Cervical cancer vaccination indications, efficacy, and side effects
José-María Bayas*, Laura Costas, Amparo Muñoz

Preventive Medicine Service, Adult Vaccination Centre, Hospital Clinic–IDIBAPS, Barcelona, Spain

Received 14 May 2008
Available online 30 June 2008

Abstract

Due to the limited contact of the human papillomavirus (HPV) with the immune system, past infection does not guarantee lasting protection. Two preventive vaccines (Gardasil® and Cervarix®) that can impede persistent HPV infection and its consequences are now available. They use structural L1 capsular proteins obtained by genetic recombination and antigens for genotypes 16 and 18, which are responsible for around 70% of cases of uterine cancer worldwide. Evaluation of their protective efficacy is based on the capacity of the vaccine to prevent persistent infection and cervical intraepithelial neoplasia (CIN).

Phase I and II trials showed the safety of these vaccines and their capacity to produce very-high titers of antibodies (low or non-existent after natural infection). Phase II and III trials have confirmed these aspects and shown an efficacy of nearly 100% in the protocol analysis in preventing infection and the CIN associated with oncogenic vaccine genotypes. Some trials have also shown cross-protection against infections produced by other genotypes (such as 45 and 31).

The optimal vaccination strategy is vaccination of girls aged 8–14 years. Other strategies should include the catch-up of adolescent and women not yet sexually-active, as well as the vaccination of sexually-active women.

The progressive development of primary prevention strategies should coexist with secondary prevention with redesigned screening programs. The successful development of vaccination programs will require the support of public health authorities, the coordination of health workers from different areas and increased public awareness.

© 2008 Published by Elsevier Inc.

Persistent infection of the genital tract by certain types of human papillomavirus (HPV) is a necessary, although insufficient, condition for the development of cervical cancer. Other cancers associated with HPV include those of the vagina, vulva, penis, anus, mouth, and oropharynx. Some HPV genotypes cause genital warts [1].

Prophylactic vaccines that can prevent persistent HPV infection and its consequences are currently available. In future years, the systematic use of these vaccines will substantially change the natural history of the diseases associated with HPV infection.

Immunologic basis of prophylactic vaccines

In most people, HPV infection induces local cellular immunity. The antibody titers in these people are low, since the capsular proteins are expressed only in the upper layers of the infected epithelium, with the consequent absence of viremia. The absence of cytolysis and inflammation limits contact with the antigen-presenting cells and macrophages. As a consequence, the antibody response produced by the B lymphocytes in the lymph nodes and spleen is very limited [2]. Nevertheless, animal models indicate that the antibodies induced by natural infection seem to protect against later HPV infections (at least by the same genotype). Therefore, it was hypothesized that the antibodies obtained after vaccination could confer long-term immunity.

Vaccines types and backgrounds

Recently, two prophylactic vaccines have become commercially available (Table 1). Both vaccines use structural capsular L1 proteins obtained by genetic recombination from the baculovirus (Cervarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) and from Saccharomyces cerevisiae (Gardasil, Merck Sharp & Dohme Pennsylvania, USA) The recombinant L1 proteins
obtained have the capacity to self-assemble and form virus-like particles (VLPs), which are free of DNA and are morphologically and antigenically similar to “real” HPV.

Both vaccines use VLPs as the vaccination antigen. Cervarix is a bivalent HPV16/18 L1 VLP vaccine, at 20/20 mg per dose that uses ASO4, which contains 500 mg aluminum hydroxide and 50 µg of 3-O-deacylated monophosphoryl lipid (MPL), derived from a detoxicated polysaccharide of *Salmonella enterica* subsp. *enterica* serovar Minnesota as an adjuvant. ASO4 is designed to improve the humoral and cellular immune response and increase the length of protection [3]. This patented adjuvant is already used in commercially available hepatitis B vaccines. Gardasil is a quadrivalent HPV 6/11/16/18 vaccine at 20/40/ 40/20 mg per dose that, in addition to the oncogenic types, includes VLPs of genotypes 6 and 11, the main types responsible for genital warts. Gardasil uses aluminum phosphate at 225 mg as an adjuvant.

**Variables of protective efficacy of vaccination**

As the natural history of the HPV infection is became known, the option of observing the appearance of the invading carcinoma as a variable of the protective efficacy of vaccination (as would be done in a disease in which the interval between exposure and disease was reduced) was unviable practically and ethically since the progression towards invasive cervical carcinoma can last for decades, clinical trials would require hundreds of thousands of subjects, and researchers would have to leave premalignant lesions untreated. For these reasons, assessing the protective efficacy of vaccinations has been based on the observation of virological (the capacity of the vaccine to prevent incident infection and persistent infection by the same viral genotype as a precursor of cervical intraepithelial neoplasia [CIN] and cancer) and clinical (prevention of CIN) variables.

**First phase II studies**

The first phase II study to demonstrate the capacity of vaccines using VLP to form neutralizing antibodies was reported in 2002 by Koutsky et al. [4] with the HPV type 16 vaccine developed by Merck Research Laboratories, West point, USA (3 doses of 40 µg of VLP HPV-16 and a schedule of 0, 2, and 6 months). This study, carried out in the United States in women aged 16–23 years, also demonstrated the efficacy and safety of the vaccine. The antibody titers obtained after vaccination were almost 60 times greater than those induced by natural infection. After a follow-up of 17.4 months, the efficacy in preventing persistent infection and CIN was 100% (95% confidence interval [CI]=90–100). The reactogenicity in the groups that received vaccine and placebo (225 µg of adjuvant of Al) was similar. The follow-up of 3.5 years showed a 100% protective efficacy against CIN 2/3 (95% CI=65–100).

In 2004, Harper et al. [5] published the first results of a clinical trial carried out in women aged 15–25 years in the United States, Canada, and Brazil with the GlaxoSmithKline bivalent adjuvant L1 VLP vaccine with AS04 using VLPs of HPV-16 and HPV-18 and a schedule of 0, 1, and 6 months. The antibody titers obtained after vaccination were 107 and 82 times greater for HPV-16 and HPV-18, respectively, than those observed after natural infection. After a follow-up of 27 months, the efficacy in preventing infection and lesions was 100% (95% CI=47.0–100) for persistent infection in the protocol analysis, 95.1% (95% CI=63.5–99.3) for persistent infection in the intention-to-treat analysis, and 92.9% (95% CI=70.0–98.3) for preventing cytological abnormalities associated with HPV-16/18. The study showed a similar general reactogenicity and slightly greater local reactogenicity in the study group than with the placebo (500 µg of A).

In 2005, Villa et al. [6] published the results of a phase II study in women aged 16–23 years from Brazil, Europe, and the United States; participants were followed for 36 months after receiving the quadrivalent HPV (types 6, 11, 16, and 18) L1 VLP vaccine of Sanofi Pasteur MSD. The study showed 90% efficacy (95% CI=71–97) in preventing infection or disease for any of the four vaccine genotypes and 100% efficacy (95% CI=16–100) in preventing clinical disease.

Long-term data from the trial by Harper et al. [5] verified the persistence of protection against persistent infection (94.3%; 95% CI=63.2–99.9) and any type of CIN (100%; 95% CI=42.4–100) 4.5 years after vaccination [7]. In addition, antibody titers against genotypes 16 and 18 remained 11 times greater than those induced by natural infection 5.5 years after vaccination. Antibody levels fell gradually after primary vaccination and reached a plateau from week 18 onwards. These findings, which remain to be confirmed, suggest that the length of protection conferred by this vaccine is prolonged and that it is unlikely that booster doses will be needed, at least in immunocompetent people. However, the role of “natural boosters” in the maintenance of protection is

---

### Table 1

**Prophylactic vaccines against HPV**

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Cervarix</th>
<th>Gardasil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin of the recombinant L1 proteins</td>
<td>Baculovirus</td>
<td><em>Saccharomyces cerevisiae</em></td>
</tr>
<tr>
<td>HPV genotypes</td>
<td>16, 18</td>
<td>6, 11, 16, 18</td>
</tr>
<tr>
<td>Adjuvant</td>
<td>AS04</td>
<td>Aluminum phosphate</td>
</tr>
<tr>
<td>Indication</td>
<td>Prevention of cervical cancer</td>
<td>Prevention of cervical cancer and genital warts</td>
</tr>
<tr>
<td>Dosing schedule</td>
<td>0, 1, and 6 months</td>
<td>0, 2, and 6 months</td>
</tr>
<tr>
<td>FDA approval</td>
<td>Scheduled for 2008</td>
<td>June 2006</td>
</tr>
<tr>
<td>EMEA approval</td>
<td>September 2007</td>
<td>September 2006</td>
</tr>
</tbody>
</table>

HPV, human papillomavirus; FDA, U.S. Food and Drug Administration; EMEA, European Medicine Agency.
unknown, as is the threshold of protection (ie, the minimum antibody titer necessary to prevent wild infection).

In December 2006, Villa et al. [8] investigated the permanence of antibodies after vaccination with the quadrivalent vaccine and found a protective efficacy of 95.6% (95% CI=83.1–99.5) in preventing persistent infection and of 100% (95% CI=12.4–100) in preventing disease (cervical dysplasia or genital warts associated with the vaccine serotypes) 5 years after vaccination. These follow-up studies by Harper and Villa, in addition to other reports, agree that vaccination-induced protection seems to be prolonged.

**Phase III clinical trials**

Partial or preliminary results have been reported from at least two of the large phase III clinical trials, which included more than 40,000 subjects from a large number of countries.

In May 2007, the New England Journal of Medicine published the results of two ongoing studies with Gardasil. The Females United to Unilaterally Reduce Endo/Ecto-Cervical Cancer (FUTURE) I study [9] was a randomized, double-blind, placebo-controlled trial with 3 years of follow-up in 5455 healthy women aged 16–24. The objective was to evaluate vaccine efficacy in preventing external anogenital lesions (genital warts, vulvar and vaginal intraepithelial neoplasia, or cancer) and cervical lesions (CIN, in situ adenocarcinoma, or cancer) caused by HPV types 6, 11, 16, and 18. Vaccine efficacy in preventing external anogenital lesions due to vaccine genotypes was 100% (95% CI=94–100) in the protocol analysis and 73% (95% CI=58–83) in the intention-to-treat analysis. Vaccine efficacy in preventing cervical lesions due to the covered genotypes was 100% (95% CI=94–100) in the protocol analysis and 55% (95% CI=40–66) in the intention-to-treat analysis. Vaccine efficacy was 34% (95% CI=15–49) in preventing external anogenital lesions and 20% (95% CI=8–31) in preventing cervical lesions due to any genotype. The FUTURE II Study [10], which also used Gardasil vaccine, was a randomized double-blind, placebo-controlled trial with 3 years of follow-up in 12,167 healthy women aged 15–26. The objective was to evaluate vaccine efficacy in the prevention of CIN 2/3, in situ adenocarcinoma, or invasive cancer caused by HPV types 16 and 18. The global vaccine efficacy in preventing any type of high-grade lesion was 98% (95% CI=86–100) in the protocol analysis and 44% (95% CI=26–58) in the intention-to-treat analysis. Vaccine efficacy in preventing any type of high-grade lesion due to any HPV genotype was 17% (95% CI=1–31).

In July 2007, The Lancet published the preliminary results of a study on vaccination efficacy of the bivalent Cervarix vaccine (the Papilloma Trial against Cancer in Young Adults [PATRICIA]) [11]. This is the largest study to date. The double-blind trial, which used the hepatitis A vaccine as a control, had a mean follow-up of 15 months after vaccination with the first dose. It was carried out in 18,664 women aged 15–25 from 14 countries in Europe, the Asian-Pacific region, Latin America, and North America. To some degree, this trial can be considered a population-based study, since a large number of women participated, many of whom were already exposed to oncogenic HPV genotypes or had cytological abnormalities. The main objective was to evaluate vaccine efficacy in preventing precancerous lesions associated with HPV types 16 and 18 in women who were DNA negatives and seronegatives for HPV 16/18. The secondary objectives were to determine the efficacy against persistent infections caused by HPV types 16 and 18 and other oncogenic HPV types at 6 and 12 months, as well as the immunogenicity and safety of the vaccine.

Vaccine efficacy in preventing high-grade lesions due to HPV types 16 and 18 was 100% (95% CI=74.2–100). A novel finding of this study was that in precancerous lesions, various oncogenic virus types can coexist; each lesion does not contain a single type, as previously thought. If the analysis of vaccine efficacy considered only the virus types detected in the lesion and not the possible presence of HPV types 16 and/or 18 in cervical samples taken in previous months, vaccination efficacy was 90.4% (95% CI=53.4–99.3). The study also demonstrated cross-protection against persistent infection (6 months) by HPV type 45 (59.9%, 95% CI=2.6–85.2), HPV type 31 (36.1%, 95% CI=0.5–59.5), and HPV type 52 (31.6%, 95% CI=3.5–51.9). Vaccine efficacy in preventing persistent infection (12 months) by 12 nonvaccine oncogenic HPV types was 27.1% (95% CI=0.5–46.8).

**Secondary effects and safety**

Most of the vaccines are used in healthy people. For this reason, the safety profile necessary is much higher than that required for therapeutic drugs.

As indicated, the prophylactic HPV vaccines developed by the two pharmaceutical companies used structural capsule viral proteins obtained by genetic recombination. This type of technology theoretically involves a high safety level, greater than the already high safety profile of inactivated vaccines.

The safety of HPV vaccines demonstrated in the first animal models was corroborated in the phase I and II studies in humans. Studies with monovalent, bivalent, and quadrivalent vaccines consistently found few differences in reactogenicity in the experimental and placebo (generally aluminum salts) groups. Some trials with vaccines using highly immunogenic adjuvant systems, such as AS04, reported greater (mainly local) reactogenicity in the experimental group. Additionally, compliance with the planned doses was similar in the experimental and placebo groups, suggesting good tolerability of the prophylactic HPV vaccines.

Long-term follow-up studies of up to 5.5 years found no differences in the number of adverse events, severe adverse events, or new-onset chronic diseases in the groups compared, thus confirming the safety of HPV vaccines.

The published results of large ongoing phase III trials have corroborated the high safety profile of these vaccines; these trials include: the FUTURE I and II studies with the quadrivalent vaccine and the PATRICIA study with the bivalent vaccine, all of which recruited thousands of women from many countries.

**Vaccination perspectives and public health repercussions**

There is wide consensus that the optimal age of vaccination with HPV vaccines is before the onset of sexual relations, which
varies considerably between countries and cultures. Girls aged 9–14 constitute the ideal age group for routine vaccination and should receive priority care. High coverage should be easier to obtain in communities where vaccination in schools is widely implemented. However, a vaccination schedule limited to this group would take more than 20 years to have an impact on the occurrence of cervical cancer (although the impact would be somewhat earlier for low- and high-grade lesions); therefore, other vaccination strategies are also necessary.

Vaccination strategies should include catch-up vaccination of sexually inactive adolescents and women and of sexually active women who may have been infected already. Vaccinating women already infected by some of the oncogenic types of HPV confers protection only against the remaining genotypes; thus, the benefit of vaccinating these groups will be more limited.

Introducing HPV vaccinations in nonindustrialized countries will be difficult. The new vaccines are relatively expensive owing to the advanced technology required for their development and current regulatory requirements for their authorization. Another potential difficulty will be that vaccines such as the pneumococcal and rotavirus vaccines will be competing for resources, as will the hepatitis B and *Haemophilus influenzae* b vaccines. The Global Alliance for Vaccines and Immunization and more recent initiatives like the Advanced Market Commitments may help to favor the availability of HPV vaccines in the neediest geographic regions [12].

Extending vaccinations to a large proportion of the at-risk population will require good coordination between various sectors, including those concerned with pediatric immunization, sexual and reproductive health, and cancer control.

The progressive development of primary prevention strategies should coexist with secondary prevention of cervical cancer by means of redesigned screening programs. The gradual extension of vaccination will progressively reduce the costs of the diagnosis and treatment of lesions detected by the screening of vaccinated cohorts.

**Final commentary**

The diseases produced by the oncogenic genotypes of HPV have the potential to be eradicated (if it is confirmed that little more than 12 genotypes cause the diseases). For this reason, a long-term eradication strategy will require universal vaccination of females and males.

Almost 300 million women worldwide carry HPV DNA, one third of which carry genotypes 16 and/or 18 [13]. We now possess the scientific basis necessary to apply primary and secondary prevention measures that are capable of substantially reducing the cervical cancer disease burden worldwide. Numerous public health organizations, including the World Health Organization and the European Centre for Disease Prevention and Control, have taken a position on the issue and have published directives favoring the use of these vaccines. The successful development of vaccination programs will also require a substantial financial effort, support of public health authorities, coordination of health workers in different fields, and greater public awareness.

**Conflict of interest statement**

J-MB has investigated vaccines of GlaxoSmithKline and Sanofi Pasteur MSD (papilloma virus vaccine and others vaccines). LC and AM have no conflicts of interest to declare.

**References**


