Human Papillomavirus Vaccination

**ABSTRACT:** The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention recommends that human papillomavirus (HPV) vaccination routinely be targeted to females and males aged 11 years or 12 years as part of the adolescent immunization platform to help reduce the incidence of anogenital cancers and genital warts associated with HPV infection. The quadrivalent HPV vaccine is approved for use in males and females, whereas the bivalent HPV vaccine is approved for use only in females. For those not vaccinated at the target age, catch-up vaccination is recommended up to age 26 years. The American College of Obstetricians and Gynecologists endorses these recommendations. Although obstetrician–gynecologists are not likely to care for many patients in the initial HPV vaccination target group, they have the opportunity to educate mothers about the importance of vaccinating their children at the recommended age and are critical to vaccinating adolescent girls and young women during the catch-up period. Obstetrician–gynecologists should advise patients and parents that HPV vaccines are most effective in preventing genital cancers when administered before the onset of sexual activity. However, sexually active individuals can receive some benefit from the vaccination because exposure to all HPV types prevented by the vaccines is unlikely in persons aged 13 years through 26 years. Although HPV vaccination in pregnancy is not recommended, neither is routine pregnancy testing before vaccination. Lactating women can receive either HPV vaccine. The need for ongoing cervical cytology screening should be emphasized in all women aged 21 years and older, even those who received HPV vaccination before the onset of sexual activity.

Human papillomavirus (HPV) is a group of more than 120 different viruses. Infection with HPV is associated with the development of anogenital cancers (including cervical, vaginal, vulvar, and anal), oropharyngeal cancer, and genital warts. Approximately 40 HPV genotypes are primarily sexually transmitted from person to person (e.g., genital–genital contact, oral–genital contact, and sexual intercourse) and infect the oral, anal, or genital areas of men and women. However, only 13 genotypes have been shown to cause cervical cancer (1). Approximately 70% of all cases of cervical cancer are caused by HPV genotypes 16 and 18, and 90% of cases of genital warts are caused by HPV genotypes 6 and 11 (2).

Each year in the United States, cervical cancer is diagnosed in more than 12,000 women, and nearly 4,000 die from the disease (3). In addition, there are more than 1 million cases of abnormal cytology screening results that require evaluation (4, 5). Although the implementation of cervical cytology screening programs and treatment of precancerous lesions has led to a decrease in deaths from cervical cancer in the United States, such deaths still occur. Approximately one half of all cases of cervical cancer are found in women who have never had a Pap test, and another 10% occur in patients who have not had one within the past 5 years (6). Both ongoing cervical cytology screening and HPV vaccination are needed to help reduce these deaths.

Human papillomavirus vaccination can also help reduce the incidence of other anogenital cancers and genital warts and may decrease the incidence of oropharyngeal cancer. Each year in the United States, HPV is believed to cause approximately 2,600 cases of vulvar and vaginal cancer, 4,300 cases of anal cancer, 360,000 cases of genital warts, and more than 8,400 cases of oropharyngeal
cancer (7). Approximately 35% of all cases of anal cancer and 80% of all cases of oropharyngeal cancer are in men (7).

**Human Papillomavirus Vaccines**

The U.S. Food and Drug Administration (FDA) has approved two vaccines shown to be effective at preventing HPV infection. The quadrivalent HPV vaccine is indicated to prevent cancers and intraepithelial neoplasias of the cervix, anus, vulva, and vagina and genital warts associated with HPV genotypes 6, 11, 16, and 18 (8). The FDA has approved administration of the quadrivalent three-dose vaccine to females and males aged 9–26 years. The bivalent three-dose HPV vaccine has FDA approval for administration to females aged 9–25 years for the prevention of cervical cancer, cervical intraepithelial neoplasia (CIN) 2 or worse and adenocarcinoma in situ, and CIN 1 caused by oncogenic HPV genotypes 16 and 18 (9).

**Efficacy**

Studies of the quadrivalent HPV vaccine have shown that among participants who were naïve to the vaccine genotypes and who followed protocol, the vaccine was nearly 100% effective in preventing CIN 2, CIN 3, and condylomatous vulvar disease related to the HPV genotypes covered by the vaccine (8). Similarly, clinical trials in men showed an efficacy of 90.4% in preventing external genital lesions associated with the HPV genotypes covered by the vaccine (10). In a substudy of men who have sex with men, the quadrivalent vaccine was 77.5% effective in preventing anal intraepithelial neoplasia related to HPV genotypes 6, 11, 16, and 18, leading to FDA approval of the quadrivalent vaccine for the prevention of anal cancer and associated precancerous lesions that are caused by these HPV genotypes (11). Results of studies of the bivalent HPV vaccine indicate that it offers protection similar to the quadrivalent vaccine against CIN 2 and CIN 3 in adolescent and young women who are naïve to the vaccine’s HPV genotypes 16 and 18 (12, 13). The bivalent vaccine does not protect against lower genital tract condyloma caused by low-risk HPV genotypes 6 and 11 (ie, associated with genital warts). There is evidence that each vaccine provides some minor degree of cross-protection against other nonvaccine HPV genotypes that are associated with disease (14).

To be maximally effective, vaccination with either vaccine should be given during the target ages (11 years and 12 years) or before the onset of sexual activity. If the vaccine is given after the onset of sexual activity, patients may have already been infected with HPV. Data from Australia, where coverage is more than 75% in the target age group (females only), showed that the diagnosis of genital warts in females decreased by 73% within 3 years of vaccine introduction (13). There also was a significant decrease in the diagnosis of genital warts in heterosexual men, suggesting herd immunity. In Sweden, data that linked multiple population registers showed that vaccine effectiveness in preventing genital warts was 93% among girls vaccinated between ages 10 years and 13 years compared with 48% and 21% if vaccinated at ages 20–22 years and 23–26 years, respectively (15). Data from the United States show that 1 month after the completion of HPV vaccination, girls aged 10–14 years generally have higher antibody levels than young women aged 15–26 years and retain these higher levels for several years (16, 17). All of these findings underscore the importance of vaccination during the target age or before the onset of sexual activity.

In the United States, the prevalence of vaccine-type HPV has decreased 56% among females aged 14–19 years since the quadrivalent vaccine was introduced in 2006 (18). The observed decrease in vaccine-associated HPV prevalence is likely due to the protection induced by a single vaccine dose, at least in the short term. According to the Centers for Disease Control and Prevention (CDC), slightly more than 50% of 13–17-year-olds in the United States have received at least one vaccine dose, and only 33% have received all three doses (19). Recent data demonstrate that individuals who received two doses of the quadrivalent vaccine at 0 and 6 months had similar antibody responses within 6 months as those receiving three doses (16). However, at 24–36 months, those who received two doses showed a lower level of antibody response than those who received three doses (16). Thus, reduced dose schedules are not currently recommended.

The need for booster doses remains to be demonstrated but is unlikely (13). The current three-dose vaccine series is designed to maximize the primary immune response and enhance long-term protection. The durability of the immune response (ie, how long protection lasts) is being monitored in various long-term studies, and there is currently no indication for a booster vaccine.

**Safety**

Safety data for both HPV vaccines are reassuring. According to the Vaccine Adverse Events Reporting System, more than 57 million doses of HPV vaccine have been distributed, and there are no data to suggest that there are any severe side effects or adverse reactions linked to vaccination (20). Ongoing surveillance of HPV vaccine side effects—which include syncope, nausea, headache, dizziness, and local pain and redness—shows no new, unexpected adverse reactions (20). Although there was an observed increase of venous thromboembolism in those vaccinated, on review it was determined that this finding was not statistically significant because all five patients had prior known risks of venous thromboembolism (21). The CDC continues to consider HPV vaccines safe.

**Vaccination of Specific Populations**

The following are recommendations for HPV vaccination of specific groups. Testing for HPV DNA is not required or recommended before vaccination in any group. If the patient is tested for HPV DNA and the results are positive, vaccination is still recommended because the
chance that the patient has been exposed to all vaccine-preventable HPV genotypes is low.

In all states, minors are allowed to give consent for the diagnosis and treatment of sexually transmitted infections. However, many of the laws that authorize them to provide such consent may only permit it after they have reached a specific age. Furthermore, these laws do not mention vaccinations (22). Clinicians should be familiar with state and local statutes regarding the rights of minors to consent to health care services and the federal and state laws that affect confidentiality.

**Girls and Boys, Adolescents, and Young Women and Men**

The Advisory Committee on Immunization Practices of the CDC recommends that HPV vaccination routinely be targeted to females and males aged 11 years or 12 years as part of the adolescent immunization platform to help reduce the incidence of anogenital cancer and genital warts associated with HPV infection. The quadrivalent HPV vaccine is approved for use in males and females, whereas the bivalent HPV vaccine is approved for use only in females. Depending on the circumstances, the vaccine can be given to individuals as young as 9 years. For those not vaccinated at the target age, catch-up vaccination is recommended up to age 26 years (see **Box 1**) (2). Once the vaccination series has begun, there is no evidence to suggest that the series needs to be restarted if there is a delay in administration of subsequent vaccine doses.

The American College of Obstetricians and Gynecologists endorses these recommendations. During a health care visit with a girl, adolescent, or a young woman in the age range for vaccination, obstetrician–gynecologists should assess the patient’s HPV vaccine status, discuss HPV and the potential benefit of HPV vaccination, offer vaccination as needed, and document this information in the patient’s medical record.

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**Box 1. Key Information Regarding the Bivalent and Quadrivalent Human Papillomavirus Vaccines**

**Dosage**

Administered intramuscularly as three separate 0.5-mL doses based on the following schedule:

1. **First dose**: at elected date
2. **Second dose**: 1–2 months after the first dose
3. **Third dose**: 6 months after the first dose

Minimum interval between first and second dose is 4 weeks, between second and third dose is 12 weeks, and between first and third dose is 24 weeks. If the vaccine schedule is interrupted, the series does not need to be restarted, regardless of the length of time between doses. Whenever possible, the same vaccine product should be used for all doses in the series.

**Recommended Age**

- **Target population**: females and males aged 11 years or 12 years (can be started as early as age 9 years)
- **Females and males** who did not receive the vaccination at the target age can be vaccinated from age 13 years through 26 years

**Contraindications**

Individuals who develop symptoms indicative of hypersensitivity to the active substances or to any of the components of either vaccine after receiving a dose of vaccine should not receive further doses of the product. Safety and effectiveness of the two formulations have not been established in pregnant women. Any exposure to it during pregnancy should be reported to the manufacturer by calling 1-877-888-4231 for the quadrivalent vaccine and 1-888-452-9622 for the bivalent vaccine.

**Precautions**

As with any vaccine, vaccination may not protect all vaccine recipients. Neither vaccine is intended to be used for treatment of active disease (ie, genital warts, cervical cancer, cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia). Human papillomavirus (HPV) vaccines can be administered simultaneously or at any time before or after a different inactivated or live vaccine administration. Because vaccinated individuals may develop syncope, sometimes resulting in falling with injury, health care providers should consider observing patients for 15 minutes after vaccine administration.

**Storage**

Both formulations should be refrigerated at 2–8°C (36–46°F), should not be frozen, and should be protected from light.

**Vaccine Adverse Event Reporting**

To report an adverse event associated with administration, go to [http://vaers.hhs.gov](http://vaers.hhs.gov).

(continued)
Sexually Active Adolescents and Young Women

Sexually active adolescents and young women can receive either the quadrivalent or bivalent HPV vaccine. These patients should be counseled that the vaccine may be less effective in individuals who have been exposed to HPV before vaccination than in individuals who were HPV naive at the time of vaccination (8, 12). However, sexually active individuals can receive some benefit from the vaccination because exposure to all HPV types prevented by the vaccines is unlikely in persons aged 13 years through 26 years. The need for ongoing cervical cytology screening should be emphasized in all women aged 21 years and older, even those vaccinated before the onset of sexual activity.

Adolescents and Young Women With Previous Cervical Intraepithelial Neoplasia or Genital Warts

The HPV vaccines can be given to patients with previous CIN or genital warts. Health care providers need to emphasize that the benefits may be limited and cervical cytology screening and corresponding management based on College recommendations must continue. The HPV vaccines are not intended to be treatment for cervical cytologic abnormalities, genital warts, or a positive HPV DNA test result. Patients with these conditions should undergo the appropriate evaluation and treatment (23, 24).

Pregnant and Lactating Women

Both the quadrivalent and bivalent HPV vaccines have been classified by the FDA as pregnancy category B. Although HPV vaccination in pregnancy is not recommended, neither is routine pregnancy testing before vaccination. Currently, there are few data on HPV vaccine administration in pregnancy; however, the available safety data regarding the inadvertent administration of the vaccine during pregnancy are reassuring (25, 26). In clinical studies, the proportion of pregnancies with adverse outcomes was comparable in women who received the HPV vaccine and in women who received a placebo (9, 27). However, it is wise to remind patients to use contraception during the period when they are receiving the vaccination series. The manufacturer should be contacted if pregnancy is detected during the vaccination schedule (see Box 1). Completion of the vaccine series should be delayed until pregnancy is completed. Lactating women can receive either HPV vaccine because inactivated vaccines, such as these vaccines, do not affect the safety of breastfeeding for mothers or infants (28).

Immunosuppressed Patients

The presence of immunosuppression, like that experienced in patients with HIV infection or organ transplantation, is not a contraindication to HPV vaccination. However, the immune response may be less robust in the immunocompromised patient (29).

Women Older Than 26 Years

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 because vaccination may provide some marginal benefit (16).
11–26 years and to offer initial vaccination and catch-up vaccination as needed. Although obstetrician–gynecologists are not likely to care for many patients in the initial HPV vaccination target group, they have the opportunity to educate mothers about the importance of vaccinating their children at the recommended age and are critical to vaccinating adolescent girls and young women during the catch-up period. It is important for health care providers to educate patients and parents of children in the target age range for HPV vaccination about HPV-related disease and be prepared to respond to questions regarding HPV vaccination, including its benefits, limitations, and safety, as discussed earlier. Studies have shown that physicians’ recommendations play a crucial role in the acceptance of HPV vaccination by patients and parents of patients (30). Many parents think that HPV vaccination is not needed and are concerned about safety and adverse reactions (31). Obstetrician–gynecologists should advise patients and parents that HPV vaccines are most effective in preventing genital cancers when administered before the onset of sexual activity, although HPV can be contracted without sexual activity. In addition, patients and parents can be counseled that HPV vaccines are safe and associated with few side effects, none of which are severe. An additional concern among some parents is that HPV vaccination may cause an increase in sexual activity among adolescents. However, health care providers can reassure parents that this is not the case. A study of 1,398 girls aged 11–12 years found that HPV vaccination was not associated with increased sexual activity outcomes that included pregnancy, sexually transmitted infection testing or diagnosis, or contraceptive counseling (32).

According to the CDC, if health care providers increase HPV vaccination coverage 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 (19). Furthermore, for every year that coverage does not increase, an additional 4,400 women will develop cervical cancer. These data highlight the overwhelming importance of HPV vaccination efforts, including discussions with patients and parents of children and adolescents about the benefit of HPV immunization for cancer prevention (19).

**American College of Obstetricians and Gynecologists’ Resources**


American Society for Colposcopy and Cervical Pathology 1530 Tilco Drive, Suite C Frederick, MD 21704 (301) 733-3640 1-800-787-7227 http://www.asccp.org

The following list is for information purposes only. Referral to these sources and web sites does not imply the endorsement of the American College of Obstetricians and Gynecologists. This list is not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.

American Cancer Society 250 Williams Street, NW Atlanta, GA 30303 1-800-227-2345 http://www.cancer.org

American Society for Colposcopy and Cervical Pathology 1530 Tilco Drive, Suite C Frederick, MD 21704 (301) 733-3640 1-800-787-7227 http://www.asccp.org

American Society for Colposcopy and Cervical Pathology 1530 Tilco Drive, Suite C Frederick, MD 21704 (301) 733-3640 1-800-787-7227 http://www.asccp.org

Center for Young Women’s Health 333 Longwood Avenue, 5th floor Boston, MA 02115 (617) 355-2994 http://www.youngwomenshealth.org

Centers for Disease Control and Prevention 1600 Clifton Road Atlanta, GA 30333 1-800-CDC-INFO (1-800-232-4636) http://www.cdc.gov

Planned Parenthood Federation of America 434 West 33rd Street New York, NY 10001 (212) 541-7800 1-800-230-7526 http://www.plannedparenthood.org

Other Resources
References


Committee Opinion No. 588 7


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ISSN 1074-861X