Literature Review

National STD Curriculum Podcast

HPV Vaccine Effects: New Data on Incidence of Cervical Cancer and Anal Dysplasia

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Season 2, Episode 4

This episode reviews recent studies on how HPV vaccines are helping to prevent cervical cancer and anal dysplasia. The episode also reviews a preteens' HPV vaccination uptake rates from 2008 to 2018 study.

Topics:

- STDs
- STIs
- HPV
- cervical cancer
- anal dysplasia

Meena S. Ramchandani, MD, MPH
Associate Editor
Associate Professor of Medicine
Division of Allergy and Infectious Diseases
University of Washington

Disclosures

Disclosures for Meena S. Ramchandani, MD, MPH
Consulting Fee: Innoviva Specialty Therapeutics

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Transcript

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In this episode:

[00.00] Introduction
Hello everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STD [sexually transmitted disease] literature review for health care professionals who are interested in remaining up-to-date on the diagnosis, management, and prevention of STDs.

[00.22] Background
We've talked a lot about bacterial STIs [sexually transmitted infections], and I'd like to focus this episode on a viral STI, specifically HPV [human papillomavirus]. This is an important topic because HPV vaccination is one of the greatest accomplishments in STI research. I'm going to review some articles that demonstrate this vaccine prevents cervical cancer, and it works well, extremely well. This is a big deal. We don't have many preventative measures for malignancies.

There are hundreds of types of HPV, with about 40 types that are spread through sexual contact. In 2006, the U.S. FDA approved the first HPV vaccine. It was a quadrivalent HPV vaccine called Gardasil, and this vaccine provides protection against HPV types 6, 11, 16, and 18, which causes about 70% of cervical cancers and about 90% of genital warts. In 2009, the FDA approved a second HPV vaccine, a bivalent vaccine known as Cervarix, that protects against types HPV 16 and 18. Later, in 2014, the third HPV vaccine was approved—it was a nonavalent vaccine called Gardasil 9 that protects against 9 HPV types, which together cause about 90% of cervical cancers and 90% of genital warts. Since 2017, the nonavalent HPV vaccine has been the only HPV vaccine used in the U.S. The dosing schedule for the Gardasil 9 has also evolved over time. Now, in the U.S., for healthy adolescents who start the vaccine series between the ages of 9 to 14 years old, they only need two doses of the vaccine for it to be effective, and for those of an older age, the vaccine is a 3-dose series. Some interesting articles have recently been published about HPV vaccination which I'd like to summarize in this episode.

[02.13] Paper #1

Lei J, Ploner A, Elfström KM, Wang J, Roth A, Fang F, Sundström K, Dillner J, Sparén P. HPV vaccination and the risk of invasive cervical cancer. N Engl J Med. 2020 Oct 1;383(14):1340-1348. **[PubMed Abstract]**

The first article for review was published in the *New England Journal of Medicine* in October 2020 by Dr. Lei and colleagues. It was titled "HPV vaccination and the risk of invasive cervical cancer." This study is important to mention because while the effectiveness of HPV vaccination on surrogates of cervical cancer, for example, for protection against HPV infection, precancerous cervical lesions, genital warts—those have already been established. There's really little data regarding the effect of vaccination on cervical cancer incidence, given the time lag from infection to clinical disease. The national vaccination programs in different countries, which were initiated more than ten years ago, they now allow for the evaluation of the incidence in cervical cancer in large number of individuals.

1. So, this study evaluated the association between HPV vaccination and the risk of invasive cervical cancer in greater than 1.6 million girls and women ages 10 to 30 years old, from 2006 to 2017 in Sweden.
2. Now, greater than 500,000 individuals received at least one dose of the quadrivalent HPV vaccine during the study period. Remember what I said in the introduction, the quadrivalent HPV vaccine, also known as Gardasil, provides protection against HPV types 6, 11, 16, and 18.
3. The authors found cervical cancer was diagnosed in only19 women who received at least one dose of the quadrivalent HPV vaccine compared to 538 women who had *not* received the vaccine.
4. With regards to those vaccinated versus unvaccinated, the cumulative incidence of cervical cancer was 47 cases per 100,000 persons among women who had been vaccinated and 94 cases per 100,000 persons among those who had not been vaccinated. It's a *huge* difference.
5. They then looked at age of vaccination to see if this made a difference in risk of cervical cancer, and what they found is that among women who had initiated vaccination before the age of 17 years, the

cumulative incidence was only 4 cases per 100,000 persons by the age of 28 years. But in women who had initiated vaccination at the age of 17 to 30 years, the cumulative incidence of cervical cancer was 54 cases per 100,000 persons by the age of 30 years.
6. So this information translates to an 88% reduction in cervical cancer among women who had been vaccinated before the age of 17 years and a 53% reduction in cervical cancer among women who had been vaccinated at the age of 17 to 30 years. So a pretty big difference.

In summary, by using a nationwide registry data from Sweden, these authors were able to examine the association between HPV vaccination and the risk of cervical cancer in a very large group of individuals. In this study, HPV vaccination was associated with a substantially reduced risk of invasive cervical cancer. And the reduction in the incidence of invasive cervical cancer was much more pronounced among women who were vaccinated at a younger age. If the vaccine is given before the age of 17 years, the risk of cervical cancer is 88% lower than among those who had never been vaccinated, so a pretty big deal.

[05.33] Paper #2

Falcaro M, Castañon A, Ndlela B, Checchi M, Soldan K, Lopez-Bernal J, Elliss-Brookes L, Sasieni P. The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: A register-based observational study. Lancet. 2021 Dec 4;398(10316):2084-2092. **[PubMed Abstract]**

The second article to discuss was published in *The Lancet* in November 2021 and is titled “The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: A register-based observational study” by Dr. Falcaro and colleagues.

1. This group looked at the early effect of routine vaccination for girls ages 12 to 13 years and a catch-up program for females ages 14-18 years with the bivalent HPV vaccine, also known as Cervarix that covers HPV 16 and 18.
2. The authors used a model to estimate the relative risk of cervical cancer and cervical intraepithelial neoplasia 3, or CIN 3, in three vaccinated cohorts of different ages and compared this to earlier cohorts not eligible for HPV vaccination. They defined the cohorts to account for the age at which women were offered HPV immunization, allowing them to then estimate the effect to the routine vaccination program offered to girls ages 12 to 13 years separately from the catch-up cohorts who might have already been exposed to certain HPV serotypes.
3. They found the estimated relative reduction in cervical cancer rates by age at when a vaccine was offered were 34% for ages 16 to 18 years, 62% for ages 14 to 16 years, and 87% for ages 12 to 13 years compared with the reference unvaccinated cohort.
4. Risk reductions in CIN3 were 39% for those offered vaccination at ages 16 to 18 years, 75% for ages 14 to 16 years, and 97% for ages 12 to 13 years.
5. They estimated that by 2019, there had been 448 fewer than expected cervical cancers and more than 17,000 fewer than expected cases of CIN3 in vaccinated cohorts in England.

So this group also demonstrated a substantial reduction in cervical cancer as well as the incidence of CIN3 in women after the introduction of the HPV immunization program in England. They found a greater effect when the vaccine was offered at a younger age, at 12 to 13 years old.

[07.58] Paper #3

Chido-Amajuoyi OG, Talluri R, Wonodi C, Shete S. Trends in HPV vaccination initiation and completion within ages 9-12 years: 2008-2018. Pediatrics. 2021 Jun;147(6):e2020012765. **[PubMed Abstract]**

So now, one of the questions is how are we doing with regards to HPV vaccination coverage in the U.S.? I’d

like to briefly review an article published in *Pediatrics* in June of 2021. This article was titled “Trends in HPV vaccination initiation and completion within ages 9-12 years: from 2008-2018,” and this was published by Dr. Chido-Amajuoyi and colleagues.

1. The authors examined trends in HPV vaccination within ages from 9 to 12 years in the U.S. They looked at HPV vaccination initiation as well as HPV vaccination up-to-date—or, the rates for fully vaccinated individuals—as well as some sociodemographic factors from 2008 to 2018.
2. Overall, what the authors found is that initiation of HPV vaccination rates increased from 17% to 63% from 2008 to 2018, and fully immunized individuals increased from 14% to 33% during this same time period, so we still have a ways to go.
3. In 2011, a gender-neutral HPV vaccination approach was recommended in the U.S. The authors found that the rate of HPV up-to-date status for fully immunized individuals among boys increased by 32% from 2011 to 2018, but for girls, it only rose up by 7% during this same period of time.
4. Hispanic populations had a higher HPV vaccination uptake rate throughout the study period. The overall HPV vaccination up-to-date rate—or, for fully immunized individuals—was higher among non-Hispanic Black populations compared to non-Hispanic White populations.
5. In 2018, rates of initiation of the HPV vaccination were greater than 60% in 32 states, greater than 70% in 16 states, and one state, the state of Rhode Island, had an 86% initiation rate!
6. For HPV vaccination up-to-date rates, unfortunately, most states were below 50%. Only Rhode Island, Colorado, Hawaii, DC, and Ohio were above 50%.

So the authors of this study found that while HPV vaccinations have increased over the years, completely vaccinated individuals ages 9 to 12 years in most U.S. states were, unfortunately, less than 50%. The authors mention that HPV vaccination at the younger ages of 9 to12 years is associated with higher levels of immunogenicity and efficacy compared with vaccination in later years. There were marked regional differences in HPV vaccinations, with Rhode Island achieving a significantly higher HPV vaccination rate than any other U.S. state. The authors point out some reasons for this: a strong public health program, school-based immunization programs, and a CDC-funded quality improvement program for practices to help with vaccination uptake in Rhode Island.

[11.02] Paper #4

Goldstone SE, Giuliano AR, Palefsky JM, Lazcano-Ponce E, Penny ME, Cabello RE, Moreira ED Jr, Baraldi E, Jessen H, Ferenczy A, Kurman R, Ronnett BM, Stoler MH, Bautista O, Das R, Group T, Luxembourg A, Zhou HJ, Saah A. Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: Results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis. 2021 Nov 12:S1473-3099(21)00327-3. **[PubMed Abstract]**

There are also emerging data that HPV vaccination reduces the risk of genital warts, anal intraepithelial neoplasia, and anal cancer in men. The next article I’d like to briefly review for this episode is one published by Dr. Goldstone and colleagues, and it was titled “Efficacy, immunogenicity, and safety of a quadrivalent HPV vaccine in men: Results of an open-label, long-term extension of a randomised, placebo-controlled, phase 3 trial,” and this was published in *Lancet Infectious Diseases* in November of 2021.

1. So, this study was a follow-up study over ten years evaluating the incidence in men of external genital warts, external genital lesions, and in MSM, or men who have sex with men, anal intraepithelial neoplasia (or anal cancer), due to specific HPV serotypes. These men were originally enrolled in a randomized, placebo-controlled study for the quadrivalent HPV vaccine.
2. There were 1800, actually over 1800, participants who enrolled in a long-term follow-up study: 936 were part of the early vaccination group, and 867 were part of the catch-up vaccination group. These were participants who were originally in the placebo group in the original study and then offered the quadrivalent HPV vaccine at the end of the base study.
3. In the early vaccine group, the incidence per 10,000 person-years of external genital warts related to

HPV 6 or 11 was 0 versus 137 in the placebo group. They used data from the original base study to make that comparison. For external genital lesions related to HPV 6, 11, 16, or 18, it was 0 versus 140, and in MSM, for anal intraepithelial neoplasia (or anal cancer), the incidence was 21 versus 906.
4. Participants in the catch-up vaccination group also had no new genital warts and a lower incidence of anal intraepithelial neoplasia (or anal cancer) compared with during the base study (i.e. before the HPV vaccine was administered).

So, in summary, the authors found in this study that HPV vaccination elicits long-term protection from HPV-related diseases in men. Although early vaccination before HPV exposure is optimal, catch-up vaccination is also beneficial in protecting against new HPV infections as well as resultant disease.

[13.32] Summary

To conclude, I'd like to summarize some key points from this session:

1. The risk of cervical cancer among a large group of participants who had initiated the quadrivalent HPV vaccine was associated with a substantially lower risk of invasive cervical cancer, especially among women who were vaccinated before the age of 17 years old.
2. A routine vaccination program in England showed a reduction of cervical cancer and incidence of cervical intraepithelial neoplasia with the bivalent HPV vaccine, with more of an effect when the vaccine was offered from the ages of 12 to 13 years.
3. While in the U.S. we've increased our rates of HPV vaccination since 2008, completely vaccinated individuals ages 9 to 12 years is less than 50% in most states. Rhode Island seems to have a successful model for HPV vaccination, which we can learn from.
4. In a ten-year follow-up study, men who received HPV vaccination had a lower incidence of HPV-related diseases, even if they received the vaccine as part of a catch-up program.
5. Overall, HPV vaccination is a success in preventing HPV-related diseases and while vaccinating at a younger age is better, getting vaccinated regardless of age is important. Now that we have this highly effective prevention tool, a key challenge for the future will be improving vaccine uptake, both in the U.S. as well as globally.

Thank you for listening. Have a wonderful day.

[15.02] Credits

This podcast is brought to you by the National STD Curriculum, the University of Washington STD Prevention Training Center, and is funded by the Centers for Disease Control and Prevention.

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