Human Papillomavirus Vaccination

ABSTRACT: Human papillomavirus (HPV) is associated with anogenital cancer (including cervical, vaginal, vulvar, penile, and anal), oropharyngeal cancer, and genital warts. The HPV vaccination significantly reduces the incidence of anogenital cancer and genital warts. Despite the benefits of HPV vaccines, only 41.9% of girls in the recommended age group, and only 28.1% of males in the recommended age group have received all recommended doses. Compared with many other countries, HPV vaccination rates in the United States are unacceptably low. The U.S. Food and Drug Administration has approved three vaccines that are effective at preventing HPV infection. These vaccines cover 2, 4, or 9 HPV serotypes, respectively. Safety data for all three HPV vaccines are reassuring. The HPV vaccines are recommended for girls and boys aged 11–12 years and can be given to females and males up to age 26 years. The Advisory Committee on Immunization Practices and the American College of Obstetricians and Gynecologists recommend routine HPV vaccination for girls and boys at the target age of 11–12 years (but it may be given from the age of 9 years) as part of the adolescent immunization platform in order to help reduce the incidence of anogenital cancer and genital warts associated with HPV infection. Obstetrician–gynecologists and other health care providers should stress to parents and patients the benefits and safety of HPV vaccination and offer HPV vaccines in their offices.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists (the College) makes the following recommendations and conclusions:

- It is crucial that obstetrician–gynecologists and other health care providers educate parents and patients on the benefits and safety of human papillomavirus (HPV) vaccination and offer HPV vaccines in their offices. A health care provider’s recommendation to vaccinate is a strong influence in parents’ decision making.
- Obstetrician–gynecologists play a critical role in women’s care and should assess and vaccinate adolescent girls and young women with HPV vaccine during the catch-up period (ages 13–26 years).
- Obstetrician–gynecologists and other health care providers play a significant role and should educate parents in their decision making regarding vaccinations for male and female children.
- Obstetrician–gynecologists and other health care providers can use well-women visits as an opportunity to provide counseling to parents and encourage them to speak to their children’s health care providers to request HPV vaccination at the targeted age range of 11–12 years.
- The Centers for Disease Control and Prevention (CDC) and the College recommend routine HPV vaccination for females and males aged 9–26 years.
- The target age for HPV vaccination is 11–12 years for girls and boys, but the HPV vaccine can be given to both genders through 26 years of age.
- For girls and boys who receive their first dose of HPV vaccine before 15 years of age, only two doses are needed. The timing of the two doses is 0 (baseline) and 6–12 months. If the interval between the two doses is less than 5 months, a third dose is recommended. If females or males receive their first dose at 15 years of age or older, three doses are needed and
Human papillomavirus (HPV) is associated with anogenital cancer (including cervical, vaginal, vulvar, penile, and anal), oropharyngeal cancer, and genital warts. Of the more than 150 HPV genotypes, 13 genotypes have been shown to cause cervical cancer (1). Most cases of HPV-associated cancer are caused by HPV genotypes 16 and 18 (2–5). In the United States, HPV genotypes 16 and 18 account for 66% of cases of cervical cancer, and HPV genotypes 31, 33, 45, 52, and 58 account for an additional 15% of cases of cervical cancer (5). For cervical intraepithelial neoplasia 2+, 50–60% of cases are caused by HPV genotypes 16 and 18, and 25% of cases are caused by HPV genotypes 31, 33, 45, 52, and 58 (6). Approximately 90% of cases of genital warts are caused by HPV genotypes 6 and 11 (7).

Despite cervical cytology screening in the United States, each year cervical cancer is diagnosed in more than 13,000 women and nearly 4,000 die from the disease (8). Most of these cases of cancer occur because of a lack of adequate screening. Human papillomavirus-associated cancer also occurs in males. The average number of anogenital or oropharyngeal cancer in males per year is 15,793, and 10,200 (65%) of these are associated with HPV 16 or HPV 18 (3).

The HPV vaccine significantly reduces the incidence of anogenital cancer and genital warts. Additionally, HPV vaccination may decrease the incidence of oropharyngeal cancer as well as the maternal transmittal of HPV to infants. Human papillomavirus in infants may result in recurrent laryngeal papillomatosis, although definitive prevention trials have not been completed for these two disease endpoints (9). In the United States, the prevalence of vaccine-type HPV decreased 56% among females aged 14–19 years between 2006 (when the quadrivalent HPV vaccine was introduced) and 2010 (10). Despite the benefits of HPV vaccines, only 41.9% of females in the recommended age group, and only 28.1% of males in the recommended age group have received all recommended doses (11). Compared with many other countries, HPV vaccination rates in the United States are unacceptably low (11).

**Human Papillomavirus Vaccines**

The U.S. Food and Drug Administration (FDA) has approved three vaccines that are effective at preventing HPV infection. These vaccines cover 2, 4, or 9 HPV serotypes, respectively. The HPV vaccine is recommended for girls and boys aged 11–12 years and can be given to females and males up to age 26 years. For girls and boys who receive their first dose of HPV vaccine before 15 years of age, only two doses are needed. The timing of the two doses is 0 (baseline) and 6–12 months. If the interval between the two doses is less than 5 months, a third dose is recommended (12). An interval greater than 12 months is not recommended in order to ensure both doses are given before the onset of sexual activity. If females or males receive their first dose at 15 years of age or older, three doses are needed and given at 0 (baseline), 1–2 months after the first dose, and 6 months after the first dose (12).

The durability of the immune response (ie, how long protection lasts) is being monitored in long-term studies, and currently there is no indication for a booster vaccine (13). The vaccine series does not need to be restarted in the case of a delay in administration of the second or third dose.

Although obstetrician–gynecologists are not likely to care for many patients in the initial HPV vaccination target group, they have the opportunity to educate women about the importance of vaccinating their children at the recommended age. Obstetrician–gynecologists and other health care providers play a significant role and should educate parents in their decision making regarding vaccinations for male and female children. Furthermore, obstetrician–gynecologists play a critical role in women’s care and should assess and vaccinate adolescent girls and young women with the HPV vaccine during the catch-up period (ages 13–26 years). Human papillomavirus vaccination is not associated with an earlier onset of sexual activity (14) or increased incidence of sexually transmitted infections (15).
Timing of Vaccination

The Advisory Committee on Immunization Practices and the College recommend routine HPV vaccination for girls and boys at the target age of 11–12 years (but it may be given from the age of 9 years) as part of the adolescent immunization platform in order to help reduce the incidence of anogenital cancer and genital warts associated with HPV infection. Bivalent, quadrivalent, and 9-valent vaccines are approved for females aged 9–26 years and quadrivalent and 9-valent vaccines are approved for males aged 9–26 years. Recently, the bivalent vaccine has been withdrawn from the U.S. market. The 9-valent vaccine, which covers five additional cancer-related HPV serotypes will soon replace the quadrivalent vaccine. Studies show that two doses of HPV vaccine given 6 months apart in individuals aged 9–14 years resulted in antibody titers equal to those in individuals aged 15–26 years who were given three doses. Hence, only two doses, 6–12 months apart, are needed if HPV vaccination is initiated before 15 years of age in boys and girls (11, 12). The 6-month interval between these two doses is critical for ensuring adequate immune titers and durability of protection. If the interval between the two doses is less than 5 months, a third dose is recommended. In addition to the ability to use two doses instead of three doses, earlier vaccination also is preferred because HPV vaccines are most effective when given before prior exposure and infection with HPV, which coincide with the onset of sexual activity. Statistics show that one in three ninth graders and two in three 12th graders have engaged in sexual intercourse (15, 16). In Sweden, vaccine effectiveness in preventing genital warts was 93% among girls vaccinated between 10 years and 13 years of age compared with 48% and 21% if vaccinated at ages 20–22 years and 23–26 years, respectively (17). All of these findings underscore the importance of vaccination at the target age (11–12 years), which is before the onset of potential exposure in the vast majority.

Vaccination is recommended regardless of sexual activity or prior exposure to HPV. Although the vaccine may be less effective in previously infected individuals, it is expected that some benefit will be experienced because prior exposure to all nine vaccine types is highly unlikely (18, 19). Vaccination is recommended even if the patient is tested for HPV DNA and the results are positive. Testing for HPV DNA is not recommended before vaccination.

9-valent Human Papillomavirus Vaccine

The 9-valent HPV vaccine was licensed by the U.S. Food and Drug Administration in December 2014. The Advisory Committee on Immunization Practices has recommended similar schedules as those for quadrivalent vaccine. In a phase III efficacy trial that made a comparison of the 9-valent HPV vaccine with the quadrivalent HPV vaccine among approximately 14,000 females aged 16–26 years, the 9-valent HPV vaccine had high efficacy for prevention of cervical intraepithelial neoplasia 2+, vulvar intraepithelial neoplasia 2 or 3, and vaginal intraepithelial neoplasia 2 or 3 due to HPV genotypes 31, 33, 45, 52, and 58 (see Table 1) (20). The antibody titer against HPV genotypes 6, 11, 16, and 18 was not reduced with the addition of the other five HPV genotypes (20).

Revaccination with the 9-valent HPV vaccine in individuals who previously completed the three-dose series with the quadrivalent HPV vaccine or the bivalent HPV vaccine currently is not a routine recommendation. If obstetrician–gynecologists or other health care providers do not know or do not have the same HPV vaccine product previously administered, or are in settings that are transitioning to the 9-valent HPV vaccine, any available HPV vaccine product may be used to continue or complete the series for females for protection against HPV genotypes 16 and 18; the 9-valent HPV vaccine or the quadrivalent HPV vaccine may be used to continue or complete the series for males (20).

Safety

Safety data for all three HPV vaccines are reassuring. According to the Vaccine Adverse Events Reporting System, more than 60 million doses of HPV vaccine have been distributed since 2006, and there are no data to suggest that there are any severe adverse effects or adverse reactions linked to vaccination (21). The 9-valent and quadrivalent vaccines had similar safety profiles, except that the 9-valent HPV vaccine had a higher rate of injection site swelling and erythema than the quadrivalent HPV vaccine, and the rate increased after each successive dose of the 9-valent HPV vaccine (20). Obstetrician–gynecologists and other health care providers should counsel patients to expect mild local discomfort after the vaccination and that such discomfort is not a cause for concern. Available data demonstrate no safety concerns in individuals who were vaccinated with the 9-valent HPV vaccine after having been vaccinated with the quadrivalent HPV vaccine (22, 23). Anyone who has ever had a life-threatening allergic reaction to any component of the HPV vaccine, or to a previous dose of the HPV vaccine, should not get the vaccine. Obstetrician–gynecologists and other health care providers should assess patients for severe allergies, including but not limited to an allergy to yeast or prior HPV vaccine dose. An individual with a moderate or severe febrile illness should wait until the illness improves before receiving a vaccine.

Considerations for Special Populations

Although HPV vaccination in pregnancy is not recommended, neither is routine pregnancy testing before vaccination. Available safety data regarding the inadvertent administration of the vaccine during pregnancy are reassuring (24, 25). Patients and obstetrician–gynecologists...
The response may be less robust in the immunocompromised patient. The three-dose regimen is recommended for immunosuppressed men and women.

Patient Education and Vaccination Efforts

High rates of HPV vaccination will reduce the burden of HPV-related disease in the United States. Current vaccination rates are unacceptably low. Studies have shown that physicians’ recommendations play a crucial role in the recommendation of HPV vaccination by patients and parents of patients. Obstetrician–gynecologists and other health care providers should stress to parents or other health care providers to register women exposed to the 9-valent HPV vaccine around the time the pregnancy began or during pregnancy by contacting the manufacturer (www.merckpregnancyregistries.com/gardasil9.html). Pregnancy registries for the quadrivalent HPV vaccine and bivalent HPV vaccine have been closed. If a vaccine series is started and a patient then becomes pregnant, completion of the vaccine series should be delayed until that pregnancy is completed. Lactating women can receive any HPV vaccine because inactivated vaccines like HPV do not affect the safety of breastfeeding for these women or their infants.

The presence of immunosuppression, like that experienced in patients with human immunodeficiency virus (HIV) infection or organ transplantation, is not a contraindication to HPV vaccination. However, the immune response may be less robust in the immunocompromised patient. The three-dose regimen is recommended for immunosuppressed men and women.

Human papillomavirus vaccines are not currently licensed in the United States for women older than 26 years. Off-label use may be indicated on a case-by-case basis.

Table 1. Use and Efficacy of the Bivalent, Quadrivalent, and 9-valent Human Papillomavirus Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>HPV Types</th>
<th>Disease Reduction</th>
<th>Efficacy*</th>
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<tbody>
<tr>
<td>Bivalent</td>
<td>16 and 18</td>
<td>HPV genotypes 16- and 18-related cervical cancer, CIN 1, CIN 2/3, and adenocarcinoma in situ</td>
<td>HPV disease related to genotypes 16 and 18; 98.1%1,2</td>
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<tr>
<td>Quadrivalent</td>
<td>6, 11, 16, and 18</td>
<td>HPV genotypes 6, 11, 16, and 18-related cervical, vulvar, and vaginal cancer; CIN 1; CIN 2/3; adenocarcinoma in situ; VIN 2/3; and vaginal intraepithelial neoplasmia 2/3 in females</td>
<td>HPV disease related to genotypes 6, 11, 16, and 18; up to 100%3,4 External genital disease in men; 90.4%5</td>
</tr>
<tr>
<td>9-valent</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, and 58</td>
<td>HPV genotypes 6, 11, 16, 18, 31, 33, 45, 52, and 58-related cervical, vulvar, and vaginal cancer; CIN 2/3; adenocarcinoma in situ; VIN 2/3; and vaginal intraepithelial neoplasmia 2/3 in females</td>
<td>HPV disease related to genotypes 6, 11, 16, 18; greater than 99% HPV related to genotypes 31, 33, 45, 52, and 58; 96.7%6</td>
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Abbreviations: CIN, cervical intraepithelial cancer; HPV, human papillomavirus; VIN, vulvar intraepithelial neoplasia.

*Efficacy rates based recipient being naive to the vaccine HPV genotypes at the time of vaccination.


and patients the benefits and safety of HPV vaccination and offer HPV vaccines in their offices. Obstetrician–gynecologists play a critical role and should assess and vaccinate adolescent girls and young women during the catch-up period (ages 13–26 years).

According to the Centers for Disease Control and Prevention, if health care providers increase HPV vaccination rates in eligible recipients to 80%, it is estimated that an additional 53,000 cases of cervical cancer could be prevented during the lifetime of those younger than 12 years (29). Furthermore, for every year that the vaccination rate does not increase, an additional 4,400 women will develop cervical cancer.

For More Information
The American College of Obstetricians and Gynecologists has identified additional resources on topics related to this document that may be helpful for ob-gyns, other health care providers, and patients. You may view these resources at: www.acog.org/More-Info/HPV.

These resources are for information only and are not meant to be comprehensive. Referral to these resources does not imply the American College of Obstetricians and Gynecologists’ endorsement of the organization, the organization’s website, or the content of the resource. The resources may change without notice.

References


