

# Human papillomavirus and HPV vaccines: a review

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**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.

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Une traduction en français de ce résumé figure à la fin de l'article. Al final del artículo se facilita una traducción al español. الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

## 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<sup>1</sup> 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<sup>2</sup> 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.<sup>3</sup> The degree of protection and

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

Site	Attributable to HPV (%)	Developed countries		Developing countries	
		Total cancers	Attributable to HPV	Total cancers	Attributable to HPV
Cervix	100	83 400	83 400	409 400	409 400
Penis	40	5 200	2 100	21 100	8 400
Vulva, vagina	40	18 300	7 300	21 700	8 700
Anus	90	14 500	13 100	15 900	14 300
Mouth	> = 3	91 200	2 700	183 100	5 500
Oro-pharynx	> = 12	24 400	2 900	27 700	3 300
All cancers	5	5 016 100	111 500	5 827 500	449 600

Adapted from: Parkin et al.,<sup>7</sup> with permission from Elsevier Sciences.

duration of immunity after natural infection are not known. Only 50–60% of women develop serum antibodies to HPV after natural infection.<sup>4</sup>

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.<sup>5</sup>

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.<sup>6</sup> Not all developed countries have successfully controlled their cervical cancer burden through screening and early treatment programmes.<sup>7</sup>

### 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,<sup>8–12</sup> 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, 35, 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.<sup>13</sup>

Genital HPV infection is primarily transmitted by genital skin-to-skin contact, usually but not necessarily during sexual intercourse.<sup>14–16</sup> HPV infection can occur at any age and has been reported in healthy young children.<sup>17</sup> In a cross-sectional study of nearly 20 000

women aged 15–74 years without cervical lesions,<sup>18</sup> 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.<sup>18</sup> 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.<sup>14</sup>

Among women infected with HIV, a recent meta-analysis found that almost 40% of those with no cervical cytological abnormalities had HPV infection.<sup>19</sup> 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.<sup>20</sup>

HPV infection risk is associated with the number of sex partners that the woman or her partner has had over a lifetime and recently.<sup>21–23</sup> Although some cross-sectional studies found no evidence of a reduction in HPV prevalence through condom use,<sup>23–25</sup> lower HPV prevalence has been reported among women using condoms with their regular partners<sup>26</sup> 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.<sup>27</sup> A protective effect against HPV infection and cervical cancer incidence has also been reported for women with circumcised partners.<sup>28</sup>

### HPV vaccines

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

Table 2. Characteristics of two candidate HPV vaccines and trial populations

Manufacturer and trade name	Quadrivalent vaccine		Bivalent vaccine	
	Merck [Gardasil]		GlaxoSmithKline [Cervarix]	
Virus-like particles [VLPs] of genotypes	6, 11, 16, 18		16, 18	
Substrate	Yeast [ <i>S. cerevisiae</i> ]		Baculovirus expression system	
Adjuvant	Proprietary aluminium hydroxyphosphate sulfate (225µg) (Merck aluminium adjuvant)		Proprietary aluminium hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)	
Schedule used in trials: 3 intramuscular doses of 0.5 ml with intervals of:	Two months between doses 1 and 2; six months between doses 1 and 3		One month between doses 1 and 2; six months between doses 1 and 3	
Countries/regions included in phase II trials	Brazil (34%); Europe (21%); USA (45%)		Brazil and North America (over 50% of women were from Brazil)	
Countries/regions included in phase III trials	N. America (25%); Latin America (27%); Europe (44%); Asia-Pacific (4%)		N. America (12%); Latin America (34%); Europe (30%); Asia-Pacific (25%)	
Adolescent safety/immunogenicity bridging trials	Females and males 9–15 years		Females 10–14 years Males 10–18 years	
Other trials in progress or due to start	Efficacy, immunogenicity bridging and safety studies in women 25–45 years; studies of administration at the same time as other vaccines; safety and immunogenicity in HIV-infected persons and other immunocompromised groups; efficacy study in males		Efficacy, immunogenicity bridging and safety studies in women > 26 years; studies of administration at the same time as other vaccines; safety and immunogenicity in African populations, including HIV-infected women	

(VLP) produced by recombinant technology.<sup>29,30</sup> 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.<sup>31–33</sup> 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 meningo-

coccal 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.<sup>31,32</sup> (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 precancerous lesions (<http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm>, and <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-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.<sup>32,34</sup> 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 in the placebo group, for an efficacy of 100% (95% CI: -7.7, 100).<sup>32</sup> For the quadrivalent vaccine, Table 3 shows results at a median of

Table 3. Efficacy of the quadrivalent vaccine against clinical endpoints among women aged 16–26 years (mean 20) in the per protocol efficacy population<sup>a</sup>

Clinical endpoint	Vaccine		Placebo		Vaccine efficacy % (95% CI)
	No. of women	No. of cases	No. of women	No. of cases	
HPV 16/18-related CIN 2/3 OR AIS	8 487	0	8 460	53	100% (92.9, 100)
HPV 6/11/16/18-related VIN 2/3	7 897	0	7 899	8	100% (41.4, 100)
HPV 6/11/16/18-related VaIN 2/3	7 897	0	7 899	5	100% (< 0, 100)
HPV 6/11/16/18-related genital warts (condyloma)	7 897	1	7 899	91	98.9% (93.7, 100)

CI, confidence interval.

<sup>a</sup> Consists of individuals who received all 3 vaccinations within 1 year of enrolment, did not have major deviations from the study protocol, and were naïve (PCR negative in cervicovaginal specimens and seronegative) to the relevant HPV type(s) (Types 6, 11, 16, and 18) prior to dose 1 and through 1 month Post-dose 3 (Month 7).

Source: <http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm>, FDA presentation, slides 31 and 48.

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/briefing/2006-4222b-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>).

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])<sup>32</sup> 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.<sup>35</sup>

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.<sup>32,36,37</sup> 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.<sup>37</sup>

Protection against persistent infection<sup>32</sup> or a combined endpoint of persistent infection and all genital diseases<sup>36</sup> 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/>. 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

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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.<sup>38</sup>

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.<sup>39</sup> In addition, the time from vaccination to prevention of genital warts is much shorter than that to cancer.<sup>40</sup>

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,<sup>41</sup> 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.<sup>42,43</sup> At lower coverage, vaccination of boys may contribute to controlling infec-

tion, 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.<sup>44</sup>

## 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.<sup>45</sup>

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.<sup>46,47</sup>

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.<sup>48</sup> 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.<sup>49</sup> ■

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## Résumé

### Virus du papillome humain et vaccins anti-VPH : bilan

Le cancer du col utérin, forme la plus courante de cancer chez les femmes des pays en développement, est due à l'infection persistante par des génotypes « à haut risque » du virus du papillome humain (PVH). Les génotypes à risque oncogène les plus courants du PVH sont les types 16 et 18, qui sont à l'origine d'environ 70 % des cancers du col utérin. Les types 6 et 11 ne contribuent pas à l'incidence des dysplasies de haut grade (lésions précancéreuses) ou des cancers du col, mais sont la cause de papillomes laryngés et de la plupart des condylomes acuminés. Le VPH est hautement transmissible et présente un pic d'incidence immédiatement après le début de l'activité sexuelle des individus.

Un vaccin anti-VPH quadrivalent (contre les types 6, 11, 16 et 18) a été récemment autorisé dans plusieurs pays après confirmation de l'acceptabilité de son profil risque/bénéfice. Dans le cadre d'essais de phase III de grande ampleur, le vaccin a prévenu 100 % des lésions cervicales précancéreuses de gravité modérée et forte associées aux types 16 et 18 chez les femmes exemptes au départ d'infection par ces génotypes. Un vaccin bivalent (contre les types 16 et 18) a aussi fait l'objet d'une évaluation complète

et a été autorisé dans un pays au moins. Ces deux vaccins sont préparés à partir de particules pseudo-virales dépourvues d'ADN et non-infectieuses, produites par génie génétique et associées à un adjuvant. Après administration en trois doses, ils induisent la production de titres d'anticorps sériques élevés chez presque tous les individus vaccinés. Chez les femmes ne présentant aucun indice d'infection antérieure ou actuelle par des VPH appartenant aux génotypes vaccinaux, ils apportent tous deux une protection de plus de 90 % contre les infections à VPH persistantes sur une période postvaccinale allant jusqu'à 5 ans (qui est aussi la plus longue durée de suivi rapportée à ce jour). L'effet de la vaccination devrait être maximal si l'on vaccine la population féminine avant qu'elle soit exposée aux VPH. Les vaccins anti-VPH n'éliminant pas le risque de cancer du col utérin, les examens de dépistage de ce cancer resteront nécessaires pour réduire au minimum son incidence. Pour que ces vaccins atteignent les populations qui en ont le plus besoin, il est extrêmement important de mettre en place une gradation des prix, des mécanismes de financement innovants et des partenariats multidisciplinaires.

## 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 laríngeos y la mayoría de las verrugas genitales. Los PVH son muy transmisibles y su incidencia máxima se registra poco después del inicio de la actividad sexual.

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 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 administración de tres 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.

## ملخص

### استعراض لفيروس الورم الحليمي البشري ولقاحاته

وقد تم الترخيص باستخدام لقاح رباعي التكافؤ ضد فيروس الورم الحليمي البشري (للأنماط 6، 11، 16، 18) في عدد من البلدان، بعد أن ثبت أن مجمل فوائده ومخاطره تقع في الحدود المقبولة. ففي تجارب المرحلة الثالثة، نجح اللقاح في إنقاذ 100% من آفات عنق الرحم المتوسطة والشديدة السابقة للتسرطن والمرتبطة بالنمطين 16 و 18، وذلك بين السيدات اللاتي لم تسبق إصابتهن بالعدوى بهذين النمطين. كما خضع لقاح ثنائي التكافؤ (من النمطين 16 و 18) لتقييم واسع النطاق ورخص باستخدامه في بلد واحد على الأقل. وكلا اللقاحين تم تحضيره من جسيمات غير معدية، شبيهة بالفيروس وخالية من حمض الدنا DNA، تم إنتاجها بتكنولوجيا المشروبات

ينجم سرطان عنق الرحم، الذي يُعد النمط الأكثر شيوعاً للسرطان بين الإناث في البلدان النامية، عن عدوى مستديمة بأنماط جينية عالية الخطار بفيروس الورم الحليمي البشري. ويُعتبر النمطان 16 و 18 من الفيروس أكثر الأنماط الجينية المسرطنة شيوعاً، إذ يتسببان في نحو 70% من جميع حالات الإصابة بسرطان عنق الرحم. أما النمطان 6 و 11 فلا يسهمان في حدوث خلل التنسج العالي الدرجة (الآفات السابقة للتسرطن) أو سرطان عنق الرحم، ولكن يسببان الأورام الحليمية للحنجرة ومعظم الأمراض التولوية التناسلية. ويتميز فيروس الورم الحليمي البشري بقدرة عالية على السراية، وتحدث ذروة وقوعه بعد بدء النشاط الجنسي مباشرةً.

أكبر الأثر. ونظراً لأن لقاحات فيروس الورم الحليمي البشري لا تقضي على مخاطر الإصابة بسرطان عنق الرحم، فسوف يستدعي الأمر مواصلة فحص عنق الرحم، بغية الحد من وقوع السرطان قدر الإمكان. كما سيستلزم الأمر تحديد أسعار متفاوتة للقاحات فيروس الورم الحليمي، واتخاذ آليات مبتكرة للتمويل، وإقامة شراكات متعددة التخصصات، لضمان وصول اللقاحات إلى الفئات السكانية الأشد احتياجاً إليها.

وأضيف إليها عامل مساعد. ويؤدي إعطاء ثلاث جرعات من اللقاحين إلى إنتاج مستويات عالية من أضداد المصل في جميع الأفراد الذين تلقوا اللقاح تقريباً. أما السيدات التي لا توجد بينات على إصابتهن بعدوى سابقة أو حالية بالأعماط الجينية لفيروس الورم الحليمي البشري الموجودة في اللقاح، فقد منحهن اللقاحان وقاية تزيد على 90% ضد العدوى المستدئمة بالفيروس لمدة تصل إلى 5 سنوات بعد التطعيم، وهي أطول مدة متابعة حتى الآن. ولوحظ أن التطعيم في سن يسبق تعرُّض الإناث للفيروس قد يكون له

## References

- Chew GK, Cruickshank ME, Rooney PH, Miller ID, Parkin DE, Murray GI. Human papillomavirus 16 infection in adenocarcinoma of the cervix. *Br J Cancer* 2005;93:1301-4.
- IARC monographs on the evaluation of carcinogenic risks to humans, volume 90, human papillomaviruses. Lyon: International Agency for Research on Cancer; 2006.
- Moscicki AB, Schiffman M, Kjaer S, Villa LL. Chapter 5: Updating the natural history of HPV and anogenital cancer. *Vaccine* 2006;24:S42-51.
- Carter JJ, Koutsky LA, Hughes JP, Lee SK, Kuypers J, Kiviat N, et al. Comparison of human papillomavirus types 16, 18, and 6 capsid antibody responses following incident infection. *J Infect Dis* 2000;181:1911-9.
- Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993;12:186-92.
- Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med* 2003;127:946-9.
- Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine* 2006;24:S11-25.
- Munoz N, Bosch FX, Castellsague X, Diaz M, De Sanjose S, Hammouda D, et al. Against which human papillomavirus types shall we vaccinate and screen? The international perspective. *Int J Cancer* 2004;111:278-85.
- Clifford GM, Smith JS, Aguado T, Franceschi S. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *Br J Cancer* 2003;89:101-5.
- Clifford GM, Smith JS, Plummer M, Munoz N, Franceschi S. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *Br J Cancer* 2003;88:63-73.
- Clifford G, Franceschi S, Diaz M, Munoz N, Villa LL. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine* 2006;24:S26-34.
- Smith JS, Lindsay L, Hoots B, Keys J, Franceschi S, Winer R, et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions: a meta-analysis update. *Int J Cancer* 2007 Aug 1;121(3):621-32.
- Clifford GM, Rana RK, Franceschi S, Smith JS, Gough G, Pimenta JM. Human papillomavirus genotype distribution in low-grade cervical lesions: comparison by geographic region and with cervical cancer. *Cancer Epidemiol Biomarkers Prev* 2005;14:1157-64.
- Munoz N, Mendez F, Posso H, Molano M, van den Brule AJ, Ronderos M, et al. Incidence, duration, and determinants of cervical human papillomavirus infection in a cohort of Colombian women with normal cytological results. *J Infect Dis* 2004;190:2077-87.
- Castle PE, Schiffman M, Herrero R, Hildesheim A, Rodriguez AC, Bratti MC, et al. A prospective study of age trends in cervical human papillomavirus acquisition and persistence in Guanacaste, Costa Rica. *J Infect Dis* 2005;191:1808-16.
- Kjaer SK, Chackerian B, van den Brule AJ, Svare EI, Paull G, Walbomers JM, et al. High-risk human papillomavirus is sexually transmitted: evidence from a follow-up study of virgins starting sexual activity (intercourse). *Cancer Epidemiol Biomarkers Prev* 2001;10:101-6.
- Antonsson A, Karanfilovska S, Lindqvist PG, Hansson BG. General acquisition of human papillomavirus infections of skin occurs in early infancy. *J Clin Microbiol* 2003;41:2509-14.
- Franceschi S, Herrero R, Clifford GM, Snijders PJ, Arslan A, Anh PT, et al. Variations in the age-specific curves of human papillomavirus prevalence in women worldwide. *Int J Cancer* 2006. Dec 1;119(11):2677-84.
- Clifford GM, Goncalves MA, Franceschi S, for the HPV and HIV Study Group. Human papillomavirus types among women infected with human immunodeficiency virus: a meta-analysis. *AIDS* 2006. Dec 20(18):2337-44.
- Palefsky JM, Gillison ML, Strickler HD. Chapter 16: HPV vaccines in immunocompromised women and men. *Vaccine* 2006;24:S140-6.
- Franco E, Villa L, Rohan T, Ferenczy A, Petzl-Erler M, Matlashewski G. Design and methods of the Ludwig-McGill longitudinal study of the natural history of human papillomavirus infection and cervical neoplasia in Brazil. Ludwig-McGill Study Group. *Rev Panam Salud Publica* 1999;6:223-33.
- Vaccarella S, Franceschi S, Herrero R, Munoz N, Snijders PJ, Clifford GM, et al. Sexual behavior, condom use, and human papillomavirus: pooled analysis of the IARC human papillomavirus prevalence surveys. *Cancer Epidemiol Biomarkers Prev* 2006;15(2):326-33.
- Vaccarella S, Herrero R, Dai M, Snijders PJF, Meijer CJLM, Thomas JO, et al. Reproductive factors, oral contraceptive use and HPV infection: pooled analysis of the IARC HPV Prevalence Surveys. *Cancer Epidemiol Biomarkers Prev* 2006. Nov;15(11):2148-53.
- Jamison JH, Kaplan DW, Hamman R, Eagar R, Beach R, Douglas JM Jr. Spectrum of genital human papillomavirus infection in a female adolescent population. *Sex Transm Dis* 1995;22:236-43.
- Young TK, McNicol P, Beauvais J. Factors associated with human papillomavirus infection detected by polymerase chain reaction among urban Canadian aboriginal and non-aboriginal women. *Sex Transm Dis* 1997;24:293-8.
- De Sanjose S, Almira R, Lloveras B, Font R, Diaz M, Munoz N, et al. Cervical human papillomavirus infection in the female population in Barcelona, Spain. *Sex Transm Dis* 2003;30:788-93.
- Winer RL, Hughes JP, Feng Q, O'Reilly S, Kiviat NB, Holmes KK, et al. Condom use and the risk of genital human papillomavirus infection in young women. *N Engl J Med* 2006;354:2645-54.
- Castellsague X, Bosch FX, Munoz N, Meijer CJ, Shah KV, De Sanjose S, et al. Male circumcision, penile human papillomavirus infection, and cervical cancer in female partners. *N Engl J Med* 2002;346:1105-12.
- Zhou J, Sun XY, Stenzel DJ, Frazer IH. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology* 1991;185:251-7.
- Hagensee ME, Yaegashi N, Galloway DA. Self-assembly of human papillomavirus type 1 capsids by expression of the L1 protein alone or by coexpression of the L1 and L2 capsid proteins. *J Virol* 1993;67:315-22.
- Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuid A, et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet* 2004;364:1757-65.
- Harper DM, Franco EL, Wheeler CM, Moscicki AB, Romanowski B, Roteli-Martins CM, 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 a randomised control trial. *Lancet* 2006;367:1247-55.
- Villa LL, Ault KA, Giuliano AR, Costa RL, Petta CA, Andrade RP, et al. Immunologic responses following administration of a vaccine targeting human papillomavirus types 6, 11, 16, and 18. *Vaccine* 2006;24:5571-83.
- Villa LL, Costa RL, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *Lancet Oncol* 2005;6:271-8.
- Smith JF, Brownlow MK, Brown MJ, Esser MT, Ruiz W, Brown DR. *Gardasil antibodies cross-neutralize pseudovirion infection of vaccine-related HPV types*. 23rd International Papillomavirus Conference and Clinical Workshop Abstract PL 1-6, Prague, September 1-7 2006.

36. Villa LL, Costa RLR, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. *Efficacy of a prophylactic quadrivalent Human Papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine through up to 5 years of follow-up*. Abstract for European Research Organization on Genital Infection and Neoplasia (EUROGIN), Paris, 2006.
37. Villa ML, Costa RLR, Petta CA, Andrade RP, Ault KA, Giuliano AR, et al. *Induction of immune memory following administration of a prophylactic quadrivalent human papillomavirus (HPV) types 6/11/16/18 L1 virus-like particle (VLP) vaccine*. 12th International Conference on Infectious Diseases, Lisbon, 2006.
38. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX, et al. *Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine*. *J Natl Cancer Inst* 2004;96:604-15.
39. Insinga RP, Dasbach EJ, Elbasha EH. *Assessing the annual economic burden of preventing and treating anogenital human papillomavirus-related disease in the US: analytic framework and review of the literature*. *Pharmacoeconomics* 2005;23:1107-22.
40. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: *Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease*. *Vaccine* 2006;24:S35-41.
41. Goldie SJ, Kim JJ, Kobus KE, Holtan MK, Kuntz KM, Salomon JA. *Cost-effectiveness analysis of prophylactic human papillomavirus vaccination and screening in Brazil*. *Poster presentation*. 23rd International Papillomavirus Conference and Clinical Workshop, 1-7 September 2006, Prague.
42. Garnett GP, Kim JJ, French K, Goldie SJ. Chapter 21: *Modelling the impact of HPV vaccines on cervical cancer and screening programmes*. *Vaccine* 2006;24:S178-86.
43. Barnabas RV, Laukkanen P, Koskela P, Kontula O, Lehtinen M, Garnett GP. *Epidemiology of HPV 16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses*. *PLoS Med* 2006;3:e138.
44. Kane MA, Sherris J, Coursaget P, Aguado T, Cutts F. Chapter 15: *HPV vaccine use in the developing world*. *Vaccine* 2006;24:S132-9.
45. Franco EL, Cuzick J, Hildesheim A, De Sanjose S. Chapter 20: *Issues in planning cervical cancer screening in the era of HPV vaccination*. *Vaccine* 2006;24 (Supl 3):S3/171-77.
46. Franco EL, Bosch FX, Cuzick J, Schiller JT, Garnett GP, Meheus A, et al. Chapter 29: *Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer*. *Vaccine* 2006;24:S242-9.
47. Hildesheim A, Markowitz L, Avila MH, Franceschi S. Chapter 27: *Research needs following initial licensure of virus-like particle HPV vaccines*. *Vaccine* 2006;24:S227-32.
48. Batson A, Meheus F, Brooke S. Chapter 26: *Innovative financing mechanisms to accelerate the introduction of HPV vaccines in developing countries*. *Vaccine* 2006;24:S219-25.
49. United Nations Family Planning Association. *Preparing for the introduction of HPV vaccines: policy and programme guidance for countries*. Geneva: WHO; 2006. WHO/RHR/06.11.