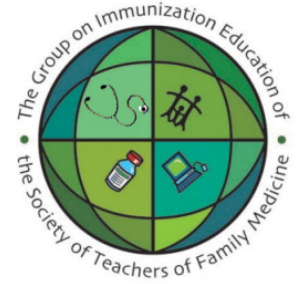


Group on Immunization Education
Society of Teachers of Family Medicine



CLINICAL SCENARIO SERIES ON IMMUNIZATION

Human Papilloma Virus Disease & Vaccination 23 year old female with abnormal pap test

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Learning Objectives:

1. review the management of abnormal pap smears
2. describe use of the preventive HPV vaccine among young adult women
3. understand the rationale for use of the preventive HPV vaccine

Scenario:

Beth, a 23 year old woman, presents for a follow-up pap smear and refill of her oral contraceptive medication. She explains that she has completed annual pap smears for the last 3 years with “normal” results before having an abnormal pap about 7 months ago. Following that abnormal pap she completed some other “test” which was “normal” and was instructed to come back in about 6 months for another pap test.



Beth denies dysuria or discharge at today’s visit. Her menstrual cycles are regular with moderate flow. She is not presently sexually active, but does report a total of 5 sexual partners in the past. For the last 4 years Beth has smoked about 10 -12 cigarettes daily. She is nulliparous.

Review of her medical chart confirms pap smear cytology results of atypical squamous cells of undetermined significance (ASC-US); reflex testing for Human Papilloma Virus (HPV) was positive for the presence of high-risk HPV. Results of colposcopy were negative.

At this visit you initiate a conversation to explore Beth’s understanding of Human Papilloma Virus (HPV) and clinical outcomes. Beth recalls some of her girlfriends mentioning something about HPV in the past but it appears that the topic of HPV has not been discussed with her. You recommend that Beth receive the HPV vaccine series with the first dose to be given today.

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Questions:

1. What is the optimal management of women with ACS-US results on pap smear screening?
2. How common is HPV infection?
3. How is HPV transmitted?
4. What disease outcomes are associated with HPV infection?
5. What is the effectiveness of HPV preventive vaccines?
6. What is known about the safety of the HPV preventive vaccines?
7. What is the duration of protection?
8. Who should receive the HPV preventive vaccine?
9. What is the dosing schedule?
10. What are sources of coverage for the vaccine?
11. What about cervical cancer screening following vaccination with the HPV vaccine?

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Answers

1. What is the optimal management of women with ACS-US results on pap smear screening?

The management of pap smear cytologic abnormalities has been summarized in consensus guidelines published in 2001 (Wright, Cox et al. 2002); an update of these guidelines by the American Society for Colposcopy and Cervical Pathology (ASCCP) is pending with anticipated release in mid- to late 2007. (<http://www.asccp.org/consensus.shtml>, accessed July 5, 2007)

While a single cytologic pap smears specimen has somewhat limited sensitivity, repeating this testing annually enhances the ability to detect cytologic abnormalities. A cytologic result of “atypical squamous cells (ACS)” is poorly reproducible but further evaluation is critical since 5-17% of women with ASC results will be found to have a grade 2 or 3 cervical intraepithelial neoplasia (CIN2/CIN3).(Wright, Cox et al. 2002)

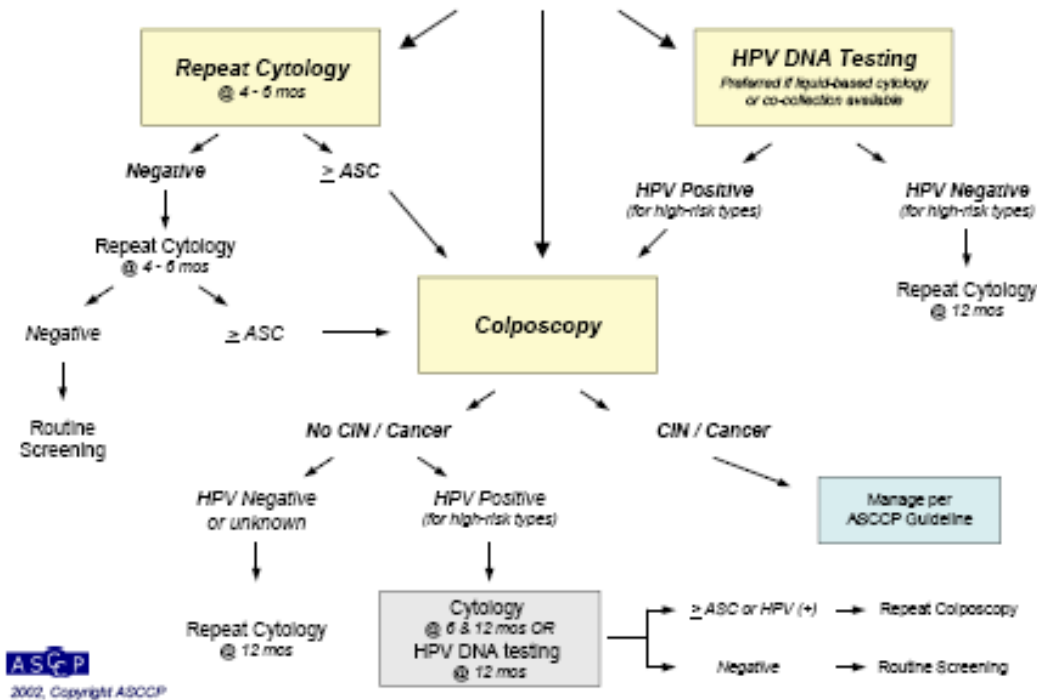
The 2001 guidelines note three options for managing an ACS-US pap result: 1) repeat cervical cytology at 4-6 months, 2) DNA testing for high-risk types of HPV, or 3) referral for colposcopy. The guidelines note testing for high risk HPV DNA as the preferred approach. Women who test positive for high risk HPV DNA should complete colposcopy. If high risk HPV DNA is not detected, cytology testing should be repeated in 1 year. (Only the high risk HPV test panel should be ordered, since the presence of low risk HPV DNA has no impact on clinical management.)

In Beth’s case of an ACS-US pap result, HPV DNA testing was positive for the presence of high risk HPV types. Colposcopy revealed no histology abnormalities and repeat cytologic testing at 6 months and 12 months was recommended. If both the 6 month and 12 month pap smear results are negative, annual screening can be resumed.

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Management of Women with Atypical Squamous Cells of Undetermined Significance (ASC-US)



Cigarette smoking and low folate levels have been identified as co-factors in the development of cervical cancers (Castellsague and Munoz 2003). Women with genital HPV infections and pap smear abnormalities should be advised to stop smoking, take a daily folic acid supplement (400 micrograms) and maintain a monogamous relationship.

2. How common is HPV infection?

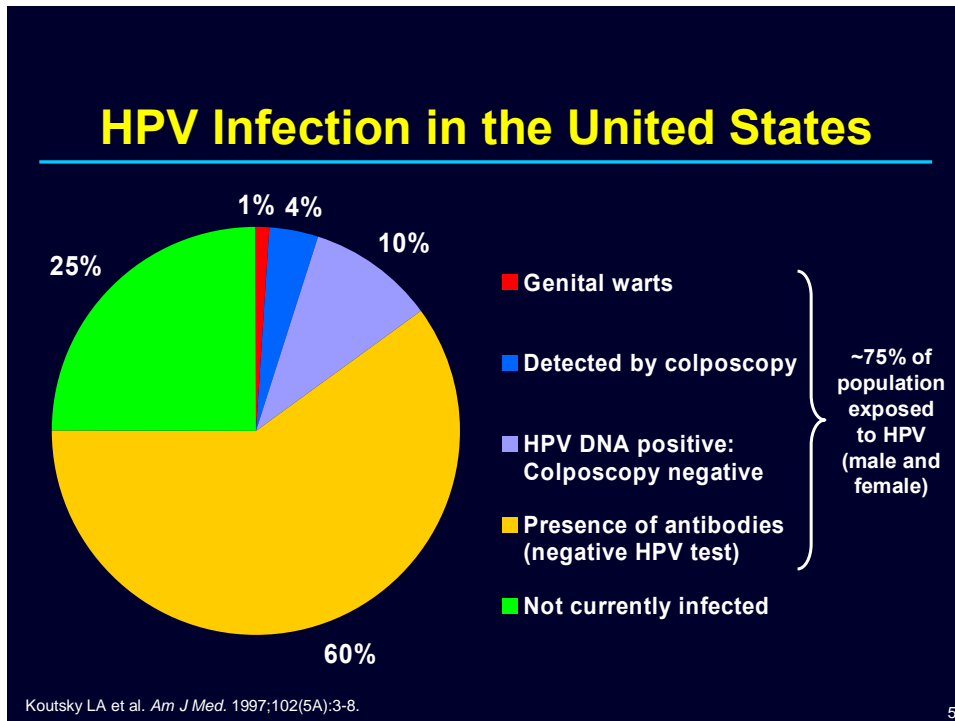
The number of prevalent HPV infections in the United States is thought to exceed 20 million, while the incidence of HPV infections acquired via intercourse is upward of 5.5 million cases annually (Cates 1999). It is estimated that 75% of sexually active men and women have been exposed to HPV at some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

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rates among adolescent and young adult males can range from 29%-48% (Kataoka, Claesson et al. 1991; Svare, Kjaer et al. 2002).



In the United States, the direct HPV-attributable costs associated with the management of abnormal Pap test results and treatment of cervical neoplasia totaled \$3.6 billion in CY 2000; most of the costs results from follow-up and treatment of abnormal pap smears (Chesson, Blandford et al. 2004). The costs attributable to HPV exceed those associated with genital herpes, chlamydia, and gonorrhea.

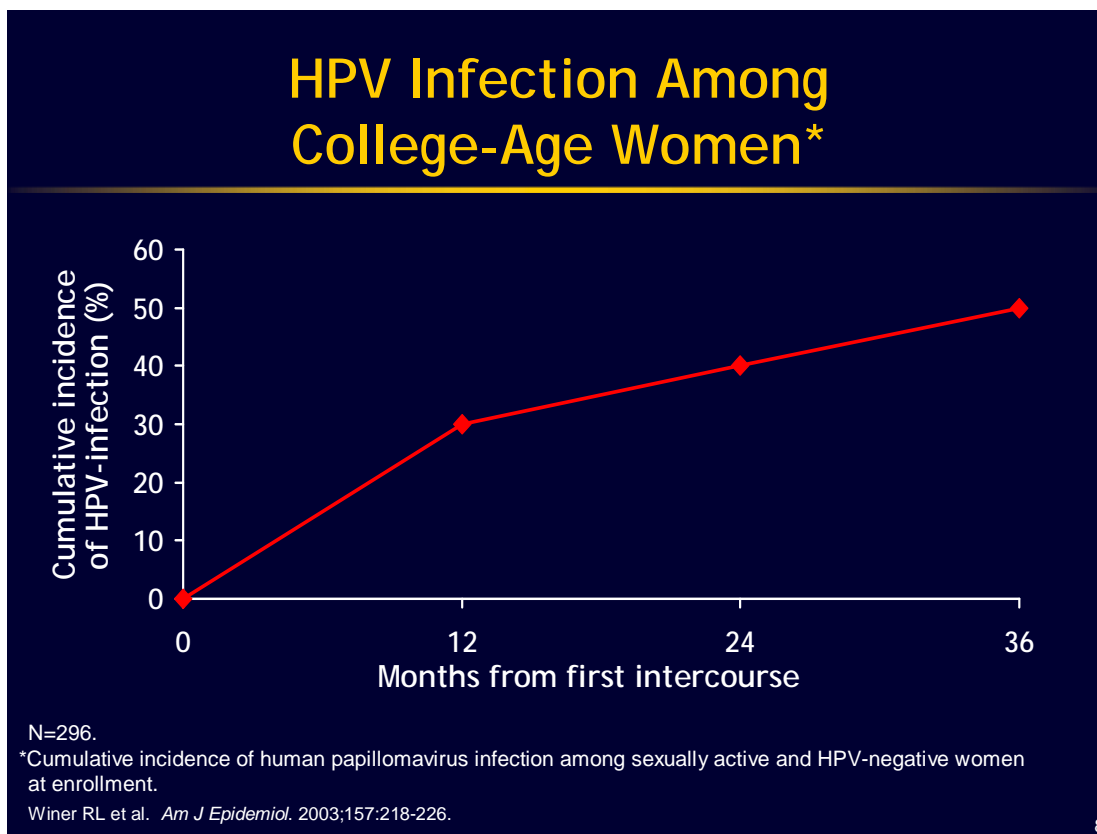
3. How is HPV transmitted?

While insertive intercourse likely represents the most efficient method of infection, HPV can be transmitted though 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).

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While the age of sexual debut is variable across different population groups, 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. A prudent risk reduction strategy should include the ABCs: Abstinence, Be faithful, Condom use.

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4. 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.

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 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 RRP.

High risk HPV infections (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).

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Cancers Attributable to High-Risk HPV

Cancer Site	Total Cancers*	% Associated With HPV**
Cervical	12,085	≥95%
Vaginal/Vulvar	3,703	50%
Penile	4,480	>50%
Anal	985	>70%
Oral/Pharyngeal	10,088	20%

*U.S. Cancer Incidence Cancer Statistics: 1999-2000. Atlanta: Department of Health and Human Services, Centers for Disease Control and Prevention, and the National Cancer Institute. Available at: www.cdc.gov/cancer/npcr/uscs/. Accessed Aug. 16, 2006.

**Gonzalez Intxaurraga MA, et al. *Acta Dermatovenerol.* 2002;11:1-8.

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 oral/pharyngeal cancers. Thus, HPV-related disease constitutes a significant burden for both men and women.

Each year >50 million pap smears are completed in the US resulting in the identification of 11,000+ new cancers of cervical cancer, 330,000 new cases of high-grade cervical dysplasia [cervical intraepithelial neoplasia (CIN) 2/3] and 1.4 million cases of low-grade cervical dysplasia (CIN 1) (Schiffman and Solomon 2003). HPV infections lead to 1 in 5 women experiencing an abnormal pap smear over their lifetimes (Sirovich and Welch 2004). The experience of an abnormal pap smear can result in emotional distress and anxiety for the patient, as well as family and friends. Moreover, 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).

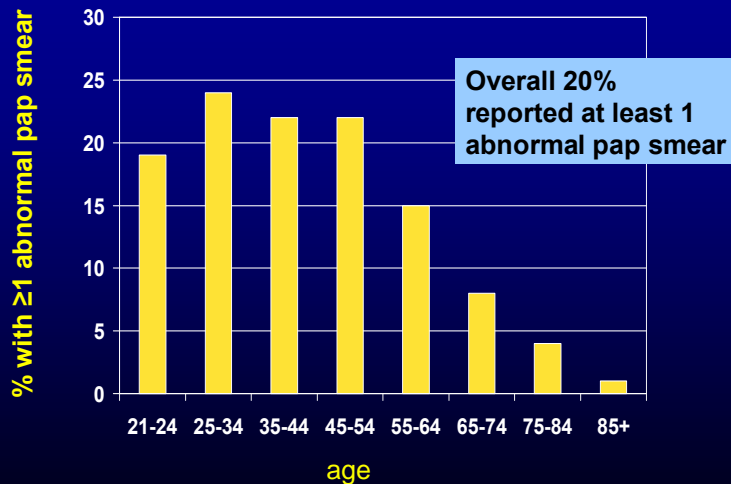
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Burden of Abnormal Pap Smears



Includes only women not reporting a hysterectomy.
Sirovich BE, Welch HG. J Gen Intern Med 2004; 19: 143-150.

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). These 2 HPV types are also thought to account for approximately 50% of CIN 2/3 cases, and close to 80% of vulvar intraepithelial neoplasia (VIN) 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 [vaginal intraepithelial neoplasia (VaIN)] 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).

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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.

4

5. 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 March 2007.

HPV vaccine efficacy is generally within the range of 90% to 100% across studies and clinical outcomes. Although published 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.

The results of two large clinical trials of the quadrivalent HPV vaccine, which together accrued 18,000 women, were recently published and affirmed high efficacy against both cervical pre-cancers and external genital lesions based on 3

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years of follow-up; sero-conversion rates after the 3 dose vaccine series are 99.5% (2007; Garland, Hernandez-Avila et al. 2007).

After 3 years of follow-up, the quadrivalent HPV vaccine was 100% effective (95% confidence interval 72-100%) against vulvar interepithelial neoplasia and vaginal interepithelial neoplasia (VIN 2/3 and VaIN 2/3) associated with HPV 16 or 18, among women naïve to these HPV types (Joura, Leodolter et al. 2007). These results suggest that the quadrivalent vaccine will contribute to reductions in HPV-related vulvar and vaginal cancers.

An interim analyses of a bivalent vaccine against HPV 16 & 18 (GlaxoSmithKline) among 18,000+ women ages 15-25 years noted efficacy of 90.4% against HPV16/18 related lesions (cervical intraepithelial neoplasia 2 or worse lesions); mean follow-up was 14.8 months (Paavonen, Jenkins et al. 2007).

These vaccines are based on virus-like particles (VLPs) derived from the 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 (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 of 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.

6. 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

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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; 2007; Ault 2007; Garland, Hernandez-Avila et al. 2007; Paavonen, Jenkins et al. 2007).

7. What is the duration of protection?

At this point it is not known if, or when, booster doses for these HPV vaccines 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.

8. 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 for FDA approval of Cervarix[™] in March 2007.)



Recommendations from the Advisory Committee on Immunization Practices (ACIP) 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 (Markowitz, Dunne et al. 2007).

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



ACIP recommendations for use of the HPV vaccine call attention to “special situations” including women with a history of equivocal/abnormal pap smears or, known to be HPV-positive to high risk HPV DNA. While it is likely that women with clinical histories similar to “Beth” have already been infected with HPV 16 and/or HPV 18 or other high risk HPV types, the results of HPV DNA testing are based on positivity to a panel of 13 high risk HPV types. As a result, there is no way to ascertain which type(s) are present. However, vaccination would protect against those HPV types to which a patients has not yet been infected. The preventive HPV vaccine has no therapeutic efficacy.

Similarly, women with a history of genital warts would likely already have been exposed to HPV 6 and/or HPV 11. The preventive HPV vaccine would provide protection against infection to those HPV types to which they have not yet been exposed that are in the vaccine.

Thus, use of HPV vaccine should be promoted among women with a history suggesting prior exposures to HPV, as the vaccine will afford protect against HPV types to which they have not yet been exposed. (Markowitz, Dunne et al. 2007).

Immunocompromised women should also be offered this vaccine, although the immune response and effectiveness are uncertain. These special situations warrant a discussion with patients regarding potential risks and potential benefits as part of an informed decision-making process.

While lactating women may receive the HPV vaccine, vaccination of pregnant females should be deferred (even though pregnancy category B).

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Schedules for recommended vaccines among children, adolescents and adults, including the HPV vaccine, are available at <http://www.cdc.gov/nip/recs/child-schedule.htm#Printable>.

9. 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). If a dose is late, it should be administered even if outside the recommended window. Effectiveness data is based on administration of all 3 vaccine doses and efficacy after just 1 or 2 doses is unknown. Immune theory and available data suggest a prime with the first dose, a boost with the second dose, and higher longer term titers from the third dose.

10. What are sources of coverage for the vaccine?

Out of pocket costs are **\$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), **nearly all health plans that have preventive services coverage** 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 disadvantaged adolescent females <19 years of age. The federal VFC program which 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 Centers for Disease Control and Prevention 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. Further information

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about the VPAP, including an application form, can be located at <http://www.merck.com/merckhelps/vaccines/home.html>.

11. What about cervical cancer screening following vaccination with the HPV vaccine?

The HPV vaccine can be considered as an adjunct to a comprehensive cervical cancer control program. 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.

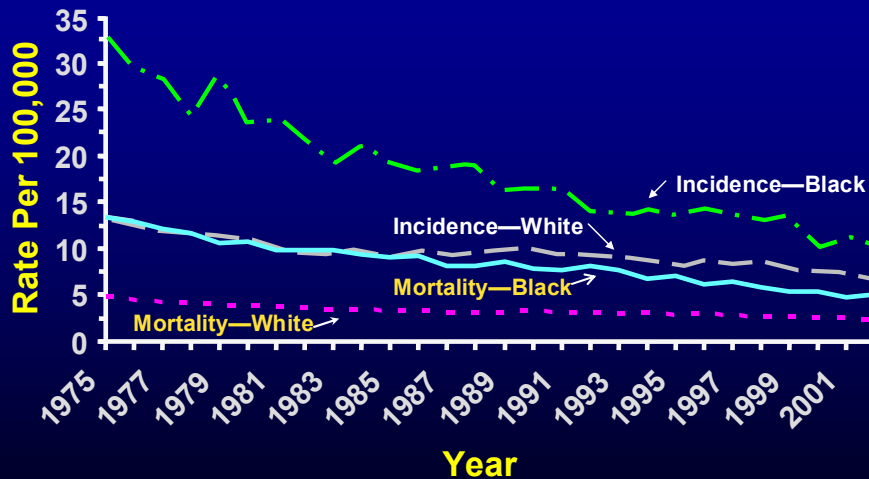
Non-compliance with recommended pap screening is a risk factor for cervical cancer. The HPV vaccine may help to address disparities in cervical cancer because HPV is covered by VFC.

Broad access to and utilization of the HPV preventive vaccines will help to address the current disparities in cervical cancer incidence and mortality. While the incidence of cervical cancer has decreased since 1992, cervical cancer incidence rates among blacks remain about 20% higher than among whites. Also, cervical cancer mortality rates among blacks are twice as high as among whites [Surveillance Epidemiology & End Results, www.seer.cancer.gov, April 2006].

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Invasive Cervical Cancer Incidence and Mortality Rates, by Race, SEER, 1975-2002



SEER = Surveillance Epidemiology and End Results; *Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population; SEER Cancer Statistics Review, 1975-2003. Available at: http://seer.cancer.gov/csr/1975_2003/. Accessed Aug. 15, 2006.

Consistent with recommendations from the Advisory Committee on Immunization Practices (ACIP) (Markowitz, Dunne et al. 2007). HPV vaccination should be actively promoted among all women ages 13-26 years. Cost should not represent a barrier to HPV vaccination. The vaccine is available through the Vaccines For Children program (up to age 18 years) and through the Merck Patient Assistance program (ages 19-26 years) [<http://www.merck.com/merckhelps/vaccines/home.html>]. ACIP recommendations for the HPV vaccine have been endorsed by major medical specialty societies providing care to girls and women including the American Academy of Family Physicians, the American Academy of Pediatrics, the Society of Adolescent Medicine, the American College of Obstetrics & Gynecology and the American College Health Association.

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