Vaccines in Women

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Even women who are vigilant about their children's vaccinations tend to neglect their own vaccinations or simply are not aware that the need for certain vaccinations continues throughout adulthood. Vaccinations are an important component of overall health, and healthcare providers should be sure their patients know this. Women, typically their family's gatekeepers to healthcare, particularly need to understand the importance of staying current with vaccinations.

There are 2 new vaccines to incorporate into women's routine immunization schedule: the human papillomavirus (HPV) vaccine, indicated for girls and younger women, and the herpes zoster vaccine, indicated for older adults. Educating patients about these new vaccines is crucial to promoting their acceptance and also gives providers the opportunity to offer other needed vaccinations.

HUMAN PAPILLOMAVIRUS AND THE HPV VACCINE

Epidemiology and Impact of HPV

HPV is the most common sexually transmitted infection (STI) in the United States.[1] An estimated 6.2 million Americans become infected with HPV each year,[2] with approximately 20 million currently infected,[3] including about 9.2 million sexually active adolescents and young adults aged 15 to 24 years.[1] This age group accounts for 74% of new HPV infections,[1] and in women younger than 25 years, prevalence of HPV infection ranges from 28% to 46%.[4,5]

Although sexual intercourse is the typical means of HPV transmission, nonpenetrative sexual contact also may transmit HPV. Infection is initiated when microabrasions in the epithelial layers of the external genitalia or cervix are penetrated by HPV virions, reaching to the basal stem cells where HPV DNA replicates.[6] Vertical transmission from mother to newborn is possible, albeit rare.[7]

For women, risk of HPV infection is highest among those younger than 25 years of age,[4] whose first sexual intercourse is at an early age,[8] and who have multiple sexual partners.[4,9] In addition, HPV infection is often acquired soon after onset of sexual activity. Nearly 40% of college-age women will acquire HPV infection within 2 years of their first sexual experience.[8] The stage of development of the cervix is another contributing factor in the incidence of HPV infection.[10,11] The transformation zone of the cervix is where approximately 99% of cervical cancers occur. The epithelium of this zone is immature at puberty, making very young women particularly vulnerable to STIs, including HPV.[12]

Clinical Manifestations of HPV

HPV infection can manifest as genital warts, low- or high-grade cervical dysplasia, cervical cancer, and recurrent respiratory papillomatosis (RRP), a rare yet potentially fatal condition in children and adults.

Every year in the United States, HPV infection is responsible for an estimated 1 million cases of genital warts[13]; 1.4 million cases of low-grade cervical dysplasia[14]; 330,000 cases of high-grade cervical dysplasia[14]; and 11,150 cases of cervical cancer.[15]

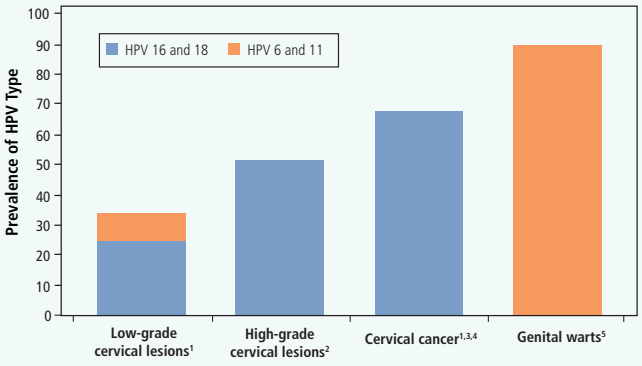
High-risk HPV Types 16 and 18

The median duration of HPV infection is 8 months, with 60% to 75% of HPV-infected women showing HPV negativity after 30 months.[16,17] Persistent HPV infection is a serious health concern because it may progress to cervical cancer. Of the 30 to 40 types of HPV that infect the genital areas,[18,19] HPV types 16 and 18 are responsible for about 70% and 80% of all cases of cervical cancer and cervical adenocarcinoma, respectively,[20,21] as well as 50% of all high-grade cervical dysplasias[22] and approximately 25% of all low-grade cervical dysplasias[23] (***Figure 1***).

Low-risk HPV Types 6 and 11

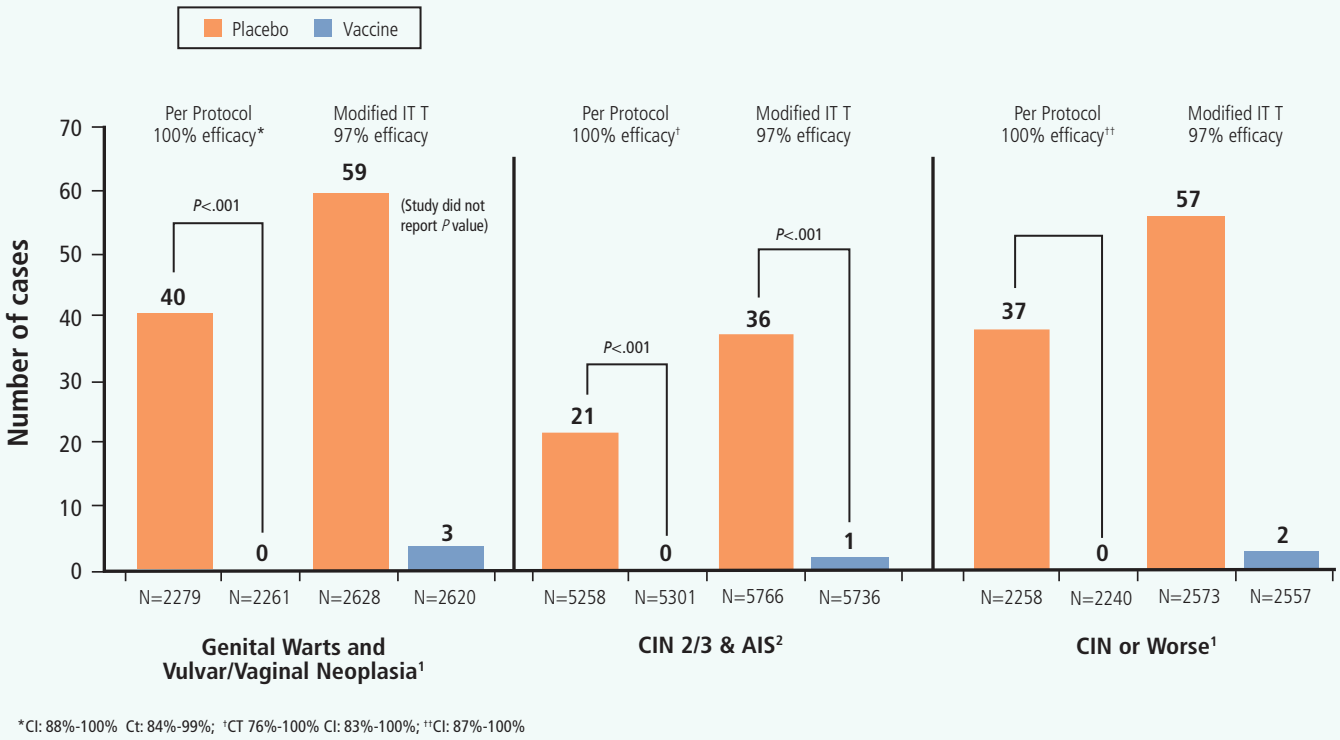
Although low-risk HPV types typically are not associated with cancer, there are significant consequences of infection with these types. Notably, HPV types 6 and 11 are responsible for more than 90% of all cases of genital warts[24,25] (***Figure 1***). Currently, 1.4 million Americans

FIGURE 1. HPV Types 6, 11, 16, and 18 in Cervical Cancer and Other Anogenital Infections



1. Clifford GM, Rana RK, Fanceschi S, et al. *Cancer Epidemiol Biomarkers Prev.* 2005;14:1157-1164.
2. Clifford GM, Smith JS, Aguado T, et al. *Br J Cancer.* 2003;89:101-105.
3. Munoz N, Bosch FX, de Sanjosé, et al. *N Engl J Med.* 2003;348:518-527.
4. Clifford GM, Smith JS, Plummer M, et al. *Br J Cancer.* 2003;88:63-73.
5. Gissmann L, Wolnik L, Ikenberg H, et al. *Proc Natl Acad Sci USA.* 1983;80:560-563.

FIGURE 2. Quadrivalent HPV Vaccine: Two-Year Phase III Results



*CI: 88%-100% Ct: 84%-99%; †CT 76%-100% CI: 83%-100%; ††CI: 87%-100%

1. Sattler C. Presented at The Interscience Conference on Antimicrobial Agents and Chemotherapy. December 2, 2005; Washington, DC.
2. Skjeldestad JO. Presented at: Infectious Diseases Society of America Annual Meeting. October 2005; San Francisco, CA.

have genital warts,[26] accounting for more than 300,000 initial visits to physician's offices annually.[27] Genital warts are most prevalent in young adults, particularly women 20 to 24 years of age (6.2 cases/1000 person years).[28] Although genital warts are almost always harmless physically, they are associated with significant psychological distress.[29] Available treatments for genital warts achieve clearance rates of 60% to 90%.[30] However, these treatments are limited by pain and discomfort[30,31] and lengthy duration. Also, recurrence rates are relatively high due to persistence of underlying infection.[30,32]

HPV 6 and 11 also cause about 80% of cases of RRP, which is typically spread through vertical transmission of HPV. Treatment for RRP is difficult and usually only palliative, often requiring several surgical procedures to remove the papillomas from the larynx.[33-35]

Economic Impact of HPV Infection

The annual direct medical cost of HPV-related diseases, which includes treatment of genital warts, precancerous lesions, carcinoma *in situ*, and invasive cervical cancer, is approximately $5 billion (in 2004 dollars).[36] Treatment costs tend to be proportionate to the grade of initial cytologic abnormality.[37] Women with negative Pap test results paid an average of $57, whereas women with abnormal Pap test results paid an average of $732 for treatment. Treatment for women with atypical squamous cells was $299, compared with $1,275 for low-grade squamous intraepithelial lesions, $1,509 for atypical glandular cells, and $2,349 for high-grade squamous intraepithelial lesions. These costs do not include treatment of cancer, only resolution of the abnormal Pap test or crossing over to cancer care services.[37]

Indirect costs of treatment for other potential complications resulting from HPV or treatment of HPV-related diseases add further economic and emotional burden. For example, a woman who has undergone treatment for an HPV-related disease may be at greater risk for premature birth or fertility problems.

Role of HPV Vaccine and Its Implications

Screening with the Pap test has reduced the incidence of cervical cancer in the United States by 75%.[38] Despite this dramatic decrease, and more than 50 million Pap tests performed annually,[39] a projected 11,150 new cases of cervical cancer will occur this year, with an estimated 3,670 resulting deaths.[15] With no treatments available for HPV infection, prevention is the most promising way to reduce HPV-related disease morbidity and mortality. A quadrivalent HPV vaccine is now available for the prevention of cervical cancer, cervical/vaginal/vulvar precancers, cervical intraepithelial neoplasia (CIN 1-3), cervical adenocarcinoma in situ (AIS), and genital warts caused by HPV types 6, 11, 16, and 18 in girls and women, specifically ages 9 to 26. By targeting these 4 HPV types and this age range, the vaccine is expected to substantially reduce the burden of HPV-related disease.

Approval of the quadrivalent HPV vaccine in June 2006 was based

TABLE 1. Limitations of Common Management Strategies for Postherpetic Neuralgia

Therapy	Limitations
Lidocaine 5% patch[1]	Short-term benefit; erythema
Capsaicin[1]	25% to 35% reduction in pain; burning sensation upon application
Anticonvulsants[1,2]	43.2% of patients report pain relief; somnolence, dizziness, memory disturbances
Tricyclic antidepressants[1,2]	47% to 67% of patients report pain relief; anticholinergic AEs, sedation, cardiac conduction abnormalities
Opioid analgesics[1,2]	38% reduction in pain; CNS- and GI-related AEs, dependence

Stankus SJ, et al. *Am Fam Physician*. 2000;61:2437-2444. Kost RG, et al. *N Engl J Med*. 1996;335:32-42.

primarily on 2 phase III studies in young women aged 16 to 26, and 2 vaccination-bridging studies in sexually naïve adolescents aged 9 to 15. In the phase III studies, referred to as Females United To Unilaterally Reduce Endo-ectocervical (FUTURE I and II) disease, the vaccine demonstrated 100% efficacy in preventing cervical cancer, all grades of CIN, AIS, vulvar/vaginal neoplasia or cancer, and genital warts related to HPV 6, 11, 16, and 18 for up to 2 years in women aged 16 to 23.[40,41] Both trials also showed 97% efficacy in women who were not completely adherent to the vaccination schedule (administered on day 1, month 2, and month 6). This suggests that even in a "real world" population, the vaccine has the potential to significantly reduce HPV infection and related diseases (***Figure 2***).[40,41]

Ideally, HPV vaccine should be administered to children and adolescents before the onset of sexual activity in order to achieve maximum protective effect. Studies in boys and girls ages 9 to 15 years support early vaccination in this age group.[42] At 1 month after the third and final vaccine injection, geometric mean titers of type-specific antibodies were 1.7 to 2.7 times higher in younger adolescents than those in older adolescents and young adults aged 16 to 23 also receiving the vaccine.[42]

It is important to note that HPV vaccination is not a replacement for routine cervical cancer screening, but should be used in conjunction with screening. Also, the HPV vaccine is preventive for HPV 6, 11, 16, and 18 only; protection against diseases caused by other HPV types has not been demonstrated. HPV vaccine is not indicated for treatment of existing HPV infection. Side effects occurring in clinical trials of HPV vaccine were minor and similar in the treatment and placebo groups, and included injection-site pain, swelling, erythema, and pruritus; and fever, nausea, and dizziness.[40,41,43,44]

The known duration of efficacy of HPV vaccine is 5 years. Because FUTURE II study participants from the Nordic region are at least 3 years ahead of their US counterparts, findings in this cohort will provide further data on longevity and the need and optimal timing for booster vaccinations. Recent results from a substudy of this group suggest that the vaccine will provide long-lasting immunity.[45]

By reducing the incidence of HPV infection, vaccination can be expected to reduce the incidence of HPV-related diseases, which would, in turn, reduce the frequency of follow-up screenings, colposcopies, and other treatments.

Make HPV Vaccine Routine: Gain Patient Acceptance

Most cases of cervical cancer can be prevented by the HPV vaccine. To fulfill this promise, the vaccine needs to be incorporated into the standard immunization schedule for appropriate patients. However, to foster patient acceptance of HPV vaccine, clinicians will need to address a number of educational, cultural, and family/parental issues.

Health-care providers are the primary source of information for patients and parents of adolescents about HPV vaccination,[46] and patient education increases acceptance of vaccination.[47] Adult patients ≤26 years of age need to be educated about the role of HPV vaccination in preventing cervical cancer and other HPV-related complications.

For parents of children at or approaching the target ages for vaccination (≥9 years), a similar educational approach may be used, with additional counseling for adults who worry that vaccination against an STI represents tacit consent to early or promiscuous sexual activity.[48] Parents can be told that the immune response to HPV antibodies is strongest in adolescents, thereby providing the greatest protection against HPV-related diseases. This information moves the focus from sexual activity to optimizing disease prevention.

Adults and adolescents often do not see their health-care providers regularly or change practitioners frequently; it is therefore important not to miss a vaccination opportunity.[49,50] Often, clinicians who focus on women's health also provide general medical care. These clinicians should be diligent in vaccinating their patients, as well as counseling patients with daughters at or approaching adolescence, to increase the likelihood of vaccinating girls at the optimal age (11-12 years, according to current recommendations).

VARICELLA-ZOSTER VIRUS AND THE HERPES ZOSTER VACCINE

Epidemiology and Impact of Varicella-Zoster Virus

Varicella-zoster virus (VZV) is responsible for herpes zoster, commonly known as shingles. In the United States, more than 90% of adults have been infected with VZV and are at risk for zoster.[51] Of the 1 million cases of herpes zoster that occur annually, 40% to 50% are in people 60 years of age and older.[52] Severity of herpes zoster, and the frequency and severity of its complications, also increase with age.[53] Risk factors for herpes zoster include history of varicella

TABLE 2. Vaccines for a Lifetime

19 – 49 Years of Age	50 – 64 Years of Age	≥65 Years of age
For all women who do not show immunity		
Tetanus, diphtheria, pertussis (Td/Tdap): initial 3-dose series, then a 1-dose booster every 10 years **Human papillomavirus (HPV):** a 3-dose series; for women ≤26 years of age **Measles, mumps, rubella (MMR):** 1 or 2 doses **Varicella (chickenpox):** 2 doses	**Tetanus, diphtheria, pertussis (Td/Tdap):** initial 3-dose series, then a 1-dose booster every 10 years **Herpes zoster:** 1 dose for women ≥60 years **Influenza:** 1 dose every year	**Tetanus, diphtheria, pertussis (Td/Tdap):** initial 3-dose series, then a 1-dose booster every 10 years **Herpes zoster:** 1 dose for women ≥60 years **Influenza:** 1 dose every year **Pneumococcal (polysaccharide):** 1 dose
For women with conditions that put them at risk for the disease		
Influenza: 1 dose every year **Pneumococcal (polysaccharide):** 1 or 2 doses **Hepatitis A:** 2 doses **Hepatitis B:** 3 doses **Meningococcal:** 1 or more doses	**Measles, mumps, rubella (MMR):** 1 dose **Varicella (chickenpox):** 2 doses; for women <60 yrs **Pneumococcal (polysaccharide):** 1 or 2 doses **Hepatitis A:** 2 doses **Hepatitis B:** 3 doses **Meningococcal:** 1 or more doses	**Hepatitis A:** 2 doses **Hepatitis B:** 3 doses **Meningococcal:** 1 or more doses

Adapted from: *Recommended Adult Immunization Schedule, United States, October 2006-September 2007.* Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention. 2006. Available at: http://www.cdc.gov/Nip/recs/adult-schedule.htm#chart. Accessed April 20, 2007.

(chickenpox) and a decrease in VZV-specific cell-mediated immunity (VZV-CMI).[51] This decline in VZV-CMI, most often related to advancing age,[51] permits the re-emergence of VZV infection, which manifests as herpes zoster. Immunosuppressive illness (eg, HIV infection, leukemia) or therapies (eg, corticosteroids), psychological stress, or physical trauma[51] are other triggers of VZV-CMI decline.

The dermatomal rash characteristic of herpes zoster may be preceded 1 to 5 days by the prodrome, which involves sensory abnormalities that may be constant or intermittent, localized or diffuse, and range from itching to tingling to severe pain.[51,54] Not every patient develops the prodrome.[55,56] Neuropathic pain is common in the acute phase, and may occur all day, every day. It has been described as sharp, throbbing, burning, stabbing, itching, or hot.[54] Neurologic, cutaneous, ophthalmic, or visceral complications may occur during or after the acute phase.

Postherpetic Neuralgia

After the herpes zoster rash heals, usually in 2 to 4 weeks following onset, some patients experience persistent, chronic pain known as postherpetic neuralgia (PHN). It is the most common complication of herpes zoster, affecting 10% to 20% of all patients.[57] PHN is typically defined as pain that persists for more than 3 months after rash resolution,[58] however, it may last for several months or even years. Severity of acute herpes zoster and age are the main risk factors for PHN, and its incidence, severity, and duration increase with advancing age.[58,59]

Patients with PHN often experience allodynia, a condition in which pain is caused by ordinary stimuli, such as clothing rubbing on the skin,[60] and hyperalgesia, an extreme response to normally painful stimuli.[61] The effect on quality of life can be debilitating, particularly for older adults who are more likely to have more severe, prolonged PHN. Psychological detriment, decreased social activity, and interference with normal daily functioning are common in patients with PHN.[58]

Management strategies for herpes zoster and PHN

Acute herpes zoster is typically treated with antiviral therapy. The antiviral agents acyclovir, famciclovir, and valacyclovir reduce the duration and severity of acute herpes zoster, but should be administered within 72 hours of rash onset for maximum effectiveness.[51] Some patients do not experience the prodrome and may not have a completely developed rash by 72 hours, and do not seek medical treatment. The benefits of antiviral therapy administered after 72 hours are not known.

Corticosteroids used in conjunction with antiviral therapy have shown benefit in relieving acute pain and speeding rash healing. However, the adverse effects of corticosteroids limit this therapy to relatively healthy individuals; it should not be used by those with diabetes, hypertension, osteoporosis, glycosuria, or peptic ulcer disease.[62] None of the treatments for herpes zoster prevent the development of PHN.[62-64]

Treatments for PHN include anticonvulsants, tricyclic antidepressants, transdermal lidocaine (lidocaine patch 5%), opioid analgesics, and topical capsaicin.[65] Randomized, controlled trials of these therapies have

demonstrated modest pain relief accompanied by adverse effects that are especially problematic in older patients (***Table 1***).[57,65]

Vaccination to prevent herpes zoster and PHN offers enormous potential in reducing the burden of herpes zoster and related complications.

Role of Herpes Zoster Vaccine and Its Implications

The herpes zoster vaccine, approved in May 2006, is indicated for use in individuals 60 years of age and older. The vaccine is not indicated for the treatment of herpes zoster or PHN, but it can prevent PHN by preventing herpes zoster.

The herpes zoster vaccine is a more potent formulation of the live, attenuated VZV vaccine that has been used in the United States since 1995 for the prevention of varicella.[66] The VZV vaccine has reduced the number of varicella cases by approximately 85%.[67] The increased potency of the herpes zoster vaccine boosts levels of VZV-CMI to provide protection in older adults with preexisting immunity through infection with wild-type VZV or latent infection established by the vaccine virus. Initial trials in adults aged 55 to >87 years have shown the vaccine to be safe and well tolerated,[68,69] significantly boosting VZV-CMI levels and sustaining them for more than 6 years.[70]

Approval of the herpes zoster vaccine was based on results from the Shingles Prevention Study, a randomized, placebo-controlled, double-blind phase III clinical trial to evaluate the efficacy of the vaccine in decreasing the incidence and severity of herpes zoster and PHN.[63] Participants included 38,546 individuals 60 years of age or older who received a single dose of vaccine or placebo and were followed for an average of 3.1 years (range, 31 days to 4.9 years).

The vaccine reduced the impact of herpes zoster by 61%, as measured by burden of illness, a compilation of incidence, severity, and duration of herpes zoster. In vaccinated individuals who developed herpes zoster, the severity of illness was reduced. The vaccine also significantly reduced the incidence of herpes zoster by 51.3%. In the general population, this translates to the prevention of more than 250,000 cases of herpes zoster every year, based on an estimated incidence of 1 million cases per year. Additionally, the incidence of PHN was reduced by 66.5% in all vaccinated subjects. Throughout the study, the cumulative incidence of herpes zoster and PHN was significantly lower in vaccinated subjects than in those receiving placebo.[63]

The rate of adverse events was low and comparable between vaccine and placebo recipients, with injection-site rash the most common complaint. However, a substudy found that more vaccine recipients (48%) had injection-site complaints than placebo recipients (17%).[63]

The herpes zoster vaccine provided 4 years of protection from zoster in the Shingles Prevention Study.[63] Further research is necessary to determine the duration of the vaccine and whether a booster will be needed.

Make Herpes Zoster Vaccine Routine

The herpes zoster vaccine gives health care providers an opportunity to reduce the incidence of herpes zoster, thereby reducing the significant morbidity associated with the illness as well as the incidence of PHN, and greatly improving quality of life in older adults. An understanding of herpes zoster and its complications can promote vaccine acceptance.

OTHER RECOMMENDED VACCINES FOR WOMEN

Healthcare providers are responsible for helping women stay up-to-date with their vaccinations. In addition to the HPV and herpes zoster vaccines (as age appropriate), women should receive vaccines according to the most recent Recommended Adult Immunization Schedule issued by the Advisory Committee on Immunization Practices (ACIP)[71] (***Table 2***). For detailed information, refer to the complete ACIP statement and schedule, available at the Centers for Disease Control and Prevention website: http://www.cdc.gov/nip/publications/acip-list.htm.

Summary

Ensuring that patients are aware of the vaccinations recommended for their age and health status, and understand the health benefits that vaccinations provide, is paramount to getting them vaccinated. Healthcare providers are the primary influence in promoting the new HPV and herpes zoster vaccines. Patients place enormous importance on their provider's recommendations. This is especially important to remember when counseling the parents of young girls about the HPV vaccine. Providing patients with the information and advice they need about these and all vaccines will promote patient acceptance, thereby helping to prevent disease and improve patient care.

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