



**DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420**

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UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

**VACCINATION TO PREVENT CERVICAL CANCER CAUSED BY CERTAIN TYPES
OF GENITAL HUMAN PAPILLOMAVIRUS**

1. Purpose. This Under Secretary for Health Information Letter provides information regarding the provision of a vaccine to prevent cervical cancer and other diseases in women caused by certain types of genital human papillomavirus (HPV).

2. Background

a. HPV infection is the most common sexually-transmitted infection in the United States (U.S.). Approximately 20 million people are currently infected, and each year an additional 6.2 million people become newly infected. The Centers for Disease Control and Prevention (CDC) estimate that at least 50 percent of sexually active men and women acquire genital HPV infection at some point in their lives. Modeling studies suggest that at least 80 percent of women in the U.S. will have become infected with HPV by age 50. The vast majority of HPV infections are asymptomatic and resolve on their own within a period of 2 years. However, persistent infection with certain oncogenic or high-risk types can lead to cervical cancer or, less commonly, to other anogenital cancers. Non-oncogenic or low-risk HPV types are responsible for causing genital warts. There are more than one hundred HPV types with more than forty types capable of infecting mucosal tissues (see subpar. 5c); HPV types 16 and 18 are the most common types found in cervical cancer ("high-risk" types) and are responsible for causing 70 percent of cervical cancer cases. HPV types 6 and 11 are the most common types found in genital warts ("low-risk" types) and are responsible for causing 90 percent of genital warts.

b. Many women with transient HPV infections may develop mild cytologic abnormalities that spontaneously regress. About 10 percent of women infected with HPV develop persistent HPV infection. Women with persistent HPV infections are at increased risk for developing high-grade cervical cancer precursor lesions (moderate-severe dysplasia and cervical intra-epithelial neoplasia) and cancer. Use of cervical cytology for screening for cervical cancer (Papanicolaou (Pap) testing) has decreased the incidence of cervical cancer by 70 percent. The estimated number of new cases of cervical cancer in the U.S. in 2006 was 9710, causing an estimated 3700 deaths. However, about 3.5 million women in the U.S. have abnormal Pap tests each year, leading to numerous repeat tests, colposcopies, and other diagnostic evaluations.

c. In June 2006, the U.S. Food and Drug Administration (FDA) licensed the first vaccine (Gardasil[®] Merck & Co., Inc.) to prevent cervical cancer and other diseases in women caused by certain types of HPV. The quadrivalent vaccine protects against the four HPV types (6, 11, 16,

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and 18) responsible for 70 percent of cervical cancers and 90 percent of genital warts. It must be emphasized that this vaccine is not a therapeutic vaccine and does not prevent or treat disease associated with HPV vaccine types in which a woman has been previously infected.

Additionally, there are thirteen other high-risk HPV types responsible for causing the remaining 30 percent of cervical cancers that are not contained in the quadrivalent vaccine (see subpar. 5c).

NOTE: A bivalent vaccine (containing types 16 and 18) is under development and may be available soon.

d. The quadrivalent vaccine has been tested in a number of studies involving nearly 20,000 girls and women. The women included in the clinical trials had no prior history of abnormal Pap smears, were between the ages of 15 and 26 years, had zero to four lifetime sexual partners (average of two) and were followed for an average of 2 years. In the primary effective analysis (which included only those women who were seronegative or polymerase chain reaction (PCR) negative to all of the four types of HPV in the vaccine, the women received all three vaccinations and did not violate the protocol), the vaccine was 100 percent effective in preventing cervical pre-cancers and nearly 100 percent effective in preventing genital warts. However, in the analysis which included all women regardless of their baseline HPV status and who received at least one vaccination, the vaccine was approximately 40 percent effective at preventing cervical pre-cancers and just under 70 percent effective in preventing genital warts and other external genital lesions. No evidence exists of protection against disease caused by vaccine types for which participants were PCR positive at baseline. Participants infected with one or more vaccine types before vaccination were protected against disease caused by the other vaccine HPV types. No evidence exists that the vaccine protects against disease caused by non-vaccine HPV types.
NOTE: Testing for pre-existing HPV infection prior to vaccination is not recommended, as commercial assays do not indicate specific HPV types.

e. In the pre-marketing clinical trials, the vaccine was observed to be safe, causing no serious side effects. The National Vaccine Information Center has been closely following the post-marketing reported adverse events. As of February of 2007, there have been an estimated 542 adverse events reported in association with the quadrivalent vaccine. A number of those reports involved fainting or loss of consciousness after vaccination. A representative from the CDC stated that the number of cases of fainting, etc. was not unexpected; however, health officials are recommending a 15 minute waiting period after vaccination prior to leaving a doctor's office.

f. Since at this time the duration of protection provided by the vaccine is unknown, it is not known whether or not a booster vaccine may be indicated.

g. In Fiscal Year (FY) 2006, there were 32,429 unique women patients ages 18 to 26 in VHA who would be potentially eligible for the HPV vaccine. The number of eligible women may decrease over time, as the Department of Defense (DOD) begins to vaccinate active-duty women. The DOD policy on HPV vaccine is to administer Gardasil consistent with the FDA-approved product label and Advisory Committee on Immunization Practices (ACIP) recommendations.

h. The quadrivalent HPV vaccine is not recommended for administration in men at this time.

3. Recommendations of CDC's ACIP

a. In June 2006, the ACIP voted to recommend use of Gardasil® in girls and women ages 9 to 26 years. This recommendation was published in CDC's Morbidity and Mortality Weekly Report in March 2007. The recommended age for vaccination is 11-12 years; however, the vaccine can be administered to females as young as age 9 years. Catch-up vaccination is recommended for females aged 13-26 years who have not yet been vaccinated. **NOTE:** *Gardasil® needs to be refrigerated (2-8 °Centigrade (C), 36-46° Fahrenheit (F)). It needs to be protected from light and should not be frozen. The vaccine needs to be shaken well immediately before use. No reconstitution or dilution is necessary. The vaccine needs to be given immediately in the deltoid region of the upper arm.*

b. The American Cancer Society (ACS) has concluded that there are currently insufficient data to recommend for, or against, universal vaccination of females aged 19 to 26 years in the general population. ACS guidelines state that "a decision about whether a woman aged 19 to 26 years should receive the vaccine should be based on an informed discussion between the woman and her health care provider regarding her risk of previous HPV exposure and potential benefit from vaccination. Ideally the vaccine should be administered prior to potential exposure to genital HPV through sexual intercourse because the potential benefit is likely to diminish with increasing number of lifetime partners."

4. Recommendations from the VA National Center for Health Promotion and Disease Prevention. It is recommended that:

a. HPV vaccination is offered to girls and women 9-26 years of age who have not been previously vaccinated. **NOTE:** *Department of Veterans Affairs (VA) formulary criteria for use is available at [http://www.pbm.va.gov/criteria/Quadrivalent%20HPV%20Vaccine%20\(Gardasil\).pdf](http://www.pbm.va.gov/criteria/Quadrivalent%20HPV%20Vaccine%20(Gardasil).pdf)). Quadrivalent HPV vaccine is administered in a three dose schedule. The second and third doses need to be administered 2 and 6 months after the first dose. Each dose of quadrivalent HPV vaccine is 0.5 milliliters (ml), administered intramuscularly, preferably in the deltoid muscle.*

b. VA staff need to be aware of the following special situations, contra-indications, and precautions:

(1) The quadrivalent HPV vaccine can be administered at the same visit when other age appropriate vaccines are provided, such as Tdap, Td, hepatitis B, and MCV4. **NOTE:** *However, data are available only for administration of the HPV vaccine at the same visit as with the hepatitis B vaccine.*

(2) The 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. Vaccine recipients need to be advised that data from clinical trials do not indicate the vaccine has any therapeutic effect on existing Pap test abnormalities, HPV infection, or genital warts. Vaccination of these females would provide protection against infection with vaccine HPV types not already acquired.

(3) Lactating women can receive the HPV vaccine.

(4) Females who are immunocompromised either from disease or medication can receive the quadrivalent HPV vaccine. However, the immune response to vaccination and vaccine effectiveness might be less than in females who are immunocompetent.

(5) The quadrivalent HPV vaccine is not recommended for use in pregnancy. The vaccine has not been associated causally with adverse outcomes of pregnancy or adverse events to the developing fetus. However, data on vaccination during pregnancy are limited. If a woman is found to be pregnant after initiating the vaccination series, the remainder of the three-dose regimen needs to be delayed until after completion of the pregnancy. If a vaccine dose has been administered during pregnancy, no intervention is needed. **NOTE:** *Any exposure to vaccine during pregnancy should be reported to the vaccine pregnancy registry (1-800-986-8999).*

(6) The quadrivalent HPV vaccine is contraindicated for people with a history of immediate hypersensitivity to yeast or to any vaccine component.

(7) The quadrivalent HPV vaccine can be administered to females 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 needs to be deferred until after the illness improves.

c. Cervical cancer screening recommendations have not changed for females who receive the quadrivalent HPV vaccine. As a result, it is important to reinforce continued routine screening for cervical cancer in vaccinated and unvaccinated women. Providers need to encourage women to continue to practice protective sexual behaviors (e.g., limiting the number of sexual partners and using condoms), since the vaccine does not prevent other sexually-transmitted infections.

d. All women receiving the vaccine should be given the current HPV Vaccine Information Statement, available from the CDC website at: <http://www.cdc.gov/nip/publications/VIS/vis-hpv.pdf>.

e. The minimum interval between the first and second doses of the quadrivalent HPV vaccine is 1 month. The minimum recommended interval between the second and third doses of vaccine is 3 months. Doses administered within shorter intervals than that recommended need to be re-administered.

f. If the vaccine schedule is interrupted, the vaccine series does not need to be restarted. If the series is interrupted after the first dose, the second dose needs to be administered as soon as possible, and the second and third doses need to be separated by an interval of at least 12 weeks. If only the third dose is delayed, it needs to be administered as soon as possible.

NOTE: For more detailed information regarding this vaccine and use in VHA, refer to the Pharmacy Benefits Management website at: <http://www.pbm.va.gov/monograph/Gardasil.pdf>.

g. The Current Procedural Terminology (CPT) code for Gardasil[®] is 90649 (HPV vaccine, types 6, 11, 16, 18 (quadrivalent), three-dose schedule, for intramuscular use). The International Classification of Diseases - 8th Edition (ICD-9) code that can be used for patients receiving vaccination is V04.89 (need for prophylactic vaccination and inoculation against certain viral diseases—other).

h. Providers are encouraged to work with clinical pharmacists to report all clinically significant adverse events, even if causal relationship to the vaccine is not certain. Web-based reporting is available at <https://secure.vaers.org/VaersDataEntryintro.htm>. Reports can also be made by telephone at: 800-822-7967. Providers are strongly encouraged to enter allergies and/or adverse reactions into the allergies and/or adverse reactions data field in CPRS, to allow others to see that the patient has had a reaction. **NOTE:** A link to “How to Enter an Allergies and Adverse Reactions for CPRS v.26” is on the Center for Medication Safety website at <http://vaww.pbm.va.gov/pbm/vamedsafe.htm>.

i. Facilities are encouraged to develop and implement vaccination protocols. Local clinical reminders may be developed, but their use is not required.

5. **References**

a. National PBM Drug Monograph. Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil[®]). VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel. February 2007

b. CDC. HPV and HPV vaccine. Information for Healthcare providers. <http://www.cdc.gov/std/hpv/STDFact-HPV-vaccine-hcp.htm>.

c. ACIP recommendations for the use of quadrivalent HPV vaccine. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr56e312a1.htm>

d. Saslow D, Castle PE, Cox JT, et al. "American Cancer Society Guideline for Human Papillomavirus (HPV) Vaccine use to Prevent Cervical Cancer and its Precursors," CA: A Cancer Journal for Clinicians (CA Cancer J Clin). 2007;57:7-28.

6. **Inquiries.** Questions regarding this information letter may be directed to the:

a. Director, VA National Center for Health Promotion and Disease Prevention (NCP) in the Office of Patient Care Services at (919) 383-7874, ext 222;

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- b. Chief Consultant, Pharmacy Benefits Management (119) at (202) 273-5086; or
- c. Chief Public Health and Environmental Hazards Officer (13) at (202) 273-8575.

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