Human Papillomavirus (HPV) Quadrivalent and Bivalent Vaccines

The Clinical Prevention Initiative (CPI) urges all medical practices and health professionals to routinely administer a series of three injections of human papillomavirus vaccine to males and females aged 11 and 12 years. Females may be given either HPV Quadrivalent Vaccine (Gardasil® from Merck) or HPV Bivalent Vaccine (Cervarix® from Glaxo Smith Kline), whereas males should be given quadrivalent vaccine (Gardasil®). This recommendation is based on observations that HPV vaccine is most beneficial when provided before sexual activity begins. Most sexually active people become infected with genital tract HPV shortly after sexual initiation. The vaccine is not effective against HPV types already acquired, but will protect against any of the HPV types to which the recipient has not been exposed.

At the discretion of the clinician, the series may be started in children as young as 9 years of age. The HPV vaccine is also indicated for adolescents and adults between the ages of 13 and 26 years of age who have not received the vaccine.

Administration to males, now a routine ACIP/CDC recommendation since October 2011, has been shown to prevent anal and penile cancer, and may also lower the risk to transmission of oncogenic and wart-producing types to sexual partners and prevent oral cancer.

Vaccines:
HPV infection is the most common sexually transmitted infection in the United States and causes a majority of atypical squamous cells of undetermined significance (ASCUS), more than 90% of all cervical intraepithelial neoplasia (CIN 1,2,3), and virtually all invasive cervical cancers. HPV 16 and 18 are responsible for up to 70% of CIN and cervical cancer and also 25 – 70% of vaginal and vulvar intraepithelial neoplasia (VaIN and VIN, respectively) as well as substantial causes of anal and penile carcinoma in males.

Gardasil® is a recombinant product of highly purified virus-like particles (VLPs) of HPV capsid proteins produced in yeast. Cervarix® contains similar VLPs produced in insect cells. Thus neither vaccine contains any live HPV viral particles and cannot transmit HPV infection.

Type of coverage* is summarized in the table below:

<table>
<thead>
<tr>
<th>HPV Type</th>
<th>Gardasil® (Quadrivalent)</th>
<th>Cervarix® (Bivalent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 and 18 Cause 70% of cervical cancer</td>
<td>Protects against type 16 and 18</td>
<td>Protects against type 16 and 18</td>
</tr>
<tr>
<td>6 and 11 Cause 90% of genital warts</td>
<td>Protects against 6 and 11</td>
<td></td>
</tr>
</tbody>
</table>

- Both vaccines may provide additional cross protective coverage for some other oncogenic types, particularly 31 and 45, but neither vaccine is specifically approved by the FDA for this indication; see each package insert for further details.
What is the administration schedule?
Both vaccines are provided as either single dose vials or prefilled syringes; neither are provided in multidose vials. Both vaccines must be stored in refrigeration at temperatures of 2-8°C (36-45°F) and must be administered as soon as possible after removed from refrigeration. Both vaccines are administered as a series of 0.5mL intra muscular injections administered by the followed schedule:

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>First dose</th>
<th>Second</th>
<th>Third</th>
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<tbody>
<tr>
<td>Cervarix® (Bivalent)</td>
<td>Females ages 11-26 (minimum age 9)</td>
<td>1 month after the first</td>
<td>6 months after the second</td>
</tr>
<tr>
<td>Gardasil® (Quadrivalent)</td>
<td>Females or males ages 11-26 (minimum age 9)</td>
<td>2 months after the first</td>
<td>6 months after the second</td>
</tr>
</tbody>
</table>

If second and third doses are delayed, there is no need to restart the series. Recommendations for maximal and minimal intervals between each dose are provided in each vaccine’s package insert.

Genital tract HPV DNA testing is not recommended to screen female patients for pre-existing HPV infections. Although these vaccines are not recommended for administration to pregnant females, routine pregnancy testing prior to doses is not recommended. (see “precautions”, below)

Cervarix® and Gardasil® are not interchangeable and once the series is started it should be competed with the same vaccine.

Giving HPV Vaccine with Other Vaccines
- The HPV series can conveniently and safely be initiated in tandem with other vaccines. It is recommended (ACIP, AAFP, and AAP) to be given with the other vaccines for 11 and 12 year olds – the Meningococcal Conjugate (MCV4) and the Tetanus, Diphtheria, Pertussis (Tdap) booster.
- HPV vaccine has been safely administered with Hepatitis B vaccine.

Side Effects:
Local: injection site pain (80-90%), swelling (25-92%), and erythema 25-45%
Systemic: low grade fever (4%–13%), headache (12-53%) nausea (4 %) and dizziness (< 3%), fatigue (55%), myalgia, or arthralgia (21-49%) gastrointestinal symptoms (3-27%)

Contraindications
Previous allergic reactions to any of the vaccine constituents.
Gardasil®: aluminum hydroxyphosphate sulfate, L-histidine, and sodium borate
Cervarix®: aluminum hydroxide, and sodium dihydrogen phosphate dehydrate, insect cell and bacterial protein. Prefilled syringes contain latex tips and plungers that may cause reactions in latex sensitive individuals.

Precautions
- Successful completion of the HPV vaccine series does not change the recommendations for periodic screening with Pap smears and testing is recommended to be completed according to ACOG guidelines..
- HPV vaccine is not recommended for use during pregnancy. If a recipient is determined pregnant, the series should be interrupted until after parturition. Merck maintains a Pregnancy Registry to monitor fetal outcomes of pregnant women exposed to Gardasil®. Patients and healthcare providers are encouraged to report any exposure to the vaccines during pregnancy by calling (800) 986-8999 for Gardasil® or 1-888-452-9622 for Cervarix®, however, the incidence of Caesarian section, pregnancy related problems, and congenital anomalies were equivalent in women receiving HPV vaccines or placebo.
- Because those being vaccinated may develop syncope, observation for 15 minutes is recommended.
How to Obtain the Vaccine

- Vaccine may be ordered through the Vaccines for Children (VFC) program at the New Mexico Department of Health for all adolescents 11 and 12 years old, and for catch-up vaccination for adolescents ages 13 through 18 years. Use the VFC vaccine order form at http://www.health.state.nm.us/immunize/forms/vaccineorder.pdf
- and fax to 505-827-1741.
- Vaccine for other age groups may be obtained at MerckVaccines.com or by calling 1-877-VAX-MERCK (1-877-629-6372) and at Glaxo Smith Kline www.gskvaccinedirect.com or 1-866-475-8222.

Suggestions for Smooth Third Party Reimbursement

VFC (not purchased) Vaccine:
Vaccine is available free of charge through the VFC program for patients, both males and females. No source can be billed for the vaccine acquired from VFC. Claims should show the vaccine code (90649) with a zero ($0.00) charge and the administration fee code (90471 or 90472). The exception is the fee-for-service, exempt Medicaid (not SALUD!) program. For exempt Medicaid providers, use only the CPT code for the vaccine (90649) and enter the usual charge for vaccine administration. Use diagnosis code V05.8 for HPV vaccine and administration.

Non-VFC (purchased) Vaccine:
Please check with your patient’s insurance plan whether HPV is a covered benefit, if it falls under the deductible, and/or if prior authorization is required. It is customary to bill for vaccine and vaccine administration. We suggest you place CPT-4 modifier -25 after your evaluation and management code (99201-99215) to indicate the office visit was unrelated to administration of HPV vaccine. Use diagnosis code V05.8 for HPV vaccine and administration.

NM Statewide Immunization Information System (NMSIIS)
It is important for providers to enter immunization data directly into NMSIIS so that a child’s complete immunization history becomes available to any health professional who has access to the system. The proper utilization of NMSIIS helps to eliminate over-immunizing a child as well as to identify those who are under-immunized. To request NMSIIS training for your office, please contact the NM Department of Health at 1-800-280-1618.

For Further Information

Centers for Disease Control and Prevention Vaccination Information Statement

Clinical Prevention Initiative at 505-828-0237 or 800-748-1596 or cpi@nmms.org