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ScienceDirect
Gynecologic Oncology 107 (2007) S19–S23
Gynecologic Oncology
www.elsevier.com/locate/ygyno

Prevention strategies against the human papillomavirus: The effectiveness of vaccination

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Received 24 July 2007

Abstract

It has been clearly established that sexually transmitted human papillomavirus (HPV) infections are the major cause of genital warts and cervical cancer and are a contributing factor in the development of other types of anogenital cancers. There is a higher risk of HPV infection with an increasing number of sexual partners. Health education measures aimed at improving the use of condoms, reducing the number of sexual partners and promoting safer sex strategies have been employed with the goal of decreasing the transmission of HPV. Of these intervention strategies, promotion of condom use has been shown to be the most effective. More recently, prophylactic HPV vaccines have been developed with the aim of reducing the burden of HPV-related diseases such as cervical cancer. Two vaccines have been developed: Gardasil®, a quadrivalent vaccine targeting HPV-6, -11, -16 and -18) and Cervarix™, a bivalent vaccine which targets HPV-16 and -18. HPV-16 and -18 are most commonly associated with cervical cancer. In clinical trials, HPV vaccination has been shown to be safe, immunogenic and highly effective against type-specific HPV infection. Predictive data also indicate that the implementation of HPV vaccination within a national screening program is likely to be cost-effective relative to current clinical practice.

Human papillomavirus infection

The human papillomavirus (HPV) plays a leading role in the development of cervical cancer and other forms of genital cancer, as well as genital warts [1,2]. HPV is a sexually transmitted disease that can result in cervical cancer 5 to 30 years after the initial infection [3]. The risk of HPV infection and subsequent development of cervical cancer is increased in women who have a higher number of sexual partners.

While in developed countries screening has contributed to a decline in rates of cervical cancer this is not the case in developing countries where access to such programs is limited [3]. Health education measures to promote the use of condoms, a reduction in the number of sexual partners, safer sex strategies, and vaccination are some recommended approaches to decreasing the transmission of HPV.

Prevention strategies against HPV infection

A systematic review of interventions targeted at reducing the spread of HPV and preventing the development of cervical cancer in 5089 sexually active and pre-sexually active women aged 13 to 64 years reported a favorable intervention effect on sexual risk reduction outcomes [1]. In these studies, measured intervention outcomes included condom use, sexual partner reduction, development of sexual negotiation skills, delayed first intercourse, abstinence and/or a clinical outcome such as sexually transmitted disease incidence and HPV/cervical cancer incidence.

Prevention strategies aimed at improving condom use appeared to be more effective, with reported increases of 25 to 56% [1]. Interventions which focused on communication skills and provided factual information were associated with the greatest effect on condom use. A recent study of female college students ($n=82$) determined that among newly sexually active women, consistent condom use by their male partners appears to reduce the risk of cervical and vulvovaginal HPV infection [4].

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doi:10.1016/j.ygyno.2007.07.068

More recently, prophylactic HPV vaccines have been developed with the aim of reducing the burden of HPV-related diseases such as cervical cancer [5–9]. Two vaccines have been developed (Gardasil® and Cervarix™) which target the two HPV types most commonly associated with cervical cancer (HPV-16 and -18). Gardasil® is the first vaccine to be approved for use in adolescent and young women aged 9 to 26 years for the prevention of cervical cancer (HPV-16 and -18) and genital warts (HPV-6 and -11), as well as vulvar and vaginal precancerous lesions [10].

HPV vaccines

In vitro, HPV virus-like particles (VLP) can be produced via the synthesis and self-assembly of the major virus capsid protein L1. Because these HPV L1 VLPs exhibit morphological and antigenic properties that are virtually identical to native virons, this has been utilized in the development of HPV L1 VLP subunit vaccines [11]. The mechanisms by which VLPs elicit protection are not completely understood. At present, all women receiving the HPV vaccine have seroconverted. As a result, there are no immune correlates which denote protection [11]. However, VLPs are highly immunogenic and anti-VLP antibody responses in VLP-immunized women are markedly greater than that identified in natural infections.

Both bivalent and quadrivalent vaccines have been shown to be safe, immunogenic and effective against type-specific HPV infection (Fig. 1) [2].

Bivalent vaccine

Cervarix™, developed by GlaxoSmithKline Biologicals, Rixensart, Belgium, is a bivalent HPV-16/18 L1 VLP vaccine. The L1 protein of each HPV type is expressed by a recombinant baculovirus vector, and the VLPs are generated separately and then combined [11]. Cervarix™ consists of purified L1 VLPs of HPV types 16/18 at 20/20 μg/dose, respectively, formulated on an ASO4 adjuvant consisting of aluminum hydroxide 500 μg and 3-deacylated monophosphoryl lipid A 50 μg. It is administered as a 0.5 mL intramuscular injection in a three-dose immunization protocol at 0, 1 and 6 months.

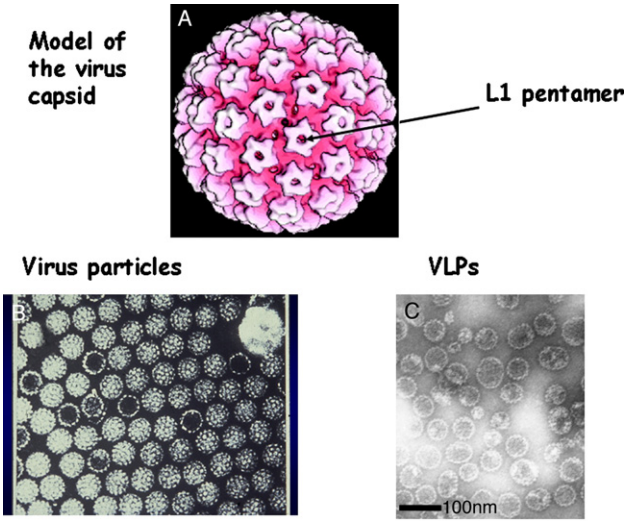

Fig. 1. Papillomavirus capsid (A); papillomavirus particles (B); human papillomavirus-16 L1 virus-like particles (C). (Reprinted with permission of Elsevier.) [11].

Table 1
Bivalent HPV vaccine efficacy in a cohort of 776 women followed for 4.5 years (per-protocol population)

Endpoint	Vaccine (n=350)	Placebo (n=344)	Vaccine efficacy (%; P-value)
Incident HPV infections: women reporting ≥1 HPV-16/18 event	1	28	96.9 (<0.0001)
Persistent HPV infections: 6 months	1	16	94.3 (<0.0001)
Persistent HPV infections: 12 months	0	7	100 (0.0062)

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HPV=human papillomavirus.

Cervical cancer

Clinical trial data indicate that vaccine protection is maintained over a period of 4.5 years with the Cervarix™ bivalent vaccine [6]. A multicenter, randomized follow-up trial (n=776) demonstrated that >98% seropositivity was maintained for HPV-16/18 antibodies at 4.5 years. The bivalent vaccine was 96.9% effective against incident HPV-16/18 infection and 100% effective against 12-month persistent infection (Table 1). A combined analysis of the initial and follow-up studies showed 100% vaccine efficacy against cervical intraepithelial neoplasia (CIN) lesions associated with HPV-16/18 (Table 2).

Quadrivalent vaccine

Gardasil®, a quadrivalent HPV-16/18/6/11 L1 VLP vaccine, has been developed by Merck & Co. Inc. [10] For each HPV VLP, the L1 protein is expressed via a recombinant *Saccharomyces pombe* vector and the vaccine is comprised of purified L1 VLPs of HPV types 6/11/16/18 at 20/40/40/20 μg/dose, respectively, formulated on a proprietary alum adjuvant [11]. Gardasil® is available as a 0.5 mL intramuscular injection

Table 2
Efficacy of the bivalent vaccine in a cohort of women followed for 4.5 years (per-protocol population)

Endpoint [a]	Vaccine (n=350)	Placebo (n=344)	Vaccine efficacy (%; P-value)
ASCUS	2	44	<0.0001
LSIL	2	26	<0.0001
CIN1+	0	8	0.0035
CIN2+	0	5	0.0292

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ASCUS=atypical squamous cells of undetermined significance; CIN=cervical intraepithelial neoplasia; LSIL=low-grade squamous intraepithelial lesions.
[a] Includes data from the initial efficacy study (27 months) plus the blinded ongoing extended follow-up study (44 to 53 months).

administered in a three-dose immunization protocol at 0, 2 and 6 months.

Cervical cancer

Data from a phase II randomized, multicenter study ($n=552$) that followed women aged 16 to 23 years for up to 5 years demonstrated that vaccination of adolescents and young adults with Gardasil® at 0, 2 and 6 months resulted in 100% vaccination coverage and effectively prevented persistent infection and disease caused by HPV types 6/11/16/18 [7]. Relative to placebo, at 5 years, there was a 96% reduction in the combined incidence of HPV-related 6/11/16/18 persistent infection or disease. At this time point there were no cases of precancerous cervical dysplasia or genital warts in the vaccinated women (versus six cases in the placebo arm) and the vaccine-induced anti-HPV geometric mean titers remained at or above those observed with natural infection [7].

These findings were confirmed in the randomized, double-blind Females United To Unilaterally Reduce Endo/Ectocervical Disease (FUTURE II) study ($n=12,167$) which demonstrated a significant reduction in the incidence of high-grade CIN related to either HPV-16 or -18 in women vaccinated with the quadrivalent HPV vaccine at 0, 2 and 6 months compared with those receiving placebo [8]. Over an average follow-up of 3 years, vaccine efficacy in the per-protocol susceptible population ($n=10,565$) which included women aged 15 to 26 years with no previous HPV-16 or -18 infection was 98%. CIN grade 2 or 3 or adenocarcinoma *in situ* developed in 1 woman receiving the HPV vaccine and 42 placebo recipients (Table 3). An immunogenicity substudy confirmed that 99% of vaccinated women demonstrated seroconversion to the relevant HPV type [8].

Pooled data from four studies in 20,583 women aged 16 to 26 years, who were followed for a mean of 3 years, indicate that the quadrivalent vaccine has the potential to substantially reduce the incidence of HPV-16 and -18-related cervical precancers and cancers [12]. In the per-protocol analysis, women who were negative for HPV-16 or -18 ($n=17,129$) demonstrated 99% vaccine efficacy for the primary endpoint of the combined incidence of HPV-16 and -18-related CIN 2/3, adenocarcinoma *in situ*, or cervical cancer. In the intention-to-treat analysis, which included women who were infected with HPV-16 and/or -18 at day 1, vaccine efficacy for the primary endpoint was 44%.

Table 3
Quadrivalent HPV vaccine efficacy against grade 2 or 3 CIN or adenocarcinoma associated with HPV type 16 or 18 (per-protocol susceptible population): [8]

Endpoint	Vaccine ($n=5305$)		Placebo ($n=5260$)		Vaccine efficacy (%; 95% CI)
	No. of cases	Rate	No. of cases	Rate	
CIN grade 2 or 3 or adenocarcinoma *in situ*	1	<0.1	42	0.3	98 (86–100)
CIN grade 2	0	0	28	0.2	100 (86–100)
CIN grade 3	1	<0.1	29	0.2	97 (79–100)
Adenocarcinoma *in situ*	0	0	1	<0.1	100 (<0–100)

CI=confidence interval; CIN=cervical intraepithelial neoplasia; FUTURE=Females United To Unilaterally Reduce Endo/Ectocervical Disease; HPV=human papillomavirus.

Genital warts

The phase III FUTURE I trial employing the 0, 2 and 6-month quadrivalent HPV vaccination schedule showed that over a 3-year follow-up period vaccination significantly reduced the incidence of HPV-associated anogenital diseases compared with placebo in 5455 women aged 16 to 24 years [9]. Vaccine efficacy was 100% in the per-protocol group; in the vaccinated women there were no reported cases of vaginal, vulvar, perianal and perianal intraepithelial lesions or warts related to the HPV vaccine types compared with 60 cases in women receiving placebo. For the primary composite endpoint of anogenital warts, vulvar or vaginal intraepithelial neoplasia grades 1 to 3, or cancer regardless of causal relation to vaccine-type HPV, vaccination was associated with a 34% reduction relative to placebo. For each of the vaccine subtypes (6/11/16/18), ≥99.5% of women in the per-protocol immunogenicity cohort had seroconversion 1 month after the third dose [9].

Cost-effectiveness of HPV Vaccination

A lack of long-term efficacy data means that it is not possible to definitively determine the cost-effectiveness of HPV vaccination [13]. However, available pharmacoeconomic data indicate that, in the US, the introduction of the HPV vaccine may be more cost-effective than current clinical practice. Although these pharmacoeconomic models and key variables still require validation before any firm conclusions can be made [2,13]. Issues that need to be resolved include who should be vaccinated, at what age should vaccination start and the implication of vaccination on current screening programs.

Within the healthcare setting, cost-effectiveness is usually measured in terms of the incremental cost-effectiveness ratio (ICER) or the ratio of the change in costs of a therapeutic intervention (compared with either no intervention or the best available alternative treatment) to the change in effects of the intervention. Quality-adjusted life years (QALYs) measure both the quality and the quantity of life lived as a means of quantifying the benefit of a medical intervention. QALYs are based on the number of years of life that would be added by a specific intervention. In three studies [14–16], a static Markov model was used to follow a hypothetical US-based cohort of women; vaccination coverage in the target group ranged from 70 to 100%. One study showed that vaccination of girls aged 12 years combined with biennial screening starting at age 24 years resulted in an ICER of $US24,300 per QALY gained [14]. Similarly, a second

Markov model based on vaccination at 12 years, screening every 2 years and boosters every 10 years, produced an ICER of $US22,755 per QALY gained compared with current practice [15].

Limitations of these studies included a failure to take into account herd immunity, the possibility of vaccinating males and the reactivation of latent infections.

A dynamic transmission model is needed to assess the epidemiological changes in type-specific HPV prevalence over time, estimate the impact of herd immunity and determine the relative value of vaccinating females only [17]. A dynamic Markov model measured the direct medical costs of vaccination of 12-year-old girls only or 12-year-old girls and boys, biennial screening and boosters every 10 years. The ICER was $US14,583 per QALY gained for the vaccination of girls only [17]. This study also determined that it is necessary to vaccinate girls only and that vaccinated individuals need only be screened once every 4 years.

Within the setting of organized cervical screening in the US, a dynamic transmission model determined that administration of the quadrivalent HPV vaccine to females aged 12 years was cost-effective and would reduce the incidence of genital warts and cervical cancer by 83 and 78%, respectively [18]. This model was based on several assumptions: up to 70% of 12-year-olds received a 3-dose vaccine, vaccine coverage increased linearly over the first 5 years of the program, the cost of the vaccine for 3 doses plus administration was $US360 (2005 values), and all costs and QALYs were discounted at 3%. The ICER of augmenting this vaccination strategy with a temporary catch-up program for 12- to 24-year-olds was $US4666 per QALY gained. The ICER for a strategy which included males was $US45,056 per QALY and would reduce the incidence of genital warts (97%), CIN (91%) and cervical cancer (91%) [18]. Removing the effects of herd immunity and the benefits of prevention of HPV-6 and -11, the ICER for the latter strategy increased to $US124,063 per QALY.

Impact of HPV vaccination

The implementation of HPV vaccination is predicted to have wide ranging impact with regard to a reduction in the use of healthcare resources. Recent data based on the US National Health Interview Surveys, conducted in 2000 and 2005, indicated that approximately 65 million Papanicolaou (Pap) cervical screening tests are performed annually [19]. Adoption of a cost-effective HPV vaccination strategy which includes biennial screening from age 24 years is predicted to reduce the annual total Pap test volume by 43%.

HPV vaccination may also contribute to a reduction in the workload at sexually transmitted disease (STD) clinics [5]. A cross-sectional analysis of medical records from a single STD clinic between 1994 and 2004 (66,537 visits) demonstrated that 10.3% of visits and 25% of 14,574 follow-up visits were related to HPV infection. Importantly, of the HPV infection-associated 'new problem' visits ($n=3085$), only 9.1% were not related to HPV infection. Data from this study suggest that a reduction in HPV-related morbidity will result in increased clinic resources to devote to the treatment of other STDs.

A reduction in Pap screening tests and STD clinic workload will be apparent relatively quickly following the implementation of HPV vaccination programs. However, the results of a Markov process model indicated that there are also substantial long-term benefits associated with the incorporation of an HPV vaccination program into a UK national cervical cancer screening program [20]. The Markov model predicted that, over the lifetime of a cohort of 12-year-old females, a 100% vaccination coverage and 95% vaccination efficacy against HPV-16 and -18 infections result in a 76% reduction in cervical cancer deaths and a 66% reduction in high-grade cervical lesions. Across all age groups, vaccination is also predicted to result in a 95% reduction in the prevalence of lesions associated with HPV-16 and -18 and a marked reduction in the prevalence of high-grade lesions, specifically CIN grade 2 and 3. Clinical benefits are also anticipated in terms of a reduction in screening tests and treatments [20].

Summary

HPV is a sexually transmitted disease that has been linked with the development of cervical and other forms of cancer. Until recently, prevention strategies have centered upon health education measures that involve promoting abstinence, increasing condom use, and reducing sexual partners. In clinical trials, HPV vaccination with bivalent or quadrivalent vaccines has shown high vaccine efficacy and seroconversion rates. Furthermore, relative to placebo, vaccination was associated with reductions in CIN, cervical cancer and anogenital warts (quadrivalent vaccine). Predictive data indicate that the implementation of HPV vaccination within a national screening program is likely to be cost-effective relative to current clinical practice. Moreover, data from a US-based model within the setting of an organized cervical screening program demonstrated that prophylactic HPV vaccination can reduce genital warts, CIN and cervical cancer. However, issues surrounding who to vaccinate, when to vaccinate and the integration of vaccination within the framework of current screening programs still need to be resolved.

Questions and answers

What is the nature of prophylactic HPV vaccines?

The current prophylactic HPV vaccines are subunit vaccines; that is, they consist of only a portion of the virus, the L1 protein of the virus coat or shell in the form of virus-like particles (VLPs). VLPs are empty protein shells immunologically identical to the virus but without the virus. Because HPV cannot be grown in tissue culture, creating the traditional live or attenuated viral vaccines is not possible. Two vaccines have been developed, and both generate high levels of neutralising antibody that is predominantly specific for the HPV types included in the vaccines. The vaccines thus provide protection against infection with the HPV types included in the vaccines, but there is no evidence that they will protect against all genital HPV types. Prophylactic HPV vaccines prevent or control infection, but they do not treat or have an effect on existing HPV infections or diseases.

What measures can be taken to prevent infection with HPV?

Health education measures aimed at improving the use of condoms, reducing the number of sexual partners, and promoting safer sex strategies have been employed with the goal of decreasing the transmission of HPV. Of these intervention strategies, promotion of condom use has been shown to be the most effective. More recently, prophylactic HPV vaccines have been developed with the aim of reducing the burden of HPV-related diseases, such as cervical cancer.

Conflict of interest statement

MS is a consultant for Merck Vaccines, GlaxoSmithKline Biologicals, and Sanofi Pasteur.

References

[1] Shepherd J, Peersman G, Weston R, Napuli I. Cervical cancer and sexual lifestyle: a systematic review of health education interventions targeted at women. Health Educ Res 2000;15(6):681–94.

[2] Newall AT, Beutels P, Wood JG, Edmunds WJ, MacIntyre CR. Cost-effectiveness analyses of human papillomavirus vaccination. Lancet Infect Dis 2007;7(4):289–96.

[3] World Health Organisation. The world health report 1998—life in the 21st century: a vision for all. Accessed at: http://www.who.int/entity/whr/1998/en/index.html.

[4] Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, King K, et al. Condom use and the risk of genital human papillomavirus infection in young women. New Engl J Med 2006;354(25):2645–54.

[5] Dempsey AF, Koutsky LA, Golden M. Potential impact of human papillomavirus vaccines on public STD clinic workloads and on opportunities to diagnose and treat other sexually transmitted diseases. Sex Transm Dis 2007;34(3):1–5.

[6] Harper DM, Franco EL, Wheeler CM, Moscicki B, Rateli-Martins C, Jenkins D, et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from randomised control trial. Lancet 2006;367:1247–55.

[7] Villa LL, Costa RLR, Petta CA, Andrade RP, Paavonen J, Iversen O-E, 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;95:1459–66.

[8] FUTURE II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. New Engl J Med 2007;356(19):1915–27.

[9] Garland SM, Hernandez-Avila M, Wheeler CM, Perez G, Harper DM, Leodolter S, et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. New Engl J Med 2007;356(19):1928–43.

[10] Gardasil®. Prescribing information. 2007. Merck & Co., Inc, Whitehouse Station, NJ 08889, USA.

[11] Stanley M, Lowy DR, Frazer I. Chapter 12: prophylactic HPV vaccines: underlying mechanisms. Vaccine 2006;24(Suppl 3):S106–13.

[12] Future II Study Group. Effect of prophylactic human papillomavirus L1 virus-like-particle vaccine on risk of cervical intraepithelial neoplasia grade 2, grade 3, and adenocarcinoma in situ: a combined analysis of four randomised clinical trials. Lancet 2007;369:1861–8.

[13] Hymel PA. Decreasing risk: impact of HPV vaccination on outcomes. Am J Manag Care 2006;12:S473–83.

[14] Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch X, et al. Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. J Natl Cancer Inst 2004;96(8):604–15.

[15] Sanders GD, Taira AV. Cost effectiveness of a potential vaccine for *human papillomavirus*. Emerg Infect Dis 2003;9(1):37–48.

[16] Taira AV, Neukermans CP, Sanders GD. Evaluating human papillomavirus vaccination programs. Emerg Infect Dis 2004;10(11):1915–23.

[17] Goldie S. A public health approach to cervical cancer control: considerations of screening and vaccination strategies. Int J Gynecol Obst 2006;94(Suppl 1):S95–S105.

[18] Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. Emerg Infect Dis 2007;13(1):28–41.

[19] Eltoum IA, Roberson J. Impact of HPV testing, HPV vaccine development, and changing screening frequency on national Pap test volume: projections from the National Health Interview Survey (NHIS). Cancer 2007;111(1):34–40.

[20] Kohli M, Ferko N, Martin A, Franco EL, Jenkins D, Gallivan S, et al. Estimating the long-term impact of a prophylactic human papillomavirus 16/18 vaccine on the burden of cervical cancer in the UK. Br J Cancer 2007;96(1):143–50.