The HPV vaccine is now recommended for adults aged 27–45: Counseling implications

Can we improve human papillomavirus (HPV) vaccination rates among boys and girls so "catch-up" vaccinations in adults are unnecessary?

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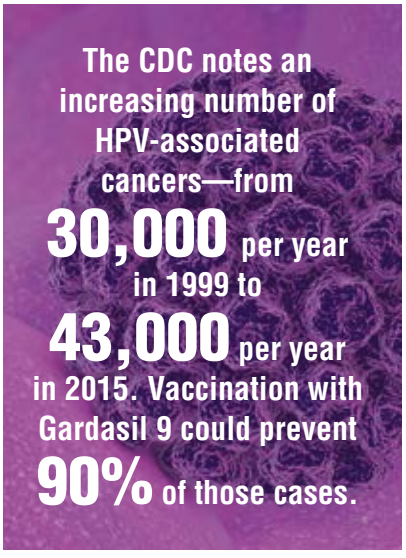
The US Food and Drug Administration (FDA) recently extended the approval for Gardasil 9 (to prevent HPV-associated cancers, cancer precursors, and genital lesions) to men and women aged 27 to 45.[1] In this editorial, we discuss the evolution of the HPV vaccine since its initial approval more than 10 years ago, the benefits of primary prevention with the HPV vaccine, and the case for the FDA's recent extension of coverage to older men and women.

The evolution of the HPV vaccine

Since recognition in the 1980s and 90s that high-risk strains of HPV, notably HPV types 16 and 18, were linked to cervical cancer, there have been exciting advances in detection and prevention of high-risk HPV infection. About 70% of cervical cancers are attributable to these 2 oncogenic types.[2] The first vaccine licensed, Gardasil (Merck), was approved in 2006 for girls and women aged 9 through 26 to prevent HPV-related diseases caused by types 6, 11, 16, and 18.[3] The vaccine was effective for prevention of cervical cancer; genital warts; and grades 2 and 3 of cervical, vulvar, and vaginal intraepithelial neoplasia. In 2008, prevention of vulvar and vaginal cancers was added to the indication. By 2009, prevention of genital warts was added, and use in males aged 9 to 15 was approved. By 2010 sufficient data were accumulated to document prevention of anal cancer and anal intraepithelial neoplasia in men and women, and this indication was added.

In 2014 Gardasil 9 was approved to extend coverage to an additional 5 oncogenic HPV types (31, 33, 45, 52, and 58), now covering an additional 20% of cervical cancers, and in 2015 Gardasil 9 indications were expanded to include boys and men 9 to 26 years of age. Immunogenicity studies were performed to infer effectiveness of a 2-dose regimen in boys and girls aged 9 to 14 years, which was recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) in late 2016.[4]

Until October 2018, Gardasil 9 was indicated for prevention of genital warts, cervical, vaginal, vulvar and anal cancers and cancer precursors for males and females aged 9 to 26 years. In October the FDA extended approval of the 3-dose vaccine regimen to men and women up to age 45.



HPV vaccine uptake

HPV vaccination has been underutilized in the United States. In 2017, a disappointing 49% of adolescents were up to date on vaccination, and 66% had received at least one dose.[5] In rural areas the vaccination rates are 11 points lower than in urban regions.[6] The CDC notes an increasing

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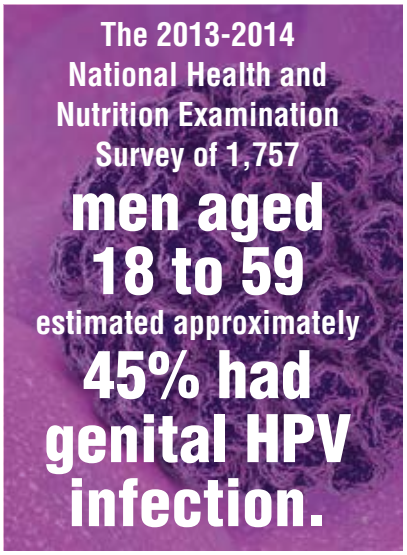
number of HPV-associated cancers—from 30,000 per year in 1999 to 43,000 per year in 2015—due mostly to increases in oral and anal carcinomas. Vaccination with Gardasil 9 could prevent 90% of those cases.[7]

Non-US successes. HPV vaccine uptake in Australia provides an excellent opportunity to study the impact of universally available, school-based vaccinations. In 2007 Australia implemented a program of free HPV vaccination distributed through schools. Boys and girls aged 12 and 13 were targeted that year, with catch-up vaccinations for those aged 13 to 18 in 2007-2009 in schools and for those aged 18 to 26 reached in the community.[8]

Ali and colleagues studied the preprogram and postprogram incidence of genital warts.[9] About 83% received at least 1 dose of vaccine, and 73% of the eligible population completed the 3-dose regimen. There was a significant reduction in warts in both men and women younger than age 21 from 2007 to 2011 (12.1% to 2.2% in men and 11.5% to 0.85% in women). In the 21 to 30 age group there were similar reductions. This study demonstrates that with universal access and public implementation, the rates of HPV-associated disease can be reduced dramatically.

Data informing expanded vaccination ages

Will vaccination of an older population, with presumably many of whom sexually active and at risk for prior exposure to multiple HPV types, have a reasonable impact on lowering HPV-associated cancers? Are HPV-detected lesions in 27- to 45-year-old women the result of reactivation of latent HPV infection, or are they related to new-onset exposure? The FDA reviewed data from 3 studies of HPV vaccination in women aged 27 to 45. The first enrolled women who were naïve to oncogenic HPV types and provided all 3 doses of quadrivalent vaccine were followed for 4 years, along with a comparison group of nonvaccinated women. The second study allowed the nonvaccinated group to receive vaccine in year 4. Both groups were followed up to 10 years with the relevant outcome defined as cumulative incidence of HPV 6/11/16/18-related CIN and condyloma. The third study looked at the same outcomes in a set of all women—whether HPV high-risk naïve or not—after receiving vaccine and followed more than 10 years.[7] This last study is most relevant to ObGyns, as it is closest to how we would consider vaccinating our patients.



The study findings are reassuring: A large proportion of HPV infections in women between 27 and 45 are the result of new exposure/infection. A study of 420 online daters aged 25 to 65 showed an annual incidence of high-risk HPV types in vaginal swabs of 25.4%, of which 64% were likely new acquisitions.[10] The 2013-2014 National Health and Nutrition Examination Survey of 1,757 men aged 18 to 59 estimated approximately 45% had genital HPV infection. There was a bimodal distribution of disease with peaks at 28 to 32 and a larger second peak at 58 to 59 years of age.[11] Bottom line: Men and women older than age 26 who are sexually active likely acquire new HPV infections with oncogenic types. Exposure to high-risk HPV types prior to vaccination—as we would expect in the real-world setting—did not eliminate the substantial benefit of immunization.

Based on these study results, and extrapolation to the 9-valent vaccine, the FDA extended the approval of Gardasil 9 to men and women from age 9 to 45. The indications and usage will remain the same: for prevention of cervical, vulvar, vaginal, and anal cancer and genital warts as well as precancerous or dysplastic lesions of the cervix, vulva, vagina, and anus related to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

Impact of the new indication on HPV-related disease

As described above, widespread vaccination of young girls and boys is going to have major impact on HPV-related disease, including precancer and cancer. Because there is evidence that older women and men are at risk for new HPV infection,[10] there likely will be some benefit from vaccination of adults. It is difficult, however, to extrapolate the degree to which adult vaccination will impact HPV-related disease. This is because we do not fully understand the rates at which new HPV infection in the cervices of older women will progress to high-grade dysplasia or cancer. Further, the pathophysiology of HPV-related cancers at other anogenital sites and new

oral-pharyngeal infection is poorly understood in comparison with our knowledge of the natural history of high-risk HPV infection in younger women. That said, because of the outstanding efficacy of HPV vaccination and the low-risk profile, even if the actual impact on prevention of cancer or morbidity from dysplasia is relatively low, adult vaccination benefits outweigh the limited risks.

It may be that increased vaccination and awareness of vaccination for adults may enhance the adherence and acceptance of widespread vaccination of boys and girls. Adult vaccination could create a cultural shift toward HPV vaccination acceptance when adult parents and loved ones of vaccine-age boys and girls have been vaccinated themselves.

Current and future insurance coverage

The Affordable Care Act, otherwise known as Obamacare, mandates coverage for all immunizations recommended by the ACIP. HPV vaccination up to age 26 is fully covered, without copay or deductible. The ACIP did consider extension of the indications for HPV vaccination to men and women up to age 45 at their October 2018 meeting. They are tasked with considering not only safety and efficacy but also the cost effectiveness of implementing vaccination. They continue to study the costs and potential benefits of extending HPV vaccination to age 45. Their recommendations may be determined at the February 2019 meeting—or even later in 2019. The American College of Obstetricians and Gynecologists (ACOG) relies upon ACIP for practice guidance. Once the ACIP has made a determination, and if new guidelines are published in the *Morbidity and Mortality Weekly Report*, insurance coverage and ACOG guidance will be updated.

How should we react and change practice based on this new indication?

Given the information reviewed by the FDA, ObGyns will want to discuss the availability of Gardasil 9 with our patients between ages 27 and 45 who have not been previously immunized. Especially for our patients with exposure to multiple or new sexual partners, immunization against oncogenic HPV viral types is effective in providing protection from cancer precursors and cancers of the cervix, vulva, vagina, and anus—and of course from genital warts. They should understand that, until formal recommendations are published by the ACIP, they are likely to be responsible for the cost of the vaccination series. These conversations will also remind our patients to immunize their teens against HPV. The more conversation we have regarding the benefits of vaccination against high-risk HPV types, the more likely we are to be able to achieve the impressive results seen in Australia. ●

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