Human papillomavirus and HPV vaccines: a review

FT Cutts, a S Franceschi, b S Goldie, c X Castellsague, d S de Sanjose, e G Garnett, f WJ Edmunds, g P Claeys, h KL Goldenthal, i DM Harper j & L Markowitz k

Abstract Cervical cancer, the most common cancer affecting women in developing countries, is caused by persistent infection with “high-risk” genotypes of human papillomaviruses (HPV). The most common oncogenic HPV genotypes are 16 and 18, causing approximately 70% of all cervical cancers. Types 6 and 11 do not contribute to the incidence of high-grade dysplasias (precancerous lesions) or cervical cancer, but do cause laryngeal papillomas and most genital warts. HPV is highly transmissible, with peak incidence soon after the onset of sexual activity.

A quadrivalent (types 6, 11, 16 and 18) HPV vaccine has recently been licensed in several countries following the determination that it has an acceptable benefit/risk profile. In large phase III trials, the vaccine prevented 100% of moderate and severe precancerous cervical lesions associated with types 16 or 18 among women with no previous infection with these types. A bivalent (types 16 and 18) vaccine has also undergone extensive evaluation and been licensed in at least one country. Both vaccines are prepared from non-infectious, DNA-free virus-like particles produced by recombinant technology and combined with an adjuvant. With three doses administered, they induce high levels of serum antibodies in virtually all vaccinated individuals. In women who have no evidence of past or current infection with the HPV genotypes in the vaccine, both vaccines show > 90% protection against persistent HPV infection for up to 5 years after vaccination, which is the longest reported follow-up so far. Vaccinating at an age before females are exposed to HPV would have the greatest impact. Since HPV vaccines do not eliminate the risk of cervical cancer, cervical screening will still be required to minimize cancer incidence. Tiered pricing for HPV vaccines, innovative financing mechanisms and multidisciplinary partnerships will be essential in order for the vaccines to reach populations in greatest need.

Introduction Cervical cancer is estimated to affect approximately 500 000 women each year, of whom 80% live in developing countries. Virtually all cervical cancer cases result from genital infection with human papillomavirus (HPV). Well-organized programmes of regular gynaecological screening and treatment of precancerous lesions have been very effective in preventing squamous cervical cancer (the most common kind) but have had less impact on adenocarcinoma and are difficult to implement in low-resource settings. In 2006, a quadrivalent vaccine was licensed in several countries, and a bivalent vaccine has recently been licensed in Australia. Countries will need to consider whether and how to use these new vaccines. This document provides an overview of key information on HPV and HPV vaccines for policy-makers. It is based on a longer document (“Human Papillomavirus and HPV vaccines: technical information for policy-makers and health professionals”) that has been reviewed by an international group of experts, available online at: http://www.who.int/vaccines-documents/DocsPDF07/866.pdf.

HPV and cancers Human papillomaviruses are DNA viruses that infect basal epithelial (skin or mucosal) cells. There is international consensus that “high-risk” genotypes, including genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66, can lead to cervical cancer and are associated with other mucosal anogenital and head and neck cancers. Infections with other genotypes, termed “low-risk,” can cause benign or low-grade cervical tissue changes and genital warts (condyloma acuminata), which are growths on the cervix, vagina, vulva and anus in women and the penis, scrotum or anus in men. They also cause epithelial growths over the vocal cords of children and adults (juvenile respiratory papillomatosis or recurrent respiratory papillomatosis) that require surgical intervention.

Most HPV infections of the cervix are asymptomatic and more than 90% of detected infections are cleared within 2 years. The degree of protection and
duration of immunity after natural infection are not known. Only 50–60% of women develop serum antibodies to HPV after natural infection.4

Early HPV infections may be accompanied by mild changes in the epithelium that are detectable by screening using virological and/or cytological techniques, allowing early treatment. Cytological examination of cervical smears can detect abnormal growth of squamous cells called squamous intraepithelial lesions (SIL) of low or high grade, depending on how much of the cervical epithelium is affected and how abnormal the cells appear. Cervical intraepithelial neoplasia (CIN) is a term for abnormal cells in the cervix that are detected by histological examination of cervical biopsies; grades from 1 to 3 are used to describe the proportion of the thickness of the cervical epithelium composed of abnormal cells seen in the histology section. In CIN 3, abnormal cells span greater than 2/3s of the cervical epithelium. Similar gradings exist for vaginal (VaIN 1–3) and vulvar (VIN 1–3) lesions. As the viral infection persists, it integrates into the human DNA and can lead to cancer precursors: moderate or severe cervical intra-epithelial neoplasia (CIN 2, CIN 3 or adenocarcinoma in situ (AIS), often grouped together as CIN 2/3 or AIS). If these remain untreated, they have a high chance of leading to cancer.5

The main burden of HPV-related disease is due to cervical cancer. HPV was estimated to cause 100% of the almost 260 000 deaths from cervical cancer worldwide in 2005 (http://www.who.int/healthinfo/statistics/bodprojections2030/en/index.html). About 80% of cancer cases attributable to HPV were in developing countries (Table 1).

The highest estimated incidence rates are in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, south-central Asia and south-east Asia. In the most developed countries, the primary economic burden of HPV disease is related to the early detection and management of precancerous lesions.6 Not all developed countries have successfully controlled their cervical cancer burden through screening and early treatment programmes.7

The epidemiology of HPV infection
There have been many studies worldwide on the proportion of cervical cancer, high- and low-grade squamous intraepithelial lesions (HSIL and LSIL) due to different HPV genotypes,8–12 but there are some gaps in Central Asia, Africa and Eastern Europe. With the possible exception of Europe, the same eight HPV genotypes were the most frequent in each region. The relative observed prevalence of HPV genotypes 31, 33, 45, 52 and 58 differed by region. These types cause a much lower proportion of all HPV infections and low-grade cervical lesions. For example, in a recent meta-analysis of HPV type distribution among women with LSIL, among 5910 HPV-positive LSIL lesions; the most common types were HPV 16 (26%), 31 (12%), 51 (11%), 53 (10%), 56 (10%), 52 (9%), 18 (9%), 66 (9%), and 58 (8%). Many other HPV types were also detected and multiple infections were frequent.13

Genital HPV infection is primarily transmitted by genital skin-to-skin contact, usually but not necessarily during sexual intercourse.14–16 HPV infection can occur at any age and has been reported in healthy young children.17 In a cross-sectional study of nearly 20 000 women aged 15–74 years without cervical lesions,18 age-standardized HPV prevalence varied more than 10-fold between populations. There is an inverse relationship between age and human papillomavirus (HPV) prevalence in many countries, but in some of the poorest areas studied HPV prevalence was high across all age groups.19 In some countries, cross-sectional and cohort studies have shown a U-shaped curve with a first peak in women under 30 years of age and a second peak in women aged 55–64 years.14

Among women infected with HIV, a recent meta-analysis found that almost 40% of those with no cervical cytological abnormalities had HPV infection.19 Simultaneous infection with multiple HPV genotypes is more common in HIV-infected women than in women without HIV. HIV-infected men and women are at increased risk of HPV-associated anal cancer.20

HPV infection risk is associated with the number of sex partners that the woman or her partner has had over a lifetime and recently.21–23 Although some cross-sectional studies found no evidence of a reduction in HPV prevalence through condom use,23–25 lower HPV prevalence has been reported among women using condoms with their regular partners26 and a longitudinal study found that consistent condom use protected American college students significantly against new HPV infections and appeared to protect against CIN lesion development.27 A protective effect against HPV infection and cervical cancer incidence has also been reported for women with circumcised partners.28

HPV vaccines
HPV vaccines are prepared from empty protein shells called virus-like particles

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Table 1. HPV-infection attributable cancer in 2002: developed and developing countries

<table>
<thead>
<tr>
<th>Site</th>
<th>Attributable to HPV (%)</th>
<th>Developed countries</th>
<th>Developing countries</th>
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<tbody>
<tr>
<td></td>
<td>Total cancers</td>
<td>Attributable to HPV</td>
<td>Total cancers</td>
</tr>
<tr>
<td>Cervix</td>
<td>100</td>
<td>83 400</td>
<td>83 400</td>
</tr>
<tr>
<td>Penis</td>
<td>40</td>
<td>5 200</td>
<td>2 100</td>
</tr>
<tr>
<td>Vulva, vagina</td>
<td>40</td>
<td>18 300</td>
<td>7 300</td>
</tr>
<tr>
<td>Anus</td>
<td>90</td>
<td>14 500</td>
<td>13 100</td>
</tr>
<tr>
<td>Mouth</td>
<td>&gt;= 3</td>
<td>91 200</td>
<td>2 700</td>
</tr>
<tr>
<td>Oro-pharynx</td>
<td>&gt;= 12</td>
<td>24 400</td>
<td>2 900</td>
</tr>
<tr>
<td>All cancers</td>
<td>5</td>
<td>5 016 100</td>
<td>11 150</td>
</tr>
</tbody>
</table>

Adapted from: Parkin et al.,4 with permission from Elsevier Sciences.
(VLP) produced by recombinant technology. They do not contain any live biological product or DNA, so they are non-infectious. Current HPV vaccines are designed to protect against HPV 16 and 18; the quadrivalent vaccine also protects against low-risk genotypes 6 and 11. Vaccine trials have been conducted predominantly in North America, Latin America and Europe and none have yet been conducted in Africa (Table 2).

One month after the third dose of HPV vaccine, nearly 100% of women aged 15–26 years in trials of either of the vaccines have detectable antibody to each HPV genotype, levels being 10–104 times higher than those in natural infections. Antibody levels achieved after vaccination are inversely related to age. The antibody responses to both the hepatitis B vaccine (recombinant) and the quadrivalent HPV vaccine were similar whether they were administered at the same visit or at different visits. Studies to evaluate the concomitant use of the quadrivalent and bivalent vaccines with other vaccines commonly given to adolescents, such as combined diphtheria, tetanus and pertussis vaccine (Tdap) and meningococcal conjugate vaccine are under way. The vaccines have not yet been evaluated among persons with HIV, severe malnutrition or intercurrent malarial or helminth infection.

For vaccine licensure, the endpoint of CIN 2/3 OR AIS has been widely accepted as a proxy for cervical cancer that can be studied feasibly and ethically among women. In children or young adolescents, bridging studies are conducted by comparing antibody responses in younger persons with those in the women for whom data on the clinical endpoint of CIN 2/3 OR AIS will also be available.

**Protection against infection and its clinical consequences**

For the bivalent vaccine, data in this report are taken from phase II trials, which were powered to detect efficacy against incident (new) or persistent infection with vaccine-type HPV. (Since writing this report, data from the phase III trials of both vaccines have been published, for example see Ault KA; Future II Study Group, *Lancet* 2007; 369:1861-8 for the quadrivalent vaccine and Paavonen et al, *Lancet* 2007; 369:2161-70 for the bivalent vaccine.)

For the quadrivalent vaccine, data in this report are taken both from published phase II trials and from the regulatory presentations for the phase III trials that evaluated efficacy against the clinical endpoints of moderate-severe cervical precancer (CIN 2/3 OR AIS), genital warts and vaginal and vulvar pre-cancerous lesions (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222b-index.htm, and http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222b-index.htm). The primary analyses were conducted among women vaccinated according to protocol (no major deviations) who did not have evidence of past or current infection with the relevant HPV genotypes included in the vaccines until at least one month after the third dose.

Both vaccines have demonstrated efficacy of over 90% against persistent infection due to genotypes 16 or 18 in women who received 3 doses of HPV vaccine. For the bivalent vaccine, phase II trials showed zero cases of 16/18-related CIN 2 among 481 vaccinated women and five cases among 470 women who received 3 doses of HPV vaccine. For the quadrivalent vaccine, Table 3 shows results at a median of

<table>
<thead>
<tr>
<th>Table 2. Characteristics of two candidate HPV vaccines and trial populations</th>
</tr>
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<tbody>
<tr>
<td><strong>Manufacturer and trade name</strong></td>
</tr>
<tr>
<td>Virus-like particles (VLPs) of genotypes</td>
</tr>
<tr>
<td>Substrate</td>
</tr>
<tr>
<td>Adjuvant</td>
</tr>
<tr>
<td>Schedule used in trials: 3 intramuscular doses of 0.5 ml with intervals of:</td>
</tr>
<tr>
<td>Countries/regions included in phase II trials</td>
</tr>
<tr>
<td>Countries/regions included in phase III trials</td>
</tr>
<tr>
<td>Adolescent safety/immunogenicity bridging trials</td>
</tr>
<tr>
<td>Other trials in progress or due to start</td>
</tr>
</tbody>
</table>

**Notes**


3. Policy and practice

4. Human papillomavirus and HPV vaccines

5. FT Cutts et al.
1.5 years after vaccination. For CIN 2/3 or AIS, the results shown are the combined results from four trials; for the remaining endpoints in the table, results are from three trials (007, 013 and 015) ([http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm](http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm)).

HPV vaccines are designed to be prophylactic (i.e. to prevent infection and consequent disease). Data on efficacy, immunogenicity and safety in women who have already been exposed to vaccine-type HPV are only available for the quadrivalent vaccine. Overall, no protective effect against CIN 2/3 OR AIS was seen among women who had already been infected with HPV 16 and 18 before vaccination ([http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm](http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm)).

Among all women enrolled in the trials (including those not vaccinated according to protocol and those with baseline evidence of past or current HPV infection), the observed efficacy against CIN 2/3 OR AIS was much lower than among the women with no evidence of past HPV infection. Nonetheless, because only a very small minority of women had already been infected with all four HPV vaccine-types at baseline, based on the possible efficacy for other vaccine types in women already infected with one vaccine-related type, it is not necessary to screen for HPV before vaccinating women.

Although screening is not needed to decide on eligibility for vaccination, screening will still be needed among vaccinated women, e.g. these women will continue to be at risk of infection with other types of HPV that can cause CIN lesions and cervical cancer.

### Cross-protection against other genotypes

In preliminary analyses, both vaccines have shown some evidence of cross-protection against HPV 31 and HPV 45, closely related HPV types to HPV 16 and 18, respectively. In the extended follow-up of the phase II trials of the bivalent vaccine, a significant reduction was found in incident infection with type 45 (1 case in 528 vaccinated women and 17 cases in 518 controls; vaccine efficiency (VE) = 94.2% [63.3, 99.9]) and type 31 (14 versus 30 cases, respectively; VE = 54.5% [11.5, 77.7])

For the quadrivalent vaccine, a study of ten vaccine recipients in the phase II trial who were seronegative and HPV DNA negative at baseline for HPV 6, 11, 16, 18, 31 and 45 showed that serum antibodies from 10 of 10 women neutralized HPV 18 pseudovirions, six out of 10 neutralized HPV type 45 pseudovirions and eight out of 10 neutralized HPV type 31 pseudovirions.

For cross-protection to be clinically meaningful, it will be necessary to demonstrate that administration of HPV vaccines reduces the incidence of persistent HPV infection and biopsy-proven CIN caused by HPV types related to HPV 16 and HPV 18. Studies are continuing for both vaccines.

### Duration of protection

Antibody levels fall by about one log between the peak after the third dose and 18 months after vaccination and then level off, and have remained as high or higher than those seen after natural infection for the approximately 5 years of follow-up analysed to date.

Note that the minimum protective antibody threshold for disease protection is not known. Early results from the quadrivalent vaccine trials show an increase in antibody titres to a challenge dose given five years after initial vaccination.

Protection against persistent infection has been demonstrated for up to 5 years post-enrollment in phase II studies, the longest reported follow-up so far. Follow-up studies are planned for both vaccines to determine duration of antibody and clinical protection among women through at least 14 years after dose 3.

### Adverse events

For the quadrivalent vaccine, detailed safety data reviewed by the US Food and Drug Administration are included in the label and are available at [http://www.gardasil.com/](http://www.gardasil.com/). Injection site pain, erythema and oedema were common and occurred significantly more often for vaccine recipients than placebo recipients. Few subjects (0.1%) discontinued due to adverse experiences. Overall, there were no differences in the proportion of women developing a serious adverse event in the vaccine or placebo group. A detailed post-licensure plan is in place to obtain additional safety data.

### Cost-effectiveness of HPV vaccine

Knowledge of the burden of disease, safety and effectiveness of HPV vaccine is not enough to decide whether to introduce HPV vaccine. The estimated costs of and benefits from HPV vaccine need to be compared to those of other interventions. The magnitude of benefit in a specific country will depend on the incidence, mortality and treatment...
costs of disease attributable to the HPV genotypes against which the vaccines protect, as well as on the vaccine efficacy, achievable coverage and duration of protection. \(^3\)

Cervical cancer is estimated to cause 91% of HPV-related cancer deaths, and its control is a high priority globally. In countries where the treatment of other HPV-associated conditions (e.g. genital warts, recurrent respiratory papillomatosis and other HPV-related cancers) is costly, there may also be substantial cost savings from avoidance of these conditions. \(^9\) In addition, the time from vaccination to prevention of genital warts is much shorter than that to cancer. \(^40\)

In countries with limited or no screening and low access to treatment, the major predicted benefit from HPV vaccination is the potential reduction in cervical cancer deaths. Preliminary results from cost-effectiveness models in low- and middle-income countries suggest that a combination of HPV vaccination and screening 1–3 times per lifetime can be cost-effective for cervical cancer prevention, \(^41\) though not at current vaccine prices. Further work is needed to assess how robust this finding is in different settings.

The coverage that is achievable with three doses of HPV vaccine among pre-adolescent girls is the major determinant of overall programme effectiveness. Modelling is ongoing to estimate the potential added benefits and costs from including older women and/or males in vaccination programmes. Direct protection of the individual is expected to decline as age at vaccination increases, as older women will be more likely to have had prior HPV infection. Catch-up campaigns may shorten the time until impact is seen on disease outcomes. The potential benefits of vaccinating males may include direct protection against certain HPV-related conditions and indirect protection of women by reducing transmission of HPV. Results of dynamic simulation models of HPV transmission suggest that if high coverage of females can be achieved, there is little additional reduction in cervical cancer to be gained by vaccinating males. \(^42\) At lower coverage, vaccination of boys may contribute to controlling infection, but because vaccination directly protects women from cervical cancer, more gains may be derived per additional girl vaccinated than per boy vaccinated. Validation of predictions based on these complex models will require long-term field implementation studies. Furthermore, the potential acceptability and coverage of a strategy targeting girls only against one including both sexes should also be considered.

The current price of the quadrivalent vaccine is over $100 per dose (with three doses recommended to achieve full protection). Manufacturers have declared their willingness to tier prices for countries with different economic settings. Vaccine price is likely to be a major determinant of the cost and affordability of any vaccine programme. Administration costs are expected to be higher than for traditional vaccines, since very few countries have universal programmes for delivering health care to pre-adolescents. \(^43\)

**Conclusions**

In developing countries, cervical cancer is the leading cause of cancer death in women, and 91% of global estimated HPV-related cancer deaths are due to cervical cancer. HPV vaccines are very effective at preventing infection and disease related to the vaccine-specific genotypes in women with no evidence of past or current HPV infection. Protection lasts for at least 5 years. Data are not yet available on the safety and efficacy of HPV vaccines in Africa, nor in populations with high HIV prevalence. HPV vaccines will reduce but not eliminate the risk of cervical cancer, and screening programmes will be important interventions for cervical cancer even after HPV vaccines are introduced, although the procedures used for screening may need to be adapted. \(^45\)

The primary target age group for HPV vaccines is likely to be pre-adolescent girls, but the cost-effectiveness of vaccinating other groups needs to be evaluated. Further data on regional and country variations in HPV epidemiology, the natural history and transmission of HPV infection, the mechanism and duration of protection by HPV vaccines, whether cross-protection is confirmed and the costs and effectiveness of different strategies for vaccination and screening will improve predictions of the benefits of these new vaccines. \(^46\) \(^47\)

If a two-dose schedule could be used or vaccination could be given at an earlier age when other vaccines are given (e.g. school-entry or even infancy), vaccine delivery could be greatly facilitated, and evaluation of these options is urgently required. Innovative methods will be needed to finance HPV vaccine introduction. \(^48\) The potential future introduction of HPV vaccines creates opportunities for strengthening health systems by rapidly establishing new partnerships for vaccine delivery, financing and monitoring of impacts. \(^49\)

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Recientemente se ha aprobado en varios países una vacuna anti-PVH tetravalente (contra los tipos 6, 11, 16 y 18) después de que se haya demostrado que presenta una relación aceptable entre los riesgos y los beneficios. En los ensayos clínicos de fase III a gran escala, la vacuna evitó el 100% de las lesiones cervicales precancerosas moderadas y graves asociadas a los tipos 16 y 18, que causan aproximadamente un 70% de los cánceres del col útero, en mujeres no infectadas previamente por estos tipos de PVH. Aunque las vacunas anti-PVH no eliminan el riesgo de cáncer cervicouterino, siguen siendo necesarias pruebas de detección de esta neoplasia para reducir al mínimo su incidencia. Los precios diferenciales de las vacunas anti-PVH, los mecanismos de financiación innovadores y las alianzas pluridisciplinarias serán esenciales para hacer llegar estas vacunas a las poblaciones que más las necesitan.

Resumen

Papilomavirus humanos y vacunas anti-PVH: revisión

El cáncer cervicouterino, el más frecuente en mujeres de los países en desarrollo, es causado por la infección persistente por papilomavirus humanos (PVH) de los genotipos llamados de alto riesgo. Los genotipos oncogénicos más frecuentes son el 16 y el 18, que causan aproximadamente un 70% de los cánceres cervicouterinos. Los tipos 6 y 11 no contribuyen a la incidencia de las displasias de alto grado (lesiones precancerosas) ni del cáncer cervicouterino, pero causan papilomas laringeos y la mayoría de las verrugas genitales. Los PVH son muy transmitibles y su incidencia máxima se registra poco después del inicio de la actividad sexual.

Recentemente se ha aprobado en varios países una vacuna anti-PVH tetravalente (contra los tipos 6, 11, 16 y 18), después de que se haya demostrado que presenta una relación aceptable entre los riesgos y los beneficios. En los ensayos clínicos de fase III a gran escala, la vacuna evitó el 100% de las lesiones cervicales precancerosas moderadas y graves asociadas a los tipos 16 y 18 en mujeres no infectadas previamente por estos tipos de PVH. También se ha evaluado exhaustivamente una vacuna bivalente (contra los tipos 16 y 18) que ha sido aprobada al menos en un país. Ambas vacunas están preparadas con partículas no infecciosas, carentes de DNA, similares a los virus, producidas mediante técnicas de recombinación y combinadas con un adyuvante. Tras la aplicación de dosis, inducen concentraciones elevadas de anticuerpos séricos en prácticamente todas las personas vacunadas. En las mujeres sin infección pasada ni actual por los genotipos de PVH presentes en esas vacunas, ambas proporcionan una protección ≥ 90% frente a la infección persistente por PVH durante periodos de hasta 5 años tras la vacunación (el máximo tiempo de seguimiento en los estudios realizados). El mayor impacto debería obtenerse con la vacunación de las mujeres antes de la edad de exposición a los PVH. Como las vacunas anti-PVH no eliminan el riesgo de cáncer cervicouterino, siguen siendo necesarias pruebas de detección de esta neoplasia para reducir al mínimo su incidencia. Los precios diferenciales de las vacunas anti-PVH, los mecanismos de financiación innovadores y las alianzas pluridisciplinarias serán esenciales para hacer llegar estas vacunas a las poblaciones que más las necesitan.
Policy and practice
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