Introduction
At its most recent meeting in October 2009, the Advisory Committee on Immunization Practices (ACIP), the federally recognized authority that makes official recommendations for civilian use of routine vaccination, approved a newly licensed vaccine, Cervarix® (GlaxoSmithKline), directed against human papillomavirus (HPV) to prevent cervical cancer. The ACIP also expanded its recommendations for HPV by giving permission to physicians to vaccinate males aged 9 to 26 years with the previously licensed vaccine, Gardasil®, to prevent genital warts, in addition to its previous recommendation for females aged 9 to 26 years to prevent cervical cancer and genital warts. The marketing, expense, safety, and reactivity of Gardasil® continue to be controversial. Reactivity refers to transient local and systemic reactions to the vaccine, such as injection site pain and syncope.
Human Papillomavirus

Human papillomavirus is a small virus with an approximately 8 million kilobase and a circular, double-stranded DNA genome. It belongs to the family Papillomaviridae, which consists of small, nonenveloped DNA viruses infecting birds and mammals. Members of this family form multiple genera, but the individual viruses are highly host-specific and tissue-restricted. Human papillomavirus has > 100 types, as defined originally by their protein serologies and later their DNA molecular hybridization. About 60 types cause common body warts, such as those found on the hands and feet. About 40 are sexually transmitted and cause mucosal, genital, or anal warts. Of those, some high-risk types cause low- and high-grade cervical changes, including precancers and anogenital cancers, whereas others are low-risk types that cause low-grade cervical changes, genital warts, and respiratory papillomas. All HPVs appear to contain 3 regions: a long control region where replication originates, which contains binding sites for regulatory transcription factors; a region consisting of 6 early genes, E1–E7 minus an E3; and a third region containing 2 late genes, L1 and L2. The early gene products control viral replication, whereas late gene products control structural components of the viral capsid. Typing appears to correlate not only with forms of disease but with risks for subsequent malignancy. A phylogenetic tree, constructed of amino acid changes on genes E6, E7, and L1, demonstrates a relationship between types associated chemically with malignancy risk. Immunity to HPV depends on both innate and adaptive immunity.

Innate immunity is nonspecific and exists independently of previous exposure; innate immunity to HPV occurs through the activation of macrophages and natural killer cells as well as the generation of interferon and other immunoregulatory molecules, which in turn stimulates the adaptive immune system. Human papillomavirus infection appears to evade the innate immune system through at least 3 mechanisms. First, the replication of HPV does not involve cell lysis and thus does not result in an inflammatory response. Second, the replication of HPV involves primarily the squamous cells of the mucosal epithelium and not the immunocompetent dendritic cells in deeper layers. Third, HPV gene products appear to inhibit certain activities of the innate immune system.

The innate immune response generates immunoregulatory molecules that can stimulate the adaptive immune system. This occurs primarily through the activation of specific naïve T cells. The milieu of immunoregulatory molecules generated by the innate response determines the terminal differentiation of the T cell to an effector T cell (type 1 or type 2) or a regulatory T cell. A response that results in predominately type 1 T-helper cells will result in a proliferation of cytotoxic T cells important for the destruction of virally infected cells. A response that results in predominately type 2 T-helper cells will result in a proliferation of B cells capable of generating specific neutralizing antibodies.

HPV Prevalence and Transmission

Human papillomavirus transmission results from direct contact with an infected person, such as during sexual intercourse. Epidemiologic estimations indicate that HPV is the most common sexually transmitted disease (STD). Most people infected with HPV do not exhibit any symptoms, and studies have found that humans clear most HPV infections within 8 months to 2 years. Epidemiologists estimate that 20 million people in the United States currently have an HPV infection, with approximately 6.2 million newly diagnosed cases annually and presumably with an equivalent number clearing their infections. In a 2003 to 2004 study of women participating in the National Health and Nutrition Examination Survey, 26.5% of subjects aged 14 to 59 years tested positive for HPV, with the highest rates of infection in women aged 20 to 24 years.

The lifetime risk of contracting an HPV infection for a sexually active man or woman is > 50%, and it is estimated that by age 50 years, 80% of women have contracted a sexually transmitted HPV infection. The predominant risk factors for HPV are age, marital status, and number of lifetime and recent sexual partners. In some studies, however, women with only one lifetime sexual partner still show a 20% HPV infection rate, likely due to the sexual experience of the partner. Young women aged < 25 years are at greatest risk of HPV infection. A second peak of HPV infection occurs in women aged > 55 years, thought to be due to changes in immune function with menopause.

Immunocompromised women, such as women with human immunodeficiency virus (HIV) and solid-organ transplant recipients, have a higher rate of HPV infection and HPV-associated neoplasms. Women infected with HIV have more than twice the rate of HPV cervical infection compared with non–HIV-infected women (64% vs 28%).

Clinical Sequelae of HPV Infection

Clinical presentation of an HPV infection depends on which type of HPV is responsible for the infection. A basic working classification system has been implemented, which divides the HPV types into high or low grade, depending on their oncogenic potential. High-grade HPV types include...
Human papillomavirus is identified in > 99% of patients with cervical cancer,17 with 70% being identified as high-grade subtype 16 or 18.18 Although HPV infection is a pre-requisite to developing cervical cancer, one does not equal the other; the infection rate greatly exceeds the progression to cancer. A variable length of time passes after infection and spontaneous clearance occurs, or persistent infection prevails, which may result in cervical histological changes. Most HPV infections are transient and clear within 8 months to 2 years.8,10 The high-grade HPV subtypes, however, are more likely to persist.19 This persistent infection can result in cervical cytological changes. High-grade precancerous lesions are estimated to take 10 years to progress into cervical cancer.20 This is one of the reasons that the American College of Obstetrics and Gynecology has recently published recommendations to delay initial Pap tests until a woman reaches age 21 years, regardless of age of onset of sexual activity.21

In the United States, from 2002 to 2006, the incidence of cervical cancer was 8.2 per 100 000.22 It is estimated that, in 2009, 11 270 women were diagnosed with new cases of cervical cancer and that 4070 women died of the disease.22 A woman’s lifetime risk of being diagnosed with cervical cancer is 1 in 145.23 Half of all women with cervical cancer never received a Pap test before diagnosis.23

Low-risk HPV types cause Condylomata acuminata, or genital warts, with 90% being of subtype 6 or 11.24 Patients with condylomata can be reassured that the HPV strains that cause genital warts are not the same strains associated with cancerous lesions. Human papillomavirus infections that manifest as genital warts may appear within weeks or months after sexual contact, if at all. It has been estimated that 1% of sexually active Americans have active genital wart infections, with 74% of new infections occurring in individuals aged 15 to 24 years.8 Genital warts in women can appear on the vulva, in or around the vagina, or anus. Genital warts on men can appear on the penis, scrotum, groin, or thigh. Lesions have varied appearance, from flat to raised, single or multiple, and large or small. Clinical course varies from patient to patient, ranging from complete resolution to an increase in number or size, or both. Treatment of warts includes topical application of cytotoxic substances or immunomodulators, intralesional injection of interferons, and ablative procedures such as excision, cryosurgery, electrosurgery, and laser surgery.

Human papillomavirus infection is also associated with vaginal, vulvar, and anal squamous cell cancers and their precursor lesions.25 The American Cancer Society estimates that United States practitioners will have diagnosed 2160 cases of vaginal cancer, 3580 cases of vulvar cancer, and 3190 cases of anal cancer in women in 2009.26–29

Patients diagnosed with certain laryngeal and oral cancers containing HPV DNA may not otherwise demonstrate symptoms of HPV. These cases therefore remain outside counts and estimates of HPV-infected individuals. A meta-analysis in 2005 of laryngeal and oral carcinogenesis epidemiological studies as well as multicenter case-control studies found HPV types detectable in 22% of oral carcinomas, 51% of tonsillar carcinomas, 33% of sinonasal papilomas, and 22% of sinonasal carcinomas of the cases analyzed for HPV.30

**HPV Vaccines**

In 2009, the US Food and Drug Administration (FDA) licensed 2 vaccines for the prevention of HPV infection: Gardasil® and Cervarix®.31 Gardasil® is a quadrivalent vaccine consisting of 4 different types of viral-like particles. These viral-like particles consist of the major capsid protein L1 from 4 serotypes of HPV (types 6, 11, 16, and 18). The vaccine is a recombinant production of the L1 proteins in virus-like particles, generated by genetically altered yeast *Saccharomyces cerevisiae*. The viral-like particles are adsorbed onto a preformed adjuvant of amorphous aluminum hydroxyphosphate sulfate. Randomized controlled trials following women over 3 years have shown that in an HPV-naïve population, Gardasil® prevented almost 90% of persistent infections and 98% of HPV 16/18-related, high-grade cervical lesions.32 Additional studies focusing on the primary endpoints of genital warts, vulvar or vaginal intraepithelial neoplasia, or cancer caused by types included in the vaccine showed that the efficacy was 100%.33 In women previously or currently infected with 1 to 3 of the HPV types included in Gardasil® vaccine, the vaccine showed 100% effectiveness against cervical intraepithelial neoplasia (CIN) or adenocarcinoma in situ for which they were initially naïve.35 When surveillance was extended to 5 years postvaccination, international trials conducted have shown the vaccine to prevent 100% of vaccine-related disease, such as CIN 1–3 or condyloma and > 95% of persistent infection with HPV 6, 11, 16, or 18.36

A randomized, double-blind, placebo-controlled, multicenter study recently demonstrated the effectiveness of Gardasil® in adolescent males and young men.37 Human papillomavirus infections in males manifest as genital warts, as well as penile, perineal, perianal and anal neoplasia, and cancer, as well as contributing to infections in women. In a study of 4065
young men aged 16 to 26 years, 97% to 99% seroconverted depending on the strain at 1 month after the third dose as compared with 2% across the strains for the placebo group. The efficacy of Gardasil® against external genital lesions was 90.4% (95% confidence interval, 69.2–98.1). GlaxoSmithKline has developed a bivalent HPV vaccine, Cervarix®, targeting HPV 16 and 18. Studies have shown it to be safe and effective in protecting against high-grade HPV infection and subsequent CIN lesions caused by HPV 16 or 18 in females. No studies of Cervarix® use in males have been conducted. Like Gardasil®, Cervarix® is adjuvanted, but with adjuvant system 04 (AS04), a monophospholipid and aluminum salt, which has been shown to activate antigen-presenting cells, producing a more rapid and pronounced immunologic response to the vaccine than with an aluminum hydroxide adjuvant. Cervarix® is produced using insect cells infected with recombinant baculovirus, which then produce the L1 virus-like particle. The primary study showing the efficacy of Cervarix® included > 18 000 women aged 15 to 25 years, including women who were naïve to HPV 16 and/or 18, as well as women who tested positive. In the entire group, Cervarix® was approximately 53% effective in preventing precancerous lesions; in the HPV 16/18-naïve group, the vaccine was about 93% effective. The current data show that Cervarix® is effective for at least 6 years.

Ongoing studies are being conducted to determine the length of immunity conferred by both HPV vaccines. At this time, studies indicate that vaccinated patients are protected for at least 5 years; the recent introduction of the vaccine makes it impossible to forecast whether booster vaccines will be necessary. Merck and GlaxoSmithKline have studies of the duration of protection underway.

Contraindications and Precautions
Like other vaccines, contraindications to the HPV vaccine include known hypersensitivity to vaccine components, particularly yeast (Saccharomyces cerevisiae) for the Gardasil® vaccine, as it is used in the fermentation process and is present in the injected vaccine (< 7 μg/dose), and latex for the Cervarix® vaccine, as it is present in prefilled syringes. Patients who had a hypersensitivity reaction to previous doses should not receive additional doses.

Pregnancy is a contraindication, as the clinical studies excluded women known to be pregnant and the protocols excluded women found to be pregnant during the study from receiving further doses. Both Cervarix® and Gardasil® are listed as pregnancy category B, and are not expected to cause harm to a developing fetus; in clinical trials, pregnant women receiving the vaccines experienced adverse events at the same rate as pregnant women receiving the placebo.

The HPV vaccines may not elicit a full immunologic response in immunocompromised or immunosuppressed patients, but because the vaccines do not contain live viruses, these patients can safely be vaccinated. No studies have been conducted, however, to determine vaccine response in immunocompromised patients. According to the ACIP, individuals with minor concurrent illness, such as low-grade fever or mild upper respiratory illness, may receive the vaccine. Individuals with moderate-to-severe illness should defer vaccination until recovery.

Licensure and Recommendations
In June 2006, the FDA licensed Gardasil® for use in females aged 9 to 26 years, and in October 2009 licensed Cervarix® for use in females aged 10 to 25 years. In March 2007, the ACIP in concert with the American Academy of Pediatrics and the American Academy of Family Physicians recommended routine vaccination of females with Gardasil® at 11 to 12 years old, starting as early as 9 years with catch-up vaccination from ages 13 to 26 years. The recommendations permit the initiation of the 3-dose series of Gardasil® vaccine starting as early as 9 years. The recommended dosing interval of the Gardasil® series is to give the second dose 2 months after the first dose, and the third dose 6 months after the first dose. The minimum dosing interval between the first 2 doses is 4 weeks and between the second and third dose is 12 weeks. Delay in delivery of any of the latter doses does not require reinitiation of the series.

In October 2009, the ACIP approved the use of Cervarix® for routine vaccination of females aged 11 to 12 years, starting as early as 10 years, with catch-up vaccination from 13 to 25 years. The 3-dose series of Cervarix® calls for a second dose to be given 1 month after the first and the third dose, 6 months after the first. The timing of the second dose of Cervarix® differs from Gardasil®, as do the age limits. The ACIP did not recommend one vaccine over the other.

In September 2009, an FDA advisory committee supported the licensure of Gardasil® for use in males aged 9 to 26 years, and in October 2009 the FDA licensed Gardasil® for use in males. On October 21, 2009, the ACIP approved a permissive recommendation for Gardasil® in males, allowing physicians to vaccinate males aged 9 to 26 years. This decision also means that Gardasil® is covered by the federal Vaccines for Children program, although the promulgation of the recommendation occurs state by state. Cervarix® is neither licensed nor approved for use in males.
In February 2007, Texas attracted national attention after its governor enacted an executive order to mandate that all females, with some exceptions, entering the sixth grade receive Gardasil® vaccine, although this order was eventually blocked by legislation. As of March 2009, 12 states have proposed HPV-related legislation or resolutions, many related to a requirement to attend public schools. Individual states determine school vaccine requirements, which are fulfilled in various ways. The legislature must consider how to provide funding for each requirement, addressing those patients covered by Medicaid and SCHIP.45

The National Childhood Vaccine Injury (NCVI) Act of 1986 requires that providers give the patient or legal guardian standardized vaccine information statements (VIS) created by the Centers for Disease Control and Prevention (CDC). The NCVI also requires that manufacturers and providers notify the Vaccine Adverse Event Reporting System (VAERS), conducted by the FDA and the CDC, for any adverse effects. The VAERS documents the occurrence of certain stipulated adverse events after the administration of vaccines. Vaccine providers and manufacturers are required to report such events and may report others as well. Parents and patients themselves may also report adverse events. Because these are only reports, cause and effect relationships are not established and care must be taken in any clinical interpretation or application to patient care.

**Adverse Events**

The most commonly reported adverse events during Gardasil® clinical trials were injection site reactions (pain, erythema, and swelling), fever, and headache.46 Pain was reported in 84% of patients receiving Gardasil® versus 75% of patients receiving the adjuvant control and 49% of patients receiving the placebo. Injection site reactions of swelling or erythema was reported in 25% of Gardasil® recipients versus 16% to 18% of patients receiving the adjuvant control and 7% to 12% of patients receiving placebo (Table 1). Fever was reported at similar rates in the vaccine group (13%) and adjuvant/placebo group (11%) within 15 days of vaccine administration. Headache was the most commonly reported systemic adverse reaction (28% in all groups) (Table 2). Much less common were serious adverse reactions, including gastroenteritis (0.032% vs 0.01% in placebo group), and appendicitis or pelvic inflammatory disease (0.02% vs 0.01% in placebo group).

Cervarix® clinical safety trials used hepatitis A vaccine or an aluminum hydroxide as controls. The most commonly reported adverse reactions to Cervarix® were local injection site reactions, with > 84% in the mild-to-moderate category, including pain (Cervarix® 91% vs HAV 64%–78% vs AL(OH)3 87%), redness (48% vs 25%–27% vs 24%), and swelling at the injection site (41% vs 17%–20% vs 21%).32 Additional adverse effects included fatigue (55% vs 42%–53% vs 54%), fever (13% vs 11%–16% vs 14%), headache (53% vs 45%–51% vs 61%), myalgia (49% vs 33%–45%), and gastrointestinal symptoms (27% vs 25%–27% vs 33%).32 Syncope is reported to have occurred, but no estimates of affected patients was given (Table 3).32

Post-vaccine syncopal events for all vaccine types are most common in adolescent female patients, and such events have been reported in patients receiving Gardasil®. Between vaccine release on June 1, 2006, and December 31, 2008, > 12 000 reports pertaining to Gardasil® were received by the VAERS.47

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**Table 1. Injection-Site Adverse Reactions with Gardasil®**

<table>
<thead>
<tr>
<th>Injection-Site Reaction (1–5 days postvaccination)</th>
<th>Gardasil® (N = 5088) (%)</th>
<th>AAHS Control (N = 3470) (%)</th>
<th>Saline Placebo (N = 320) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>84</td>
<td>75</td>
<td>49</td>
</tr>
<tr>
<td>Swelling</td>
<td>25</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>Erythema</td>
<td>25</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3.2</td>
<td>2.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Bruising</td>
<td>2.8</td>
<td>3.2</td>
<td>1.6</td>
</tr>
</tbody>
</table>

*The injection-site adverse reactions observed among recipients of Gardasil® were at a frequency of at least 1% and also at a greater frequency than that observed among AAHS control or saline placebo recipients. Abbreviation: AAHS, amorphous aluminum hydroxyphosphate sulfate.*

**Table 2. Common Systemic Adverse Reactions with Gardasil®**

<table>
<thead>
<tr>
<th>Adverse Reactions (1–15 days Postvaccination) (N = 5088) (%)</th>
<th>Gardasil® (%)</th>
<th>AAHS Control or Saline Placebo (N = 3790) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>13.0</td>
<td>11.2</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.7</td>
<td>6.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Cough</td>
<td>3.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Toothache</td>
<td>2.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Upper</td>
<td>2.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Malaise</td>
<td>1.5</td>
<td>1.4</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Nasal</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*The adverse reactions in this table are those observed among recipients of Gardasil® at a frequency of at least 1% and those observed among AAHS control or saline placebo recipients. Abbreviation: AAHS, amorphous aluminum hydroxyphosphate sulfate.*
Syncope was the mostly frequently reported adverse event, with a frequency of 8.2 events per 100,000 Gardasil® doses. New ACIP recommendations are to observe patients for 15 minutes after Gardasil® administration, as 70% of all syncopal episodes have been reported to occur within 15 minutes of vaccination, and serious injury may result from syncopal episodes. An Australian study of adverse events after Gardasil® administration found a higher-than-average rate of anaphylactic reactions compared with other vaccines. This study reported 7 cases of anaphylaxis with 260,000 vaccine administrations, an incidence rate of 2.6 per 100,000 doses. In comparison, the rate of identified anaphylaxis was 0.1 per 100,000 doses for the conjugated meningococcal vaccine. While this is an increased incidence, the rate was still relatively low and the episodes were managed appropriately without more serious effects.

In a review of adverse events reported to VAERS after the licensure of Gardasil®, venous thromboembolic events (VTE) were reported at a disproportionately high rate compared with other vaccinations which, though still rare, were reported at a frequency of 0.2 events per 100,000 doses of Gardasil. Of these cases, 90% of the women had a known risk factor for VTE, such as oral contraceptive pill use or positive family history. The mean age of women having VTE after immunization was 21 years. Guillain-Barré syndrome after Gardasil® administration was reported in 42 cases representing a rate of 0.2 cases per 100,000 vaccine doses, no greater than the expected rate if it were not related to the vaccine; the diagnosis was confirmed in 12 cases. Only 8 of these cases occurred within the 42 days after vaccine administration, which is the theoretical window for any causal link. No comparable data are yet available for Cervarix®.

Table 3. Solicited Local Adverse Reactions and General Adverse Events in Females Aged 10 to 25 Years within 7 Days of Vaccination with Cervarix®

<table>
<thead>
<tr>
<th>Local Adverse Reactions</th>
<th>Cervarix® (10–25 years) (%)</th>
<th>HAV 720 (15–25 years) (%)</th>
<th>HAV 360 (10–14 years) (%)</th>
<th>Al(OH)3 Control (15–25 years) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>91.8</td>
<td>78.0</td>
<td>64.2</td>
<td>87.2</td>
</tr>
<tr>
<td>Redness</td>
<td>48.0</td>
<td>27.6</td>
<td>25.2</td>
<td>24.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>44.1</td>
<td>19.8</td>
<td>17.3</td>
<td>21.3</td>
</tr>
<tr>
<td>General Adverse Events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>55.0</td>
<td>53.7</td>
<td>42.3</td>
<td>53.6</td>
</tr>
<tr>
<td>Headache</td>
<td>53.4</td>
<td>51.3</td>
<td>45.2</td>
<td>61.4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>27.8</td>
<td>27.3</td>
<td>24.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Fever (≥ 99.5°F)</td>
<td>12.8</td>
<td>10.9</td>
<td>16.0</td>
<td>13.5</td>
</tr>
<tr>
<td>Rash</td>
<td>9.6</td>
<td>8.4</td>
<td>6.7</td>
<td>10.0</td>
</tr>
</tbody>
</table>

Vaccination Rates and Barriers to Vaccination

The most recent vaccination rates available are from 2008; the CDC reported that the rate of female adolescents aged 13 to 17 receiving at least one dose of Gardasil® had increased from 25% to 37.2%, which is comparable to the rate of meningococemia vaccination (41.8%) and Tdap booster (40.8%). Of those who had received the first dose > 6 months before the survey, 59% had received the entire 3-dose course. Vaccination rates were highest among Hispanic adolescent females (9.4% higher than white females), and those living below the poverty line (10.6% higher than those living at or above the poverty line). The authors of the report theorize that the higher vaccination rates for adolescent females below the poverty line is due to vaccine availability through the federally funded Vaccine for Children program, which removes the cost barrier for these patients.

The price for the 3-dose series of Gardasil® is about $399 and $386 for Cervarix®. Most insurance companies cover the cost of ACIP recommended vaccines, but some may not. Parents should check with their insurance company before vaccinating their children. Cervarix® and Gardasil® are available through the Vaccines for Children program if patients are Medicaid eligible, uninsured, or American Indian or Alaska Native.

Long-Term Economic Impact

The long-term economic benefits from HPV immunization of adolescent females are difficult to project. Prevention of costs related to genital warts, costs related to cervical cancer screening, and ultimately costs associated with cervical cancer treatment should all be considered when performing a
cost-benefit analysis. A recent analysis in the New England Journal of Medicine looked at costs related to diagnosis and treatment of genital warts, cervical cancer screening, and treatment. Assuming that the vaccine confers lifelong immunity, and that 75% of eligible patients (female patients age 12 years) receive the vaccine, then the vaccine was found to be “economically attractive,” ie, < $50000 per quality-adjusted life year (QALY); the cost for targeted 12-year-old females was projected to be $34900. The addition of catch-up programs for older girls and young women increased the costs, as did the assumption that booster immunizations would be needed. While cost-effectiveness data offer little support for the use of the HPV vaccine at a population level in older adolescents, young women, and even older women, new preliminary data indicate that the HPV vaccine is both safe and effective in women aged 25 to 45 years.

A recent cost-effectiveness analysis for use in males in the United States failed to approach conventionally accepted levels of expense for the benefits obtained, unlike analyses with females. The analysis not only included the direct benefit to males but the effect of vaccinating males upon the rates of infection among females. Despite this, vaccinating preadolescent females (with no change to the current program of cervical cancer screening) gave a cost-effectiveness ratio of $40310 per QALY gained, compared with the current program of cervical cancer screening. Vaccinating males in addition to this gave a cost-effectiveness ratio of $290290 per QALY compared with vaccinating females only while continuing the current program of cervical cancer screening.

The American College of Obstetrics and Gynecology recently updated and revised its recommendations for cervical screening examinations to delay initial Pap tests until a woman reaches age 21 years, regardless of age of onset of sexual activity, and then every 2 years between 21 and 29 years of age, not because of the vaccine but because of the timing of cervical changes after HPV infection. One recent study showed that the cervical cancers caused by HPV 16 and 18 presented earlier than those caused by other HPV types; if the rate of cervical cancers caused by HPV-16 and HPV-18 is as drastically reduced as are the goals, this could have an impact on the schedule of cervical cancer screening.

Summary

Human papillomavirus as a cause of genital warts, cervical, vulvar, anogenital, and laryngeal cancers is also a significant cause of medical morbidity, mortality, and health care-related costs. Current efforts at early identification and treatment of HPV-related disease have lowered the rates of HPV-related mortality, but at a great cost, with recent estimates of the annual direct medical costs of screening $4 billion in the US, the treatment of cervical intraepithelial neoplasia II and III another $2 billion, and the treatment of cervical cancer itself $300 to $400 million. Both HPV vaccines have been shown to prevent infection with the most common carcinogenic strains, for at least 5 years post vaccination, with generally mild, predictable side effects. The ACIP recommends routine vaccination of females at ages 11 to 12 years with either Gardasil® or Cervarix® and gives permission for the use of Gardasil® in males aged 9 to 26 years. Though females will still need to undergo cancer screening at the current recommended schedule, vaccination in females appears cost-effective in preventing costs related to genital warts (in the case of Gardasil®) and cervical, vulvar, and anogenital cancers. Future recommendations for cervical screening may be influenced by the success of the vaccine.

Conflict of Interest Statement

Eileen M. Broomall, MD, Sonya M. Reynolds, MD, and Robert M. Jacobson, MD disclose no conflicts of interest.

References


