Human Papillomavirus and HPV Vaccines

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Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States, with more than 14 million new cases each year. Most infections are subclinical and undiagnosed, so the exact prevalence is unknown. However, it has been suggested that almost all sexually active individuals acquire HPV at some point during their lifetimes. Factors that increase an individual's risk of becoming infected with HPV include age younger than 25 years, sexual debut before 16 years of age, having multiple sexual partners, and having a partner who has had multiple partners. More than 120 strains of HPV have been identified, more than 40 of which are sexually transmitted and can infect the genital regions. HPV strains are divided into oncogenic (high-risk) types and nononcogenic (low-risk) types based on their potential to cause cancer.

Infection with high-risk or oncogenic types (most commonly types 16 and 18) may lead to cellular changes of the cervix, which can be detected on Papanicolaou smear. These cellular changes are asymptomatic and usually self-resolve, especially among healthy adolescent females. In a study of 187 adolescent females with low-grade squamous intraepithelial lesions on Papanicolaou smear, the median time to complete resolution of the lesions was 8 months, and only 3% of the study participants progressed to a high-grade squamous intraepithelial lesion. Furthermore, a high percentage of high-grade lesions also self-resolve in this age group, with very few females younger than age 21 years progressing to cervical cancer (0.15 per 100,000 females). Because most HPV-induced cellular changes are transient and rates of cervical cancer in this population are low, initial Papanicolaou smear testing is not recommended before age 21 years. Delaying the initial Papanicolaou smear to age 21 years reduces the chance of detecting an abnormality that would likely self-resolve with no clinical consequence but may lead to unnecessary, costly, and anxiety-provoking diagnostic or therapeutic procedures.

Infections with low-risk HPV subtypes (most commonly types 6 and 11) have the potential to cause genital warts, also known as condylomata acuminata. Condylomata are usually flesh-colored cauliflower-like genital lesions, although they may also appear flat, smooth, thorny, or hyperpigmented. Genital warts are most commonly detected on the external genitals (penis, scrotum, and perianal area in males; vulva, perineum, and perianal area in females) and less commonly in the urethral meatus, vagina, or cervix. Warts tend to be asymptomatic but occasionally may cause mild itching or irritation. Additional symptoms may develop, depending on the size and location of the warts. For example, warts located within the urethral meatus may cause dysuria or hematuria, vaginal warts may cause irregular vaginal bleeding, and perianal warts may cause hematochezia or pain with defecation.

Genital warts are primarily diagnosed by clinical inspection and must be differentiated from similar-appearing normal variants, such as pearly penile

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TABLE. **Treatment Options for Genital Warts**

CATEGORY	TREATMENT	USE	ADVERSE EFFECTS
Patient Applied	Imiquimod 5% (or 3.75%*) cream	Apply at bedtime 3×/week (*or every night), wash off in morning; use up to 16 weeks	Skin irritation, vesicles, hypopigmentation, may weaken condom
	Podofilox 0.5% solution or gel	Apply twice daily for 3 days, no therapy for 4 days; may repeat up to 4 weeks	Pain or irritation
	Sinecatechins 15% ointment (green tea extract)	Apply 0.5 cm ointment strand 3×/day, do not wash off; use up to 16 weeks	Skin erythema, itching, burning, rash, pain
Clinician Applied	Cryotherapy (liquid nitrogen)	Must be trained appropriately	Pain, necrosis, blistering
	Trichloroacetic acid or bichloracetic acid 80%-90% solution	Apply small amount to wart, allow to dry, will see white frost on tissue; repeat weekly if necessary	Pain, irritation

papules (asymptomatic flesh-colored papules in rows along the corona of the penis) and vestibular papillae (pink frond-like papules symmetrically lined along a female's vestibule). Warts should also be differentiated from molluscum contagiosum (small, firm, clustered viral lesions with a central umbilication) and condylomata lata (a sequela of secondary syphilis that appears flatter, smoother, and moister than warts).

Application of 5% acetic acid to a wart produces a whitening appearance, but routine use is not recommended to make a definitive diagnosis because many other common conditions, such as candidiasis and herpes, can also produce a positive result. Biopsy of typical lesions is not necessary, although biopsies of atypical-appearing lesions or those not responding to therapy may be performed to rule out malignancy. HPV DNA testing for genital warts is also not recommended.

Multiple treatment options are available for genital warts, primarily to remove symptomatic lesions or those causing cosmetic concerns. Genital warts may regress spontaneously, so patients with asymptomatic lesions may opt to delay treatment. Furthermore, treatment does not eradicate the underlying virus, and it is not known if viral transmission is diminished by treatment. Warts generally improve within 3 months of treatment, although they frequently recur within a few months. Treatment modalities are separated into patient-applied and clinician-applied methods (Table). Because no specific treatment has been shown to be most effective, the choice of method should be based on the clinician's experience, cost of treatment, and number and location of warts.

The only vaccine approved by the Food and Drug Administration and available in the United States is the 9-valent vaccine. This vaccine is approved for use in both males and females and protects against the nononcogenic HPV strains 6 and 11 (responsible for approximately 90% of genital warts) and 7 oncogenic strains including strains 16 and 18 (responsible for approximately 70% of cervical cancers). The 9-valent vaccine has replaced the bivalent vaccine (which protected against strains 6 and 11) and the quadrivalent vaccine (which protected against strains 6, 11, 16, and 18), both of which have been discontinued in favor of the newer 9-valent vaccine. The American Academy of Pediatrics and the Advisory Committee on Immunization Practices (ACIP) recommend vaccination against HPV for all adolescent females and males at age 11 to 12 years. All unvaccinated females (age 13 to 26 years) and males (age 13 to 21 years) and immunocompromised or high-risk males (such as men sexually active with men) age 21 to 26 years should also be vaccinated, as should unvaccinated adolescents who have genital warts or abnormal cervical changes.

The Centers for Disease Control and Prevention's ACIP has recently recommended that individuals initiating the vaccine series at 9 through 14 years of age should receive only 2 doses, administered 6 to 12 months apart. Older patients receiving the initial HPV vaccine after 15 years of age should continue to receive the 3-dose series on a 0, 1 to 2 months, and 6 months schedule. Vaccination series do not need to be restarted if patients are late for the second or third doses, and patients who have received 3 doses of the bivalent or quadrivalent vaccine do not require extra doses of the newer 9-valent vaccine.

The HPV vaccines have been shown to be effective in preventing more than 95% of precancerous cervical changes from types 16 and 18, more than 90% of genital warts in males and females, and more than 96% of precancerous cervical changes from the 5 additional oncogenic types covered by the 9-valent vaccine. In addition, the HPV vaccine is safe and well tolerated, with a safety profile similar to those of other routine vaccines. The most common adverse effects are pain, edema, and erythema at the injection site. Adolescents may occasionally develop dizziness or syncope following an injection, so they should be observed for 15 minutes following vaccination.

Rates of HPV vaccination among adolescents in the United States remain low for several reasons: lack of knowledge about the vaccine, less-than-strenuous recommendations by clinicians, parental perception that the vaccine is not necessary, and discomfort about vaccinating preteens against a sexually transmitted infection. Clinicians should counsel patients and parents that the vaccine is most effective when administered at a younger age and before patients have become sexually active. They should stress that the vaccines are very safe and effective in preventing cancer and that receiving the vaccine does not influence an adolescent's decision to initiate sexual activity.

COMMENT: A vaccine to prevent cancer is something of a medical holy grail, and the pity is that this one really works (even better than originally predicted) and we're not close to taking full advantage. By 2012, 6 years after its introduction, the quadrivalent HPV vaccine had reduced the prevalence of its 4 covered strains of virus among girls ages 14 to 19 years by nearly two-thirds. Yet fewer than 50% of adolescent girls and only about 20% of teenage boys in the United States have received a full course of the vaccine. Further, only 2 states, Rhode Island and Virginia, as well as Washington DC, require it. Although the vaccine has primarily been promoted for its role in preventing cervical cancer, which currently kills more than 4,000 women each year, HPV can also cause anal, penile, and oropharyngeal cancers, providing the rationale for immunizing boys along with girls. Another rationale is that, as with all vaccines, the larger the immunized population, the smaller the pool of virus in the community. We have an effective tool at hand, and other countries are using it far more efficiently than we. Australia has an immunization rate greater than 70% among teenage girls, and Rwanda has a rate greater than 90%. Overcoming unreasonable resistance to the HPV vaccine is well worth the effort.

– Henry M. Adam, MD
Associate Editor, *In Brief*

Retractions

1. NOTICE OF RETRACTION: Visual Diagnosis: 7-year-old Girl With Swelling in the Arm. Shahnawaz M. Amdani, Magda Mendez. *Pediatrics in Review.* May 2015; 36(5):e14-e17, DOI: 10.1542/pir.36-5-e14. The American Academy of Pediatrics has removed this article from circulation because it contained citation and attribution errors. We apologize to our readers.
2. NOTICE OF RETRACTION: Visual Diagnosis: 3-Year-Old Boy With Persistent Right Chest Wheezing. Shahnawaz M. Amdani, Naresh Reddivalla, Magda Mendez, Orlando Perales. *Pediatrics in Review.* Dec. 2014; 35(12):e61-e63, DOI: 10.1542/pir.35-12-e61. The American Academy of Pediatrics has removed this article from circulation because it contained citation and attribution errors. We apologize to our readers.
3. NOTICE OF RETRACTION: Index of Suspicion: Rash, Recalcitrant Tachycardia, and Hypertension in a 16-Year-Old Girl. Seshashree Seshadri, Samhar Al-Akash, Salam Gharaybeh. *Pediatrics in Review.* Jan. 2015; 36(1):31-32, DOI: 10.1542/pir.36-1-31. The American Academy of Pediatrics has removed this article from circulation because it contained citation and attribution errors. We apologize to our readers.

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