

Louisiana Drug Utilization Review (LADUR) Education

Human Papillomavirus: Focus on Prevention

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Human Papillomavirus (HPV)

Genital HPV is the most common sexually transmitted infection (STI) in the United States, with an estimated 6.2 million new infections occurring annually.¹ Papillomaviruses initiate infection in the basal layer of the epithelium causing normally nondividing epithelial cells to remain in an active cell cycle; this may result in a thickened epithelial lesion. Because papillomaviruses are restricted to the epithelium, HPV infections are largely shielded from the host immune response, although 90% of cases are cleared naturally.^{2,3} HPV is transmitted by direct contact, usually sexual, with an infected person. Transmission occurs most frequently with sexual intercourse but may occur following nonpenetrative sexual activity. The affected genital areas of men and women include the skin of the penis, vulva, and anus, as well as the linings of the vagina, cervix, and rectum.⁴

Many HPV types have been identified; over 40 types affect the epithelial mucosa.² (See Table 1) Genital wart-causing HPV types are often referred to as "low-risk" and cancer-causing HPV types as "high-risk." High-risk HPV types are detected in 99% of cervical cancers with types 16 and 18 together accounting for approximately 70% of cases.² With 30% of cervical cancers caused by HPV types that are not contained in available vaccines, cervical cancer screening programs are still a necessity.⁵

Genital Warts

Population-based estimates, primarily from clinics treating persons with STIs, indicate that about 1% of the sexually active adolescent and adult population in the United States have clinically apparent genital warts. All anogenital warts are caused by HPV, and approximately 90% are associated with HPV types 6 and 11.² After infection with HPV types 6 or 11, the average time to development of new anogenital warts is 2 to 3 months. However, not all persons infected with HPV types 6 or 11 acquire genital warts due to the body's ability to clear the infection. And unlike cervical cancer, anogenital warts can be treated locally.³

Typically appearing externally as painless, pink or flesh colored swellings of the skin of the genital region, perineum, and perianal region, genital warts can appear singly or in clusters. Genital warts can also manifest internally on the cervix, vaginal walls, and anus or within the urethra, in which case the patient is unlikely to be aware of the infection. Signs of infection may take months to appear or the infected person may never develop symptoms. Viral transmission may occur despite a lack of visible signs of infection.⁶

Cervical Cancer

The American Cancer Society estimates that in 2009, 11,270 cases of invasive cervical cancer are expected to be diagnosed and 4,070 deaths from cervical cancer are expected. Over the past several decades, mortality rates due to cervical cancer have declined steadily due to prevention and early detection as a result of screening.⁷

The primary cause of cervical cancer is infection with certain types of HPV.⁷ Uncomplicated HPV infection in the lower genital tract can progress to cervical intraepithelial neoplasia (CIN). This lesion precedes invasive cervical carcinoma and is classified as low-grade squamous intraepithelial lesion (SIL), high-grade SIL, and carcinoma in situ. Carcinoma in situ demonstrates cytologic evidence of neoplasia without invasion through the basement membrane and can persist unchanged for 10 to 20 years, but most of these eventually progress to invasive carcinoma. Approximately 70% of invasive cervical cancers are squamous cell tumors, 20 to 25% are adenocarcinomas, and 2 to 5% are adenosquamous with epithelial and glandular structures.⁸

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It is important to note that HPV infections are common in healthy women and only rarely result in cervical cancer. Risk factors for HPV infection and cervical cancer include having sex at an early age and/or having multiple sexual partners. However, a woman may be infected with HPV even if she has had only one sexual partner.⁷ Persistent HPV infection is the most important risk factor for the development of precancerous cervical lesions while immunosuppression, multiple pregnancies, and cigarette smoking may influence progression of precancerous lesions to cervical cancer.^{2,7}

Prevention of HPV in Females

While physical barriers such as condoms may reduce the risk of HPV transmission, vaccination against pathologic HPV appears to be an effective cervical cancer prevention strategy.^{2,8} Vaccines are made with inactivated virus-like particles that are noninfectious but highly immunogenic. Despite a history of genital warts, abnormal Papanicolaou test, or positive HPV DNA test, HPV vaccination is recommended because vaccination may offer protection from HPV types of which the patient is not infected. Ideally, the vaccine should be administered before potential exposure to HPV through sexual activity. However, females who are sexually active should still be vaccinated consistent with age-based recommendations.^{9,10}

Currently, one quadrivalent vaccine product (Gardasil®, Merck) containing HPV types 6, 11, 16, and 18 and one bivalent vaccine product (Cervarix®, GlaxoSmithKline) containing HPV types 16 and 18 have been licensed in the United States and recommended by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC) for administration to girls and young women.^{9,10,11}

Gardasil® is approved for the prevention of cervical, vulvar and vaginal cancers caused by HPV types 16 and 18; precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18; and genital warts caused by HPV types 6 and 11.¹² Cervarix® is approved for the prevention of cervical cancer and cervical pre-cancers caused by oncogenic HPV types 16 and 18.¹³

In 2007, the CDC reported that 25.1% of adolescent females (13 to 17 years of age) initiated the Gardasil® vaccine series (≥ 1 dose).¹⁴ A rise in vaccination to 37.2% of adolescent females initiating the vaccination series (≥ 1 dose) occurred in 2008, with 17.9% of females receiving ≥ 3 doses. In 2008, vaccine initiation rates for Louisiana were 36.6% compared to 22.4% in Arkansas, 15.8% in Mississippi, and 31.6% in Texas.¹⁵

HPV vaccination with Gardasil® is FDA-approved for use in all females aged 9 through 26 years. Gardasil® is administered in 3 separate 0.5 mL intramuscular injections in the deltoid region of the upper arm or in the higher anterolateral area of the thigh over a 6-month period at 0, 2, and 6 months.¹² (See Table 2.) The series does not need to be restarted if the schedule is interrupted.² The ACIP recommends HPV vaccination at age 11 to 12, although it may be administered as young as 9 years, with catch-up vaccination for 13 to 26 year old females who have not yet received or completed the vaccine series.^{2,9,10}

The most commonly reported adverse event associated with Gardasil® vaccination is headache. Fever, nausea, dizziness, injection-site pain, swelling, erythema, pruritus, and bruising are still common, but have been reported less frequently. Syncope, sometimes associated with tonic-clonic movements and other seizure-like activity, has been reported following vaccination. It is recommended that patients undergo observation for 15 minutes after administration to monitor for syncope. When syncope is associated with tonic-clonic movements, the activity is usually transient and typically responds to restoring cerebral perfusion by maintaining a supine or Trendelenburg position.¹²

Women who have had a previously severe reaction to yeast should not receive Gardasil®. And while the vaccine is Pregnancy Category B, there are no well-controlled studies in pregnant women; vaccination during pregnancy should occur only if clearly needed.¹²

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In October 2009, the FDA approved a second HPV vaccine, Cervarix®, which provides protection from HPV 16 and 18.¹⁶ The vaccine was approved based on findings from the PATRICIA (PApilloma TRIal against Cancer In young Adults) trial, which demonstrated a vaccine efficacy rate of 93% and suggested additional protection from HPV types not covered by the vaccine (HPV types 31, 33, and 45).^{17,18,19} The ACIP also voted to add Cervarix® to its list of recommended HPV immunization options for females. Routine administration is recommended among 11 and 12 year old girls with catch-up vaccination for females 13 to 25 years old who have not previously been vaccinated.¹¹

Cervarix® is indicated for the prevention of cervical cancer and cervical pre-cancers caused by oncogenic HPV types 16 and 18, in females 10 to 25 years of age. It is administered as 3 separate 0.5 mL doses by intramuscular injection at 0, 1, and 6 months.¹³ (See Table 2.) The preferred site of administration is the deltoid region of the upper arm. Common adverse events include injection site reactions as well as fatigue, headache, myalgia, gastrointestinal symptoms, and arthralgia.¹³

Like Gardasil®, Cervarix® carries a warning regarding the risk of syncope. Both vaccines are Pregnancy Category B and should only be used in pregnancy if clearly needed.^{12,13} Each vaccine appears highly effective in preventing its particular HPV infections, and protection has persisted for at least 4.5 years after three injections over a 6-month period.⁸ Differences between the vaccines include approved indications, dosing schedule, and approved age of vaccination.^{12,13}

Prevention of HPV in Males

Also in October 2009, the FDA approved the use of Gardasil® in males aged 9 - 26 years for the prevention of genital warts caused by HPV types 6 and 11.²⁰ The decision was based on a phase III study of 4,065 boys and men who were randomized to receive the three-dose Gardasil® vaccine or placebo with the vaccine offering a nearly 90% protection against genital warts.¹⁹ The ACIP voted that Gardasil® should be optional for males rather than part of the approved childhood vaccination schedule.

According to the ACIP, the benefits of vaccinating all boys did not outweigh the costs of such a program.²² Therefore, male HPV vaccination is left to a physician's discretion or patient/guardian choice.²²

Table 1 Association of HPV with Clinical Lesions ^[1]

HPV Type	Clinical Lesion	Suspected Oncogenic Potential
1	Plantar warts	Benign
2, 4, 27, 57	Common skin warts	Benign
3, 10, 28, 49, 60, 76, 78	Cutaneous lesions	Low
5, 8, 9, 12, 17, 20, 36, 47	Epidermodysplasia verruciformis	Mostly benign, but some progress to malignancy
6, 11, 40, 42-44, 54, 61, 70, 72, 81	Anogenital warts; laryngeal papillomas; dysplasias and intraepithelial neoplasias (mucosal sites)	Low
7	Hand warts of butchers	Low
16, 18, 30, 31, 33, 35, 39, 45, 51-53, 56, 58, 59, 66, 68, 73, 82	High-grade dysplasias and carcinomas of genital mucosa; laryngeal and esophageal carcinomas	High correlation with genital and oral carcinomas, especially cervical cancer

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Table 2 Gardasil® vs. Cervarix® [12,13]

	Gardasil®	Cervarix®
Indication	Prevention of: <ul style="list-style-type: none"> • Cervical, vulvar, and vaginal cancer caused by HPV types 16 and 18 • Genital warts caused by HPV types 6 and 11 Prevention of precancerous or dysplastic lesions caused by HPV types 6, 11, 16, and 18: <ul style="list-style-type: none"> • CIN grade 2/3 and cervical adenocarcinoma in situ • CIN grade 1 • Vulvar intraepithelial neoplasia grade 2 and grade 3 • Vaginal intraepithelial neoplasia grade 2 and grade 3 Prevention of genital warts caused by HPV types 6 and 11 in males 9 to 26 years	Prevention of the following caused by HPV types 16 and 18: <ul style="list-style-type: none"> • Cervical cancer • CIN grade 2 or worse and adenocarcinoma in situ • CIN grade 1
Approved ages	9 to 26 years	10 to 25 years (females only)
Dosing schedule	0.5 mL IM at 0, 2, and 6 months	0.5 mL IM at 0, 1, and 6 months

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