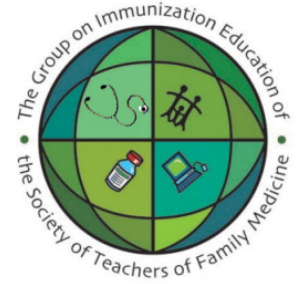


Group on Immunization Education
Society of Teachers of Family Medicine



CLINICAL SCENARIO SERIES ON IMMUNIZATION

Human Papilloma Virus Pre-adolescent Female

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Clinical Scenario – Human Papilloma Virus Pre-adolescent Female



Clinical Scenario – Human Papilloma Virus Vaccination

Learning Objectives:

1. Describe use of the preventive HPV vaccine among pre-adolescent/young adult females and issues relevant to patients/caregivers
2. Understand the rationale for use of the preventive HPV vaccine

Scenario:

Abigail and Mom

Abigail, a 12 year old girl, presents to your office accompanied by her mother for a “check-up”. They have brought with them sports physical paperwork so that Abigail can participate on the middle school soccer team. As part of assessing preventive care issues, you recommend that Abigail be started on the human papilloma virus (HPV) vaccine series.

Abigail’s mother has a sister who had a high-grade squamous interepithelial lesion (HSIL) pap screening result; colposcopic evaluation revealed a cervical interepithelial neoplasia, grade 2 (CIN 2, or moderate dysplasia) which was successfully ablated. Abigail’s aunt had mentioned that the cervical dysplasia was due to HPV. Abigail’s mother recalls reading a magazine article about HPV, but is initially ambivalent and wonders whether this is really necessary.



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Questions:

1. How common is HPV infection?
2. How is HPV transmitted?
3. What disease outcomes are associated with HPV infection?
4. What is the effectiveness of HPV preventive vaccines?
5. What is known about the safety of HPV preventive vaccines?
6. What is the duration of protection?
7. Who should receive the HPV preventive vaccine?
8. What is the dosing schedule?
9. What are sources of coverage for the vaccine?
10. What about pap screening among females who receive the HPV vaccine?



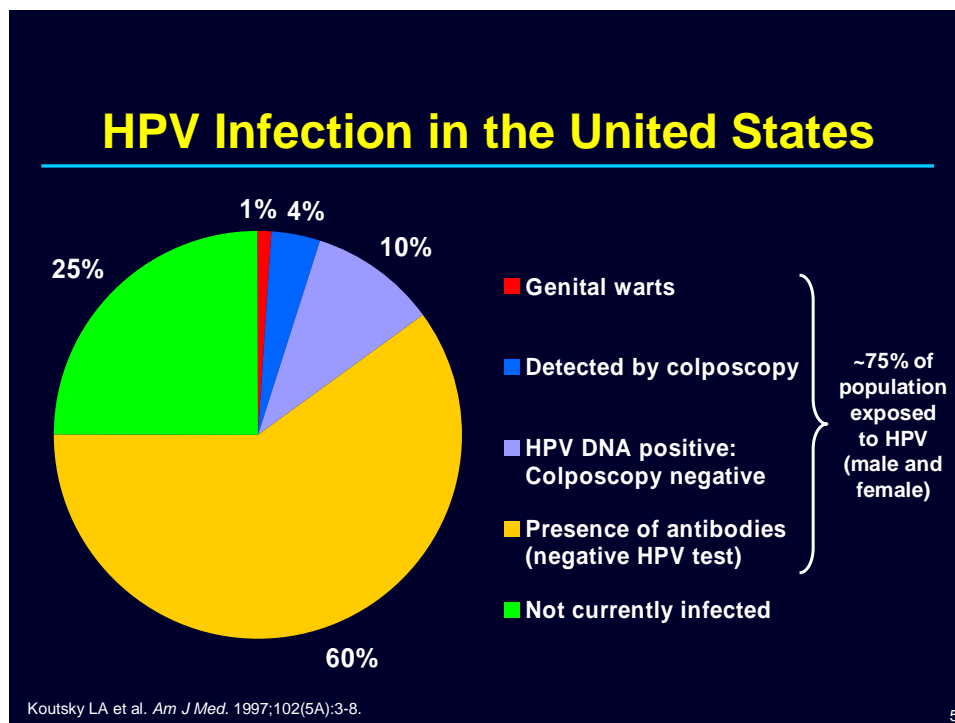
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Answers

1. How common is HPV infection?

The number of prevalent HPV infections in the United States is thought to exceed 20 million, while the incidence of HPV infections acquired via intercourse is upward of 5.5 million cases annually (Cates 1999). It is estimated that 75% of sexually active men and women have been exposed to HPV at some point in their lives (Koutsky, Galloway et al. 1988).

Males and females appear to be equally affected. Studies among adolescent girls and young adult women have reported HPV prevalence rates ranging from 28%-82% (Burk, Ho et al. 1996; Brown, Shew et al. 2005), while prevalence rates among adolescent and young adult males can range from 29%-48% (Kataoka, Claesson et al. 1991; Svare, Kjaer et al. 2002).



In 2000, the direct medical costs of HPV infection among persons 15 to 24 years of age were estimated to total \$2.9 billion, thereby ranking HPV ahead of genital herpes, chlamydia, and gonorrhea; the bulk of these costs are derived from the management of abnormal Pap smears (Chesson, Blandford et al. 2004).

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2. How is HPV transmitted?

While insertive intercourse likely represents the most efficient method of infection, HPV can be transmitted through any skin-to-skin contact. Within 36 months of first intercourse, the cumulative incidence of HPV infection among female college students who were HPV negative at time of enrollment reached 50% (Winer, Lee et al. 2003).

While the age of sexual debut is variable across various populations, national surveys note that about ¼ of US 15-year-olds report a history of vaginal intercourse, increasing to 62% of males and 70% of females by age 18 years (Mosher, Chandra et al. 2005). These figures suggest that other risk behaviors for HPV transmission are likely occurring at earlier ages.

Condoms are known to decrease the risk of infection with human immunodeficiency virus, chlamydia, gonorrhea, and herpes, as well as the risk of pregnancy. A recent paper reported that the risk of genital HPV infection among women reporting consistent condom use by male partners was reduced by 70% (Winer, Hughes et al. 2006). Thus, while the risk of HPV infection, pregnancy, and sexually transmitted infections can be decreased, condoms are not universally effective in preventing HPV infection. You emphasize to both Abigail and her mother that a prudent risk reduction strategy should include the ABCs: abstinence, be faithful, condom use.

3. What disease outcomes are associated with HPV infection?

The clinical burden of disease resulting from human papillomavirus (HPV) infection is substantial and extends from genital warts to cytologic abnormalities to cervical, vaginal, and vulvar cancers and their associated precursor lesions.

The family of HPV viruses includes more than 100 distinct viral types, that can be sub-divided based upon their tropism for infecting mucosal or cutaneous epithelial tissues (Mahoney 2006). HPV viral types are generally classified using a numbering system, for example HPV-6.

HPV infections involving cutaneous surfaces result in flat warts or plantar warts. The 40 types of mucoso-trophic HPV viruses include both “high-risk” and “low-risk” types based upon the type of disease outcomes resulting from infection. High risk types are associated with the development of cancers and pre-cancers.



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High risk HPV infection (e.g., HPV-16, -18, -31, -33, etcetera) manifest as pap smear abnormalities – low grade interepithelial lesions (LSIL), high grade interepithelial lesions (HSIL), cervical cancers and other malignancies of the anogenital region (Cox 1995; Munoz, Bosch et al. 2003). Nearly all cervical cancer specimens have detectable high risk HPV-DNA (Bosch, Lorincz et al. 2002; Munoz, Bosch et al. 2003) and the International Agency for Research on Cancer (IARC) identifies a dozen high risk HPV types as human carcinogens; chronic, persistent infection with high risk HPV represents a necessary cause of cervical cancer (IARC 2005). In addition, persistent infection with high risk HPV is implicated in the development of anal, penile, and head and neck cancers. Thus, HPV-related disease constitutes a significant disease burden for both men and women.

Cancers Attributable to High-Risk HPV

Site	Total Cancers*	HPV Attributable Fraction (%)	Estimated No. Attributable to HPV
Cervix	12,085	100	12,085
Anus	3,703	85	3,148
Vulva/vagina	4,480	50	2,240
Penis	985	40	394
Oral/pharyngeal	10,088	15	1,514

*U.S. Cancer Statistics Working Group (2005), United States Cancer Statistics: 1999-2002 Incidence and Mortality Web-based Report Version. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, and National Cancer Institute. Available at: www.cdc.gov/cancer/npcr/uscs/. Accessed Aug. 16, 2006; Parkin M (2005), Presented at the 22nd International Papillomavirus Conference and Clinical Workshop, Vancouver, Canada; April 30-May 6; Trotter H, Franco E (in press), Vaccine.

Infection with low risk HPV types (e.g., HPV-6, -11, etcetera) manifests as low grade pap smear abnormalities and genital warts. While these low grade pap smear abnormalities are largely reversible, the process of dealing with an abnormal pap smear is very distressing to both these patients and their families/friends. Among women exposed to HPV-6 or -11, about 2/3 will develop genital warts by 36 months (Winer, Kiviat et al. 2005). HPV-6 and -11 are also responsible for recurrent respiratory papillomatosis (RRP), where obstructive



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papillomas form on the larynx and vocal cords, causing considerable morbidity among affected infants and young children; there is also an adult onset form of RFRP.

The emotional impact of HPV infections includes feeling of anxiety, rejection, shame, loss of sexual interest and fears about cancer (Anhang, Goodman et al. 2004).

Most HPV infections are transient and will clear on their own; generally these infections are asymptomatic. However, chronic and persistent infection with high-risk HPV is associated with the development of malignancies and precursor lesions. At this time, there is no strategy to identify patients at risk of developing persistent HPV infection.

In summary, HPV types 16 and 18 are generally considered to account for approximately 70% of all cervical cancers in high-grade cervical lesions (e.g., cervical intraepithelial neoplasia grade 3 [CIN 3]) (Munoz, Bosch et al. 2003), and for more than 90% of cervical adenocarcinomas (Castellsague, Diaz et al. 2006). HPV types 16 & 18 are also thought to account for approximately 50% of CIN 2/3 cases, and close to 80% of vulvar intraepithelial neoplasia (VIN), grades 2/3 (Koutsky 1997). Low-risk HPV types, type 6 and 11, are thought to account for one-third to one-half of all low-grade cervical lesions (CIN 1) as well as low-grade vaginal and vulvar lesions (VaIN 1 and VIN 1) (Koutsky 1997). HPV types 6 and 11 account for more than 90% of cases of genital warts (Brown, Schroeder et al. 1999).



Common HPV Types Associated With Benign and Malignant Disease

	HPV Types	Manifestations
High-Risk	Types 16, 18, 31, 33, and 45	Low-grade cervical changes High-grade cervical changes Cervical cancer Anogenital and other cancers
Low-Risk	Types 6 and 11	Benign low-grade cervical changes Condylomata acuminata (Genital warts)

Co JT, 1995; Munoz et al., 2003.

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4. What is the effectiveness of HPV preventive vaccines?

Data on preventive HPV vaccines is derived from clinical trials of the quadrivalent HPV vaccine (Gardasil[®], Merck & Co., Inc., Whitehouse Station, NJ), which protects against HPV-16, -18, -6, and -11, and from clinical trials of a bivalent HPV vaccine (Cervarix[™], GlaxoSmithKline, London, UK), which protects against HPV 16 and 18. Gardasil[®] was FDA-approved in June 2006 while an application for Cervarix[™] was submitted in 2007.

HPV vaccine efficacy is generally within the range of 90% to 100% across studies and clinical outcomes. Although these studies examined somewhat different end points, the clinical outcomes are overlapping. Results provide consistent evidence confirming high levels of efficacy against incident and persistent HPV infection, cytologic abnormalities, histological changes, and HPV-related disease, including cancers and precursor lesions.

These vaccines are based on virus-like particles (VLPs) derived from non-infectious L1 outer capsid proteins which induce an immunologic response (Fife, Wheeler et al. 2004). Nearly all participants in clinical trials of HPV vaccines have demonstrated seroconversion to each of the component HPV antigens with antibody levels several-fold higher than those observed following natural infection

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(Harper, Franco et al. 2004; Sattler and Investigators. 2005; Skjeldestad and Committee 2005; Villa, Costa et al. 2005). However, minimal antibody levels considered to provide protection against each of the HPV subtypes have not yet been established. Moreover, antibody levels are HPV type–specific and assay-specific, and it is not possible to compare antibody levels across or within trials.

Studies of the immunogenicity of the preventive HPV vaccine among boys and girls ages 9-15 years, provide evidence of immunologic responses to the quadrivalent HPV vaccine that are least comparable to that observed among young women (Nolan, Block et al. 2005; Reisinger, Block et al. 2006). Thus, these data can be used to “bridge” efficacy data from studies that included young women to other age groups not included in the efficacy trials completed to date.

5. What is known about the safety of HPV preventive vaccines?

Consistent with other trials of vaccines, injection site reactions such as pain, swelling, and redness were common among participants in the HPV preventive vaccine trials and were somewhat more frequent in the vaccine group. Pain severity was typically reported as mild to moderate and generally lasted for 1 to 2 days. Systemic symptoms such as fatigue, headache, rash, upset stomach, and temperature elevation were comparable between groups. The occurrence of serious adverse events was infrequent, and vaccine-related serious adverse events were extremely rare. Taken together, the data on adverse events from these trials suggest that the HPV preventive vaccines are well tolerated (Harper, Franco et al. 2004; Sattler and Investigators. 2005; Skjeldestad and Committee 2005; Villa, Costa et al. 2005).

6. What is the duration of protection?

At this point it is not known if, or when, booster doses for these HPV vaccine might be needed. Follow-up data extending out to about five years show continued efficacy and immunogenicity for both the quadrivalent HPV vaccine (Villa, Ault et al. 2006) and for the bivalent HPV vaccine (Harper, Franco et al. 2006). Studies monitoring long term effectiveness remain underway.

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7. Who should receive the HPV preventive vaccine?

The quadrivalent HPV vaccine (Gardasil[®], Merck) is approved for administration to girls and women ages 9 to 26 years as a 3 dose series (initial dose, then 2nd dose 2 months after the 1st dose and the 3rd dose 6 months after the 1st dose). GlaxoSmithKline filed an application for FDA approval for the bivalent vaccine Cervarix[™] in March, 2007.



Recommendations from the Advisory Committee on Immunization Practices include routine use of the quadrivalent HPV vaccine (HPV-6,-11,-16,-18; Gardasil[®]) among girls at the 11-12 year visit; this “pre-adolescent visit” is intended to serve as an opportunity to emphasize health promotion and prevention (e.g., immunization). Clinicians may opt to vaccinate girls as young as age 9 years as part of a systematic approach to vaccination. The

HPV preventive vaccine should also be offered to all girls and women ages 13-26 years as part of a catch-up vaccination strategy (Markowitz, Dunne et al. 2007).



Schedules for recommended vaccines among children, adolescents and adults, including the HPV vaccine, are available at <http://www.cdc.gov/vaccines/recs/schedules/default.htm>.

The greatest benefit from vaccination with the HPV preventive vaccine will be derived among those persons/groups who have not yet been exposed to the HPV types included in the vaccine.

The ACIP recommendations for use of the HPV vaccine call attention to special situations including women with a history of equivocal/abnormal pap smears, HPV-positive, and/or with a history of genital warts. Use of the preventive HPV vaccine could provide protection against infection by those HPV types to which they have not yet been exposed. Immunocompetent women should also be offered this vaccine, although the immune response and effectiveness are uncertain. These special situations warrant a discussion of potential risks and potential benefits with patients as part of an informed decision-making process.



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While lactating women may receive the HPV vaccine, vaccination of pregnant females should be deferred.

8. What is the dosing schedule?

The HPV vaccine is a 3 dose series, administered over a period of 6 months. Dose #2 is recommended 2 months after the initial dose, but can be administered between 1 and 3 months following the initial dose. Dose #3 is recommended 6 months following dose #1, but can be administered between 4 and 8 months after the initial dose. The minimal interval between the first and second doses of HPV vaccine is 4 weeks and 12 weeks between the second and third doses (Markowitz, Dunne et al. 2007). Effectiveness data is based on administration of all 3 vaccine doses and efficacy after just 1 or 2 doses is unknown.

9. What are sources of coverage for the vaccine?

In 2007, the cost is **\$120 per dose** or \$360 for the full 3 dose series. Because the vaccine is recommended for routine use in targeted groups (Markowitz, Dunne et al. 2007), **most health plans that offer preventive services will cover the purchase and administration cost for the HPV vaccine** among girls and women ages 9-26 years of age

The HPV vaccine is included as part of the **Vaccines for Children (VFC) program** assuring access for adolescent females <19 years of age. The federal VFC program provides free vaccine for children through age 18 years who are Medicaid eligible, uninsured, American Indian/Alaska Native, or underinsured. Physicians can refer patients to VFC sites in their community or register to participate in the VFC program, administered by the National Immunization Program within the Centers for Disease Control National Immunization Program, at <http://www.cdc.gov/vaccines/programs/vfc/providers/default.htm>.

For women 19-26 years of age who are uninsured or underinsured, the **Merck Vaccine Patient Assistance Program (VPAP)** provides an important resource for eligible adults to access the HPV vaccine without charge. A VPAP application form can be downloaded at <http://www.needymeds.com/papforms/mervac1100.pdf>

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10. What about pap screening among females who receive the HPV vaccine?

Clinicians should emphasize to patients who receive the HPV vaccine that regular pap smear screening for cervical cancer early detection should continue at the recommended intervals (Saslow, Runowicz et al. 2002). It is important to understand that the maximal public health benefits of the preventive HPV vaccine will not be realized until vaccine recipients reach the ages of peak incidence for cervical, vaginal and vulvar malignancies, generally ages 50 years and older. Also, the HPV vaccines do not protect against infection with all high risk HPV types associated with the development of anogenital cancers.

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