State of California—Health and Human Services Agency
California Department of Public Health

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TO: California Vaccines for Children (VFC) Program Providers

FROM: John Talarico, D.O., M.P.H., Chief
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SUBJECT:

- BIVALENT HUMAN PAPILLOMAVIRUS (HPV) (TYPES 16, 18) RECOMBINANT VACCINE IS NOW AVAILABLE FROM VFC;
- QUADRIVALENT HUMAN PAPILLOMAVIRUS (HPV) (TYPES 6, 11, 16, and 18) RECOMBINANT VACCINE AVAILABLE FOR MALES, AND
- UPDATED ACIP PROVISIONAL HARMONIZED HPV VACCINE RECOMMENDATIONS

This memo is divided into sections to enable you to quickly access the information you need:

SUMMARY

On October 16, 2009, United States Food and Drug Administration (FDA) licensed a bivalent human papillomavirus (HPV) vaccine, *Cervarix*®, GlaxoSmithKline Biologicals, for use in females 10 through 25 years of age. This bivalent HPV vaccine is indicated for the prevention of cervical cancer, cervical intraepithelial neoplasia, and adenocarcinoma in situ. The federal Advisory Committee on Immunization Practices (ACIP) voted to harmonize recommendations between the newly licensed bivalent HPV vaccine with the previously licensed quadrivalent HPV vaccine. The bivalent HPV vaccine is now available from VFC (http://www.cdc.gov/vaccines/programs/vfc/acip-vfc-resolutions.htm) for females 9 through 18 years of age.

The FDA also expanded the licensure for the quadrivalent HPV vaccine, *Gardasil*®, Merck & Co., for use in males ages 9 through 26 years for the prevention of genital warts. ACIP voted for permissive use of the quadrivalent HPV vaccine in males ages 9 through 26 years to prevent genital warts. The VFC Program announced in February that the quadrivalent HPV vaccine was available for males 9 through 18 years of age.

This letter summarizes information about the use of the bivalent HPV vaccine in the VFC program and updated information on the quadrivalent HPV vaccine. The Immunization Branch is following ACIP's updated harmonized provisional recommendations for use of HPV vaccines.

BACKGROUND AND COMPOSITION

Human papillomavirus types 16 and 18 cause approximately 70% of cervical cancer cases, approximately 40% of vulvar and vaginal cancers, and thousands of cases of anogenital and head and neck cancers in United States.

Cervarix® is a non-infectious recombinant, adjuvanted bivalent vaccine prepared from purified virus-like particles (VLPs) of the major capsid (L1) protein of human papillomavirus types 16 and 18. The product does not contain preservatives. The prefilled syringes contain latex in the tip cap and rubber plunger. Bivalent HPV vaccine single dose vials contain no latex.

In a recently published clinical trial, efficacy of the bivalent HPV vaccine against incident infection (95.3% (95% CI: 87.4-98.7)), persistent infection (100% (95% CI: 81.8-100)), and cervical intraepithelial neoplasia (CIN) grade 2 or higher (100% (95% CI: 51.3-100)) related to HPV types 16 and 18 remained high up to 6.4 years after vaccination. [The GlaxoSmithKline Vaccine HPV -007 Study Group, 2009]

Separately, the quadrivalent HPV vaccine has been found to have 90.4% (95% CI: 69.2-98.1)) efficacy against external genital lesions, and 89.4% (95% CI: 65.5-97.9) efficacy against condyloma in males for the vaccine HPV types. [http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf]

PROVISIONAL HARMONIZED HPV VACCINE RECOMMENDATIONS

Routine immunization with three doses of either the bivalent or quadrivalent HPV vaccine is recommended for females 11 or 12 years of age. The vaccination series can be started as young as 9 years of age. Catch-up vaccination is recommended for females 13 through 26 years of age who have not been vaccinated previously or who have not completed the full vaccine series, though persons older than 18 years of age are not eligible for the VFC Program.

Males ages 9 through 26 years may receive the quadrivalent HPV vaccine to reduce their likelihood of acquiring genital warts; however, males older than 18 years of age are not eligible for the VFC Program.

Ideally, HPV vaccine should be administered before potential exposure to HPV through sexual contact; however, persons who are already sexually active can still be vaccinated. Providers should continue to educate women about the importance of recommended cervical cancer screening.

Both HPV vaccines should be administered intramuscularly as a series of three separate 0.5 mL doses. The second dose should be given one to two months after the first dose, and the third dose should be given six months after the first dose.

The minimum interval between the first and second dose of vaccine is 4 weeks, and the minimum interval between the second and third dose is 12 weeks. The minimum interval between the first and third dose is 24 weeks.

Whenever possible, the same HPV vaccine product should be used for all doses in the series; however, for protection against cervical cancer, a combination of three doses of either vaccine would be considered valid. For protection against genital warts, three doses of the quadrivalent HPV vaccine are recommended.

ADMINISTRATION OF THE BIVALENT HPV VACCINE (CERVARIX®)

Thoroughly shake the vial or syringe prior to withdrawal and use. The vial or syringe should be inspected visually for cracks prior to administration. The vaccine should be inspected visually for particulate matter and discoloration prior to administration. If the vaccine vial or syringe is cracked or particulate matter or discoloration is noted, the vaccine should not be administered. After shaking, the vaccine should be a homogeneous, white, cloudy suspension. For single dose vials, vaccine should be withdrawn from the single-dose vial using a sterile needle and syringe. The vaccine should be administered by intramuscular injection in the deltoid region of the upper arm.

ADMINISTRATION OF HPV VACCINES WITH OTHER VACCINES

Both the bivalent and quadrivalent HPV vaccines may be given at the same visit when other age appropriate vaccines are provided, such as Tdap and MCV4.

OBSERVATION PERIOD

Syncope can occur after vaccination, most commonly among adolescents and young adults. To avoid serious injury related to a syncopal episode, vaccine providers should consider observing patients for 15 minutes after they are vaccinated. To decrease the risk of injury from syncope, providers should consider having their patients seated during both vaccination and the observation period.

HOW SUPPLIED FOR CALIFORNIA VFC PROGRAM PROVIDERS

Cervarix® is supplied as:

- Package of 10 single dose vials (NDC 58160-830-11)
- Package of 5 single dose pre-filled TIP-LOK™ syringes (packages without needles) (NDC 58160-830-46)

Storage

- DO NOT FREEZE
- Bivalent and quadrivalent HPV vaccines are freeze-sensitive vaccines and should be stored at 36 - 46°F (2 - 8°C). To avoid freezing temperatures, refrigerator temperatures should be maintained between 40 -42°F.
- Vaccines exposed to freezing temperatures should not be used.

POTENTIAL VACCINE REACTIONS

CDC and the FDA have reviewed the data from clinical trials and postlicensure and consider HPV vaccines to be safe and effective. Continuing studies are ongoing to monitor HPV vaccine safety. See above discussion about observation periods and the risk of syncope.

Bivalent HPV Vaccine
The most common adverse reaction reported was pain at the injection site. Other commonly reported adverse reactions included redness and swelling at the injection site, fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.

Quadrivalent HPV Vaccine
Local injection site reactions (pain, swelling, erythema), headache, fever, nausea, and dizziness were reported after administration with the quadrivalent HPV vaccine.

Providers should report suspected reactions to the HPV vaccine or other vaccines to the Vaccine Adverse Events Reporting System (VAERS) at 800-822-7967 (toll-free) or http://vaers.hhs.gov.

CONTRAINDICATIONS

- History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine.
- Patients with a history of anaphylaxis to latex should not receive Cervarix™ in the pre-filled syringe presentation as the rubber tip cap and plunger contain latex. The Cervarix™ single-dose vial does not contain latex.
- History of immediate hypersensitivity to yeast is a contraindication to the quadrivalent HPV vaccine.

PRECAUTIONS

- HPV vaccines can be administered to persons 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.

PREGNANCY

- HPV vaccines are not recommended for use in pregnant women. HPV vaccines have not been causally associated with adverse outcomes of pregnancy or adverse events to the developing fetus. However, data on vaccination during pregnancy are limited. Until additional information is available, initiation of the vaccine series should be delayed until after completion of pregnancy. Pregnancy testing is not needed before vaccination. If a vaccine dose has been administered during pregnancy, no intervention is needed.

- Any exposure to an HPV vaccine during pregnancy should be reported to the manufacturer's vaccine pregnancy registry:
    - Merck (*Gardasil*®): 1-800-986-8999

- GlaxoSmithKline (*Cervarix*®): 1-888-452-9622

SPECIAL SITUATIONS

- Abnormal Pap test/Genital Warts: 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. Vaccine recipients should be advised that data from clinical trials do not indicate the vaccine will have 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.
- Immunocompromised: Females who are immunocompromised either from disease or medication can receive either the bivalent or the quadrivalent HPV vaccine. However, the immune response to vaccination and vaccine effectiveness might be less than in females who are immunocompetent.
- Lactating women can receive either the bivalent or quadrivalent HPV vaccine.

ORDERING AND BILLING

Eligible Persons for Receipt of VFC Vaccine
Females ages 9 through 18 years are eligible for both the bivalent and the quadrivalent HPV vaccine provided by the VFC program. Males ages 9 through 18 years are eligible for the quadrivalent HPV vaccine provided by the VFC program.

How to Order
VFC Providers may order either the bivalent or the quadrivalent HPV vaccine using the attached revised order form (DHS 8501 [04/10]). Remember to complete all the boxes in the four columns of the order form. Maintain a copy of your order forms for your office files. Please be aware that your orders of the bivalent or quadrivalent HPV vaccine may be adjusted depending upon your existing inventory and reported usage.

Billing Information for VFC HPV Vaccine
CHDP: The CHDP administration fee will be $9.00 using CHDP code **85** for doses of bivalent HPV vaccine administered to females 9 years through 18 years, 11 months enrolled in the CHPD program.

The CHDP administration fee is $9.00 using CHDP code **76** for doses of quadrivalent HPV vaccine administered to males 9 years through 18 years, 11 months enrolled in the CHDP program.

However, providers should wait until notified by CHDP to submit claims for the bivalent HPV vaccine. CHDP Provider Information Notices can be found at http://www.dhcs.ca.gov/formsandpubs/publications/Pages/CMSLetters.aspx.

Medi-Cal Fee-For-Service (FFS): The code for administration of the bivalent HPV vaccine is **90650-SL** for female VFC recipients' ages 9 through 18 years. The code for administration of the quadrivalent HPV vaccine is **90649-SL** for both male and female VFC recipients' ages 9 through 18 years of age. For more information on Medi-Cal billing for the HPV vaccines, please see the February 2010 Provider Bulletin http://files.medi-cal.ca.gov/pubsdoco/publications/bulletins/gm/archive/pdf/gm20100201.pdf and also the Medi-Cal provider manual: http://files.medical.ca.gov/pubsdoco/publications/mastersmtp/part2/vaccine_m00o03o04o11.doc
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Other codes for the use of HPV vaccines that are not supplied by VFC:

- The CPT code for quadrivalent HPV vaccine is **90649**.
- The CPT code for bivalent HPV vaccine is **90650.**

DOCUMENTATION

- Bivalent HPV vaccine Product Insert: contains additional vaccine information: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM186981.pdf
- Quadrivalent HPV vaccine Product Insert: contains additional vaccine information: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM111263.pdf
- The GlaxoSmithKline Vaccine HPV-007 Study Group. Sustained efficacy and immunogenicity of the human papillomavirus (HPV)-16/18 ASO4-adjuvanted vaccine: analysis of a randomized placebo-controlled trial up to 6.4 years. Lancet 2009; 374: 1975-1985.
- Vaccine Information Statement (VIS): The VIS for HPV vaccines may be found at: http://www.cdc.gov/vaccines/pubs/vis/default.htm#hpv
- CDPH HPV Vaccine Information website: http://www.HPVVaccineCa.org
- CDC Fact Sheet: Information on HPV disease and the HPV vaccine can be found at: http://www.cdc.gov/vaccines/vpd-vac/hpv/default.htm
- ACIP recommendations: Provisional ACIP recommendations may be found at: http://www.cdc.gov/vaccines/recs/provisional/default.htm. Final updated ACIP recommendations for use of HPV vaccines will later be published at http://www.cdc.gov/vaccines/pubs/ACIP-list.htm
- AAP recommendations and other information about HPV will be available to AAP members at http://www.cispimmunize.org/
- VFC resolution No. 10/09-1: The VFC resolution on HPV vaccines may be found at: http://www.cdc.gov/vaccines/programs/vfc/downloads/resolutions/1009hpv-508.pdf
- Vaccine Injury Compensation Program (VICP): HPV vaccine is covered by the federal VICP. Information on the federal VICP and HPV vaccines will be found at: http://www.hrsa.gov/vaccinecompensation/.

Enclosures: Order Form (04/10) http://www.eziz.org/PDF/CDPH-8501.pdf

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