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Using the new HPV vaccines in clinical practice

■ ABSTRACT

Gardasil, a vaccine against human papillomavirus (HPV), recently became available in the United States for use in girls and women 9 to 26 years of age. A second HPV vaccine, Cervarix, is under development. These vaccines constitute the most significant development in cervical cancer prevention in the last 60 years, having the potential to reduce the incidence of cervical cancer by up to 70%.

■ KEY POINTS

Gardasil provides protection against HPV types 16 and 18, which are the high-risk types responsible for 70% of cases of cervical cancer, as well as HPV types 6 and 11, which are low-risk types responsible for 97% of cases of genital warts. Cervarix provides protection against HPV types 16 and 18.

Current Papanicolaou screening and follow-up recommendations must still be followed regardless of a woman's vaccination status. This testing is still necessary because 30% of cases of cervical cancer are caused by HPV types not contained in the vaccines.

Gardasil has not been approved for use in men in the United States because clinical efficacy data are not yet available. However, the vaccine appears to be highly immunogenic and safe in men, and once efficacy data are available, this use may be approved.

Physicians should continue to reinforce prevention messages related to safer sexual behaviors. The discussion of the vaccine provides an opportunity to discuss these issues with both parents and adolescents.

*Dr. Kahn has disclosed that she has received a consulting fee from the SciMed and Merck corporations for editing a journal supplement on HPV vaccines.

THE US FOOD AND DRUG ADMINISTRATION (FDA) recently unanimously approved a vaccine against human papillomavirus (HPV), the virus that causes cervical cancer.

Gardasil (quadrivalent HPV recombinant vaccine; Merck) is one of two vaccines designed to prevent HPV acquisition and is the first prophylactic vaccine against cervical cancer approved by the FDA. It is approved for use in girls and women 9 to 26 years of age for the prevention of cervical cancer; genital warts; cervical intraepithelial neoplasia grades 1, 2, and 3; vulvar intraepithelial neoplasia grades 2 and 3; and vaginal intraepithelial neoplasia grades 2 and 3.

A second HPV vaccine, Cervarix (GlaxoSmithKline Biologicals) has been submitted for regulatory review in Europe and is expected to soon be submitted to the FDA for approval for use in the United States to prevent cervical cancer.

In clinical trials, both vaccines have been 100% effective against HPV types 16 and 18, which cause 70% of cases of cervical cancer. The widespread use of these vaccines in the appropriate populations, along with continued use of screening, could markedly cut the incidence of cervical cancer.

In this article, we will review the virology and epidemiology of HPV infection, the spectrum of HPV-related diseases, the safety and efficacy of HPV vaccines, the current vaccine recommendations, and key issues related to vaccine acceptability and delivery.

■ VIROLOGY AND EPIDEMIOLOGY OF HPV

HPV is a small DNA virus that replicates in squamous epithelial cells, causing warts and

HPV 16 and 18 account for nearly 70% of cases of cervical cancer

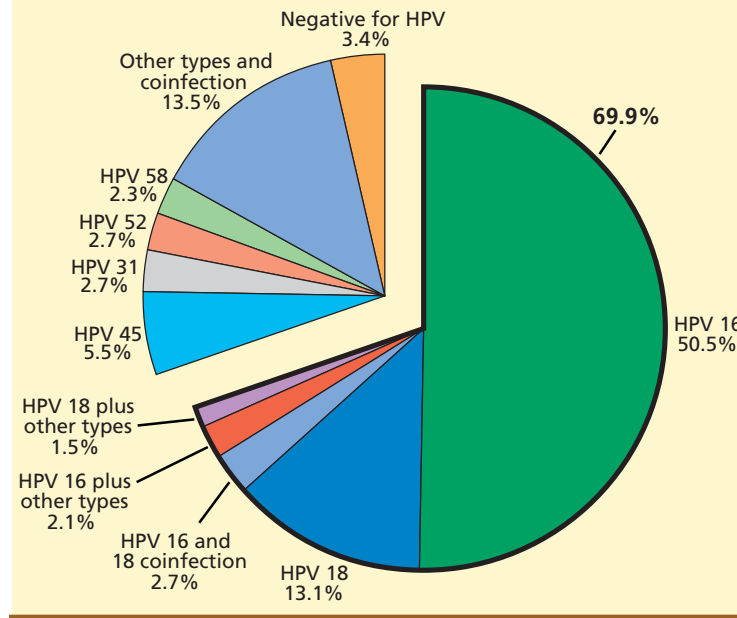


FIGURE 1. Human papillomavirus (HPV) types identified in squamous-cell cervical cancer worldwide.

DATA FROM MUNOZ N, BOSCH FX, DE SANJOSE S, ET AL. EPIDEMIOLOGIC CLASSIFICATION OF HUMAN PAPILLOMAVIRUS TYPES ASSOCIATED WITH CERVICAL CANCER. *N ENGL J MED* 2003; 348:518–527.

Infection with high-risk HPV is a necessary precursor to cervical cancer

other lesions of the mucosal epithelium in the oral pharynx, esophagus, or genital tract.

HPV virions consist of DNA within a capsid shell. The capsid consists of two proteins: L1 (the major structural and antigenic protein) and L2 (the minor, infectivity-enhancing protein). Each HPV type has a unique L1 protein. More than 130 types of HPV have been identified, and approximately 40 of these infect the genital tracts of men and women.

Genital HPV types are classified as high-risk or low-risk on the basis of their association with cervical cancer. More than 15 high-risk types have been identified, of which two types, HPV 16 and 18, cause about 70% of cases of invasive cervical cancer (FIGURE 1).¹

Low-risk types such as HPV 6 and 11 cause genital warts and other benign lesions including mild abnormalities on Papanicolaou (Pap) testing, such as low-grade squamous intraepithelial lesions. Genital HPV types do not cause common skin or plantar warts.

HPVs are easily transmitted through skin-to-skin contact, often via microabrasions in

the genital skin. The virus does not require sexual intercourse for transmission.^{2,3}

HPV is considered to be the most common sexually transmitted infection, and age-specific prevalence rates are highest in adolescent and young adult women.⁴ Prevalence data vary depending on the population studied and the method used to detect HPV, but it is estimated that 75% to 80% of sexually active men and women in the United States will become infected at some point in their lives.^{5,6}

As with other sexually transmitted infections, the risks associated with HPV acquisition are related to sexual behaviors such as age of onset of sexual activity, number of lifetime sexual partners, and number of recent sexual partners. However, positive HPV status does not imply multiple sexual partners and is not a marker for current sexual activity. It can represent an infection acquired many years ago. HPV is common in people with few sexual partners, and infection often occurs soon after sexual initiation.⁷ Rates of HPV infection are 20% to 46% among women with only one lifetime partner, and increase to almost 70% in women with 10 or more partners.^{8,9}

Consistent condom use has been shown to reduce the risk of acquiring HPV in newly sexually active women. With less than 100% condom use, however, HPV appears easily transmitted.^{10,11}

■ HPV-RELATED DISEASE

Cervical cancer

Much as epidemiologic and biologic evidence established the causal association between smoking and lung cancer, such evidence has also demonstrated that infection with high-risk HPV types is a necessary cause of cervical cancer.¹²

The association between HPV infection and cervical cancer is one of the strongest in cancer epidemiology.⁴ In one international study,¹³ more than 99.7% of cervical tumor specimens contained detectable HPV DNA.

Persistent infection with high-risk HPV types, indicating active viral replication, is a key factor in the development of precancerous cervical lesions and cervical carcinoma. Research has shown that two proteins encoded by high-risk HPV types, E6 and E7, contribute to carcinogenesis by inactivating the

Cervical cancer is more common in less developed countries

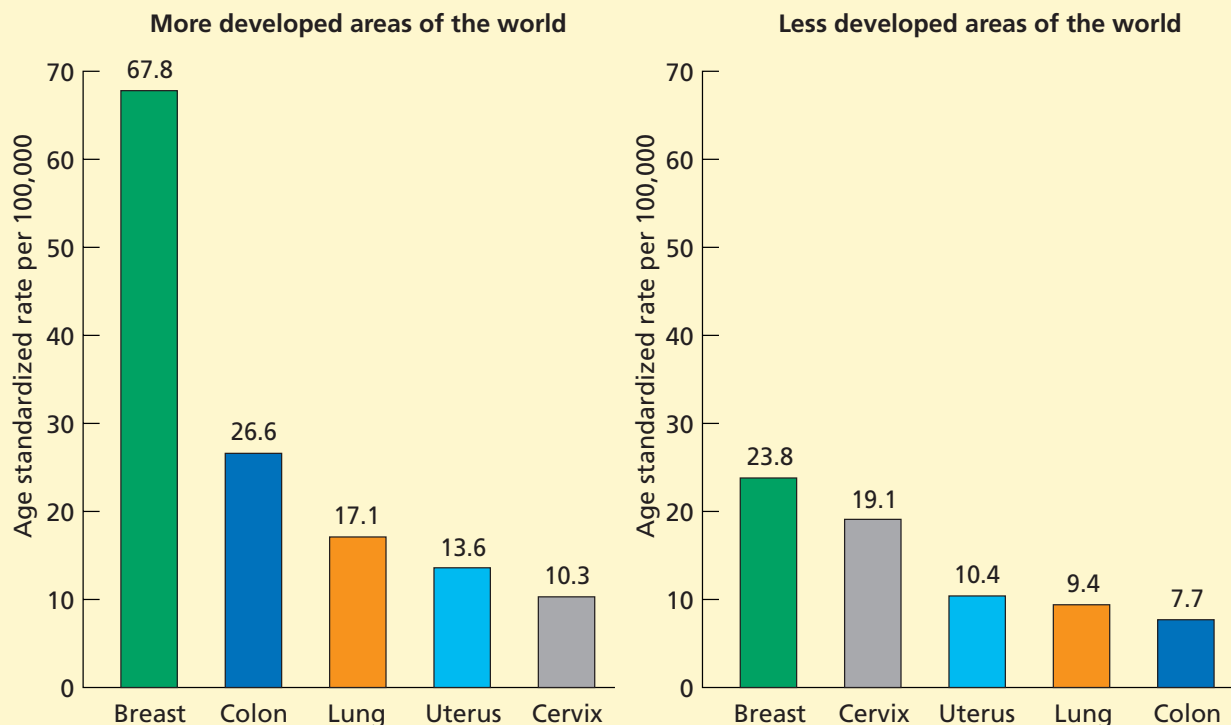


FIGURE 2. Age-standardized cervical cancer rates among women in more developed and less developed regions of the world. Rates are age standardized per 100,000.

DATA FROM CANCERMONDIAL, INTERNATIONAL AGENCY FOR RESEARCH ON CANCER, WWW-DEPIARC.FR/.

host cell's tumor-suppressor gene products p53 and retinoblastoma protein.¹⁴

Despite widespread cervical cancer screening programs involving periodic Pap testing and more recently HPV DNA testing, cervical cancer remains the fifth most commonly diagnosed cancer among women living in more developed regions of the world.¹⁵ Almost 10,000 women are expected to be diagnosed with cervical cancer in the United States in 2006.¹⁶

Racial disparities exist in both cervical cancer incidence and mortality. Among black women, the age-adjusted rates of incidence and mortality are, respectively, 11/100,000 and 5.3/100,000, whereas among white women the corresponding rates are 8.7/100,000 and 2.5/100,000.¹⁷ In developing countries, where established Pap screening programs are often nonexistent, cervical cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related death in women (FIGURE 2). Cervical cancer is responsible for approxi-

mately 230,000 deaths per year worldwide.¹⁵

In addition to causing cervical cancer, high-risk HPV infection has also been linked to epithelial cancers of the oropharynx, esophagus, vulva, vagina, and penis.^{7,18-20}

Genital warts, other diseases

Infection with low-risk HPV types may cause nonmalignant conditions that include genital warts, mild Pap test abnormalities such as low-grade squamous intraepithelial lesions, and, in the respiratory tract, recurrent respiratory papillomatosis.

Genital warts can occur on the vulva, perineum, vagina, cervix, penis, and perianal and intra-anal areas. HPV types 6 and 11 cause about 97% of genital warts.^{7,21} Although they do not progress to malignancy, genital warts may cause substantial psychological distress to patients,²² and treatment can be uncomfortable, time-consuming, and expensive. Recurrences are common after treatment.²³

This is not a virus

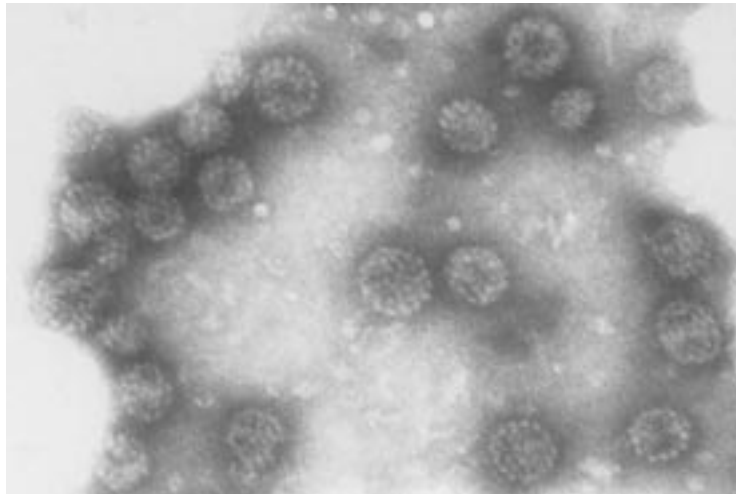


FIGURE 3. Electron photomicrograph of human papillomavirus (HPV) virus-like particles, composed of L1 major capsid proteins after self-assembly. Each particle is about 55 nanometers in diameter (stained with phosphotungstic acid 2%).

USED WITH PERMISSION FROM DR. ROBERT ROSE,
WWW.URMC.ROCHESTER.EDU/GEBS/FACULTY/ROBERT_ROSE.HTM.

Recurrent respiratory papillomatosis is most often considered a childhood disease caused by vertical transmission of low-risk HPV types from mother to neonate during delivery, but it occasionally presents in adulthood. Squamous papillomas associated with HPV types 6 and 11 develop along the entire length of the airway, most commonly at the larynx, leading to presenting symptoms of hoarseness and airway obstruction. The prevalence is 3 to 5 per 100,000 population.

The mainstay of treatment is repeated surgical debulking. Lesions may spontaneously regress but recur years later. Death may occur if papillomas spread to surgically inaccessible areas, causing airway obstruction, or transform into squamous cell carcinoma.²⁴

■ TWO HPV VACCINES

Prophylactic HPV vaccines consist of virus-like particles, which are empty protein shells composed of the major L1 capsid proteins of specific HPV types. These particles are identical morphologically to HPV capsids (**FIGURE 3**). Thus, virus-like particles induce a type-specific host immune response, but because they contain no viral DNA, pose no infectious or oncologic risk to the individual receiving the vaccine.

Gardasil

Gardasil comprises four virus-like particles—types 6, 11, 16, and 18—and an adjuvant, aluminum hydroxyphosphate sulfate, that boosts the immune response. It contains no DNA, RNA, mercury, egg, or animal products.

Gardasil is given as three 0.5-mL intramuscular injections (at 0, 2, and 6 months) and may be given at the same time as hepatitis B vaccine (at a separate injection site), as stated in the package insert. The Advisory Committee on Immunization Practices (ACIP) of the US Centers for Disease Control and Prevention provisionally recommends giving it with other age-appropriate vaccines such as tetanus-diphtheria-pertussis (Tdap), tetanus-diphtheria (Td), and meningococcal conjugate vaccine (MCV4).²⁵ Gardasil is expected to cost approximately \$360 for three doses.

Cervarix

Cervarix contains virus-like particles for HPV types 16 and 18, aluminum hydroxide, and an additional adjuvant called ASO4. Like Gardasil, it is given as three 0.5-mL intramuscular injections. However, the timing is different: it is given at 0, 1, and 6 months. Cervarix is expected to become available in the United States after it receives FDA approval.

Side effects have been minor

Side effects reported by women receiving the vaccines in clinical trials were minor, consisting primarily of mild local and systemic reactions. Pain was the most commonly reported local reaction (84% with vaccine, 75% with placebo with preservative), and fever was the most commonly reported systemic side effect related to the Gardasil vaccine (10% with vaccine, 8.6% with placebo; Gardasil package insert).²⁶ In clinical trials of both Gardasil and Cervarix, no serious vaccine-related adverse events have been reported to date.²⁶

Both vaccines are effective

Although both HPV vaccines were developed and tested independently, clinical trials have demonstrated similarly high efficacy rates for both vaccines.

Since cervical cancer usually requires decades to develop, the FDA granted Gardasil

HPV vaccine is not yet approved for boys and men, but it appears effective and safe in males

approval on the basis of surrogate end points associated with the development of cancer as measures of efficacy: namely, cervical infection with HPV types contained in the vaccines, cervical cellular abnormalities associated with HPV infection (ie, abnormal Pap tests), and cervical cancer precursors (ie, cervical dysplasia).

The most recent data available from Gardasil clinical trials show that in women who received all three doses and followed the study protocol, 0 of 5,301 women in the vaccine group and 21 of 5,258 women in the placebo group developed HPV 16/18-associated cervical intimal neoplasia grade 2 or 3, adenocarcinoma in situ, or cervical cancer.²⁷ Thus, Gardasil was 100% effective in preventing these conditions.

Cervarix also appears to be up to 100% effective in preventing infection with HPV 16 and 18, as well as Pap test abnormalities and cervical dysplasia associated with these types.²⁸ A recent report²⁸ also suggested that Cervarix may provide cross-protection against HPV types 31 and 45.

Clinical trials are still ongoing for both vaccines to determine the need for booster immunizations. The most recent data suggest that immunity extends beyond 4 years for both Gardasil and Cervarix.^{28,29}

Assuming that the HPV vaccine has an efficacy rate of 75% in the general population and that Pap screening patterns do not change now that a vaccine is available, vaccination is expected to reduce the lifetime risk of cervical cancer by 70% to 83%.³⁰

Women must still get Pap tests

It is imperative that women continue to obtain regular Pap tests after they have been vaccinated, for the following reasons:

- Thirty percent of cases of cervical cancer are caused by HPV types not contained in the vaccines, such as 31 and 45 (FIGURE 1).
- Women may not be protected fully against HPV types contained in the vaccines if they have been infected with these types prior to receiving the vaccine.
- The duration of immunity provided by either Gardasil or Cervarix is not absolutely clear and is still being monitored.

WHO SHOULD BE VACCINATED?

The ACIP recently recommended that girls 11 and 12 years of age be targeted for vaccination, with catch-up immunization for girls and women 13 to 26 years of age and vaccination of girls ages 9 and 10 at the provider's discretion.²⁵

Once a person has been infected with a specific HPV type, vaccination likely will not prevent the development of disease related to that particular type. Therefore, it is optimal to complete the immunization series before the patient becomes sexually active. However, the ACIP recommends that even women with a history of sexual contact should receive the vaccine because they may not have acquired the HPV types contained in the vaccine. Furthermore, it would not be feasible to determine whether women are positive for types contained in the vaccine prior to vaccination.

Gardasil has not been approved for use in men in the United States because clinical efficacy data are not yet available. However, the vaccine appears to be highly immunogenic and safe in men,³¹ and once efficacy data are available the FDA may approve its use in boys and men. Men could benefit directly from vaccination because HPV is linked to genital warts as well as oropharyngeal, esophageal, penile, and anal cancers in men. Vaccination of men may also prevent transmission to women.³²

OVERCOMING BARRIERS TO VACCINATION

Studies have shown that pediatricians, family physicians, and gynecologists are likely to recommend HPV vaccines.^{33–35}

Physicians are more likely to recommend HPV vaccination if it is endorsed by a professional organization, if they are knowledgeable about HPV, if they see many adolescents in their practice, if they believe that vaccination will facilitate discussion of sexuality issues with adolescents, and if there are fewer perceived barriers to vaccination. However, in general, physicians reported they would be more likely to vaccinate older than younger adolescents,^{33,35} which is worrisome, given the importance of completing the vaccination series before the onset of sexual activity to gain optimal benefit from the vaccine.

Girls 11 and 12 years old are the prime targets for HPV vaccination

In general, adolescent and young adult women find HPV vaccines to be acceptable, particularly if vaccination will prevent genital warts in addition to cervical cancer.³⁶⁻³⁸

Addressing parental concerns

Because parental consent likely will be required for vaccination of minors, parental attitudes are paramount in terms of effective vaccine delivery.

Studies have shown that parents generally accept vaccination, regardless of the route of transmission of the disease, because they naturally want to protect their children from harm.^{39,40} Parents are more likely to accept HPV vaccination for their children if they believe that the vaccine is safe and effective, if the physician recommends it, if they know how severe HPV-related disease can be, and if they believe their children may be susceptible to HPV infection.³⁹ The fact that HPV is sexually transmitted did not influence acceptability in one study.⁴¹

However, some parents may be concerned that agreeing to vaccinate their child implies that they condone premarital sexual activity, or may fear that vaccinated adolescents will practice riskier sexual behaviors. Other parents may have concerns about vaccines in general, or oppose vaccines for religious or cultural reasons.

If the physician is aware of the parent's specific concerns, he or she can address them on an individual basis,^{42,43} which may make the parent more willing for the child to be vaccinated. Physicians should explain to parents the rationale for vaccinating prior to sexual initiation and should reassure parents that there is no evidence that HPV vaccination increases risky sexual behaviors.

In fact, discussions with parents as well as adolescents provide an opportunity to reinforce safe-sex messages. Adolescents must understand that HPV vaccines do not protect

against all HPV types or against other sexually transmitted diseases. Physicians can advise adolescents that they should still postpone sexual initiation, limit their number of sexual partners, and use condoms consistently to prevent HPV and other sexually transmitted diseases. In addition, physicians should reinforce the importance of continued Pap screening, as noted previously.

Simply providing education about HPV vaccines may enhance parental acceptance. One study demonstrated that brief, written educational materials about HPV vaccines markedly increased acceptability among parents, especially among parents initially undecided about whether to allow their child to be vaccinated.⁴⁴

Using practice-based systems to boost vaccination rates

Practice-based systems have been shown to be highly effective in boosting vaccination rates. These systems will be particularly important, given that HPV vaccination involves a series of three vaccinations over 6 months in an age group that until recently has not been targeted for routine vaccination.

Practice-based policies and procedures that have been shown to be effective in increasing vaccination rates include:

- Automatically reminding patients and their parents to come in for vaccination
- Automatically placing reminders for providers in the patient's chart or electronic medical record when vaccinations are due or overdue
- Setting up systems for auditing and providing feedback to providers
- Writing standing orders for vaccination.

Other strategies that may promote adolescent vaccination should be explored, such as vaccination in school-based health centers and other community settings and efforts to promote insurance coverage for HPV vaccines. ■

Some parents worry that vaccination implies they condone premarital sex

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