

Assessing Human Papillomavirus Vaccine Efficacy and Safety

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Clinical trials have documented the safety, efficacy, and immunogenicity of the quadrivalent and bivalent human papillomavirus (HPV) L1 virus-like particle vaccines. These vaccines have demonstrated greater than 90% efficacy in preventing HPV-related neoplasias of the lower genital tract. The quadrivalent HPV vaccine has been found to be more than 95% efficacious in preventing genital warts. These vaccines have been shown to protect against a wider range of oncogenic HPV types. Nonetheless, women must continue to have routine cervical cytologic screening. This article reviews the clinical trials document the efficacy of the HPV vaccines.

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Historically, vaccines have represented a cost-effective way to prevent disease induced by infective or microbial agents. Persons older than 50 years may have seen not only an active case of poliomyelitis, but also in their lifetime, the development of the Salk killed virus vaccine (1952) and the Sabin live, oral vaccine (1963).¹ These two vaccines essentially eradicated this crippling disease. In the Americas, the number of cases fell from 2525 in 1960 to 61 by 1965, and an average of only 8 cases per year occurred between 1980

and 1990; most of them were the result of vaccination.¹ By 1980, the last indigenous case of polio was reported in the United States.

Current attention is focused on vaccines that can reduce the incidence of human papillomavirus (HPV) infections and thereby reduce the incidence of cervical cancer and its precursor lesions—vulvar and vaginal neoplasias—and genital warts. The potential of reduction through prevention also exists for the other HPV-associated lower genital tract (anal and penile) neoplasias and recurrent respiratory papillomatosis (RRP).²

The HPV is ubiquitous, living on every mammal. Birds and animals carry this virus, making it difficult to prevent HPV infection and its related diseases.

The HPV vaccine that was created is

clearly designed to prevent infection and anogenital neoplasia. Vaccines are not live and do not contain viral DNA, so these vaccines are not infectious or oncogenic. They are essentially empty shells that consist of virus-like particles (VLP). The L1 protein is the capsid protein around the HPV. The vaccines reproduce the capsid protein in yeast cells. (A discussion of the L2 protein is beyond the scope of this article.) Five L1 proteins self-assemble into a pentamer. Then, a huge 72-pentamer becomes the virus-like particle (*Figure*) that is injected and causes the humoral response and antibody formation.

The HPV vaccine is not a therapeutic vaccine to be given to patients who have active disease. But there is speculation, especially in the RRP literature, that if

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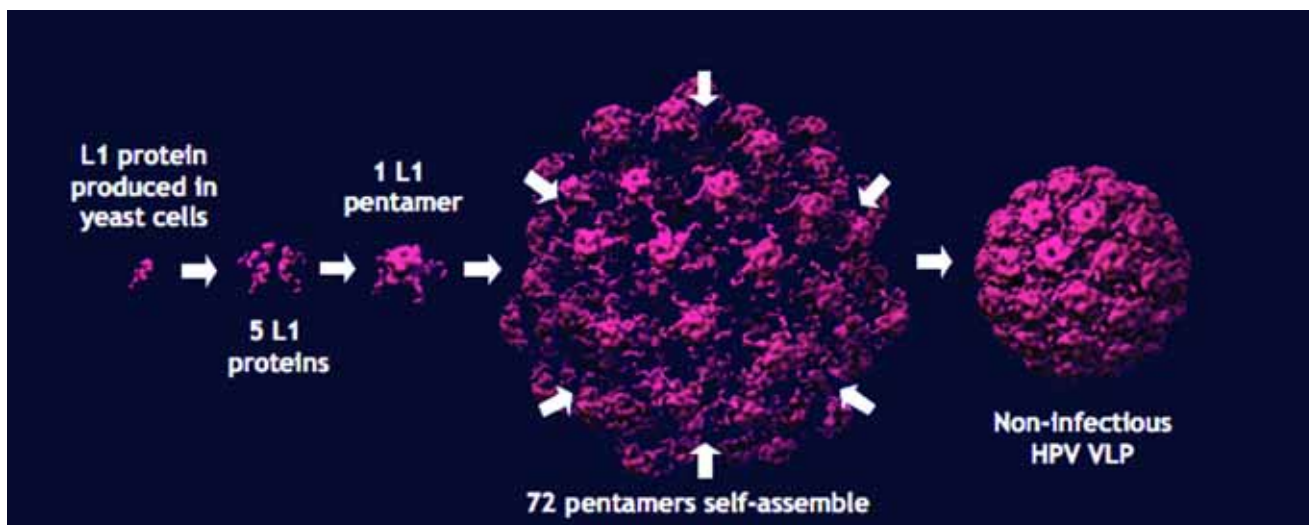


Figure. Sequence in formation of noninfectious human papillomavirus (HPV) virus-like particle (VLP) in quadrivalent HPV L1 VLP vaccine.

the vaccine is administered to patients who have RRP, it may induce regression of other HPV subtypes that they may have, including head and neck cancer.

This article looks at the critical issues of the safety and efficacy of the HPV VLP-1 vaccines by reviewing the clinical trials that were done by both companies that have developed HPV vaccines, one of which is currently approved, while the other is awaiting approval. The other company was first to start development of the HPV vaccine and initiated the original clinical trials with a bivalent vaccine designed specifically to prevent cancer and viral subtypes 16 and 18.

Bivalent Vaccine Clinical Trial

In a phase III double-blind, multicenter randomized control clinical trial, 18,525 females aged 15 to 25 years were randomly assigned to receive at least one dose of either HPV 16/18 vaccine (n=9319) or hepatitis A vaccine (n=9325) intramuscularly.³ Injections were given at baseline (day 0), 1 month, and 6 months. The primary objective was to assess vaccine efficacy against cervical intraepithelial neoplasia (CIN) grade 2 or greater associated with HPV 16 or HPV 18 in young women who were seronegative and DNA negative at baseline. The secondary objectives were to assess vaccine efficacy against CIN grade 1, 2, or 3 associated with HPV 16/18, persistent HPV 16/18 at 6 and 12 months or other oncogenic types at 6 months, and immuno-

genicity and safety. Interim assessments were done on a modified intention-to-treat basis.

Although the final clinical trial studying this vaccine has not yet been published because of ongoing negotiations with the US Food and Drug Administration (FDA), the interim analysis showed the vaccine efficacy to be high: 90% or greater for CIN grade 2 and 3 and 89.2% for CIN grade 1. For persistent infection, the vaccine had 80% efficacy at 6 months and 75.9% at 12 months.³

Adverse events associated with the HPV vaccines are much the same as with any vaccine that is administered in the physician's office: pain, redness, and swelling. These events were slightly greater in the group receiving the bivalent HPV vaccine than in the control group. General symptoms were nearly identical. No differences existed between the groups with respect to fatigue, headache, myalgia, gastrointestinal complaints, arthralgia, elevated temperature, rash, or urticaria.³

Quadrivalent Vaccine Trials

The quadrivalent HPV L1 VLP vaccine, which is currently the only HPV vaccine available in the United States, is protective against four viral subtypes, 6, 11, 16, and 18, thus making it effective for prevention of cervical cancer as well as for vulvar and vaginal condylomata acuminata (vulvar and vaginal warts).

FUTURE I Trial

The Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I) study was a smaller study of 5455 females 16 to 23 years old who were not pregnant, who had no abnormal cells on Papanicolaou (Pap) smear tests, and who had had no more than four male sex partners.⁴ Virgins were enrolled if they were seeking contraception and were probably going to have intercourse in the future during the trial. The young women were excluded if they had an allergy to any of the vaccine components. Injections were given intramuscularly at day 0 and at 2 and 6 months.

The placebo in this clinical trial was an aluminum adjuvant that is used to make the quadrivalent vaccine. A different aluminum-based adjuvant is used in the bivalent vaccine. The aluminum adjuvant that is used in the quadrivalent vaccine is the same as that used in the manufacturer's hepatitis B vaccine that is currently available and has been for more than 20 years. The adjuvant is important with respect to a vaccine's having long-lasting effects or untoward effects that are not preventable. The adjuvant in the quadrivalent HPV vaccine therefore has been around for a long time and has been well tested and found to be safe.⁴

Primary end points were CIN, adenocarcinoma in situ (AIS), cancer of the cervix, genital warts, and vulvar and vaginal neoplasia. The population was unrestricted and included all women

who were seronegative and polymerase chain reaction (PCR) negative at enrollment. For the analysis, the women were separated into the groups to which the investigators were completely blinded. Four-year follow-up evaluation at 6-month intervals included liquid-based cytology, HPV testing of external genitalia/cervix, HPV serology, and colposcopy. A panel of four gynecology pathologists read the slides.

When evaluating the data in the various clinical trials, the FUTURE I investigators wanted to look at two groups: the one called “per-protocol”, which is the group of women who received the vaccine before they had HPV serology positive and before they had been exposed to the virus, and who remained HPV negative through 1 month of the follow-up testing. Disease may be completely prevented if young girls are vaccinated at 11 or 12 years of age.

The intent-to-treat population comprises the rest of the young women who participated in the trial: those whose disease or virus status was not known at enrollment. In the practice setting, these may be 16- to 18 year-olds who may have been sexually active; they may have had a negative Pap test; or they may even have had a positive Pap test. Should such young women be vaccinated? They were not excluded from participating in the FUTURE I study, but they were excluded from the per-protocol analysis if they were seropositive and/or PCR positive to the relevant vaccine HPV type at day 1 during the vaccination phase (ie, 6 months and 1 month after). If they violated protocol, if they had one dose or two doses, they were excluded from the per-protocol analysis. Missed or improperly timed visits were also a protocol violation.⁴ Women could stray somewhat from the dose series schedule and still not be a protocol violator. If they received all three doses within 1 year, they did not violate protocol.

The case counting was done at 1 month after administration of dose 3 for the per-protocol population. The intent-to-treat population included everyone who was enrolled, and the investigators looked at all subjects who received at least one vaccine. So even if the subjects did not receive their remaining injections,

Table 1						
Prophylactic Efficacy Against Human Papillomavirus (HPV) 16- and 18-Related Cervical Intraepithelial Neoplasia (CIN) Grades 2 and 3 or Adenocarcinoma in Situ						
Population	Group				HPV Vaccine Efficacy, %	95% CI
	Quadrivalent HPV Vaccine		Placebo			
	n	Cases, No.	n	Cases, No.		
Protocol 005*	755	0	750	12	100	65.1-100
Protocol 007	231	0	230	1	100	−3734.9-100
FUTURE I	2200	0	2222	19	100	78.5-100
FUTURE II	5301	0	5258	21	100†	80.9-100
Combined Protocols	8487	0	8460	53	100†	92.9-100

*Evaluated only the HPV 16 L1 virus-like particle component of quadrivalent HPV vaccine.

†P values were computed for the prespecified primary hypothesis tests. All P values were .001, supporting the following conclusions: efficacy against HPV 16- and 18-related CIN grades 2 and 3 is greater than 0% (FUTURE II), and efficacy against HPV 16- and 18-related CIN grades 2 and 3 is greater than 25% (combined protocols).

Sources: Koutsky LA, et al. *N Engl J Med.* 2002;347:1645-1651; Villa LL, et al. *Lancet Oncol.* 2005;6:271-278; Garland SM, et al. *N Engl J Med.* 2007;356:1928-1943; FUTURE II Study Group. *N Engl J Med.* 2007;356:1915-1927.

Table 2						
Prophylactic Efficacy Against Human Papillomavirus (HPV) 6-, 11-, 16-, and 18-Related Cervical Intraepithelial Neoplasia (CIN) Grades 1 and 2/3 or Adenocarcinoma in Situ						
Population	Group				HPV Vaccine Efficacy,%	95% CI
	Quadrivalent HPV Vaccine		Placebo			
	n	Cases, No.	n	Cases, No.		
Protocol 007	235	0	233	3	100	–137.8-100
FUTURE I	2240	0	2258	37	100*	89.5-100
FUTURE II	5383	4	5370	43	90.7	74.4- 97.6
Combined Protocols	7858	4	7861	83	95.2	87.2- 98.7

*Pvalues were computed for the prespecified primary hypothesis tests. All Pvalues were <.001, supporting the following conclusions: efficacy against HPV 6-, 11-, 16-, and 18-related CIN is greater than 20% (FUTURE I).

Sources: Koutsky LA, et al. *N Engl J Med.* 2002;347:1645-1651; Villa LL, et al. *Lancet Oncol.* 2005;6:271-278; Garland SM, et al. *N Engl J Med.* 2007;356:1928-1943; FUTURE II Study Group. *N Engl J Med.* 2007;356:1915-1927.

the investigators could assess protection according to the number of received doses. At 3 years in FUTURE I, there were 65 cases with CIN or worse in the group receiving the placebo in the per-protocol population. In the per-protocol analysis, the efficacy was 100%, and the vaccine group had no case.

For the subjects who may have had

the virus at the time of their injection, there were 89 cases in the placebo group and 2 cases in the vaccinated group, for an unrestricted, or general, population 98% efficacy rate. Thus, a 100% efficacy rate can be achieved in preventing CIN or worse if girls or women are vaccinated before becoming sexually active. The vaccine is 98% effective in women who

become sexually active after vaccination.⁴

For genital warts and vulvar and vaginal neoplasia, case counting yielded similar results. In the group receiving placebo, there were 60 cases; in the group receiving vaccine, the case count was 0, for 100% efficacy for the per-protocol group. In the unrestricted or the general population, the efficacy was 95%, with 81 cases in the placebo group and 4 cases in the vaccine group.

FUTURE II Trial

FUTURE II was the primary clinical trial that the FDA used to approve the quadrivalent vaccine against HPV types 6, 11, 16, and 18.⁵ More than 12,000 young women between the ages of 16 and 26 years were enrolled. Inclusion criteria were similar to those in the FUTURE I trial: subjects could not be pregnant, could have no history of abnormal cells on Pap smear tests, and could have a history of no more than four male sex partners. Virgin subjects were enrolled if they were seeking contraception.

The exclusion criterion was allergy to any of the vaccine components. Injections were given intramuscularly at day 0 and at 2 and 6 months. Again, the placebo was the same aluminum adjuvant used in the hepatitis B vaccine.

End points were similar to those in the FUTURE I trial. At 3 years, there were 42 cases of cervical disease, AIS, or cancer related to HPV 6, 11, 16, or 18 in the placebo group, 1 case in the vaccine group for the per-protocol population, for a 98% efficacy rate, and 62 cases in the placebo group and three cases in the vaccine group, for a 95% efficacy rate for the prevention of CIN grade 2 or 3, or AIS.

For vaginal and vulvar precancerous lesions, the quadrivalent vaccine had 100% efficacy at preventing HPV 16- and HPV 18-related vulvar intraepithelial neoplasia (VIN) grade 2 or 3, and vaginal intraepithelial neoplasia (VaIN) grade 2 or 3; in the unrestricted group, the vaccine had 95% efficacy. For prevention of all HPV-related CIN or AIS, there was 98% efficacy. By lesion type, efficacy for prevention of CIN grade 2 was 99%; for CIN grade 3, 97% efficacy; and for AIS, 100% efficacy.

Table 1 summarizes all of the protocols that were done in assessing the effi-

Population	Group				HPV Vaccine Efficacy, %*	95% CI
	Quadrivalent HPV Vaccine		Placebo			
	n	Cases, No.	n	Cases, No.		
Protocol 007	235	0	233	3	100	–139.5-100
FUTURE I	2261	0	2279	29	100*	86.4-100
FUTURE II	5401	1	5387	59	98.3	90.2-100
Combined Protocols	7897	1	7899	91	98.9	93.7-100

*The efficacy of quadrivalent HPV vaccine against HPV 6-, 11-, 16-, and 18-related vulvar intraepithelial neoplasia grade 1 and vaginal intraepithelial neoplasia grade 1.

Sources: Koutsky LA, et al. *N Engl J Med*. 2002;347:1645-1651; Villa LL, et al. *Lancet Oncol*. 2005;6:271-278; Garland SM, et al. *N Engl J Med*. 2007;356:1928-1943; FUTURE II Study Group. *N Engl J Med*. 2007;356:1915-1927.

cacy of the quadrivalent HPV L1 VLP vaccine.⁴⁻⁷ Protocol 005 was the original monovalent vaccine study; it evaluated only the HPV type 16 L1 VLP component of the quadrivalent HPV vaccine.⁶ Protocol 007 was the original phase 2⁷ trial, followed by the phase 3 trials—FUTURE I⁴ and FUTURE II.⁵ All these studies combined have demonstrated 100% prophylactic efficacy against HPV 16- and 18-related CIN grades 2 and 3 and AIS: no case occurred in the group receiving the vaccine; 53 cases occurred in the group receiving placebo.

When protocol 007, FUTURE I, and FUTURE II for CIN grades 1, 2, and 3, or AIS are combined,⁶ four cases occurred in the vaccinated group compared with 83 cases in the placebo group in FUTURE II, for a trial efficacy rate of 90.7% (Table 2). For the four combined protocols, the prophylactic efficacy rate was 95.2%. In all four of the cases in the vaccinated group in FUTURE II, the subjects became seropositive before their 1-month follow-up visit at month 7 (after they had received all their vaccine doses). Therefore, they had become infected some time during the vaccination process; but even then, the vaccine was 90.7% effective in preventing the development of disease.⁶

Table 3 summarizes the results for the quadrivalent vaccine's efficacy in preventing genital warts. In FUTURE I, there

was 1 case in the group receiving the quadrivalent HPV L1 VLP vaccine, whereas there were 91 cases in the groups receiving placebo.^{4,7} Again, that single case that occurred in the groups receiving the vaccine was in a person who became infected some time during the vaccination process. The cumulative incidence during the 3 years was slightly more than 1% for the quadrivalent HPV L1 VLP vaccine, with a doubling of that incidence in the placebo group.

Clearly, many of the women in the general population group became exposed some time during the vaccination process, so disease might have been prevalent in them. Also the disease could have happened because of other non-HPV 6, 11, 16, or 18 subtypes that may have infected the cervix.

In the FUTURE II trial, the recipients of the vaccine compared with the recipients of the placebo had a 16.5% reduced need for a loop electrosurgical excision procedure (LEEP) of the cervix or conization, and a 26.5% reduced need for excision of warts. During the trial, no clear evidence of protection against disease caused by HPV type was found for those subjects who were PCR-positive or seropositive for one of the HPV types found in the vaccine at baseline (day 0).

Again, the quadrivalent HPV L1 VLP vaccine is not a therapeutic vaccine, it is a prophylactic vaccine. Individuals

who were already infected with one or more HPV types were protected from the other HPV types, which supports the rationale for vaccinating a woman if she has had abnormal cells demonstrated on a Pap smear test. The vaccine may confer protection against the other subtypes (probably three) that have not caused her infection.

The quadrivalent HPV L1 VLP vaccine is indicated currently by the FDA for girls and women 9 to 26 years of age for the prevention of cervical cancer and genital warts, diseases caused by HPV types 6, 11, 16, and 18. The vaccine is also indicated for the prevention of cervical AIS, CIN grades 2 and 3, VIN grades 2 and 3, VaIN grades 2 and 3, and CIN grade 1.

Efficacy Through 5 Years of Follow-up

In 2006, Villa and colleagues⁸ published 5-year follow-up data from the phase 2 trial of the quadrivalent HPV L1 VLP vaccine in which 552 women were enrolled for 3 years. A subset of 241 of the originally enrolled women were followed up for 2 additional years; 226 of these women completed the study. The vaccine reduced the combined incidence of HPV 6-, 11-, 16-, and 18-associated persistent infection or disease by 96% (2 cases in the vaccinated group vs 46 cases in the control group) and related CIN or genital warts by 100% (no cases in vaccine recipients vs 46 in placebo recipients).

Recommended Immunization

The ideal age for the administration of the quadrivalent HPV L1 VLP vaccine is between 11 and 12 years. The vaccine is available in a single-dose (0.5 mL) vial or prefilled syringe; no dilution or reconstitution is required. The vaccine is administered intramuscularly as three 0.5-mL doses, injected into the deltoid region of the upper arm or in the higher anterolateral area of the thigh. The time for administering the first dose is an

elected date. The second and third doses are injected 2 months and 6 months, respectively, after the first dose.

The quadrivalent HPV L1 VLP vaccine is a category B vaccine, so it is not to be administered to women who are pregnant; however, if a woman becomes pregnant during an interval after vaccination, scheduled administration is discontinued during her pregnancy and resumed after her delivery, usually at 6 weeks. The vaccine may be given to women who are breastfeeding postpartum.

Women should not be prescreened with HPV testing; the vaccine can be given to women who have known HPV-associated disease. Serologic titers are not necessary; nearly 100% seroconversion occurs. It is important that patients continue having regular Pap smear screening because cervical disease may still develop.

In January 2008, the phase 3 study of the quadrivalent HPV L1 VLP was completed. Studies examining the efficacy and safety of this vaccine in the mid-adult female population is ongoing, as is a program looking at the vaccine's efficacy in young men and boys. Data may be forthcoming within a year and hold promise of vaccinating men and establishing herd immunity.

Comment

In summary, the HPV L1 VLP vaccines are safe and well tolerated. They are highly immunogenic. Both the quadrivalent and the bivalent vaccines have shown greater than 90% efficacy in preventing HPV-associated neoplasia of the lower genital tract, and the quadrivalent vaccine was greater than 95% efficacious in preventing genital warts. The vaccines have been shown to protect against a wide range of oncogenic HPV types and infections. Nonetheless, it is necessary for women to continue having routine cervical screening.

References

1. Okonek BAM, Morganstein, eds. Development of polio vaccines. In: Access Excellence Classic Collection. Available at: <http://www.accessexcellence.org/AE/AEC/CC/polio.html>. Accessed March 30, 2008.
2. Lowy DR, Frazer IH. Chapter 16: Prophylactic human papillomavirus vaccines. *J Natl Cancer Inst Monogr*. 2003;31:111-116.
3. Paavonen J, Jenkins D, Bosch FX, Naud P, Salmerón J, Wheeler DM, et al: HPV PATRICIA study group. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a Phase III double-blind, randomised controlled trial [published correction appears in *Lancet*. 370:1414]. *Lancet*. 2007;369:2161-2170.
4. Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al; Females United to Unilaterally Reduce Endo/Ectocervical Disease (FUTURE I) investigators. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *N Engl J Med*. 2007;356:1928-1943.
5. FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *N Engl J Med*. 2007; 356:1915-1927.
6. Koutsky LA, Ault KA, Wheeler CM, Brown DR, Barr E, Alvarez FB, et al; for the Proof of Principle Study Investigators. A controlled trial of a human papillomavirus type 16 vaccine. *N Engl J Med*. 2002;347:1645-1651.
7. Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomized double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol*. 2005;6:271-278.
8. Villa LL, Costa RL, Petta CA, Andrade RP, Paavonen J, Iversen OE, et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *Br J Cancer*. 2006;95:1459-1466.