HPV Vaccination for the Prevention of Cervical Intraepithelial Neoplasia
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This Journal feature begins with a case vignette that includes a therapeutic recommendation. A discussion of the clinical problem and the mechanism of benefit of this form of therapy follows. Major clinical studies, the clinical use of this therapy, and potential adverse effects are reviewed. Relevant formal guidelines, if they exist, are presented. The article ends with the author's clinical recommendations.

A sexually active 18-year-old woman presents to her internist for an annual examination. During the review of her family history, she notes that her mother recently received a diagnosis of “pre-cervical cancer” and underwent a loop electrosurgical excision procedure. The patient’s mother has advised her to get the “cervical-cancer shot.” Should this patient receive a human papillomavirus (HPV) vaccine, and how effective would vaccination be in preventing cervical cancer?

The Clinical Problem
Genital HPV infection is usually acquired through sexual contact and is extremely common. In a nationally representative study of women in the United States, 25% of persons between the ages of 14 and 19 years and 45% of persons between the ages of 20 and 24 years were HPV-positive. It is estimated that more than 80% of both men and women in the United States will be infected with HPV at some point in their lives. HPV is often acquired within months after the first sexual intercourse: in a study of university women who had recently had sexual intercourse for the first time and reported having only one partner, almost 30% became HPV-positive within 1 year. Although HPV infection is usually asymptomatic, anogenital warts or cancers or other HPV-associated cancers develop in a subgroup of infected women and men. The clinical outcome of greatest significance for public health is cervical cancer. Globally, cervical cancer is the second most frequent cancer among women; each year, approximately 490,000 women receive this diagnosis and 270,000 die from cervical cancer.

In the United States, the implementation of cytologic screening programs with the Papanicolaou (Pap) test has led to a decrease in rates of cervical cancer, since screening identifies precancerous cervical lesions that can be treated before they
progress to cancer. Despite such screening, in 2008, approximately 11,000 women in the United States received a diagnosis of cervical cancer and 3900 died from the disease. The direct medical costs associated with the prevention and treatment of HPV-related anogenital warts and cervical disease in the United States are estimated to be $4.0 billion annually, and productivity losses due to deaths from cervical cancer are estimated to be $1.3 billion annually.

Pathophysiological Features and Effect of Therapy

HPVs are double-stranded DNA viruses that infect cutaneous or mucosal epithelial surfaces. The genome of the virus encodes two nucleocapsid proteins (L1 and L2) and at least six early proteins (E1, E2, and E4 through E7) that allow for replication of viral DNA and the assembly of viral particles. More than 130 HPV genotypes have been cloned from clinical lesions, and classification is based on genetic similarities in the L1 nucleocapsid protein DNA sequence.

Approximately 30 to 40 HPV genotypes infect the mucosa of the genital tract and are categorized as low-risk or high-risk according to their clinical sequelae: low-risk types are associated primarily with benign anogenital warts, and high-risk types are associated primarily with anogenital cancers. Two low-risk types, HPV type 6 (HPV-6) and HPV type 11 (HPV-11), cause more than 90% of anogenital warts and recurrent respiratory papillomatosis. Infection with high-risk HPV types causes virtually 100% of cervical cancers, approximately 90% of anal cancers, 50% of vulvar, vaginal, and penile cancers, and 12% of oropharyngeal cancers. HPV type 16 (HPV-16), HPV type 18 (HPV-18), or both cause approximately 70% of cervical cancers, whereas types 16, 18, 45, 31, 33, 52, 58, and 35 cause approximately 95% of cervical cancers. HPV-16 and HPV-18 cause approximately 50% of cervical-cancer precursors.

The HPV life cycle occurs only in keratinocytes undergoing differentiation. In most cases, infection occurs without malignant transformation. In such cases, the viral DNA is maintained separately from the host DNA as an episome. In the subgroup of HPV infections leading to malignant transformation, the viral DNA is often integrated into the host genome during progression of the cancer. Carcinogenesis is associated with the expression of proteins E6 and E7, which inactivate tumor suppressors p53 and retinoblastoma protein (pRb), respectively.
The human papillomavirus (HPV) infects basal keratinocytes through microabrasions in the skin or mucosa; with viral DNA replication, the copy number of the virus is amplified to approximately 50 to 100 copies per cell. The initial genome amplification is followed by an episomal maintenance phase. Infected basal cells then enter the suprabasal compartment, where abundant expression of early and late genes and productive genome amplification to high copy numbers is triggered in the terminally differentiating compartments. Viral assembly occurs in the upper layer of the squamous epithelium, and virions are then released and may infect adjacent tissue. Because of the mechanism by which HPV infects and replicates in the host's epithelial cells, the virus is able to largely evade the host's immune system. Thus, the innate and adaptive immune responses to natural infection are limited, and although most infections are controlled eventually, antibody concentrations tend to be low or undetectable.

The progression of HPV infection to cervical cancer is accompanied by a sequence of histologic changes. Cervical intraepithelial neoplasia (CIN) is a histologic abnormality of the cervical squamous epithelium that is associated with HPV infection and is regarded as a potential precursor of cervical cancer. CIN is classified into three grades. In CIN grade 1 (CIN 1), mild dysplasia is present, with abnormal cells occupying the lowest third of the cervical epithelium. In CIN grade 2 (CIN 2), dysplasia is moderate, with abnormal cells occupying the lower two thirds of the epithelial layer, and in CIN grade 3 (CIN 3), dysplasia is severe, with abnormal cells occupying the full thickness, or nearly the full thickness, of the cervical epithelium. Natural-history data indicate that 70 to 90% of CIN 1 lesions undergo spontaneous regression. In contrast, rates of persistence or progression to invasive cancer among CIN 2 and CIN 3 have been estimated at 57% and 70%, respectively.

Two vaccines that prevent primary infection with HPV have been developed. The HPV L1 protein, the antigen in both vaccines, is produced with the use of recombinant techniques. The proteins assemble themselves into virionlike particles that are identical.
to HPV virions morphologically, but they have no viral DNA core. Thus, viruslike-particle vaccines induce a virus-neutralizing antibody response but pose no infectious or oncogenic risk. Gardasil (also marketed as Silgard) is a quadrivalent vaccine manufactured by Merck. It contains viruslike-particle antigens for HPV types 6, 11, 16, and 18. Cervarix, a bivalent vaccine, is manufactured by GlaxoSmithKline. It contains viruslike-particle antigens for HPV-16 and HPV-18. Neither vaccine contains thimerosal or antibiotics. In contrast to natural infection, vaccination is highly immunogenic, activating both humoral and cellular immune responses. Vaccination generates high concentrations of neutralizing antibodies to L1, and it is thought that vaccination may provide protection against HPV infection through neutralization of virus by serum IgG that transudes from capillaries to the genital mucosal epithelium.9

Clinical Evidence

Several international, randomized, controlled trials involving approximately 50,000 young women have evaluated either the quadrivalent or the bivalent vaccine. Seroconversion rates among clinical-trial participants were 97.5% or higher for both vaccines.22232425 An antigen challenge 5 years after vaccination with the quadrivalent vaccine resulted in a strong anamnestic response.26 In an extended study of the bivalent vaccine, preventive efficacy against incident infection with HPV-16 or HPV-18 was 94.4% at 42 months among women who had received all three per-protocol doses.27

In terms of clinical efficacy, neither the incidence of invasive cervical cancer nor the rate of death due to cervical cancer has been assessed as a trial end point for either vaccine. Although the prevention of such outcomes is of course the ultimate purpose of HPV vaccination, they are infrequent enough that a very large, long-term trial would be necessary to establish such a benefit. Such studies are ongoing.28 Furthermore, treatment for precancerous lesions would be expected to reduce event rates still further, since it would not be ethical to allow the development of advanced disease without intervention in a trial participant with a known precursor. Therefore, the major trials have used prevention of CIN 2, CIN 3, and adenocarcinoma in situ as the efficacy end points.

Trials of both vaccines have shown more than 90% efficacy in preventing CIN 2, CIN 3, and adenocarcinoma in situ caused by HPV-16 or HPV-18 among women not infected with those HPV types and who adhered to the study protocol.22232425273031 Vaccination does not protect women who are already infected with HPV-16 or HPV-18 at the time of vaccination.2329 Furthermore, although the current vaccines may offer some degree of cross-protection against other high-risk HPV genotypes,27 this effect is probably modest.32 In one of the efficacy trials, the efficacy of the quadrivalent vaccine in preventing high-grade cervical lesions in study participants who may have previously been infected and may not have received all vaccine doses was 44% against high-grade lesions caused by HPV-16 or HPV-18 and only 17% against lesions caused by any HPV type.29

Clinical Use

The quadrivalent HPV vaccine was licensed in June 2006 by the Food and Drug Administration (FDA), and the indication for its use was expanded in September 2008. Currently, the vaccine is indicated for use in women who are between 9 and 26 years of age for the prevention of the following: cervical, vulvar, and vaginal cancer caused by
HPV-16 or HPV-18; genital warts caused by HPV-6 or HPV-11; and lesions caused by HPV types 6, 11, 16, or 18 (CIN 1, CIN 2, and CIN 3; cervical adenocarcinoma in situ; and vulvar or vaginal intraepithelial neoplasia grades 2 and 3). The bivalent vaccine is not yet licensed in the United States.

Ideally, young women should be vaccinated before they have sexual intercourse for the first time, since they often acquire HPV infection within months after their first sexual intercourse, and the peak incidence of HPV infection occurs within a few years after that. In the United States, 6.2% of adolescents have sexual intercourse for the first time before 13 years of age, and the median age at the time of first sexual intercourse is 16 to 17 years.

The vaccine should not be given to women with a history of an immediate hypersensitivity to yeast or to any component of the vaccine, and immunization should be deferred in young women with moderate-to-severe acute illness. Immunocompromised women may receive the quadrivalent vaccine. Although the safety and immunogenicity of HPV vaccination in this population are not well established, the vaccine is not infectious and could be especially beneficial in these women, since they are at increased risk for HPV-related cancers.

Vaccination is not recommended for pregnant women, but neither vaccine has been shown to be causally associated with adverse outcomes in pregnant women or their fetuses. If pregnant women are vaccinated inadvertently, completion of the series should be delayed until after the pregnancy. (The manufacturer of the quadrivalent vaccine requests that patients and clinicians report vaccination during pregnancy to a company safety registry at 800-986-8999.)

Although HPV vaccines are not effective in preventing cervical disease in young women infected with vaccine-type HPV, HPV testing is not recommended before vaccination primarily because few women are infected with both HPV-16 and HPV-18 before vaccination. Women who have genital warts or an abnormal Pap test may be vaccinated, since they are unlikely to be infected with all vaccine-type HPVs, but clinicians should inform these women that vaccination will have no therapeutic effect on existing vaccine-type HPV infection or disease.

Other options for primary prevention of HPV infection are abstinence until marriage and the use of condoms. The potential effectiveness of abstinence is limited by the low proportion of young women who choose to abstain from sexual intercourse until their mid-20s (the average age when women in the United States marry) and the fact that young women who intend to abstain from sexual intercourse until marriage may still acquire HPV through sexual abuse or from an infected marriage partner. Correct, consistent condom use provides partial protection against HPV infection. Options for secondary prevention of cervical cancer include Pap screening and HPV DNA testing.

The dose of both HPV vaccines is 0.5 ml, administered intramuscularly. The quadrivalent vaccine is administered at 0, 2, and 6 months, and the bivalent vaccine is administered at 0, 1, and 6 months. The quadrivalent vaccine should be readministered if it was given at a shorter interval than recommended or if the full dose was not successfully administered. The vaccine series does not need to be restarted if it is interrupted. Although there are limited data on coadministration of HPV vaccines with other vaccines, experts have concluded that the quadrivalent HPV vaccine may be
administered at the same visit as other recommended vaccines, such as the diphtheria and tetanus toxoid vaccine and the meningococcal conjugate vaccines. Because syncope due to vasovagal reactions may occur in adolescents after vaccination, the clinician should observe the recipient for 15 minutes after vaccination, while the patient is seated or lying down.

Cervical-cancer screening is still strongly recommended in vaccinated women, since some vaccine recipients may already be infected and since approximately 30% of cervical cancers are caused by nonvaccine HPV types. Current guidelines advise beginning screening 3 years after the first sexual intercourse, but not later than at 21 years of age, with repeat screening at least every 3 years. Widespread use of HPV vaccination may lead to a change in the screening guidelines, but it is not yet clear what change, if any, will be recommended (see Areas of Uncertainty, below).

The retail price of the quadrivalent vaccine in the United States is about $125 per dose, or $375 for the full series. These figures do not include any office or physician charges related to vaccine administration; these charges may vary. Vaccination is covered by some, but not all, health insurance plans, and some, but not all, states have passed legislation providing state funding for vaccination.

Adverse Effects

In clinical trials of the quadrivalent vaccine, mild adverse events that were more common in vaccine recipients than in placebo recipients included pain, erythema, and swelling at the injection site, as well as headache, fatigue, and myalgia. Rates of serious adverse events were not higher among recipients of vaccine than among recipients of placebo for either vaccine.

Postlicensing monitoring of HPV vaccine safety is conducted by the Centers for Disease Control and Prevention (CDC) through the Vaccine Adverse Event Reporting System (VAERS) and the Vaccine Safety Datalink. As of December 31, 2008, more than 23 million doses of the quadrivalent HPV vaccine had been distributed in the United States; as of that date, the VAERS database included 11,916 reports of adverse events after HPV vaccination. Of these events, 94% were considered to be nonserious; they included dizziness, syncope, nausea, pain at the injection site, headache, fever, and rash. The 6% of events that were considered to be serious included Guillain-Barré syndrome, venous thromboembolism, and death. The CDC and the FDA have concluded that these events do not appear to be causally linked to the vaccine.

Clinically significant adverse events should be reported by clinicians or patients to VAERS so that they can be investigated. VAERS reporting forms and information are available at www.vaers.hhs.gov or by calling 800-822-7967.

Areas of Uncertainty

Several areas of uncertainty remain with regard to HPV vaccination. First, the duration of immunogenicity and clinical efficacy is unknown. Long-term cohort studies of vaccinated women are being conducted to address this question and to establish whether boosters are needed. Second, the efficacy of vaccination in men is not well

http://ovidsp.tx.ovid.com/spa/ovidweb.cgi
defined. The immunologic response to the quadrivalent vaccine in boys is equivalent to that in girls, and preliminary data suggest that the quadrivalent vaccine is effective in preventing HPV infection and HPV-related anogenital disease among uninfected young men. However, some models suggest that if high vaccination rates are achieved among women, vaccination of men may not be cost-effective and may not lead to substantial, additional reductions in the incidence of cervical cancer.

Third, the true effect of vaccination on the incidence of cervical cancer and other HPV-related cancers is not actually known, since the end points of clinical trials were rates of CIN 2, CIN 3, and adenocarcinoma in situ. Ongoing studies that use population-based cervical-cancer registries are evaluating the effect of vaccination on cervical-cancer incidence and mortality. Fourth, the health benefits of vaccinating women who are older than 26 years of age are not yet well defined. Vaccine trials suggest that these vaccines are immunogenic and may be effective in older women. However, the effect on public health and the cost-effectiveness of HPV vaccination are expected to be lower in older women than in younger women. Fifth, little is known about the safety and efficacy of these vaccines in immunocompromised persons, although these data are of critical importance, given the increased risk of HPV-related cancers among immunocompromised women and men.

Sixth, it is unclear how cervical-cancer screening guidelines will change in the vaccination era. Widespread HPV vaccination may decrease the clinical usefulness of Pap tests and colposcopy by decreasing the prevalence of high-grade lesions, and adding HPV vaccination to existing cytologic screening programs without decreasing the frequency of screening will be costly. Thus, recommendations regarding cervical-cancer screening are likely to change; screening may start later (e.g., at 25 years of age), and the interval between Pap tests may be extended. Finally, concerns have been raised that HPV vaccination may lead to riskier sexual behaviors or nonadherence to future Pap screening, though there is no evidence to support such concerns.

Guidelines

The Advisory Committee on Immunization Practices recommends routine vaccination of girls who are 11 to 12 years of age and “catch-up” vaccination of girls and young women who are 13 to 26 years of age. The vaccine can be administered to girls as young as 9 years of age. Professional organizations such as the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, and the Society for Adolescent Medicine have published similar guidelines. The American Cancer Society guidelines differ in that catch-up immunization is recommended for girls 13 to 18 years of age; these guidelines note that there are insufficient data to make a recommendation for or against universal vaccination of women who are 19 to 26 years of age, and they state that the decision to vaccinate women in that age range should be based on a discussion between the patient and the clinician.

In countries, other than the United States, where national immunization programs have recommended HPV vaccines, guidelines are generally similar to those in the United States. The World Health Organization has recently stated that “routine HPV vaccination should be included in national immunization programs, provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in that...
The recommendations also note that HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer that includes education and cervical-cancer screening.

**Recommendations**

The young woman described in the vignette is 18 years of age and therefore an appropriate candidate for HPV immunization. I recommend that the HPV vaccine be universally administered to young women of this age, regardless of their history of sexual activity, unless there are contraindications to vaccination. In order to avoid vaccination during pregnancy, I would assess the risk of pregnancy and perform a pregnancy test, if indicated, in this sexually active young woman. I would also explain that although she may have already been exposed to HPV through sexual contact, she is unlikely to be infected with both of the cancer-associated HPV types targeted by the quadrivalent HPV vaccine, so vaccination would be expected to protect her at least partially. Finally, I would use this opportunity to reinforce the importance of both practicing safe sexual behaviors to prevent sexually transmitted infections and returning for future Pap screening, since current vaccines do not target all high-risk HPV types and the duration of efficacy is unknown.

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