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TO: Vaccines for Children (VFC) Providers

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SUBJECT: GARDASIL<sup>®</sup> 9, NINE-VALENT HUMAN PAPILLOMAVIRUS VACCINE, IS NOW AVAILABLE FROM VFC

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## SUMMARY

In December 2014, the United States (U.S.) Food and Drug Administration (FDA) licensed a 9-valent human papillomavirus vaccine (HPV9), Gardasil<sup>®</sup> 9 (Merck and Co., Inc.), for use in females 9 through 26 years of age and males 9 through 15 years of age. HPV9 is indicated for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52, and 58 and genital warts caused by HPV types 6 and 11. It is also indicated for the prevention of cervical intraepithelial neoplasia (CIN) grades 1-3, cervical adenocarcinoma *in situ*, vulvar intraepithelial neoplasia grade 2 and 3, vaginal intraepithelial neoplasia grade 2 and grade 3, and anal intraepithelial neoplasia grades 1-3 caused by the vaccine HPV types. HPV9 is a preventive vaccine and does not treat current HPV infection or disease.

The Advisory Committee on Immunization Practices (ACIP) voted to include Gardasil® 9 in the VFC program at their February 2015 meeting. The vaccine is now available from VFC for both females and males 9 through 18 years.

This letter summarizes information about the use of the newly licensed 9-valent HPV vaccine. The California Department of Public Health, Immunization Branch is following ACIP's recommendations for use of HPV vaccines.

## **IMPORTANCE OF A STRONG MESSAGE FOR HPV VACCINE**

Providers should give a strong recommendation for the HPV vaccine series along with the other adolescent vaccines for preteen girls and boys. Focus the recommendation for HPV vaccination as a way to protect against a number of forms of cancers. According to CDC research, HPV vaccination as cancer prevention is a message that strongly resonates with parents. Providers should not miss any opportunity to vaccinate preteens with all recommended immunizations, including HPV vaccine.

California is far from meeting the Healthy People 2020 Objective for 3 doses HPV vaccine.<sup>1</sup> As shown below, rates for first-dose HPV and meningococcal conjugate vaccine lag that of Tdap. Providers should strongly recommend HPV vaccine and meningococcal vaccine at age 11-12 years, along with Tdap. Based on data from the National Immunization Survey – Teen for 2013, immunization rates for California teens ages 13-17 years of age were estimated to be:

- Tdap: 91%
- Meningococcal conjugate vaccine 81%
- HPV (one dose) for females: 68%
- HPV (three doses) for females: 46%
- HPV (one dose) for males: 51%
- HPV (three doses) for males: 17%

For additional tips and resources, please see: <http://eziz.org/resources/immunization-promo-materials/> under “Preteen” and [www.cdc.gov/vaccines/youarethekey](http://www.cdc.gov/vaccines/youarethekey). Contact your local health department to order select CDPH educational materials.

## **BACKGROUND AND COMPOSITION**

Human papillomavirus (HPV) is associated with cervical, vulvar, and vaginal cancer in females, penile cancer in males, and anal cancer and oropharyngeal cancer in both females and males. HPV infection also is associated with cervical precancers. The majority of all HPV-associated cancers are caused by HPV 16 or 18, types targeted by all licensed HPV vaccines. In the United States, 64% of invasive HPV-associated cancers are attributable to HPV 16 or 18 (~21,300 cases annually). Ten percent are attributable to the five additional HPV types (~3400 cases annually; 14% for females; 4% for males). HPV 16 and 18 account for 66% of cervical cancers and approximately 50% of ≥CIN2. The five additional types account for approximately 15% of

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<sup>1</sup> Healthy People 2020 Objectives for 13-15 year olds are 80% for each of the following three adolescent immunization measures: Tdap, meningococcal conjugate vaccine, and three doses of HPV vaccine

cervical cancers and approximately 25% of  $\geq$ CIN2. HPV 6 and 11 cause 90% of anogenital warts and most cases of recurrent respiratory papillomatosis.

HPV9 is a noninfectious, recombinant virus-like particle (VLP) vaccine of the major capsid (L1) protein of 9 HPV types. HPV9 contains HPV 6, 11, 16, and 18 VLPs (similar to HPV4); HPV9 also contains HPV 31, 33, 45, 52, and 58 VLPs. The L1 proteins are produced by fermentations using recombinant *Saccharomyces cerevisiae*. The VLPs are released from the yeast cells by cell disruption and then purified. The VLPs then are adsorbed on aluminum-containing adjuvant (amorphous Aluminum hydroxyphosphate sulfate). Each 0.5 mL dose contains approximately 30 mcg of HPV type 6 L1 protein, 40 mcg of HPV Type 11 L1 protein, 60 mcg of HPV type 16 L1 protein, 40 mcg of HPV type 18 L1 protein, 20 mcg of HPV type 31 L1 protein, 20 mcg of HPV type 33 L1 protein, 20 mcg of HPV type 45 L1 protein, 20 mcg of HPV type 52 L1 protein, and 20 mcg of HPV type 58 L1 protein. Each dose also contains approximately 500 mcg of aluminum and <7 mcg yeast protein. The product does not contain a preservative or antibiotics.

Studies showed high efficacy (96% or higher) of HPV9 in the prevention of grade 2 or 3 cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia caused by HPV types 31, 33, 34, 52, or 58 in females aged 16 through 26 years. Geometric mean antibody titers (GMTs) were significantly higher in adolescent girls and boys ages 9 through 15 years compared with females aged 16 through 26 years. Immunogenicity in males aged 16 through 26 years were compared to females in the same age group. Over 99% seroconverted to all nine HPV vaccine types, and GMTs in males were noninferior to those in females.

## **RECOMMENDATIONS FOR USE OF GARDASIL® 9 IN THE VFC PROGRAM**

### **Eligible Persons for Receipt of VFC Supplies**

Females and males ages 9 through 18 years are eligible for the 9-valent HPV vaccine (HPV9) provided by the VFC program.

Note: Although HPV9 is licensed for females ages 9 through 26 years and males ages 9 through 15 years only, ACIP recommended the use of the vaccine in males through age 26 after review of additional data on HPV9 in males aged 16 through 26 years that was not yet available during the FDA licensure process. This decision was the basis for allowing the use of this vaccine in both VFC-eligible females and males 9-18 years.

### **ACIP HPV Vaccine Recommendations**

Routine Recommendation: HPV vaccination is recommended routinely for all persons at 11 or 12 years of age. The vaccination series may be initiated as early as age 9 years. Vaccination beginning at age 9 years is recommended for children and youth with any history of sexual abuse or assault.

HPV vaccines are administered in a three-dose schedule. The second dose should be administered 1-2 months after the first dose. The third dose should be administered 6 months after the first dose. If the vaccine schedule is interrupted, the vaccination series does not need to be restarted.

If a patient started the HPV vaccination series with HPV2 (Cervarix®) or HPV4 (Gardasil®), HPV9 may be used to continue or complete the HPV vaccination series.

**Catch-up Recommendations:** Vaccination is also recommended for females ages 13 through 26 years and for males ages 13 through 21 years who have not yet started or completed the three-dose HPV vaccination series. The HPV vaccination series may also be given to males through the age of 26 years. If a person reaches age 27 years before the vaccination series is complete, the second and/or third doses of vaccine can be administered after age 26 years to complete the vaccine series.

**High-risk Recommendations:** HPV vaccination is also recommended through age 26 years for men who have sex with men and for immunocompromised persons (including those with HIV infection) if they have not been previously vaccinated or have not completed the three-dose vaccination series.

**Minimum intervals:** The first and second doses should be separated by an interval of at least four weeks. The second and third doses should be separated by an interval of at least 12 weeks, with a minimum interval of 24 weeks between the first and third doses.

**Important Note:** The full HPV vaccine recommendations are provided for your information; VFC HPV vaccines are only available for eligible patients ages 9 through 18 years.

## **ADMINISTRATION OF GARDASIL® 9**

For both single-dose vial and prefilled syringe: Shake well before use to maintain suspension of vaccine, which should appear as a white, cloudy liquid after agitation. Inspect visually for particulates or discoloration prior to administration. If particulates or discoloration are present, do not administer vaccine.

**Single-Dose Vial:** Withdraw vaccine from the single-dose vial using a sterile needle and syringe and administer preferably in the deltoid region.

**Prefilled Syringe:** Attach needle by twisting clockwise until the needle fits securely on the syringe. Administer the entire dose intramuscularly, preferably in the deltoid region.

Providers should consider observing patients (with patients seated or lying down) for 15 minutes after they are vaccinated.

Providers should report any vaccine administration error and associated contributing factors to the National Vaccine Errors Reporting Program (VERP) at <http://verp.ismp.org/>. Examples of potential errors include HPV2 (licensed only for females) administered to a male or DTaP administered to a teenager. As a part of the report, providers can make recommendations for error prevention. This surveillance program aims to prevent future errors by identifying trends, creating targeted education efforts, and making changes to product labeling and design.

## **ADMINISTRATION OF GARDASIL® 9 WITH OTHER VACCINES**

Gardasil® 9 can be given at the same visit when other age-appropriate vaccines are provided, such as Tdap and meningococcal conjugate vaccine. Do not mix this vaccine or any of its components with any other vaccine or diluent in the same syringe or vial. All vaccines should be given at separate anatomic sites with separate syringes. The California VFC program recommends that the HPV vaccine be given at the same visit as other recommended adolescent vaccines.

## **HOW GARDASIL® 9 IS SUPPLIED FOR CALIFORNIA VFC PROGRAM PROVIDERS**

Gardasil® 9 is supplied as:

- A carton of ten 0.5 mL single-dose vials

### **STORAGE**

- Please keep all syringes or vials stored in the original carton.
- Gardasil® 9 should be refrigerated at 35 to 46 degrees F (2 to 8 degrees C).
- Do not freeze. Protect from light.

### **POTENTIAL VACCINE REACTIONS**

In preclinical trials, safety was evaluated in over 13,000 subjects. The vaccine was well tolerated; most adverse events were injection site-related pain, swelling, and erythema that were mild to moderate in intensity. The safety profile was similar to that of HPV4, but recipients of HPV9 reported more injection-site adverse events, including swelling (40.3% vs. 29.1%) and erythema (34% vs. 25.8%). Males had fewer injection site adverse events (26.9% with swelling and 24.9% with erythema). Swelling and erythema increased following each successive dose of HPV9.

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 (with patients seated or lying down) for 15 minutes after they are vaccinated.

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

### **CONTRAINDICATIONS**

- History of immediate hypersensitivity to any vaccine component, including yeast.

### **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. However, if a woman is found to be pregnant after receiving HPV vaccine during pregnancy, no intervention is needed. The remainder of the three-dose series should be delayed until after the completion of the pregnancy. Women who were administered Gardasil® 9 around the time of conception or during pregnancy should report this to the Merck pregnancy registry at 1-800-986-8999.

### **CERVICAL CANCER SCREENING**

Cervical cancer screening continues to be recommended beginning at age 21 years and continuing through age 65 years for both vaccinated and unvaccinated women. Screening recommendations will continue to be evaluated as additional data becomes available.

## **ORDERING AND BILLING**

### **How to Order**

Supplemental orders will be accepted for all VFC providers to start receiving HPV9 vaccine. HPV9 is now available on VFC's online ordering system, MYVFCVaccines. To manage existing HPV4 vaccine inventories, the VFC program began limiting all HPV4 orders to approximately a 4-week supply, in an effort to reduce provider inventories of HPV4 prior to the introduction of HPV9.

Providers who may still have HPV4 doses on inventory once HPV9 is available for ordering, may consider using HPV9 doses in female patients, while using existing supply of HPV4 doses in non-high risk VFC-eligible male patients.

### **Ordering Other HPV Products**

#### **HPV4**

With the introduction of HPV9, HPV4 will no longer be available for routine ordering through the California VFC Program.

#### **HPV2**

Due to the limited VFC eligibility and indication of HPV2 (Cervarix®), this product will be considered a "special order vaccine." Cervarix® is only indicated for females. This vaccine is not recommended for males 9 through 18 years of age. HPV2 will be available in the "Special Order Vaccines" section of the VFC Order form on MYVFCVaccines.

Providers are allowed to order only one brand of vaccine, if multiple brands are available for the same vaccine type. As with other VFC products, providers serving primarily female populations, such as Women's Health Clinics, will be limited to only one brand of HPV vaccine.

### **Billing Information for VFC HPV9 Vaccine**

Information for billing the Child Health and Disability Prevention (CHDP) program and Medi-Cal for HPV9 will be forthcoming from Department of Health Care Services.

- CHDP Provider Information Notices <http://www.dhcs.ca.gov/services/chdp/Pages/CHDPPLPIN.aspx>.
- Medi-Cal Provider Bulletins [http://files.medi-cal.ca.gov/pubsdoco/Bulletins\\_menu.asp](http://files.medi-cal.ca.gov/pubsdoco/Bulletins_menu.asp).
- Medi-Cal Provider Manual [http://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/vaccine\\_m00o03o04o11.doc](http://files.medi-cal.ca.gov/pubsdoco/publications/masters-mtp/part2/vaccine_m00o03o04o11.doc).

Other codes for the use of Gardasil® 9 that is not supplied by VFC:

- The CPT code for HPV9 vaccine is 90651.
- The ICD-9-CM code for the need for prophylactic vaccination against other viral disease V08.9.

## DOCUMENTATION - HYPERLINKS

- 1) ACIP recommendations:
  - Use of 9-Valent Human Papillomavirus (HPV) Vaccine: Updated HPV Vaccination Recommendations of ACIP. MMWR, 2015; 64(11): 300-304.
  - Human Papillomavirus Vaccination: Recommendations of the ACIP. MMWR, 2014 ; 63(5):1-30.
- 2) Product Inserts:
  - Gardasil® 9
- 3) Vaccine Information State (VIS) for Gardasil® 9 vaccine
- 4) AAP recommendations (members-only): <http://www.cispimmunize.org/>
- 5) VFC resolution No. 02/15-2 on HPV vaccines
- 6) Vaccine Injury Compensation Program (VICP): HPV vaccines are covered by the federal VICP.
- 7) HPV Vaccine Resources for Healthcare Professionals – CDC  
<http://www.cdc.gov/vaccines/who/teens/for-hcp/hpv-resources.html>