Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals

Initiative for Vaccine Research
Department of Immunization, Vaccines and Biologicals
World Health Organization

World Health Organization

Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals

Contents

Acknowledgements

This document is based on the deliberations of the following experts, who attended a meeting of the WHO Human Papillomavirus Expert Advisory Group, held on 3-4 August 2006 in Geneva, Switzerland:

Jan Agosti, Daniel Barth-Jones, Robin Biellik, Nathalie Boswell, Loretta Brabin, James Cheyne, Patricia Claeys, Mahima Datla, Ciro de Quadros, Ketayun Dinshaw, John Edmunds, Elamin Elbasha, Silvia Franceschi, Patricia Garcia, Geoffrey Garnett, Karen Goldenthal, Sue Goldie, Diane Harper, Rob Hecht, David Jenkins, Jessica Kahn, Ryoko Krause, Jovelle Laoag-Fernandez, Lauri Markowitz, Nubia Munoz, Jay Pearson, Punnee Pitisuttithum, Amy Pollack, David Ross, Alfred Saah, Maria Stella de Sabata, Silvia De Sanjose Llongueras, Helen Saxenian, Jacqueline Sherris, Vivien Tsu, Jimmy Whitworth. Additional comments were provided by Ian Frazer, Jeffrey Partridge and Margaret Stanley.

The following WHO staff attended the meeting:

Teresa Aguado, Okwo Bele, Venkatraman Chandra-Mouli, Thomas Cherian, Felicity Cutts, Peter Fajans, Joachim Hombach, Dale Huntington, Raymond Hutubussy, Marie-Paule Kieny, Merle Lewis, Annick Manuel, Sonia Pagliusi, Kenji Shibuya, Jin-Ho Shin, and Andreas Ullrich.

The document was prepared by: Xavier Castellsague, Patricia Claeys, Felicity Cutts, John Edmunds, Silvia Franceschi, Geoff Garnett, Sue Goldie, Diane Harper, Lauri Markowitz, Silvia de Sanjosé, Nathalie Broutet, and Kathleen Irwin.

Abbreviations and acronyms

AIDS	acquired immunodeficiency syndrome
AIS	adenocarcinoma in situ
ASIR	age-standardized incidence rate
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CMH	Commission on Macroeconomics and Health
DNA	deoxyribonucleic acid
GDP	gross domestic product
HIV	human immunodeficiency virus
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IARC	International Agency for Research on Cancer
LSIL	low-grade squamous intraepithelial lesion
PATH	Program for Appropriate Technology in Health
RRP	recurrent respiratory papillomatosis
SAE	serious adverse event
SIL	squamous intraepithelial lesion
UNFPA	United Nations Population Fund
VE	vaccine efficacy
VLP	virus-like particle
WHO	World Health Organization
YLL	years of life lost
YLS	years of life saved

Summary

Cervical cancer is the most common cancer affecting women in developing countries. It has been estimated to have been responsible for almost 260 000 deaths in 2005, of which about 80% occurred in developing countries. Cervical cancer is caused by human papillomavirus (HPV).

Recently a vaccine that has the potential to prevent certain HPV infections, and hence reduce the incidence of cervical cancer and other anogenital cancers, has been licensed. Another vaccine is in advanced clinical testing. This document provides key information on HPV, HPV-related diseases and HPV vaccines, and is intended to underpin the guidance note on HPV vaccine introduction, recently produced by WHO and the United Nations Population Fund (UNFPA).*

HPV are DNA viruses that infect skin or mucosal cells. There are more than 100 known HPV genotypes, at least 13 of which can cause cancer of the cervix and are associated with other anogenital cancers and cancers of the head and neck; they are called "high-risk" genotypes. The two most common of these (genotypes 16 and 18) cause approximately 70% of all cervical cancers. HPV (especially genotypes 6 and 11) can also cause genital warts, a common benign condition of the external genitalia that causes significant morbidity. HPV is highly transmissible, with peak incidence of infection soon after the beginning of sexual activity. Most people acquire the infection at some time in their life. Factors contributing to development of cervical cancer after HPV infection include immune suppression, multiparity, early age at first delivery, cigarette smoking, long-term use of hormonal contraceptives, and co-infection with *Chlamydia trachomatis* or Herpes simplex virus.

HPV vaccines are prepared from virus-like particles (VLPs), produced by recombinant technology. They do not contain any live biological product or DNA, so are non-infectious. A quadrivalent vaccine, containing VLPs related to HPV genotypes 6, 11, 16 and 18, has recently been licensed, and a bivalent vaccine, containing VLPs related to HPV genotypes 16 and 18, is in advanced clinical testing. The vaccines are designed to prevent infection and disease due to their respective genotypes, and are not designed to treat persons who have already been infected with them. The vaccines are given as a series of three 0.5-ml intramuscular injections over a six-month period. HPV vaccines induce high levels of serum antibodies in virtually all vaccinated individuals and are generally well tolerated. Adverse events at the injection site (pain, erythema and oedema) occur more often in vaccine recipients than controls, but the incidence of serious adverse events (SAEs) was not significantly higher among vaccine recipients in any of the trials.

In women who have no evidence of past or current infection with vaccine-related HPV genotypes, both vaccines give over 90% protection against persistent HPV infection with those genotypes. The quadrivalent vaccine has shown 100% protection (95% confidence interval (CI): 92.9–100) against moderate or severe precancerous lesions associ-

* WHO, UNFPA. *Preparing for the introduction of HPV vaccines: policy and programme guidance for countries.* Geneva; World Health Organization:2006.

ated with HPV 16 or 18. Results from a phase II trial of the bivalent vaccine, which included 1113 women, showed an efficacy of 100% (95% CI: –7.7–100) against moderate precancerous cervical lesions. Data from larger trials of the bivalent vaccine are expected soon. Data on vaccine effects among women who had already been infected with HPV 16 and 18 are available only for the quadrivalent vaccine, and show no protective effect against moderate or severe precancerous lesions. However, women who had been exposed to one vaccine-related HPV genotype were protected against disease related to other vaccine-related HPV genotypes. Because only a very few women had already been infected with all four vaccine-related HPV genotypes before first vaccination, almost all women could therefore potentially benefit from vaccination. These data suggest that there is no need to screen for HPV before offering vaccine to women.

The very high clinical efficacy in women without evidence of infection with vaccine-related HPV genotypes, and the lower efficacy among those already exposed to HPV, show that vaccinating girls before they are exposed to HPV would have the greatest impact. Although the duration of protection is not yet known, there is evidence of protection for at least five years after vaccination. Studies are continuing to evaluate the longer-term protection. The safety and efficacy of HPV vaccines have not yet been evaluated in Africa, or in populations with a high prevalence of human immunodeficiency virus (HIV) infection.

Vaccines that protect against HPV genotypes 16 and 18 have the potential to reduce, but not eliminate, the risk of cervical cancer. Women will still be at risk from other high-risk genotypes, and other interventions – including cervical screening – will still be required. The cost of HPV vaccines will be a major determinant of the cost-effectiveness of vaccination. Delivery costs are also likely to be important, since in many settings new systems will be needed to reach young adolescents. If a two-dose schedule could be used, or if vaccination could be given at an earlier age with other vaccines (e.g. at school entry or even in infancy), the cost of vaccine delivery could be reduced. Studies to evaluate these options are planned. HPV vaccines can improve comprehensive cervical cancer control programmes as well as stimulate new partnerships for advocacy, information and communication, as well as service delivery, stewardship and financing.

Introduction

Human papillomavirus (HPV) is common throughout the world. Although most infections with HPV cause no symptoms and are self-limiting, persistent genital HPV infection can cause cervical cancer in women.[1, 2] HPV can also cause other types of anogenital cancer, head and neck cancers,[3] and genital warts, in both men and women.[4] HPV is estimated to cause about half a million new cancers every year, most of them affecting women in developing countries.

For many years, the main way to prevent cervical cancer has been through screening programmes. Well organized screening and early treatment programmes have been effective in preventing squamous cervical cancer (the most common kind), but have had less impact on adenocarcinoma.[5] Unfortunately, they are difficult to implement in low-resource settings.

In 2006, a vaccine that protects against infection with four HPV genotypes was licensed; a second vaccine that protects against two HPV genotypes is likely to be licensed soon. Countries need to consider whether and how to use these new vaccines. The decision to introduce a new vaccine depends on factors such as:[6]

- public health priority (based on, for example, the burden of disease);
- the effectiveness and safety of vaccines;
- the availability of other interventions;
- the costs and cost-effectiveness of vaccines;
- programme strength and ability to deliver vaccines.

This document aims to provide policy-makers and health professionals with key information on HPV, HPV-related diseases and HPV vaccines, and to underpin the guidance note recently published by WHO and UNFPA.[7] Information on implementation of cervical cancer screening programmes is available in a related document;[8] while not covered here, such programmes should be considered an important part of comprehensive cervical cancer control.

1. What is HPV?

- Human papillomaviruses are DNA viruses that infect epithelial (skin or mucosal) cells. There are more than 100 known HPV genotypes, which are numbered in order of their discovery. [9]
- At least 13 HPV genotypes can cause cancer.[10]
- The two genotypes most commonly associated with cervical cancer are genotypes 16 and 18.

HPV genotypes that infect the genital mucosa are considered “high-risk” or “low-risk”, according to their link with cancer.[11] The high-risk genotypes – genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 – can lead to cervical cancer,[10] and are also associated with other anogenital, head and neck cancers. Infection with low-risk genotypes very rarely causes cancer, but can cause benign or low-grade changes in cervical cells that are indistinguishable from those caused by high-risk HPV genotypes.

2. What is the burden of disease caused by HPV?

HPV can cause a number of cancers. It also causes genital warts (condyloma acuminatum) which grow on the cervix, vagina, vulva, or anus in women and the penis, scrotum, or anus in men. Genital warts very rarely progress to cancer. HPV can also cause recurrent respiratory papillomatosis (RRP), an uncommon, but serious, condition of the larynx.

2.1 Cancers

- The main burden of HPV-related disease is due to cervical cancer.
- It is estimated that there were almost 260 000 deaths from cervical cancer in 2005, and 2.7 million years of life lost (YLL) in 2000 (http://www.who.int/healthinfo/statistics/bodprojections2030/en/index.html).
- Of the total estimated HPV-attributable cancers, 94% affect women and 80% are in developing countries.
- In Latin America, the Caribbean and eastern Europe, cervical cancer makes a greater contribution to YLL than does tuberculosis, maternal conditions or acquired immunodeficiency syndrome (AIDS).
- On the basis of epidemiological and virological studies, HPV is estimated to cause 100% of cases of cervical cancer, 90% of anal cancer, 40% of cancers of the external genitalia (vulva, vagina and penis), at least 12% of oropharyngeal cancers and at least 3% of oral cancers.[12]

Data on cancer burden are obtained from cancer registries. The most recent summary of registry data,[13] published in 2002, covered 186 registries. Data were available from 24 developing countries (see Annex) mainly for urban areas. In the majority of developing countries, which do not have registries, several methods are used to estimate cancer incidence and mortality.[14–16] Table 1 shows the estimated number of cancer cases attributable to HPV in developed and developing countries.[12] Estimated incidence is highest in sub-Saharan Africa, Melanesia, Latin America and the Caribbean, and south-central and south-east Asia (Figure 1).

Cervical cancer occurs rarely women under 30 years of age, and occurs most commonly in women over 40 (Figure 2). In developed countries, the primary economic burden of HPV disease is related to early detection and management of precancerous lesions. In the United States of America, for example, screening with Papanicolaou (Pap) smears produces about 4.7 million abnormal results each year, which need to be followed up.[17] Not all developed countries, however, have successfully controlled their cervical cancer burden through screening and early treatment programmes, because of inadequate coverage and/or quality of screening programmes in some countries.[12]

Table 1. Number of cancers attributable to HPV infection, 2002: developed and developing countries[12]

		Developed countries		Developing countries	
Site of cancer	**Attributable to HPV (%)**	**Total no. of cancers**	**Attributable to HPV (%)**	**Total no. of 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
Oropharynx	≥12	24 400	2 900	27 700	3 300
Total		237 000	111 500	678 900	449 600

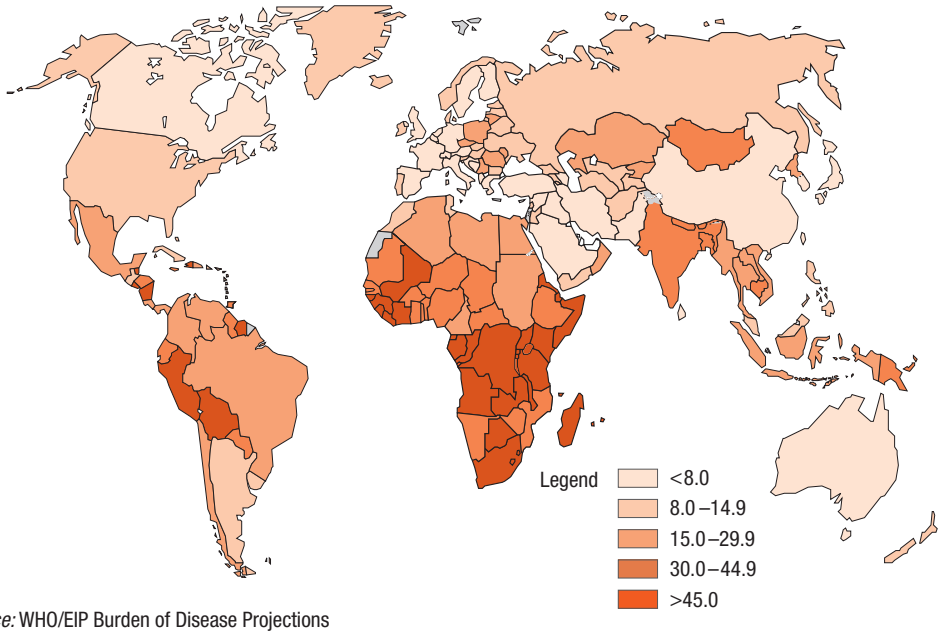
Source: Reprinted from ref. 12 with permission from Elsevier.

2.2 Genital warts

- Genital warts are very common and are highly infectious.
- Between 90% and 100% of genital warts are caused by HPV genotypes 6 and 11.[18]
- Although they do not usually result in death, genital warts cause significant morbidity and entail substantial health care costs.

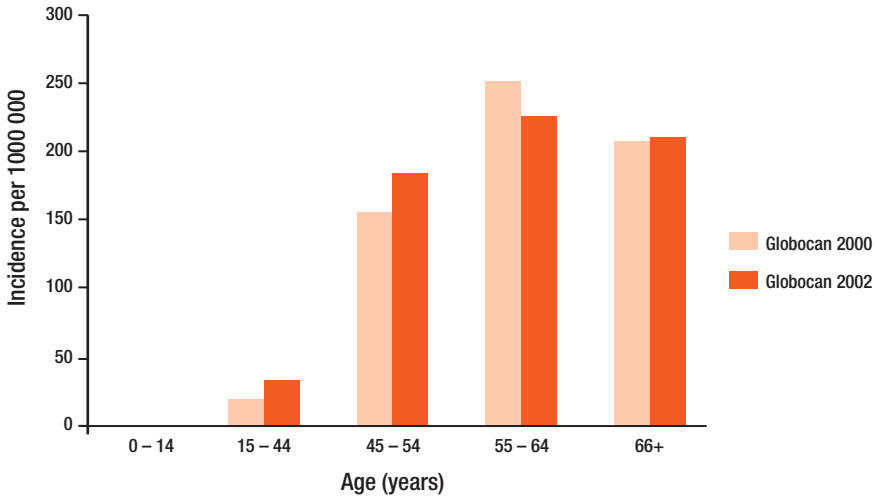
Incidence rates for genital warts rise sharply in women aged 15–24 years and in men aged 20–29 years; peak rates are seen in 20–29-year-olds in both sexes. Incidence then falls sharply in females but remains high in males up to age 40 years.[19] Almost 50% of women infected with HPV 6 or 11 will develop genital warts within 12 months, and 64% within 36 months.[20] Consistent use of condoms decreases the risk of genital warts by 60–70%. Human immunodeficiency virus (HIV) infection is associated with an increased prevalence of genital warts. Giant condylomas (Buschke-Löwenstein tumours) have also been observed in HIV-positive patients.[21]

Figure 1. Worldwide incidence of cervical cancer per 100 000 females (all ages), age-standardized to the WHO standard population, 2005



Source: WHO/EIP Burden of Disease Projections
(http://www.who.int/healthinfo/statistics/bodprojections2030/en/index.html).

Figure 2. Age-specific cervical cancer incidence



Source: ref.14.

Studies in the USA have reported that 1–2% of the sexually active population aged 15–49 years has had genital warts.[4] Much higher figures of 10% of women aged 18–45 years were obtained in a random sample of almost 70 000 women in Denmark, Iceland, Norway and Sweden.[22] There are data to suggest that the incidence has been rising over time.[19, 22] A minority of cases resolve without treatment. Recurrence is common, even after treatment. Recurrent respiratory papillomatosis (RRP) is caused by transmission of HPV genotypes 6 or 11 from mother to child during birth. Although it is uncommon, a maternal history of genital warts is associated with a 231-fold increased risk of RRP in a newborn child.[23] RRP is a potentially devastating disease, characterized by the growth of wart-like benign neoplasms throughout the respiratory and digestive tracts, and often requires repeated surgical intervention.[24]

3. What are the stages leading up to cervical cancer after HPV infection?

- HPV infection of the cervix is associated with cellular changes, which can be detected early on microscopic examination. Changes cannot be detected reliably by the naked eye until the later stages of precancerous lesions or invasive cancer.
- HPV infection usually clears within a few months; about 90% of infections clear within two years. Persistence of infection beyond 12 months is associated with an increased risk of cancer.[25]

HPV infects the basal layer of the epithelium. Most infections of the cervix are asymptomatic and the virus is cleared without treatment (median time for clearance, eight months).[26] More than 90% of infections are cleared within two years.[26–29] Early HPV infections may be accompanied by mild changes in the epithelium. An abnormal growth of squamous cells of the cervix, detected by cytological examination of a cervical smear, is called a squamous intraepithelial lesion (SIL). The changes in the cells are described as low-grade (LSIL) or high-grade (HSIL), depending on how much of the cervical epithelium is affected and how abnormal the cells appear. Equivocal changes seen on cervical smears are called “atypical squamous cells” or “atypical glandular cells”. Abnormal cells in the cervix detected by histological examination of cervical biopsies are classified as cervical intraepithelial neoplasia (CIN); they are graded from CIN1 to CIN3 according to the proportion of the cervix affected. Similar gradings exist for precancerous vaginal (VaIN1–3) and vulvar (VIN1–3) lesions. The majority of LSIL or CIN1 lesions disappear within a few months without treatment.[30] If HPV infection persists, however, it can lead to moderate or severe cervical intraepithelial neoplasia (CIN2 or CIN3), or to adenocarcinoma in situ (AIS), often grouped together as “CIN2/3 or AIS”, which if untreated has a high probability of progressing to cancer.[30]

4. What proportion of cases of cervical cancer is associated with different HPV genotypes in different regions?

- Worldwide, HPV 16 and 18 cause approximately 70% of cervical cancer, AIS, CIN3, VIN2/3, and VaIN2/3, and 50% of CIN2.[31–35]

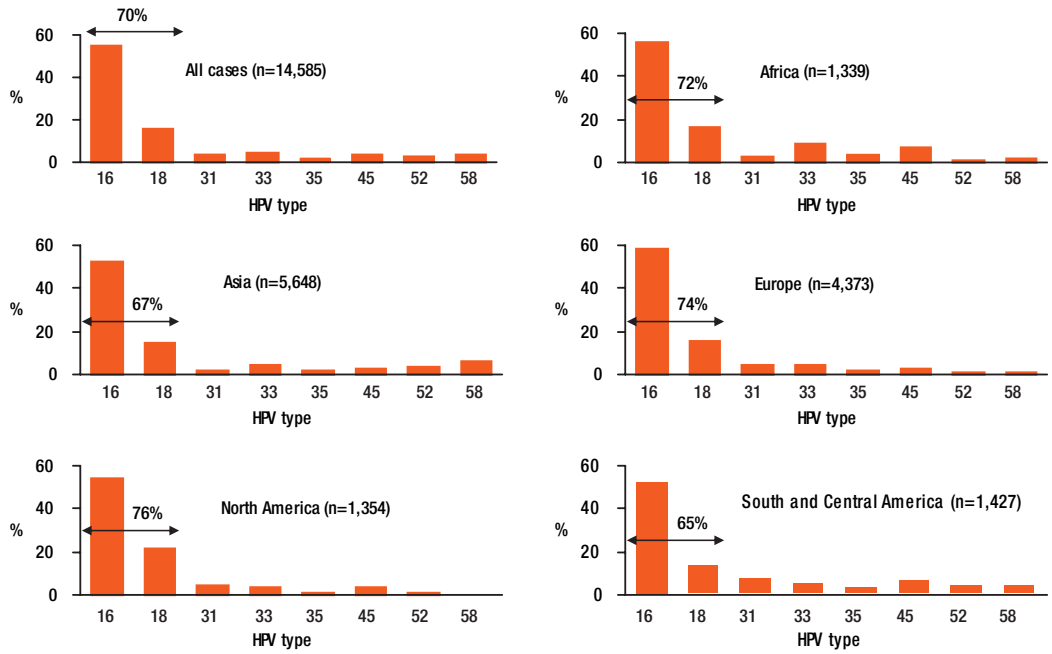
- The eight most common high-risk genotypes (HPV 16, 18, 45, 31, 33, 52, 58 and 35) account for 90% of cases of cervical cancer.[31–35] Apart from HPV 16 and 18, each individual genotype causes a small (<5%) proportion of cases.
- The same eight genotypes are the most common in each region.
- The proportion of cervical cancer cases due to HPV 16 varies little across regions (minimum 52% in Asia, maximum 58% in Europe).
- HPV 18 is more common in adenocarcinoma than in squamous cell cervical cancer.[32, 36]
- HPV 6, 11, 16, and 18 cause 35–50% of all CIN1, VIN1, and ValN1 cases.[37]

There have been many studies throughout the world on the proportion of cervical cancer, HSIL and LSIL due to different HPV genotypes.[31–35]

However, information for Africa, Central Asia and eastern Europe is incomplete. The HPV genotypes most commonly found in women with cervical cancer, by region, are shown in Figure 3. With the possible exception of Europe, where HPV 56 was the eighth most common high-risk genotype (rather than HPV 52), the same eight HPV genotypes were the most frequent in each region. The relative importance of HPV genotypes 31, 33, 35, 45, 52 and 58 differed by region, HPV 58 prevalence being high in Asia.

Within regions, the relative importance of HPV 16 appears most heterogeneous across Asia. In women with cervical cancer, HPV 16 prevalence tends to be higher in India and the Eastern Mediterranean than in east Asia.[35] HPV 16 may also be more prevalent in the north of Africa than in sub-Saharan Africa.[31]

Figure 3. Percentages of cervical cancer cases attributed to the most frequent high-risk HPV genotypes, by region



Source: Adapted from ref. 35 with permission from Wiley.

5. What are the risk factors for HPV infection and cervical cancer?

- HPV infection is highly transmissible, and the majority of men and women will acquire HPV infection at some time in their life.[38] However, only a very small proportion will go on to develop cancer.
- The risk of infection is highest soon after sexual activity begins.[39–43] In many populations, there is another peak among women at the menopause.[40, 44]
- Although HPV is sexually transmitted, penetrative sex is not required for transmission: skin-to-skin genital (e.g. penile–vulvar) contact is a well recognized mode of transmission.[43, 45–48]
- Data on age-specific prevalence of HPV suggest that the pattern of infection varies between regions and socioeconomic groups.[49]
- HIV-infected individuals are at higher risk of HPV infection and persistence, and are infected by a broader range of HPV genotypes.[50]
- Factors contributing to development of cervical cancer after HPV infection include, in addition to immune suppression:[51] multiparity, early age at first delivery, cigarette-smoking, long-term use of hormonal contraceptives, and co-infection with *Chlamydia trachomatis* or Herpes simplex virus. [52]
- Less information is available on risk factors for, and the natural history of, HPV infection in men.

Genital HPV infection is primarily transmitted by genital contact, usually but not necessarily through sexual intercourse.[4] HPV infection can occur at any age and has been reported in healthy young children.[46–48] Most studies of HPV epidemiology have focused on women of childbearing age, among whom it may be more acceptable and practicable to obtain a cervical sample for HPV DNA testing.

In a cross-sectional study of nearly 20 000 women aged 15–74 years from 15 areas in four continents, carried out by the International Agency for Research on Cancer (IARC),[53] age-standardized HPV prevalence varied more than 10-fold between populations. The shape of the age-specific prevalence curves also varied. An inverse relationship between age and HPV prevalence was found in many, but not all, countries. In some of the poorest areas studied, e.g. India and Nigeria, HPV prevalence was high in all age groups.[53] One of the limitations of cross-sectional studies is the absence of information on when infection was acquired. In Colombia and Costa Rica, the peak prevalence of HPV infection is seen in women under 30 years of age and in those aged 55–64 years.[54] Longitudinal studies have shown a similar bimodal curve for incidence of HPV infection in Colombia,[40] but with only a minor second peak in Costa Rica.[55] In the longitudinal study in Costa Rica, the acquisition of new HPV infections was greatest in young women, whereas persistent infections gradually became more prominent with age. Further work is needed to clarify how data on age patterns of infection can be used to guide vaccination strategies and to monitor the future impact of vaccination.

Although most women will acquire an infection with at least one HPV genotype during their lifetime, particular factors have been found to be associated with increased risk for HPV infection.[38] HPV infec-

tion is common among people infected with HIV. A recent meta-analysis found that nearly 40% of HIV-infected women with no cervical cytological abnormalities had HPV infection.[56] Simultaneous infection with multiple HPV genotypes is more common in HIV-infected women than in non-HIV-infected women.[57] There is very little published data on the distribution of HPV genotypes in HIV-infected women with cervical cancer,[56] however, and further data are urgently needed. HIV-infected men and women are also at increased risk of HPV-associated anal cancer.[58–60]

Many longitudinal and cross-sectional studies have shown that HPV infection is associated with the number of sex partners, over the lifetime or recently.[26–29, 61, 62] In the largest prevalence study, conducted by IARC in over 11 000 women in 4 continents, the prevalence of HPV among women who had had two or more sexual partners in their lifetime was double that in women who had had only one partner. Women whose husbands had had extramarital sexual relationships had a 50% higher HPV positivity rate.[62]

Cross-sectional studies have generally failed to find evidence of a lower HPV prevalence in people who use condoms.[62–64] A detailed longitudinal study in the USA, however, found that consistent condom use significantly protected college students against new HPV infection. No cervical intraepithelial lesions occurred in women whose partners always used condoms, compared with 14 lesions in women whose partners used condoms inconsistently or never.[65]

There have been fewer studies of HPV epidemiology among men than women, for two main reasons: (1) HPV-related morbidity and mortality are much greater in women, and (2) sensitive methods for collecting and testing specimens for HPV DNA have only recently been developed for use in men.[66] High rates of anal HPV infection have been reported in men who have sex with men, resulting in an increased risk of HPV-related anal cancer.[67] Longitudinal observational studies, and data from ongoing vaccine trials in men, will help to elucidate this important area of HPV epidemiology.

6. What is the immune response to HPV infection?

- Genital HPV infections do not promote a vigorous immune response because they are not cytolytic and do not induce local inflammation.[68]
- Only 50–60% of women develop serum antibodies to HPV after natural infection.[69]
- The degree of protection and duration of immunity after natural infection are not known. Reinfections with the same genotype are thought to occur.
- The role of cellular immunity in clearance of infection is not well elucidated, but infection persists longer in immunosuppressed individuals (e.g. HIV-infected women). [70, 71]

Many viral vaccines, e.g. those against hepatitis B, measles and rubella, protect against infections that have a phase when the virus circulates in the bloodstream. The antibody response to natural infection with these viruses is vigorous and sustained. An important difference with HPV is that it is a purely mucosal infection and has no

bloodstream phase. Only about half of infected women develop serum antibodies,[69] and the levels are lower than those seen after vaccination. These differences mean that it is difficult to extrapolate from experience with other viral vaccines to predict what will happen after HPV vaccination.

Another factor that has hindered epidemiological studies of infection and comparison of results from different vaccine trials (see below) is the lack of a standardized assay for measurement of antibody titres.[72] WHO is coordinating work to develop such an assay.[73]

7. What are HPV vaccines and how have they been evaluated?

- There are currently two HPV vaccines: both are designed to protect against HPV 16 and 18, and one also protects against low-risk genotypes 6 and 11.
- The vaccines are prepared from virus-like particles (VLPs) produced by recombinant technology.[74, 75]
- They do not contain any live biological product or DNA, so they are non-infectious.
- The vaccines are given as a series of three 0.5-ml intramuscular injections over a six-month period. Robust data on their effects are available only for this three-dose schedule.

The HPV genome is enclosed in a capsid shell made up of two proteins, L1 and L2. Purified L1 protein self-assembles to form empty shells that resemble HPV (virus-like particles (VLPs)). VLPs are the basis of the vaccines discussed in this document, and of serological tests for HPV.

Both HPV vaccines have been evaluated in randomized, placebo-controlled, clinical trials. The characteristics of the two vaccines and key features of the trials are shown in Table 2. Details of the quadrivalent vaccine trials contributing to the analyses of efficacy described below are available in full at 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 advantages and disadvantages of assessing different outcomes, or endpoints, in HPV vaccine trials have been reviewed in depth.[76] For vaccine licensing, the endpoint of CIN2/3 or AIS has been widely accepted as a proxy for cervical cancer that can be studied ethically. This endpoint can be evaluated among young women. In children or young adolescents, however, it is not practical to study this endpoint, since cervical specimens would be required, and the endpoint is rare in young people. Bridging studies are therefore conducted, in which the antibody responses of young people are compared with those of women for whom data on the clinical endpoint (CIN2/3 or AIS) will be available.

For each endpoint, vaccine efficacy (VE) is calculated by comparing the incidence of the endpoint in women who receive the vaccine with that in women who receive placebo (controls), where:

- Incidence in vaccinated women = number of cases in vaccinated women/total number of vaccinated women
- Incidence in control women = number of cases in control women/total number of control women.

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

	Quadrivalent vaccine (licensed in many countries)	**Bivalent vaccine (in advanced clinical testing)**
Manufacturer and trade name	Merck; Gardasil	Glaxo Smith Kline;Cervarix
Virus-like particles of genotypes:	6, 11, 16, 18	16, 18
Substrate	Yeast (*Saccharomyces cerevisiae*)	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: 3 doses at intervals of:	2 months between doses 1 and 2; 6 months between doses 1 and 3	1 month between doses 1 and 2; 6 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	North America (25%); Latin America (27%); Europe (44%); Asia-Pacific (4%)	North America (12%); Latin America (34%); Europe (30%); Asia-Pacific (25%)
Adolescent safety and 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 study in males Efficacy study in women aged over 26 years Studies of administration at the same time as other vaccines Safety and immunogenicity in HIV-infected and other immunocompromised groups	Efficacy, immunogenicity, bridging and safety studies in women over 26 years Studies of administration at the same time as other vaccines Safety and immunogenicity in African populations, including HIV-infected women

- $VE = 1 - \frac{\textit{incidence in vaccinated women}}{\textit{incidence in control women}}$

The VE is usually expressed as a percentage, with corresponding 95% confidence interval (CI), which indicates the range within which the true value for the total population has a 95% chance of lying. (Since the trial population is only a sample of the total population, the trial VE is only an estimate of the population VE, and is subject to sampling error, which is captured in the confidence interval.)

In the vaccine trials, the primary analyses were conducted among the "according-to-protocol" population, i.e. women who received three doses of vaccine or placebo according to the study protocol, and did not have evidence of past or current infection with the vaccine-related HPV genotypes until at least one month after the third dose.

8. What is the antibody response to HPV vaccines, and what affects it?

- The major basis of protection against infection is neutralizing antibody.
- HPV vaccines induce serum antibodies in virtually all vaccinated individuals.[77–79]
- Antibody levels after vaccination are several times higher than those seen after natural HPV infection in all age groups evaluated.
- Antibody levels after vaccination are higher in young adolescents (under 15 years old) than in older people.
- The minimum protective antibody level is not known.
- Antibody responses to the quadrivalent vaccine have not been affected by race, ethnic origin, concomitant administration of hepatitis B vaccine or oral contraceptive use.
- Women who had evidence of past or current HPV infection at enrolment also developed an antibody response to the quadrivalent vaccine.[79]
- Antibody responses have been affected only slightly by receipt of vaccine doses earlier or later than the recommended schedule, but the range of intervals evaluated to date is not very wide (1–3 months between doses 1 and 2, and 4–8 months between doses 1 and 3).

In experimental studies on dogs, cows and rabbits, immunization with L1 VLPs induced high titres of genotypes-specific neutralizing antibodies, which prevented infection after challenge with large amounts of the relevant animal papillomavirus genotype.[80] Neutralizing antibody is considered to be the major basis for protection by VLP-based vaccines in humans.

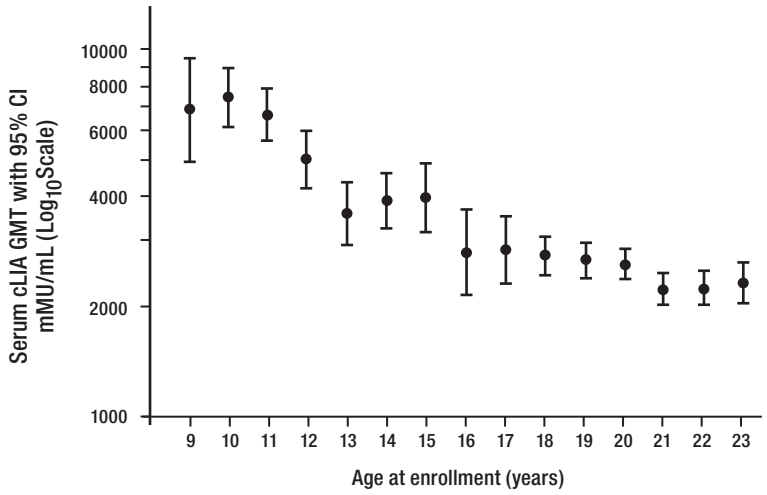
After three doses of either of the HPV vaccines, practically 100% of women aged 15–26 years had detectable antibody to each HPV genotype; the levels were between 10 and 104 times higher than those in natural infections.[77–79] In studies of older women, aged 26–55 years, antibody levels were also several times higher than after natural infection.[81] Data on vaccine efficacy in older women are not yet available. The antibody levels achieved after vaccination were inversely related to age. Figure 4 shows levels of antibody to HPV 6 achieved after vaccination of girls and women with the quadrivalent vaccine (http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm).

The absolute values of specific titres cannot be compared for different HPV genotypes (because of different values of the reference sera), or for the assays used in the trials of the quadrivalent and bivalent vaccines.

In the vaccine trials to date, cases of the endpoint in vaccinated individuals have been rare, and have mostly occurred in women with antibody levels similar to those in the rest of the vaccinated trial population. Thus, the minimum antibody level required for protection is not known, and additional follow-up of vaccinated cohorts will be required to determine this.

Co-administration of the quadrivalent HPV vaccine with hepatitis B vaccine (recombinant) (injections in separate sites at same visit) was evaluated in a randomized study. The immune response to both hepatitis B vaccine (recombinant) and the quadrivalent HPV vaccine was not significantly different, whether they were administered at the same visit or at a different visit. A study to evaluate the concomitant use of the quadrivalent vaccine with combined diphtheria, tetanus and pertussis vaccine and meningococcal conjugate vaccine in adolescents is underway (http://www.clinicaltrials.gov/ct/show/NCT00325130;jsessionid=43B3BB2A3006A0A7874B19EE2942B2B4?order=34). The effects of HIV, severe malnutrition, and intercurrent malarial or helminth infection have not yet been studied.

Figure 4. Antibody titres to HPV 6 after 3 doses of quadrivalent vaccine, by age



Number of subjects evaluable (n)															
Age	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23
n	67	131	165	142	165	150	109	80	135	423	506	594	550	527	375

HPV =Human papillomavirus; cLIA = Competitive Luminex immuneassay. GMT = Geometric mean titer mMU = Mili Merck units.

Source: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm

9. How much protection from infection and disease do HPV vaccines give?

- The HPV vaccines are designed to be prophylactic (i.e. to prevent infection and consequent disease), not therapeutic.
- The protection provided by the vaccines is therefore lower among women who have already been infected with the vaccine-related HPV genotypes than among those who have not been infected.
- The overall population benefit from vaccinating women aged 15–26 years would depend on the epidemiology of HPV in the population (including age-specific rates of infection, and the proportion of infections and clinical endpoints due to the vaccine-related HPV genotypes). The benefit cannot be directly extrapolated from the efficacy results of current vaccine trials.

For the bivalent vaccine, data are available from phase II trials, which were designed to measure efficacy against new or persistent infections with HPV genotypes 16 and 18.[77, 78] Data from phase III trials are expected to be made public in 2007. For the quadrivalent vaccine, data are available from published phase II trials and large phase III trials, which were designed to measure efficacy against the clinical endpoints of moderate to severe cervical precancer (CIN2/3 or AIS), genital warts, and vaginal and vulvar precancerous lesions.[82] Women who had laboratory evidence of having already been infected with HPV were excluded from the phase II trials of the bivalent vaccine, but included in the phase II trials of the quadrivalent vaccine and in the phase III trials of both vaccines. The women included in the efficacy trials of the quadrivalent vaccine had a mean age of 20 years (range 16–26 years), and received all three doses within a one-year period.

9.1 Efficacy in women without evidence of previous or current infection with vaccine-related HPV genotypes

- In women who, at enrolment in the trials, had no evidence of exposure to, or infection with, the vaccine-related HPV genotypes, both vaccines showed high efficacy against HPV infection and against clinical endpoints associated with these vaccine-related HPV genotypes.
- Efficacy against persistent infection with genotypes 16 or 18 was over 90% in women who received three doses of HPV vaccine.[78, 83]
- Efficacy against CIN2/3 and AIS due to genotypes 16 or 18 was 100% (95% CI: 92.9–100) for the quadrivalent vaccine (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm).

Both vaccines showed high efficacy, with over 90% fewer persistent infections in the vaccinated women, and close to 100% fewer moderate or severe cervical lesions and, for the quadrivalent vaccine, genital warts, and vulvar and vaginal precancerous lesions. For the bivalent vaccine, extended follow-up of phase II trials found no cases of HPV 16/18-related CIN2 among 481 vaccinated women, and five cases among 470 women in the control group, giving an efficacy of 100% (95% CI: –7.7–100).[78] Further data on the efficacy of the bivalent vaccine against CIN2/3 and AIS are

expected in 2007. Table 3 shows results for the quadrivalent vaccine at a median of 1.5 years after completion of the 3-dose vaccination series. The results shown for CIN2/3 and AIS are the combined results from four trials (numbered 005, 007, 013 and 015); for the remaining endpoints, results are from three trials (007, 013 and 015) (http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4222b-index.htm).

9.2 Efficacy in women who have already been infected with vaccine-related HPV genotypes

- Data on efficacy, immunogenicity and safety in women who have already been infected with vaccine-related HPV genotypes are available only for the quadrivalent vaccine.
- 27% of women in the quadrivalent vaccine trials had evidence of prior exposure to, or ongoing infection with, one or more of the four vaccine-related genotypes.
- Among women who were infected with one vaccine-related HPV genotype at entry into the trial, high-level protection was observed against infection with the other three vaccine-related HPV genotypes and related diseases.
- The vaccine did not appear to alter the course of infections already present at the time of starting the 3-dose vaccination regimen.

Among the 1763 women who were HPV DNA-negative and had HPV-specific antibodies of the relevant genotypes at recruitment (so-called "cleared HPV infection"), there were four cases of CIN2/3 or AIS in the control group over the study

Table 3. Efficacy of the quadrivalent HPV vaccine among women who received three doses of vaccine according to protocol and had no evidence of past or current infection with the vaccine-related HPV genotypes

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	8487	0	8460	53	100% (92.9–100)
HPV 16/18 related VIN 2+	7897	0	7899	8	100% (41.4–100)
HPV 16/18 related ValN 2+	7897	0	7899	5	100% (<0–100)
HPV 6/11/16/18-related genital warts (condyloma)	7897	1	7899	91	98.9% (93.7–100)

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

period and none in the vaccinated group, giving a non-significant protective efficacy of 100% (95% CI: –63.6–100). Among the 1287 women who were HPV DNA-positive but had no HPV-specific antibodies at recruitment, the incidence of HPV 16 or 18-related CIN2/3 or AIS was more than tenfold higher than among women who were HPV-naïve at recruitment. There were 57 cases in the control group and 42 in the vaccinated group; vaccine efficacy was 31.2% (95% CI:–4.5–54.9). Most of these cases were caused by the HPV genotype with which the woman was already infected at the time of recruitment. Among the 972 women who were both HPV DNA-positive and HPV antibody-positive at recruitment (many of whom already had early precancerous lesions), there were more cases of CIN2/3 or AIS caused by genotype 16 or 18 among vaccinated (79 cases) than unvaccinated women (69 cases), but the difference was not significant.

It is important to note that, among subjects with evidence of infection with one or more vaccine-related HPV genotypes, the quadrivalent vaccine was highly effective in protecting against infection and disease caused by the other vaccine-related HPV genotypes, to which the subject was naïve on day 1.[84]

Overall, the lack of impact of these vaccines on the course of vaccine-related HPV genotype infections present at the start of vaccination was expected, since the vaccines were not designed to be therapeutic or to clear existing infections. It is possible that results would be different in the long term, since the vaccines could reduce re-infections with the same genotype, but such results will only be available once longer follow-up is done. The apparent differences between subgroups should be treated with caution, since the numbers of events in some subgroups were small. They raise hypotheses, however, about potential biological reasons for the apparent differences between groups and further study of these differences will be of interest.

9.3 What was the overall efficacy of the quadrivalent HPV vaccine among all women enrolled in the trials?

- The total study population included women with past exposure to, or current infection with HPV, or abnormal cytology at entry.
- The observed vaccine efficacy among all women depends on the duration of observation. Early on, the efficacy of the vaccine is lower because of the consequences of infections already present at the time of first vaccination (against which the vaccine has little impact).
- Women who had been exposed to one vaccine-related HPV genotype were protected against disease related to other vaccine-related HPV genotypes. Nonetheless, efficacy in the total population was much lower than in women without evidence of previous infection with a vaccine-related HPV genotype.
- The very high clinical efficacy in women without evidence of infection with vaccine-related HPV genotypes, and the lower efficacy among those already exposed to HPV, show that vaccinating girls before they are exposed to HPV would have the greatest impact.

Table 4 shows the efficacy of the quadrivalent vaccine among all women enrolled in the trials. The majority of CIN, genital warts, VIN, and VaIN detected in vaccinated women was a consequence of infection with the HPV genotype already present at the time of first vaccination. The observed vaccine efficacy among all women was dependent on the duration of observation. Early on, the efficacy of the vaccine was lower, because of the consequences of infections already present at the time of first vaccination (against which the vaccine had little impact). Thus, the efficacy results shown in Table 4 are only preliminary estimates and those from longer follow-up are likely to be different.

The quadrivalent HPV vaccine was well tolerated by women who had HPV infection or disease on entry into the study. Women who had been exposed to one vaccine-related HPV genotype were protected against disease related to other vaccine-related HPV genotypes. Only a very few women had already been infected with all four vaccine-related HPV genotypes on entry. Thus, almost all women could potentially benefit from vaccination. These data suggest that there is no need to screen for HPV before offering vaccine to women.

Table 4. Efficacy of the quadrivalent vaccine against clinical endpoints related to HPV genotypes 16, 18, 6 and 11, among all women enrolled

	Vaccine		Placebo		Vaccine efficacy (%) (95% CI)
Clinical endpoint	**No. of women**	**No.of cases**	**No. of women**	**No. of cases**	
HPV 6/11/16/18-related CIN 2/3 or AIS	9831	122	9896	201	39.0 (23.3–51.7)
HPV 16-related CIN 2/3 or AIS	9831	115	9896	184	37.2 (20.3–50.7)
HPV 18-related CIN 2/3 or AIS	8814	7	8846	33	78.7 (51.0–92.0)
HPV 6/11/16/18-related VIN 2/3	8954	7	8962	22	68.1 (22.7–88.5)
HPV 6/11/16/18-related VaIN 2/3	8954	2	8962	9	77.7 (<0–97.7)
HPV 6/11/16/18-related genital warts	8954	58	8962	184	68.5 (57.5–77.0)

Source: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4222s-index.htm, FDA presentation, slides 32, 38 and 48.

10. Is there any cross-protection against other genotypes?

- For the bivalent vaccine, protection against new infections by two other genotypes has been reported in HPV-naïve women.[78]
- For the quadrivalent vaccine, neutralizing antibodies against genotypes 31 and 45 have been demonstrated following immunization.[85]

In preliminary analyses, both vaccines have shown evidence of cross-protection against HPV 31 and HPV 45, two closely related HPV genotypes. The extended follow-up of the phase II trials of the bivalent vaccine found a significantly lower incidence of infection with genotype 45 (one case in 528 vaccinated women and 17 cases in 518 controls; VE = 94.2% (95% CI: 63.3–99.9)) and genotype 31 (14 versus 30 cases; VE = 54.5% (95% CI: 11.5–77.7)). No significant effect was seen for other genotypes examined (genotypes 33, 52 and 58).[78] There were insufficient cases of CIN related to HPV 31 and HPV 45 to assess vaccine efficacy against clinical disease.

For the quadrivalent vaccine, a study was conducted to determine whether vaccine-induced antibodies could neutralize HPV 31 and HPV 45 infectivity. Serum antibodies from 10 of 10 vaccine recipients neutralized HPV 18 pseudovirions, 6 out of 10 neutralized HPV genotype 45 pseudovirions, and 8 out of 10 neutralized HPV genotype 31 pseudovirions. The study concluded that vaccination with the quadrivalent HPV vaccine induces antibody responses capable of neutralizing infection with the vaccine-related HPV genotypes and related non-vaccine-related HPV genotypes.[85]

For cross-protection to be clinically meaningful, administration of HPV vaccines will need to reduce the incidence of CIN caused by HPV genotypes other than HPV 16 and HPV 18. Studies are continuing for both vaccines.

11. Is the duration of protection known?

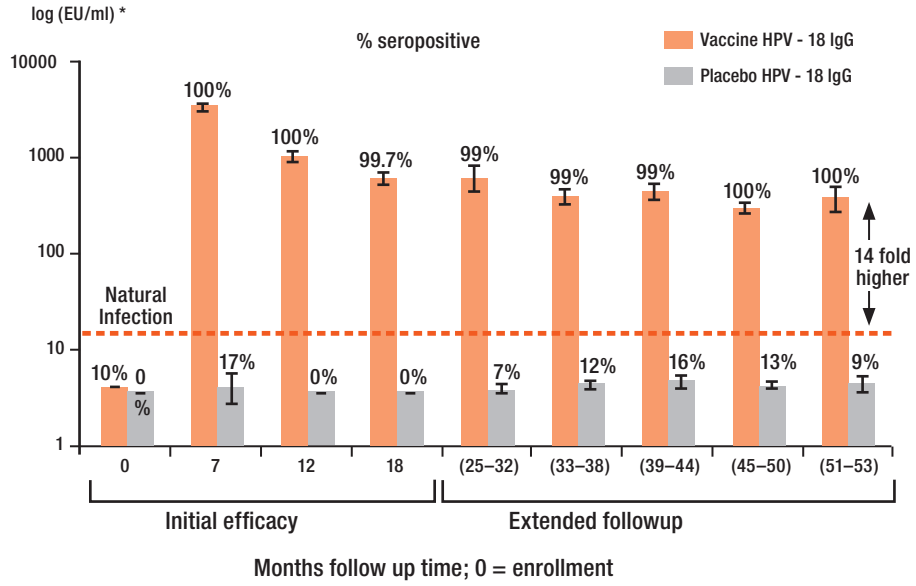
- Antibody persistence, and protection against persistent HPV infection, have been shown for up to five years post-vaccination (this being the longest duration of follow-up)
- A fourth dose of the quadrivalent HPV vaccine at five years leads to a rapid increase in antibody levels, consistent with the presence of immune memory.[86]
- Further studies are planned to evaluate more fully the duration of protection.

Data have been published on immune response up to 54 months after first vaccination for the bivalent vaccine[78] and 60 months for the quadrivalent vaccine. [86, 87] Antibody levels peak after the third dose, then fall by about one log unit until 18 months after first vaccination; they then level off, and remain as high as, or higher than, those seen after natural infection (Figure 5). It is not yet known whether seropositivity (according to the thresholds used) correlates with clinical protection; there have been too few cases of vaccine-type disease in vaccinated women to know if the small proportion of women who become seronegative are susceptible to disease.

Early results from a challenge study, in which 241 vaccinated women were given a fourth dose of the quadrivalent vaccine five years after enrolment, suggest that HPV vaccination induces immune memory.[86]

Protection against persistent infection,[78] or a combined endpoint of persistent infection and all genital diseases,[87] has been demonstrated for up to five years after enrolment; this is the longest reported follow-up so far. Both vaccine manufacturers plan follow-up studies of at least 14 years after the third dose, to determine the duration of antibody and clinical protection among women enrolled in the phase III studies.

Figure 5. Antibody levels to HPV-18 after vaccination, bivalent vaccine [78]



* EU - enzyme-linked immunosorbent assay (ELISA) units

Source: Reprinted from ref. 78, with permission from Elsevier.

12. Are HPV vaccines safe?

- HPV vaccines do not contain any live biological product or DNA, so they are non-infectious.
- Both HPV vaccines appear to be generally well tolerated.
- Adverse events at the injection site (pain, erythema and oedema) occur more often in vaccinated women than in controls.
- The incidence of serious adverse events (SAEs) was not significantly higher in vaccinated women than in controls in any of the trials.

In the phase II trials of both vaccines, and the phase III trials of the quadrivalent vaccine, pain, erythema and oedema at the injection site were common, and occurred significantly more often in those given vaccine than in those given placebo. None of the women in the phase IIb trials experienced an SAE that the clinical site physician considered to be probably, possibly or potentially vaccine-related. There were no deaths in either phase II vaccine trial. There are as yet no data on safety or efficacy in immunocompromised persons.

For the quadrivalent vaccine, the detailed safety data reviewed by the United States Food and Drug Administration are included in the label, and are available at http://www.gardasil.com/. Few subjects (0.1%) discontinued because of adverse experiences. Seventeen deaths were reported among 21 464 male and female subjects. The events reported were consistent with events expected in healthy adolescent and adult populations. The most common cause of death was motor vehicle accident.

A total of 102 out of 21 464 subjects (9–26-year-old girls and women and 9–15–year-old boys) reported an SAE on days 1–15 following any vaccination visit; these included one case of bronchospasm and two cases of asthma. The most frequently reported SAEs, regardless of causality were:

- headache (0.03% Gardasil versus 0.02% placebo),
- gastroenteritis (0.03% Gardasil versus 0.01% placebo),
- appendicitis (0.02% Gardasil versus 0.01% placebo),
- pelvic inflammatory disease (0.02% Gardasil versus 0.01% placebo).

In the quadrivalent vaccine clinical studies, subjects were evaluated for new medical conditions for up to four years of follow-up. In the vaccinated group (n=11 813), five subjects developed non-specific arthritis, two rheumatoid arthritis, one juvenile arthritis and one reactive arthritis. In the placebo group (n=9701), two subjects developed arthritis and one systemic lupus erythematosis.

12.1 Vaccination during pregnancy

The clinical trial protocols excluded women who were pregnant. A pregnancy test was done prior to administration of each vaccine dose. If a woman was found to be pregnant, vaccination was delayed until after completion of pregnancy (in the quadrivalent trials), or discontinued (in the bivalent trials). Among participants in the quadrivalent vaccine trial, there were 1244 pregnancies in the vaccine group and 1272 in the placebo group. In each group, 3.6% of women who reported a

pregnancy experienced an SAE. The proportions of these that could potentially result in a need for Caesarean section were comparable in the two groups. There were 15 congenital anomalies in babies born to women in the vaccine group, and 16 in the placebo group. Further sub-analyses were conducted to evaluate pregnancies with estimated onset less than or more than 30 days from administration of vaccine or placebo. For pregnancies with estimated onset within 30 days of vaccination, five cases of congenital anomaly were observed in the vaccine group and none in the placebo group. By contrast, in pregnancies with onset more than 30 days following vaccination, 10 cases were observed in the vaccine group and 16 in the placebo group. The types of anomalies observed (regardless of when pregnancy occurred in relation to vaccination) were consistent with those generally observed in women aged 16–26 years. Animal studies in rats have shown no evidence of impaired fertility or harm to the fetus. Merck & Co. Inc. maintains a pregnancy registry to monitor fetal outcomes among pregnant women given Gardasil.

12.2 Vaccination during lactation

In the clinical trials, 995 subjects in the evaluated population (500 in the vaccine group and 495 in the control group) were breastfeeding during the vaccination period. A total of 17 (3.4%) infants of breastfeeding women who received quadrivalent HPV vaccine experienced an SAE, compared with 9 (1.8%) of those who received placebo. None of the events was judged by investigators to be vaccine-related.

13. Are HPV vaccines cost-effective?

- In settings with established cervical cancer screening programmes, the addition of HPV vaccination to the programmes is predicted to be cost-effective, especially if screening costs are reduced by increasing the age of initiation or reducing the frequency of screening.
- The benefits, in terms of averted costs associated with following up abnormal screening tests, and treating cancers, genital warts, and other HPV-related diseases, will depend greatly on the country. Cost savings related to outcomes such as genital warts and follow-up of abnormal tests for cervical precancer would occur sooner than those associated with avoiding cancer.
- Preliminary data show that HPV vaccination may be cost-effective in developing countries, but more work is needed before firm conclusions can be reached.

Knowledge of the burden of disease and the effectiveness of HPV vaccines is not enough to decide whether to introduce vaccines. The costs and benefits of vaccines need to be estimated and compared with those of other potential interventions; this can be done using modelling techniques. Most developed countries have greatly reduced cervical cancer deaths as a result of screening programmes. In such settings, the expected benefits from introduction of HPV vaccine include a reduction in morbidity, and in costs associated with follow-up of mild or equivocal cervical lesions and treatment of CIN2/3, AIS and cancer. Eventually it

may be economically more efficient to delay the age of first screening and reduce the number of screening visits.[88] The situation is likely to be very different in countries where screening does not exist or is very limited, and where access to treatment is poor. In these settings the potential reduction in cervical cancer deaths would be by far the major benefit of HPV vaccination.

In countries where the burden of HPV-related disease from conditions other than cervical cancer (including genital warts,[22] RRP, and cancers of the head, neck, anus, vagina and vulva) is well documented and their treatment is costly, the potential cost savings related to avoidance of these conditions may be substantial.[89] In addition, the time from vaccination to prevention of genital warts and RRP is much shorter than the time to prevention of cancer.[90]

In Brazil, a middle-income country, cervical cancer screening is opportunistic and coverage is incomplete. The estimated impact of HPV vaccination of girls in Brazil, from the perspective of cervical cancer control, will depend mainly on the proportion of cervical cancer attributable to HPV genotypes 16 and 18, the effectiveness of the vaccine in the target population, and the coverage achievable. Table 5 shows the estimated mean percent reduction in cases of cancer for each strategy, together with the range of estimates taking into account the uncertainty in the data and assumptions used for the analysis (i.e., probabilistic uncertainty analysis). Vaccination in adolescents (between ages 9 and 12) with 70% coverage (assuming 100% efficacy) is expected to reduce the incidence of cancer by between 34% and 55% in the long term. Screening 70% of the eligible population two or three times per lifetime, between age 35 and 45 years, using HPV DNA testing at 5-year intervals is expected to be less effective. Although the effect of secondary prevention with screening is not limited to HPV 16, 18-associated disease, this scenario assumes that screening tests are not perfectly sensitive, there is loss to follow-up with diagnosis and treatment, and that screening would only occur two or three times.

Using primary and published data from Brazil, a cost-effectiveness analysis was conducted in which the cost per vaccinated woman (inclusive of three doses of vaccine, wastage, and programmatic costs of delivery) was assumed to be US$25, US$50, or US$75; all of these are a fraction of the current cost in the USA.[91] In general, using the assumptions specified above, the results of the analysis show the following:

1) vaccination alone is likely to be more effective and cost-effective than screening two or three times per lifetime;
2) the cost-effectiveness ratio associated with vaccination is most influenced by assumptions about the vaccine cost. At $75 per vaccinated woman the cost-effectiveness ratio of vaccination alone (compared to no vaccination) ranges between $500 and $2,000 dollars per year of life saved (YLS), while at $25 per vaccinated women, the cost-effectiveness ratio is consistently less than $100 per YLS;
3) a combination of vaccination and screening three times per lifetime is more effective than vaccination alone, but also more costly. If the cost per vaccinated woman was below $25, however,

this strategy would consistently cost less than $2,000 per YLS. Thus, while it could cost more, the additional expenditure may be deemed worth while. The per capita gross domestic product (GDP) for Brazil is US$7400; thus, using the threshold of GDP per capita, as suggested by the Commission on Macroeconomics and Health, this combination strategy would be deemed very cost-effective.

It should be noted that the information on cost-effectiveness is only one input for priority-setting and additional criteria, such as affordability, capacity to achieve coverage, and distributional equity, are equally important to consider.

Cost-effectiveness studies have used different types of mathematical models, and their respective advantages and disadvantages have been discussed in detail in several excellent reviews.[92,93] The accuracy of model results depends on the appropriateness of the assumptions used to build the models, and the quality of the data used to develop and validate them. Several groups are modelling various approaches to cervical screening and vaccination in developing countries, and results should be available for several countries within the next 12–24 months. Some factors are being found consistently to influence the estimated costs and benefits (see questions 14 and 15), indicating which data it will be important to collect in the future.

Table 5. Expected reduction in the lifetime risk of cervical cancer in Brazil using different vaccination and screening strategies

Strategy*	Estimated mean cancer reduction (%) (range)
Screen 2x lifetime	18 (12–22)
Screen 3x lifetime	26 (19–31)
Vaccination alone	43 (34–55)
Vaccination and screening 3x lifetime	61 (51–68)

* Screening strategies assume HPV DNA testing between age 35 and 45 years, at 5-year intervals; 70% coverage with 15% loss to follow-up at each clinic visit. Vaccine strategies: assume 70% vaccine coverage of girls aged 9 to 12, 100% vaccine efficacy, and no waning of immunity.

14. What factors have most influence on the estimated benefits from HPV vaccination?

- The magnitude of benefit from HPV vaccination in a country will depend on:
  - the burden of HPV disease attributable to the genotypes against which the vaccines protect or, if confirmed, cross-protect;
  - vaccine efficacy;
  - achievable vaccine coverage;
  - duration of protection.

- These factors may differ in different age groups and in populations with high HIV prevalence.
- Both direct protection of those vaccinated and indirect protection of others as a result of reduced HPV transmission in the community need to be considered when different vaccination strategies are evaluated.[89, 92, 94]
- The introduction of HPV vaccines may affect – positively or negatively – the effectiveness of screening programmes, which may have important consequences.[94]
- Poorly understood features of HPV epidemiology and natural history (e.g. age- and sex-specific transmission rates, duration of natural immunity, whether reactivation occurs, HPV genotype interaction, natural history of CIN2 and CIN3) hinder modelling work; better data are urgently required.

In general, the most important determinant of overall programme effectiveness will be the coverage of pre-adolescent girls with three doses of HPV vaccine. Direct protection of individuals would be expected to decline as age at vaccination increases, since HPV vaccines are prophylactic and older women will be more likely to have had prior exposure to HPV. However, catch-up campaigns (sometimes used at the start of routine vaccination with a new vaccine) can hasten the decline in incidence and result in indirect protection of the population. Mathematical models can help to determine the costs and benefits of catch-up campaigns; these are likely to depend on the age-specific rates of HPV infection in different countries.

The potential gains from vaccinating males also need to be considered from a population perspective, including indirect (reduced HPV transmission) and direct effects (e.g. prevention of genital warts, penile cancer, anal cancer, RRP, and certain head and neck cancers). The direct cancer prevention effect in boys will be less than in girls, as the incidence of HPV-related cancer is lower in men than in women. Results of dynamic simulation models of HPV transmission suggest that, if high coverage of females can be achieved, little additional reduction in cervical cancer is gained by vaccinating males.[94, 95] At lower coverage, vaccination of boys may contribute to controlling infection. However, because vaccination directly protects women, more gains may be derived per girl vaccinated than per boy vaccinated. Whether any additional benefits are worth the costs of vaccinating males can be evaluated further in different settings using mathematical models. Validation of predictions based on these complex models will require long-term implementation studies. Furthermore, considerations of the acceptability and likely coverage of a strategy targeting girls only, against one including both sexes, will also be relevant in determining the usefulness of vaccinating boys.

The most important risk period for acquisition of HPV appears to be late adolescence and early adulthood. To obtain maximum benefit from vaccines, protection must cover this period. The clinical trials have shown that efficacy is sustained for at least 4–5 years, and it seems likely that protection may last longer. Thus, declining vaccine efficacy is unlikely to be a major determinant of the benefits of a pre-adolescent programme, though data to confirm this are clearly required.

In countries with organized screening, it will be important to evaluate the effect of HPV vaccination on the screening programme. If those who have been vaccinated no longer attend for screening, because they (wrongly) believe that they are fully protected against cervical cancer, the number of deaths could even increase, especially if vaccine protection wanes over time.[94] It is important, therefore, to use the opportunity presented by the introduction of HPV vaccine to increase awareness of the need for screening.

15. What factors have most influence on the estimated costs of HPV vaccination?

- The cost of HPV vaccines is likely to be the major determinant of the cost of a vaccination programme.
- Delivery costs for HPV vaccines are likely to be much higher than for existing vaccines given to infants, since in most developing countries a new programme will be needed.
- Data on costs and coverage of different vaccination strategies will be obtained from demonstration projects planned in four developing countries over the next 1–2 years.

The licensed vaccine is not yet widely available, but where it has been licensed, its current price is over US$100 per dose (i.e. over US$300 for the full course). Manufacturers have declared that they are willing to set different prices for countries with different economic conditions. The price of the vaccine is almost certainly going to be a major determinant of the cost and affordability of any vaccine programme.

Administration costs are likely to vary by country and region. Very few countries have universal programmes for delivering health care to pre-adolescents, so the costs of establishing and maintaining a new system for HPV vaccination are likely to be considerable.[96] Demonstration projects planned by the Program for Appropriate Technology in Health (PATH) in India, Peru, Uganda, and Viet Nam, will help to gather data on the costs of HPV vaccination programmes. If a two-dose schedule could be used, or if vaccines could be given at an earlier age, together with other vaccines (e.g. at school entry or even in infancy), the costs could be reduced. Evaluation of these options is therefore urgently needed.

Conclusions

In developing countries, cervical cancer is the leading cause of cancer death in women; it is estimated that 91% of all HPV-related cancer deaths in the world are due to cervical cancer. HPV vaccines are very effective in preventing infection and disease resulting from vaccine-related HPV genotypes in women who are negative for both HPV DNA and serum antibodies at the time of first vaccination. Protection lasts for at least 5 years and probably much longer. Data are not yet available on the safety and efficacy of HPV vaccines in Africa, or in populations with high HIV prevalence. HPV vaccines will reduce, but not eliminate, the risk of cervical cancer. Screening programmes will still be needed to prevent cervical cancer, even after HPV vaccines are introduced, although the procedures used for screening may need to be adapted.[97] The primary target group for HPV vaccines is likely to be pre-adolescent girls (e.g. aged 9–12 years), 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, and the costs and effectiveness of different strategies for vaccination and screening will improve predictions of the benefits to come from these new vaccines.[98, 99] More information on the cost-effectiveness of different strategies will become available to guide policy-makers once the price of the vaccine itself is known for countries at different income levels, and when associated delivery costs have been assessed. If a two-dose schedule could be used, or if HPV vaccines could be given at an earlier age with other vaccines (e.g. at school entry or even in infancy), vaccine delivery could be greatly facilitated. Innovative methods will be needed to finance the introduction of HPV vaccines.[100] The introduction of HPV vaccines will create opportunities to strengthen health systems. Such opportunities should be taken through the rapid establishment of new partnerships for vaccine delivery, financing and monitoring of impact.[7]

References

1. zur Hausen H. Papillomaviruses in human cancer. *Appl Pathol.* 1987;5:19–24.

2. Walboomers JM, Jacobs MV, Manos MM, Bosch FX, Kummer JA, Shah KV et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol.* 1999;189:12–19.

3. Hobbs CG, Sterne JA, Bailey M, Heyderman RS, Birchall MA, Thomas SJ. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. *Clin Otolaryngol.* 2006;31:259–266.

4. Koutsky L. Epidemiology of genital human papillomavirus infection. *Am J Med.* 1997;102:3–8.

5. 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;93:1301–1304.

6. Department of Immunization, Vaccines and Biologicals. *Vaccine introduction guidelines. Adding a vaccine to a national immunization programme: decision and implementation.* Geneva: World Health Organization; 2005 (WHO/IVB/05.18).

7. WHO, UNFPA. Preparing for the introduction of HPV vaccines. *Policy and programme guidance for countries.* Geneva: World Health Organization; 2006 (WHO/RHR/06.11).

8. World Health Organization. *Comprehensive cervical cancer control. A guide to essential practice.* Geneva; 2006.

9. de Villiers EM. Papillomavirus and HPV typing. *Clin Dermatol.* 1997;15:199–206.

10. International Agency for Research on Cancer. *Human papillomaviruses.* Lyon; 2006 (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 90).

11. Munoz N, Bosch FX, De Sanjose S, Herrero R, Castellsague X, Shah KV et al. Epidemiologic classification of human papillomavirus types associated with cervical cancer. *N Engl J Med.* 2003;348:518–527.

12. Parkin DM, Bray F. The burden of HPV-related cancers. *Vaccine.* 2006;24 (Suppl 3):S11–S25.

13. Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer incidence in five continents. Volume VIII.* Lyon: International Agency for Research on Cancer; 2002 (IARC Scientific Publications No. 155).

14. Ferlay J, Bray F, Pisani P, Parkin DM. *GLOBOCAN 2000: Cancer incidence, mortality and prevalence worldwide, Version 1.0.* Lyon: IARC Press; 2001 (IARC Cancer Base No. 5).

15. Mathers CD, Shibuya K, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: I. Application of regional cancer survival model to estimate cancer mortality distribution by site. *BMC Cancer.* 2002;2:36.

16. Shibuya K, Mathers CD, Boschi-Pinto C, Lopez AD, Murray CJ. Global and regional estimates of cancer mortality and incidence by site: II. Results for the global burden of disease 2000. *BMC Cancer.* 2002;2:37.

17. Schiffman M, Solomon D. Findings to date from the ASCUS-LSIL Triage Study (ALTS). *Arch Pathol Lab Med.* 2003;127:946–949.

18. Greer CE, Wheeler CM, Ladner MB, Beutner K, Coyne MY, Liang H et al. Human papillomavirus (HPV) type distribution and serological response to HPV type 6 virus-like particles in patients with genital warts. *J Clin Microbiol.* 1995;33:2058–2063.

19. Koshiol JE, Laurent SA, Pimenta JM. Rate and predictors of new genital warts claims and genital warts-related healthcare utilization among privately insured patients in the United States. *Sex Transm Dis.* 2004;31:748–752.

20. Winer RL, Kiviat NB, Hughes JP, Adam DE, Lee SK, Kuypers JM et al. Development and duration of human papillomavirus lesions, after initial infection. *J Infect Dis.* 2005;191:731–738.

21. Chin-Hong PV, Vittinghoff E, Cranston RD, Browne L, Buchbinder S, Colfax G et al. Age-related prevalence of anal cancer precursors in homosexual men: the EXPLORE study. *J Natl Cancer Inst.* 2005;97:896–905.

22. Kjaer SK, Munk C, Tran TN, Tryggvadottir L, Sparen P, Dasbach E, Liaw K-L, Nygaard J, Nygaard M. The burden of genital warts. A study of nearly 70,000 women from four Nordic countries. *Proceedings of European Research Organization on Genital Infection and Neoplasia (EUROGIN), April 23–26 2006, Paris, France (Abstract SS21-04).*

23. Silverberg MJ, Thorsen P, Lindeberg H, Grant LA, Shah KV. Condyloma in pregnancy is strongly predictive of juvenile-onset recurrent respiratory papillomatosis. *Obstet Gynecol.* 2003;101:645–652.

24. Derkay CS, Hester RP, Burke B, Carron J, Lawson L. Analysis of a staging assessment system for prediction of surgical interval in recurrent respiratory papillomatosis. *Int J Pediatr Otorhinolaryngol.* 2004;68:1493–1498.

25. Ho GY, Burk RD, Klein S, Kadish AS, Chang CJ, Palan P et al. Persistent genital human papillomavirus infection as a risk factor for persistent cervical dysplasia. *J Natl Cancer Inst.* 1995;87:1365–1371.

26. Ho GY, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *N Engl J Med.* 1998;338:423–428.

27. 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;6:223–233.

28. Moscicki AB, Shiboski S, Broering J, Powell K, Clayton L, Jay N et al. The natural history of human papillomavirus infection as measured by repeated DNA testing in adolescent and young women. *J Pediatr.* 1998;132:277–284.

29. Moscicki AB, Schiffman M, Kjaer S, Villa LL. Updating the natural history of HPV and anogenital cancer. *Vaccine.* 2006;24 (Suppl 3):S42–S51.

30. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol.* 1993;12:186–192.

31. 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;111:278–285.

32. 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;89:101–105.

33. 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.

34. Clifford G, Franceschi S, Diaz M, Munoz N, Villa LL. HPV type-distribution in women with and without cervical neoplastic diseases. *Vaccine.* 2006;24 (Suppl 3):S26–S34.

35. Smith JS, Lindsay L, Keys J, Hoots B, Winer R, Franceschi S, Clifford G. HPV type distribution in invasive cervical cancer and high-grade cervical neoplasia: an update of meta-analyses and identification of global data gaps. *Int J Cancer.* 2007; in press.

36. Castellsague X, Diaz M, De Sanjose S, Munoz N, Herrero R, Franceschi S et al. Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: implications for screening and prevention. *J Natl Cancer Inst.* 2006;98:303–315.

37. 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;14:1157–1164.

38. Myers ER, McCrory DC, Nanda K, Bastian L, Matchar DB. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol.* 2000;151:1158–1171.

39. 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;191:1808–1816.

40. 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;190:2077–2087.

41. Schiffman MH. Recent progress in defining the epidemiology of human papillomavirus infection and cervical neoplasia. *J Natl Cancer Inst.* 1992;84:394–398.

42. 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;10:101–106.

43. Winer RL, Lee SK, Hughes JP, Adam DE, Kiviat NB, Koutsky LA. Genital human papillomavirus infection: incidence and risk factors in a cohort of female university students. *Am J Epidemiol.* 2003;157:218–226.

44. Smith EM, Johnson SR, Ritchie JM, Feddersen D, Wang D, Turek LP et al. Persistent HPV infection in postmenopausal age women. *Int J Gynaecol Obstet.* 2004;87:131–137.

45. Fairley CK, Gay NJ, Forbes A, Abramson M, Garland SM. Hand-genital transmission of genital warts? An analysis of prevalence data. *Epidemiol Infect.* 1995;115:169–176.

46. Antonsson A, Karanfilovska S, Lindqvist PG, Hansson BG. General acquisition of human papillomavirus infections of skin occurs in early infancy. *J Clin Microbiol.* 2003;41:2509–2514.

47. Rintala MA, Grenman SE, Jarvenkyla ME, Syrjanen KJ, Syrjanen SM. High-risk types of human papillomavirus (HPV) DNA in oral and genital mucosa of infants during their first 3 years of life: experience from the Finnish HPV Family Study. *Clin Infect Dis.* 2005;41:1728–1733.

48. Rintala MA, Grenman SE, Puranen MH, Isolauri E, Ekblad U, Kero PO et al. Transmission of high-risk human papillomavirus (HPV) between parents and infant: a prospective study of HPV in families in Finland. *J Clin Microbiol.* 2005;43:376–381.

49. Clifford GM, Gallus S, Herrero R, Munoz N, Snijders PJ, Vaccarella S et al. Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis. *Lancet.* 2005;366:991–998.

50. Strickler HD, Burk RD, Fazzari M, Anastos K, Minkoff H, Massad LS et al. Natural history and possible reactivation of human papillomavirus in human immunodeficiency virus-positive women. *J Natl Cancer Inst.* 2005;97:577–586.

51. De Sanjose S, Valls I, Paz CM, Lloveras B, Quintana MJ, Shah KV et al. Human papillomavirus and human immunodeficiency virus infections as risk factors for cervix cancer in women prisoners. *Med Clin (Barc).* 2000;115:81–84 (in Spanish).

52. Castellsague X, Munoz N. Cofactors in human papillomavirus carcinogenesis-role of parity, oral contraceptives, and tobacco smoking. *J Natl Cancer Inst Monogr.* 2003;31:20–28.

53. 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; 119: 2677–2684.

54. Herrero R, Castle PE, Schiffman M, Bratti MC, Hildesheim A, Morales J et al. Epidemiologic profile of type-specific human papillomavirus infection and cervical neoplasia in Guanacaste, Costa Rica. *J Infect Dis.* 2005;191:1796–1807.

55. 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;191:1808–1816.

56. Clifford GM, Goncalves MA, Franceschi S. Human papillomavirus types among women infected with human immunodeficiency virus: a meta-analysis. *AIDS.* 2006; 20: 2337–2344.

57. Strickler HD, Palefsky JM, Shah KV, Anastos K, Klein RS, Minkoff H et al. Human papillomavirus type 16 and immune status in human immunodeficiency virus-seropositive women. *J Natl Cancer Inst.* 2003;95:1062–1071.

58. Palefsky JM, Gillison ML, Strickler HD. HPV vaccines in immunocompromised women and men. *Vaccine.* 2006;24 (Suppl 3):S140–S146.

59. Palefsky J. Human papillomavirus-associated malignancies in HIV-positive men and women. *Curr Opin Oncol.* 1995;7:437–441.

60. Palefsky JM. Human papillomavirus infection and anogenital neoplasia in human immunodeficiency virus-positive men and women. *J Natl Cancer Inst Monogr.* 1998;23:15–20.

61. 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;15:326–333.

62. 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; 15:2148–2153.

63. 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;22:236–243.

64. 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;24:293–298.

65. 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;354:2645–2654.

66. Partridge JM, Koutsky LA. Genital human papillomavirus infection in men. *Lancet Infect Dis.* 2006;6:21–31.

67. Chin-Hong PV, Vittinghoff E, Cranston RD, Buchbinder S, Cohen D, Colfax G et al. Age-specific prevalence of anal human papillomavirus infection in HIV-negative sexually active men who have sex with men: the EXPLORE study. *J Infect Dis.* 2004;190:2070–2076.

68. Stanley M. Immune responses to human papillomavirus. *Vaccine.* 2006;24 (Suppl 1):S16–S22.

69. 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;181:1911–1919.

70. Koshiol J, Schroeder J, Jamieson DJ, Marshall SW, Duerr A, Heilig CM et al. Smoking and time to clearance of human papillomavirus infection in HIV-seropositive and HIV-seronegative women. *Am J Epidemiol.* 2006;164:176–183.

71. Koshiol JE, Schroeder JC, Jamieson DJ, Marshall SW, Duerr A, Heilig CM et al. Time to clearance of human papillomavirus infection by type and human immunodeficiency virus serostatus. *Int J Cancer.* 2006;119:1623–1629.

72. Ferguson M, Heath A, Johnes S, Pagliusi S, Dillner J. Results of the first WHO international collaborative study on the standardization of the detection of antibodies to human papillomaviruses. *Int J Cancer.* 2006;118:1508–1514.

73. Pagliusi SR, Dillner J, Pawlita M, Quint WG, Wheeler CM, Ferguson M. International Standard reagents for harmonization of HPV serology and DNA assays-an update. *Vaccine.* 2006;24 (Suppl 3):S193–S200.

74. 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;185:251–257.

75. 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;67:315–322.

76. Pagliusi SR,.Teresa AM. Efficacy and other milestones for human papillomavirus vaccine introduction. *Vaccine.* 2004;23:569–578.

77. Harper DM, Franco EL, Wheeler C, Ferris DG, Jenkins D, Schuind 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;364:1757–1765.

78. 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;367:1247–1255.

79. 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;24:5571–5583.

80. Stanley MA. Human papillomavirus vaccines. *Curr Opin Mol Ther.* 2002;4:15–22.

81. Schwartz TF, Dubin GO, HPV Vaccine Study Investigators for Adult Women, GlaxoSmithKline Biologicals. An AS04-containing human papillomavirus (HPV) 16/18 vaccine for prevention of cervical cancer is immunogenic and well-tolerated in women 15–55 years old. ASCO Annual Meeting Proceedings, Part 1. *J Clin Oncol.* 2006;24(18S): 1008.

82. Villa LL. Efficacy of a quadrivalent HPV (Types 6, 11, 16, 18) L1 VLP vaccine against external genital disease: a combined analysis. *Proceedings of European Research Organization on Genital Infection and Neoplasia (EUROGIN), April 23–26 2006, Paris, France (Abstract SS17–04).*

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;6:271–278.

84. Ferris D, For the FUTURE II study group. Efficacy of a quadrivalent HPV (types 6/11/16/18) L1 virus-like particle (VLP) vaccine in women with virologic evidence of HPV infection: a combined analysis. *Proceedings of European Research Organization on Genital Infection and Neoplasia (EUROGIN), April 23–26 2006, Paris, France (Abstract S11-2).*

85. Smith JF, Brownlow MK, Brown MJ, Esser MT, Ruiz W, Brown DR. GardasilTM antibodies cross-neutralize pseudovirion infection of vaccine-related HPV types. *Proceedings of 23rd International Papillomavirus Conference and Clinical Workshop. September 1–7 2006, Prague (Abstract PL 1–6).*

86. 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. *Proceedings of 12th International Conference on Infectious Diseases, Lisbon, Portugal.* 2006.

87. 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. *Proceedings of European Research Organization on Genital Infection and Neoplasia (EUROGIN), April 23–26 2006, Paris, France (Abstract in Addendum).*

88. 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;96:604–615.

89. 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;23:1107–1122.

90. Lacey CJ, Lowndes CM, Shah KV. Burden and management of non-cancerous HPV-related conditions: HPV-6/11 disease. *Vaccine*. 2006;24 (Suppl 3):S35–S41.

91. Goldie SJ, Kim JJ, Kobus KE, Holtan MK, Kuntz KM, Salomon JA. Cost-effectiveness analysis of prophylactic human papillomavirus vaccination and screening in Brazil. *Proceedings of 23rd International Papillomavirus Conference and Clinical Workshop, 1–7 September 2006, Prague, Czech Republic (Abstract PS25-7)*.

92. Dasbach EJ, Elbasha EH, Insinga RP. Mathematical models for predicting the epidemiologic and economic impact of vaccination against human papillomavirus infection and disease. *Epidemiol Rev*. 2006;28:88-100.

93. Goldie SJ, Goldhaber-Fiebert JD, Garnett GP. Public health policy for cervical cancer prevention: The role of decision science, economic evaluation, and mathematical modeling. *Vaccine*. 2006;24 (Suppl 3):S155–S163.

94. Garnett GP, Kim JJ, French K, Goldie SJ. Modelling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine*. 2006;24 (Suppl 3):S178–S186.

95. 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.

96. Kane MA, Sherris J, Coursaget P, Aguado T, Cutts F. HPV vaccine use in the developing world. *Vaccine*. 2006;24 (Suppl 3):S132–S139.

97. Franco EL, Cuzick J, Hildesheim A, De Sanjose S. Issues in planning cervical cancer screening in the era of HPV vaccination. *Vaccine*. 2006;24 (Suppl 3):S171–S177.

98. Franco EL, Bosch FX, Cuzick J, Schiller JT, Garnett GP, Meheus A et al. Knowledge gaps and priorities for research on prevention of HPV infection and cervical cancer. *Vaccine*. 2006;24 (Suppl 3):S242–S249.

99. Hildesheim A, Markowitz L, Avila MH, Franceschi S. Research needs following initial licensure of virus-like particle HPV vaccines. *Vaccine.* 2006;24 (Suppl 3):S227–S232.

100. Batson A, Meheus F, Brooke S. Innovative financing mechanisms to accelerate the introduction of HPV vaccines in developing countries. *Vaccine*. 2006;24 (Suppl 3):S219–S225.

Annex

Cancer registries and age-standardized incidence rates (ASIR) of cervical cancer by country *

Region and country or area	No. of registries meeting inclusion criteria	Population represented	No. of cases	ASIR / 100 000 (if >1 registry, median and range shown)
Latin America and the Caribbean				
Argentina	2	655 114	273	14.6–30.6
Brazil	2	1 849 664	940	14.1–38.2
Colombia	1	1 672 854	1 102	29.8
Costa Rica	1	3 369 415	568	20.1
Cuba	1	849 703	143	9.6
Ecuador	1	1 401 389	675	26.0
Martinique	1	381 427	231	19.3
Uruguay	1	1 372 431	476	17.8
Eastern Mediterranean				
Algeria	1	1 882 000	506	12.5
Kuwait (Kuwaitis)	1	2 000 000	34	4.2
Oman (Omanis)	1	1 684 850	154	7.7
Pakistan	1	1 724 915	74	6.8
Sub-Saharan Africa				
Gambia	1	1 038 145	171	29.8
Mali	1	1 016 167	182	35.9
Réunion	1	642 600	109	17.7
Uganda	1	1 141 992	465	41.7
Zimbabwe	1	1 486 944	613	55.0
South-East Asia				
India	9	38 951 927	12 567	22.5 (10.9–30.1)
Singapore	1	2 705 115	1 119	9.9 (8.2–15.0)
Thailand	5	11 562 626	4 405	20.9 (16.5–25.3)
Western Pacific				
China				
- Mainland	6	18 032 032	1 658	2.3 (1.2–3.9)
- Hong Kong	1	6 484 300	2 337	12.3
- Province of Taiwan	1	21 000 000	2 855	24.9
Philippines	2	10 329 364	3 400	17.5–21.9
Republic of Korea	4	16 639 847	7 723	20.2 (15.2–22.3)
Viet Nam	2	7 003 235	2 633	6.7–28.8

* Adapted from: Parkin DM, Whelan SL, Ferlay J, Teppo L, Thomas DB. *Cancer incidence in five continents, volume VIII.* Lyon; International Agency for Research on Cancer: 2002 (IARC Scientific Publications No. 155).