



Vaccines for Preventing HPV-Related Anogenital Infection and Neoplasia

Daron G. Ferris, MD

Human papillomavirus (HPV) is a common sexually transmitted pathogen. Although most anogenital HPV infections resolve within several years, persistent infection may lead to neoplasia of the cervix, vagina, vulva, anus, and penis, and also genital warts. High-risk HPV types 16 and 18 are known to cause approximately 70% of all cervical cancers, and low-risk HPV types 6 and 11 are the main causes of genital warts. Prophylactic HPV vaccines have the potential to block the acquisition of HPV and hence subsequent development of anogenital neoplasia. Results from several clinical trials have demonstrated that the HPV L1 virus-like-particle vaccines are safe and highly immunogenic. These trials have documented a 100% vaccine efficacy in prevention of persistent HPV infection and, more important, of HPV-associated anogenital neoplasia in per-protocol analyses. Widespread vaccination of sexually naïve preadolescent children could substantially reduce the morbidity and mortality associated with anogenital malignancies. Furthermore, such a primary prevention program would also reduce healthcare costs.

Human papillomavirus (HPV) is the most common sexually transmitted infection in the United States.¹ It is estimated that 20 million individuals are currently infected with HPV and

more than 6 million individuals become infected each year. The infection could be considered ubiquitous because approximately 75% to 80% of individuals will become infected sometime during their lifetime.^{2,3} The young are especially at risk as nearly 75% of HPV infections occur in 15- to 24-year-old persons.⁴ However, in approximately 70% to 90% of cases, HPV infection resolves spontaneously within 2 years of acquisition.^{5,6} Clearance of infection is less likely to occur in the immunosuppressed, older individuals, and women infected with high-risk or multiple types of HPV.⁵ Persistence of HPV infection is considered a significant risk

factor for the development of anogenital neoplasia.⁷⁻⁹

High-Risk and Low-Risk Types of Human Papillomavirus

Infection with HPV is a necessary, but not uniquely sufficient, cause of cervical cancer.¹⁰⁻¹² Of the many types of HPV, 30 to 40 have a tropism for epithelia found in the lower genital tract. High-risk HPV type 16 and HPV type 18 cause approximately 70% of all cervical cancers.^{13,14} Most squamous cell cervical cancers are caused by HPV type 16, and HPV type 18 is the main cause of cervical adenocarcinoma. High-risk HPV types are also considered the cause of vaginal, vulvar, and perianal dysplastic and malignant lesions in women.

The same high-risk HPV types are known causes of penile and anal cancers in men. In addition, HPV type 16 is associated with approximately 20% of head and neck cancers. Low-risk HPV type 6 and HPV type 11 cause the majority of anogenital warts in both men and women. These low-risk types are also the main cause of recurrent respiratory papillomatosis, a rare, but chronic, condylomatous infection of the larynx and vocal cords affecting children born to women harboring a productive lower genital tract HPV infection.¹⁵

Burden of Human Papillomavirus

Currently, no cure for HPV infection exists. Fortunately, normal epithelium infected by the virus initially transforms into precancerous lesions prior to advancing to cancer. This process occurs slowly in most cases, allowing for early detection and successful treatment. Although cytologic screening for cervical cancer has substantially reduced the rate of this malignancy, approximately 5% of Papanicolaou (Pap) tests are diagnosed as abnormal.¹⁶ Evaluation involves some discomfort for women, considerable cost, and an understandable emotional toll. Treatment of lower genital tract neoplasia and genital warts causes further physical, financial, and psychological burdens. Because Pap screening is not universally available nor always sensitive in detecting disease, cervical cancer remains the second most frequent malignancy in women worldwide.¹⁷ Relief

Dr Ferris is a professor in the departments of Family Medicine and Obstetrics and Gynecology, and director of the Gynecologic Cancer Prevention Center, at the Medical College of Georgia in Augusta.

Dr Ferris has received grants/research support from Merck & Co, Inc, and GlaxoSmithKline and is a consultant to Merck & Co, Inc, and GlaxoSmithKline.

Address correspondence to Daron G. Ferris, MD, Director, Gynecologic Cancer Prevention Center, Medical College of Georgia, 1120 15th St, Augusta, Georgia 30912-0006.

E-mail: dferris@mail.mcg.edu

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from the morbidity and mortality associated with HPV may be forthcoming soon. Prophylactic HPV vaccines are poised to help reduce the burdens affecting so many.

Human Papillomavirus L1 Virus-like-Particle Vaccines

Cutaneous trauma facilitates HPV infection that induces the humoral immune system to produce antibodies. When exposed to the L1 capsid protein, or capsule surrounding the HPV DNA, a type-specific antibody response occurs. Mimics of the HPV capsid protein called L1 virus-like particles (VLPs) can be manufactured using yeast or insect cell recombinant technology. The L1 VLPs are highly immunogenic, producing large amounts of neutralizing antibodies.¹⁸ However, because the VLP is hollow and contains no essential early HPV genes (ie, E6, E7), it is noninfectious and nononcogenic.^{18,19} Because antibodies are thought to be type specific, HPV type 16 antibodies do not protect against other types of HPV.¹⁸ However, there exists some evidence that antibodies produced in response to HPV VLPs may convey cross-protection against phylogenetically related HPV types.²⁰ Further studies are needed to confirm this finding and determine the magnitude of resulting efficacy.

Vaccine Trials

Multiple HPV vaccine trials have been conducted, and many more are ongoing. The vaccines have been evaluated in regard to their safety for local reactions, systemic reactions, and serious adverse events, and for immunogenicity. In addition, vaccine efficacy in the prevention of persistent HPV infection, cervical neoplasia, and reduction in cytologic abnormalities has been evaluated.

Phase 1 Trials

Phase 1 and dose-ranging trials established the preliminary safety and immunogenicity of L1 VLP vaccines. Results demonstrated that injection-site pain was the most frequent adverse event across studies.²¹⁻²³

Human papillomavirus types 11, 16, and 18 L1 VLP vaccines were found to be highly immunogenic.²¹⁻²³ Consistently high levels of neutralizing antibodies

Table Human Papillomavirus Type 16 and Type 18 Vaccine Trial: Reduction of Cytologic Abnormalities (≥ASCUS)*†			
Cohort	Cytologic Abnormality (No.)	Vaccine Efficacy (%)	95% Confidence Interval
■ According to Protocol			
<input type="checkbox"/> Vaccine (n=366)	1	93.5%	51.3-99.1
<input type="checkbox"/> Control (n=355)	15		
■ Intention to Treat			
<input type="checkbox"/> Vaccine (n=560)	2	92.9%	90.0-98.3
<input type="checkbox"/> Control (n=553)	27		

* ASCUS indicates atypical squamous cells of undetermined significance.
† Source: Harper DM, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet*. 2004;364:1757-1765.

were produced that remained elevated above prevaccination levels for at least 3 years.²³ Vaccine-induced antibody titers were as much as 60 times higher than those produced by naturally occurring infection.²² Based on these findings of reasonable safety and robust immune responses, larger phase 2 and 3 trials were undertaken.

Phase 2 and 3 Clinical Trials

The first proof-of-principle trial randomly assigned approximately 2400 females aged 16 to 23 years old to receive three doses of HPV type 16 VLP vaccine or placebo.²⁴ Genital samples, to test for HPV DNA, were obtained at enrollment, month 7, and at regular 6-month intervals after month 7. Colposcopically directed biopsy specimens were examined for the presence of cervical neoplasia and HPV type 16 DNA, which was assessed by polymerase chain reaction testing. The participants were followed up for approximately 17 months after the third vaccination. Forty-one cases of persistent HPV type 16 infections were detected in the placebo group and no cases in the vaccine group, demonstrating 100% vaccine efficacy.²⁴ The monovalent vaccine demonstrated a robust and sustained immune response and an acceptable safety profile.

A phase 2 trial also reported results for a bivalent HPV type 16 and HPV type 18 vaccine.²⁵ Females aged 15 to 25 years

who had had six or fewer sexual partners and no history of abnormal Pap test results, and who were seronegative for HPV type 16 and HPV type 18 and HPV DNA-negative for 14 high-risk HPV types were randomly assigned to receive either vaccine (n=560) or placebo (n=533). Doses were administered at day 0, month 1, and month 6, and participants were followed up for 18 months. Pap tests and HPV DNA testing were done at regular intervals throughout the study. Primary study endpoints were prevention of HPV type 16 or HPV type 18 infection; secondary endpoints included prevention of persistent infection and the prevention of HPV type 16- or HPV type 18-related low-grade squamous intraepithelial lesions (LSIL), high-grade squamous intraepithelial lesions (HSIL), cervical intraepithelial neoplasia grade 1 (CIN 1) through grade 3 (CIN 3), and adenocarcinoma.²⁵

In the according-to-protocol analysis,²⁵ the bivalent vaccine reduced incident cervicovaginal HPV type 16 and HPV type 18 infection by 73.6% ($P<.0001$) during the 27 months of patient follow-up; the reduction in the intention-to-treat analysis was 67.6% ($P<.0001$). Results of the secondary analyses showed the bivalent vaccine was 100% effective at reducing persistent cervicovaginal HPV type 16 or HPV type 18 infections ($P<.0001$) present in two or more sequential visits; the reduction was 87.5% in the

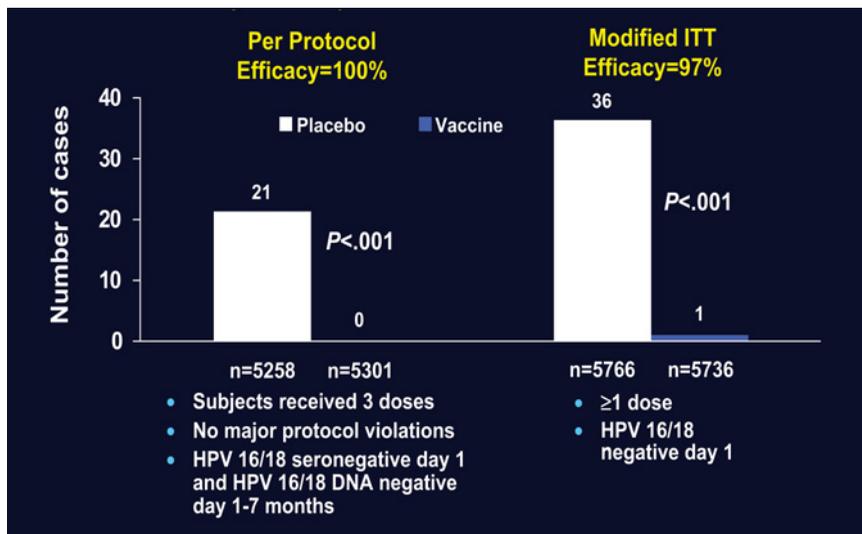


Figure. Efficacy of human papillomavirus (HPV) types 6, 11, 16, and 18 vaccine in 2-year phase 3 trial: Results for cervical intraepithelial neoplasia (CIN) grades 2 and 3 and adenocarcinoma in situ (AIS). (Adapted from Skjeldestad FE, and FUTURE II Steering Committee. Prophylactic quadrivalent human papillomavirus (HPV) (types 6, 11, 16, 18) L1 virus-like particle (VLP) Vaccine (Gardasil™) reduces cervical intraepithelial neoplasia (CIN) 2/3 risk. Presented at: 43rd Annual Meeting of the Infectious Diseases Society of America; October 6-9, 2005; San Francisco, Calif. Abstract.)

intention-to-treat analysis ($P < .0001$). Human papillomavirus type 16- or HPV type 18-related disease greater than or equal to atypical squamous cells of undetermined significance (ASCUS) was reduced by 92.9% in the intention-to-treat cohort ($P < .0001$; Table).²⁵

Antibodies to HPV type 16 developed at month 7 in all the subjects receiving three doses of vaccine, whereas antibodies to HPV type 18 developed at month 7 in 99.7% of those receiving three doses of vaccine. The bivalent vaccine, like the quadrivalent vaccine, was highly immunogenic.²⁵

The bivalent vaccine was well tolerated. Injection-site reactions were common, the most common being pain, which was more frequent in the group receiving vaccine (93.4% vs 87.2%, $P = .006$). There were no statistically different findings between the two groups with respect to adverse systemic events. Further, no serious vaccine-related adverse events occurred.²⁵

A phase 2 clinical trial of a quadrivalent HPV vaccine established its efficacy in preventing persistent infection with HPV types 6, 11, 16, and 18, and in preventing disease associated with these HPV types.²⁶ Young females aged 16 to 23 who had no prior abnormal Pap test result and four or fewer male sexual partners were assigned to receive three injections of either placebo ($n = 275$) or quadrivalent vaccine ($n = 277$) at day 1, month 2, and month 6 and were followed up for 36 months. Gynecologic examinations, Pap tests, and swabs for HPV testing

were done at regular intervals. Primary study endpoints were: (1) persistent infection with HPV types 6, 11, 16, or 18, defined as the presence of HPV types 6, 11, 16, or 18 in two or more cervicovaginal samples at least 4 months apart, both taken 7 months after the initiation of the study; or (2) HPV-associated disease, which included intraepithelial neoplasia or cancer of the vulva, vagina, or cervix, or genital warts.

The quadrivalent vaccine reduced the incidence of persistent HPV infection and associated disease by 90% (95% CI, 71%–97%, $P < .0001$) in the per-protocol cohort. That cohort included females who were HPV types 6, 11, 16, and 18 negative at baseline and during the vaccination period (the first 6 months), who received all three doses, and who did not otherwise violate the study protocol. In the modified intention-to-treat cohort, vaccine efficacy was 89% (95% CI, 73%–96%, $P < .0001$).²⁶

Secondary analysis of immunogenicity supported previous findings that HPV L1 VLP vaccines are highly immunogenic: antibody responses to HPV types 6, 11, 16, and 18 developed by 7 months in all those subjects who received the active vaccine, and the level of antibodies produced were as much as 10-fold higher than those produced by natural infection.²⁶

The quadrivalent HPV vaccine was also well tolerated. Adverse injection-site reactions, the most common of which was pain, were more common in subjects who received active vaccine (86%

vs 77% for placebo). The most common systemic reaction was headache. Approximately 94% of all adverse events were classified as mild or moderate, and there were no vaccine-related serious adverse events.²⁶

A phase 3 trial was designed to assess the ability of the quadrivalent HPV vaccine to prevent HPV type 16- and type 18-related CIN 2 or CIN 3, adenocarcinoma in situ (AIS), and cervical cancer.²⁷ Approximately 12,167 females, 16 to 23 years of age, were randomly assigned to receive three injections of either placebo or vaccine during a 7-month period; vaccine efficacy was assessed via Pap test and HPV testing at regular intervals for 48 months.

In the per-protocol analysis of females who were HPV type 16 and HPV type 18 seronegative at day 1 and HPV type 16 and HPV type 18 DNA negative for months 1 through 7, no HPV type 16- or HPV type 18-related CIN 2 or CIN 3, AIS, or cervical cancer occurred in the group that received the vaccine, whereas there were 21 such occurrences in the group that received placebo (100% efficacy; 95% CI, 76%–100%, $P < .001$; Figure). The efficacy in the modified intention-to-treat cohort, which included subjects who received at least one dose of vaccine and were HPV type 16 and HPV type 18 seronegative at day 1 was 97% (95% CI: 83%–100%, $P < .001$). This analysis provides a better estimate of real-world response than does the according-to-protocol analysis. The most common adverse event was pain at the injection site.²⁷

Trials in Special Populations and Ongoing Clinical Trials

A study has also been conducted assessing the immunogenicity and safety of the quadrivalent vaccine in young adolescents and males. Sexually naïve young adolescents 10 to 15 years of age (510 male; 506 female) and young females (16 to 23 years of age; n=513) received three injections of the quadrivalent vaccine. Geometric mean antibody titers (GMT) were 1.7-2.7 times higher in young adolescents than in young adults ($P<.001$), whereas antibody titers were 1.1 to 1.3 times higher in young adolescent males than in young adolescent females. Adverse events were similar between groups. This study found that the quadrivalent vaccine is safe and immunogenic in both male and female adolescents.²⁸ The vaccines will initially target this adolescent age group.

Clinical trials of the bivalent vaccine are currently being conducted in more than 30,000 females 15 to 25 years of age. The quadrivalent vaccines are also being studied in young adult males and mid-adult women. The Nordic Registry will provide long-term follow-up data on the safety and efficacy of the quadrivalent vaccine, and the efficacy of a year-5 booster dose is also being assessed.

Cost-Effectiveness of Prophylactic HPV Vaccination

HPV-related diseases generate substantial healthcare costs. A survey of 3.5 million patients was conducted to assess the frequency and costs of genital warts. Most episodes of genital warts required 3.1 patient visits during the course of 3 months, at an average cost of \$436, though some cases of warts lasted for more than 1 year, and no doubt incurred greater healthcare costs. Genital warts were most prevalent and most expensive among people between 20 and 29 years of age. Women had the greatest incidence and highest healthcare costs between 20 and 24 years of age: 6.2 cases per 1000 patient years, at a cost of \$1692 per 1000 patient years, and men had peak incidence and healthcare costs between ages 25 and 29 years: 5.0 cases per 1000 patient years and a cost of \$1717 per 1000 patient years.²⁹

Cervical neoplasia screening generates even greater healthcare costs. In total,

HPV-related cervical disease costs \$26,415 per 1000 enrollees. Routine cervical screening is the greatest expense, accounting for 63.4% of total costs; false-positive Pap test results account for an additional 9.1% of costs. The average abnormal Pap test result incurs costs of \$732, whereas a negative Pap test result costs only \$57. Women with higher grades of cytologic abnormality require more treatment and incur greater costs: atypical squamous cells diagnosed by Pap test costs \$299, necessitates 2.6 visits and 7.4 months of treatment, whereas an HSIL costs an average of \$2349 and requires 6.8 visits and 17.4 months of follow-up.³⁰

Reducing the incidence of HPV-associated disease should reduce healthcare costs. Several mathematical modeling studies have assessed the costs and benefits of vaccination against high-risk HPV as a means of reducing the costs of cervical healthcare. Estimates of vaccine cost and HPV-related healthcare costs can be combined with estimates of vaccination age, percentage of population vaccinated, and vaccine efficacy to generate cost-to-benefit ratios. The models can then be manipulated to assess the effects of different vaccine efficacies, ages of vaccination, and other variables.

Sanders and Taira³¹ assumed a vaccine that was 75% effective against all HPV types would be administered to all 12-year-old girls via three injections in a school-based program at a cost of \$300.

It was estimated that vaccine-induced immunity would last 10 years, and that booster shots (\$100 each) would be needed every 10 years. Under these conditions, vaccination against high-risk HPV was more expensive than the current regimen of screening and treatment but resulted in a greater quality-adjusted life expectancy, at a cost of \$22,755 per quality-adjusted life year (QALY). If vaccination permitted a decrease in Pap test frequency to once every 4 years, however, real savings would be seen in contrast to current practice.³¹

Decreasing vaccine efficacy or increasing vaccine cost (pr bpth) would increase the overall cost of vaccination, screening, and treatment, but it would still be below \$50,000 per QALY, an economic threshold considered acceptable. More frequent booster shots (eg, every 3

years) would also increase cost but keep it well below the cap of \$50,000 per QALY.³¹

Kulasingam et al³² assessed the potential benefit of universally vaccinating 12-year-old girls against HPV. Their vaccine assumptions were closer to those of the vaccines currently in clinical trials; ie, that the vaccine would be targeted to HPV type 16 and HPV type 18, and that the vaccine would be 90% effective against these types of HPV. As in Sanders and Taira,³² the assumption was made that the vaccine would confer 10 years' immunity. Vaccine costs were slightly lower, and it was assumed that all three doses of the vaccine could be administered within regularly scheduled office visits. Vaccination was found to be cost-effective when it delayed the onset of screening. In addition, combining vaccination with delayed onset of screening actually resulted in fewer predicted cancer deaths, especially among younger women.³²

The implications of vaccinating males for both public health and healthcare costs need to be studied further. Vaccination of males against low- and high-risk types may be cost-effective, and would incur benefits for the vaccinees, as well as contribute to herd immunity. In addition, it should be noted that historically, attempts to vaccinate just one gender have not been particularly successful. England originally chose to vaccinate just females against rubella, but the decision was later made to extend vaccination to both males and females to further reduce disease incidence.^{33,34}

These models may underestimate the benefits and healthcare savings that would be associated with a vaccine that offers protection against low- and high-risk HPV. Protection against low-risk types of HPV, like that provided by the quadrivalent vaccine, will reduce the incidence of LSIL and genital warts and incur additional healthcare savings. Furthermore, the recent phase 3 data for the quadrivalent vaccine suggest that vaccines may be even more effective than estimated in these experiments.

Comment

The two HPV vaccines currently in clinical trials have demonstrated efficacy in

preventing persistent HPV infection and associated disease in young females ranging from 90% to 100%. All trials, phases 1 through 3, have consistently found these vaccines to be safe and highly immunogenic.

Although safety and efficacy have been well established in young females, some questions are still unanswered. Until recently, it was not known whether the vaccines would be effective in men. Recent studies, however, confirmed that the quadrivalent vaccine, which protects against genital warts and thus offers a benefit to male vaccinees, is even more immunogenic in males than it is in females.²⁸ It is also not known how long vaccine-induced immunity lasts; follow-up data are being collected to answer this question, but the longer vaccine-induced immunity lasts, the longer it will be before we can answer this question.

Currently, HPV-associated disease is a major public health burden; these new vaccines, however, promise to reduce the incidence of genital warts, cervical dysplasia, and cervical cancer. In addition, some analyses suggest that in addition to improving public health, these vaccines may also be cost-effective, and in some situations, even result in health-care savings.

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