Human Papillomavirus Vaccines

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OBJECTIVE: To review the pharmacology, efficacy, safety, tolerability, and pharmacoeconomics of Cervarix and Gardasil, 2 human papillomavirus (HPV) vaccines.

DATA SOURCES: English-language articles were obtained by MEDLINE search (1966–February 2006) using the key words human papillomavirus vaccine, Cervarix, and Gardasil. Bibliographies of selected articles were used to identify additional sources.

STUDY SELECTION AND DATA EXTRACTION: All available published articles or abstracts reporting the results of human studies of HPV vaccines were reviewed for inclusion in this article. Additional information about ongoing clinical trials was obtained from manufacturers' Web sites.

DATA SYNTHESIS: Cervarix and Gardasil are recombinant vaccines against HPV. Cervarix targets HPV-16 and -18, which are responsible for 70% of cervical cancers. Gardasil also targets HPV-16 and -18, plus the HPV-6 and -11 types responsible for more than 80% of genital warts. Both vaccines have been effective in preventing persistent infection with targeted HPV types and in preventing cervical intraepithelial lesions, while Gardasil has also been effective in preventing vulvar and vaginal neoplasia and genital warts. Both vaccines have been well tolerated, with the most common adverse effects occurring at the injection site. Phase III trials are ongoing to further evaluate vaccine efficacy.

CONCLUSIONS: Cervarix and Gardasil are effective for prevention of HPV infection and cervical lesions. Issues remaining to be addressed include duration of protection, efficacy for prevention of cervical cancer, optimal age for vaccination, feasibility of application to the developing world, the ideal combination of HPV subtypes, and the most efficient combination of vaccination and cervical cancer screening.

KEY WORDS: Cervarix, Gardasil, human papillomavirus vaccine.

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Genital human papillomavirus (HPV) infection is the most common sexually transmitted disease in the US. It is estimated that approximately 20 million Americans are infected with HPV, with as many as 6.2 million new cases occurring annually.[1] Epidemiologic studies have reported that 75% of all sexually active men and women will develop HPV infection during their lifetimes, with peak prevalence occurring from adolescence through age 29.[2,3] More than 40 types of HPV infect the human genital tract and are associated with cancers, condylomata acuminate (genital warts), and other intraepithelial lesions.[4]

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Cervical cancer is unique among human cancers in that an etiologic agent is firmly established: oncogenic types of HPV establish persistent infections in the cervical epithelium, leading to dysplastic lesions and invasive carcinoma.[5] An odds ratio of 158 is estimated for the association between HPV infection and cervical cancer in case–control studies.[4] HPV-16 and -18 are responsible for about 70% of cervical cancer cases in the US; worldwide, the figure ranges from about 64% in Subsaharan Africa to about 74% in Asia.[4,6] HPV types 31, 33, 45, 52, and 58 account for another 15–23% of cases, depending on region.[6,7] While anal and penile cancers are much rarer than cervical cancer, with an incidence in the US of 2.5 and 1.5 cases per

100 000 population, respectively, oncogenic HPV types are associated with 80–90% of these cancers as well.[8,9] Some HPV types are low risk for cancer but cause genital warts, which occur in approximately 1% of sexually active adults.[2] The low-risk types HPV-6 and -11 are associated with more than 80% of genital warts.[10] Many HPV infections are transient and, for those that become persistent, the outcome depends heavily on the type of HPV involved.[5]

Globally, 470 000 new cases of cervical cancer occur annually, with 80% occurring in women in developing nations, and cervical cancer kills an estimated 230 000 women each year worldwide.[11] In contrast, in the US about 10 000 new cases of cervical cancer were expected to occur in 2005, and about 3700 women were expected to die of the disease.[12] The disparity in morbidity and mortality between developed and developing nations is largely attributable to screening for cervical lesions by the Papanicolaou (Pap) method. It is estimated that more than 50 million Pap smears are done each year in the US alone.[13] In countries where routine Pap smears are economically impossible for most women, a means to prevent cervical cancer by preventing HPV infection could spare thousands of lives. In the developed world, prevention of HPV infection may also spare some of the economic and emotional costs that accompany detection and treatment of cervical lesions.

This article reviews data for 2 vaccines designed to prevent HPV infection. Cervarix is a bivalent vaccine targeting HPV-16 and -18 that is currently in Phase III clinical trials. Gardasil is a quadrivalent vaccine targeting HPV-6, -11, -16, and -18 that was approved in June 2006 by the Food and Drug Administration (FDA) for the prevention of cervical cancer, genital warts, and certain precancerous lesions in females aged 9–26 years.

Data Sources

Literature citations were obtained by a MEDLINE search (1966–February 2006) of English-language articles, using the key words human papillomavirus vaccine, Cervarix, and Gardasil. The bibliographies of these articles were reviewed to determine other relevant citations. Information about the design of ongoing clinical trials was obtained from meeting abstracts and manufacturers' Web sites.

Natural History of Human Papillomavirus Infection

HPV is a double-stranded DNA virus that infects keratinocytes in the cervical epithelium.[14,15] The virus encodes several proteins (eg, E4, E6, E7) that appear to be involved in regulating viral replication, gene expression, and host immune response. Other viral proteins (L1, L2) make up the capsid that encloses the circular viral chromosome. HPV enters keratinocytes in the suprabasal layer of squamous epithelium. As infected cells reach the upper layers of the epithelium, HPV capsid proteins are produced, virions assemble, and infectious virus is released.[15] The rate of spontaneous resolution of HPV infections is high, demonstrating that the human immune system can mount an effective response. However, HPV can thwart this response, leading to persistent infections.[14]

HPV-infected cells become dysplastic when they escape cell cycle regulation. Viral proteins E6 and E7 have been implicated in this transformation. E6 is thought to speed turnover of the key tumor suppressor protein p53, while E7 has been implicated in blocking the function of the retinoblastoma tumor suppressor protein.[16]

The progression from persistent HPV infection to cervical cancer follows a predictable pattern of histologic changes. Low-grade squamous intraepithelial lesions are HPV-related dysplasias (including low-grade cervical intraepithelial neoplasia [CIN1]), which often regress spontaneously.[17] Within a year or two of infection with an oncogenic HPV type, high-grade squamous intraepithelial lesions (HSIL) may occur, which include those lesions classified as CIN2 and CIN3/cancer in situ.[10,17,18] Eventually, invasive cervical cancer may develop. Generally, women are treated when HSIL is discovered because current diagnostic tools cannot determine which lesions will progress to invasive cancer.[17]

Vaccine Design

The outer capsid of HPV is an icosahedron composed primarily of several hundred copies of the viral protein L1.[15] Purified recombinant L1 protein self-assembles into virus-like particles (VLPs), which are empty icosahedral shells virtually indistinguishable from native HPV virions by electron microscopy.[19-21] L1 VLPs lack viral DNA and, as such, are noninfectious. Recombinant L1 protein cross-reacts with antibodies to native HPV in a type-specific manner.[22]

HPV vaccine development has been hindered by inability to produce large quantities of virus; HPV neither grows readily in tissue culture nor infects nonhuman species. The relatively easy production of VLPs, therefore, makes them attractive candidates for vaccine development. Experiments conducted in the mid-1990s demonstrated that vaccination of rabbits or dogs with species-specific VLPs produced high titers of antibodies and protected against papillomavirus infection.[23,24]

Both Cervarix and Gardasil are VLP-based. Cervarix vaccine includes 2 types of VLPs assembled from recombinant HPV-16 and -18 L1. The L1 protein is produced using a baculovirus/insect cell expression system.[25] Gardasil vaccine consists of 4 types of VLPs assembled from recombinant HPV-6, -11, -16, and -18 L1 protein expressed in the yeast *Saccharomyces cerevisiae*.[26]

The adjuvant included in these vaccines differs. Gardasil vaccine contains amorphous aluminum hydroxyphosphate sulfate,[26] while Cervarix vaccine utilizes AS04, which is composed of aluminum hydroxide and 3-deacylated monophosphoryl lipid A.[25] AS04 is a novel adjuvant reported to produce higher and persistent antibody titers, which may result in an enhanced immune response.[27]

Clinical Trials

PHASE I

The first human studies of VLP-based vaccines involved the nononcogenic type HPV-11,[28,29] but interest soon shifted to the oncogenic HPV types. One early randomized, placebo-controlled, double-blind trial used VLPs from HPV-16 to vaccinate healthy subjects.[30] Antibody titer peaked after the third vaccination of the series, and the majority of vaccinated subjects achieved an HPV-16 antibody titer approximately 40 times higher than the initial titer observed in 6 subjects who had been naturally exposed to HPV-16.

Research groups associated with the development of quadrivalent HPV vaccine have conducted Phase I studies on VLP vaccines for HPV-11, -16, and -18 with similar results.[31,32] Vaccination with HPV-18 VLP vaccine at 0, 2, and 6 months resulted in a high antibody titer by 7 months, with peak titer approximately 60 times higher than that observed with natural exposure to HPV-18.[32] Vaccination with HPV-11 or -16 vaccine at months 0, 2, and 6 resulted in high titers of HPV-11 antibodies by month 7 in 100% of subjects and high titers of HPV-16 antibodies in 85% of subjects.[31] Antibodies continued to be detectable at month 36, and titers typically remained higher in vaccinated women than in women naturally exposed to HPV.

Although these Phase I studies of HPV-11 and HPV-16 were not designed to evaluate efficacy, investigators conducted a post hoc analysis of the rates of HPV-16 infection.[33] Among the 129 participants who either received placebo in the HPV-16 trial or were enrolled in any arm of the HPV-11 trial, there were 15 new cases of HPV-16 detected by polymerase chain reaction (PCR), representing 5 cases per 100 person-years at risk. Among the 66 participants who received HPV-16 vaccine, there were no new cases of HPV-16 detected by PCR during the 36 months of follow-up, suggesting that HPV-16 vaccine was protective against new HPV-16 infection.

PHASE II

Vaccine efficacy, as determined by Phase II clinical trials, is summarized in Table 1. The earliest Phase II trial of an HPV VLP vaccine was published in 2002 by a group associated with the development of quadrivalent vaccine. The findings offered the first strong evidence that VLP-based vaccine could offer protection against persistent HPV-16 infection and, therefore, potentially reduce cervical lesions and cervical cancer.

This multicenter, randomized, placebo-controlled, double-blind trial enrolled 2392 women during the late 1990s.[34] Women were accepted into the trial if they were 16–23 years old, had had no more than 5 male sex partners, and had never had an abnormal Pap smear. Participants received HPV-16 vaccine or placebo at months 0, 2, and 6. The primary endpoint was persistent infection with HPV-16 occurring after month 7 of the study. Persistent infection was defined as HPV-16 infection detected on 2 visits at least 4 months apart or at the last visit, or HPV-16–associated CIN or cervical cancer demonstrated by biopsy. Women were excluded from analysis of the primary endpoint if they demonstrated HPV-16 infection detectable by PCR at enrollment or prior to month 7, if they withdrew from the study before month 7, or if they had a protocol violation, such as incorrect vaccine or incorrect timing of visits.

A total of 768 women in the vaccine group and 765 women in the placebo group were analyzed for the primary endpoint; median follow-up after the final vaccination was 17.4 months. Forty-one primary endpoint events were detected after month 7 of the study, including 31 persistent HPV-16 infections, 5 cases of HPV-16–related CIN1, 4 cases of HPV-16–related CIN2, and 1 case of positive HPV-16 DNA at the last visit prior to being lost to follow-up. All of these events occurred in the placebo group, leading to an incidence of primary events of 3.8 per 100 woman-years at risk. There were no events in the vaccine group. The calculated efficacy was 100% (Table 1).[34]

The duration of antibody response was further confirmed for HPV-16 vaccine in a Phase IIa dose-ranging study in 480 women.[35] All doses of vaccine tested resulted in antibody titers 38–76 times higher than those observed in women after natural HPV-16 infection. Titers more than doubled after the third dose in most participants and, while titers waned during the 24 month study period, at the end of the trial they remained above levels seen in women who have been naturally infected with HPV-16.

In 2004, the first Phase II study was published by researchers associated with the development of a bivalent VLP vaccine against HPV-16 and HPV-18.[25] This double-blind, randomized, placebo-controlled trial enrolled 1113 women between the ages of 15 and 25 years. Exclusion criteria included history of abnormal Pap smear or treatment of cervical lesions, more than 6 sexual partners, or current treatment for genital warts. Subjects were accepted only if they had tested as seronegative for HPV-16 and -18 and DNA-negative for oncogenic HPV types within 90 days prior to enrollment. Five hundred sixty subjects were randomized to receive bivalent HPV-16, -18 VLP vaccine at 0, 1, and 6 months; 553 were randomized to receive placebo at those timepoints.

The investigators carried out both intent-to-treat (ITT) and according-to-protocol (ATP) analyses. Women excluded from the ATP analysis included those who had cervical lesions, were HPV-16 or -18 seropositive or DNA positive for oncogenic HPV at the start of the study, became PCR positive for HPV-16 or -18 before study month 6, were nonadherent to the vaccine schedule or other protocols or had missing laboratory results, or dropped out of the study before month 18. Included in the ATP analysis were 366 women in the vaccine group and 355 in the placebo group.[25]

The primary efficacy endpoint was prevention of incident HPV-16 and -18 infection between study months 6 and 27. In the ATP group, the rate of infection with HPV-16 or -18 was 1.8% in the vaccine group and 6.6% in the placebo group, resulting in a combined efficacy of 73.6%. The analogous efficacy in the ITT group was 67.6%. When only persistent infection with HPV-16 or -18 was considered, detected on 2 separate visits at least 6 months apart, there were no cases in the vaccine group in the ATP analysis and 16 cases in the placebo group, leading to an efficacy estimate of 100%. The comparable result in the ITT analysis was an efficacy of 87.5%. Secondary endpoints in the study of bivalent vaccine included incidence of cytologic and histologic abnormalities. Twenty-seven women in the placebo group and 2 women in the vaccine group developed cytologic abnormalities associated with HPV-16 or -18. Six women in the placebo group developed histologically confirmed CIN1 or CIN2. Only 1 woman in the vaccine group developed a CIN1 lesion, and it was found to contain HPV-51 by biopsy.[25]

The first published clinical trial of a quadrivalent VLP vaccine against HPV-6, -11, -16, and -18 appeared in 2005.[26] HPV-6 and -11 were included in the expectation that this vaccine may protect against genital warts as well as cervical lesions. In this randomized, double-blind trial, 277 women aged 16–23 years were assigned to receive vaccine and 275 were assigned to receive placebo. Women were enrolled if they had never had an abnormal Pap smear and had had no more than 4 male sex partners. Par-

Table 1. Efficacy of HPV VLP Vaccines in Clinical Trials

Trial	Incident HPV Infection, % (95% CI)	Persistent HPV Infection, % (95% CI)	Cytologic Abnormalities, % (95% CI)	Other Endpoints, % (95% CI)
Phase II				
HPV-16[34]		100 (90 to 100) p < 0.001		
HPV-16,-18[25]				
ATP analysis	73.6 (49.7 to 86.1) p < 0.0001	100 (76.8 to 100) p < 0.0001	93.5 (51.3 to 99.1) p = 0.0002 (ASCUS/LSIL/HSIL)	
ITT analysis	67.6 (48.9 to 79.4) p < 0.0001	87.5 (64.6 to 95.6) p < 0.0001		
HPV-6,-11,-16,-18[26]				
ATP analysis		89 (70 to 97) p < 0.0001		
MITT analysis		88 (72 to 96) p < 0.0001		
Phase III				
HPV-6,-11,-16,-18[39]				
ATP analysis			100 (76 to 100) p < 0.001 (CIN2/3)	
MITT analysis			97 (83 to 100) p < 0.001 (CIN2/3)	
HPV-6,-11,-16,-18[40]				
PP analysis			100 (87 to 100)[a] p < 0.001 (CIN or worse)	100 (88 to 100)[a] p < 0.001 (genital warts,vulvar/ vaginal neoplasia)
MITT analysis			97 (87 to 100) p = NR (CIN or worse)	95 (84 to 99) p = NR (genital warts, vulvar/ vaginal neoplasia)

ASCUS = atypical squamous cells of undetermined significance; ATP = according-to-protocol; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesions; ITT = intent-to-treat; LSIL = low-grade squamous intraepithelial lesions; MITT = modified intent-to-treat; NR = not reported; PP = per protocol; VLP = virus-like particle.
[a]For the PP analysis, a 97.5% confidence interval was used.

ticipants received the study drug at months 0, 2, and 6. The primary outcome was a combined endpoint of persistent infection with HPV-6, -11, -16, or -18, or cervical lesions or genital warts detected at 7 months after vaccination. Diagnosis of persistent infection required detection of HPV DNA at 7 months after vaccination plus at 2 more study visits at least 4 months apart or at last study visit.

Investigators conducted a modified intent-to-treat (MITT) analysis excluding women seropositive to HPV-6, -11, -16, or -18 at enrollment or with detection of HPV DNA from these types before the end of the vaccination period. Investigators also performed an ATP analysis, in which women were excluded for the above reasons and also for protocol violations, such as incomplete or incorrect vaccination. Seventy-three percent of participants were included in the ATP efficacy analysis for HPV-16, 83% for HPV-18, and 78% for HPV-6 and -11. The ATP analysis revealed 36 primary endpoint events in the placebo group and 4 in the vaccine group, leading to an efficacy estimate of 90% (95% CI 71 to 97; $p < 0.0001$) for the combined primary endpoint. HPV-16 DNA was found in 3 women in the vaccine group at last study visit; 1 woman had persistent HPV-18 infection. Vaccine efficacy calculated from the MITT analysis was 89% (95% CI 73 to 96; $p < 0.0001$) for the combined primary endpoint.[26]

These trials had similar limitations. Because they were designed to detect prevention of HPV infection, none was powered to determine efficacy in prevention of cervical lesions, nor was study duration sufficient to determine prevention of cervical cancer. Published trials have not examined whether the vaccine might afford protection against development of cervical lesions in women already persistently infected with oncogenic HPV. Efficacy estimates have been higher with ATP analyses, but the number of subjects excluded from these analyses has been large. Thus far, only 1 or 2 oncogenic HPV subtypes per vaccine have been tested, while a vaccine expected to prevent 90% of cervical cancer would need to include 7 or more oncogenic subtypes. Finally, comparison of efficacy between vaccines is difficult, given the differing endpoints evaluated in each trial.

PHASE III

Phase III clinical trials are underway for both bivalent and quadrivalent HPV vaccines. Cervarix is being tested in approximately 18 000 women aged 15–25 years in the US, South America, Europe, and Asia.[36] The National Cancer Institute is sponsoring a second 8 year trial in 12 000–15 000 Costa Rican women aged 18–25 years.[37] Gardasil is being tested in more than 25 000 people worldwide.[38] Trials include about 17 800 women aged 16–26 years, 3800 women aged 24–45 years, 3700 men aged 16–24 years, as well as about 1000 girls and boys aged 10–15 years.[36,38]

Interim results from Future II, an ongoing Phase III trial for Gardasil, have confirmed efficacy reported in Phase II trials (Table 1). This multicenter, double-blind, randomized, placebo-controlled trial enrolled 12 167 women aged 16–23 years.[39] Subjects received quadrivalent HPV-6, -11, -16, and -18 VLP vaccine or placebo, administered at 0, 2, and 6 months, and were followed for an average of 2 years. The investigators carried out ATP (n = 10 559) and MITT (n = 11 502) analyses. The ATP analysis included women who received all study injections, were without major protocol violations, and were seronegative and DNA negative for HPV-16 and -18 on day 1 and day 1 through month 7, respectively. The MITT analysis included subjects who received at least one injection and were without HPV-16 and -18 infections on day 1. In the ATP analysis, no subjects in the vaccine group were diagnosed with high-grade cervical lesions or carcinoma in situ compared with 21 subjects in the placebo group, resulting in 100% efficacy. Efficacy for the MITT analysis was similar at 97%.

Future I investigators published initial results of a Phase III trial that evaluated the impact of quadrivalent HPV-6, -11, -16, and -18 vaccine on anogenital cancers/high-grade precancers, low-grade dysplastic lesions, and external genital warts over 18 months (Table 1).[40] Women aged 16–23 years were randomly assigned to receive vaccine (n = 2620) or placebo (n = 2628) at months 0, 2, and 6. Per protocol (PP) analysis (women who received all doses, had no major protocol violations, and were seronegative at day 1 and DNA negative day 1 to month 7 for HPV-6, -11, -16, or -18) and MITT analysis (women who received at least one dose and were negative at day 1 for HPV-6, -11, -16, or -18) were reported. In the PP analysis, 100% efficacy was reported when vaccinated subjects were compared with placebo subjects for CIN or worse and for genital warts and vulvar/vaginal neoplasia. Comparable efficacy in the MITT analysis was 97% and 95%, respectively.

Limitations to these trials include exclusion of significant numbers of patients from the MITT analyses and lack of long-term data. Each trial has been published only in abstract form. Gardasil may be an attractive option for prevention of genital warts in young men, but the single trial published does not include males.

It is anticipated that the manufacturers of Cervarix may file for regulatory approval during 2006.[41] The manufacturers of Gardasil received FDA approval in June of 2006 to market the vaccine for use in females 9 to 26 years of age for prevention of cervical cancer, genital warts, and certain precancerous lesions.[42] To date, the supporting Phase III trials have not been published.

Dosage and Administration

In clinical trials, Cervarix and Gardasil vaccines were administered as 0.5 mL intramuscular injections at day 1

and months 1 and 6 and at day 1 and months 2 and 6, respectively.[25,26] Antibody titers have typically peaked after the third injection and remained elevated throughout study periods that have extended as long as 36 months.[30-32,35] Further studies are needed to determine whether protection against HPV is long-lasting or whether booster vaccinations will be needed. Although no clear contraindications to the HPV vaccine are currently known from published studies, one that may be anticipated is allergy to any vaccine component.

Safety and Tolerability

In published clinical trials, VLP vaccines against HPV appear to be safe and generally well tolerated, although long-term data are not currently available.[25,26,28-33,35] Table 2 lists the most common, as well as any serious, adverse events reported. The most common adverse event is local injection site reaction, with a majority of recipients of both vaccine and placebo experiencing pain at the injection site. In most trials, erythema and swelling at the injection site are more frequently associated with vaccine than with placebo. The most frequent systemic adverse event has been headache. Two cases of urticaria have been reported in subjects receiving vaccine, necessitating termination of study injections.

Pharmacoeconomic and Social Issues

As Phase III clinical trials address some remaining scientific questions about HPV vaccines, various social and economic issues will come to the fore. In the developed world, one of the most pressing matters will be implementation of a public health policy for cervical cancer prevention combining timely vaccination with appropriately spaced screening for cervical lesions.

Women become infected with HPV soon after they become sexually active. A recent study examined the incidence of HPV infection in college women who tested negative for HPV at study enrollment.[43] After 5 years, 60% of the women had become infected with HPV; 40% became infected within 2 years of their first sexual intercourse experience. According to the Centers for Disease Control and Prevention, approximately 28% of girls in the US have had sexual intercourse by the 9th grade and 7% by the age of 13.[44] These figures suggest that, to maximize protection against HPV and cervical cancer, the optimal time for vaccination is during the preteen years. In a recent survey of gynecologists, however, resistance was noted to vaccinating 13 year olds against HPV,[45] and parental choice is likely to be an issue in any discussion of universal HPV vaccination.

Another challenge will be finding an acceptable balance between vaccination and screening for cervical lesions. Two pharmacoeconomic studies have addressed this question for vaccines targeting HPV-16 and -18. The first study predicted a favorable balance between cancer incidence and incremental cost effectiveness for a program of vaccination at age 12 plus screening every 2 years, starting at age 24.[46] The cost-effectiveness calculations were highly sensitive to age at vaccination. The second analysis predicted that a program of vaccination at 12 years of age plus screening every 3 years, starting at age 25, would be the most effective in preventing cervical cancer among all plans that offered a cost effectiveness of less than $60 000 per quality-adjusted-year of life saved.[47]

Regarding the developing world, discussion is centered on optimal design of future vaccines and challenges of vaccine availability. HPV-16 and -18 account for about 64–74% of cervical cancer in the developing world.[6] The remaining cases are accounted for by differing HPV types from region to region, and debate is expected regarding which types to include in the next generation of vaccines. It has been suggested that a vaccine against the 7 most common oncogenic types (16, 18, 31, 33, 45, 52, 58) would be appropriate to prevent about 87% of cervical cancer with little variation from region to region.[6] Even if a vaccine with ideal coverage can be devised, any vaccination plan for developing nations will face barriers posed by cost, the likely requirement for refrigeration, and the need for a series of 3 injections. There will also be variation among differing cultures regarding the acceptability of and preferred timing for vaccination.

Summary

Published clinical trials have demonstrated nearly 100% efficacy of bivalent and quadrivalent HPV vaccines in preventing persistent HPV infection and cervical lesions. Quadrivalent vaccine is also effective for prevention of vulvar and vaginal neoplasia and genital warts. Both vaccines have been well tolerated. Results of ongoing Phase III trials are needed before efficacy against cervical cancer can be assessed. Other issues remaining to be addressed include duration of protection and long-term safety. The healthcare community will need to answer several questions as these vaccines are introduced, including determination of the optimal age for vaccination and the optimal program for screening for cervical lesions. Developing nations will face further obstacles, but if vaccination programs are successful, the worldwide burden of cervical cancer may be greatly reduced.

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Table 2. Safety and Tolerability of HPV VLP Vaccines in Published Trials

Vaccine, Sponsor	Subjects (n)	ADEs	vaccine, %	placebo, %
HPV-11,[29] MedImmune	49 vaccine 16 placebo 44 vaccine and 15 placebo subjects received full course	pain within 4 days of injection headache within 4 days of injection itching or rash urticaria	73 31 8 (n = 4) 2 (n = 1)	70 4 6 (n = 1)
HPV-16,[30] National Institutes of Health	60 vaccine 12 placebo 58 vaccine and 10 placebo subjects received full course	reaction within 1 wk of injection pain erythema induration headache transient transaminase elevation	 23.3–93.3 (depending on dose or adjuvant) 0– 16.7 3.3–16.7 6.7–16.7 2 (n = 1)	 22.9 2.9 2.9 5.7
HPV-11,[31,33] Merck	112 vaccine 28 placebo 24 subjects withdrew during vaccination phase; no break-down by treatment group	reaction within 2 wk of injection pain erythema swelling (≤1 inch) swelling (1–2 inches) systemic ADE 1 hospitalization for depression judged to be unrelated to vaccine no participants withdrew due to ADE	 56 12 14 4 21	 36 14 7 0 18
HPV-16,[31,33] Merck	82 vaccine 27 placebo 5 vaccine and 1 placebo subject withdrew during vaccination phase	reaction within 2 wk of injection pain erythema swelling (≤1 inch) swelling (1–2 inches) systemic ADE no participants withdrew due to ADE	 70 18 18 1 52	 56 11 0 0 56
HPV-18,[32] Merck	27 vaccine 13 placebo 5 vaccine and 2 placebo subjects excluded from endpoint analysis	reaction within 2 wk of injection pain erythema swelling systemic ADE severe systemic ADE headache 1 participant experienced urticaria and was withdrawn	 96 41 37 70 6.6 48	 85 8 23 85 15.7 62
HPV-16,[34] Merck	1194 vaccine 1198 placebo 200 vaccine subjects withdrew before month 7 vs 158 placebo subjects	reaction within 2 wk of injection injection site pain systemic ADE systemic ADE judged to be possibly, probably, or definitely related to study drug serious ADE withdrew due to ADE no subjects withdrew due to serious ADEs	 86.3 71.4 41.6 (n = 4) (n = 4)	 82.3 71.7 43.5 (n = 3) (n = 5)
HPV-16,[35] Merck	428 vaccine 52 placebo 88 vaccine subjects and 8 placebo subjects withdrew during vaccination phase	reaction within 2 wk of injection fever ≥37.8 ˚C injection site ADE systemic ADE systemic ADE judged to be possibly, probably, or definitely related to study drug most common systemic ADE was headache 3 serious ADEs judged to be nonvaccine related occurred in vaccine group: gastroenteritis, a suicide attempt, pneumonia 1 subject in the placebo group withdrew due to headache	 3.5 84 71 44	 1.9 88 70 44
HPV-16,-18,[25] GlaxoSmithKline	560 vaccine 553 placebo 36 vaccine subjects and 31 placebo subjects withdrew before month 18	reaction within 1 wk of injection pain at injection site swelling at injection site redness at injection site systemic ADE headache 22 serious ADEs occurred in vaccine group and 19 in placebo group; none judged to be related to study drug 3 placebo subjects and 1 vaccine subject withdrew due to an ADE	 93.4 34.3 35.6 86.3 62.3	 87.2 21 24.3 85.9 61.2

ADE = adverse drug event; HPV VLP = human papillomavirus virus–like particle.

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Table 2. Safety and Tolerability of HPV VLP Vaccines in Published Trials (continued)

Vaccine, Sponsor	Subjects (n)	ADEs	vaccine, %	placebo, %
HPV-6,-11,-16,-18,[26] Merck	277 vaccine 275 placebo 20 vaccine subjects and 15 placebo subjects withdrew during vaccination phase	reaction within 2 wk of injection injection site adverse event systemic ADE systemic ADE judged to be associated with study drug most common injection site ADE was pain; most common systemic ADE was headache 94% of ADEs were mild or moderate; no serious ADEs were judged to be related to treatment 1 pt. withdrew from placebo group due to ADEs	 86 69 38	 77 69 33

ADE = adverse drug event; HPV VLP = human papillomavirus virus–like particle.

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EXTRACTO

OBJETIVO: Repasar la farmacología, la eficacia, la seguridad, la capacidad de ser tolerada, y la farmacoeconomía de Cervarix y Gardasil, 2 vacunas del papilomavirus humano (HPV, por sus siglas en inglés), en investigación.

FUENTES DE INFORMACIÓN: Los artículos en el idioma inglés fueron obtenidos a través de una búsqueda en MEDLINE (1966–febrero 2006) utilizando los términos claves en inglés: human papillomavirus vaccine, Cervarix, y Gardasil. Las bibliografías de artículos seleccionados fueron utilizadas para identificar fuentes adicionales.

SELECCIÓN DE FUENTES: Todos los estudios disponibles en humanos, publicados como artículos o extractos de vacunas del HPV, fueron revisados para inclusión en este artículo. Información adicional sobre pruebas clínicas en curso fue obtenida de los sitios de los fabricantes en el Web.

SÍNTESIS: Cervarix y Gardasil son vacunas recombinantes contra el HPV. Cervarix tiene como objetivo el HPV-16 y -18, que son responsables por 70% de los cánceres cervicales. Gardasil está dirigida contra el HPV -16 y -18, en adición a los tipos HPV-6 y -11 responsables por más de 80% de las verrugas genitales. Ambas vacunas han sido efectivas en prevenir infecciones persistentes por los tipos del HPV a los que están dirigidas y en prevenir lesiones intraepiteliales cervicales, mientras que Gardasil también ha sido efectiva en prevenir neoplasia vulvar y vaginal y verrugas genitales. Ambas vacunas han sido bien toleradas, con los efectos adversos más comunes ocurriendo en el lugar de administración de la inyección. Se están llevando a cabo pruebas clínicas en Fase III para evaluar más a fondo la eficacia de la vacuna.

CONCLUSIONES: Cervarix y Gardasil ofrecen potencial en la prevención de la infección por el HPV y lesiones cervicales. Asuntos que permanecen por discutir incluyen la duración de la protección, la eficacia en la prevención de cáncer cervical, la edad óptima para la vacunación, la viabilidad de aplicación a los países en desarrollo, la combinación ideal de los sub-tipos del HPV, y la combinación más eficiente de vacunación y screening para cáncer cervical.

Brenda R Morand

RÉSUMÉ

OBJECTIF: Analyser le profil pharmacologique, l'efficacité clinique, la tolérance, et la pharmacoéconomie du Cervarix et du Gardasil, 2 vaccins HPV en expérimentation.

REVUE DE LITTÉRATURE: De 1966–février 2006, une recherche bibliographique MEDLINE d'articles en anglais a été menée à l'aide des termes suivants: vaccins papillomavirus humains, Cervarix, et Gardasil. D'additionnelles informations ont été identifiées à l'aide de bibliographies d'articles sélectionnés.

SÉLECTION DE L'ÉTUDE ET SÉLECTION DE L'INFORMATION: Toutes les études cliniques chez l'homme publiées, telles que des articles ou extraits sur les vaccins papillomavirus humains, ont été analysées pour leur potentielle inclusion dans cet article. D'additionnelles informations sur les essais cliniques en cours furent obtenues via les sites Web des fabricants.

RÉSUMÉ: Le Cervarix et le Gardasil sont des vaccins recombinants contre le papillomavirus humains. Le Cervarix cible les HPV de type 16 et 18, qui rendent compte de 70% des cancers cervicaux. Le Gardasil cible les HPV de type 16 et 18 et les HPV de type 6 et 11 qui rendent comptent de plus de 80% des verrues génitales. Les 2 vaccins ont été efficaces dans la prévention de l'infection HPV persistante et dans la prévention des lésions cervicales intra-épithéliales, tandis que le Gardasil a montré également une efficacité dans la prévention des néoplasies intra-épithéliales et des verrues génitales. Les 2 vaccins ont été bien tolérés, avec les plus communs effets secondaires se produisant sur le lieu de l'injection. Les essais cliniques de phase III sont en cours afin d'approfondir l'évaluation de l'efficacité du vaccin.

CONCLUSIONS: Le Cervarix et le Gardasil sont prometteurs pour la prévention de l'infection HPV et pour la prevention des lésions cervicales. Les problèmes restant à aborder incluent la durée de protection, l'efficacité pour la prévention du cancer cervical, l'âge optimal pour la vaccination, la faisabilité pour l'application dans les pays en voie de développement, la combinaison idéal de sous-types HPV, la plus efficace combinaison vaccinale, et le dépistage du cancer cervical.

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