Review article

Vaccination as a prevention strategy for human papillomavirus-related diseases

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Abstract

Childhood vaccines have had an enormously beneficial impact on human health. Large-scale vaccination programs have controlled diseases associated with high morbidity and mortality such as poliomyelitis, smallpox, diphtheria, tetanus, yellow fever, pertussis, Haemophilus influenzae, Streptococcus pneumoniae, measles, mumps, and rubella. Human papillomavirus (HPV) is a significant source of morbidity and mortality throughout the world. In the United States, HPV is the most common sexually transmitted infection (STI), and sexually active adolescents are at particularly high risk for HPV acquisition. Genetic and epidemiologic studies have clearly demonstrated that HPV infection is a necessary cause of both cervical cancer and genital warts. More than 99% of cervical cancers contain at least one high-risk HPV type, and approximately 70% contain HPV types 16 or 18. Moreover, low-risk HPV types 6 or 11 are responsible for approximately 90% of genital warts and almost all cases of recurrent respiratory papillomatosis. Thus, a vaccine that could prevent HPV acquisition would have the potential to significantly reduce the incidence of both childhood and adult diseases. © 2005 Society for Adolescent Medicine. All rights reserved.

Keywords: Public health; HPV; Vaccinations

Childhood vaccines have had an enormously beneficial impact on human health. Large-scale vaccination programs have controlled diseases associated with high morbidity and mortality such as poliomyelitis, smallpox, diphtheria, tetanus, yellow fever, pertussis, Haemophilus influenzae, Streptococcus pneumoniae, measles, mumps, and rubella. Figure 1 summarizes the public health impact of routine vaccination against a number of common childhood diseases.

Although infection with human papillomavirus (HPV) does not commonly cause disease during childhood, vertical transmission of specific HPV types from mother to child rarely may cause recurrent respiratory papillomatosis (RRP) in young children, and casual contact or sexual abuse may cause genital warts in children. In sexually active adolescents, HPV infection is highly prevalent, with reported cumulative prevalence rates up to 82% in adolescent girls [1]. Infection in adolescents may cause abnormal cervical cytology, cervical dysplasia, or external genital warts. As noted in the previous article, over 100 HPV types have been identified, and approximately one-third of these infect the genital tract. Infection with low-risk types, such as 6 and 11, may cause RRP or external genital warts. Infection with high-risk types, such as 16 and 18, may cause cervical cancer in women and other oral and genital malignancies in both men and women [2–7].

Evidence from genetic, immunologic and epidemiologic studies all provided the initial impetus for HPV vaccine development. Immunologic research demonstrated that natural HPV acquisition induces both cellular and humoral immunity, which appear to correlate with regression of infection. However, immunity after natural infection is limited [8]. Genetic and epidemiologic studies demonstrated that HPV infection is a necessary cause of cervical cancer and genital warts [3]. At least 99% of cervical cancers contain at least one high-risk type, and approximately 70% contain HPV types 16 or 18 (Figure 2) [9]. Approximately
90% of genital warts and almost all cases of recurrent respiratory papillomatosis are caused by low-risk HPV types 6 or 11 [10,11].

Thus, a vaccine that could prevent HPV acquisition would have the potential to reduce the incidence of childhood and adult diseases responsible for significant morbidity and mortality worldwide. For example, vertical transmission of maternal HPV infection rarely may lead to the development of multiple warts in the upper respiratory tract of an affected child. These respiratory papillomas often cause significant upper airway compromise and may necessitate repeated surgical procedures [10,12]. Genital warts are also caused by low-risk HPV types but are far more common than RRP. Although population-level prevalence data are not available, experts have estimated that prevalence rates vary from 1% to 5% [13,14]. Prevalence rates are substantially higher in specific populations; for example, rates up to 40% have been reported among men and women attending sexually transmitted infection clinics [15–17]. Because the prevalence of HPV infection is higher in sexually active adolescents than in adults, the prevalence of genital

Fig. 1. Public health impact of routine vaccine implementation against common childhood diseases. The graph illustrates the maximum number of disease cases reported before introduction of each vaccine, the number of reported cases in 2003, and the percent decrease in the number of cases of each disease. Implementation of routine vaccination programs in the US has had a substantial impact on the prevalence of these diseases today. Adapted from: Needle tips and the Hepatitis B coalition news. October 2004, Vol 14, No.3. Available at http://www.immunize.org/nslt.d/n31/n31.pdf.

Hib = Haemophilus influenzae type b

Fig. 2. Worldwide distribution of HPV types in cervical cancer. It has become clear that although there are at least 15 HR HPV types, a small number cause most cervical cancers. In this study, Munoz and colleagues pooled data from 11 case-control studies from nine countries. The percentage of squamous cell cancer caused by HPV 16 is shown in blue, 18 in purple, and 16/18 in dark green. Together, HPV 16, HPV 18, or both cause approximately 70% of cervical cancers worldwide. Adapted from: Munoz et al, N Engl J Med 2003;348:518–27.
warts also is likely to be relatively high in adolescents. The diagnosis of genital warts often is associated with significant psychological distress [18,19]. Treatment consists of multiple provider- or patient-applied topical treatments that may cause discomfort; if topical treatment is not effective or warts are extensive, surgical procedures may be necessary. Current treatment modalities have varying success rates, and even after treatment genital warts may recur [7]. Finally, although cervical cancer rates have fallen dramatically in more developed regions of the world as a result of large-scale Pap screening, cervical cancer remains the fourth most commonly diagnosed cancer in women residing in these regions. Cervical cancer is the second most commonly diagnosed cancer and the leading cause of cancer-related mortality among women in less developed regions, accounting for approximately 230,000 deaths per year (GLOBOCAN 2002 data, http://www-depdb.iarc.fr/globocan/GLOBOframe.htm). High-risk HPV infection is also associated with the development of other malignancies including oral, vulvar, penile, and anal cancers [4–6].

An effective HPV vaccine could also reduce the substantial costs associated with HPV infection and related diseases, although the cost savings may not be realized for many years. In developed countries such as the United States, costs are incurred primarily through cervical cancer screening programs and follow-up of abnormal cytology results. Insinga et al examined administrative and laboratory records from approximately 100,000 female enrollees of the Kaiser Permanente Northwest health plan to examine the health care costs of HPV-related disease in this setting [20]. Estimated overall annual cervical cancer prevention and treatment costs were $26,415 per 1000 female enrollees. The authors extrapolated results to the general U.S. population, and suggested that cervical HPV-related disease accounted for total health care costs of $3.4 billion in 1998. Routine cervical cancer screening accounted for the highest proportion of expenditures, comprising 64% of total costs, whereas the remainder of expenditures were related to the management of precancerous lesions, treatment of cervical cancer, and managing false-positive Pap test results (Figure 3). Costs associated with HPV infection also include those related to the diagnosis and treatment of recurrent respiratory papillomatosis, genital warts, and other HPV-associated diseases, as well as the indirect costs (e.g., lost work) associated with infection [21]. Thus, an HPV vaccine could lead to cost savings if it allowed for later initiation of Pap screening or less frequent Pap screening, and if it decreased the prevalence of abnormal Pap tests and genital warts and thus the need for diagnostic and treatment procedures.

Features of an ideal HPV vaccine would include safety, efficacy, ease of delivery, and cost-effectiveness. Safety is an essential feature, because HPV vaccines likely will be given to young and healthy individuals, most of whom would not develop HPV-related diseases such as cervical cancer even if they acquired HPV infection [22]. Vaccines should be effective enough so that widespread immunization would lead to a substantial reduction in the incidence of genital warts and cervical cancer, and preferably would result in long-lasting immunity so that booster immunizations would not be needed. Ideally, vaccines would be feasible for low-resource settings; that is, they would be inexpensive, would not require refrigeration, would be effective after a single dose, and could be administered without an injection. Finally, vaccination should reduce overall cervical cancer mortality as well as the costs and morbidity associated with screening for and treatment of HPV-related diseases.

**HPV vaccines in development**

Remarkable progress has been made in the development of HPV vaccines over the past 20 years [22–25]. Vaccines in development fall into two categories. *Prophylactic vaccines* are designed to prevent primary HPV infection by inducing virus-neutralizing antibody that provides protection against incident infection. These vaccines target the L1 and L2 proteins of the viral capsid. *Therapeutic vaccines* are designed to prevent progression of HPV infection to low-grade or high-grade squamous intraepithelial lesions, to achieve regression of cervical intraepithelial neoplasia (CIN) or condylomata, or to eradicate residual cervical cancer. One of the goals of therapeutic vaccines is to elicit a cell-mediated cytotoxic T cell response, leading to elimination of cells expressing viral proteins such as the cancer-associated proteins E6 and E7. A recent review provided an excellent and comprehensive overview of therapeutic vaccines under development [24]. This article will focus on prophylactic HPV vaccines because they will be recommended for children or young adolescents and because they are likely to be available soon for clinical use.

Prophylactic vaccines in development consist of virus-like particles (VLPs), which are recombinant viral capsids created by inducing expression of the major HPV capsid protein L1 in eukaryotic cells [26,27]. VLPs are identical to
HPV virions morphologically, so they can induce a neutralizing antibody response. However, because they do not contain viral DNA, they cannot replicate and therefore pose no infectious or oncogenic risk. Phase I and II clinical trials have been completed and phase III clinical trials are underway that test vaccines targeting HPV types 16 and 18, with or without types 6 and 11. These trials have shown that the vaccines are highly immunogenic at relatively low antigen doses, and induce HPV genotype-specific serum antibody responses that are at least 40 times higher than those found after natural infection [28,29]. Although the mechanism of protection is not yet clear, some experts believe that virus-neutralizing antibodies (primarily IgG and IgA) transudate from the serum into the cervical mucus where they confer protection at the site of infection [23].

Initial phase I and II trials involved univalent HPV vaccines targeting types 11, 16 or 18, and were studied as a proof of concept [28,29]. In the trials of HPV 11 and 16 vaccines, escalating doses of each vaccine type were given to healthy 18- to 25-year-old women at day 0, month 2, and month 6 [28]. The immune response to the HPV 11 vaccine is shown in Figure 4; the results of the HPV 16 trail were similar. The figure demonstrates that vaccination led to a robust immune response within one month after the third dose. Vaccine doses of 20, 50, and 100 μg led to acceptable immune responses as defined by the proportion of participants with high serum antibody titer, and somewhat higher immune responses were obtained in those who received a booster at 12 months compared with those who did not. Antibody titers declined slowly over the 30 months after the initial series was completed.

The first study evaluating the efficacy of a VLP vaccine in preventing incident HPV infection was published in 2002 [30]. This was a randomized, double-blind study in which 2392 women aged 16 to 23 years received three doses of a univalent HPV 16 vaccine (40 μg per dose, vaccine manufactured by Merck Research Laboratories, West Point, Pennsylvania) or placebo at day 0, month 2, and month 6. Participants were then followed for a median of 17.4 months. Samples to test for HPV 16 DNA were obtained at enrollment, one month after the third vaccination, and every six months thereafter. Colposcopy was performed as indicated and tissue obtained from biopsies was used to evaluate for CIN and HPV positivity. The primary endpoint of the study was persistent HPV 16 infection, defined as detection of HPV 16 DNA in samples obtained at two or more consecutive visits four or more months apart. The secondary endpoint was tolerability. In the according-to-protocol analysis, a total of 41 cases of persistent HPV 16 infection occurred in participants who received placebo. Thirty-one of these participants had persistent HPV 16 infections without CIN, five had HPV 16-related CIN 1, and four had HPV 16-related CIN 2. Conversely, none of the participants who received vaccine developed persistent HPV 16 infection. Thus, the vaccine was 100% effective (95% confidence interval [CI] 90.0–100.0%) in preventing persistent HPV 16 infection. Vaccine efficacy was identical in the analysis that included women with general protocol violations. Sixty-eight participants who received placebo developed either persistent or transient HPV 16 infection, whereas only six who received vaccine developed HPV 16 infection. All nine of the HPV 16-related cases of CIN developed in participants who received placebo. Thus, the vaccine was 91.2% effective (95% CI 80.0–97.0%) in preventing transient or persistent HPV 16 infection. In this study, no vaccine-related serious adverse events occurred in either the vaccine or the placebo group. During the study, serious adverse events occurred in 4% of individuals (n = 4) in the vaccine group and 3% of individuals (n = 3) in the placebo group. The percentage that withdrew from the study due to vaccine-related adverse events or serious adverse events was minimal. The most common vaccine-related adverse event was pain at the injection site. Follow-up data presented recently suggest that four years after vaccination, those who received vaccine compared with those who received placebo had a 72.7% reduction in incidence of CIN 3. None of the CIN cases in those who received the vaccine appeared to be caused by HPV 16 (abstract presented by Ferris D et al, Society for Gynecologic Oncologists annual meeting, March 20, 2005). Follow-up data also have demonstrated that following immunization, HPV 16 antibody titers peak at month 7, decline until month 18, then remain fairly stable between months 30 and 48 (abstract presented by Mao C et al, Society for Gynecologic Oncologists meeting, March 20, 2005).

The first randomized, double-blind, placebo-controlled trial evaluating the clinical efficacy of a bivalent HPV vaccine was published in 2004 [31]. The vaccine contained 20 μg each of HPV 16 and HPV 18 VLP (GlaxoSmithKline Biologicals, Rixensart, Belgium) with AS04 adjuvant containing 500 μg aluminum hydroxide and 50 μg 3-deacetylated monophosphoryl lipid A (MPL, Corixa, Montana). A total of 1113 women aged 15 to 25 years were

**Fig. 4. Immunogenicity of an HPV 11 vaccine-like particle vaccine.** Adapted from: Fife et al, Vaccine 2004;22:2943–52.
randomized to receive HPV 16/18 vaccine or placebo at day 0, month 1 and month 6, then underwent periodic Pap testing, HPV testing, and serologic testing for immune response during the follow-up period of up to 27 months. Endpoints included its efficacy in preventing HPV 16 and/or 18 infections and efficacy in preventing cytological abnormalities, CIN, and cervical cancer. In the according-to-protocol analysis, the vaccine was 100% effective (95% CI 47.0–100.0%) against persistent infection with HPV 16, 18, or both. The vaccine was 91.6% effective (95% CI 64.5–98.0%) against incident infection with HPV 16, 18, or both. In the intention-to-treat analysis, which included all enrolled participants who received at least one dose of vaccine or placebo and had any data available for analysis, vaccine efficacy was 95.1% (95% CI 63.5–99.3%) against persistent cervical infection with HPV 16, 18, or both. Efficacy was 92.9% (95% CI 70.0–98.3%) against HPV 16/18-related cytological abnormalities. During the study, serious adverse events occurred in 4% of individuals in the vaccine group and in 3.5% of individuals in the placebo group; this difference was not statistically significant. There were no serious adverse events related to vaccination. The proportion of participants that withdrew from the study due to vaccine-related adverse events or serious adverse events was minimal, and did not differ significantly between vaccine and placebo recipients. A large-scale efficacy trial involving approximately 28,000 women is underway.

The results of a randomized, double-blind placebo-controlled multicenter phase II trial of a quadrivalent VLP vaccine were published recently [32]. The vaccine included four recombinant HPV type-specific VLPs consisting of the L1 major capsid proteins of HPV 6, 11, 16, and 18 (Merck Research Laboratories) adsorbed onto amorphous aluminum hydroxyphosphate sulfate adjuvant. Women (n = 1106) from Brazil, Europe, and the United States who participated in the study received three preparations of the vaccine containing different dosages of the four VLPs at day 1, month 2, and month 6. Subsets were randomized to receive low-dose vaccine (n = 277) or placebo (n = 275). In the according-to-protocol cohort, the incidence of persistent HPV 6, 11, 16 or 18 infection or associated disease decreased by 90% (95% CI 71–97%) in women who received the low-dose vaccine compared with placebo. The results were similar in an intention-to-treat analysis. All women who received vaccine developed HPV antibody to the four HPV types after the series was completed, and antibody titers were substantially higher than in placebo recipients who had a previous HPV infection. Mean antibody titers at month 36 remained at or above the titers in women who had a natural HPV infection and cleared the virus. Pain was the most common injection-site adverse event and headache the most common systemic adverse event. There were no vaccine-related serious adverse events. A phase III trial of the quadrivalent vaccine, involving 17,800 women aged 16 to 23 years, is ongoing [33]. Data from this clinical trial, the Females United to Universally Reduce Endo-ectocervical disease (FUTURE II) study, were presented recently [34]. In a subsample of 12,167 women who were randomized to receive vaccine or placebo and who followed the protocol closely, the vaccine was 100% effective in preventing incident HPV 16/18-related CIN 2/3, adenocarcinoma-in-situ, and cervical cancer during two years of follow-up. The vaccine was well-tolerated and there were no vaccine-related serious adverse events.

Delivery of prophylactic HPV vaccines

Prophylactic HPV vaccines are likely to be available for clinical use in the near future. However, questions remain concerning the clinical outcomes of vaccination, duration of antibody response after vaccination, and impact of vaccination on cervical cancer screening and other health-related behaviors [23,24]. Questions also remain concerning factors that will ensure vaccine uptake; for example, provider willingness to recommend vaccine to patients, HPV vaccine acceptability among adolescents and parents, and development of effective public health strategies for immunization in various settings [35,36].

Although prophylactic vaccines appear to be highly effective in preventing incident HPV infection, more information is needed concerning their efficacy in preventing HPV-associated diseases. Published data do not adequately address the efficacy of prophylactic HPV vaccines in preventing genital warts and malignancies other than cervical cancer, such as vulvar, anal, penile, or oral cancers. Transudation of serum IgG, which is thought to protect the cervix, may not protect cutaneous areas such as the vulva or anus. The results of ongoing large-scale clinical trials should provide additional efficacy data. It is also unclear whether HPV vaccines in development will be effective in individuals who are immunocompromised as a result of HIV infection, organ transplants, or other disorders. Immunocompromised individuals may be less likely to respond to vaccination and are at increased risk for HPV-related disease [37]. The efficacy of vaccines containing HPV 16 and 18 also may vary by geographic region, race/ethnicity, or other factors. For example, types 16 and 18 appear to be more common in Asia, Europe and North America than in sub-Saharan Africa and Central/South America [38,39]. Finally, there has been concern that oncogenic types not contained in vaccines could replace types 16 and 18 after widespread vaccine implementation, limiting its effectiveness in preventing cervical cancer. The inclusion of additional HPV genotypes may help to optimize the public health impact of these vaccines.

Additional information is needed about the duration of protection after vaccination as well. If vaccines are administered to children and adolescents, levels of protective antibody must remain high over several decades or booster
vaccinations will be required. Persistence of neutralizing antibody at mucosal surfaces may be the most important factor determining protection, and it is unknown how rapidly these antibodies decline [22]. Follow-up data from large-scale trials are likely to provide information about duration of protection.

Target populations for vaccination are still being defined. Because prophylactic vaccines should be given before sexual initiation, older children and early adolescents are likely to be targeted. However, it is unclear whether men as well as women should be vaccinated. If the vaccines are effective in men, then vaccinating men could maximize the public health impact of HPV vaccines because of herd immunity [40]. Men could also benefit directly from a vaccine that prevents genital warts and anogenital cancers. However, it is unclear whether the vaccine prevents HPV infection in men or decreases HPV transmission from men to women.

Concerns have been raised about the impact of HPV vaccination on both sexual risk behaviors and screening behaviors. Some have expressed concern that adolescents who receive an HPV vaccine may feel less vulnerable to STI infection and thus practice riskier sexual behaviors; however, there are no published data to support this concern. Women of all ages who are vaccinated must understand that they should continue to obtain regular Pap tests even after vaccination. Although HPV types 16 and 18 are responsible for most cases of cervical cancer, at least 13 other genotypes may cause approximately 30% of cervical cancers. In addition, the vaccine may not be 100% effective against types 16 and 18, and immunity may wane over time. Guidelines will need to be developed regarding the safety of lengthening the screening interval in vaccinated women [41].

Vaccination of early adolescents against an STI may pose unique challenges. Adolescents often do not visit their health care provider routinely, and HPV vaccination will require three visits over a six-month period. Adolescents who may be particularly vulnerable to STI acquisition, such as street youth or incarcerated youth, are less likely to receive preventative health services in general and thus may be more difficult to reach with existing vaccination programs. Parental and adolescent acceptance of vaccination against an STI and provider willingness to recommend such vaccines will also be key determinants of successful vaccine delivery [36]. Recent studies demonstrate that although parents generally find STI vaccines acceptable, some do not believe their children are at risk for STIs or express concern that adolescents who are vaccinated may practice riskier sexual behaviors [42–44]. In the next article, Dr. Zimet will explore these issues in detail.

Finally, questions remain concerning the feasibility of prophylactic HPV vaccines for large-scale immunization programs in less developed countries, where most cervical cancer deaths occur (GLOBOCAN 2002 data, http://www.depdb.iarc.fr/globocan/GLOBOframe.htm). The vaccines under development require multiple doses and refrigeration, which make administration difficult in developing countries. In addition, it is unclear how to accomplish large-scale vaccination of early adolescents, given that current global vaccination programs are designed to implement vaccination of infants and young children [22].

In conclusion, prophylactic HPV vaccines may reduce substantially the morbidity and mortality associated with cervical cancer, other oral and genital malignancies, recurrent respiratory papillomatosis, and genital warts. Clinical trials suggest that they are safe, well-tolerated, highly immunogenic, and prevent both HPV infection and CIN. Additional research should provide information on the efficacy of HPV immunization in preventing other HPV-related diseases, duration of protection after vaccination, groups that should be targeted for vaccination, vaccine acceptability, and feasibility of vaccine delivery in less developed countries.

References


