Human Papillomavirus Vaccination

**ABSTRACT:** Human papillomavirus (HPV) causes significant morbidity and mortality in women and men. The HPV vaccine significantly reduces the incidence of anogenital cancer and genital warts in women and in men. Human papillomavirus vaccines are among the most effective vaccines available worldwide, with unequivocal data demonstrating greater than 99% efficacy when administered to women who have not been exposed to that particular type of HPV. Obstetrician–gynecologists and other health care professionals should strongly recommend HPV vaccination to eligible patients and stress the benefits and safety of the HPV vaccine. Further, obstetrician–gynecologists are encouraged to stock and administer HPV vaccines in their offices when feasible. Ideally, the HPV vaccine should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity. Unvaccinated women age 26 years and younger should receive the HPV vaccine series regardless of sexual activity, prior exposure to HPV, or sexual orientation. The HPV vaccine is now licensed in the United States for women and men through age 45 years. For some women aged 27–45 years who are previously unvaccinated, obstetrician–gynecologists and other health care professionals may use shared clinical decision making regarding HPV vaccination, considering the patient’s risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit.

**Recommendations and Conclusions**

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

- The Advisory Committee on Immunization Practices and ACOG recommend routine human papillomavirus (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.
- Obstetrician–gynecologists and other health care professionals should strongly recommend HPV vaccination to eligible patients and stress the benefits and safety of the HPV vaccine.
- Obstetrician–gynecologists should assess and vaccinate adolescent girls and young women with the HPV vaccine during the catch-up period (ages 13–26 years), regardless of sexual activity, prior exposure to HPV, or sexual orientation, if they were not vaccinated in the target age of 11–12 years.
- Obstetrician–gynecologists and other health care professionals should educate parents in their decision making regarding vaccinations for their daughters and sons.
- For some women aged 27–45 years who are previously unvaccinated, obstetrician–gynecologists and other health care professionals may use shared clinical decision making regarding the HPV vaccination, considering the patient’s risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit.
- The American College of Obstetrician–Gynecologists does not recommend that an individual who received the quadrivalent HPV vaccine be revaccinated with 9-valent HPV vaccine, including those aged 27–45 years who previously completed some, but not all, of the vaccine series when they were younger.
- Obstetrician–gynecologists are encouraged to stock and administer HPV vaccine in their offices when feasible.
Vaccination is recommended for women through age 26 years even if the patient is tested for HPV DNA and the results are positive.

Testing for HPV DNA is not recommended before vaccination.

Human papillomavirus vaccination is not recommended during pregnancy; however, routine pregnancy testing is not recommended before vaccination.

The HPV vaccine can and should be given to breastfeeding women age 26 years and younger who have not previously been vaccinated.

In children with a history of sexual abuse or assault, the HPV vaccine should be given as early as possible, starting at age 9 years.

**Background**

Human papillomavirus (HPV) causes significant morbidity and mortality in women and men. Human papillomavirus infection is associated with anogenital cancer (including cervical, vaginal, vulvar, penile, and anal) and oropharyngeal cancer (back of tongue, tonsil) (see Table 1 Number of Human Papillomavirus–Associated and Estimated Number of Human Papillomavirus–Attributable Cancer Cases Per Year). Human papillomavirus also is associated with genital warts. Of the more than 150 HPV genotypes, 13 genotypes have been shown to cause cervical cancer (1). Despite the success of cervical cancer 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 (2). Most cases of cervical cancer occur in women who have had inadequate screening. Approximately 90% of cases of genital warts are caused by HPV genotypes 6 and 11 (3). Human papillomavirus–associated cancer in men is increasing in the United States, as are HPV–associated anal and vulvar cancer in women (4).

Despite the benefits of HPV vaccines, only 54% of women and 49% of men in the recommended age groups have received all recommended doses (5). Compared with many other countries, HPV vaccination rates in the United States are unacceptably low (5). According to the Centers for Disease Control and Prevention, if health care professionals increase HPV vaccination rates in eligible recipients to 80% in the target age range, it is estimated that an additional 53,000 cases of cervical cancer could be prevented during the lifetimes of those younger than 12 (6). Furthermore, for every year that HPV vaccination rates do not increase, an additional 4,400 women will develop cervical cancer.

<table>
<thead>
<tr>
<th>Cancer Site</th>
<th>Average Number of Cases of Cancer Per Year in Sites Where HPV Often Is Found (HPV-Associated Cancer)</th>
<th>Percentage of Cases of Cancer Probably Caused by Any HPV Type</th>
<th>Estimated Number of Cases of Cancer Probably Caused by Any HPV Type</th>
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<tbody>
<tr>
<td>Cervix</td>
<td>12,015</td>
<td>91%</td>
<td>10,900</td>
</tr>
<tr>
<td>Vagina</td>
<td>862</td>
<td>75%</td>
<td>600</td>
</tr>
<tr>
<td>Vulva</td>
<td>4,009</td>
<td>69%</td>
<td>2,800</td>
</tr>
<tr>
<td>Penis</td>
<td>1,303</td>
<td>63%</td>
<td>800</td>
</tr>
<tr>
<td>Anus†</td>
<td>6,810</td>
<td>91%</td>
<td>6,200</td>
</tr>
<tr>
<td>Female</td>
<td>4,539</td>
<td>93%</td>
<td>4,200</td>
</tr>
<tr>
<td>Male</td>
<td>2,270</td>
<td>89%</td>
<td>2,000</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>19,000</td>
<td>70%</td>
<td>13,500</td>
</tr>
<tr>
<td>Female</td>
<td>3,460</td>
<td>63%</td>
<td>2,200</td>
</tr>
<tr>
<td>Male</td>
<td>15,540</td>
<td>72%</td>
<td>11,300</td>
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<tr>
<td>Total</td>
<td>43,999</td>
<td>79%</td>
<td>34,800</td>
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<tr>
<td>Women</td>
<td>24,886</td>
<td>83%</td>
<td>20,700</td>
</tr>
<tr>
<td>Men</td>
<td>19,113</td>
<td>74%</td>
<td>14,100</td>
</tr>
</tbody>
</table>

Abbreviation: HPV, human papillomavirus.

*Estimates were rounded to the nearest 100. Estimated counts might not sum to total because of rounding.

†HPV types detected in genotyping study; most were high-risk HPV types known to cause cancer.

‡Includes anal and rectal squamous cell carcinomas.

Human Papillomavirus Vaccination

The U.S. Food and Drug Administration has approved three vaccines that prevent HPV infection. These vaccines cover 2, 4, or 9 HPV serotypes, respectively. Bivalent and quadrivalent vaccines are approved for women and men aged 9–26 years, and the 9-valent vaccine is approved for women and men aged 9–45 years. Currently, the 9-valent vaccine is the only HPV vaccine available in the United States (7).

The Advisory Committee on Immunization Practices and ACOG 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 to reduce the incidence of anogenital cancer and genital warts associated with HPV infection (8). Although obstetrician–gynecologists are not likely to care for many patients in the recommended HPV vaccination target population, they have the opportunity to provide catch-up vaccination for girls and women age 13 and older and to discuss HPV vaccination with parents of children in the target age. Obstetrician–gynecologists should assess and vaccinate adolescent girls and young women with the HPV vaccine during the catch-up period (ages 13–26 years), regardless of sexual activity, prior exposure to HPV, or sexual orientation, if they were not vaccinated in the target age of 11–12 years. Further, obstetrician–gynecologists and other health care professionals should educate parents in their decision making regarding vaccinations for their daughters and sons. Finally, for some women age 27–45 years who are previously unvaccinated, obstetrician–gynecologists and other health care professionals may use shared clinical decision making regarding the HPV vaccination, considering the patient’s risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit (7, 9, 10).

Human Papillomavirus Vaccination Timing and Number of Doses

Children and Adolescents (9–14 years)

The target age for HPV vaccination is 11–12 years. For immunocompetent girls and boys who receive their first dose of HPV vaccine before 15 years of age, only two doses are needed because the immune response that develops at this age provides antibody levels equivalent to those in patients who receive three doses at the age of 15 years or older (11). The timing of the two doses is 0 (baseline) and 6–12 months. 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 (8). 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 (5, 8).

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 exposure and infection with HPV, which coincide with the onset of sexual activity. Statistics show that 20% of 9th graders and more than 55% of 12th graders have engaged in sexual intercourse (12, 13). In Sweden, vaccine effectiveness in preventing genital warts was 93% among girls vaccinated between 10 years of age and 13 years of age compared with 48% and 21% if vaccinated at ages 20–22 years and 23–26 years, respectively (14). 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 of adolescents. Human papillomavirus vaccination is not associated with an earlier onset of sexual activity (15, 16) or increased incidence of sexually transmitted infections (12).

Teens and Adults (15–26 years)

If girls or boys receive their first dose at age 15 years 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 (8).

Unvaccinated women age 26 years and younger should receive the HPV vaccine series regardless of sexual activity, prior exposure to HPV, or sexual orientation. Although the vaccine is 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 (17, 18). Vaccination is recommended for women through age 26 years even if the patient is tested for HPV DNA and the results are positive. Testing for HPV DNA is not recommended before vaccination.

Adults (27–45 years)

The HPV vaccine is now licensed in the United States for women and men through age 45 years. Although administration of the HPV vaccine is safe in patients aged 27–45, and can prevent new infections in women not previously exposed to the HPV-type protection generated by the vaccine, most women in this age range will have been exposed to HPV already. The overall public health benefit of HPV vaccination in women aged 27–45 years is markedly diminished compared with use in the target age range (7).
Ideally, the HPV vaccine should be given in early adolescence because vaccination is most effective before exposure to HPV through sexual activity. For some women aged 27–45 years who are previously unvaccinated, obstetrician–gynecologists and other health care professionals may use shared clinical decision making regarding HPV vaccination, considering the patient’s risk for acquisition of a new HPV infection and whether the HPV vaccine may provide benefit. Those women aged 27–45 years who are most likely to benefit from vaccination are those at greater risk for HPV exposure or acquisition: younger women, women who are not in committed monogamous relationships, and women with recently diagnosed sexually transmitted infections. When counseling patients, clinicians should explain that women aged 27–45 years in long-term monogamous relationships are not likely at risk of acquiring a new HPV infection. It is not routinely recommended that these women receive the vaccine.

Clinicians should keep in mind that catch-up HPV vaccination is not recommended for all adults older than 26 years and that HPV vaccination does not need to be discussed with most adults older than 26 years. The American College of Obstetricians and Gynecologists does not recommend that an individual who received the quadrivalent HPV vaccine be revaccinated with 9-valent HPV vaccine, including those aged 27–45 years who previously completed some but not all, of the vaccine series when they were younger. Further, having a new partner increases the risk of a new HPV infection at any age; however, with increasing age and more past exposure to HPV, it is less likely that vaccination provides benefit.

Typically, routine vaccine recommendations are made for specific at-risk populations (identified either by age group or underlying health-related conditions) after considering vaccination cost, availability, and public health impact. The 9-valent HPV vaccine is costly and in short supply globally. In addition, routine HPV vaccination of all women age 27–45 would be expected to have a very limited effect on the global fight to prevent cervical cancer. Thus, in this case, the shared clinical decision making approach is recommended by the Centers for Disease Control and Prevention and ACOG.

**Considerations for Special Populations**

Human papillomavirus vaccination is not recommended during pregnancy; however, routine pregnancy testing is not recommended before vaccination. When the vaccine has been inadvertently administered to a pregnant woman, safety data are reassuring, although the data are somewhat limited because the vaccine is not used routinely in pregnancy (19–21). Patients and obstetrician–gynecologists or other health care professionals are encouraged 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. It is not necessary to restart the series. The HPV vaccine can and should be given to breastfeeding women age 26 years and younger who have not previously been vaccinated. The HPV vaccine has not been shown to affect the safety of breastfeeding for these women or their infants (22).

The presence of immunosuppression, like that experienced in patients with human immunodeficiency virus infection or organ transplantation, is not a contraindication to HPV vaccination. However, the immune response may be less robust in an immunocompromised patient (23). Thus, the three-dose schedule is recommended for immunocompromised women and men, adults and adolescents, even if younger than 15 years.

In children with a history of sexual abuse or assault, the HPV vaccine should be given as early as possible, starting at age 9 years (8).

**Boosters, Revaccination, and Series Completion**

The durability of the immune response (ie, how long protection lasts) of the HPV vaccine is being monitored in long-term studies, and currently there is no indication for a booster vaccine (24). The vaccine series does not need to be restarted in the case of a delay in administration of the second or third dose, regardless of the amount of time of the delay. Further, 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 is not a routine recommendation. The bivalent and quadrivalent vaccines have been shown to be extremely effective at preventing HPV-related disease (20; 25).

If obstetrician–gynecologists or other health care professionals 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 women 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 men (26).

**Vaccine Safety**

Safety data for all three HPV vaccines are reassuring. According to the Vaccine Adverse Events Reporting System, more than 270 million doses of HPV vaccine have been distributed worldwide since 2006, and there are no data to suggest that there are any severe adverse effects or adverse reactions linked to vaccination (27). 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 (26). The Vaccine Adverse Events Reporting System reports from December 2014 to December 2017 demonstrated no additional or unexpected safety concerns related to the 9-valent HPV vaccine (28). 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 (29, 30).

Anyone who has 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 professionals 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. Obstetrician–gynecologists and other health care professionals should counsel patients to expect mild local discomfort after the vaccination and that such discomfort is not a cause for concern. Syncope and site reactions are common after this vaccine, but serious adverse events are rare. Adolescents should be observed for at least 15 minutes after vaccination because of the risk of fainting.

Vaccine Efficacy

Human papillomavirus vaccines are among the most effective vaccines available worldwide, with unequivocal data demonstrating greater than 99% efficacy when administered to women who have not been exposed to that particular type of HPV (26). The HPV vaccine significantly reduces the incidence of anogenital cancer and genital warts in women and in men (31, 32). Additionally, HPV vaccination may decrease the incidence of oropharyngeal cancer. In the United States, the prevalence of vaccine-type HPV infection decreased 71% among women aged 14–19 years between 2006 (when the quadrivalent HPV vaccine was introduced) and 2014 (31). Additionally, a marked reduction in genital warts has occurred in countries with high HPV vaccine coverage (33).

The 9-valent HPV vaccine protects against more than 99% of HPV disease related to genotypes 6, 11, 16, and 18 and up to 96.7% for HPV disease related to genotypes 31, 33, 45, 52, and 58 (26). This includes prevention of cervical, vaginal, vulvar, and anal disease caused by these HPV types. The HPV vaccine is a prophylactic vaccine used to prevent disease. Studies are ongoing currently as to whether it may be helpful to prevent recurrent disease, but current data does not support its use as a therapeutic vaccine (34).

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 have the strongest influence in the acceptance of HPV vaccination by patients and parents of patients (35). Obstetrician–gynecologists and other health care professionals should strongly recommend HPV vaccination to eligible patients and stress the benefits and safety of the HPV vaccine. Further, obstetrician–gynecologists are encouraged to stock and administer HPV vaccines in their offices when feasible. Obstetrician–gynecologists play a critical role and should assess and vaccinate adolescent girls age 11–12 years and previously unvaccinated young women during the catch-up period (ages 13–26 years). Health care professionals should use shared clinical decision making with previously unvaccinated women aged 27–45 years to assess the benefit of HPV vaccination.

References


