Chapter 2
Case of a Girl Due for Human Papillomavirus Immunization

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Case

JH is a healthy 12-year-old female with an unremarkable past medical history who presents for a sports pre-participation physical for soccer. When discussing her gynecologic history, JH reports menarche 6 months ago around her 12th birthday. She has monthly periods without excessive bleeding or cramping. Family history is only notable for celiac disease in her mother and rheumatoid arthritis in her paternal grandmother.

During a confidential social history, JH shares that she lives with her parents and older brother. Her family is health conscious: her father is a salesman for a nutritional supplement company, and her mother only buys organic fruits and vegetables. The family is also very religious, and JH is active in her church youth group. JH is about to start seventh grade and typically receives As and Bs. She has a lot of friends on the soccer team and wants to be a teacher and coach. She feels safe at home and denies any mood concerns and abuse history or that she or any of her teammates have tried tobacco, alcohol, and other drugs. She identifies as female and has crushes...
on boys but is not allowed to have a boyfriend now and reports that she does not plan to even kiss a boy until she gets married.

On physical examination, vital signs and body mass index are within normal limits. JH appears healthy, athletic, and cooperative with tanner IV breast and pubic hair and no abnormalities on comprehensive examination.

JH is cleared for sports and developmentally appropriate anticipatory guidance is offered. However, when routine immunizations are discussed, her mother consents to the meningococcal, tetanus, diphtheria, and acellular pertussis vaccines but hesitates with the human papillomavirus (HPV) vaccine. She wants to avoid “unnecessary” vaccines and has several questions:

1. Does my daughter really need the HPV vaccine if she is not going to have sex until marriage?
2. My son never got the vaccine; should he get it?

Discussion

Messages for patient and family: You welcome the family’s questions and strongly recommend the vaccine for both the patient and her brother. You discuss with both the patient and her family that HPV is a common infection that can lead to cancer and genital warts. HPV is well known to cause cervical cancer in females and is associated with oropharyngeal, penile, anal, and other genital cancers. Her older brother should also be immunized to decrease both the acquisition and spread of HPV between himself and his future partner(s).

Background discussion: HPV is the most common sexually transmitted infection in the USA with 20–24-year-old females having among the highest prevalence [1]. Certain HPV types can lead to cutaneous manifestations (common skin warts), while others are associated with genital or oropharyngeal lesions (precancer and cancers) [2]. Genital HPV infections are generally acquired via skin-to-skin contact, most often sexual intercourse [2]. Though HPV infections can cause clinical manifestations, most HPV infections are asymptomatic and clear spontaneously in 2 years [3]. In addition, cervical cancer is very rare in females under age 20, and it takes years for cancer to develop after exposure to the virus leading to the recommendation to delay Pap smears until age 21 [3]. It is the persistence of infection with high-risk HPV types (such as HPV 16, 18, 31, 33, 45, 52, 58) which leads to cancers in women and men, many of which could be prevented by the HPV vaccine [2]. Low-risk HPV types 6 and 11 cause about 90% of genital warts (condylomata acuminata) and are associated with recurrent respiratory papillomatosis and conjunctival papillomas [2]. Genital warts are not precancerous lesions but still can be bothersome, as well as difficult to treat [2].

Each year in the USA, around 30,000 cases of HPV-related cancers are diagnosed [2]. HPV infections are responsible for nearly all cervical and anal cancers and most oropharyngeal, vaginal, and vulvar cancers [4]. The incidence of anal and
oropharyngeal cancers have been increasing in the USA [5]. These cancers are most commonly caused by the HPV types found in the licensed HPV vaccines [6] (Table 2.1).

**Messages for patient and family:** You can let the family know that HPV vaccines have been in use for over a decade and studied in clinical trials for even longer. Further, HPV vaccine is strongly recommended by the major medical groups. The most recently released 9-valent vaccine protects against even more high-risk HPV types.

**Background discussion:** Several vaccines have been developed to help decrease risks and subsequent sequelae related to acquisition of HPV infection. The US Food and Drug Administration (FDA) has approved the use of three HPV vaccines, which protect against two, four, or nine types of HPV. After FDA licensing and review of available studies, recent Advisory Committee on Immunization Practices’ (ACIP) vaccination guidelines (March 2015) reaffirmed the recommendations for vaccination of all males and females at ages 11–12 with catch-up for females aged 13–26 and males aged 13–21 [7]. The recommendations permit use in males and females as young as age 9 and males ages 22–26. However, it is important to note that the vaccine is specifically recommended in several special populations including cases of sexual abuse or assault (starting at age 9), catch-up vaccination through age 26 for men who have sex with men, and both males and females who are immuno-compromised [7, 8] (Table 2.2). All guidelines from major medical organizations agree with ACIP regarding the age group for routine immunization. In December 2016, the Centers for Disease Control and Prevention (CDC) approved the use of a two-dose series for boys and girls initiating HPV vaccination prior to age 15; the three-dose series is still recommended for those who start HPV immunization between ages 15 through 26 [9].

**Messages for patient and family:** For maximum protection, the patient should complete the entire series of shots. You can also emphasize the recommendation of universal vaccination at ages 11–12, since, even if the patient is not exposed to HPV prior to marriage, younger adolescents achieve a better antibody response to the vaccine than older teens. It is important to emphasize that this is a cancer prevention

### Table 2.1 HPV-associated cancers

<table>
<thead>
<tr>
<th>Site</th>
<th>Average annual #</th>
<th>% Attributable HPV</th>
<th>% Caused by HPV 16 or 18</th>
<th>% Additional caused by HPV 31, 33, 45, 52, 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervix</td>
<td>11,967</td>
<td>96%</td>
<td>66%</td>
<td>15%</td>
</tr>
<tr>
<td>Vulva</td>
<td>3136</td>
<td>51%</td>
<td>49%</td>
<td>14%</td>
</tr>
<tr>
<td>Vagina</td>
<td>729</td>
<td>64%</td>
<td>55%</td>
<td>18%</td>
</tr>
<tr>
<td>Penis</td>
<td>1046</td>
<td>36%</td>
<td>48%</td>
<td>9%</td>
</tr>
<tr>
<td>Anus: F</td>
<td>3089</td>
<td>93%</td>
<td>79%</td>
<td>11%</td>
</tr>
<tr>
<td>Anus: M</td>
<td>1678</td>
<td>93%</td>
<td>79%</td>
<td>4%</td>
</tr>
<tr>
<td>Oropharynx: F</td>
<td>2370</td>
<td>63%</td>
<td>51%</td>
<td>10%</td>
</tr>
<tr>
<td>Oropharynx: M</td>
<td>9356</td>
<td>63%</td>
<td>63%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Data from [6, 14]
Background discussion: HPV vaccines were initially recommended as a three-dose series, with the minimum time between doses 1 and 2 being 4 weeks and between doses 2 and 3 being 12 weeks [2]. There must be a minimum of 24 weeks between doses 1 and 3. A two-dose series has been approved by the CDC for males and females beginning HPV vaccination before the age of 15, with doses given 6–12 months apart [9]. Completion of a vaccine series with the same type of HPV vaccine is ideal in order to be consistent with the vaccine research studies. However, in cases where the previous vaccine type is unknown or unavailable, ACIP recommends completing the series, with the available HPV vaccine, rather than restarting the entire three-dose series [7].

Completion of the vaccine series results in production of vaccine-type HPV antibodies, or seropositivity, in over 99% of healthy individuals, and the antibody response produced by the two-dose series is non-inferior to that of the three-dose series [9]. Antibody titers decrease in the first 2 years after vaccination but then tend to stabilize at levels which are significantly higher than those resulting from natural HPV infection [2]. Furthermore, HPV antibody responses are significantly higher in

**Table 2.2** Characteristics of HPV vaccines and ACIP recommendations

<table>
<thead>
<tr>
<th>Characteristic or recommendation</th>
<th>Bivalent (2vHPV)</th>
<th>Quadrivalent (4vHPV)</th>
<th>9-valent (9vHPV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brand name</strong></td>
<td>Ceravix</td>
<td>Gardasil</td>
<td>Gardasil 9</td>
</tr>
<tr>
<td><strong>Viruslike particles contained</strong></td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
<td>6, 11, 16, 18, 31, 33, 45, 52, 58</td>
</tr>
<tr>
<td><strong>Manufacturer</strong></td>
<td>GlaxoSmithKline</td>
<td>Merck</td>
<td>Merck</td>
</tr>
<tr>
<td><strong>Recommendations</strong></td>
<td>• Females only</td>
<td>• Females and males</td>
<td>• Females and males</td>
</tr>
<tr>
<td></td>
<td>• Routine at age 11 or 12</td>
<td>• Routine at age 11 or 12</td>
<td>• Routine at age 11 or 12</td>
</tr>
<tr>
<td></td>
<td>• Can be started at age 9</td>
<td>• Can be started at age 9</td>
<td>• Can be started at age 9</td>
</tr>
<tr>
<td></td>
<td>• Catch-up for females ages 13–26</td>
<td>• Catch-up for females ages 13–26 (including immunocompromised)</td>
<td>• Catch-up for females ages 13–26 (including immunocompromised)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Catch-up for males ages 13–21</td>
<td>• Catch-up for males ages 13–21</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Catch-up for MSM and immunocompromised males ages 22–26</td>
<td>• Catch-up for MSM and immunocompromised males ages 22–26</td>
</tr>
<tr>
<td><strong>Proven protection against</strong></td>
<td>• Cervical cancer precursors in females</td>
<td>• Cervical, vulvar, and vaginal cancer precursors in females</td>
<td>• Protection over the 4vHPV from five additional HPV types for cervical, vulvar, and vaginal cancer precursors in females</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Genital warts in females and males</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anal precancers in males</td>
<td></td>
</tr>
</tbody>
</table>

MSM men who have sex with men; recommendations from [7]
9–15-year-olds compared to older adolescents and young adults, contributing to the recommendation to vaccinate all 11–12-year-olds [2, 7]. The antibody titers for the 9-valent vaccine are non-inferior to the quadrivalent vaccine [2].

In the HPV vaccine research studies, there was no identified lower threshold of antibody level below which an individual would not be protected from vaccine-related HPV types [2]. In practical terms, HPV antibody titers are not commercially available nor used in the clinical setting. We do know, however, that these vaccines are incredibly effective at preventing HPV-related disease [2] (Table 2.2). The protection from the bivalent and quadrivalent vaccines does not decrease even a decade after vaccination, as evidenced by the lack of breakthrough disease in 8–10-year follow-up studies [2]. Though HPV vaccines are most effective if given before a patient’s sexual debut, the vaccines can be used in patients who have been sexually active or even have evidence of current or past HPV infection. Individuals are unlikely to be infected with all vaccine-preventable types of HPV and will receive protection from the types to which they have not been exposed. It should also be noted that the vaccine is not therapeutic [2]. In other words, HPV vaccines do not treat disease but only can prevent disease.

Messages for patient and family: You can reassure the family that the HPV vaccine’s safety is monitored closely and patients usually only have minor side effects with the injection, similar to all vaccines given to children and adolescents. The vaccine is even safe and recommended in patients with a family history of autoimmune diseases, such as celiac disease and rheumatoid arthritis.

Background discussion: HPV vaccines are generally well tolerated and safe. The vaccines cannot cause infection since they are not live viruses but consist of bioengineered viruslike particles from the capsid proteins of the HPV types contained in the vaccine [2, 7]. HPV vaccination can be given to patients who are immunocompromised although the immunologic response may not be as robust as in immunocompetent individuals. It is also can be used by those who are breastfeeding (note: quadrivalent and 9-valent vaccines are considered safe in lactating women, but the bivalent vaccine has not been studied in breastfeeding patients) [2, 4]. Although there is no evidence of adverse pregnancy outcomes (pregnancy category B) and a pregnancy test is not required before vaccination, there have been no specific HPV vaccine studies in pregnant women. As such, HPV vaccines are not recommended in pregnant women and should be postponed until the pregnancy is completed (providers can notify the pregnancy registry for pregnant women who inadvertently receive the 9-valent vaccine at 1-800-672-6372; other HPV vaccine pregnancy registries have been closed with concurrence from the FDA) [2]. HPV vaccines have also not been shown to increase the risk of autoimmune diseases. Though some case reports have associated vaccination with development of multiple sclerosis, larger studies have shown no causal relationship [10].

It is common for parents to state concerns that consenting to the HPV vaccine will give their son or daughter license to become sexually active. Immunization with the HPV vaccine has not been shown to increase risky sexual activity [11]. In one recent study, researchers utilized a retrospective medical chart review, over a 3-year period, in order to prevent self-reporting bias and documented clinical outcome.
markers of sexual activity. The study found that females who received the HPV vaccine were no more likely than those who never received the vaccine to seek contraception and testing for pregnancy or STIs or be diagnosed with a pregnancy or STI. This study also showed that HPV vaccination was not associated with earlier age of initiation of sexual activity. As with all STIs, it is important to provide counseling that HPV transmission can also be reduced by abstinence, consistent condom use, and circumcision in males [1].

All three vaccine types have a similar side effect profile [7]. The most common adverse event is injection site pain, swelling, or redness [2]. Less commonly, systemic symptoms, such as headache, dizziness, fever, nausea, or fatigue, can be seen [2]. Syncope has been noted in adolescents following any vaccine, including the HPV vaccine [2]. To prevent syncopal episodes, patients should be observed sitting or lying for 15 minutes after injection [2]. The only HPV-specific serious adverse event reported has been rare anaphylaxis in patients allergic to vaccine components [1]. Therefore, the vaccine is contraindicated in individuals with an allergy to any vaccine components, including yeast in the quadrivalent and 9-valent or latex in the syringe stopper of the bivalent vaccine. The Vaccine Adverse Event Reporting System, among other vaccine surveillance programs, continuously collects and reviews potential adverse events [4]. No deaths have been caused by the vaccine [12]. As with all vaccines, the HPV vaccine can be given during mild illness but should be deferred during moderate-to-severe acute illness [2]. HPV vaccination does not change cervical cancer screening recommendations, because there are other HPV types that can cause cervical cancer that are not covered by the vaccine [7].

Despite what is known about the impressive immunogenicity, efficacy, and safety profiles of these vaccines, HPV vaccine uptake in the USA has been poor (Fig. 2.1).

![Fig. 2.1](image-url)
Although HPV vaccine uptake is much lower than the healthy children 2020 goal of 80%, it is also notable that uptake is lower than other vaccines on the adolescent platform [13]. As of 2014, in the USA, only 39.7% of females and 21.6% of males had completed three doses of the HPV series, and 60% of females and 41.7% of males had received at least one dose of the HPV series [14]. The promising news is that even with the poor immunization rate, vaccine-type HPV prevalence in the US population has decreased which suggests herd immunity, and there are fewer cases of genital warts in the adolescent age group [15, 16]. Other countries have been successful in achieving high rates of vaccination by including the HPV vaccine in their national vaccine program [3]. Some countries have also found decrease in genital warts and cervical dysplasia [16]. After just 3 years of the HPV vaccine program, Australia noted a decrease in cervical dysplasia [3].

Studies have evaluated various strategies to help increase vaccination rates, and one study showed high rates of series completion when families could choose the method by which they were reminded, whether via text, email, phone call and multiple methods or also by reminding the adolescent themselves [17]. More importantly, families are more likely to vaccinate against HPV if their physician strongly recommends the vaccine [12]. It is considered best practice to update vaccines at all patient visits and not miss opportunities by only reserving immunizations for the annual well visit.

**Clinical Pearls and Pitfalls**

1. HPV is the most common sexually transmitted virus in the USA. Genital warts result from low-risk HPV types and cancers can result from persistent infection with high-risk types.
2. HPV is responsible for most cervical, anal, oropharyngeal, vaginal, and vulvar cancers, along with some penile cancers.
3. HPV vaccines are safe and effective at protecting against HPV-related cancers and genital warts.
4. HPV vaccination should be routinely recommended to females and males ages 11 and 12. Vaccination can start at age 9 and recommended at this age with a history of sexual abuse. Catch-up vaccination is recommended for females ages 13–26 (bivalent, quadrivalent, or 9-valent) and males ages 13–21 (quadrivalent or 9-valent). Vaccination is also recommended for MSM and all immunocompromised individuals including males ages 22–26.
5. HPV antibody response is more robust when given at younger ages.
6. HPV vaccines are most effective if given before a patient becomes sexually active and is exposed to the virus, but neither sexual activity nor evidence of current or past HPV infection is a contraindication to vaccination.
7. Though the HPV vaccine is not approved in pregnant females, no safety concerns have been identified during pregnancy, and a pregnancy test is not required prior to vaccination.
8. HPV vaccines are generally well tolerated. The most common side effect is injection site discomfort. The most common adverse event is syncope, as is seen with other adolescent vaccines. No deaths have been caused by the vaccine.

9. HPV series completion rates are low in the USA, but a strong recommendation from a physician is one of the most important factors in increasing vaccination rates.

References

Suggested Educational Reading, References, and Policies

Tips and Toolkits


Chapters, Policy Statements, and Guidelines

Adolescent Gynecology
A Clinical Casebook
Talib, H.J. (Ed.)
2018, XXV, 275 p. 25 illus., 14 illus. in color., Softcover
ISBN: 978-3-319-66977-9