

Decreasing Risk: Impact of HPV Vaccination on Outcomes

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Abstract

Cervical cancer, caused by oncogenic types of human papillomavirus (HPV), remains a major health problem worldwide. The recent introduction of a quadrivalent vaccine (Gardasil®), which targets HPV strains responsible for approximately 70% of cervical cancer cases and 90% of genital warts, has ushered in new hope of substantially reducing global prevalence of HPV disease. A further bivalent HPV vaccine (Cervarix™) is in the offing. However, many issues still need to be addressed, including actual vaccine efficacy in preventing cervical cancer, public acceptance, use of the vaccine in men, vaccine access, costs, and impact of the vaccine on cervical cancer screening programs. This review analyzes some of these issues, and emphasizes the need for a coordinated effort of patients, parents, health professionals, hospitals, and policymakers to ensure successful implementation of vaccination programs in the United States.

(Am J Manag Care. 2006;12:S473-S483)

Worldwide, cervical cancer is second only to breast cancer as the leading cause of cancer-related mortality in women.¹⁻³ About 500 000 cases of cervical cancer are seen globally each year, accounting for close to a quarter of a million deaths.^{2,4,5} The largest burden of cervical cancer—approximately 80% of cases—is seen in developing countries, related to lack of infrastructure and resources required to establish and maintain high-quality Papanicolaou (Pap)-based screening programs.^{4,6-8}

Although organized Pap-based screening has led to a significant reduction in incidence rates of cervical cancer and attendant mortality in the United States over the past several decades,^{8,9} the current rates are by no means acceptable. Cervical cancer represents the eleventh most frequent cancer in

the United States and was responsible for more than 3500 deaths in the United States in 2005; more than 10 000 new cases were diagnosed during that year alone.³ Screening and cytological evaluations performed in the United States exact an enormous economic burden,^{10,11} and many annual cases of cervical cancer in the United States are still seen in women who are being screened.⁵ Although current interventions for treating precursor cervical lesions are effective, response is still not seen in some women, and there is room for improvement. Thus, cervical cancer still constitutes a major health problem in all geographic regions.

There is indisputable evidence that cervical cancer is related to persistent infection with sexually transmitted, oncogenic types of human papillomavirus (HPV), also labeled cancer-associated HPV or high-risk HPV.^{1,7,12,13} There is also evidence of non-sexual transmission of the virus. With use of sensitive polymerase chain reaction techniques, high-risk HPV deoxyribonucleic acid was seen in at least 99% of cervical cancers.^{2,12,14} Of the 15 types of high-risk HPV, any one type can result in cervical cancer; however, the most predominant are HPV-16 and HPV-18, which account for approximately 70% of cases (50%-60% and 10%-20%, respectively).^{1,2,14} Other HPV types, such as 31, 33, 45, 52, and 58, account for most other additional cases, depending on geographic region.^{5,7}

Cancers caused by a viral agent are unique in that they are subject to immunologic intervention via vaccines. In developing countries, an effective HPV vaccine may

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be the only practical method of reducing disease and cervical cancer in ensuing decades. In the United States, HPV vaccination has the potential to significantly reduce health-care costs and the emotional burden related to detection of cervical lesions, in addition to further limiting disease in conjunction with screening programs.^{1,7}

This article will discuss the development and clinical efficacy of emerging HPV vaccines, the potential impact of vaccination programs in the United States, the cost-effectiveness of vaccination, and issues related to US vaccine implementation. The epidemiology of HPV and natural course of infection are discussed elsewhere in this supplement.

HPV Vaccines

Initial attempts at development of an HPV vaccine were met with difficulty, because of the poor growth of HPV in cell cultures and inability to cause infection in nonhuman species.^{7,14} The presence of viral oncogenes in a developed live attenuated vaccine was also problematic. Research focus shifted to potential use of subunit vaccines, based on the major capsid protein of the virus, L1. It was discovered that L1 proteins were capable of self-assembling into virus-like particles (VLPs) when expressed in cells. These VLPs share great similarity to native HPV virions, are noninfectious and nononcogenic, and can induce high levels of neutralizing antibodies; vaccination with VLPs has protected against HPV infection in animal models.^{7,14,15}

Several VLP vaccines directed at specific types of HPV are either under development, in the clinical evaluation phase, or have reached US Food and Drug Administration (FDA) approval status.^{1,7,9,16} To assess vaccine efficacy, the most relevant outcomes recommended by an FDA advisory panel are reductions in vaccine type-specific persistent HPV infection and cervical intraepithelial neoplasia (CIN)2+. CIN1 represents low-grade dysplasia, which is not thought to be a true cancer precursor, whereas CIN2 and CIN3 are moderate- and high-grade dysplasias, respectively, and immediate precursors of cervical cancer.^{1,17} In keeping with these outcome markers, a controlled proof-of-

principle efficacy study (n = 2392) conducted by Koutsky et al¹³ demonstrated 100% efficacy of an HPV-16 VLP vaccine in women. All cases of new HPV-16 infections, including HPV-16-related CIN, occurred in the placebo group. Additional follow-up of these patients revealed protection against persistent infection and HPV-16-related CIN2-3 for an average of 3.5 years.¹⁷

Two of the initial vaccines incorporating more than 1 HPV type have focused on types most frequently associated with cervical cancer. Thus, a bivalent VLP vaccine (Cervarix™, GlaxoSmithKline) is composed of VLPs assembled from recombinant HPV-16 and HPV-18 L1. Cervarix is in phase III trials and will likely be considered for FDA approval before 2007. A quadrivalent VLP-based vaccine (Gardasil®, Merck & Co) encompasses HPV-16 and HPV-18, as well as HPV-6 and HPV-11; the latter types, combined, cause the majority of genital warts (approximately 90%) in both men and women.^{1,16} Although HPV-6 and HPV-11 can cause cervical infection, they are not associated with cervical cancer. Gardasil was approved by the FDA in June 2006 for use in women 9 to 26 years of age to prevent cervical cancer, as well as genital warts and precancerous lesions (cervical, vaginal, vulvar).

Cervarix and Gardasil differ with respect to adjuvants. The former uses AS04 (aluminum hydroxide plus 3-deacylated monophosphoryl lipid A [MPL]), whereas the latter employs amorphous aluminum hydroxyphosphate sulfate.^{2,7,16} It is unclear if greater and more sustained antibody responses are obtained with the AS04 adjuvant compared with aluminum salt-based adjuvants without MPL, as some investigators suggest.^{2,7} Direct comparisons of the immunogenicity of HPV vaccines are lacking.

Published and unpublished double-blind, placebo-controlled phase II and phase III trials have demonstrated the efficacy of the bivalent and quadrivalent vaccines in producing high rates of seroconversion and significant type-specific protection against HPV infection (incident and persistent) and cervical intraepithelial lesions.^{1,2,7,13,16-20} Based on according-to-protocol analyses, efficacy rates for clinical outcomes (infection, cervical lesions) have approached 100% with each

vaccine. Gardasil has also shown efficacy in protecting against vulvar/vaginal neoplasia and anogenital warts.^{7,18} Some relevant findings for both vaccines from clinical trials are shown in **Table 1**.

Approval of Gardasil in very young girls was not based on clinical efficacy, but rather “bridging immunogenicity and safety studies,” where efficacy was inferred from immunologic responses in women aged 9 to 15 years of age when compared with immunologic responses in women aged 16 to 26 years of age with known efficacy against HPV disease.^{18,21,22} Significant antibody responses were seen in more than 99% of these girls, and were higher than those observed in 16- to 26-year-old women.¹⁸

Effect on Cervical Cancer. The ultimate goal of immunization against HPV types is to prevent cervical cancer. At present, no study

has clearly demonstrated a reduction in cervical cancer with vaccine use, owing to short trial durations. Long-term efficacy data from ongoing phase III trials and extensions are needed to fully assess vaccine effects on this outcome, although modeling techniques predict high efficacy.

Ongoing Studies in Various Age Groups. Cervarix is currently being evaluated in phase III trials in the United States and other countries that involve women up to 55 years of age.^{7,23} Results from these trials are not yet available. In addition to the phase III data in **Table 2**, Gardasil is undergoing phase III investigations in girls and boys 10 to 15 years of age, women 16 to 45 years of age, and men 16 to 24 years of age.⁷

Duration of Immunity. The duration of vaccine protection is uncertain at present,

Table 1. Clinical Trials with Bivalent and Quadrivalent HPV Vaccines: Effect on Outcomes*

HPV Vaccine Type	Type of Study and Reference	Total Number of Subjects; Age (yr); Vaccine Doses	Duration of Follow-up	Prevention of Persistent Infection	Prevention of Cytologic Abnormalities or Other End Point
16,18	Phase II ²	1113; 15-25; 0, 1, 6 mo	Up to 27 mo	100% (ATP analysis) [†]	93% (ITT analysis) [†]
6,11,16,18	Phase II ⁴²	552; 16-23; 0, 2, 6 mo	2.5 yrs	89% (ATP analysis)	Other: 90% for primary end point (combined incidence of persistent infection with HPV 6, 11, 16, or 18, or cervical or genital lesions caused by the HPV types)
16,18	Phase III ⁷	18 000 (approx); 15-25; (Dosage not available)	Initial results unavailable		
6,11,16,18	Phase III ⁴¹	12 167; 16-23; 0, 2, 6 mo	2 yrs		CIN2-3: 100% (ATP analysis)
6,11,16,18	Phase III ⁷	5248; 16-23; 0, 2, 6 mo	1.5 yrs		CIN1 or worse: 100% (PP analysis); Other: 100% for genital warts, vulvar or vaginal neoplasia (PP analysis)

*All trials placebo-controlled; many are ongoing.

[†]Further follow-up of patients in this trial revealed sustained efficacy for up to 4.5 years.¹⁹

HPV indicates human papillomavirus; ATP, according-to-protocol; ITT, intention-to-treat; CIN, cervical intraepithelial neoplasia; PP, per protocol.

Table 2. ACIP Recommendations for the FDA-approved Quadrivalent HPV Vaccine in Women

HPV Types Covered	6,11,16,18 <ul style="list-style-type: none"> • 16 and 18: Most common high-risk types found in cervical cancer • 6 and 11: Most common low-risk types found in genital warts and respiratory tract warts
Optimum Time for Vaccination	Before onset of sexual activity
Recommended Age for Vaccination	11-12 yrs
Alternative Age Recommendations	Can begin as early as 9 yrs 13-26 yrs in women who have not been vaccinated or have not completed vaccination series
Vaccine Dose Schedule	3 doses at 0, 2, and 6 mo Dose: 0.5 mL intramuscularly May use at the same visit with other age-appropriate vaccines, such as Td, Tdap, MCV4, or hepatitis B vaccines
Cervical Screening	Screening recommendations have not changed in women receiving the vaccine (routine screening visits should continue after vaccination) Vaccine may be given if equivocal or abnormal Pap smear, a positive Hybrid Capture II high-risk test, or genital warts <ul style="list-style-type: none"> • However, the quadrivalent vaccine has not shown efficacy in pre-existing infection or HPV-related disease* • The vaccine would provide protection against HPV types not already acquired
Pregnancy and Breast-feeding Period	The quadrivalent vaccine can be given to lactating women, but not during pregnancy <ul style="list-style-type: none"> • No adverse sequelae have been observed in pregnancy, but data are limited • The vaccine pregnancy registry should be notified if exposure to the vaccine during pregnancy occurs (1-800-986-8999)
Immunocompromised Patients	The vaccine may be given, although immune response and clinical efficacy may be reduced
Concurrent Illness	Vaccine may be given to patients with minor acute illnesses, such as URI or diarrhea In patients with moderate-severe acute illness, the vaccine should be deferred until after the illness improves
History of Hypersensitivity	Avoid the vaccine in those with prior hypersensitivity to yeast or other vaccine components
Duration of Protection	Unclear, but studies suggest a duration of protection of at least 5 yrs (based on studies with 5-yr follow-up)
Thimerosal and Mercury Content in Vaccine	None
Adverse Effects	Mainly injection-site reactions, such as pain and erythema

*Some evidence of therapeutic responses has been observed.

ACIP indicates Advisory Committee on Immunization Practice; FDA, US Food and Drug Administration; HPV, human papillomavirus; Td, tetanus-diphtheria toxoids; Tdap, combined tetanus, diphtheria, and pertussis; MCV4, meningococcal conjugate vaccine; Pap, Papanicolaou; URI, upper respiratory infection.

Adapted from References 22 and 25.

and will be determined by long-term follow-up of vaccinated subjects. The longest duration of effective immunogenicity with Gardasil comes from published data of Harper and associates,¹⁹ who found significant protection against infection with HPV-16 and HPV-18 and associated cervical lesions for up to 4.5 years. Unpublished study data suggest duration vaccine protection of about 5 years for Gardasil.²²

There are no data at present regarding the efficacy or required frequency of booster doses, or even if boosters will be required. This is an important cost consideration. Antibody titers postvaccination have been higher than after natural infection, suggesting a potentially longer duration of protection compared with natural infection.^{2,8} However, 1 or 2 decades may be required to define the need for a clear booster interval; determination of therapeutic antibody titers, or if these even exist, is also needed. Both of these areas will likely be the focus of much debate, as seen with hepatitis B vaccine.

Cross-immunogenicity. There is evidence (published and unpublished) that Cervarix and Gardasil may confer some degree of cross-immunogenicity against HPV-31 and HPV-45, each of which has been associated with cervical cancer.^{1,19} This protection was not as complete as that against HPV-16 and HPV-18, and results of long-term studies are needed to clarify clinical significance (eg, whether this phenomenon will confer significant protection against precursor lesions). It is also unclear if cross-immunogenicity may occur against other HPV types.

Safety. All VLP HPV vaccines have been relatively well tolerated in clinical trials. Local reactions are by far the most common events compared with placebo, including injection-site pain, swelling, and erythema; in some studies, however, these effects were seen with similar frequency in the placebo group. Injection-site reactions have not compromised adherence with a full vaccine course.

Systemic adverse effects have generally been similar in placebo and vaccine groups. Headache and fever (usually low-grade) have

occurred more often than placebo in some studies. Urticaria and bronchospasm were reported rarely.

There are no data from available studies to suggest superior tolerability of one vaccine over another. Long-term safety of VLP-type vaccines against HPV will be determined in ongoing trials.

Recommendations of the Advisory Committee on Immunization Practices (ACIP).

In June 2006, the ACIP (convened by the Centers for Disease Control and Prevention [CDC]) recommended that FDA-approved Gardasil be administered to 11- and 12-year-old girls.^{22,24,25} The committee also indicated the vaccine could be started in girls as young as 9 years of age, and recommended catch-up vaccination in women 13 to 26 years of age who have not been previously vaccinated or have not completed the vaccination series. Use of the vaccine before onset of sexual activity was strongly advocated. ACIP recommendations require CDC approval.

Expansion of the age range in ACIP guidelines may occur based on results of ongoing studies with Gardasil in women older than 26 years of age. A summary of the current ACIP recommendations is found in Table 2.

Projected Impact and Cost-effectiveness of Vaccination Programs

Estimated healthcare costs incurred by cervical HPV disease are presented in Table 3. The lack of long-term trial data precludes actual assessment of the impact of HPV VLP vaccines on disease burden and their true cost-effectiveness. However, there is a general consensus—ranging from simple estimates based on what we know about HPV to complex mathematical models and cost-benefit analyses—that implementation of HPV vaccine programs with continuation of appropriate screening will significantly reduce the prevalence of precursor lesions and cervical cancer and will be significantly cost-effective.^{1,5,10,22,26-30} For example, considering only 90% type-specific efficacy for VLP HPV-16,18 vaccines, and that HPV-16 and HPV-18 account for approximately 70% of precursor lesions, it has been estimated that the short-term impact in the United States would be a 33% to 50% reduction in overall CIN2+ cases

Table 3. Estimated Annual Costs Associated with Cervical HPV-related Disease in the United States

Cost Level	Total Healthcare	Routine Screening	False + Pap Results	CIN1	CIN2-3	Cervical Cancer
Health Plan* (cost per 1000 enrollees)	\$26 415	\$16 746	\$2394	\$1142	\$3393	\$2629
US Population (extrapolated from above data; 2002 dollars)	\$3.4 billion†	\$2.1 billion†	\$300 million	\$150 million	\$450 million	\$350 million

*Based on data for female enrollees of the Kaiser Permanente Northwest health plan 1997-2002 (all ages), adjusted to 1-year period of 1998; not all expenditure-parameters are included.

†A figure of at least \$4 billion was estimated in another analysis for annual direct costs associated with anogenital warts and cervical disease¹¹; the total cost/year was expected to be higher if indirect costs (eg, work and productivity losses) were included.¹¹

*Other data suggest figures that ranged from \$2.3 billion to \$6 billion per year.^{11,14}

HPV indicates human papillomavirus; Pap, Papanicolaou; CIN, cervical intraepithelial neoplasia.

Adapted from Reference 10.

in vaccinated women (with a booster, if needed) compared with nonvaccinated women.¹ The reduction in the incidence of cervical cancer is similarly anticipated.

Using a computer-based decision analytic approach (Markov model), which incorporated the natural history of HPV, Goldie et al³⁰ found that use of an HPV-16,18 vaccine (with a conservative efficacy estimate of 70%-100%), in conjunction with current US cervical cancer screening programs, would result in a decrease of the lifetime risk of cervical cancer by 46% to 66% compared with current screening practices. This corresponds to a reduction in absolute lifetime risk from 0.86% to approximately 0.4%. The incremental cost-effectiveness ratio (ie, the additional cost of a strategy divided by its additional clinical benefit compared with the next most expensive strategy) in this setting ranged from \$20 600 per quality-adjusted life-year (QALY) to \$33 700 per QALY for vaccine efficacy rates ranging from 100% to 70%. Their model suggested that the optimal strategy was vaccination at 12 years of age, followed by triennial screening initiated at 25 years of age; this was projected to reduce the lifetime risk of cervical cancer by 94% relative to no intervention, and would correspond to an incremental cost-effectiveness ratio of less than \$60 000 per QALY. In general, a cost-effectiveness ratio of less than \$75 000 per QALY gained is considered a good value for resources in the United States (ie, a cost-effective intervention).

Data from Taira et al²⁸ suggested a similar estimated reduction in cervical cancer (62%) by vaccination of 12-year-old girls with VLP HPV-16,18. These investigators used disease transmission models for HPV-16 and HPV-18, which estimated HPV prevalence in the US population as a whole and by age, sex, and level of sexual activity. A booster every 10 years was assumed. This reduced risk was associated with a cost-effectiveness ratio of \$14 583. In contrast, including men in a vaccination program was found not to be cost-effective when compared with vaccination only in women in this model.²⁸

Some Issues in Implementation of Vaccine Programs

Based on studies of successful implementation of vaccines, it is clear that introduction of an HPV vaccine must be country-driven and well planned, with full support and involvement of policymakers, parents, district and hospital managers, medical personnel, and community groups.^{8,14} Strong and effective public education programs, easy access to the vaccine, clear vaccination populations and protocols, low-cost services, health system linkages, information services, well-trained providers, adequate insurance coverage, school vaccination requirements, strong infrastructure (for storage and dissemination of the vaccine supplied via federal sources to the non-insured or underinsured), and quality

control mechanisms have been identified as key elements for success.^{1,8,31,32}

Specific Targeted Populations

Young Girls. Infection with HPV is highly prevalent in the United States. More than half of men and women in the United States will be infected during their lifetime, with most infections occurring in the teens and early 20s; most women acquiring infection will contract HPV shortly after becoming sexually active.^{22-24,33} CDC data indicate that approximately a quarter of all girls in the United States have had sexual intercourse before the ninth grade; high rates of HPV infection also accumulate in women during college years.⁷ Thus, the ideal time for vaccine administration is before the onset of sexual activity, with the most apparent population being preteens, which is consistent with ACIP recommendations. As previously indicated, immunogenic responses are greater in young girls compared with older women.

Should Men Be Vaccinated? Whether men should receive HPV vaccination is controversial. Vaccine-induced immunogenicity in men is similar to that in women, and there are indirect benefits to women with male vaccination.^{1,22} However, clinical outcome data in men are lacking. Anogenital cancer is relatively rare in American men, with the exception of human immunodeficiency virus infection and men who have sex with men, which limits efficacy evaluation.²⁰ The role of Gardasil in preventing genital warts in men will need to be addressed. Clinical efficacy studies in men are ongoing, but the absence of these data at present emphasizes a focus on women.

Underserved and "Hidden" Populations. Vaccination of these groups should be a focus of US vaccine implementation efforts; examples of this include prisons and other correctional facilities, sexually transmitted disease clinics, lower socioeconomic areas with limited access to medical care, and emergency rooms and walk-in clinics. Although beyond the scope of this article, implementation of vaccination programs in developing countries with limited screening capabilities is a complex but high priority.

Public, Parental, and Patient Acceptance. Lack of knowledge about HPV infection and its sequelae, and concerns regarding vaccine safety, are key barriers to vaccine acceptance.³⁴

Education Is Mandatory. A clearly focused public and patient education program is mandatory for acceptance,^{14,34} which would present the risk of cervical cancer with HPV, a sensitive portrayal of the sexual link (that is particularly important in preteens and teens), and benefits of an HPV vaccine. Educational efforts must be consistent, using terminology appropriate to the audience, and should be supplied through various sources. Many are under way and include television health announcements, articles in young women's magazines, and pharmaceutical company "direct-to-consumer" advertising. Health education efforts in elementary, middle, and high schools would also be beneficial.

Some awareness is already apparent, as evidenced by results of a recent online *Wall Street Journal*/Harris Interactive Health Care Poll, demonstrating that about half of those polled had knowledge of the HPV vaccine, and 70% favored vaccination in teenage girls and women.³⁵

Health Professional Advocacy. Promotion by physicians, nurses, and other health professionals in the community sends a strong message. In one US study involving adolescents and adults, physician advocacy was one of the most important factors leading to a decision to be vaccinated.⁸

Gathering the support of national medical associations can also play an important role in facilitating vaccine implementation. A published survey of Fellows of the American College of Obstetricians and Gynecologists indicated the willingness of gynecologists to use the vaccine in their office practice.³⁶

Continuing education programs for practicing physicians that are directed at enhancing knowledge of HPV and HPV vaccines would likely have a positive effect on vaccine usage, as well as advocacy. Inclusion of HPV-related education in medical-school curricula might elicit a persistent impact on physician attitudes toward vaccination in the future.

Safety Concerns. Further determination of vaccine safety will play a major role in acceptance and the ultimate impact of vaccination programs. Judicious and responsible media handling of safety results from ongoing trials will be important, especially if any serious or life-threatening sequelae are seen with similar frequency in placebo groups, or if preventable/treatable underlying or background factors are contributory or causal. In the United Kingdom, negative reporting of the media in regard to pertussis vaccination led to a decline in the vaccination rate by 50% from 1974 to 1976, resulting in a significant increase in rates of pertussis.⁸

Vaccine Efficacy Issues. As mentioned, the duration of effective immunity will be an important issue with respect to the need for boosters. The potential for what has been termed “cross protection” against HPV strains not in the vaccine is also an area requiring additional study. Each of these has potential cost implications.

Preliminary data suggest that HPV VLP vaccines in women with pre-existent infection with vaccine-oncogenic types of HPV may prove beneficial. Limited studies have reported a significant antibody response to the HPV-6,11,16,18 L1 VLP vaccine and the HPV-16 L1 VLP vaccine in women with vaccine-type antibodies at baseline; levels were higher and more persistent compared with baseline HPV naïve women.¹⁶ Whether a therapeutic effect of HPV vaccines is possible, and whether this might consistently protect against persistent infection and cervical pathology in women who already have HPV infection, will be resolved only by results of ongoing long-term trials. Present data from the manufacturer of Gardasil indicate that the vaccine is not therapeutic.¹⁸

Other vaccines with intended therapeutic effects are under investigation. These vaccines are designed to target E6 and E7 oncoproteins (encoded by HPV genes and expressed in cervical cancers), such as the E7-chimeric VLP vaccine, which may have prophylactic and therapeutic application.^{14,15}

Infection with all HPV types with Gardasil is rare. To a lesser extent, the same can be said of Cervarix. Clinicians should be aware

that women would also gain protection from vaccine types they have not acquired.²² The vaccines appear safe in women who have 1 or more HPV types in the vaccine at baseline.

Vaccine Access: Payment Issues and Employer Views

Insurers and Sponsors. Widespread vaccine availability is central to implementation of the HPV vaccine in the United States. The relatively high cost of the now-marketed Gardasil (\$119.75/dose or approximately \$360 for the full series) may in itself present a barrier to implementation, because insurance coverage is not guaranteed.^{22,37} However, history suggests that most federal and private insurers cover vaccines recommended by the ACIP and/or CDC.^{22,23,31,33} Ultimately, individual states will determine whether insurance coverage should be mandated for HPV vaccination.³¹

California already requires insurers to cover the vaccination of individuals in age groups recommended by the ACIP; as of September 28, 2006, California also requires insurers to cover costs for HPV testing during cervical cancer screening.^{31,38} Similar mandates for HPV testing have been made in New Mexico, Maryland, West Virginia, and Texas.³⁸ States will also determine if HPV vaccination will be required for school entrance.^{23,31}

For low-income individuals younger than 19 years of age, and those who are uninsured, underinsured, American Indian, Medicaid-eligible, or Alaskan Native, the Vaccines for Children (VFC) program will provide free vaccinations.^{22,33} VFC vaccines can be obtained through hospitals, public clinics, and federally qualified or rural health centers.^{22,31} For women who are too old for the VFC program, uninsured, or younger than 26 years of age, free vaccinations may be obtained via a program sponsored by the manufacturer of Gardasil. Many states may also offer free vaccinations under the federal 317 grant program or through public health department clinics, or states may consider Medicaid coverage requirements.

Employers. Most large US employers will cover insurer-approved vaccines recom-

mended by the ACIP. This includes coverage for childhood and adult immunizations. However, vaccines that fall outside ACIP recommendations, or those used for travel prophylaxis, are often not included. As more employers look at prevention and keeping employees healthy, there is a swing toward broad benefits coverage for immunizations.

A vaccine to prevent cervical cancer is certainly of interest to most employers. By preventing the onset of a chronic and potentially deadly disease, costs of medical care could potentially be defrayed by this preventive measure. Although the current recommendation for cervical cancer vaccines is for women from 9 years to 26 years of age, studies are still being conducted to determine the optimum window of opportunity for this immunization. But, as the current age range touches on young women entering the workforce, a large portion of the targeted population will be dependents. Because more employers view themselves in the role of population health management for employees and their dependents, it is reasonable to assume they will be supportive of covering a vaccine to prevent cervical cancer for its current workforce as well as future workers.

It is hopeful that employers will disseminate information on the HPV vaccine in some of the preventive care media used to engage employees in taking better care of themselves. It will be important information to include in education about women's health issues. Most employers are making a concerted effort to help employees gain access to this type of information. With more employers moving toward consumer-directed plans, education on the importance of the HPV vaccine for cervical cancer prevention will be needed. Easily understandable information that can be made available to employees and their dependents through employer healthcare communications will be particularly important in adoption of the vaccine by adolescents and young women.

Impact on Cervical Screening. Because HPV vaccines do not protect against all HPV types, women receiving the vaccine should continue to undergo routine Pap-based

screening.^{1,8,22,24,33} In addition, some women may not achieve full vaccine effects if there is pre-existent infection or if they fail to receive all 3 vaccine doses.²²

There is concern that introduction of an effective HPV vaccine would result in a significant reduction in adherence with Pap-screening programs, with the risk of an actual rise in cases of cervical cancer.¹⁴ Perhaps the most exigent need in the United States is a public health policy directed at timely vaccination in conjunction with prescheduled screening times to detect and treat cervical lesions.⁷ An HPV DNA test and liquid-cytology test are available for use during screening.²²

The belief that HPV vaccination will increase the risk of sexual promiscuity or risky sexual behavior¹⁴ does not appear likely to manifest.^{39,40} Parents have generally indicated that this is not the most important issue. However, because the vaccine will not protect against all types of HPV, all genital warts, or other sexually transmitted diseases, education for all vaccine-approved age groups that stresses the need for continuous practice of protective sexual behavior is encouraged.

Conclusion

Bivalent and quadrivalent HPV vaccines offer realistic hope of reducing the risk of cervical neoplasia and the prevalence of cervical cancer worldwide. These vaccines have demonstrated significant efficacy in preventing persistent infection and cervical lesions associated with their specific targeted HPV types, and they are cost-effective. However, successful implementation of an effective vaccination program in the United States will require a coordinated effort of insurers, employers, hospitals, healthcare professionals, parents, and community groups. Highly focused educational programs will be paramount, including emphasis on the need for continued cervical screening. Many unanswered questions remain about HPV vaccines that will impact acceptance and implementation of US vaccine programs, such as their actual ability to impart a meaningful reduction in the occurrence of cervical cancer, duration of vaccine protection, need for boosters, vaccine safety, and effica-

cy and use in men. Answers to these questions should emerge from ongoing clinical trials.

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