LEARNING OBJECTIVES
Upon completion of this activity, participants should be better able to:
• Discuss the latest Advisory Committee on Immunization Practices recommendations for human papillomavirus (HPV) vaccination in male and female adolescents
• Implement practical approaches to counseling patients and their parents on the benefits of HPV vaccination
• Evaluate the safety and efficacy data of the HPV vaccines

INTRODUCTION
Human papillomavirus (HPV) is a ubiquitous infection, and is the most common sexually transmitted infection in the United States.1,2 More than 79 million people in the United States are currently infected with HPV, with 14 million new infections occurring each year.3 About one-half of these new infections will occur among teens and young adults aged 15 to 24 years,3 and most sexually active men and women will acquire HPV during their lifetimes.4 Although 90% of HPV infections are cleared by the immune system within 2 years, persistent infection can cause precancer or cancer years later.5,6 In addition, immunocompromised persons, such as those infected with human immunodeficiency virus, have higher rates of HPV acquisition and disease progression.7

The HPV vaccine offers an unprecedented potential for cancer prevention, but coverage rates among adolescents remain suboptimal.
Fortunately, the efficacy and safety of the bivalent (2vHPV) and quadrivalent (4vHPV) vaccines have been well established in protecting patients against genital warts, precancers, and cancers caused by the HPV strains contained in the vaccines. In 2014, the Food and Drug Administration approved a 9-valent vaccine (9vHPV) formulation, which provides protection against 5 additional HPV types, with similar efficacy to that of the 2vHPV and 4vHPV vaccines. However, despite the proven effectiveness of these vaccines, the HPV vaccination rate in the United States is still suboptimal, and the vaccines are not being used to their full potential. Increasing vaccination rates from 30% to 80% would prevent 53,000 cervical cancer cases among girls now aged 12 years and younger. For every year that increases in coverage are delayed, another 4400 women in each birth cohort will develop cervical cancer during their lifetimes.8

Healthcare clinician recommendation is the strongest predictor of HPV vaccination among adolescents. Despite the well-established connection between HPV infection and the development of certain cancers and precancers, clinicians miss many opportunities to vaccinate adolescents against HPV. Compared with other adolescent vaccination rates in the United States, such as those for the quadrivalent meningococcal conjugate vaccine (Men–ACWY) or tetanus, diphtheria, and pertussis (Tdap) vaccines, the HPV vaccination rate is low (Figure 1).9 In 2014, only 60% of females aged 13 to 17 years had received at least 1 dose of the HPV vaccine, and 39.7% had received the 3-dose series. For males, the numbers were even lower: 41.7% had received at least 1 dose, while only 21.6% had received the 3-dose series.9 While these rates represent an increase from the 2013 HPV vaccination rates, national coverage remains suboptimal, and large variations in state and local vaccination coverage persist. In an analysis of adolescent females born before 2000, coverage with at least 1 dose of the HPV

![Figure 1. Compared with other adolescent vaccines, the US HPV vaccination rate is low.](https://example.com/figure1.png)

*Figure 1. Compared with other adolescent vaccines, the US HPV vaccination rate is low.*

- Ages 13-17 years; ≥1 dose Tdap vaccine on or after age 10 years; ≥1 dose of Men–ACWY vaccine;
- Either 2vHPV or 4vHPV vaccine; Either 2vHPV or 4vHPV vaccine. ACIP recommends the 4vHPV vaccine for males; however, some males might have received the 2vHPV vaccine.
Vaccine before the age of 13 years could have reached 91.3% if opportunities to administer the HPV vaccine were not missed when administering other adolescent vaccines.\textsuperscript{10} The objective of HealthyPeople 2020, which sets target goals for certain healthcare objectives by the US government, is to increase HPV vaccination coverage for females and males with the 3-dose series to 80% by the year 2020.\textsuperscript{11}

Parents cite myriad reasons for not wanting to have their children vaccinated against HPV. The 2013 National Immunization Survey-Teen asked parents who did not intend to vaccinate their daughters in the next 12 months the principal reasons behind this decision. The parents’ responses, highlighted in Table 1,\textsuperscript{8} show that sometimes all that is needed to allay parental fears is clinician recommendation and education about the vaccine.

As with other vaccines, the most effective time to vaccinate against HPV is before exposure—and the younger, the better. In an analysis of 1552 adolescents and young adults, a subset of 1014 (65%) reported having engaged in sexual intercourse; 2% at 11 years of age or younger and 7% at ages 12 to 13 years, indicating low potential for exposure to HPV. By age 18 years,

\begin{table}
\centering
\begin{tabular}{|l|c|}
\hline
Parental Reason & Percent \\
\hline
Not needed or necessary & 19.1 \\
Not recommended by clinician & 14.2 \\
Safety concerns/side effects & 13.1 \\
Lack of knowledge & 12.6 \\
Daughter not sexually active & 10.1 \\
\hline
\end{tabular}
\caption{Top 5 Parental Reasons for Not Vaccinating a Daughter Against HPV\textsuperscript{8}}
\end{table}

\begin{table}
\centering
\begin{tabular}{|l|l|l|}
\hline
Mucosal/Genital (approximately 40 types) & Nonmucosal/ Cutaneous (approximately 60 types) \\
\hline
High-risk: Types 16, 18, 31, 33, 45, 52, 58 & Low-risk: Types 6, 11 \\
- Low-grade cervical abnormalities & - Benign or low-grade cervical abnormalities \\
- High-grade cervical abnormalities that are cancer precursors & - Genital warts \\
- Genital cancers (cervical, vaginal, vulvar, penile, anal) & - Laryngeal papillomas \\
- Head and neck cancers & - Skin warts: Types 1, 2 (hands and feet) \\
\hline
\end{tabular}
\caption{HPV Types and Disease Association\textsuperscript{1}}
\end{table}
77% of cohorts reported having had sexual intercourse. It is also important to emphasize that HPV transmission can occur with any skin to skin contact.

HPV-ASSOCIATED DISEASES

As shown in Table 2, HPV types are divided into 2 categories, mucosal and nonmucosal. Nonmucosal types infect cutaneous tissue and are responsible for plantar and flat warts. Mucosal or genital HPV types include low- and high-risk types, with the risk referring to oncogenic potential. Low-risk HPV types 6 and 11 can cause genital warts and laryngeal papillomas, while high-risk types, or oncogenic HPV, can result in low- and high-grade cervical lesions, precancerous genital lesions, and anogenital cancers.

Cancer

Approximately 27,000 HPV-associated cancers are diagnosed annually in the United States. HPV types 16 and 18 cause nearly two-thirds of the more than 21,000 invasive HPV-associated cancers in men and women each year. Specifically, 66% of cervical, 55% of vaginal, 79% of anal, and 62% of oropharyngeal cancers are attributable to HPV types 16 and 18. An additional 10% of invasive HPV-associated cancers (14% for females and 4% for males), or 3400 cases annually, are associated with HPV types 31, 33, 45, 52, and 58, the additional 5 HPV types in the 9vHPV vaccine, as well as approximately 15% of cervical cancers. The average numbers of annual HPV-attributable cancers in the United States from 2006 to 2010 are highlighted in Table 3. While rates of many cancers are decreasing in the United States, rates of anal, oral, and vulvar cancers are increasing.

Genital Warts

Approximately 1% of sexually active adults in the United States have genital warts, with more than 90% of cases associated with HPV types 6 and 11. These warts might regress, grow larger, or remain the same; however, recurrence is common, occurring in approximately 30% of patients. Genital warts occur in approximately 360,000 people annually in the United States.

<table>
<thead>
<tr>
<th>Site</th>
<th>Male</th>
<th>Female</th>
<th>Total No. of Cancers</th>
<th>Percent Attributable to HPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>0</td>
<td>10,400</td>
<td>10,400</td>
<td>96</td>
</tr>
<tr>
<td>Anus</td>
<td>1400</td>
<td>2600</td>
<td>4000</td>
<td>93</td>
</tr>
<tr>
<td>Vagina</td>
<td>0</td>
<td>600</td>
<td>600</td>
<td>64</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>7200</td>
<td>1800</td>
<td>9000</td>
<td>63</td>
</tr>
<tr>
<td>Vulva</td>
<td>0</td>
<td>2200</td>
<td>2200</td>
<td>51</td>
</tr>
<tr>
<td>Penis</td>
<td>700</td>
<td>0</td>
<td>700</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 3. Average Annual HPV-Attributable Cancers in the United States, 2006-2010
costing an estimated $300 million per year. In addition, patients with genital warts often report a lower quality of life, in part due to the social stigma of having a sexually transmitted infection.

HPV VACCINES

Three vaccines against HPV are now licensed in the United States. The 2vHPV vaccine protects females against infection with virus types 16 and 18, preventing cervical cancers and precancers. Two vaccines are available for use in females and males—the 4vHPV vaccine, which protects against infection with virus types 6, 11, 16, and 18, and the 9vHPV vaccine, which protects against virus types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Table 4). Both the 4vHPV and 9vHPV vaccines protect against cervical, vulvar, vaginal, and anal cancers and precancers and genital warts.

HPV Vaccine Efficacy in Females

The Advisory Committee on Immunization Practices (ACIP) recommends routine HPV vaccination with the 2vHPV, 4vHPV, or 9vHPV vaccine for girls aged 11 to 12 years. Vaccinations can be started in females as young as 9 years. If not previously vaccinated, females aged 13 through 26 years should complete catch-up immunization.

The efficacy of the 4vHPV vaccine was assessed in 20,541 females aged 16 to 26 years and the 2vHPV vaccine in 19,778 females aged 15 to 25 years. For these vaccines, efficacy was measured using cervical intraepithelial neoplasia (CIN) 2/3 or adenocarcinoma in situ (AIS) caused by HPV types 16 and 18. The 4vHPV vaccine also measured efficacy against CIN or AIS for HPV types 6, 11, 16, and 18, and genital warts caused by HPV types 6 and 11. Efficacy rates for these vaccines are summarized in Table 5. Several other measures were assessed when measuring the efficacy of the 9vHPV vaccine, and the results are summarized in Table 6.

For female patients, clinicians should recommend the 2vHPV, 4vHPV, or 9vHPV vaccine for the prevention of cervical precancers and cancers and the 4vHPV or 9vHPV vaccine for the additional prevention of vulvar, vaginal, and anal cancers and precancers and genital warts.
HPV VACCINATION

HPV Vaccine Efficacy in Males
The ACIP recommends routine HPV vaccination for boys aged 11 to 12 years with either the 4vHPV or 9vHPV vaccine.7,13 Both vaccines can be started in males as young as 9 years, and if not previously vaccinated, the 4vHPV vaccine is recommended for men up through age 26 years, and the 9vHPV vaccine is recommended through age 15 years.7 Previously unvaccinated immunocompromised males and men who have sex with men, aged 22 through 26 years, should be vaccinated; other males in this age group may also be vaccinated.7 Clinicians should recommend the 4vHPV or 9vHPV vaccine for the prevention of anal precancers and cancers and genital warts, emphasizing the importance of completing the 3-dose series.23 The 2vHPV vaccine is not licensed for use in males.7

The efficacy of the 4vHPV vaccine against HPV types 6, 11, 16, and 18 was assessed in 4065 males aged 16 to 26 years. For genital wart prevention, the efficacy rate was 89.4% (95% CI, 65.5-97.9) and for the prevention of anal intraepithelial neoplasia grades 1, 2, and 3, the rate was 77.5% (95% CI, 39.6-93.3).7 When the 9vHPV vaccine was studied in males aged 9 through 26 years, immunogenicity was found to be noninferior to that in females and was the basis of current licensure for males aged 9 to 15 years and application for licensure for males aged 16 to 26 years.13,22

HPV Vaccine Interval, Duration of Immunity, and Interchangeability
The routine vaccination schedule consists of a second dose 1 to 2 months after the first dose and a third dose 6 months after the first dose. The minimum interval between the first and second dose is 4 weeks; between the second and third dose, 12 weeks; and between the first and third dose, 24 weeks. There is no maximum interval between doses.1,19,20,22,24

The 3-dose series does not have to be restarted if it has been interrupted.25 Any HPV vaccine may be used to complete the series for females; the 4vHPV or 9vHPV vaccine may be used to complete the series for males.1 The HPV vaccine should be administered at the same time as any of the other age-appropriate vaccines (e.g., Tdap, Men-ACWY, influenza).1,19,20,22,24

Table 5. 4vHPV and 2vHPV Vaccine Efficacy in Femalesa,19,20

<table>
<thead>
<tr>
<th>End Point</th>
<th>Efficacy of 4vHPV, % (95% CI) (N = 20,541)</th>
<th>Efficacy of 2vHPV, % (96.1% CI) (N = 19,778)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CIN 2/3 or AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV types 16/18-related</td>
<td>98 (93.3-99.8)</td>
<td>93 (79.9-98.3)</td>
</tr>
<tr>
<td>CIN or AIS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV types 6/11/16/18</td>
<td>96 (92.3-98.2)</td>
<td></td>
</tr>
<tr>
<td>Genital warts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HPV types 6/11</td>
<td>99 (96.2-99.9)</td>
<td></td>
</tr>
</tbody>
</table>

aAmong 15- to 26-year-old females.
The importance of completing the 3-dose series cannot be overemphasized. While the duration of immunity afforded after completion of the 3-dose schedule is not fully known, multiple studies suggest protection for at least 7 to 10 years. Notably, younger adolescents have 2- to 3-fold higher HPV antibody levels after immunization compared to older adolescents and young adults. This may result in longer lasting immunity. If a female is vaccinated before exposure, the efficacy rate is 99% to 100.

**HPV Vaccine Impact: United States**

A study that examined the reduction in HPV prevalence among young women following HPV vaccine introduction in the United States using data collected during National Health and Nutrition Examination Interview Surveys found that within 4 years of the first vaccine being introduced, vaccine-type HPV prevalence decreased 56% among females aged 14 to 19 years (Table 7). This decline was higher than expected, and may be due to a number of factors, including herd immunity from vaccination, effectiveness of a less than complete 3-dose vaccine series, or unmeasured changes in sexual behavior.

In Connecticut, data from a statewide surveillance registry documented a significant decline from 2008 to 2011 in rates of high-grade cervical lesions in women aged 21 to 24 years. The annual rate of high-grade cervical lesions per 100,000 women declined from 834 to 688 in just 4 years (P <.001), which also corresponded with a 16% increase in HPV vaccine initiation among adolescent females.

**HPV Vaccine Safety**

Vaccine safety and monitoring studies have not identified any serious safety concerns or long-term side effects associated with the HPV vaccines, which have a safety profile similar to that
of other adolescent vaccines. From June 2006 through March 2014, approximately 68 million doses of the HPV vaccine had been distributed in the United States.10

During that time, the Vaccine Adverse Event Reporting System (VAERS) received 25,176 adverse event reports that occurred after HPV vaccination. The 4vHPV vaccine was cited in 99% of the reports (22,897 females and 2196 males), 92.4% of which were classified as non-serious. Among nonserious adverse events, the most commonly reported generalized symptom was syncope, and the most commonly reported local symptoms were injection-site reactions (pain, swelling, and erythema), dizziness, nausea, and headache.10,19,20

In addition to VAERS, the Centers for Disease Control and Prevention gathers safety data from the Vaccine Safety Datalink (VSD), a collaboration with 9 integrated healthcare organizations that allows for active surveillance and research,30 and the Clinical Immunization Safety Assessment Network. Reports from these 2 US population-based safety studies and VAERS have found increased risk of syncope with HPV vaccines; however, immunizations in general have been linked to syncope among adolescents.31 Syncope following vaccination is not uncommon among adolescents (aged 11-18 years), regardless of vaccine. The majority of syncopal episodes (70%) have occurred within 15 minutes of vaccination. Therefore, it is good practice to observe patients for at least 15 minutes after they are vaccinated, independent of vaccine. Presyncopal manifestations should also be monitored and appropriate measures taken to prevent injury.7

Data from the VSD have shown that following more than 600,000 doses of the 4vHPV vaccine administered to females, no statistically significant increased risks for Guillain-Barré syndrome, stroke, venous thromboembolism, appendicitis, seizures, syncope, allergic reactions, or anaphylaxis have been observed. Studies in males are ongoing.30

**Special Precautions**

Females can still be vaccinated if they have a history of an equivocal or abnormal Papanicolaou test, cervical dysplasia, a positive HPV DNA test, genital warts, immunosuppression, or are breastfeeding.1,23 The HPV vaccine is contraindicated in patients with a severe allergic reaction

### Table 7. HPV Vaccine Impact in Females Aged 14 to 19 Years28

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Prevalence, % (95% CI)</th>
<th>Change, % (decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2003-2006</td>
<td>2007-2010</td>
</tr>
<tr>
<td>Any HPV</td>
<td>32.9 (29.5-36.4)</td>
<td>26.1 (22.4-30.2)</td>
</tr>
<tr>
<td>High-risk nonvaccine-type HPV</td>
<td>20.7 (17.9-23.9)</td>
<td>16.4 (12.9-20.6)</td>
</tr>
<tr>
<td>Vaccine-type HPV</td>
<td>11.5 (9.2-14.4)</td>
<td>5.1 (3.8-6.6)</td>
</tr>
<tr>
<td>High-risk vaccine-type HPV</td>
<td>7.2 (5.8-8.7)</td>
<td>3.6 (2.5-5.0)</td>
</tr>
</tbody>
</table>
to a vaccine component or following a prior dose, and during pregnancy. In pregnant women, further HPV vaccination should be deferred until completion of the pregnancy. Precautions should be taken with patients who have moderate or severe acute illnesses, and vaccination should be deferred until symptoms improve.¹

PRACTICAL APPROACHES FOR CLINICIANS
Healthcare clinician recommendation and support are the most important predictors of vaccine acceptance.³² The HPV vaccine should be recommended by clinicians with the same urgency and commitment they have for other adolescent vaccines, emphasizing that HPV is a commonly occurring sexually transmitted infection. Clinicians should provide a clear, strong, and unequivocal recommendation for the HPV vaccine, emphasizing effectiveness, safety, and, most importantly, cancer prevention.³³-³⁵

Every office visit offers an opportunity to check patient vaccination status and to improve vaccination rates. Unless contraindicated, the HPV vaccine should be administered at the same time as other adolescent vaccines. Altering the order in which vaccines are recommended may have an impact on the patient and parent’s responsiveness (eg, mention HPV first in the list of vaccines recommended for adolescents).³⁶ Patient reminders, including phone calls, postcards, and/or letters all improve immunization rates. Patients and parents should be reminded that the full series is 3 shots.³²,³⁷,³⁸

Conversations with parents and adolescent patients should be initiated early, focusing on long-term cancer prevention. If possible, clinicians should tell parents a personal story; for example, that their own children have completed a 3-dose series. Finally, questions from parents should always be invited and welcomed. However, parents want and often respond better to decisive and direct communication from the clinician compared with participatory discussions.³⁹,⁴⁰

As a component of long-term wellness care, it is imperative that clinicians educate women about the importance of cervical cancer screening and especially that screening needs to be continued following HPV vaccination, because some cervical cancers are caused by HPV types not prevented by the HPV vaccine. In addition, females could have been infected prior to vaccination.¹

SUMMARY
HPV infection, which is common in both males and females, can become a chronic and persistent infection that, when caused by oncogenic types, may lead to cancers and precancers. The 2vHPV, 4vHPV, and 9vHPV vaccines are safe and effective in preventing genital warts, precancers, and cancers in both males and females, but they are not being used to their full potential. The bottom line is that increasing the HPV immunization rates for the full 3-dose series, particularly among girls aged 12 years and younger, could prevent tens of thousands of future cases of cervical cancer.
**CASE: A 12-Year-Old Boy Whose Mother Is Reluctant to Vaccinate Him With the HPV Vaccine**

**PRESENTATION**
Justin is 12 years old. On routine checkup, you note that he has not received the recommended vaccines for 11 to 12 year olds, including Tdap, HPV, and meningococcal vaccines. Justin's mother, Martha, has heard about the HPV vaccine for girls, but not for boys. She tells you that she is not interested in Justin receiving the HPV vaccine, because her son is young and not sexually active, and she has heard that receiving the HPV vaccine increases sexual activity.

**Clinical Decision Point**
*Based on Martha's reluctance, you decide to:*
A. Discuss Tdap and meningococcal vaccines in more detail  
B. Emphasize the importance of vaccinating against HPV now, before exposure, as with other childhood vaccines  
C. Resume the discussion about HPV vaccines just before Justin becomes sexually active  
D. Wait to discuss the HPV vaccine at Justin's next wellness office visit

**COMMENT**
You allay Martha's fears by explaining that medical research has shown that there is no correlation between receiving the HPV vaccine and an increase in sexual activity, and that HPV is so common that almost everyone is infected at some point during their lifetimes. What is most important is that she understands that HPV is associated with anal, oral, and penile cancers in males, and that sexual partners can infect each other. The 4vHPV and 9vHPV vaccines can prevent anal precancers and cancers as well as genital warts in males. Although not a label indication, available data suggest that HPV vaccination is also likely to be effective in preventing HPV-attributable oropharyngeal cancers.

You explain that just as with measles and other recommended childhood vaccines, clinicians vaccinate people before they are exposed to an infection. In fact, vaccinating early will give Justin the best protection possible, prior to exposure and long before the start of any sexual activity. Boys as young as 9 years of age can be immunized, and younger adolescents have a more robust immune response to the HPV vaccine. *Correct answer: B*

**CASE (cont’d)**
Despite being informed of the positive benefits of having Justin vaccinated against HPV, Martha remains unconvinced. From what she has read on the Internet, she does not believe that the vaccine is effective. You cite studies from the CDC showing that in males who had
not been previously exposed to targeted HPV types, the HPV vaccines achieve 90% efficacy in preventing genital warts and 75% efficacy in preventing anal precancers.\textsuperscript{15}

**CASE CONCLUSION**
Martha and Justin discuss what they have heard and Justin tells his mother he is willing to be vaccinated. You administer the first dose and schedule Justin to return in 2 months for the next injection and in 6 months for the final of the 3-dose vaccine series.

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**REFERENCES**


