IPVS interview with Dr. Laura Koutsky

Winner of the 2020 Maurice Hilleman Award

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Introducing Dr. Laura Koutsky

Dr. Koutsky is a Professor Emeritus in the School of Public Health at the University of Washington and holds a PhD in Epidemiology. She is recognized internationally for her studies on HPV infections and the diseases they cause. Laura is acknowledged as a pioneer in HPV research beginning in the late 1980s when she started studies on the acquisition and natural history of genital human papillomavirus (HPV) infections and the prevention of HPV-related genital tract neoplasms.

Let's learn about Laura's professional journey and why it is so appropriate that she receive the 2020 Maurice Hilleman Award.

Q1: Dr. Koutsky, what was it that stimulated you to become one of the first epidemiological researchers to investigate HPV back in the 1980s? Can you tell us a bit about how that happened?

It happened pretty much by chance. I was in Seattle and I needed a job before starting graduate school. A friend of mine happened to be leaving a job that involved studying sexually transmitted infections (STI), led by the renowned researcher in that area, Dr. King Holmes. As it turned out, I took over the position and began researching a variety of sexually transmitted infection topics affecting young women, like whether *Chlamydia trachomatis* was a cause of preterm birth. When that work was done, we moved on to studying the natural history of genital herpes infections in young women and looking into whether *Mycoplasma hominis* was developing resistance to tetracyclines.

When it came time for me to submit a topic for my doctoral dissertation, I met with King Holmes and this is where **the big chance** comes in: I proposed the topic "The Polymicrobial Etiology of Cervical Neoplasia," which would have involved looking at most sexually-transmitted agents, except HPV, which at the time, was known only as a virus that caused warts.

However, just a few days earlier, Dr. Holmes had spoken with a Finnish gynecologist who had told him about incredible work that was coming out of the zur Hausen group in Germany. When I finished presenting my proposed dissertation topic, I recall Dr. Holmes saying something like, "That's interesting, but I really think you should take a look at HPV." So, I got a hold of Dr. zur Hausen's two key publications linking the newly discovered HPV types, HPV16 and HPV18, with cervical cancer, and that did it - I was sold on HPV.

Q2: Did you put the first dissertation topic entirely aside?

A: Not really. We were well on our way to doing extensive testing for other sexually transmitted infections, and in the end, the beauty of our overall design was that we were able to clearly show that HPV, not another STI, was *the* leading etiologic agent for cervical neoplasia.

Q3: Were you on your own or part of a big team?

A: I was very much part of a multidisciplinary team. I was the epidemiologist working with gynecologists, pathologists, molecular biologists, biostatisticians, virologists, and others.

Q4: How long did you have to work at it before you had some breakthrough results?

From coming up with the idea, to getting funding, to doing the study and publishing results – that all took about 7 years.

Q5: How do you think these results contributed to the HPV sector at that time?

Our study led to better understanding of the infectious epidemiology of HPV itself, which was a milestone. At that time there were other groups out there who were focused on HPV-related cancer, but in Seattle we were looking upstream - into the early infectious aspects of the virus.

And we accomplished much of what we set out to do. The major results of our study were published in the New England Journal of Medicine, which helped to solidify the connection between HPV and cervical neoplasia in the medical community. The importance of documenting the behavior of a virus in its early stages is clear: if you want to develop a prophylactic (preventative) vaccine, you need to know what is going on at the outset in order to time vaccination to precede that age. So, we needed to determine the ages at which people are likely to become infected, and if infected, how often and when a precancerous cervical lesion develops.

Q6: By the late 1980s, was the connection between HPV and cervical cancer clearly accepted in the medical scientific community?

A: Well, I would say that the connection was still subject to some debate at that time. Many careers had been devoted to studying other potential causes of cervical cancer. Even as late as the mid-1990s a few medical researchers maintained that it was herpes that led to cervical cancer. Sometimes old ideas take a while to dissipate.

Q7: Is it fair to say that your research laid part of the foundation for the connection between HPV and cancer to be made?

A: Yes, you can say that. While HPV DNA was being detected much more frequently in cervical cancer specimens than in normal cervical tissue, for an epidemiologist, that was insufficient. It was critical to show that HPV infection consistently occurs *before* the cancer develops. We were one of the first groups to provide strong evidence showing that HPV infection precedes precancerous lesions.

Q8: Back in 1998-2000, you were the principal investigator in the first proof-of-principle HPV-16 VLP vaccine trial of females between 16-23 years of age. Tell us about it - what were the challenges and why this age group?

The proof-of-principal trial was designed to find **evidence of protection**, and to find out if our research plan worked as is or needed tweaking before we went on to conduct much larger and more diverse vaccine trials, the results of which one would submit for licensing of the vaccine.

The most significant challenges in the proof-of-principle trial had to do with the design of the trial itself. Team members from various disciplines weighed in with different perspectives on how best to structure the trial, and it took some discussion to reach

consensus about our approach. For example, some thought it better to look at an older population of women because the average age of a precancerous cervical lesion was thought to be 35 years. However, when it came to determining the final characteristics and protocols for our testing population, we drew from earlier experience studying genital HPV infections and risk of precancerous cervical lesions in a younger age group. We knew we could leverage our understanding of young women; we knew their concerns. Bear in mind, participation in such a study is quite a bit to ask of someone over a long period of time – 3-5 years. These women needed to interface with highly dedicated clinical staff who could provide clinical care and support and assure them that their participation mattered - the information they were providing was important and worthwhile.

The study itself went smoothly as I recall. I enjoyed it, we had a good team and were ready to work with whatever the results would tell us. We tested about 2400 young women in a double-blind placebo-controlled trial, meaning neither the clinicians and investigators nor the patients knew whether they received the vaccine or the placebo. We met with these women every six months. Events got recorded without bias. When testing a new medical intervention, it is critical to have the conditions of complete objectivity that come with the double-blind placebo-controlled trial. The statistician kept track of how many positive HPV infections came in (also not knowing whether they were in the vaccine or placebo group) and when we reached the predefined number of persistent HPV infections, about 2 years later, the statistician broke the code so that the results could be revealed. It was incredibly exciting! Among those without HPV16 infection at the beginning of the trial, all new persistent HPV-16 infections were found in the placebo participants and none were found in the participants who received the vaccine!

Q9: Can you describe how you felt when the results came through?

I had a sense that I had just reached a true highlight of my professional career. It slowly sunk in just how much potential the vaccine had to prevent cervical cancer and therefore save lives. *If* the vaccine became readily available to women around the world (we will get to that topic in a minute). Most of the time researchers make incremental progress in their work (with one of the rare exceptions being Maurice Hilleman!), but I knew this was a major advancement.

Q10: Part of me is envious. Not too many people get to play a fundamental role in that kind of life-saving scientific achievement. It must feel amazing.

A: Yes, I know exactly what you are saying. I marvel at the fact that really my career was based on chance. At every important juncture I happened to have an opportunity and I went with it. And lo and behold I found myself with this terrific chance to be involved with the discovery of a life-saving intervention.

Q11: What do you think about where we are today in terms of HPV vaccine effectiveness and the prospect of eliminating HPV-related cancer?

A: We are in a terrific position! We have excellent vaccines that are safe and highly effective. Also important - we are now about 14 years down the road, and the body of evidence about the preventive power of the vaccine keeps growing. Data from countries throughout the world that have implemented HPV vaccination programs continue to prove that vaccination leads to substantial declines in the numbers of oncogenic HPV infections and the precancerous cervical lesions that they cause. That is important.

Our problem is going to be finding the funding to get these vaccines to the low and middle-income countries that do not have the resources but do have the most cervical cancer. The WHO has come up with a good plan for moving forward, but it will require a huge financial, political and structural commitment in order to make it happen. It's doable. Let's not forget, global childhood vaccination programs have been realized before. If you'd asked me this question four months ago, I would have said 'Yes, we can definitely implement a plan similar to this and yes, cervical cancer can be eliminated.' However, unfortunately another virus, SARS-CoV-2, the cause of COVID-19, has emerged and taken center-stage, calling for urgent attention and significant resources. That changes the situation.

Q12: The coronavirus pandemic has pushed vaccines into the global spotlight. How do you think the public's focus on finding an effective vaccine against COVID-19 will impact on vaccination uptake?

I have always been a big believer in vaccines, and as I get older, I have become even more appreciative. Vaccines are a major element of public health. I look forward to getting my adult vaccines, it clears up 'mental real estate', shortening the list of things to worry about. The fact that HPV vaccines reduce the risk for HPV-related cancers among both

females and males and, for females, reduces the need to undergo routine Pap smear examinations every few years before the age of 35 is a gift of time and a big relief.

COVID-19 is a major global wake up call, and if one good thing can come out of this pandemic, I think it is causing people to remember the importance of vaccines. Vaccines defeat viruses. We won't really know how the COVID-19 vaccine impacts uptake until it is actually here, but I am hopeful that it will reduce vaccine hesitancy. Ideally, it will also put a lid on the pseudo-science out there that generates so much fear and misunderstanding. It is a perfect time to remind people around the world about Maurice Hilleman and all the lives he saved with his vaccines.

Q13: What are you working on now?

Once the vaccine was launched in the mid-2000s, the focus of the work at that point shifted to cost effectiveness and implementation. I looked around and thought about different research ideas, but nothing seemed to strike a deep chord in me. In the meantime, my husband was outfitting a camper van so we could travel and soak up some of North America's beautiful nature. The last seven years have been mainly spent exploring hidden places and enjoying my family.

Q14: So, once you knew that the path of the vaccine was in good hands, you decided that you had done your part and focused on having fun outside of work?

That's pretty much it. I was intrigued by an incredibly talented HIV investigator I knew who was doing excellent work but chose to retire early in the midst of her success. I realized that the decisions we make about how we spend our lives are really our own, and what we choose to do with our time is up to us. I wanted this time for myself. And professionally I felt it was time to make room for the next generation of young, talented, energetic researchers to take over and forge onward.

Q15: What's been the best thing about working in the HPV field?

HPV research met my 'best job ever' criteria. I was always interested in learning about biological systems. I went from learning about epidemiology to getting the opportunity to explore a new epidemiological topic in collaboration with great people from many different disciplines. The cross-functional team of molecular biologists, virologists, pathologists, and other epidemiologists was fertile intellectual ground. We could ask each other questions and gain a deeper understanding of our subject thanks to all these

different perspectives. Ultimately, the greatest reward was knowing that I did something significant that makes peoples' lives better. I cannot imagine any other work that would have given me as much joy and satisfaction. It has been magical.