HPV AND HPV VACCINE

Information for Healthcare Providers

August 2006

OVERVIEW

On June 8, 2006, the Food and Drug Administration (FDA) licensed the first vaccine developed to prevent cervical cancer and other diseases in females caused by certain types of genital human papillomavirus (HPV). The quadrivalent vaccine, Gardasil®, protects against four HPV types (6,11,16, 18), which are responsible for 70% of cervical cancers and 90% of genital warts. On June 29, 2006, the Advisory Committee on Immunization Practices (ACIP [1]) voted to recommend use of this vaccine in females, ages 9-26 years.

This prophylactic vaccine, made from non-infectious HPV-like particles (VLP), offers a promising new approach to the prevention of HPV and associated conditions. However, this vaccine will not replace other prevention strategies since it will not work for all genital HPV types.

PROVISIONAL HPV VACCINE RECOMMENDATIONS

- The HPV vaccine is recommended for 11-12 year-old girls, but can be administered to girls as young as 9 years of age. The vaccine also is recommended for 13-26 year-old females who have not yet received or completed the vaccine series.
- Ideally, the vaccine should be administered before onset of sexual activity. However, females who are sexually active also may benefit from vaccination. Females who have not been infected with any vaccine HPV type would receive the full benefit of vaccination. Females who already have been infected with one or more HPV type would still get protection from the vaccine types they have not acquired. Few young women are infected with all four HPV types in the vaccine. Currently, there is no test available for clinical use to determine whether a female has had any or all of the four HPV types in the vaccine.

HPV VACCINE SAFETY

- The HPV vaccine has been tested in over 11,000 females (9-26 years of age) in many countries around the world, including the United States (U.S).
- These studies found that the HPV vaccine was safe and caused no serious side effects. Adverse events were mainly injection site pain. This reaction was common but mild.
- A detailed and coordinated post-licensure safety monitoring plan is in place.
- There is no thimerosal or mercury contained in the vaccine.

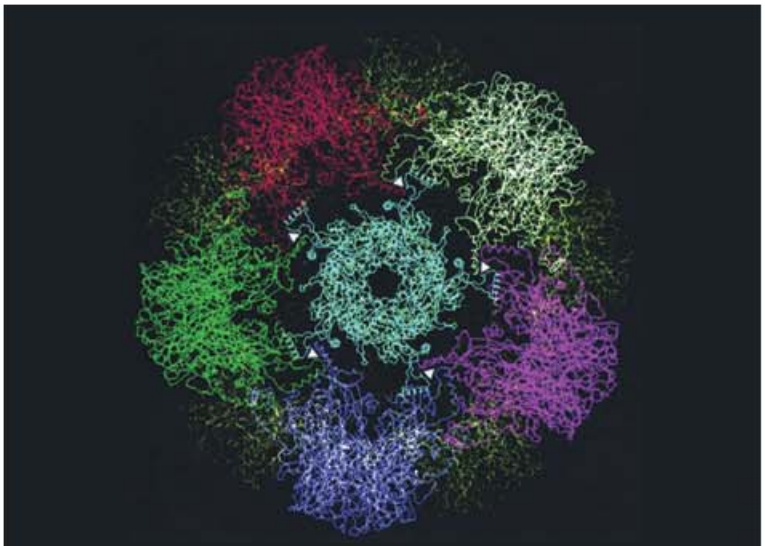
1 The ACIP advises the director of CDC and the Secretary of Health and Human Services (HHS) on the control of vaccine-preventable disease and vaccine usage. The ACIP is comprised of 15 members appointed by the Secretary of HHS. Recommendations made by the ACIP become CDC policy when they are accepted by the director of CDC and are published in CDC's Morbidity and Mortality Weekly Report (MMWR).

HPV VACCINE EFFICACY

- The efficacy of this vaccine has mainly been studied in young women (16-26 years of age) who previously had not been exposed to any of the four HPV types in the vaccine. These clinical trials have demonstrated 100% efficacy in preventing cervical precancers caused by the targeted HPV types, and nearly 100% efficacy in preventing vulvar and vaginal precancers and genital warts caused by the targeted HPV types.
- The vaccine has no therapeutic effect on HPV-related disease. If a girl or woman is already infected with one of the HPV types in the vaccine, the vaccine will not prevent disease from that type.
- The ACIP recommendation for vaccine use in girls as young as 9 years of age is based on 'bridging' immunogenicity and safety studies, which were conducted in about 1, 100 females, 9-to-15 years of age. These studies demonstrated that over 99% of study participants developed antibodies after vaccination; titers were higher for young girls than for older females participating in the efficacy trials.
- While it is possible that vaccination of males with the quadrivalent vaccine may offer direct health benefits to males and indirect health benefits to females, there are currently no efficacy data available to support use of HPV vaccine in males. Efficacy studies in males are ongoing. Information will be available in the future.

DURATION OF VACCINE PROTECTION

- The duration of vaccine protection is unclear. Current studies (with five-year followup) indicate that the vaccine is effective for at least five years. There is no evidence of waning immunity during that time period. This information will be updated as additional data regarding duration of immunity become available.



Virus-like Particles (VLPs) Assembled from the L1 Protein of Human Papillomavirus 16

HPV VACCINE DELIVERY (PROVISIONAL RECOMMENDATIONS)

- The vaccine should be delivered through a series of three intramuscular injections over a six-month period. The second and third doses should be given 2 and 6 months after the first dose.
- The vaccine can be administered at the same visit as other age-appropriate vaccines, such as Tdap, Td, MCV4, and hepatitis B vaccines.
- The HPV vaccine can be given to females who have an equivocal or abnormal Pap test, a positive Hybrid Capture II® high risk test, or genital warts. However, women should be advised that data do not indicate that the vaccine will have any therapeutic effect on existing Pap test abnormalities, HPV infection or genital warts.
- Lactating women can receive the HPV vaccine.
- Immunocompromised females, either from disease or medication, can receive this vaccine; however, the immune response to vaccination and vaccine efficacy might be less than in immunocompetent females.
- The HPV vaccine is not recommended for use in pregnancy. The vaccine has not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus. However, data on vaccination in pregnancy are limited. Any exposure to vaccine in pregnancy should be reported to the vaccine pregnancy registry (800-986-8999).
- The HPV vaccine is contraindicated for persons with a history of immediate hypersensitivity to yeast or to any vaccine component.
- The HPV vaccine can be administered to people with minor acute illnesses (e.g., diarrhea or mild upper respiratory tract infections, with or without fever). Vaccination of people with moderate or severe acute illnesses should be deferred until after the illness improves.
- Cervical cancer screening recommendations have not changed for females who receive the HPV vaccine.
- Vaccine providers should notify vaccinated women that they should continue to receive regular cervical cancer screening for three reasons. First, the vaccine will NOT provide protection against all types of HPV that cause cervical cancer. Second, women may not receive the full benefits of the vaccine if they do not complete the vaccine series. Third, women may not receive the full benefits of the vaccine if they receive the vaccine after they have already acquired a vaccine HPV type.
- Vaccine providers should notify vaccinated women that they should continue to practice protective sexual behaviors (e.g., abstinence, monogamy, limiting the number of sex partners, and using condoms, which may have a protective effect on HPV acquisition, reduce the risk for HPV-associated diseases, and mitigate the adverse consequences of infection with HPV[1]), since the vaccine will not prevent all cases of genital warts—nor will it prevent other sexually transmitted infections (STIs).
- CDC has developed a list of vaccine questions and answers, which vaccine providers may find useful for patient discussions.

HPV VACCINE DELIVERY

- The private sector list price of the vaccine is $119.75 per dose (about $360 for full series).
- The federal Vaccines for Children (VFC) Program will provide free vaccines to children and adolescents under 19 years of age, who are either uninsured, Medicaid-eligible, American Indian, or Alaska Native. There are over 45,000 sites that provide VFC vaccines, including hospital, private, and public clinics. The VFC Program also allows children and adolescents to receive VFC vaccines through Federally Qualified Health Centers or Rural Health Centers, if their private health insurance does not cover the vaccine. For more information about the VFC, visit http://www.cdc.gov/nip/vfc/
- Some states also provide free or low-cost vaccines at public health department clinics to people without health insurance coverage for vaccines.
- While some insurance companies may cover the vaccine and cost of administration, others may not. Most large group insurance plans usually cover the costs of recommended vaccines. However, there is often a short lag-time after a vaccine is recommended, and before it is available and covered by health plans.

COST EFFECTIVENESS OF HPV VACCINE

- Published cost-effectiveness studies of HPV vaccination suggest that the cost per quality-adjusted life year (or QALY) saved due to vaccination against HPV types 16 and 18 would be in the $15,000 to $25,000 range per QALY. These published estimates were calculated without including the benefits of preventing HPV types 6 and 11. If such benefits were included, the cost effectiveness of vaccination would appear more favorable.
- Both the impact and cost-effectiveness of HPV vaccination were estimated assuming that vaccination occurs in addition to current cervical cancer screening programs in the U.S.

POLICIES FOR HPV VACCINATION

- There are no federal laws requiring immunization of children with HPV vaccine. School and childcare entry laws for all immunizations are state laws and vary from state to state.

OTHER VACCINES IN DEVELOPMENT

- A bivalent HPV vaccine is in the final stages of clinical testing in females. This vaccine would protect against the two types of HPV (16,18) that cause 70% of cervical cancers.

GENITAL HPV INFECTION

HPV infection is the most common STI in the U.S., with approximately 20 million people currently infected. Each year, an additional 6.2 million people become newly infected in the U.S.[2] As many as half of infected males and females with HPV are adolescents and young adults, 15-24 years of age.[3]

While most HPV infections are asymptomatic and transient, HPV is of clinical and public health importance because persistent infection with certain oncogenic types can lead to cervical cancer. Cervical cancer is one of the most common cancers in women worldwide. Certain oncogenic types also have been associated with other, less common anogenital cancers. Moreover, non-oncogenic HPV types can cause genital warts and, rarely, respiratory tract warts in children.

Over 40 types of HPV infect mucosal surfaces, including the anogenital epithelium (i.e., cervix, vagina, vulva, rectum, urethra, penis, and anus). Genital HPV can be divided into "high-risk" (i.e., oncogenic or cancer-associated) types, and "low-risk" (i.e., non-oncogenic) types.

- HPV 16 and 18 are the most common high-risk types found in cervical cancer
- HPV 6 and 11 are the most common low-risk types found in genital and respiratory tract warts

Natural History of HPV

Over half of sexually active women and men are infected with HPV at some point in their lives.[4] Approximately 90% of women with HPV infection become HPV-negative within two years.[5] The gradual development of an effective immune response is thought to be the likely mechanism for HPV DNA clearance. However, it is possible that the virus remains in a non-detectable dormant state and then reactivates many years later.

Many women with transient HPV infections may develop mild cytologic (Pap test) abnormalities that spontaneously regress.

About 10% of women infected with HPV develop persistent HPV infection. Women with persistent high-risk HPV infections are at greatest risk for developing high-grade cervical cancer precursor lesions (cervical intra-epithelial neoplasia or CIN 2,3) and cancer.

HPV-Associated Disease

Persistent infection with high-risk types of HPV is associated with almost all cervical cancers. The age-adjusted incidence rate for invasive cervical cancer in the U.S. was 8.7 per 100,000 women in 2002 (most recent year for which data are available).[6] In that same year, 3,952 women died from cervical cancer in the U.S.

Persistent infection with high-risk types of HPV also is associated with cancers of the vulva, vagina, penis and anus. However, these cancers are considerably less common than cervical cancer.

Genital HPV infection with low-risk types of HPV is associated with genital warts in men and women. About 1% of sexually active adults in the U.S. have visible genital warts at any point in time.[2]

Rarely, perinatal transmission of low-risk HPV infections can result in respiratory tract warts in infants and children, a condition known as recurrent respiratory papillomatosis (RRP).

Prevention of Cervical Cancer

Cervical cancer once claimed the lives of more American women than any other type of cancer. But over the last 40 years, widespread cervical cancer screening using the Pap test and treatment of pre-cancerous cervical abnormalities have resulted in a marked reduction in cervical cancer incidence and mortality in the U.S.[7] New technologies, such as liquid-based cytology and an HPV DNA test, are now commercially available and licensed for use in women for cervical cancer screening and management, although they are not recommended by all professional associations.

Today, as many as 82% of women in the U.S. have been screened with a Pap test in the past three years.[8] Despite this, U.S. screening programs are not reaching all women in the U.S. It is estimated that half of the women diagnosed with cervical cancer have never been screened for cervical cancer, and an additional 10% have not been screened in the previous 5 years.[5,9] Cervical cancer disproportionately affects women of lower socioeconomic status, without regular access to health care, who are uninsured, and who are recent immigrants.[6,10]

Additional Sources of Information

www.cdc.gov/std/hpv
www.cdc.gov/ncidod
www.cancer.org
www.fda.gov/bbs/topics/NEWS/2006/NEW01385.html

References

1 Sexually Transmitted Diseases Treatment Guidelines, 2006. MMWR 2006; 55 [No. RR-11].

2 Weinstock H, Berman S, Cates W, Jr. Sexually transmitted diseases among American youth: incidence and prevalence estimates, 2000. Perspect Sex Reprod Health. 2004; 36(1):6-10.

3 Cates W, Jr. Estimates of the incidence and prevalence of sexually transmitted diseases in the United States. American Social Health Association Panel. Sex Transm Dis. 1999; 26(4):Suppl):S2-7.

4 Koutsky LA. Epidemiology of genital human papillomavirus infection. *Am J Med.* 1997; 102(5A):3-8.

5 Ho GY, Bierman R, Beardsley L, et al. Natural history of cervicovaginal papillomavirus infection as measured by repeated DNA testing in adolescent and young women. N Engl J Med. 1998; 338(7):423-428.

6 U.S. Cancer Statistics Working Group. *United States Cancer Statistics: 1999–2002 Incidence and Mortality Web-based Report.* Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2005. Available at: www.cdc.gov/cancer/npcr/uscs. Accessed December 6, 2005.

7 National Institutes of Health (NIH). *NIH Consensus Statement: Cervical Cancer.* 1996; 14:1-38.

8 Swan J, Breen N, Coates RJ, Rimer BK, Lee NC. Progress in cancer screening practices in the United States: Results from the 2000 National Health Interview Survey. Cancer, 2003; 1528-1540

9 Leyden WA, Manos MM, Geiger AM, Weinmann S, Mouchawar J, Bischoff K, et al.. Cervical cancer in women with comprehensive health care access: Attributable factors in the screening process. J Natl Cancer Inst. 2005;97(9):675-83.

10 Singh GK, Miller BA, Hankey BF, Edwards BK. Persistent area socioeconomic disparities in U.S. incidence of cervical cancer, mortality, stage, and survival, 1975-2000. Cancer, 2004;101(5):1051-7.