJECTIVE NORMS, AND INTENTIONS TO VACCINATE AGAINST HUMAN PAPILLOMAVIRUS

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Pharmacists and pharmacy interns who have completed an immunization training certification can administer human papillomavirus vaccine doses. Little is known about these pharmacy professionals' intentions and influences on human papillomavirus vaccination behavior.
Methods: This cross-sectional study utilized a 52-item survey to explore Arizona pharmacists' and pharmacy interns' behaviors, intentions, attitudes, subjective norms, and perceived behavioral control related to human papillomavirus vaccination. Guided by the Theory of Reasoned Action, a member of the research team created a survey to assess pharmacy interns' and pharmacists' intentions and behaviors related to human papillomavirus vaccination. The survey was conducted at a statewide pharmacy conference. The main outcomes of this study included human papillomavirus vaccination behavior and intentions to administer the vaccine. Multiple regression was performed to determine significant predictors of vaccination. A path analysis determined factors that contributed to vaccine intentions.
Results: Overall, most pharmacy professionals held positive attitudes about the human papillomavirus vaccine. However, the majority of participants responded that they either never or rarely administered the human papillomavirus vaccine to their age-eligible patients. Attitude, perceived behavioral control, and subjective norm all influenced human papillomavirus vaccination intentions. However, the strongest predictor of human papillomavirus vaccination intention were subjective norms to administer this vaccine.
Conclusions: This work highlights the need to increase pharmacy professionals' subjective norms to vaccinate against human papillomavirus as a means to increase pharmacy-based human papillomavirus immunization. Future human papillomavirus vaccine promotion could engage pharmacy leadership to encourage pharmacy professionals to administer this vaccine. Additionally, raising patient awareness of pharmacy professionals' ability to administer adolescent vaccines could increase human papillomavirus vaccination rates.

MOLECULAR CHARACTERIZATION OF HUMAN PAPILLOMA VIRUS AMONG WOMEN IN IBADAN, OYO STATE

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: Cervical cancer is the secind mst common cancer among women in Africa and especially Nigeria. WHO recommended cervical cytology as well as HPV DNA screening as one of the main prevention strategies for the disease. This study investigated the prevalence HPV genotype among women presenting for routine cytology check-up in Ibadan, Oyo State.
Methods: Method: women attending the cytology clinic at the Gynaecology clinic of the University College Hospital, Ibadan, Oyo State. Cervical swabs and smears were collected from 335 consenting patients. Papanicolaou staining of smears was performed and HPV DNA was detected and genotyped using conventional multiplex nested PCR as described by Sotla et al (2004).
Results: Result: Of the 335 samples tested 23 (6.9%) showed varied degree of abnormal cytology. Eighty-six (25%) samples were positive for HPV DNA. Majority, 12 (3.9%) were genotype 16 while 8 (2.4%) were genotype 18 DNA. Co-infection was seen in only one participant. The highest rates (26.4%) of HPV infection was observed among females aged 40-49 years. Multiparity ($P<0.1971$) and attainment of menopausal age($P<0.1236$) were significant factors for abnormal cytology but not for HPV DNA presence by PCR ($P>0.0001$),
Conclusions: Conclusion: This study revealed a high prevalence of HPV infection among women in Ibadan hence the need for increased advocacy for vaccination of females against HPV as well as increased accessibility to HPV screening programs.

HPV 18 GENETIC VARIATION AND CERVICAL DISEASE IN US

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Introduction: HPV18 is second only to HPV16 as an etiologic factor in cervical cancer but is not well represented in precancers. Whole genome sequencing of HPV18 may shed light on the molecular changes with cervical disease progression.
Methods: Methods: Whole genome sequencing following HPV target enrichment (eWGS) was performed with Illumina Hiseq 2500 and interpreted following published methods on samples from the Early Detection Research Network cervical cancer biorepository. HPV types were identified if ≥511 reads mapped to reference genome (CLC Genomics). Multiple sequence alignment of the HPV18 consensus and sublineage reference sequences with MUSCLE 3.8.31, and maximum likelihood phylogenetic analysis were used to determine HPV18 lineage/sublineages. HPV integration was identified by deletions (>50 bp) in the mapped reads with at least 10X depth of coverage.
Results: Results: eWGS identified HPV18 in 49 samples: 16 from women with no cervical disease (No-CIN), 11 from cervical intraepithelial neoplasia grade 1 (CIN 1), 13 CIN 2, 6 CIN 3 and 3 invasive cancer. HPV 18 was the only type detected in 5 samples, the remaining had 1 to 18 additional types (mean 5 types). HPV16 was co-identified with HPV18 in 16 samples. Most HPV18 belonged to A lineage (41), 8 were B, none in C lineage. Within A lineage, there were 8 A1 (16.3%), 25 A3 (51%); 7 A4 (14.3%) and 1 A5 (2%). B sublineages included B1 (4, 8%) and B3 (4, 8%). HPV18 lineage/sublineage was not associated disease. HPV18 was integrated in 5 samples, all with at least CIN2 (3 invasive cancer, 1 CIN 3 and 1 CIN 2) Integration of HPV18 genome resulted in deletions ranging from 224-3958 bp (mean, 2283bp), affecting E1, E2, E5 and L2 genes.
Conclusions: Conclusion: Using eGWS provides direct information on genetic variants and integration of HPV 18. This method will be used to study additional samples.

ADJUDICATION OF FINAL HISTOLOGICAL DIAGNOSIS OF CERVICAL BIOPSIES USING A THREE-STEP STANDARDISED PROTOCOL: AN INTER-OBSERVER REPRODUCIBILITY ANALYSIS WITHIN THE ESTAMPA STUDY (NCT01881659)

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: p16 immunohistochemistry is recommended for distinction between high-grade and low-grade cervical lesions under the Lower Anogenital Squamous Terminology (LAST), by which CIN2/p16-positive, CIN3, and adenocarcinoma in-situ diagnoses represent histological high-grade intraepithelial lesions (HSIL). Using a LAST-based standardised protocol, we evaluated the inter-observer reproducibility between local and reviewed histological diagnoses within the ESTAMPA study.
Methods: ESTAMPA is a multicentric study in Latin America. Women aged 30-64 are screened with HPV and cytology and referred to colposcopy (with biopsy collection as appropriate) if any screening positive result. Histological slides (H&E) are prepared locally and treatment is offered according to local histologic interpretation. Two expert pathologists blind to local results and additional women's data reviewed H&E slides following a three-step protocol. If first review disagreed with local interpretation, then a second blind review (along with all slides belonging to the same subject) was done. If first and second reviews disagreed, then a third review between the two experts was done using a multi-head microscope (adjudication meeting). p16 was required at any step as needed. Based on fully reviewed diagnosis, decisions for upgrading (local-based <CIN2 to reviewed-based HSIL+) or downgrading (local-based CIN2+ to reviewed-based <HSIL) were made. Agreement, positive agreement (positive concordant results over total positive results) and unweighted kappa were calculated.
Results: 4389 H&E and 196 p16 slides (corresponding to 1716 subjects in 10 study centres) were fully reviewed. The agreement, positive agreement and kappa were 94.5% (95%CI 94.2-95.6), 58.0% (53.8-62.2) and 0.71 (0.67-0.75), respectively. The concordance varied widely among study centres (positive agreement and kappa ranges: 38.3-100, 0.53-1.00). This process led to 26 (2% among 1515) upgrades and 56 (28% among 201) downgrades.

Conclusions: A LAST-based standardised protocol may yield reliable final study endpoints and clinical outcomes. If routinely implemented, it could improve the identification of women in need of urgent treatment reducing overtreatment-related harms.

VARIATION OF PREVALENCE AND VIRAL LOAD OF HIGH RISK HUMAN PAPILLOMAVIRUS IN FEMALE GENITAL TRACTS IN A REFERRAL POPULATION

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: There have been a lot of studies on the prevalence or viral load of human papillomavirus (HPV) in cervix, but very few data showed the variation of HPV prevalence and viral load throughout female genital tract.
Methods: 489 colposcopy referral women with valid Hybrid Capture Ⅱ (HC2) and Linear Array (LA) detection results in 4 sites of female genital tract (perineum, lower vagina, upper vagina and cervix) were included into the study. Positive rate of high risk HPV(HR-HPV) was estimated using linear-by-linear association test and Chi-square test, the Geometric mean of HC2 result (RLU/CO) was described as viral load, statistical significance was assessed with α level of 0.05.
Results: The overall prevalence of HR-HPV single infection was significantly different among 4 sites of genital tract (P<0.001), but no trend was observed ($P_{for\ trend}$=0.951), slightly higher single infection rates were found in upper vagina (46.2%) and cervix (44.2%). As for multi-infection, the overall prevalence decreased significantly from perineum to cervix ($P_{for\ trend}$ <0.001), but no significant trend was observed in women diagnosed as CIN1 ($P_{for\ trend}$=0.063) or CIN2+ ($P_{for\ trend}$ =0.156). In cervix, viral load increased with the elevation of disease severity, while in other 3 genital sites, higher viral load was found in CIN1 lesion. The overall viral load of HR-HPV single infection or multiple infections decreased significantly from cervix to perineum ($P_{for\ trend}$<0.001). Whatever the grades of cervical lesions, viral load of multi-infection was higher than that of single infection.
Conclusions: Prevalence of single infection tend to be higher in cervix while multi-infection was higher in lower genital tract. HR-HPV viral load decreased significantly from cervix to perineum for both single and multiple infections.

MICRORNAS AS PREDICTIVE BIOMARKERS OF LOW-GRADE CIN OUTCOMES

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Low-grade cervical dysplasia is frequently managed by observation because most dysplasia will resolve without intervention. Currently there are no clinical tests that will identify women at risk for progression to high-grade dysplasia from among those that will resolve naturally. A molecular biomarker that predicts the outcome of low-grade CIN could be used clinically to triage women for definitive care.
Methods: We conducted a retrospective case-control study to reveal microRNAs that could predict the outcome of low-grade CIN. Women were identified through electronic medical records as having a diagnosis of low-grade CIN. Women with a subsequent diagnosis of high-grade CIN were designated as cases (n=22). Women with a significant history of normal cervical tests following the low-grade CIN diagnosis and without evidence of clinical intervention were included as controls (n=29). Total RNA was isolated from the archived diagnostic specimen with the low-grade CIN diagnosis. MicroRNA expression was analyzed using arrays with probes for all known human microRNAs (LC Sciences, Houston, TX). Differential microRNA expression between cases and controls was calculated.
Results: Twenty-nine microRNAs were differentially expressed at the $p<0.01$ level when comparing cases to controls. Notably, miR-638 was significantly downregulated and miR-1260a was significantly upregulated in women with low-grade CIN that progressed to high-grade CIN. Literature supports a role for miR-638 as a tumor suppressor miRNA, while miR-1260a has been shown to promote migration and invasion properties. These findings are consistent with a possible role for miR-638 and miR-1260a in the pathophysiology of cervical dysplasia progression.
Conclusions: MicroRNA testing, either alone or in combination with other biomarkers, may have a role in future clinical tests to direct management of women with low-grade CIN. Dysregulated microRNAs may also play a role in the pathophysiology of dysplasia progression.

A PILOT EVALUATION OF INTERLABORATORY AGREEMENT IN ASSESSMENT OF GYNAECOLOGICAL CYTOLOGY IN POLISH CERVICAL CANCER SCREENING PROGRAMME (PCCSP)

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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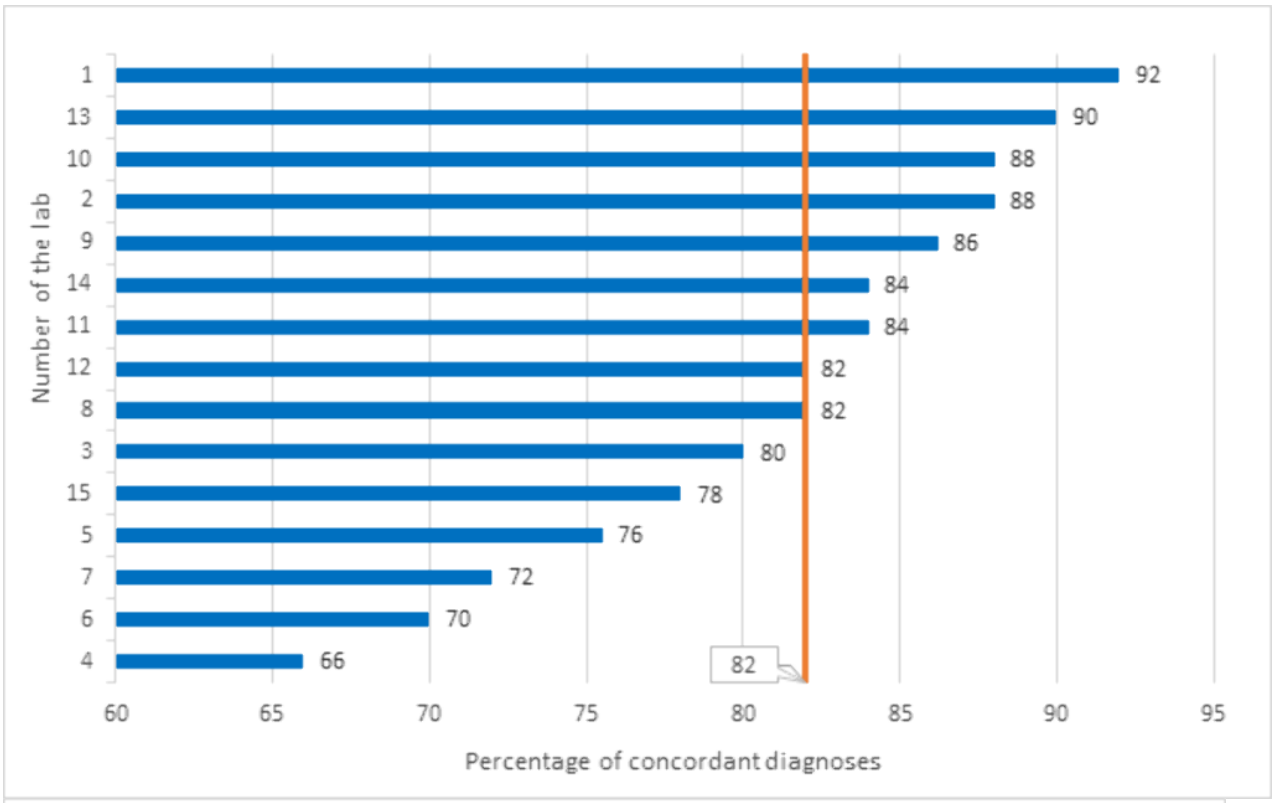
Introduction: In 2018 a pilot study was carried out to assess interlaboratory variability of cytological diagnoses in selected laboratories participating in Polish Cervical Cancer Screening Programme (PCCSP) to establish grounds for certification system for cytologists and monitor the quality of services.
Methods: A set of 50 expert-selected cytological slides with clinical, colposcopic and histological confirmation of diagnoses was prepared. Smears were selected to form a set representative for each category of diagnoses according to the Bethesda 2001 system. The set with each-time blinded and mixed slides was sent to 15 laboratories in 4 different voivodeships. Cytodiagnosticians were asked to assess the slides as a routine practice. Three types of coding were applied and slides were classified respectively: general: inadequate for evaluation, normal, abnormal (atypical squamous cells of undetermined significance (ASC-US) or more severe diagnosis), aggregated: inadequate for evaluation, normal, low-grade lesions (ASC-US, low-grade squamous intraepithelial lesion (LSIL)), high-grade lesions (atypical squamous cells cannot exclude HSIL (ASC-H), high-grade squamous intraepithelial lesion (HSIL), atypical glandular cells (AGC), squamous cell carcinoma (SCC)); detailed: inadequate for evaluation, normal, ASC-US, LSIL, ASC-H, AGC, HSIL, SCC). The proportion of correct diagnoses and unweighted kappa coefficients were estimated for each laboratory.
Results: Unweighted kappa coefficients among labs ranged from 0.40 to 0.86 for general coding, from 0.37 to 0.76 for aggregated coding and from 0.34 to 0.73 for detailed coding and median unweighted kappa coefficients correspond with substantial (0.66), moderate (0.58) and moderate agreement (0.51), respectively. The median percentage was calculated as 82% in general coding (Figure 1), 72% in aggregated coding (Figure 2) and 66% in detailed coding (Figure 3).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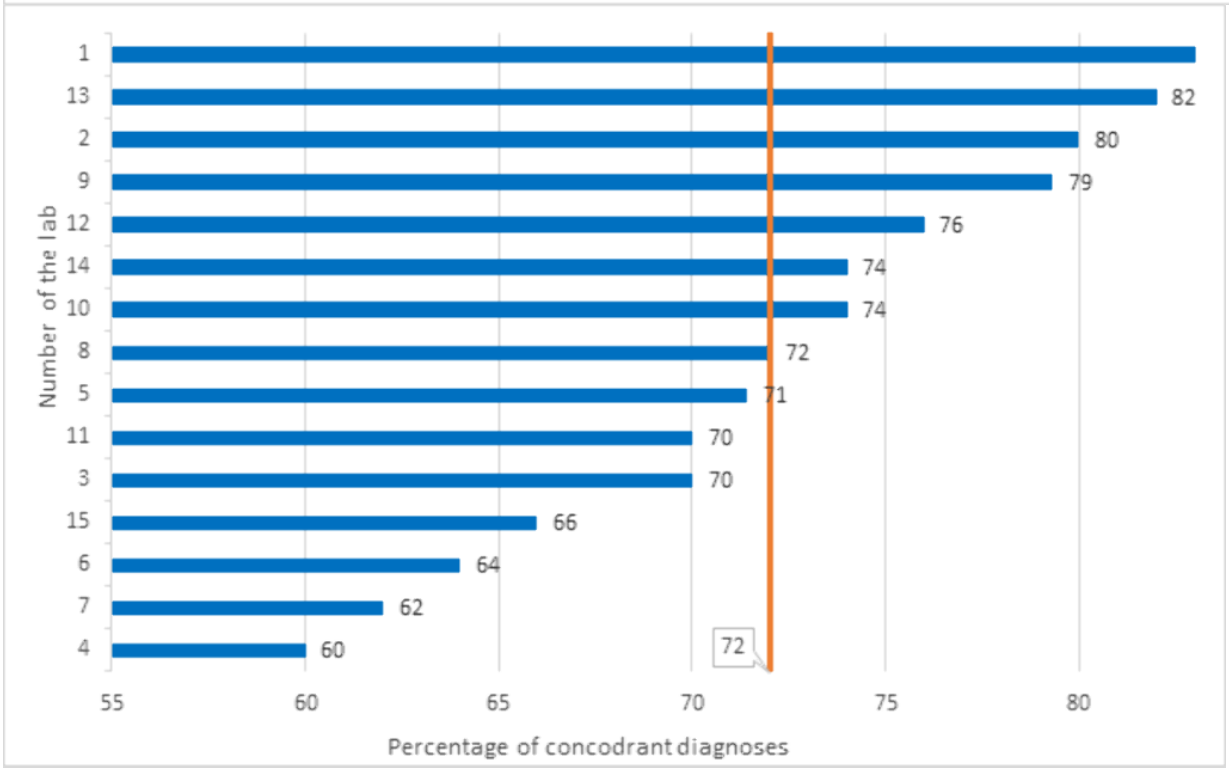
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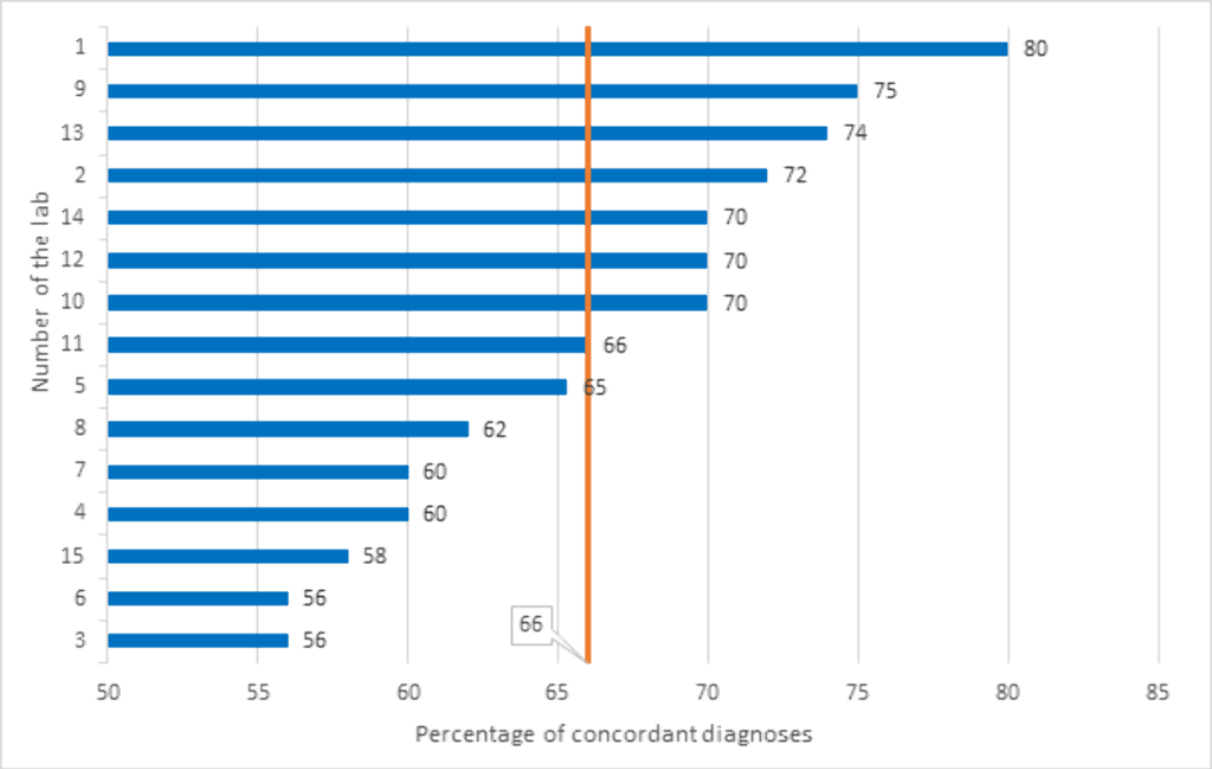

Conclusions: Conducted analysis shows relatively high level of agreement between labs and expert's diagnoses. Further lab verification is underway to establish final certification system for cytologists. Benchmark level of agreement for laboratories/cytomorphologists should be established to guide corrective actions.

HPV VACCINATION, ARE WE OVERLOOKING ADDITIONAL OPPORTUNITIES TO CONTROL HPV INFECTION AND TRANSMISSION?

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Due to distinctive immunogenic properties of human papillomavirus virus like particles (HPV VLPs) HPV vaccination generates a durable antibody response producing high-quality neutralizing antibodies. The viral survival strategy which includes hiding from the systemic immune system, is overruled by intramuscular injection generating huges amounts of vaccine induced antibodies. As other circulating immuno globulines G, vaccine inducted IgGs, are easily transuded to the genital mucosa and are detectable in genital secretions.
Methods: It is well accepted that these antibodies interact with the virions presented by an infected partner and inhibit infection.
Results: However, much less attention has been paid to the role of anti-HPV vaccine-induced antibodies in HPV-infected individual where infectious virions are encountered by neutralizing antibodies in mucosal secretions. Indeed, in these women vaccination may interfere with the auto-innoculation obstructing infectious virions to spread from sites with low potential for malignant progression to the transformation zone with higher potential for progression. Secondly, anti-HPV IgGs may potential also decrease the likelihood that women with a productive infection transmit the infection to their sexual partner.
Conclusions: Although it is challenging to investigate experimentally or epidemiologically this concept because of it potential impact there is a clear need to further investigate and document this concept. Indeed, if HPV vaccination of HPV-infected women has an effect on HPV transmission, auto-inoculation, and relapse after treatment this may influence how we model, assess and implement HPV vaccination programmes.

HIGH-RISK HPV PREVALENCE IN HUNGARY: A POPULATION-BASED, GEOGRAPHICALLY-REPRESENTATIVE, CROSS-SECTIONAL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Estimated age-standardized incidence and mortality rates of cervical cancer is substantially higher in Hungary than European average. Evidence-based continuous improvement of national prevention strategy requires representative monitoring data according to European guidelines. In many countries Human papillomavirus testing became first-line method of cervical pre-cancer screening in women above the age of 30 due to its superior sensitivity, automatization and less frequent effective screening intervals.
Methods: 4731 Thinprep cervical samples were collected during 8 months in 84 sampling sites until 4000 eligible samples from the screening target population of patiens between 25-65 years of age with addresses matching the representative geographic distribution (county and 4 major settlement types) and with valid laboratory results was reached. hrHPV genotyping was performed using sequentially Confidence HPV-X (Neumann Diagnostics) and Linear Array HPV Genotyping (Roche) commercial IVD CE tests. Collecting parallel epidemiology (education, HPV vaccination) and cervical anamnestic data with questionnaire enabled presentation of hrHPV genotype distribution in age, geographic, education, cytology, vaccination population subgroups.
Results: 446 samples were high-risk positive showing a 11.2% prevalence similar to world average, higher than Europe average, lower than Eastern-Europe average. Prevalence decreases with age from 19,4% in age group 25-29 to 5,0% and 5,3% in age groups 55-59 and 60+ respectively. Immediately following genotype 16 and 31 in order of frequency, certain non-vaccine high-risk HPV genotypes (51,66, 56) have unexpectedly high prevalence compared to international data.
Conclusions: Evidence supports introducing primary HPV-screening in Hungary. Our study provides the first geographically-representative genotype-specific hrHPV prevalence base-line database for supporting and evaluating policy-making efforts. Further follow-up should reveal probable genotype distribution shifts over time along with our nation-wide HPV vaccination and cervical screening prevention programs, both in random screening population and among those hopefully less and less women with cervical pre-cancer and cancer.

CAN FEMALE COMMUNITY HEALTH VOLUNTEERS HELP INCREASE CERVICAL CANCER SCREENING UPTAKE IN NEPAL?

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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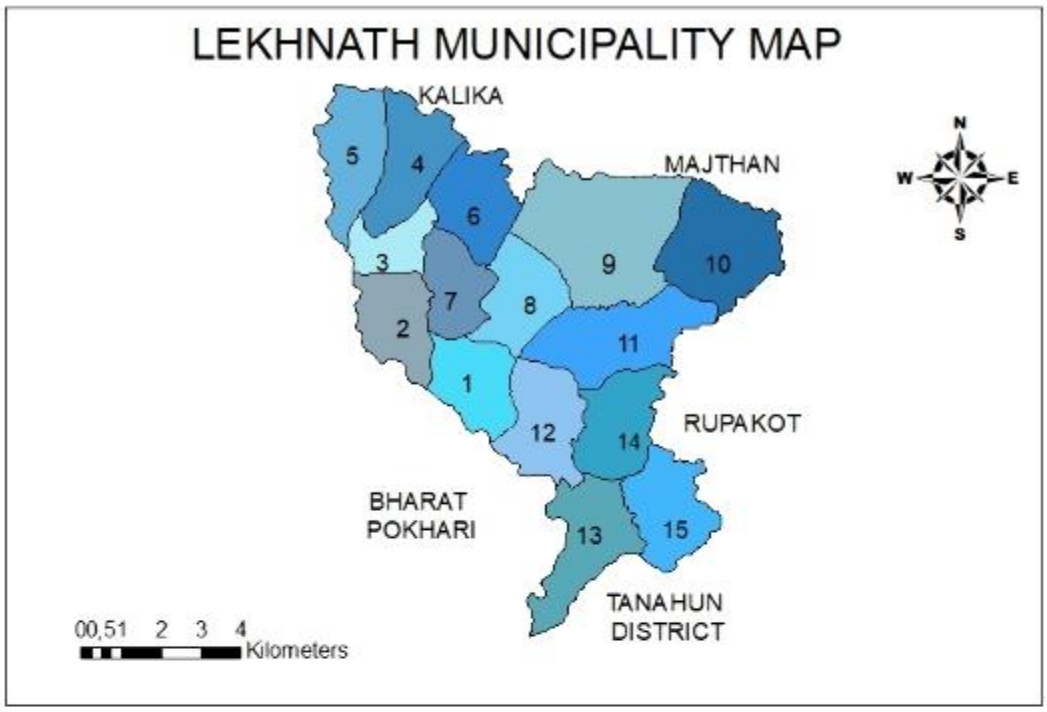
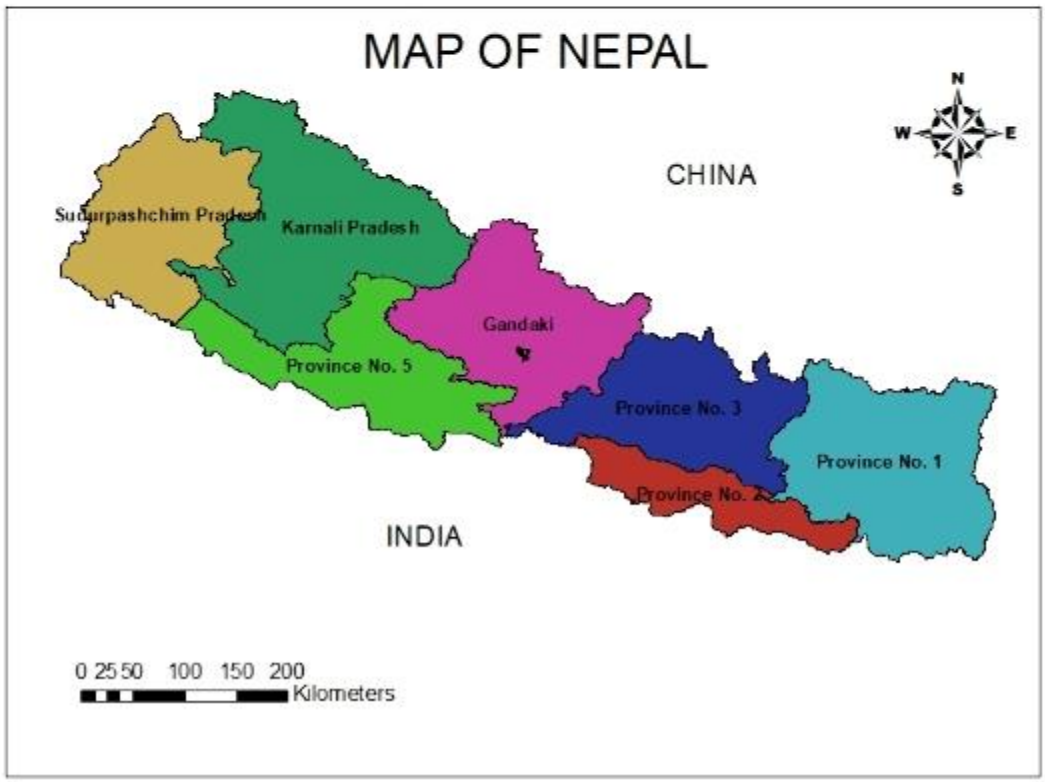
Introduction: Cervical cancer is the major cause of cancer death among women in Nepal with an estimated 2,942 new cases and 1,928 deaths in 2018 (GLOBOCAN 2018). Screening is one of the most effective tools for early diagnosis and prevention. A single-visit approach with Visual Inspection with Acetic acid (VIA) and cryotherapy is safe, acceptable, feasible and is a potentially efficient method of cervical cancer prevention in low resource settings. Current studies reveal Nepalese women's participation in cervical cancer screening is low. There is a need for appropriate, cost-effective and sustainable interventions increasing VIA screening uptake in Nepal.
Methods: The aim of the study is to evaluate the effect of a community based educational intervention delivered by the Female Community Health Volunteers (FCHVs) to increase cervical cancer screening through home visits. The study is a community-based cluster randomized controlled trial, open-label with two-groups to be implemented in a semi-urban area of Pokhara Metropolitan city (former Lekhnath Municipality) of Nepal. The estimated sample size of the prevalence and intervention study will be 884 and 690, respectively.





Results: Prevalence, knowledge, attitude and cervical cancer screening practices will be measured in the baseline survey. The primary outcome is the increase of women participation in the cervical cancer screening program and the difference in knowledge and awareness level will be measured as secondary

outcomes.
Conclusions: Female Community Health Volunteers (FCHVs) can play a key role in increasing the cervical cancer-screening uptake through a community-based, culturally tailored education intervention in Nepal. It may contribute to the implementation of the National Cervical Cancer Screening and Prevention policy and help reduce cervical cancer mortality in the long term in Nepal.

DURABILITY OF THE NEUTRALIZING ANTIBODY RESPONSE TO VACCINE AND NON-VACCINE HPV TYPES 7 YEARS FOLLOWING IMMUNIZATION WITH EITHER CERVARIX® OR GARDASIL® VACCINE

BASIC RESEARCH / PAPILLOMAVIRUS VACCINES (I.E NEW DEVELOPMENTS)

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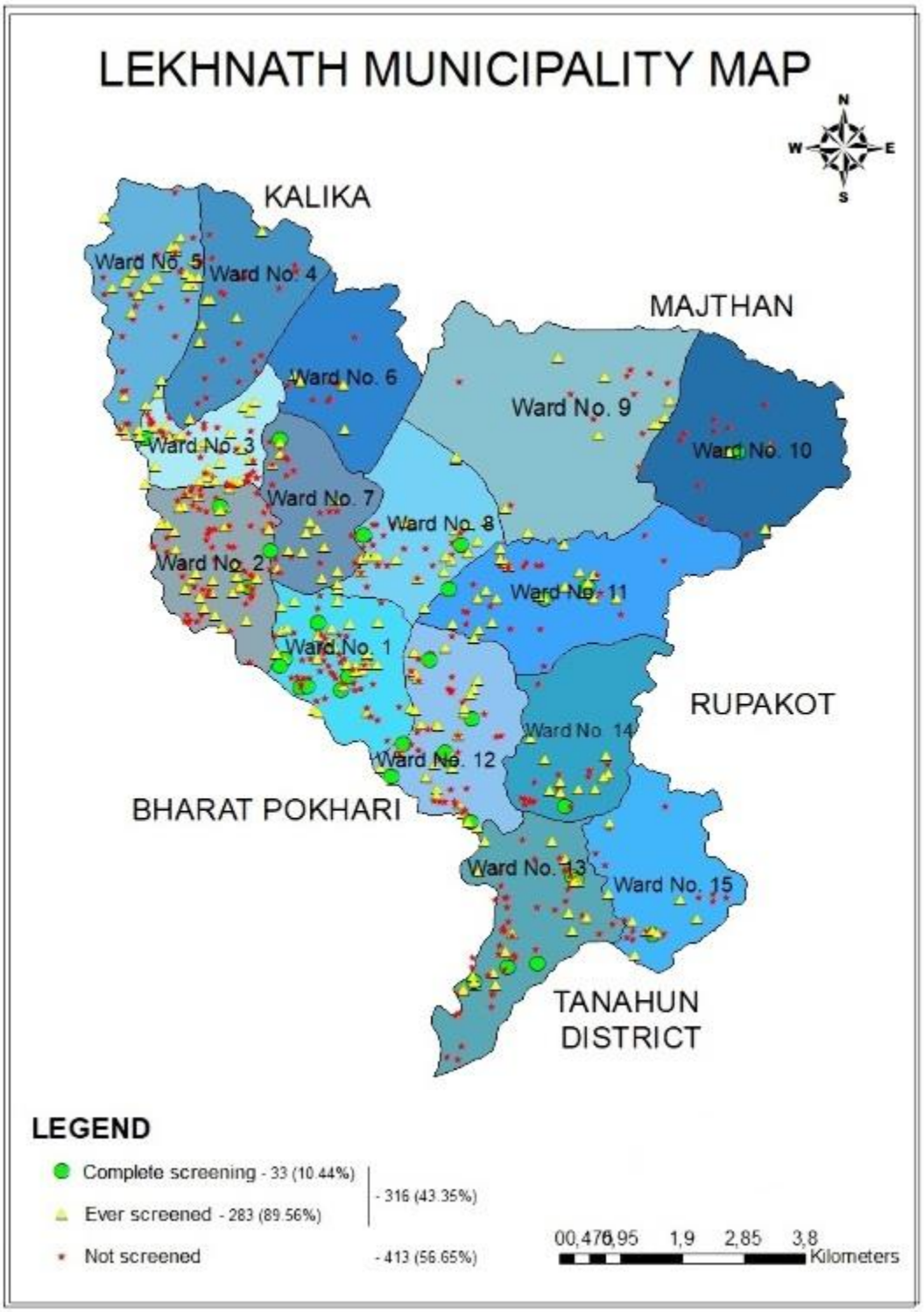
Introduction: Bivalent (Cervarix®) and quadrivalent (Gardasil®) Human Papillomavirus (HPV) vaccines demonstrate remarkable efficacy against the targeted genotypes, HPV16 and HPV18, but also a degree of cross-protection against non-vaccine incorporated genotypes, HPV31 and HPV45. These outcomes seem to be supported by observations that the HPV vaccines induce high titer neutralizing antibodies against vaccine types and lower responses against non-vaccine types. Few data are available on the robustness of the immune response against non-vaccine types.
Methods: We examined the durability of vaccine and non-vaccine antibody responses in a follow up of a head-to-head study of 12-15 year old girls initially randomized to receive three doses of Cervarix® or Gardasil® vaccine.
Results: Neutralizing antibodies against both vaccine and non-vaccine types remained detectable up to 7 years following initial vaccination and a mixed effects model was used to predict the decline in antibody titers over a 15 year period. The decline in vaccine and non-vaccine type neutralizing antibody titers over the study period was estimated to be 30% every 5-7 years, with Cervarix® antibody titers expected to remain 3 – 4 fold higher than Gardasil® antibody titers over the long term. The antibody decline rates in those with an initial response to non-vaccine types were similar to that of vaccine types and are predicted to remain detectable for many years.
Conclusions: Empirical data on the breadth, magnitude, specificity and durability of the immune response elicited by the HPV vaccines contribute to improving the evidence base supporting this important public health intervention. Original trial: ClinicalTrials.gov NCT00956553

BARRIERS, KNOWLEDGE, ATTITUDE, AND PRACTICE ON HUMAN PAPILLOMAVIRUS (HPV) AND CERVICAL CANCER SCREENING AMONG WOMEN IN A SEMI-URBAN AREA OF NEPAL

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

A. Shrestha[1,2], D. Neupane[3], S. Ghimire[4], C. Campbell[5], P. Kallestrup[1]
[1]Aarhus University, Department Of Public Health, Aarhus C, Denmark, [2]Nepal Development Society, Cobin, Pokhara, Nepal, [3]Johns Hopkins Bloomberg University, Department Of Epidemiology, Aarhus C, United States of America, [4]Nepal Cancer Care Foundation, Cancer Screening Program, lalitpur, Nepal, [5]University of Edinburgh, Usher Institute, Edinburgh, United Kingdom

Introduction: Cervical cancer is a major cause of cancer deaths among women in Nepal which is largely preventable. Knowledge, attitude, and practice (KAP) are important elements for designing and monitoring screening programs. This study aims to assess the barriers, knowledge, attitude, and practice of cervical cancer screening among women of age group (30 – 60) years in a semi-urban area of Nepal.
Methods: A population-based cross-sectional survey was conducted including 729 women of 30-60 years from a semi-urban area of Lekhnath Municipality of Nepal, from April to June 2019. We used the validated tools, modified and translated into Nepalese language. Data collection on socio-demography, pregnancy, knowledge, attitude and screening practice regarding cervical cancer was conducted through face-to-face interviews during a door-to-door visit.

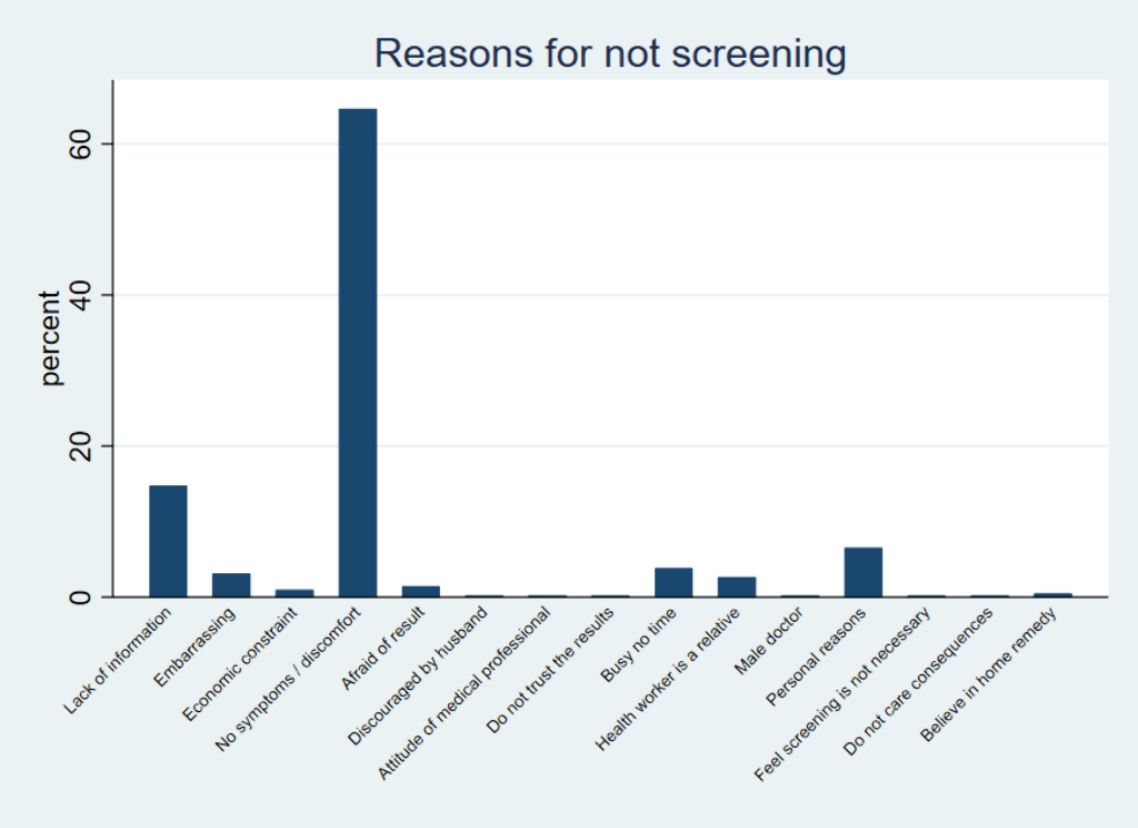


Results: The mean age of the participants was 45.92 ± 7.69 years, they were mostly married (632; 86.69 %). The majority of women have not completed their primary school education (393; 53.92 %). Most of the women's occupation was agriculture (326; 44.72 %) and homemaker (265; 36.35 %). Almost all

women (704; 96.57%) had heard about cervical cancer. Among those who have heard about cervical cancer 181; 25.71 % know about the sign and symptoms, 429; 60.94 % knows about risk factors and the majority of them had heard about cervical cancer screening (399; 54.73). Only 39; 5.54 % of participants answered that cervical cancer means abnormal growth of the cells of the cervix when asked 'What do they mean by cervical cancer?' Furthermore, the majority (694; 98.6% & 672; 95.5%) of the participants have not heard about Human Papilloma Virus (HPV) and its vaccine. Almost half (305; 43.3%) have not heard about cervical cancer screening.

Characteristics	Frequency (%)	Knowledge			Practice		
		OR	(95% CI)	*p*-value	OR	(95% CI)	*p*-value
Age (Years)							
30-34	54 (7.41)	1.00			1.00		
35-39	118 (16.19)	1.34	0.67-2.70	0.406	1.85	0.92-3.71	0.086
40-44	152 (20.85)	1.23	0.63-2.39	0.546	2.53	1.29-4.97	0.007*
45-49	158 (21.67)	1.38	0.71-2.70	0.343	2.81	1.43-5.49	0.003*
50-54	121(16.60)	0.76	0.39-1.49	0.425	2.10	1.05-4.20	0.037*
55-60	126 (17.28)	0.55	0.28-1.07	0.078	1.25	0.62-2.53	0.528
Education							
< Primary	393 (53.91)	1.00			1.00		
Primary	165 (22.63)	2.14	1.44-3.19	0.001*	1.65	1.14-2.38	0.008*
≥ Secondary	171 (23.46)	3.97	2.53-6.24	0.001*	2.08	1.45-3.01	0.001*
Ethnicity							
Non-upper caste‡	336 (46.09)	1.00			1.00		
Upper caste	393 (53.91)	1.66	1.22-2.27	0.001*	1.49	1.11-2.00	0.008*
Current marital status							
Non-married§	97 (13.31)	1.00			1.00		
Married	632 (86.69)	1.88	1.22-2.90	0.004*	1.75	1.11-2.76	0.016*
Household monthly income							
< 25000 NPR or < 220 USD	320 (43.90)	1.00			1.00		
≥ 25000 NPR or ≥ 220 USD	409 (56.10)	1.64	1.20-2.24	0.002*	1.46	1.09-1.97	0.012*

Note: OR: Odds ratio; CI: Confidence interval; *Significantly associated factors $p < 0.05$; ‡Non-upper caste: (Dalit, disadvantaged janajatis and relatively advantaged janajatis); §Non-married: (Unmarried, separated, divorced, widow)



Conclusions: The findings of the study call for exploring barriers to cervical cancer screening uptake, educate and empower women at the community level.

PATTERNS OF HPV CLEARANCE AFTER CONIZATION

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: To assess hrHPV-DNA detection after treatment for High Grade Cervical Lesions (CIN2/3), Adenocarcinoma In Situ (AIS) or microinvasive carcinomas treated with Large Loop Electrosurgical Excision of Transformation Zone (LLETZ).
Methods: 208 patients diagnosed between 2011-2015, with CIN2/3/AIS or IA1 carcinomas were included. Three controls were scheduled after conization with their frequency depending on positive or negative margin. When positive, the first control (co-testing, hrHPVDNA -with Cobas 4800- and cytology) was done at 3 months and if negative at 6 months. If both were negative, second and third controls were performed yearly for 2y and then normal screening. Otherwise, in 6 months, another test was repeated or new treatment was performed. HPV and cytology results were registered and so were biopsies. Cured patient was defined as negative test result. HPV persistence, ASC-US or greater cytology, and biopsy LSIL or more was considered as positive result.
Results: Follow-up ranged from 4 to 96 months, mean 48 months. A mean of 3 controls were done (range 1-9). Average time for first was 7 months, 13 for second and 26 for third. HPV clearance tended to increase with time, from 76% at first, 84% second, 86% third and 90% the last test. Cytology behaved in similar way, ranging from 80-92%. Only 38 biopsies were performed, 50% of them negative. HPV status changed in 47 of 208 patients (23%). From them 31 (15%) had persistent HPV that finally cleared, and 16 (7%) switched to positive after being negative. 7 (3%) patients never cured.
Conclusions: One control is insufficient to determine whether or not a patient is cured. On the other hand, too many test may be confusing for patients and clinicians. Cured status was achieved in 88,9% of patients. A constant switching HPV result suggests that latency can occur in a small group of patients.

MATHEMATICAL MODELLING OF HPV DYNAMICS IN STRATIFIED SQUAMOUS EPITHELIA

BASIC RESEARCH / VIRUS LIFE CYCLE

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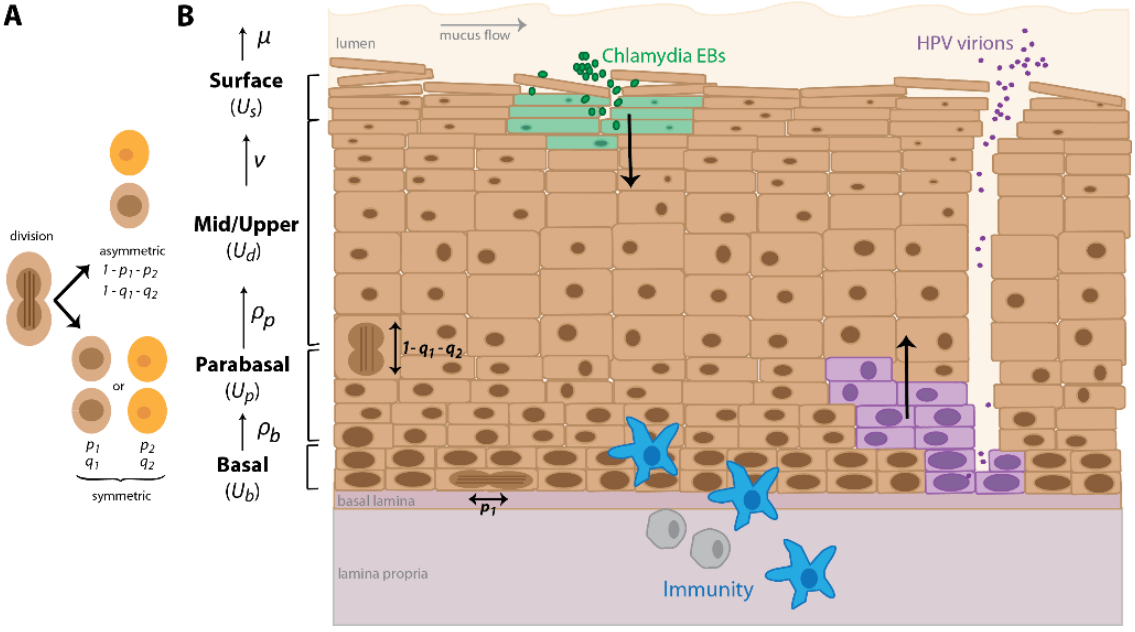
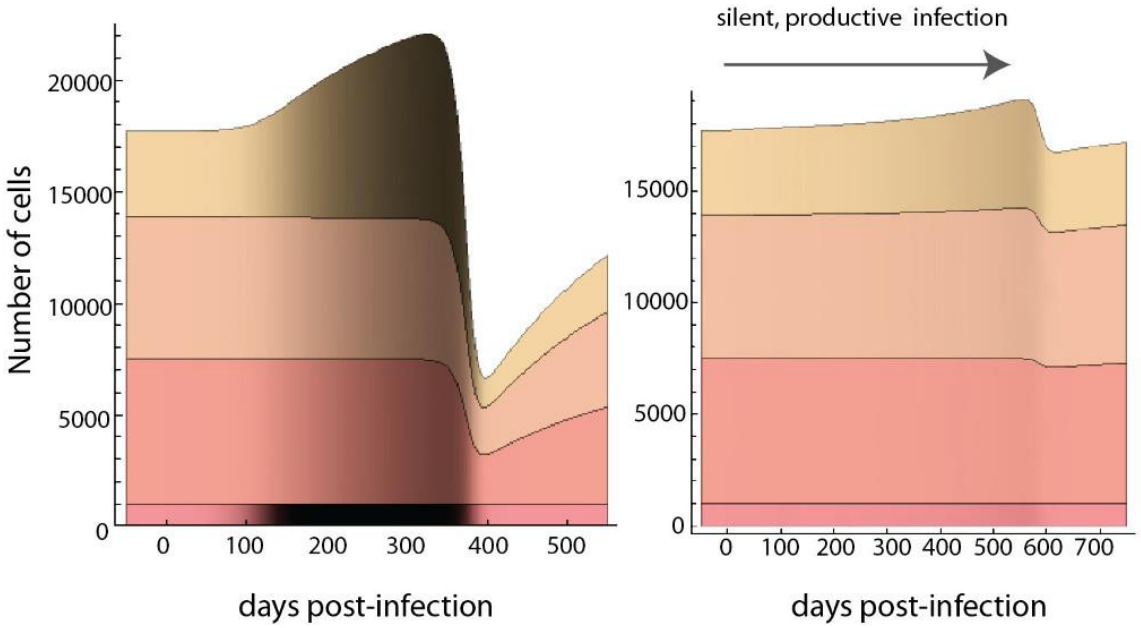
Introduction: Over the last 20 years, mathematical modelling of within-patient temporal virus dynamics, also known as 'viral kinetics', has improved our understanding of infections and the effect of treatments, especially when combined to data. This is the case for HIV and HCV, but few such models currently exist for HPV and, more generally, for non-lytic viruses infecting structured epithelia.
Methods: We developed a model to capture HPV infection dynamics in squamous stratified epithelia using a deterministic approach based on ordinary differential equations. This ecology-inspired model is stage-structured and features several classes of epithelial cells (basal, parabasal and differentiated keratinocytes), as well immune effectors. In order to parameterise the model, we used published estimates from the literature but also performed raft cultures using a spontaneously immortalized human cell line (NIKS cells), which we fitted to infection-free epithelium models to infer realistic parameter ranges.



Results: Our parameterised model reproduces cellular and viral dynamics that are consistent with clinical observations (Figure 1). In particular, we find that key infection symptoms can be explained by differential interactions with the layers, while clearance and pathogen burden appear to be bottom-up processes. Cell protective responses to infections (e.g. mucus trapping) generally lowered virus load. Finally, we show that the most parsimonious way to explain differences between wart-like or lesion-like infection dynamics in the model relies on the 'burst size', i.e. if wart-causing HPVs tend to release more virions.



Conclusions: HPV kinetics can be simulated using simple models with biologically-relevant parameterisation. This mathematical modelling of HPV kinetics opens new perspectives for analysing infections in 3D tissue culture experimental systems and, more generally, for developing and testing hypotheses related to infections of stratified epithelia. Reference Murall CL, Jackson R, Zehbe I, Boulle N, Segondy M, Alizon S (2019) Epithelial stratification shapes infection dynamics. *PLoS Comput Biol* 15(1):e1006646. https://doi.org/10.1371/journal.pcbi.1006646

EVALUATION OF NANOSTRING TECHNOLOGY FOR HUMAN PAPILLOMAVIRUS DETECTION AND TYPING

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Introduction: High throughput HPV typing assays with increased automation, faster turnaround and digital readout are needed to facilitate studies monitoring the impact of HPV vaccination. We evaluated NanoString technology (Seattle WA) adapted for detection of DNA as a platform for digital readout of 48 HPV types in a single reaction.
Methods: Methods: NanoString used proprietary software to design code sets: type specific probe pairs targeting the L1 region of 48 HPV types and human globin gene. We tested residual DNA extracts from epidemiologic specimens (n=40) and eight defined samples (HPV plasmids at 10 to 104 copies/reaction) directly (no PCR) as well as after L1 consensus PCR (45 or 15 cycles). Assay and interpretation followed NanoString recommendations. We evaluated NanoString results using 2 x 2 comparisons with prior typing results (Linear Array, Roche, Indianapolis IN).
Results: Results: NanoString results on samples tested without amplification showed good type-specific agreement with LA (k=0.621) but lower sensitivity (65%) and 104 copies limit of plasmid detection. NanoString results on amplicons from 45 cycles showed almost-perfect type-specific agreement with LA (k=0.862), 82% sensitivity and 10 copies of plasmids were detected. NanoString results on amplicons from 15 cycles showed substantial type-specific agreement with LA (K=0.796), 92% sensitivity, and 10 copies of plasmids were also detected.
Conclusions: Conclusions: This proof-of-principle study demonstrates the potential of using the NanoString platform for highly multiplexed, high throughput detection and typing of HPV with a low number of PCR cycles. This could improve the quality and reliability of data management, and has the potential to reduce the cost of HPV surveillance. Additional studies are in progress to evaluate assay reproducibility and validation with large sample size.

ANALYZING THE VIRAL PROPERTIES OF HUMAN PAPILLOMAVIRUS 16 IN VACCINATED AND NON-VACCINATED WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: In 2009, a bivalent vaccine targeting oncogenic HPV-16/18 was introduced in the Netherlands. The vaccine proved highly effective (vaccine effectiveness >90%) against persistent HPV-16/18 infections. However, HPV-16 is occasionally detected in vaccinated women and little to nothing is known about the underlying mechanisms. Therefore, our aim is to analyze potential differences in viral properties (i.e. viral load and variants) of HPV-16 isolated from vaccinated and non-vaccinated women.
Methods: We utilized data from the cross-sectional PASSYON study. The study includes STI-clinic visitors, who provide a genital swab and fill in a questionnaire including vaccination status. Self-collected vaginal swabs were tested for presence of HPV-DNA using the SPF10-DEIA-LiPA-25 platform. HPV-16 positive vaginal swabs were further analyzed. Viral load (VL) was quantified with a HPV-16 L1-specific qPCR assay. In addition, a fragment-PCR was designed to amplify HPV-16 in ten overlapping amplicons which were sequenced with next-generation sequencing.
Results: In total, 15 of the 1367 vaccine-eligible vaccinated women and 91 of the 842 vaccine-eligible non-vaccinated women tested positive for HPV-16 and were further analyzed. Currently, HPV-16 VL has been successfully determined in 13 vaccinated and 50 non-vaccinated women. Median VL was significantly lower in vaccinated compared to non-vaccinated women (0.064 vs. 0.77 copies/cell, respectively; p-value < 0.05). Nine out of 15 and nine out of 91 HPV-16 positive samples from vaccinated and non-vaccinated women respectively, were successfully sequenced on whole-genome basis. Maximum-parsimony analyses showed a high degree of HPV-16 host-unique sequences with a similar clustering-pattern, independent of vaccination-status.
Conclusions: The HPV-16 viral load is reduced in vaccinated women, thereby aiding in the prevention of persistent infection and cancer risk. HPV-16 shows high sequence diversity among vaccinated and non-vaccinated women. On the contrary, phylogenetic analyses showed no differences in HPV-16 clustering pattern.

A NONINVASIVE CLINICAL INTERVENTION OF REBACIN® FOR HIGH-RISK HUMAN PAPILLOMAVIRUS PERSISTENT INFECTION

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: Objectives: Evaluate clinical effect of REBACIN® in the treatment of hrHPV persistent infection and cervical lesions.
Methods: 92 hrHPV-positive volunteer patients (infected more than 12 months) with or without cervical lesions were enrolled and randomly divided into a REBACIN® group, an interferon group and a no-treatment control group. Participants in REBACIN® group (32 cases) and interferon group (30 cases) received vaginal administration for 3 months while no treatment in control group (30 cases). HPV test and liquid-based cytology were performed for all patients at 1-, 4-, 8-, and 12-month after drug withdrawal. If necessary, colposcopy and histopathology were also performed. HPV clearance, TCT, colposcopy and histopathological changes were compared between the two groups. Removal of all hrHPV types were considered as hrHPV negative. The transformation from CINI to normal cells or chronic cervicitis was considered as CINI regression.
Results: HPV negative conversion rates in REBACIN® group were 71.88% (23/32), 75.00% (24/32), 81.25% (26/32), and 90.63% (29/32) at 1-, 4-, 8-, and 12-month after drug withdrawal respectively, interferon group were 20.00%(6/30), 33.33%（10/30）, 53.33%（16/30）, and 63.33%（19/30） respectively, while they were 13.33% (4/30), 23.33% (7/30), 43.33% (13/30), and 46.67% (14/30) in blank control group. The negative conversion rate and effective rate of HPV infection in the REBACIN® group were significantly higher than those in the other groups at each time point, and the difference in the negative conversion rate was statistically significant ($P < 0.05$). Moreover, CIN1regression rate was 81.82% (9/11) in REBACIN® group, while it was 28.57% (2/7) the blank control group.
Conclusions: As a new type of anti-HPV drug, REBACIN® has a significant clearance effect on high-risk HPV infection, especially in the early stage of treatment, which is more different from that of other groups. At the same time, it has regression effect on CINI caused by high risk HPV infection.

BIASED HUMAN PAPILLOMAVIRUS GENOTYPING IN TISSUE-BASED STUDIES WITHOUT REGARD TO THE MOST SEVERE HISTOLOGY DIAGNOSIS AT INDIVIDUAL LEVEL

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Accurate human papillomavirus(HPV) genotyping within cervical tissues is important to inform prophylactic vaccines and cervical cancer screening strategies. We aim to explore the impact of the most severe histology diagnosis at individual level to tissue-based HPV genotyping in cervical intraepithelial neoplasia(CIN) to avoid bias.
Methods: We collected cervical tissues in 113 Chinese women referred for loop electrosurgical excision procedure (LEEP). LEEP specimens were divided into 12 clock-position segments for pathological diagnosis and genotyping. Tissue diagnosis was defined as the histology diagnosis of every single segment. Source-case diagnosis was defined as the most severe diagnosis among 12 segments. All segments were divided into 6 disease categories: CIN1-CIN1, CIN1-CIN2, CIN1-CIN3, CIN2-CIN2, CIN2-CIN3 and CIN3-CIN3 according to tissue diagnosis(the former part in category name) and source-case diagnosis(the latter part in category name) (Table 1). We further explored HPV type-distribution difference with a tissue-segment based approach(analyzing all tissue segments, regardless of source-case diagnosis) and a source-case based approach(selecting tissue segment with the most severe diagnosis at individual level).

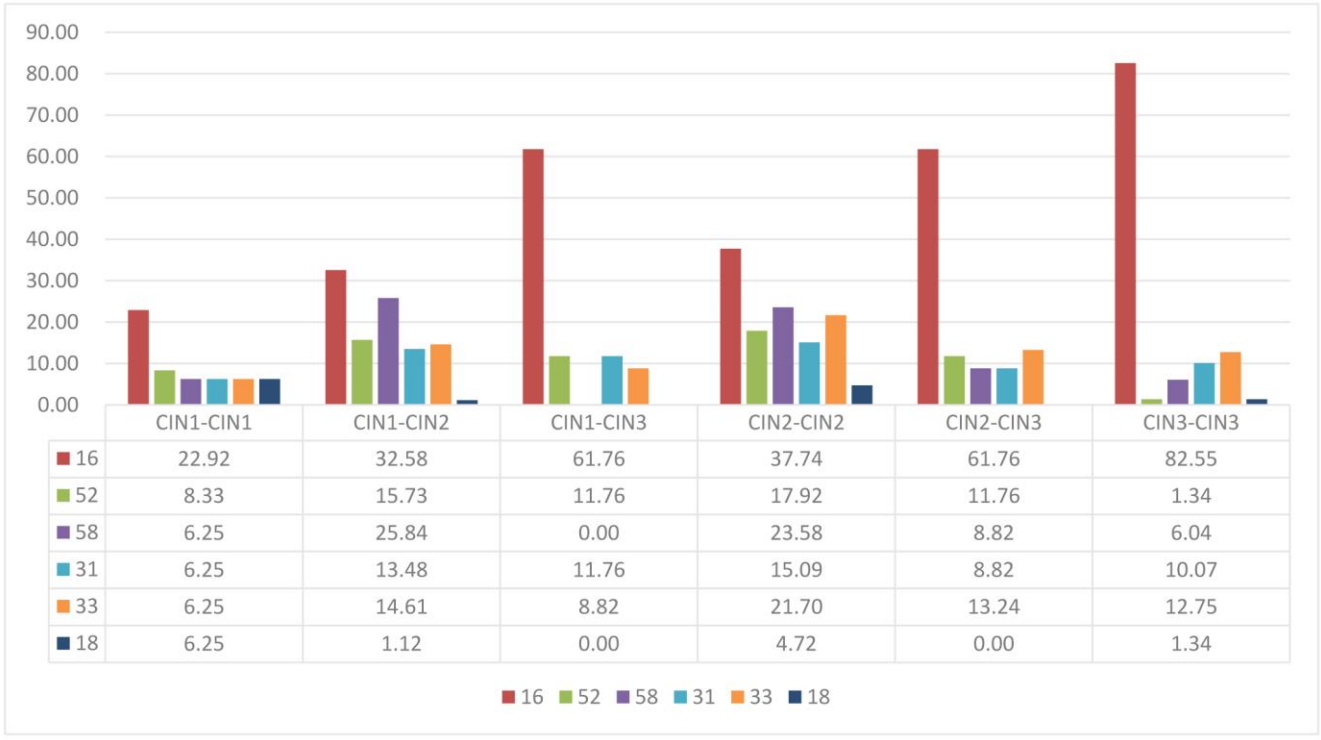
Table 1. Category options in combination of histology diagnosis at both Tissue level and individual level

Category number	Category name	Tissue Diagnosis	Source case diagnosis
1	CIN1-CIN1	CIN1	CIN1
2	CIN1-CIN2	CIN1	CIN2
3	CIN1-CIN3	CIN1	CIN3
4	CIN2-CIN2	CIN2	CIN2
5	CIN2-CIN3	CIN2	CIN3
6	CIN3-CIN3	CIN3	CIN3

*CIN: Cervical intraepithelial neoplasia

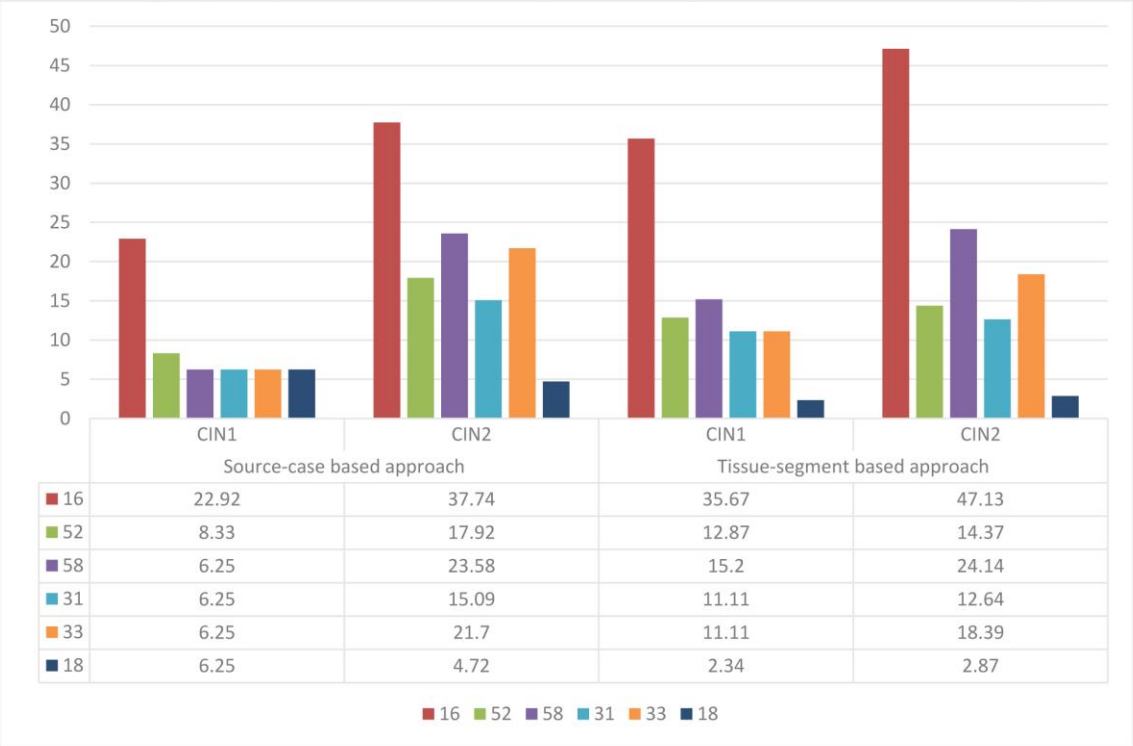
Results: A total of 494 tissue segments were included in final analysis. HPV16 was the most frequent genotype among all 6 categories. Compared with category CIN1-CIN1, the relative prevalence of HPV16 was 2.69(95%CI:1.50, 4.82) in category CIN1-CIN3, 2.70(1.55, 4.68) in category CIN2-CIN3 and 3.60(2.13, 6.08) in category CIN3-CIN3. Prevalence of type-specific HPV was quite similar between category CIN1-CIN2 and category CIN2-CIN2 but generally higher than that in category CIN1-CIN1 (Figure 1). Compared with a source-case based approach, tissue-segment based approach overestimated HPV 16 prevalence and single-type proportions in both CIN1 and CIN2(Figure 2).

Figure 1. HPV type-specific prevalence in 6 categories



	CIN1-CIN1	CIN1-CIN2	CIN1-CIN3	CIN2-CIN2	CIN2-CIN3	CIN3-CIN3
16	22.92	32.58	61.76	37.74	61.76	82.55
52	8.33	15.73	11.76	17.92	11.76	1.34
58	6.25	25.84	0.00	23.58	8.82	6.04
31	6.25	13.48	11.76	15.09	8.82	10.07
33	6.25	14.61	8.82	21.70	13.24	12.75
18	6.25	1.12	0.00	4.72	0.00	1.34

Figure 2. HPV type-specific prevalence using tissue-segment based approach and source-case based approach



	Source-case based approach		Tissue-segment based approach	
	CIN1	CIN2	CIN1	CIN2
16	22.92	37.74	35.67	47.13
52	8.33	17.92	12.87	14.37
58	6.25	23.58	15.2	24.14
31	6.25	15.09	11.11	12.64
33	6.25	21.7	11.11	18.39
18	6.25	4.72	2.34	2.87

Conclusions: HPV type-specific prevalence was biased if analyzing all tissue segments, without regard to the most severe histology diagnosis at individual level. Genotyping using tissue segments with the most severe diagnosis are suggested in genotyping-attributable and biomarker expression studies to avoid bias.

EXTENDED GENOTYPING OF HIGH RISK HPV AS A METHOD IN RISK ASSESSMENT OF CERVICAL CANCER

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: There is growing interest in methods of triaging HPV-positive women in terms of risk. Extended genotyping is one of the methods of assessment of an increased risk of developing cervical carcinoma. This study aims to assess in a private practice scenario the validity of utilising extended genotyping as a method of choice.
Methods: We undertook an investigation of HPV genotype prevalence within specific subsets of cervical cancer screening patients within South Africa. There were three patient cohort arms included in this study: (i) high-risk HPV positive (non-16/18) patients; (ii) high-grade cytology cases; and (iii) invasive cervical cancer. All specimen were collected in BD SurePath vials and HPV genotyping analysis was conducted using the BD Onclarity HPV Assay. All biopsy specimens were analysed from FFPET.
Results: The first arm involved triage of Roche cobas “other 12” positive cases irrespective of the Pap test results. Preliminary data from the Roche cobas “other 12” positive cases (N=113) were generated by genotype analysis using the Onclarity HPV assay. Surprisingly, approximately one-third of the Roche cobas cases were negative to high-risk HPV genotypes using the Onclarity assay. Of the remaining positive cases (N=75): 56/59/66 (32%); 35/39/68 (24%); 31 (18%); 52 (16%); 33/58 (16%); 45 (11%); and 51 (9%). The second arm is investigating extended genotyping on HSIL, ASC-H, AGC and malignant pap tests. The third arm includes biopsy specimens of cervical malignancies to establish the prevalence of high risk HPV genotypes.. Additional data will be presented on the prevalence of HPV genotypes within these different categories.
Conclusions: Emerging clinical evidence in the peer-reviewed literature has identified HPV extended genotyping as a potential triage method for high-risk HPV positive patients and atypical cytology cases. We have undertaken a systematic investigation of extended HPV genotyping as a triage tool applicable to the South African cervical cancer screening.

LOCAL IMMUNITY IN HPV GENITAL INFECTIONS IN YOUNG WOMEN

BASIC RESEARCH / IMMUNOLOGY

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Introduction: The vast majority of HPV infections in young adults clears naturally within three years but we still have a limited mechanistic understanding of the process. Some studies have described immunological profiles in the cervico-vaginal environment but few are in the context of HPV infections and even fewer follow longitudinal variations.
Methods: The PAPCLEAR study follows longitudinally 150 young women from 18 to 25 every two or four months depending on their HPV status. At each visit, a gynaecological exam is carried out and samples are collected to detect and type potential HPVs, measure systemic HPV antibodies, local virus load, cytokine production and immune cell response. For the latter, we set-up a 10-color panel for flow cytometry including markers for classical T lymphocytes and for TCR-γδ, MAIT cells and NK cells. For cytokine profiling in cervical secretions, we investigate a panel of 20 analytes using MesoScale Discovery technology. Given the size and the dimensionality of the dataset, we combine manual and computational approaches for data analysis. For flow cytometry data, we first perform manual gating using the FlowJo software and then follow an automated analysis using the OpenCyto R-package.
Results: Using a model selection approach for multi-factor linear models, we identify statistically significant changes in cytokine concentrations (e.g. IFN-α2a, IL-1α) depending on the infection status at the first visit. Further analysis of cytokine correlation networks identify IL-15 as a key player associated with HPV infection. For the flow cytometry data, data has been collected for all 150 participants for multiple visits and analyses are ongoing.
Conclusions: This work addresses technical and computational challenges regarding multi-parametric flow cytometry data collection and analysis, and cytokine profiling in exfoliated cervical cells. It contributes to increasing our knowledge about the immune response in the female genital tract and its interaction with HPV infection as well as other factors (e.g. microbiota, vaccination).

IMPLEMENTATION OF HPV DNA TEST AS AN ALTERNATIVE TO CYTOLOGY ONLY METHOD IN AN OPPORTUNISTIC NATIONAL CERVICAL CANCER SCREENING PROGRAM.

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: HPV DNA test is superior in sensitivity detecting precancerous cervical lesions compared to cytology only method in primary cervical cancer screening. HPV DNA test was introduced as an alternative to national cytology only method, in a tertiary hospital in Singapore. Cervical cancer remains one of the top ten most common cancer in Singapore despite having a national cervical cancer screening program. The aim was to increase detection of precancerous lesion leading to establishing local data to aid national policies in future.
Methods: The Kotter's change method was adopted for the project and divided into 3 main categories. 1. Creating climate for change, 2. Engaging/enabling the organization and 3. Implementing/sustaining change. HPV test were offered to women between ages of 30 to 69 years old. Cotesting was initially implemented. HPV primary screening (partial genotyping with cytology triage for HPV non16/18 positive)were introduced in September 2016 following audit findings. Implementation findings were presented to the Ministry of Health leading to update of the national cervical screening guideline (May 2019).
Results: A total of 1678 HPV DNA tests were performed (February 2015 to December 2017). Majority (93%) were primary screening; cotesting (48.7%) and HPV primary screening (44.3%). Majority (78.4%) had negative HPV result. Positive HPV result included HPV 16 (3.7%), HPV 18 (1.3%), HPV non16/18 (16.1%) and HPV16/HPV18 (0.1%). Indeterminate result were seen in 0.3% of the cohort. A 37% increase in histological diagnosis of CIN2+ were seen. Grade 1 colposcopy findings with CIN2+ histology (18% in HPV 16 and 4% in HPV non 16/18 positive) plays some part in the increment.
Conclusions: Scientific evidence alone is not enough to ensure compliance and success to implementation of HPV primary screening without clear goals and careful implementation strategy. Changes in colposcopy practice will need to be seriously acknowledged in the light of current findings following implementation.

READINESS OF HEALTHCARE PROVIDERS TO IMPLEMENT HPV TESTING IN PRIMARY SCREENING FOR CERVICAL CANCER: A REVIEW AND SYNTHESIS OF PSYCHOSOCIAL DETERMINANTS OF HPV TESTING ACCEPTABILITY

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Guidelines for primary cervical cancer screening are evolving rapidly to include HPV DNA testing, which is a more sensitive test than cytology (Pap) in detecting cervical intraepithelial neoplasias (CINs). Many professional and public health organisations worldwide have endorsed these new recommendations. However, healthcare providers (HCPs) practice changes have been slow. To better understand this barrier, we conducted a comprehensive review and synthesis of the literature regarding HCPs' knowledge, attitudes and practices related to HPV testing and the influence of psychosocial factors on HCPs acceptability of HPV testing in primary cervical cancer screening.
Methods: Eligible journal articles published from January 1, 1980 to July 25, 2018 were identified in Medline, Embase, PsycINFO, CINAHL, Global Health, and Web of Science. We present a narrative synthesis of HCPs' knowledge, attitudes and practices related to HPV testing. The influences of psychosocial factors on HCPs' HPV testing acceptability were synthesized using the Patient Pathway framework.
Results: Barriers and facilitators of HCPs' acceptability of HPV testing were grouped into: 1) HCP-specific, 2) patient-specific, 3) related to HCP's practice environment, and 4) healthcare system dependent. Important HCP knowledge gaps remain in understanding the higher sensitivity of the HPV test to detect CIN, and new age-specific guidelines for HPV testing. Many HCPs (35%) report negative attitudes in that they consider current guidelines unreliable and inconsistent in their current environment.
Conclusions: Adherence of HCPs to guidelines including HPV testing for primary cervical cancer screening is sub-optimal and compounded by gaps in HPV test knowledge and inconsistencies across guidelines. Screening at shorter intervals than recommended by new, age-specific guidelines continues to be a widespread practice. Multi-level interventions are needed targeting HCPs, practice environments, and patient-specific barriers to HPV testing. Implementing organized HPV-based screening programmes and use of self-collected cervical samples should decrease the cervical cancer health burden over time.

CORRELATES OF HPV VACCINE UPTAKE AMONG GAY, BISEXUAL, AND OTHER MEN WHO HAVE SEX WITH MEN IN ONTARIO, CANADA: RESULTS FROM THE #ICRUISE STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Gay, bisexual, and other men who have sex with men (gbMSM) are at higher risk for HPV-related diseases, particularly anal cancer. In September 2016, the province of Ontario, Canada, began offering free HPV vaccine to young gbMSM aged up to 26 years.
Methods: #iCruise is an Ontario-wide study of gbMSM seeking sexual health information online. Men were recruited through websites and mobile socio-sexual apps from 07/2017-01/2018. At baseline, a questionnaire assessed experience with the HPV vaccine. We used multivariable Poisson regression to explore independent correlates of vaccine uptake (1+ dose) according to demographic characteristics and healthcare engagement. Results are reported as adjusted prevalence ratios (aPR) with 95% confidence intervals.
Results: Among 865 participants aged 14-89 years, 34.7% were aged ≤26. Receipt of at least 1 dose of HPV vaccine was reported by 18.3% (≤26:25.3% versus >26:14.5%; p<0.001). Uptake was higher among all men who reported looking for sexual health information online in the last 3 months (21.3%), particularly in younger men (≤26:28.4%) compared to older men (>26:17.4%, p=0.002). Independent correlates of vaccine uptake were being aged ≤26 years (aPR=2.22;1.69-2.9), identifying as gay (aPR=2.06;1.11-3.82), having disclosed one's sexual orientation to a doctor/nurse (aPR=2.45;1.65-3.64); and looking for sexual health information online in the last 3 months (aPR=1.65;1.15-2.36). Vaccination status was not associated with ethnicity, citizenship, education, income, employment, or recent HIV testing. Vaccination correlates were similar among men age-eligible for free vaccine (aged ≤26) compared to ineligible men aged >26.
Conclusions: Access to welcoming healthcare is a key barrier to overcome, given that one of the strongest correlates of vaccine uptake was having disclosed one's sexual orientation to a doctor/nurse. Additionally, age-eligibility for free vaccine under the public program suggests that cost is another crucial barrier. Online environments are promising venues to promote HPV vaccine to this population.

INVESTIGATION OF TEMPERATURE AND TIME STABILITY OF SELF-COLLECTING SAMPLES

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: In our previous research, Japanese women's acceptance of self-collecting HPV tests was positive and they preferred them much greater than the conventional cytology. Due to global warming, summer temperatures in Japan often soar to over 35 degrees Celsius and have reached 40 degrees in some parts recently. As a result, public mailbox temperature in some towns has reached around 50 degrees Celsius in summer. We need to ensure whether the high temperature negatively affects self-collection samples or not, as the samples are sent to the testing laboratory through the postal service and samples could be exposed to sweltering environments. We wish to investigate if the self-collecting HPV test sample using Evalyn Brush is stable in a high temperature environment. If we can precisely measure the maximum high temperature the sample can sustain, the results are most certainly relevant and useful in other parts of Asia.
Methods: We receive 2 samples from the same participant via physicians using Evalyn Brush. One sample is tested as a normal test and another one is kept in 4 conditions and tested as an experimentally high temperature environmental test; The first in 50 degrees Celsius for 2 weeks; The second in the same temperature for 4 weeks; The third in 30 degrees Celsius for 2 weeks; And the fourth in the same temperature for 4 weeks. We then compare the results of the samples from the same participant and confirm if there is a disparity.
Results: We investigated 66 pairs of samples in total including 23 pairs kept in 50 degrees Celsius for 4 weeks, and 24 pairs at 50 degrees Celsius for 2 weeks. We will report the entire results at the IPV 2020 conference.
Conclusions: After being kept in 50 degrees Celsius for 4 weeks, almost all of the samples tested properly.

EXPLORING THE USE OF A CANCER REGISTRY AND LARGE POPULATION SCREENING PROGRAM DATA LINKAGE TO MONITOR HPV TESTING AND HPV-RELATED DISEASE

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Cervical cancer and other HPV-related diseases continue to disproportionately burden disadvantaged populations in the United States (US) despite recommendations for routine screening and HPV vaccination. This study examines statewide cervical cancer disparities among underserved women in New Jersey, one of the most densely populated and geographically diverse states in the US.
Methods: Using data from the New Jersey State Cancer Registry (NJSCR) and New Jersey Cancer Education and Early Detection (NJCEED) program, we established a NJSCR-NJCEED linkage of invasive cervical cancer cases diagnosed between 2000 and 2014. We compared tumor characteristics of cervical cancer cases linked from the NJCEED screening program with other cervical cancer cases during the same time period. We then conducted an exploratory study to assess the feasibility of obtaining HPV-specific data from NJSCR records.
Results: Among the 4,835 invasive cervical cancers cases in NJSCR, 312 women were screened through NJCEED (linked cases). A higher proportion of NJSCR-NJCEED linked cases were Hispanic (41%) compared to non-linked cases (18%) ($p<0.001$). HPV testing data from NJSCR records were explored for 160 of the 312 cases. Of these, 86% had no documentation of prior HPV testing, 5% had HPV-testing related abstracted text, and 9% had HPV testing related pathology reports. We were unable to explore differences by sociodemographic or tumor characteristics given the few cases with HPV testing information.
Conclusions: We established a large population-level data linkage to characterize cervical cancer screening and follow-up care among underserved women statewide. Availability of HPV testing-related data within our state cancer registry was limited. Future efforts to monitor HPV testing and obtain HPV-specific data among populations screened for HPV-associated cancers are needed.

DIGITAL INTERVENTIONS TO IMPROVE HPV VACCINE UPTAKE: RECENT TRIAL RESULTS

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: The U.S. uptake of HPV vaccine remains substantially below the Healthy People 2020 goal of 80% series completion, particularly for young adolescents, when immunogenic response to the vaccine is strongest. Physician and clinic-based interventions have shown some limited positive effect on vaccine uptake. However, parental barriers to HPV vaccination (e.g., confusion, uncertainty, and misinformation about HPV vaccine schedule, safety, and effectiveness) may be addressed by digital interventions (i.e., smartphone applications) that are tailored to their concerns. Diffusion of Innovations Theory principles were used to guide mobile app development in English and Spanish (*Vacteens/VacunaAdolescente.org*) to encourage HPV vaccination in New Mexico, an ethnically-diverse U.S. state with insufficient vaccine uptake.
Methods: Parents and adolescents were recruited from pediatric clinics in New Mexico to a randomized trial evaluating the mobile web app, focused on daughters (ages 11-14). Parents were randomized to receive either the *Vacteens/VacunaAdolescente* mobile web app or the Usual and Customary CDC HPV vaccination pamphlet online. Adolescent vaccine records were collected for daughters at a 9-month assessment point.
Results: Vaccine uptake results from the trial found that parents who received the *Vacteens/VacunaAdolescente* web app were significantly more likely to have their daughters vaccinated, having a 2.5 times greater odds of obtaining the first dose *(Pearsons Chi Square=6.45, p=.01, OR=2.85)* and of completing the multi-dose vaccination series (*Pearsons Chi Square=7.54, p=.006, OR=2.60).*
Conclusions: Digital information delivered to parents in a community setting may be an effective way to reach HPV vaccine uptake goals in the United States. An ongoing trial with parents and sons will provide further evidence on whether a mobile web app, widely available on popular mobile digital platforms, can improve HPV vaccine uptake.

GAY AND BISEXUAL MEN IN THE U.S. LACK BASIC INFORMATION ABOUT ANAL CANCER

PUBLIC HEALTH / EPIDEMIOLOGY / DISSEMINATION/COMMUNICATION RESEARCH

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Introduction: Gay and bisexual men (GBM) are disproportionally affected by high-risk anal HPV infection and the subsequent development of anal cancer. Widespread awareness and knowledge of HPV and anal cancer among GBM is important to the success of targeted HPV vaccination and anal cancer screening. The purpose of this study is to provide population-based estimates of HPV awareness and knowledge in GBM and identify differences across demographic subgroups.

Methods: Data were pooled from three cycles of the Health Information National Trends Survey (2017, 2018, 2019). Results are reported for the subset of adults (≥18 years) who identified as GBM (N=226). Awareness was assessed as ever having heard of HPV and knowledge was assessed as knowing that HPV can cause anal cancer. Knowledge was assessed only among respondents who were previously aware of HPV. Differences in awareness and knowledge were evaluated (chi-square and multiple logistic regression) by age, race/ethnicity, education, marital status, and sexual identity.
Results: Awareness of HPV and knowledge of anal cancer were stable over the survey years (75.3% and 38.8% pooled awareness and knowledge, respectively). Awareness was significantly lower among GBM with a high school education or less (44.4%), and among those who were single/never married (71.1%) or divorced/widowed (67.7%). These differences were statistically significant after adjusting for other covariates. Of the 165 GBM who had previously heard of HPV, a larger percentage of gay (44.2%) compared to bisexual (24.4%) men new HPV could cause anal cancer. This difference remained significant after adjusting for other covariates.
Conclusions: GBM in this study were largely aware of HPV, but did not know HPV can cause anal cancer. This was consistent across age groups and other demographic factors. Low anal cancer knowledge limits informed decision making about HPV vaccination and anal cancer screening among this at-risk population.

SEXUALLY TRANSMITTED INFECTIONS AND HPV CO-INFECTION AMONG HIV-INFECTED AND HIV-UNINFECTED FEMALE SEX WORKERS FROM MUMBAI, INDIA

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: This study estimated the prevalence of bacterial and viral sexually transmitted infections (STIs) and high-risk HPV co-infection among HIV-infected and HIV-uninfected female sex workers (FSW) receiving care at a women's health clinic in Mumbai, India.
Methods: A convenient sample of 347 consecutive HIV-infected (N=122) and HIV-uninfected (n=225) FSWs, 18 years and older were enrolled in a cross-sectional study. Participants were clinically evaluated using blood, vaginal and endocervical swabs for eight STIs: high-risk HPV (HR-HPV), HCV, HSV-2, HBV, syphilis, chlamydia, gonorrhea and trichomonas. HPV/STI co-infection patterns were assessed among HIV-infected and uninfected FSWs using Pearson's Chi Square.
Results: Median age of FSWs was 35 (range: 20-60) years; 72% (248/347) of participants had no education; 31% (108/347) reported a stable partner. Approximately 31.5% (106/247) reported excessive vaginal discharge. Overall, irrespective of HIV status, 44.4%, (154/347) of FSWs were infected with at least one STI; 2.6% (9/347) were infected with 2 STIs, and one woman had 3 STIs. HR-HPV infection had the highest prevalence (40%) followed by syphilis (2.3%, 8/347) and hepatitis B (2.3%); chlamydia, HSV-2 and HCV had a prevalence of <2% with no cases of gonorrhea or trichomoniasis. HR-HPV prevalence was not significantly higher (p=0.09) among HIV-infected FSWs (45%) than HIV-uninfected (37%). Among FSWs harboring HR-HPV, four were co-infected with hepatitis B, two were co-infected with syphilis, two were coinfected with HSV-2 and one was co-infected with chlamydia. Of these nine HR-HPV/STI co-infected women, six were HIV-infected.
Conclusions: Although bacterial STI prevalence was low in this population, possibly due to syndromic STI management, high-risk HPV prevalence was elevated among both HIV-infected and uninfected FSWs. Integrating regular cervical screening with STI screening is essential irrespective of HIV status for early detection and treatment of cervical disease in this high-risk population. Further, HPV-negative FSWs may benefit from HPV vaccination

A POTENT INHIBITOR OF HUMAN PAPILLOMAVIRUS INFECTIONS VIA PHYSICALLY BLOCKING

BASIC RESEARCH / OTHER BASIC RESEARCH

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Introduction: HR-HPV detection has been considered an important tool for cervical cancer screening around the world. However, therapy strategies to eliminate HPV are still very limited so far. The current study was designed to assess a potent inhibitor of HPV infection, named H protein, using an in vitro pseudovirion assay.
Methods: The H protein was extracted from mushroom and had been chemically modified with relatively increased surface negative charges. HPV6, 16 and 18 pseudoviruses with luciferase reporter plasmid were produced by co-transfected 293FT cells. Fresh 293FT cells were infected with pseudoviruses. Virion infections with or without H protein treatment were determined by luciferase quantification.
Results: Here we found that H protein exhibited highly potent antiviral activity against infection by HPV6, HPV16 and HPV18 (IC50 = 0.25~5 μg/mL). The H protein could strongly bind to the positively charged peptides derived from the L1 and L2 proteins of HPV. Its anti-HPV activity was correlated with the percentage of modified lysine and arginine residues. The negative charges on H protein bind to viral capsids and envelopes, which physically block infection and entry of HPV into cells. Skin allergy test in mice showed no signs of inflammation related to the topical application of H protein.
Conclusions: We demonstrated that H protein is a potent inhibitor of human papillomavirus infections. Our results suggest that H protein has good potential to be developed as an effective and safe antiviral agent for treatment and prevention of HPV infections. Acknowledgements: This work was supported in part by the National Key Research and Development Program of China (No. 2016YFC1302900).

CLINICAL VALIDATION OF A HIGH VOLUME HUMAN PAPILLOMAVIRUS ASSAY WITH EXTENDED VACCINE RELEVANT GENOTYPING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: With a growing number of countries moving to large regional, or national, HPV-based screening programs there is a growing need for high volume (>1000 tests per day) clinically validated HPV assays to support these programs. The introduction of the Gardasil vaccine has also driven interest in understanding the role of HPV31,33,45,52, and 58 in screening programs and pathways.
Methods: The Abbott alinity m HPV assay run on the alinity m instrument was compared to the reference Roche cobas 4800 HPV test using the Meijer Criteria framework to examine sensitivity and specificity for histologically confirmed cervical intraepithelial neoplasia grade two or above (CIN2+). Intra- and Inter-laboratory reproducibility was also examined. The alinity m HPV assay is currently not approved for clinical use but this is expected to change in late 2019. Samples for this study are from the Compass Trial which is a consent-based trial and this current study has ethics approval.
Results: Relative Sensitivity for histologically confirmed CIN2+ is 96.7% (95%CI 88.5-99.6%). Currently (n = 300 of 805 tested to date) relative specificity for CIN2+ is over 99%. Final results, including sensitivity, specificity and inter- and intra-laboratory reproducibility will be presented.
Conclusions: Current data suggests that the Abbott alinity m HPV assay has sensitivity and specificity that is comparable to Roche cobas 4800 HPV reference test with the additional utility of producing a more detailed HPV genotyping profile (HPV16, HPV18, HPV45, HPV31/33/52/58, HPV35/39/51/56/59/66/68) which may be useful in monitoring Gardasil9 vaccine impacts on screening programs.

CLINICAL VALIDATION OF AN EXTENDED GENOTYPING HUMAN PAPILLOMAVIRUS ASSAY USING A VERSATILE, SMALL LABORATORY SYSTEM

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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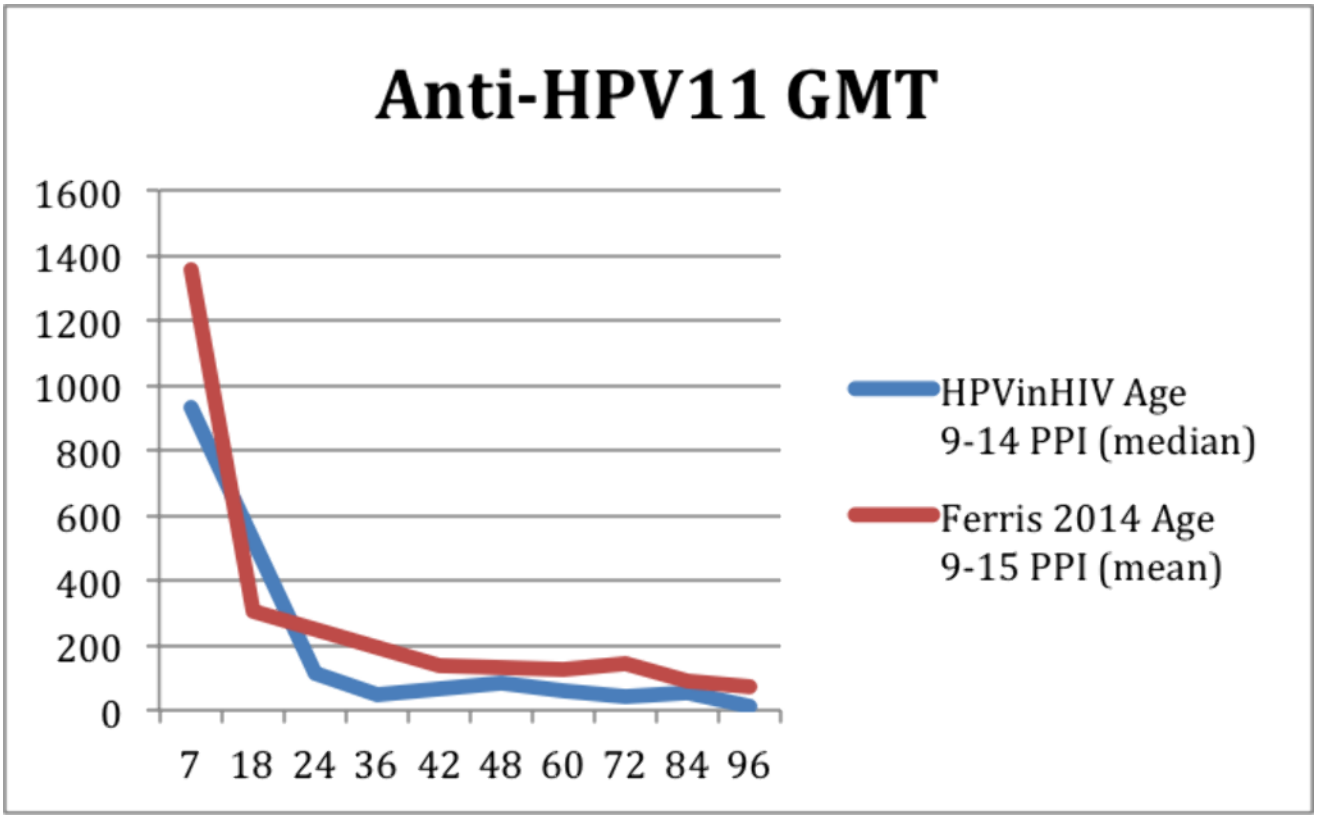
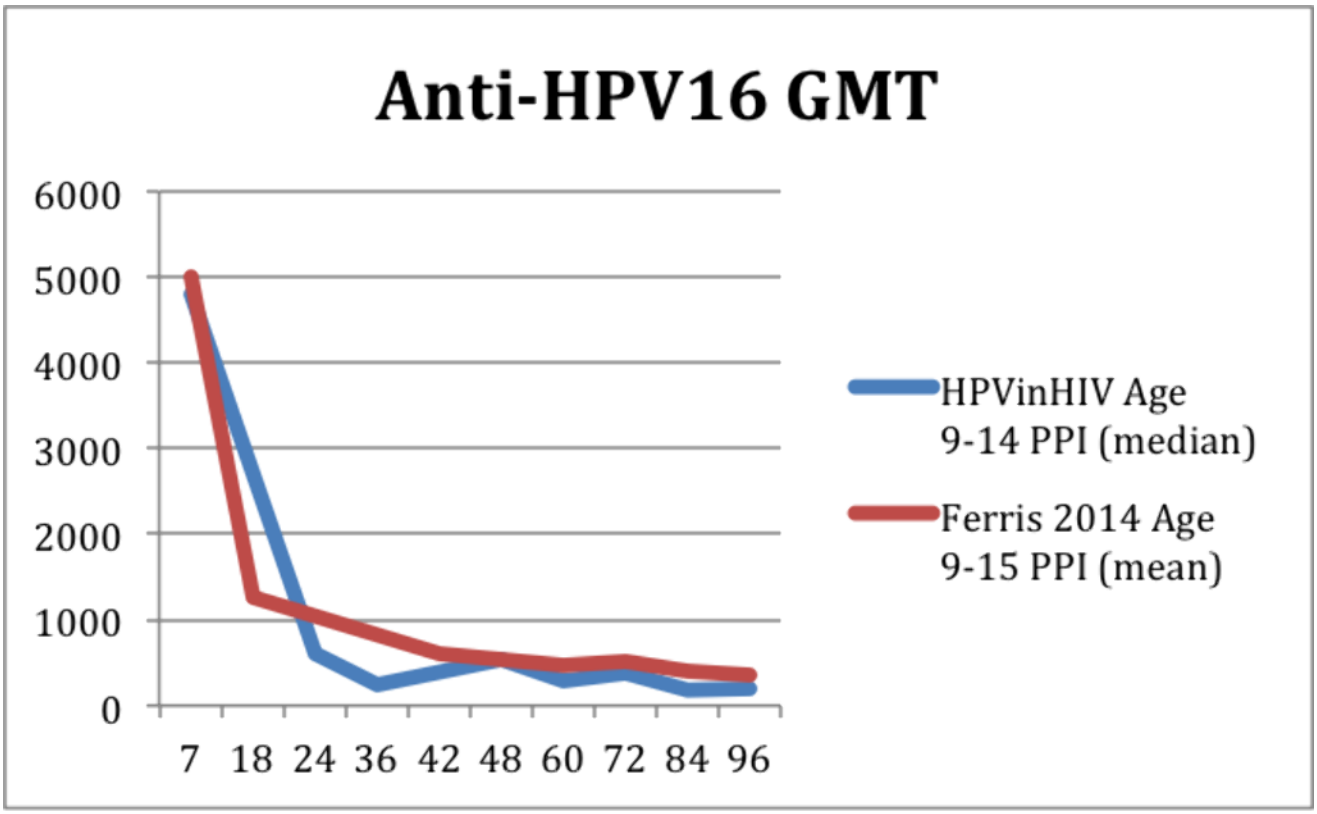
Introduction: Whilst most HPV-based screening programs focus on high volume HPV assays and accompanying instrumentation, there is also emerging interest in HPV assays which can be run on small, flexible platforms on which a wide range of other assays can be utilised. Such systems may have considerable usefulness in low and middle income settings.
Methods: The AusDiagnostics High-Risk HPV panel was compared to the reference Roche cobas 4800 HPV test using the Meijer Criteria framework to examine relative sensitivity and specificity for histologically confirmed cervical intraepithelial neoplasia grade two or above (CIN2+). Intra- and Inter-laboratory reproducibility was also examined. Samples for this study are from the Compass Trial which is a consent-based trial and this current study has ethics approval.
Results: Relative sensitivity for histologically confirmed CIN2+ was 100% (95%CI 94.8-100%). Relative specificity for CIN2+ is 98.9% (95%CI 97.8-99.5%). Intra-laboratory reproducibility had a lower confidence interval of >87% and inter-laboratory data will also be presented.
Conclusions: The AusDiagnostics High-Risk HPV panel is as sensitive and specific as the Roche cobas 4800 HPV reference test. The AusDiagnostics High-Risk HPV panel also presents individual genotyping for the twelve oncogenic HPV types and HPV66 and HPV68a/b.


Anti-HPV11 GMT
1600
1400
1200
1000
800
600
400
200
0
7
18
24
36
42
48
60
72
84
96
HPVinHIV Age 9-14 PPI (median)
Ferris 2014 Age 9-15 PPI (mean)



Conclusions: The reduction in GMTs over time to a level where many girls are no longer seropositive presents concerns for this population of girls, particularly at an age where they require longstanding protection to endure through their lifetime. Assessment of efficacy in this population was not possible at this time due to the relatively young age of participants at time of follow up.

TIME-OF-FLIGHT SECONDARY ION MASS SPECTROMETRY (TOF-SIMS) TISSUE IMAGING USING A MOUSE PAPILLOMAVIRUS MODEL

BASIC RESEARCH / ANIMAL MODELS

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Introduction: We have established a mouse papillomavirus (MmuPV1) model used as a surrogate for biomarker discovery of HPV-associated diseases. Imaging mass spectrometry allows us to examine tissues at the chemical level without labeling. We aimed to compare the peak intensities and spatial distributions of small molecules in virus-induced muzzle lesions and normal muzzle tissues using ToF-SIMS tissue imaging.
Methods: Lesion (n = 3) and normal (n = 3) muzzle tissue sections were collected and thaw-mounted on conductive ITO-coated glass slides. The samples were freeze-dried in a Labconco FreeZone 18L Lyophilizer. ToF-SIMS tissue imaging experiments were performed using a Phi NanoTOF II equipped with a Bi liquid metal ion gun (LMIG) and an electron flood gun for charge neutralization. The LMIG generated a pulsed Bi_3^+ beam impacting the target at an angle of 45° and had a beam spot of 1-2 μm in the high-current bunched mode. 500 μm × 500 μm raster scans with 256 × 256 pixels and 40 frames per scan were analyzed. Negative ion spectra were calibrated. Mass spectra were exported to Matlab for further processing.
Results: 605 mass peaks with a minimum prominence equal to the 50th percentile prominence of the mean normalized ion intensities were identified. Of those, 36 peaks showed a statistically significant difference in intensity between the lesion and normal tissues ($P < 0.01$). The intensity of a peak with m/z of 465.3 identified as cholesterol sulfate in the lesion tissue was 3.5 times of that in normal tissues. Additionally, the ion is primarily located at the top of the epidermis in normal skin tissue, but in the lesion tissue the signal was more intense and accumulated around hair follicles in addition to epidermis.
Conclusions: ToF-SIMS tissue imaging is a promising tool for biomarker discovery of papillomavirus-associated diseases. Cholesterol sulfate may be related to papillomavirus infection.

E7 VARIANTS OF HPV 16 AND ITS ASSOCIATION WITH CERVICAL CANCER AND PRECURSOR LESIONS IN WOMEN OF SOUTHERN MEXICO.

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: The E7 protein is one of the two proteins responsible for maintaining the oncogenicity of HPV16. E7 HPV16 can immortalize epithelial cells and this ability is enhanced by E6 protein. E7 presents genetic hypovariability, however, variants of the oncoprotein has been reported. Some of the variants have been associated with the risk of developing cervical cancer due to the alteration of its oncogenic potential. In Mexico, there are no reports of E7 variants of HPV 16.
Methods: DNA were extracted from 190 cervical exfoliated cells and biopsies specimens HPV16 positive from women of southern Mexico with cervical cancer, precursor lesions and normal cytology. E7 HPV16 was amplified and sequenced to identify variants of the oncoprotein. We analyzed the association between E7 variants and the risk or cervical cancer.
Results: We found 8 mutations in E7 gene, 2 missense mutations (A647G, C712A) and 6 synonymous mutations (G666A, T678C, T732C, C765T, T789C and T795G). E7-prototype was the most frequent in our study (74.35 %). The second one was a variant with 3 silent mutations (E7-C732/C789/G795) in 20.42 % of all samples and this variant presented a 3.8 (95% CI, 1.46-9.85) higher risk of cervical cancer development.
Conclusions: This report is the first that presents the distribution of E7 variants of HPV 16 in women from southern Mexico with cervical cancer, precursor lesions and normal cytology, which differs from that observed in Asian countries. E7 prototype was the most frequent, which is consistent with the reported hypovariability of the oncoprotein. This study provides evidence for the association of E7-C732/C789/G795 genetic variant with the risk of cervical cancer.

HUMAN PAPILLOMAVIRUS KNOWLEDGE AND VACCINE ACCEPTABILITY AMONG MALE MEDICAL STUDENTS IN SAUDI ARABIA: A CROSS-SECTIONAL STUDY

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Human Papillomavirus (HPV) is the most common sexually- transmitted infection worldwide, with a global prevalence of 11.7%. The HPV vaccines developed during the last two decades can help prevent this infection and its potentially devastating carcinogenic outcomes. Due to the scarce data in the literature on HPV vaccine acceptability, especially in males, the aim of our study was to assess the level of knowledge of HPV and its vaccine uptake, and to evaluate HPV vaccine acceptability among a sample of medical students in Jeddah, Saudi Arabia.
Methods: This cross-sectional study was conducted on 3rd and 4th year male medical students enrolled in three medical universities in Jeddah, from February to December 2018. A validated 40-item survey was distributed among the students consisting of the following sections: sociodemographic characteristics, questions about HPV infection knowledge (16-tems), HPV vaccine knowledge (7-items), and questions assessing vaccine acceptability.
Results: The sample comprised of 517 participants with a mean age of 21 years. The majority of them were non-smokers (73%), and more than half received the Hepatitis B vaccine (56.2%). Almost 73% of the students have previously heard of HPV, with a mean knowledge score of 8.1/16 (±3.3). However, 42% have heard of the HPV vaccine, achieving a mean knowledge score of 2.3/7 (SD± 1.7). Factors that significantly correlated with better vaccine acceptability were receiving the Hepatitis B vaccine and smoking status (p-value 0.001 and 0.05, respectively).
Conclusions: It is of great importance to improve medical undergraduates' knowledge on HPV as they are the future healthcare providers. Promotion of HPV vaccine uptake in this potentially influential group is crucial for a better disease prevention for our society.

AURORA KINASE INHIBITION IS EFFECTIVE IN HPV TUMOURS AND ITS EFFICACY IS FURTHER ENHANCED WITH RADIATION OR THE USE OF BCL-2 FAMILY INHIBITORS.

CLINICAL RESEARCH / TREATMENT OF HPV-RELATED DISEASE

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Introduction: We have previously shown that HPV E7 sensitizes cells to the inhibition of Aurora A/B kinases (AKi) and treatment is effective at eliminating early tumours and reducing late tumours [1, 2]. Functionally, AKi's cause HPV cells to take 5X longer to traverse mitosis and key anti-apoptotic proteins degrade and apoptosis is induced. Here we wish to enhance the effect of AKi's by adding inhibitors of Bcl-2, Bcl-XL and Mcl1. We also wish to test the combination of radiation therapy (RT) with AKi in cervical PDX models. ls.
Methods: Drugs were added to HeLa /Caski cells and cell viability via MTT and cell imaging undertaken. Dose-response curves and isobolograms for synergy were generated. A PDX expressing HPV16E7 was implanted orthotopically in the cervix and treated with RT (30Gy;2Gy/day), with or without Alisertib (30mg/kg/day) given concurrently with RT daily (3wks). Expression of anti-apoptotic and DNA damage response proteins were evaluated by western blot and IHC respectively.
Results: The combination of Alisertib and Venetoclax was more effective than either drug alone. Enhanced apoptosis was observed with increased PARP cleavage. A1210477 and A1331852 were similar. In the PDX model, RT plus Alisertib showed tumour growth delay compared with RT alone. Reduced lymph node metastasis was observed with Alisertib alone. Combination treatment resulted in the loss of RT-induced anti-apoptotic expression andenhanced γ-H2AX phosphorylation. Loss of Aurora activity reduced the ability of cells to manage DNA damage induced by RT.
Conclusions: Combination of AKi's with Bcl-2 family inhibitors was highly effective at killing HPV cells, likely by accelerating apoptosis during mitotic delay. Alisertib may enhance RT response in patients and appears to reduce metastasis on its own. These studies present a promising approach to treating aggressive HPV cancers and may apply to other HPV-related cancers. 1. Martin D et al. MCT 2017;16:1934-41. 2. Gabrielli B, et al. MCT 2015;14:2753-61

A NOVEL, RAPID, QUANTITATIVE AND COMPREHENSIVE COST-EFFICIENT HPV AND SEXUALLY TRANSMITTED INFECTIONS ASSAY USING NEXT-GENERATION SEQUENCING

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Sexually transmitted infections (STIs) have become increasingly prevalent and impose a major global health and economic burden for the patients, populations and healthcare. Many STIs are silent, hidden infections and can have serious impact on individual's health. There is an urgent need for a comprehensive assay to detect a broad-spectrum of STIs simultaneously in a single reaction at an extremely low-cost.
Methods: Type/species-specific primers were designed for clinically relevant 27 HPVs and 13 STIs and two internal human gene controls, which are used to estimate copy number per cell and to monitor cross-contamination, respectively. Amplification and barcoding/indexing of each sample is performed in a single-tube PCR reaction and all the amplicons are pooled together and sequenced by NGS. The HPV samples used in this study were previously analyzed by Roche Cobas HPV test and all the HPV/STI samples were previously tested with other validated assays.
Results: Our results show that the new assay can detect all intended types/species with high sensitivity, specificity and uniformity. The entire workflow consists of four steps of DNA extraction, single-well and one-step amplification, sample pooling/library preparation and sequencing. The assay can be completed within 24 hours including 17 hours sequencing. Using this comprehensive assay, our results show that many samples are found to have more than one clinically important type/species present that go undetected in routine clinical and diagnostic testing.
Conclusions: We have developed a highly multiplex and comprehensive STI assay that uses low amount of DNA, detects and quantifies 27 HPVs and 13 STIs in one single-tube and one-step amplification reaction. Due to its simple procedure, the comprehensive STI assay is very low-cost and can be easily automated for low/medium and high throughput sample scales. The comprehensive STI assay can be used for screening, detection, research and epidemiological settings.

THE GLOBAL IMPACT OF CERVICAL CANCER ELIMINATION ON OTHER HPV-RELATED CANCERS

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: The WHO has recently called for coordinated action to eliminate cervical cancer globally. Although it has been estimated that the impact of elimination strategies will prevent around 13 million cervical cancer cases globally by 2070, the wider impact on other HPV-related cancers had not been analysed. Large scale uptake of the HPV vaccine will have the additional benefit of preventing other cancers caused by HPV, such as a proportion of vulvar, vaginal, anal, penile and oropharyngeal cancers. In this study we aim to expand the analysis of cervical cancer elimination to also capture its effect on these other cancers.
Methods: A deterministic incidence-based model was developed to estimate the reduced burden of other HPV cancers. The proportion of each cancer attributable to HPV types targeted by the vaccine was obtained using published estimates. The HPV incidence reductions predicted by previously published elimination studies were then applied to the HPV attributable cancer incidence, resulting in an estimated cancer incidence reduction. Age and sex specific cancer incidence rates were used.
Results: If the cervical cancer elimination targets of 90% female HPV vaccination for ages 9-14, the incidence of other-HPV related cancers will be reduced by 20-29% globally in 2070.
Conclusions: If achieved, the global push for cervical cancer elimination will have an additional, previously unquantified, societal benefit of reducing the global burden of other cancers associated with HPV by 20-29% by 2070, on top of preventing the previously reported 13 million cervical cancer cases.

PREVALENCE OF HPV INFECTION IN AN ARGENTINIAN POPULATION SCREENED FOR CERVICAL CANCER WITH CO-TEST. 5 YEARS OF EXPERIENCE

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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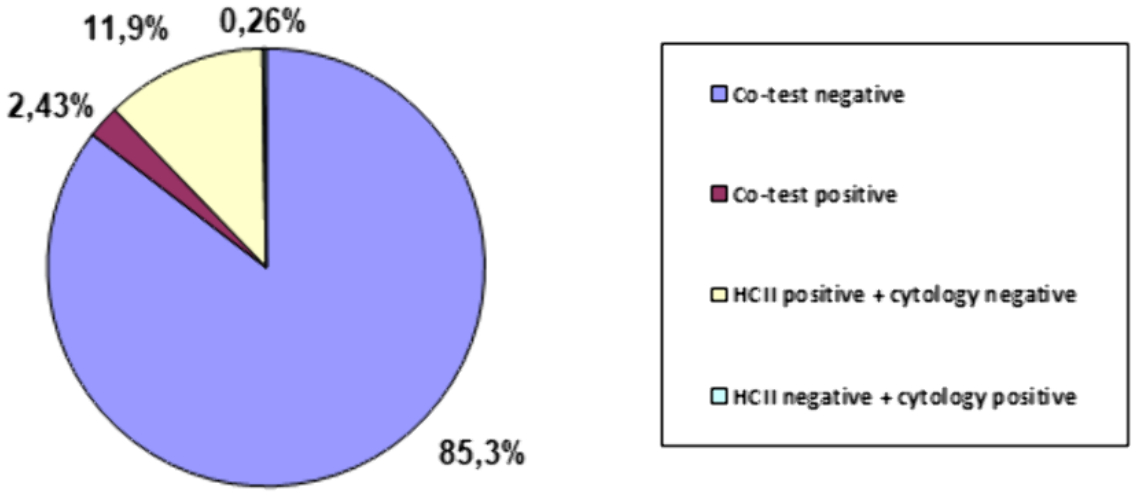
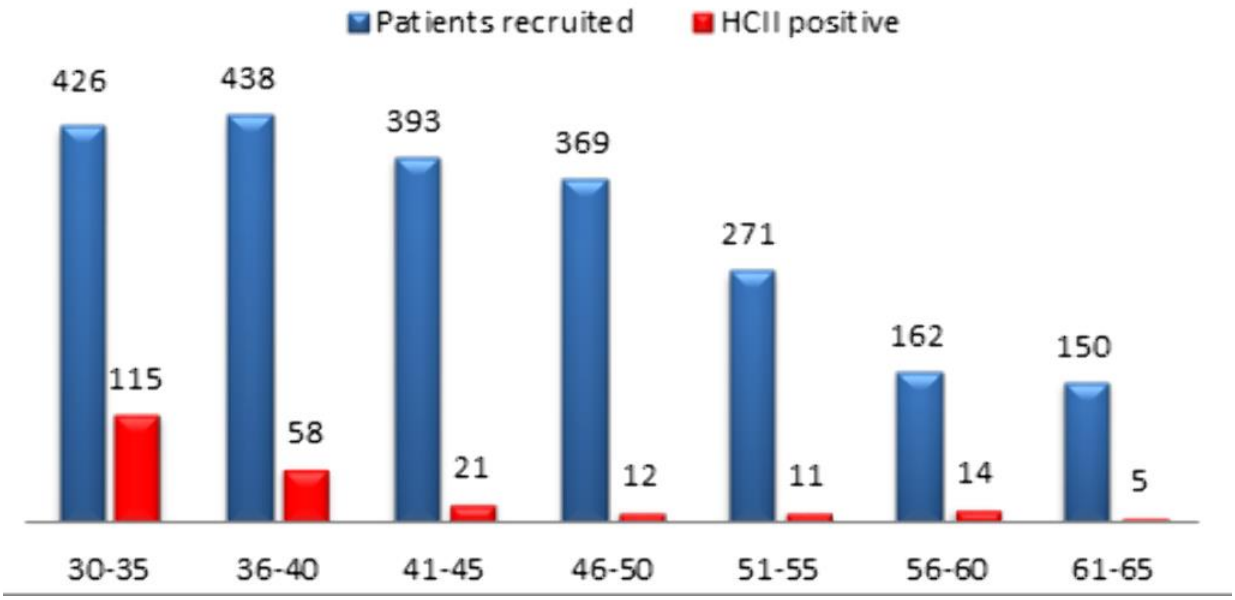
Introduction: Cervical cancer is the second most common cancer in women between 35 and 64 years of age worldwide. In Argentina around 4,000 new cases are diagnosed each year, and 1,800 women die from this disease. The aim of this study is to assess the prevalence of HPV infection in a group of women screened for cervical cancer with Co-test (Hybrid Capture – HCII – and Cytology).
Methods: A retrospective, descriptive and cross section study which included 2304 women between 30 and 65 years of age, recruited from a Community Private Health Care setting (CEMIC), who were screened for cervical cancer with Co-test between 08/2013 and 07/2018.
Results:





The negative rate of Co-tests was 85.3%. Six women (0.26%) showed a negative HCII and ASCUS cytology; they were instructed to perform a new test in 3 years' time. 331 women (14.4%) had a positive HCII, of which 56 (2.43%) showed a positive Co-test and were referred for evaluation by the Lower Genital Tract Disease Section. 275 (11.9%) showed a positive HCII and a negative cytology; they remained on follow-up.

Conclusions: The positive rate of HCII was 14.4%. HPV screening allows us to identify a minority of women with CIN2+ risk.

ELEVATED VAGINAL PH LEVELS AND HPV AMONG SENEGALESE WOMEN

PUBLIC HEALTH / EPIDEMIOLOGY / EPIDEMIOLOGY: NATURAL HISTORY/RISK FACTORS

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Introduction: Sub-Saharan Africa has the greatest global burden of cervical cancer. While elevated levels of vaginal pH have been associated with vaginal inflammation and infection, evidence demonstrating the relationship between vaginal pH and HPV infection is not well characterized. Elevated vaginal pH may serve as a biomarker in determining risk of HPV acquisition and persistence and may inform the underlying biological mechanisms driving the interplay between the vaginal microbiota, HPV infection, and development of cervical cancer.
Methods: Between 2006 and 2011, 462 adult women participated in a longitudinal study at two outpatient clinics in Senegal, West Africa. At each of 1361 study visits, samples were collected for assessment of vaginal pH and HPV infection, and women contributed from 1 to 11 samples. A liquid bead microarray assay was utilized to identify 37 HPV types. We performed logistic regression using generalized estimating equations to calculate odds ratios for risk of HPV detection associated with level of vaginal pH, and assessed the potential impact of subject age/menopausal status, sexual partnerships, douching, and HIV status on this association.
Results: HPV was detected at 49.0% of study visits. In adjusted analyses, among pre-menopausal women, vaginal pH was not significantly associated with HPV infection. However, in menopausal/post-menopausal women, increased vaginal pH $\geq$ 5.0 was strongly associated with increased HPV infection: pH 5-5.9, OR=3.0, 95% CI 1.2-7.3; pH 6.0-6.9, OR=3.5, 95% CI 1.4-8.8; pH $\geq$7.0, OR=4.8, 95% CI 1.8-12.7.
Conclusions: We found that elevated vaginal pH, known to be associated with bacterial vaginosis and indicative of an imbalanced vaginal microbiome, is associated with detection of HPV in older, menopausal/post-menopausal women. Further research to determine the composition of vaginal bacteria as it relates to HPV infection acquisition and persistence, and to assess the impact of interventions to alter the vaginal microbiome on risk for HPV, are warranted.

USE OF CHILDREN'S SERA TO ESTABLISH NEGATIVE CUT-OFF VALUES FOR HPV SEROLOGY ASSAYS

PUBLIC HEALTH / EPIDEMIOLOGY / VACCINATION: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Pseudovirion based neutralization assays (PBNA) are closest to a gold standard for HPV serology, however viral-like particle enzyme linked immunosorbent assay (ELISA) binding assays correlate well and are more convenient. Binding assays may be more sensitive than neutralization assays, so establishing cut-off values (COV) for ELISA seropositivity is challenging. We compared antibody multiplex ELISA and PBNA results in samples from children unlikely to be HPV-exposed, to select and evaluate ELISA COV.
Methods: Residual sera/ EDTA-plasma from 200 children between the ages of 2-8 years were purchased from a hospital in Atlanta, Georgia, USA and tested using a multiplex ELISA and nano-luciferase PBNA for 4-valent HPV types. Antibody titers for ELISA were calculated using parallel line method. For PBNA, positive titers (neutralization ≥50%) were calculated using a 4-parameter curve. The median of the ELISA titers for non-neutralizing samples was calculated after removal of statistical outliers. This median plus 2 or 3 standard deviations (SD) was used as ELISA COV. We compared agreement between PBNA and ELISA seropositivity with each COV.
Results: PBNA found 6.5 -10.5% of children's sera to be positive for at least one 4v HPV type; 4.5% were positive for all 4v HPV types. The ELISA COVs (2 SD) for HPV 6,11,16,18 were 0.5 Arbitrary Units (AU)/ml, 0.6 AU/ml, 1.1 International Units (IU)/ml, 2.5 IU/ml respectively. The proportion of PBNA negative/ ELISA positive ranged from 25.7-31.1% and PBNA positive/ELISA negative ranged from 15.8 % (HPV11) to 38.5% (HPV18). Neutralizing titers in the PBNA positive/ELISA negative group were 2-7 fold less than those positive by both assays. With ELISA COV (3 SD), the proportion of PBNA negative/ELISA positive was reduced to 17.6%-24%.
Conclusions: Varying COV parameters are being evaluated and will be extended to 9-valent HPV types. Establishing COV in IU is important for inter-laboratory comparisons.

ULTRASOUND AND HUMAN PAPILLOMAVIRUS (HPV) 16 E6 ANTIBODIES ARE SENSITIVE FOR DETECTION OF OROPHARYNGEAL CANCER

CLINICAL RESEARCH / HPV DIAGNOSTICS AND BIOMARKERS FOR EARLY DETECTION AND PROGNOSIS OF HPV-RELATED CANCERS

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Introduction: Human papillomavirus 16 (HPV16) E6 seropositivity is a promising early marker of HPV-driven oropharyngeal cancer (HPV-OPC); yet, it is unclear if current imaging modalities can visualize early tumors within the oropharynx. The objective was to determine the sensitivity of ultrasound for detecting HPV-OPC compared to CT and PET/CT.
Methods: Fifty-one patients with known or suspected OPC, without prior treatment or cancer (other than non-melanoma skin cancer) were recruited from the Vanderbilt Head and Neck Clinic. Eight standard ultrasound images (transverse/sagittal views of tonsils, transverse/coronal views of tongue base [BOT], and bilateral long-axis lateral BOT) were obtained using the Lumify portable ultrasound system and mobile application (Philips Healthcare, Bothwell, WA). Blood was collected for HPV serologic analyses. Pathologic details, p16 status, final staging, and radiologic findings were abstracted from the medical record. The sensitivity of each imaging modality was compared to the final clinical diagnosis (gold-standard), as determined by the combined findings from the clinical and radiologic workup (excluding ultrasound), and biopsy of the primary site (as required).
Results: Following the clinical work-up, 24 (51%) BOT, 22 (43%) tonsil, and 2 (4%) unknown primaries were diagnosed; 3 patients (6%) had benign disease. 47 of 48 tumor and/or nodal specimens were tested for p16; all were positive. The presence or absence of primary oropharyngeal lesions were correctly identified in 90.2% (95%CI:78.6%-96.7%) using ultrasound; 69.4% (95%CI:54.6%-81.7%) using CT; 83.3% (95%CI:68.6%-93.0%) using PET/CT and 92.9% (95%CI:80.5%-98.5%) using biopsy. Ultrasound correctly identified 10 out of 14 tumors missed by CT and identified the absence of tumors in 3 cases where CT and/or PET/CT incorrectly identified a tumor. The smallest tumor was 0.51cm in greatest dimension; average size was 2.29cm. 76.1% (95%CI:61.2%-87.4%) of p16 positive patients had detectable HPV16 E6 antibodies.
Conclusions: Transcervical ultrasound and HPV16 E6 antibodies are sensitive for the diagnosis of HPV-OPC.

EVALUATION OF NOVAPLEX II HPV28 DETECTION ASSAY FOR USE IN FORMALIN-FIXED EMBEDDED (FFPE) TISSUE

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: The Novaplex II HPV28 assay (Seegene Inc. US subsidiary, Walnut Creek, CA), a multiplex real-time PCR assay detection and identification of 28 HPV types, recently became available in the United States (available elsewhere as Anyplex II HPV 28). The assay is validated for cervical swabs in a variety of collection media, but not for FFPE specimens. This study was conducted to evaluate Novaplex II HPV 28 for use with FFPE specimens.
Methods: DNA extracts from 507 prospectively collected FFPE cervical specimens from an ongoing study were tested with Linear Array (LA, Roche, Indianapolis, IN) and Novaplex assays. Assay comparisons were restricted to the 26 HPV types identified by both assays. Analyses included % inadequate (failure to detect any HPV and endogenous control), type-specific concordance, and concordance at the level of the specimen.
Results: Of the 507 extracts tested, 1.8% (9) were inadequate with LA and none with Novaplex. Type-specific positive agreement, negative agreement and accuracy were all ≥ 0.98 for Novaplex in reference to LA (Table 1). Cohen's kappa was 0.88, indicating substantial agreement between both assays. Positive concordance was 0.79 indicating moderate to strong agreement for type-specific HPV positive results. Significantly more types were discordantly detected by Novaplex (136 LA negative/ Novaplex positive) than by LA (13 LA positive,/Novaplex negative) McNemar p-value <0.00001. The overall concordance between Novaplex and LA at the specimen level was 0.95 (Table 2).

Table 1: Type-specific concordance between Novaplex and LA

Comparison (Evaluated Test/ Reference Test)	+/+, +/-, -/+, -/-	Propor. Discrep. Types	Positive Agreement (95% CI)	Negative Agreement	Accuracy (Relative to LA)	Positive Concord	Kappa (95% CI)	McNemar p-value
	A, B, C, D	$\frac{C+B}{A+B+C+D}$	$\frac{A}{A+C}$	$\frac{D}{B+D}$	$\frac{A+D}{A+B+C+D}$	$\frac{A}{A+B+C}$		
Novaplex / LA Run	557, 136, 13, 12476	0.002	0.98 (0.96, 0.99)	0.99 (0.99 0.99)	0.99	0.79	0.88 (0.86, 0.89)	<0.00001

Conclusions:

Table 2. Concordance of overall HPV status at level of specimen[1]

Overall HPV Status (by specimen)		LA			Type Agreement		
		Positive	Negative	Inadequate	Full Concordance	Partial Concordance	Full Discordance
Novaplex	Positive	464 (0.92)	17 (0.03)	4 (0.01)	390 (0.77)	95 (0.19)	22 (0.04)
	Negative	1 (0.00)	16 (0.03)	5 (0.01)			
	Inadequate	0 (0)	0 (0)	0 (0)			

[1]*Data not shown as number of specimens (Proportion)*

For the 26 types in common, the performance of Novaplex and LA on FFPE tissues generally was comparable. No FFPE specimens were inadequate with Novaplex and Novaplex detected more individual HPV types and more HPV positive samples than LA. Validation of Novaplex use in FFPE tissues is continuing.

ASSESSMENT OF THE VALIDITY OF ANAL CYTOLOGY AND HPV TYPING IN THE DETECTION OF ANAL HSIL IN A CLINIC-BASED POPULATION IN PUERTO RICO

PUBLIC HEALTH / EPIDEMIOLOGY / PRIMARY HPV VS CO-TESTING WITH HPV AND CYTOLOGY

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Introduction: Anal cytology tends to underestimate lesion grade when compared to high-resolution anoscopy (HRA). We assessed the validity of anal cytology and high-risk (HR) HPV typing against HRA in the detection of anal high-grade squamous intraepithelial lesions (HSIL).
Methods: Cross-sectional analysis of the baseline visit of men and women that attended the Anal Neoplasia Clinic of the University of Puerto Rico Comprehensive Cancer Center (2014-2019). Eligible patients (n=406) completed an anal cytology and HRA with biopsy. HR-HPV detection was done with the Cobas 4800 test. Weighted-kappa coefficient, sensitivity, specificity, and positive and negative predictive values were calculated using HRA with biopsy as the gold standard test.
Results: 68.2% of patients were men, 77.1% were HIV-positive, and 76.9% had anal HR-HPV infection; prevalence of HPV-16 (33.7%) was higher than for HPV-18 (16.9%). Squamous intraepithelial lesions were detected with anal cytology and histology in 70.7% and 83.0% of patients, respectively. Weighted-kappa statistic between the tests (cytology and histology) was 0.26 ($p<0.001$). Measured against the results from histology, the sensitivity and specificity of anal cytology alone to detect histologically confirmed anal HSIL was 82.3% (95% CI: 75.6%-87.8%) and 37.2% (95% CI: 31.1%-43.6%), respectively. The HPV test had higher sensitivity (92.7%, 95% CI=87.6%-96.2%) than the cytology, with slightly lower specificity (33.9%, 95% CI=27.9%-40.2%). The two tests combined (positive results to anal cytology or HR-HPV) had the best sensitivity to detect anal HSIL (97.6%, 95% CI: 87.6%-99.3%), although the specificity decreased (18.2%, 95% CI: 13.5%-23.6%). Similar results were seen in analyses stratified by sex and HIV-status.
Conclusions: While anal cytology in combination with HR-HPV typing improved the detection of histologically, confirmed anal HSIL in this Hispanic population, HR-HPV testing by itself had better performance in the detection of anal HSIL as compared to cytology alone. Findings support the importance of HPV testing in anal screening. AMC-NCI Grant# UM1 CA121947.

ROBUSTNESS OF HUMAN PAPILLOMAVIRUS (HPV) TYPESEQ ASSAY DEMONSTRATED THROUGH SUCCESSFUL TECHNOLOGY TRANSFER BETWEEN LABORATORIES

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: To reduce cost and increase throughput of HPV typing, the Cancer Genomics Research (CGR) Laboratory at the National Cancer Institute developed the TypeSeq Assay, which leverages Next Generation Sequencing and bioinformatics pipeline for automated type calling. Transferring this technology to a laboratory at the Centers for Disease Control (CDC) would demonstrate feasibility of TypeSeq adoption in other settings.
Methods: Assay transfer involved three steps: 1) CDC personnel selected DNA extracts from 65 samples with Linear Array results (LA, Roche Diagnostics, IN) and performed TypeSeq onsite at the NCI laboratory with Illumina MiSeq, while CGR personnel performed TypeSeq with Ion S5 sequencing. Bioinformatics pipelines corresponding to each sequencing platform generated typing results. 2) Using CGR-provided reagents, TypeSeq was performed at CDC by CDC personnel on a different sample set using MiSeq, and genotyping results generated using NCI's pipeline. 3) Bioinformatics pipeline was transferred to CDC and CDC generated results verified along with TypeSeq testing of additional samples (total 151 samples). Type-specific concordance between LA and TypeSeq, restricted to the 37 LA types, was calculated along with kappa coefficient (k).
Results: TypeSeq passed quality controls and all synthetic controls demonstrated detection of 51 types at the level of 25 copies/reaction in both labs. Testing at NCI (n=65) using MiSeq showed substantial type-specific agreement with LA (k=0.781; 95% CI: 0.735 - 0.827; concordance 96.6%; sensitivity relative to LA 88.0%). TypeSeq type-specific results between Ion S5 and MiSeq platforms were almost in perfect agreement (k=0.988; 95% CI 0.977 - 1.00). TypeSeq at CDC (n=151) also showed almost perfect type-specific agreement with LA (k=0.821; 95% CI=0.792 – 0.850; concordance 97.6%; sensitivity relative to LA 83.3%).
Conclusions: The TypeSeq assay is readily transferrable when reagents are provided. Additional validation of TypeSeq using primers, barcodes and synthetic DNA controls ordered and prepared at CDC is in progress.

SCREENING STRATEGIES FOR ANAL HISTOLOGIC HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION (HHSIL) DETECTION IN WOMEN LIVING WITH HIV (WLHIV) – AIDS MALIGNANCY CONSORTIUM (AMC)-084

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: Compared to U.S. women WLHIV have >10-fold higher risk for anal squamous cell carcinoma (a-SCCA). Strategies to prevent a-SCCA include detection and treatment of anal hHSIL. Currently, there is no consensus on anal-hHSIL screening strategies for WLHIV.
Methods: 256 WLHIV were enrolled in AMC-084. Evaluations included anal high-risk (hr)HPV testing, using hrHPV-HC2™ and APTIMA™, anal cytology (anal-cyt) and concurrent high-resolution anoscopy, where ≥2 biopsies were obtained. Screening test characteristics for predicting anal hHSIL, validated by central pathology, were estimated: sensitivity (SN), specificity (SP), positive predictive value (PPV) and false-omission rate. Paired and clustered analyses compared screening test characteristics for (1) hrHPV single tests to anal-cyt (2) triage (both anal-cyt>ASC-US and hrHPV tests positive) to single test strategies. P values <0.05 were considered significant.
Results: 229 (89%) of 256 enrolled WLHIV had complete anal assessment data and were included in this analysis. Mean age was 50, 62% were Black, 22% Hispanic, and 60 (26%) had hHSIL. Anal-cyt≥ASC-US, hrHPV-HC2, and APTIMA SN estimates were similarly high (83%, 75%, 77% respectively) and the false-omission rates were similarly low (11-13%). The SP for APTIMA (67%) and hrHPV-HC2 (61%) were higher than SP for anal-cyt (83%). the PPV for APTIMA (45%) was higher than PPV for anal-cyt (37%), but PPV for hrHPV-HC2 (41%) was not. Anal-cyt of ASC-H/HSIL showed the highest SP (97%) and lowest SN (27%) compared with other screening tests. Triage strategies (anal-cyt≥ASC-US and hr-HPV test) had significantly higher SP (73-76%) and PPV (46-51%), and significantly lower SN (65-70%) compared with single test strategies.

Table: Comparison of Test Characteristics for Performance of Anal Cancer Screening Test Strategies for Predicting Anal Histological HSIL (hHSIL) in 229 Women living with HIV

Test Strategy	hHSIL+* N (%)	SN (95% CI)		SP (95% CI)		PPV (95% CI)		False Omission Rate (95% CI)	
Single test									
Anal Cytology									
≥ASC-US	135 (59%)	83%	(71%, 92%)	50%	(42%, 57%)	37%	(29%, 46%)	11%	(5%, 19%)
ASC-H/HSIL	21 (9%)	27%	(16%, 40%)	97%	(93%, 99%)	76%	(53%, 92%)	21%	(16%, 27%)
hrHPV									
APTIMA	102 (45%)	77%	(64%, 87%)	67%	(59%, 74%)	45%	(35%, 55%)	11%	(6%, 18%)
hrHPV-HC2	111 (48%)	75%	(62%, 85%)	61%	(53%, 68%)	41%	(31%, 50%)	13%	(7%, 20%)
Triage (Both screening tests positive)									
ASC-US+ anal Cytology and APTIMA	82 (36%)	70%	(57%, 81%)	76%	(69%, 83%)	51%	(40%, 62%)	12%	(7%, 19%)
ASC-US+ anal Cytology and hrHPV-HC2	84 (37%)	65%	(52%, 77%)	73%	(66%, 80%)	46%	(35%, 58%)	14%	(9%, 21%)

* Based on observed prevalence of 26% anal hHSIL.

Conclusions: Anal hrHPV testing demonstrated similar SN for anal-cyt≥ASC-US in predicting anal hHSIL. SP was highest for triage strategies and higher for hrHPV single tests compared to anal-cyt. Thus, anal hrHPV testing appears to be an alternative single test strategy or effective triage for anal-cyt≥ASC-US for anal hHSIL screening among WLHIV.

PROVIDER RECOMMENDATION AND PARENTAL REFUSAL OF HPV VACCINE IN DIFFERENT ADOLESCENT AGE GROUPS: INSIGHTS FROM CLINICIAN STAKEHOLDERS ACROSS INDIANA, U.S.A.

PUBLIC HEALTH / EPIDEMIOLOGY / PSYCHOLOGICAL ASPECTS ON HPV-RELATED INTERVENTIONS

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Introduction: Clinician recommendation is one of the strongest predictors of HPV vaccination in the U.S. Previous research suggests clinicians often over-estimate parental hesitancy about HPV vaccine. The purpose of this study was to explore the association of frequency of clinician recommendation with perceptions of the frequency of parental refusal of HPV vaccine.
Methods: Using online and phone methodologies, we surveyed clinic vaccine coordinators (clinicians) across Indiana about the frequency of HPV vaccination recommendations for male and female adolescents ages 9-10, 11-12, and 13-17 years. We also queried perceptions of how often parents refuse vaccination for each age and sex group. Responses for both measures ranged from never (1) to always (5).
Results: Surveys were completed by 94 clinicians from across Indiana. Clinicians reported increasing recommendation frequency as age increased in both males (9-10 = 3.1, 11-12 = 4.7, 13-17 = 4.8) and females (9-10 = 3.2, 11-12 = 4.8, 13-17 = 4.9). Clinicians also reported decreasing parental refusal as age increased in both males (9-10 = 3.5, 11-12 = 3.2, 13-17 = 3.0) and females (9-10 = 3.5, 11-12 = 3.1, 13-17 = 3.0). Correlations (Kendall's Tau) indicated that provider recommendation and parental refusal were significantly negatively correlated for girls 9-10 years old ($\tau = -0.38$, $p < .001$) and 13-17 years old ($\tau = -0.20$, $p < .05$), and for boys 9-10 years old ($\tau = -0.26$, $p < .01$), suggesting that clinicians who perceived greater levels of parental refusal reported less frequent recommendations of HPV vaccination.
Conclusions: The findings of this study suggest that clinicians may base decisions to recommend vaccination on perceptions of frequency of parental refusal. With HPV vaccination rates still sub-optimal in both sexes, particularly in Indiana, it is important to help clinicians make routine strong recommendations for HPV vaccination to all parents of HPV-vaccine-eligible adolescents.

SERUM TESTOSTERONE AND ESTRADIOL MODIFY RISK OF ANAL HPV16/18 INFECTIONS BUT ONLY ESTRADIOL INFLUENCES RISK FOR HISTOLOGICAL HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESIONS (HSIL)

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF ANAL CANCER AND ITS' PRECURSORS

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Introduction: Higher serum free testosterone (FT) and increased anal-HPV16/18 infection prevalence in MSM. Associations of serum-Total/FT, and -estradiol with anal-HPV16/18 infections and histological HSIL (hHSIL) indicate an important underlying role of SHBG levels. Data suggest Estrogen Receptor-*α* (ERα) in stroma underlying tumors, not epithelial cells promotes cervical cancer.
Methods: Two cross-sectional analyses were performed. For 340 HIV-infected/HIV-uninfected Multicenter AIDS Cohort MSM, anal cytology residuals were evaluated for 37 HPVs (PCR). A total of 336 HRA/biopsy were performed for 214 men. Serum specimens collection preceded HPV and HRA visits by 24(±9) months and were tested for albumin, SHBG (radioimmunoassay), total testosterone and estradiol (TE2) (LC/MS); serum-FT (pg/mL) was estimated. HPVs were classified: HPV16/18+, other Group-1 and -2 high-risk HPVs+ (hrHPVs); low-risk HPVs+ (lrHPVs), and HPV-uninfected. Biopsies were evaluated as hHSIL vs. <hHSIL. Multivariable-adjusted GEE logistic regression models assessed relationships between $\log_e$-transformed FT and TE2, and HPV16/18+ and hHSIL, separately. Sociodemographic/behavioral covariates were included. ERα immunohistochemistry explored median expression intensity for hHSIL(n=3) and <hHSIL(n=3) specimens of six HPV16-infected subjects.
Results: Adjusted models showed higher FT increased odds of HPV16/18-infection (OR=1.9(1.2-2.9)), but odds were inversely associated with TE2 (OR=0.68(0.49-0.94)). White race and other Group-1-hrHPVs+ increased odds for HPV16/18 infection (OR=2.6(1.2-5.9) and (OR=1.7(1.1-2.5)), but HIV-infection/CD4+count, receptive anal intercourse partnerships, exogenous-testosterone, or tobacco use did not increase HPV16/18-infection odds. Serum-FT was not associated with odds of hHSIL (OR=1.1(0.7-1.8)), but serum-TE2 was protective for hHSIL (OR=0.5(0.3-0.9)). Men testing HPV16/18+ alone showed higher odds of hHSIL than hrHPV-negative men (OR=4.3(1.7-10.7)). Median IHC ERα-expression intensity was 10% (hHSIL) vs. 40% (<hHSIL).
Conclusions: Higher serum-FT increased odds of anal HPV16/18-infection but not hHSIL. Consistent across both analyses, and unexpectedly, higher serum-TE2 lowered odds of both HPV16/18+ and hHSIL in these MSM. More research evaluating sex hormones, binding proteins and ERα expression in stroma and epithelial cells of HPV-associated HSIL/<HSIL-affected tissue is needed.

HPV TESTING AMONG WOMEN IN SOUTHERN INDIA: SELF-COLLECTED VERSUS PHYSICIAN COLLECTED SWABS

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: A large proportion (27%) of the world's cervical cancer deaths annually can be attributed to India. To address the burden of cervical cancer, the Indian Ministry of Health implemented a nation-wide cancer-screening program in November 2016. Literature suggests the use of human papillomavirus (HPV) self-tests to increase participation in cervical cancer screening. This study aims to assess the inter-rater reliability between self-collected and physician collected swabs HPV testing.
Methods: Participants completed a survey including socio-demographic, reproductive, and health data, as well as an assessment of knowledge regarding cervical cancer. After the screening questionnaire was completed, the participant used a private room to self-collect a vaginal swab. A clinician then performed a pelvic examination and a specimen collected from the cervical os using a speculum. The digene Hybrid Capture 2 HPV DNA Test was used to test for HPV. Cohen's Kappa was calculated to assess agreement between the results of self-collected and physician collected swabs.
Results: There were 119 women included in the study of mean age 42.4 (±8.07) years. Most women received formal education; 43.6% (1-8 years) and 32.7% (≥9 years). However, 23.6% of women received no formal education. Most women were married (87.7%) and Hindu (95.6%). Cohen's kappa was determined to be 0.71 (95% CI: 0.50-0.9; $p<0.01$) indicating significant agreement between the test results of self-collected and physician collected swabs.
Conclusions: Our findings indicate that there is substantial agreement between self-collected and physician collected swabs used for HPV testing. Self-collected swabs are a viable method to improve cervical cancer screening initiatives in Southern India.

MMUPV1 INFECTION IN GENETICALLY OUTBRED MICE AS A MODEL OF NATURAL INFECTION AND DIVERGENT OUTCOMES OF HPV INFECTION

BASIC RESEARCH / ANIMAL MODELS

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Introduction: HPV exposure leads to divergent clinical outcomes, potentially due to genetic factors and/or differential immunologic responses. HPV exposure can result in failed infection, transient infection that is cleared, persistent infection, or productive infection and disease. Current models of HPV infection utilize genetically identical mouse strains and are not suitable models to recapitulate the outcomes of HPV exposure in humans. We aimed to investigate mouse papillomavirus (MmuPV1) infection in genetically outbred SKH-1 to model the divergent outcomes of papillomavirus challenge.
Methods: 55 female SKH-1 mice were pretreated with Depo-Provera and 50 infected intravaginally with MmuPV1, with 5 used as virus-free challenge controls. Blood was collected periodically to measure global immune alterations and capsid-specific antibodies by PsV ELISA. 48 days after initial challenge, mice were euthanized, and tissue was collected for downstream analysis. Vaginal tract was harvested for FFPE and used for qPCR analysis of infection status by 757/3139 spliced viral mRNA expression, histological analysis, and in situ hybridization (ISH) using E6/E7 probes. Draining lymph node was collected and used to measure E6/E7-specific T-cell responses by peptide pool stimulation and intracellular cytokine staining for IFNg.
Results: In challenged mice divergent outcomes of infection were observed. 63% tested positive for viral mRNA, 16% displayed histological changes consistent with cervical intraepithelial hyperplasia, and 7% tested positive by ISH. 37% had no evidence of persistent infection. Essentially all mice (95%) showed a robust peripheral capsid antibody response, whereas 14% had T-cell responses to E6/E7 peptides. This T-cell response correlated with a lack of persistent infection. Controls were negative for all assays.
Conclusions: MmuPV1 infection in genetically outbred SKH-1 mice potentially provides a unique platform to query factors contributing to divergent outcomes of HPV infection. Ongoing studies are investigating immunologic factors contributing to long-term infection and the development of papillomavirus-associated diseases.

DETECTION OF HUMAN PAPILLOMAVIRUS (HPV) DNA IN FORMALIN-FIXED PARAFFIN-EMBEDDED (FFPE) TISSUES: IMPACT OF STORAGE TIME

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Pathology archives of routinely processed FFPE tissues are important for HPV studies. Formalin introduces cross-links that preserve histology indefinitely, but processing and storage variables could affect molecular preservation. We conducted this analysis to determine if storage times of up to 10 years affect HPV detection.
Methods: We conducted a retrospective analysis of data from studies of HPV-associated diseases that included FFPE samples stored up to 10 years. All studies used the same laboratory methods: [Linear Array HPV (LA; Roche) followed by reflex testing with LiPA HPV (LiPA; Innogenetics) for samples with negative or inadequate LA results. LA detects 450 bp amplicons and LiPA detects 65 bp amplicons.] We classified results as HPV positive (positive for ≥ one HPV type), HPV negative (negative for all HPV types and positive for globin), or inadequate (negative for all HPV and globin). We calculated storage time as the difference between dates of diagnosis and DNA extraction. Multinomial logistic regression measured the association between storage time and HPV results (positive, negative and inadequate based on LA alone or with LiPA reflex testing).
Results: We had data from >13,000 archived blocks stored up to 10 years. Overall, using LA, 80% were positive; 10% negative and 9% inadequate. With LiPA reflex testing, less than 3% were negative and 0.6% inadequate. Longer storage time was associated with higher inadequate (p=0.106) and negative (p=0.0226) and correspondingly fewer positive (p=0.0219) LA results (Figure 1). However, storage time was not associated with HPV results using the combination of LA and reflex LiPA [negative/inadequate (p=0.577), negative (p=0.372) and positive (p=0.319)] (Figure 2).

Figure 1. Proportion of inadequate, negative and positive LA results by number of specimen storage years at time of DNA extraction. Note difference in y-axis scales among plots.

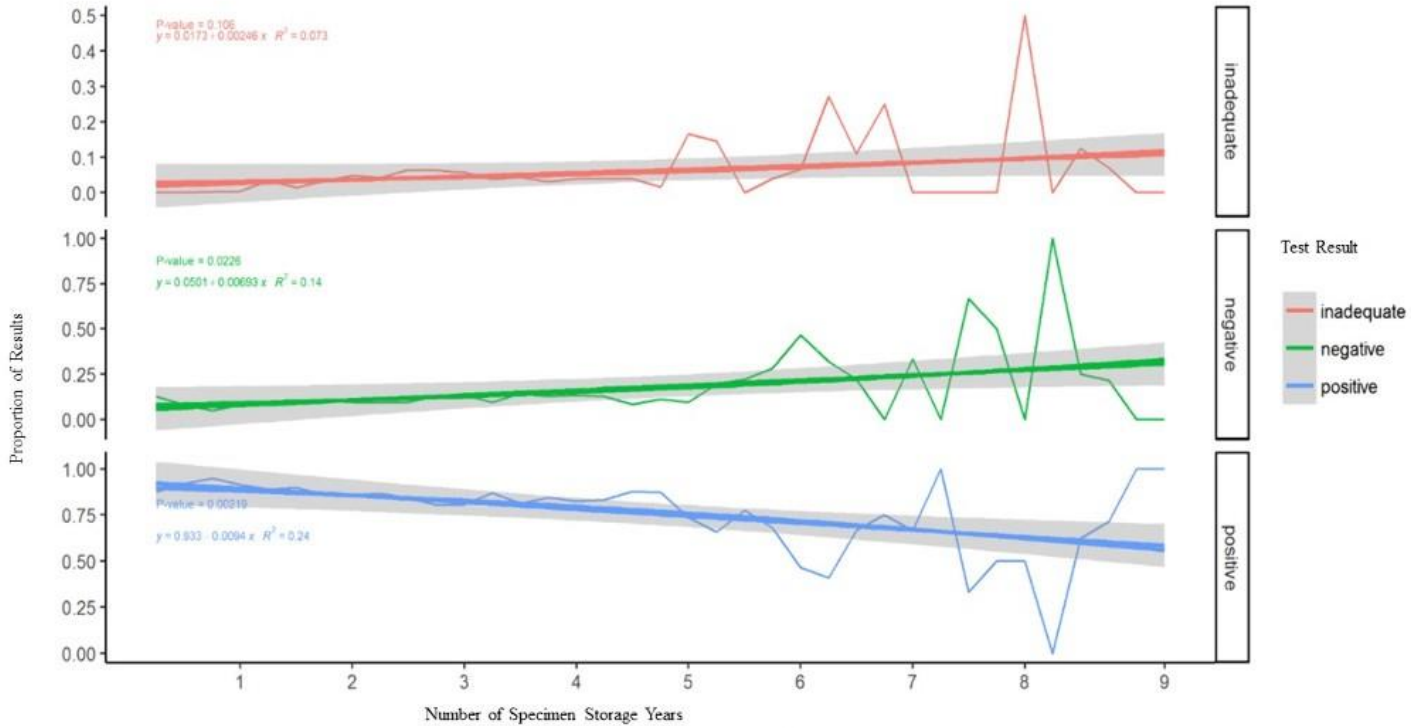
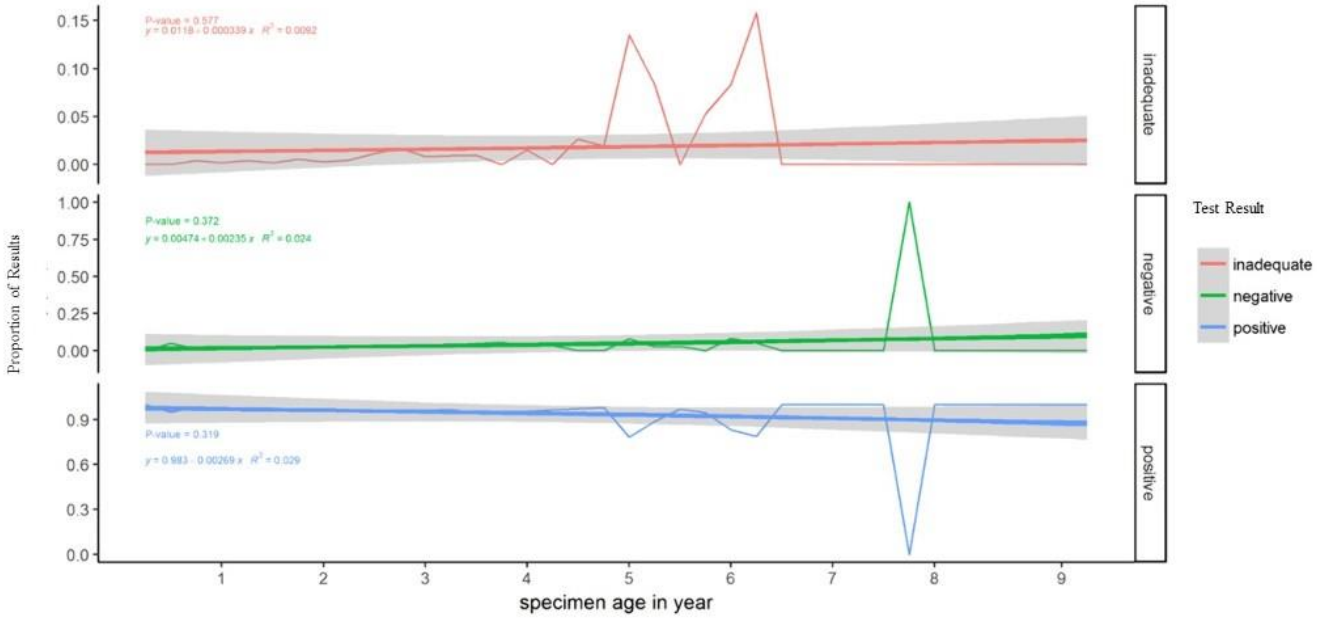


Figure 2. Proportion of inadequate, negative and positive LA with reflex LiPA results by number of specimen storage years at time of DNA extraction. Note difference in y-axis scales among plots.



Conclusions: Within 10 years of storage, nucleic acid amplification from FFPE tissues, especially for larger amplicons, is impaired. Use of smaller amplicons and sequential testing by multiple assays can

mitigate the impact of routine tissue processing and storage effects.

EVALUATION OF THE USE OF RESIDUAL CLINICAL SPECIMENS FOR SURVEILLANCE OF ANAL HUMAN PAPILLOMAVIRUS (HPV) IN MALES

CLINICAL RESEARCH /HPV SELF-COLLECTION

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Introduction: Men who have sex with men (MSM) are at high risk for HPV infection and related disease. As part of an existing research study assessing HPV prevalence and HPV vaccine impact among MSM attending sexual health clinics (Vaccine Impact in Men), we compared two types of self-collected anal specimens as a pilot evaluation of the performance of residual clinical specimens for secondary HPV testing.
Methods: Participants in the HPV research protocol self-collected an anal swab in digene Specimen Transport Medium (STM). If clinically indicated, an additional anal specimen was self-collected for Chlamydia trachomatis/Neisseria gonorrhoeae (CT/NG) testing using the Aptima Multitest Swab Specimen Collection Kit. Residual Aptima specimens were retrieved after CT/NG testing was completed. All specimens were coded and sent to CDC where replicates of each specimen were tested for HPV using Roche Linear Array. After HPV testing was completed, results of specimen pairs from each participant were linked. Analyses included % inadequate specimens and type-specific reproducibility by collection method, type-specific concordance between collection methods and concordance at the specimen level.
Results: Both specimens were received from 48 participants. In repeat runs inadequate samples ranged from 2.1-6.3% and did not differ by collection method. Run-to-run type-specific reproducibility for identification of HPV was similar and high (99%) for both collection methods (Table 1). The type-specific concordance between collection methods was also high (97%) (Table 2). The overall concordance by samples between Aptima and STM samples was 0.81 to 0.90.

Table 1: Run-to-Run Type-specific Reproducibility of Linear Array HPV Results by Collection Method

Comparison (Run 1/Run 2)	+/+, +/-, -/+, -/-	Proportion Discrepant Types	Positive Agreement (95% CI)	Reproducibility	Positive Concordance	Kappa (95% CI)
Formula	A, B C, D	$\frac{C+B}{A+B+C+D}$	$\frac{A}{A+C}$	$\frac{A+D}{A+B+C+D}$	$\frac{A}{A+B+C}$	Cohen's Kappa coefficient
STM[a] Run 2/Run 1	105, 21, 5, 1693	0.0055	0.95 (0.90, 0.99)	0.99	0.80	0.88 (0.84, 0.93)
Aptima (residual)[b] Run 2/Run 1	124, 8, 19, 1673	0.021	0.87 (0.80, 0.92)	0.99	0.82	0.89 (0.85, 0.94)

[a]Anal specimen self-collected for Vaccine Impact in Men study in STM; [b]Anal specimen self-collected for Aptima CT/GC test

Table 2: Type-Specific Concordance of Linear Array HPV Results between Collection Methods

Comparison (Evaluated Test/ Reference Test)	+/+, +/-, -/+, -/-	Proportion Discrepant Types	Positive Agreement (95% CI)	Accuracy (Relative to STM)	Positive Concordance	Kappa (95% CI)
Run1: Aptima (residual)/STM	99, 44, 11, 1670	0.012	0.90 (0.83, 0.95)	0.97	0.64	0.77 (0.72, 0.81)
Run 2: Aptima (residual)/STM	101, 31, 25, 1667	0.027	0.80 (0.72, 0.87)	0.97	0.64	0.77 (0.72, 0.81)

Conclusions: Specimens remaining after Aptima GC/CT testing are suitable for surveillance of anal HPV. Use of anonymized residual clinical specimens to monitor HPV prevalence can reduce specimen collection burden for patients and clinic staff.

REVISED RECOMMENDATIONS FOR CERVICAL CANCER SCREENING IN FRANCE

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: A national organized cytology-based cervical cancer screening programme was launched in 2018 and rollout is ongoing. The High Authority for Health (HAS) recently assessed new evidence on primary HPV testing to adapt screening recommendations.
Methods: The HAS commissioned systematic reviews and meta-analyses to evaluate HPV testing compared with cytology screening; accuracy of HPV testing on self-samples; effectiveness of self-sampling to reach under-screened women; and performance of triage methods to manage HPV positive women. The evidence was examined, considering the specific French healthcare system. Recommendations were produced by the HAS and reviewed by a multidisciplinary group.
Results: Compared with cytology screening, HPV screening is more sensitive to detect pre-cancers but less specific. In women ≥ 30 years, if the test is negative, HPV screening greatly reduces the risk to develop pre-cancer and cancer for at least 5 years. HPV testing is as sensitive and slightly less specific on self-samples than on clinician-taken samples, provided the HPV test is a validated PCR. Self-sampling is more effective to reach under-screened women than sending invitations. Two-time triage strategies result in the highest sensitivity for pre-cancers and the lowest burden of colposcopies.
Conclusions: The HAS recommends to screen women aged 25-29 years with cytology every 3 years. Women aged ≥ 30 years should be screened with HPV testing and the screening interval should be extended to 5 years for women with negative HPV test. Self-sampling kits should be provided to under-screened women aged ≥ 30 years. HPV-positive women should be triaged with cytology. Those with abnormal cytology (ASC-US+) should be referred for colposcopy; those with normal cytology should be re-tested for HPV 12 months later. The HAS recommends that the HPV test be fully reimbursed and that communication materials on HPV testing for health workers and for women be developed.

USING FOCUS GROUPS TO DETERMINE KNOWLEDGE, ATTITUDES AND PERCEPTIONS ABOUT HPV AND CERVICAL CANCER SCREENING IN GRENADA, WI

PUBLIC HEALTH / EPIDEMIOLOGY / SCREENING FOR HPV-RELATED DISEASE: IMPLEMENTATION, EVALUATION AND IMPACT

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Introduction: Using focus groups, we gathered knowledge, attitudes and perceptions about cervical cancer screening and HPV in Grenada, West Indies, a small, tri-island nation in the Eastern Caribbean. Cervical cancer is a leading source of morbidity and mortality in Latin America and the Caribbean, including Grenada. While high-risk (HR) HPV testing is not yet available in Grenada, it is important to determine its cultural acceptability by Grenadian women ahead of implementation.
Methods: Ten focus groups comprising over 70 participants were conducted with women in several locations in the capital city of St. Georges (and including women from the surrounding parishes). Participants were asked about their baseline knowledge of pelvic exams, Pap smears, and HPV. They were asked about their reasons for seeking (or avoiding) cervical cancer screening and about how different aspects/modalities of testing (e.g., self-collection, HR HPV testing, timely reporting of results, use of mobile clinics) might affect their decision-making. Focus groups were recorded and transcribed. Participant responses were coded and organized into common themes.
Results: While many respondents had heard of HPV, far fewer knew about HPV prevention or its causative role in cervical cancer. Many focus group participants were aware that cervical cancer screening was beneficial, but many barriers to obtaining that screening were noted, including concerns about privacy and stigma, potential discomfort, and the cost and inconvenience involved.
Conclusions: These findings have important implications for future cervical cancer control efforts in Grenada. While there is some awareness of the importance of screening, translating this awareness into action will require addressing outstanding issues of access and stigma. A focus on educating the population about the role of HPV in cervical cancer and the importance of early detection of cervical cancer should be central to these efforts.

TREATMENT OF THE PRECANCEROUS LESIONS OF THE UTERINE COLLAR WITH THE CHU GABRIEL TOURÉ

CLINICAL RESEARCH / DIAGNOSIS AND MANAGEMENT OF CERVICAL CANCER AND ITS' PRECURSORS

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Introduction: The cancer of the cervix especially remains true public health problems in the developing countries. It constitutes the 4th cancer at the woman in the world; whereas it occupies the 2nd position in the developing countries, especially in south sahara Africa .
Methods: Our study proceeded in all the health systems of the district Bamako of the first January 2010 at December 31st, 2017 (8ans). It was about a retro study prospective and descriptive.
Results: For the study period we detected 121904 women by test IVA and or IVL whose 8016 biopsies is 6,57% of the detected women. The average age is 34,23 years with extremes from 14 to 100 years We then have a total frequency of 2,55% for the precancerous lesions that of the cancerous lesions is 1,05%. We carried out the cryotherapy (09.6%), RAD (12%), Hysterectomy (1%)
Conclusions: The assumption of responsibility of the lesions can reduce considerably the burdens of cancer in the developing countries.

IMPACT OF A MASS PROGRAM OF CERVICAL CANCER SCREENING UPTAKE REINFORCEMENT IN MALIAN CAPITAL CITY, BAMAKO: LESSONS FROM WEEK-END 70 PROJECT

PUBLIC HEALTH / EPIDEMIOLOGY / GLOBAL IMPACT OF HPV AND CERVICAL CANCER PREVENTION

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Introduction: Cervical cancer is the second cancer in women from Sub Sahara Africa. The aim of this study was to evaluate the impact of free of charge cervical cancer screening each weekend during18 months in Bamako, Mali.
Methods: We conducted a cross-sectional from cervical cancer screening data the District of Bamako from January 1st, 2010 to December 31st, 2017. The target population was women aged 20 years or higher. We included 27 healthcare structures where cervix screening is routinely available for clients. From July 2016 to December 31st, 2017 we used communications lines to reinforce adherence to screening, and screening services were free a charge each weekend during this period. Descriptive statistics were calculated.
Results: During the study period, 182 741 women were screened for cervical cancer in the District of Bamako. Among these, 145,000 women were screened during the period of free of charge services. Screening coverage has increased from 35% between 2010 - 2015 to 46% in 2016 - 2017. The age groups 20-24, 25-29, 30-34 and 35-39 years old were the most represented; while women aged 65 and over were less represented. Prevalence rate of precancerous lesions was 2.7% and 1.1% for cancerous lesions. Since 2017, we observed a significant decrease of annual prevalence rate of precancerous and cancerous lesion. There was a significant decrease in the prevalence rate of invasive cervical cancer. This decrease was mainly observed for advance stages III and IV.
Conclusions: A well organized screening program is feasible in developing settings and can decrease the burden of cervical cancer.

PERFORMANCE OF HPV16/18 GENOTYPING AS A TRIAGE TEST OF HPV POSITIVE WOMEN IN LATIN AMERICA

PUBLIC HEALTH / EPIDEMIOLOGY / OTHER PUBLIC HEALTH/EPIDEMIOLOGY RESEARCH

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Introduction: Persistent infection with high-risk HPV is the main cause of cervical cancer; however, most HPV+ women will not develop cervical disease. A second test, triage, to select HPV+ women at high-risk of cervical precancer and cancer should be considered. The ESTAMPA study is evaluating several techniques/strategies for triage of HPV+ women in nine Latin American countries. The performance of HPV16/18 genotyping alone or combined with cytology ASCUS+ (ASCUS or worse) for CIN2+ detection in HPV+ ESTAMPA participants.
Methods: In five ESTAMPA centres, 12,764 women were screened with cytology and COBAS; those positive for either test were referred to colposcopy/biopsy and treatment as appropriate. COBAS provides individual results for HPV16 and HPV18 and a group result for other 12 high-risk HPV types. Sensitivity and specificity of HPV16/18 genotyping alone or combined with cytology ASCUS+ for CIN2+ detection among HPV+ women were estimated.
Results: Among 1,689 HPV+ women (334 HPV16+, 123 HPV18+, 12 HPV16+/18+ and 1220 positive for other high-risk types) with colposcopy/biopsy results, 241 CIN2+ (52 CIN2, 178 CIN3, 11 cancer) were detected. In 469 HPV16/18+, 138 CIN2+ were identified (sensitivity of HPV16/18 genotyping: 57.3%, 95% CI 50.9-63.3; specificity: 77.2%, 95% CI 75.0-79.3). Among 1220 women positive for non-16/18 high-risk HPV types, 103 CIN2+ cases were detected: 36 in women with ASCUS+ cytology and 67 in those with normal cytology. Thus, the combined sensitivity for CIN2+ detection was 72.2% (95% CI 66.2-77.5), 14.9% significantly higher ($p<0.001$) than that of HPV16/18 alone but at the expense of a reduction in specificity of 10.3% (66.9% combined specificity vs 77.2% HPV16/18, p-value<0.001).
Conclusions: Using for referral to colposcopy, HPV16/18 positivity or ASCUS+ among HPV+ women, leads to higher detection of CIN2+, reducing the overall referral (all HPV+) and the proportion of women to be recalled for a second HPV test in 12-24 months.