Human Papillomavirus (HPV) Vaccine
Background Paper

September 2008
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<th>Definition</th>
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<tbody>
<tr>
<td>AAHS</td>
<td>amorphous aluminium hydroxyphosphate sulphate</td>
</tr>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices (United States)</td>
</tr>
<tr>
<td>AE</td>
<td>adverse event</td>
</tr>
<tr>
<td>AFRO</td>
<td>World Health Organization Regional Office for Africa</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immune deficiency syndrome</td>
</tr>
<tr>
<td>AIN</td>
<td>anal intraepithelial neoplasia</td>
</tr>
<tr>
<td>AIS</td>
<td>adenocarcinoma in situ</td>
</tr>
<tr>
<td>AMC</td>
<td>advance market commitment</td>
</tr>
<tr>
<td>AORRP</td>
<td>adult onset recurrent respiratory papillomatosis</td>
</tr>
<tr>
<td>AS04</td>
<td>GlaxoSmithKline Inc.’s adjuvant containing aluminium hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A</td>
</tr>
<tr>
<td>ASC-H</td>
<td>atypical squamous cells, where cannot exclude high-grade intraepithelial lesion</td>
</tr>
<tr>
<td>ASC-US</td>
<td>atypical squamous cells of undetermined significance</td>
</tr>
<tr>
<td>ASCUS</td>
<td>atypical squamous cells of undetermined significance (category may also include those in which high-grade intraepithelial lesions (ASC-H) cannot be excluded)</td>
</tr>
<tr>
<td>AUS$</td>
<td>Australian dollar</td>
</tr>
<tr>
<td>CAN$</td>
<td>Canadian dollar</td>
</tr>
<tr>
<td>CAR</td>
<td>Central African Republic</td>
</tr>
<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention (United States)</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CIN(1,2,3)</td>
<td>cervical intraepithelial neoplasia (grade 1, 2, 3)</td>
</tr>
<tr>
<td>DALY</td>
<td>disability-adjusted life year</td>
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</table>
DNA  deoxyribonucleic acid
dT  diphtheria/tetanus vaccine
dTaP  diphtheria/tetanus/pertussis vaccine
dTaP-IPV  diphtheria/tetanus/pertussis/poliomyelitis vaccine
DPT3  diphtheria/tetanus/pertussis vaccine
DTP  diphtheria/tetanus/pertussis vaccine
dTpa  diphtheria/tetanus/pertussis vaccine
E4, E6, E7  human papillomavirus (HPV) genes associated with carcinogenesis that code for proteins produced early in infection with HPV
ECDC  European Centre for Disease Prevention and Control
ELISA  enzyme-linked immunosorbent assay
EMEA  European Medicines Agency
EMRO  World Health Organization Regional Office for the Eastern Mediterranean region
EPAR  European Public Assessment Report
EPI  Expanded Programme on Immunization
Eudravigilance  European post-marketing surveillance system
EURO  World Health Organization Regional Office for Europe
FDA  Food and Drug Administration (United States)
Fendrix®  GlaxoSmithKline Inc.’s hepatitis B vaccine for patients aged over 15 years with renal insufficiency
GACVS  Global Advisory Committee on Vaccine Safety
GAVI  Global Alliance for Vaccines and Immunization
GDP  gross domestic product
GIVS  Global Immunization Vision and Strategy
GMT  geometric mean titre
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>GNI</td>
<td>gross national income</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline Inc.</td>
</tr>
<tr>
<td>HBsAg</td>
<td>hepatitis B surface antigen</td>
</tr>
<tr>
<td>HBV</td>
<td>hepatitis B virus</td>
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<tr>
<td>HEAG</td>
<td>Human Papillomavirus Expert Advisory Group</td>
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<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
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<tr>
<td>HPV</td>
<td>human papillomavirus</td>
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<tr>
<td>HSIL</td>
<td>high-grade squamous intraepithelial lesion</td>
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<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>HSV-2</td>
<td>herpes simplex virus type 2</td>
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<tr>
<td>HVAC</td>
<td>HPV Vaccine Advisory Committee</td>
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<tr>
<td>IS$</td>
<td>international dollar</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IAVI</td>
<td>International AIDS Vaccine Initiative</td>
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<tr>
<td>ICER</td>
<td>incremental cost-effectiveness ratio</td>
</tr>
<tr>
<td>ICO</td>
<td>Institut Català d’Oncologia</td>
</tr>
<tr>
<td>IFFIm</td>
<td>International Financing Facility for Immunization</td>
</tr>
<tr>
<td>IgA</td>
<td>immunoglobulin A</td>
</tr>
<tr>
<td>IgG</td>
<td>immunoglobulin G</td>
</tr>
<tr>
<td>IUD</td>
<td>intrauterine device</td>
</tr>
<tr>
<td>IVB</td>
<td>Immunization, Vaccines and Biologicals (World Health Organization programme)</td>
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<tr>
<td>IVR</td>
<td>Initiative for Vaccine Research</td>
</tr>
<tr>
<td>JORRP</td>
<td>juvenile onset recurrent respiratory papillomatosis</td>
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<tr>
<td>L1, L2</td>
<td>human papillomavirus structural proteins</td>
</tr>
<tr>
<td>LEEP</td>
<td>loop electrosurgical excision procedure</td>
</tr>
<tr>
<td>Low-risk HPV</td>
<td>human papillomavirus types with low oncogenic potential</td>
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<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>LSIL</td>
<td>low-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>LY</td>
<td>life year</td>
</tr>
<tr>
<td>MCV4, Menactra®</td>
<td>Sanofi Pasteur’s meningococcal (groups A, C, Y and W-135) conjugate vaccine</td>
</tr>
<tr>
<td>MDG</td>
<td>United Nations Millennium Development Goal</td>
</tr>
<tr>
<td>Merck</td>
<td>Merck &amp; Co.</td>
</tr>
<tr>
<td>MPL</td>
<td>adjuvant substance 3-O-desacyl-4’- monophosphoryl lipid A</td>
</tr>
<tr>
<td>NCT</td>
<td>clinical trial registry number</td>
</tr>
<tr>
<td>OPV</td>
<td>oral polio vaccine</td>
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<tr>
<td>PAHO</td>
<td>World Health Organization Regional Office for the Americas</td>
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<tr>
<td>Pap test</td>
<td>Papanicolaou test</td>
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<tr>
<td>PATH</td>
<td>Program for Appropriate Technology in Health</td>
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<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>PPP</td>
<td>purchasing power parity</td>
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<tr>
<td>PPV</td>
<td>positive predictive value</td>
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<tr>
<td>QALY</td>
<td>quality-adjusted life year</td>
</tr>
<tr>
<td>RNA</td>
<td>ribonucleic acid</td>
</tr>
<tr>
<td>RRP</td>
<td>recurrent respiratory papillomatosis</td>
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<tr>
<td>SAGE</td>
<td>World Health Organization Immunization Strategic Advisory Group of Experts</td>
</tr>
<tr>
<td>SEARO</td>
<td>World Health Organization Regional Office for South-East Asia</td>
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<tr>
<td>SJS</td>
<td>Stevens–Johnson syndrome</td>
</tr>
<tr>
<td>STD</td>
<td>sexually transmitted disease</td>
</tr>
<tr>
<td>STI</td>
<td>sexually transmitted infection</td>
</tr>
<tr>
<td>TCG</td>
<td>Technical Consultative Group</td>
</tr>
<tr>
<td>TdaP</td>
<td>tetanus/diphtheria/acellular pertussis vaccine</td>
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<td>UAE</td>
<td>United Arab Emirates</td>
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<tr>
<td>UN</td>
<td>United Nations</td>
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<tr>
<td>UNFPA</td>
<td>United Nations Population Fund</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>US$</td>
<td>United States dollar</td>
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<tr>
<td>Vaccine-related HPV types</td>
<td>types of HPV for which type-specific virus-like particles serve as vaccine antigens</td>
</tr>
<tr>
<td>VAERS</td>
<td>Vaccine Adverse Event Reporting System (United States)</td>
</tr>
<tr>
<td>VaIN</td>
<td>vaginal intraepithelial neoplasia</td>
</tr>
<tr>
<td>VE</td>
<td>vaccine efficacy</td>
</tr>
<tr>
<td>VIA</td>
<td>visual inspection of the cervix with acetic acid</td>
</tr>
<tr>
<td>VILI</td>
<td>visual inspection of the cervix with Lugol’s iodine</td>
</tr>
<tr>
<td>VIN</td>
<td>vulvar intraepithelial neoplasia</td>
</tr>
<tr>
<td>VLP</td>
<td>virus-like particle</td>
</tr>
<tr>
<td>VSD</td>
<td>Vaccine Safety Datalink project (United States)</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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<tr>
<td>WPRO</td>
<td>World Health Organization Regional Office for the Western Pacific</td>
</tr>
<tr>
<td>YLL</td>
<td>year of life lost</td>
</tr>
<tr>
<td>YLS</td>
<td>year of life saved</td>
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</table>
Executive summary

Purpose of document (Introduction)
This background paper summarizes data published to the end of 2007, plus, in Annex 2, publicly available data (including unpublished reports) from January to the end of September 2008, much of which was reviewed by the World Health Organization (WHO) Human Papillomavirus (HPV) Vaccine Advisory Committee (HVAC).

This summary includes the key points and evidence available to the end of September 2008 that are most relevant to the WHO Immunization Strategic Advisory Group of Experts (SAGE), and that provide the basis for HVAC’s candidate recommendations about HPV vaccines for consideration by SAGE (see Section 7).

Topic headings and order in this summary are not identical to those in the background paper. For each topic, the indicated section in the background paper provides further details.

Epidemiology of genital HPV infection (Section 1)

- HPV is a family of deoxyribonucleic acid (DNA) viruses that infect skin or mucosal epithelial cells. Of the more than 100 types of HPV, at least 13 can cause cancer of the cervix, other anogenital organs, or the head and neck. Other HPV types with low oncogenic potential cause non-malignant lesions, such as warts.
- Genital HPVs are highly transmissible, and infection with HPV is the most common viral infection of the genital tract. Infection is extremely common throughout the world.
- Genital HPV types are transmitted through penetrative and non-penetrative sexual contact. Because HPV is usually acquired within the first few years after onset of sexual activity, peak incidence usually occurs between the ages of 16 and 20 years. Incidence and prevalence increase with increasing sexual activity. Most people will acquire the infection at some time in their life.
- Risk factors for transmission of HPV infections include multiple sex partners, lack of condom use, smoking and coinfection with other sexually transmitted infections (STIs), including human immunodeficiency virus (HIV).
- HPV is a purely mucosal infection and has no bloodstream phase. Only about half of women develop serum antibodies after natural infection, and antibodies do not necessarily prevent subsequent infection.
- Most HPV infections of the cervix are asymptomatic and transient; most clear within 2 years (i.e. are no longer detectable by commonly used molecular methods).
- The small proportion of HPV infections that persist can cause neoplastic changes.

Role of HPV infection in malignant and non-malignant diseases (Section 1)

- Persistent HPV infections can lead to development of precancerous lesions, cancer, notably cervical cancer, and non-malignant disease.
- Persistent cervical infection causes cellular changes in the epithelium that can be detected through cytology screening. Persistent infection can cause cervical intraepithelial neoplasia (CIN), which is graded as CIN1, CIN2 or CIN3 according to the extent of affected epithelium, and adenocarcinoma in situ (AIS). Moderate to high-grade CIN (CIN2/3) and AIS – diagnoses confirmed by cervical biopsy – have a high probability of progression to cancer and are considered precancerous lesions.
• The time between initial HPV infection and development of cervical cancer is usually decades.
• High-grade anal, vaginal and vulvar intraepithelial neoplasia have a high probability of progressing to cancer.
• Several factors contribute to HPV persistence and development of cervical cancer: older age, immune suppression due to HIV or other factors, multiparity, early age at first delivery, long-term hormonal contraceptive use, smoking and infection with other STIs.
• Oncogenic types of HPV are estimated to cause 100% of cervical cancers; 90% of anal cancers; 40% of cancers of the vulva, vagina, and penis; and at least 12% of head and neck cancers.
• HPV 16 and 18 cause approximately 70% of cervical cancer cases globally. Together, HPV 16, 18, 31, 33, 35, 45, 52 and 58 account for about 90% of cervical cancer cases in all regions.
• HPV 16 is the most common cause of cervical cancer, causing 52–58% of cases in all regions.
• HPV 16 is the most common cause of non-cervical anogenital cancers.
• Together, HPV 6, 11, 16 and 18 cause about 35–50% of CIN1, vulvar intraepithelial neoplasia (VIN)1 and vaginal intraepithelial neoplasia (VaIN)1 cases.
• HPV types 6 and 11, two types with very low oncogenic potential, cause 90–100% of external anogenital warts, and nearly all cases of recurrent respiratory papillomatosis (RRP).

**Burden of malignant disease related to oncogenic HPV (Section 1)**

• Cervical cancer is the most common HPV-related malignancy. It is the leading cause of cancer among women in developing countries, and the second leading cancer in women worldwide.
• In 2005, nearly 500 000 new cases of cervical cancer occurred. If current incidence trends continue, incidence of cervical cancer will rise to an estimated 1 million cases per year by 2050.
• Incidence rates are highest in parts of Latin America and the Caribbean, sub-Saharan Africa, Melanesia and parts of south Asia. In 2002, 54% of cervical cancer cases occurred in Global Alliance for Vaccines and Immunization (GAVI)-eligible countries, of which about half were in India alone. Incidence rates range from less than 1–50 per 100 000.
• In 2005, more than 260 000 cervical cancer deaths occurred, resulting in 2.7 million years of life lost. If current trends persist, cervical cancer deaths are expected to rise by nearly 25% in the next 10 years.
• About 80% of cervical cancer deaths occur in developing countries; if current mortality trends continue, this proportion is expected to increase to 90% by 2020. In most developing countries, more than 60% of women with cervical cancer will die of their disease due to late detection.
• Incidence and mortality of cervical cancer is highest in countries where effective screening, diagnosis and treatment services are absent or limited.
• In the Caribbean, Eastern Europe and Latin America, cervical cancer contributes more to years of life lost than tuberculosis, maternal conditions or acquired immune deficiency syndrome (AIDS).
• Most cervical cancer cases occur in women aged over 40 years, an age when women maximize their familial, economic, social, and educational contributions, including workforce and community participation, child and elder care, and support of child education.
• The HIV pandemic has increased the global cervical cancer burden; HIV-infected females are more likely to acquire oncogenic HPV types that progress rapidly to neoplasia.
• Cancers of the vulva, vagina, penis, anus, and head and neck due to HPV are far less common than cervical cancer; age-standardized incidence rates are less than 2 per 100 000.
• Incidence of HPV-related vulvar, anal, and head and neck cancer is rising in some regions or subpopulations.
• Most HPV-related anogenital and head and neck cancer cases occur in adults aged over 50 years.
Burden of non-malignant disease related to HPV 6 and 11 (Section 1)

- Anogenital warts are common among sexually active persons. Global burden estimates are imprecise, but some surveys indicate that up to 10% of women have had anogenital warts.
- Warts are highly infectious; they generally appear in adolescence or young adulthood shortly after onset of sexual activity, usually in the late teens and 20s.
- Warts may cause pain, bleeding, genital or urethral obstruction, pregnancy complications, shame and embarrassment. Warts infrequently resolve without treatment, and recurrence is common despite treatment. In HIV-infected or immunocompromised persons, warts may be severe and require inpatient treatment.
- Warts incur substantial health-care costs, especially in high-income countries that routinely provide wart diagnosis and treatment.
- RRP is a rare but serious condition of the larynx. In children, it results from perinatal exposure during delivery, while in adults it results from oral–genital sexual contact.
- RRP often requires repeated surgical treatment, especially if the airway is compromised.

Limitations of current strategies to prevent cervical cancer and other HPV-related disease (Section 2)

- Most HPV-related precancerous lesions of the cervix are asymptomatic; thus, they can only be detected through screening tests that rely on cytologic or histologic examination of cervical cells or tissue collected by a health professional during an internal pelvic examination.
- In settings where cervical cancer screening is absent or limited, most women present with symptomatic late-stage disease that is often complex and costly to treat, untreatable or fatal.
- In many high-income countries, and a few middle-income countries, organized cervical cytology screening programmes with high population coverage have substantially reduced cervical cancer incidence and mortality. However, even when screening is available, many women are unaware of it, do not access it or cannot afford it. Cytology screening is more effective in detecting precancers and cancers of squamous cell type than AIS or adenocarcinoma, because the endocervical glands from which these lesions arise are more difficult to sample using cytology.
- Screening programmes are absent or very limited in most low and middle-income countries. They are complex, costly, labour intensive, and hard to sustain with quality. Five percent of women in developing countries have been screened in the last 5 years, compared with 75% in other countries.
- Because cytology screening is not feasible in most low-resource settings, WHO recommends visual cervical inspection and cryotherapy for lesions. Access to these services in developing countries is limited, partly because preventive care for women (other than family planning) is rare.
- Access to diagnosis, treatment and palliative care for cervical cancer and other HPV-related cancers is limited in many low and middle-income countries. Consequently, individuals with cancer often suffer prolonged, painful deaths that may isolate them from family and friends.
- Abstinence and condom use can reduce the risk of acquiring warts, but limited use of these methods reduces their impact at a population level. Condoms cannot prevent skin-to-skin HPV transmission in genital areas not covered by the condom or during non-penetrative intercourse.
- Anogenital warts can be treated with patient or provider-applied medication, ablation and surgery. Access to these therapies is limited in many countries.
Characteristics of marketed HPV vaccines (Section 3)

- Two prophylactic HPV vaccines are currently marketed. Both vaccines are designed to prevent HPV infection and HPV-related disease; they are not designed to treat women with current HPV infection or HPV-related disease.
- Both vaccines are made with recombinant technology in which proteins form virus-like particles (VLPs). They are non-infectious and lack live biological products and genetic material.
- Cervarix®, hereafter referred to as the bivalent vaccine, is manufactured by GlaxoSmithKline (GSK). It contains VLP antigens for HPV 16 and 18 reassembled from L1 proteins of HPV 16 and 18, and is designed to protect against infection and disease due to these types. It is produced using a novel recombinant baculovirus expression system and a cell line derived from Trichoplusia ni cells, and contains the adjuvant AS04, which includes monophosphoryl lipid A (MPL). It is given as three intramuscular injections at 0, 1 and 6 months.
- Gardasil® (also marketed as Silgard®), hereafter referred to as the quadrivalent vaccine, is manufactured by Merck. It contains VLP antigens for HPV 6, 11, 16 and 18, reassembled from L1 proteins of HPV 6, 11, 16 and 18, and is designed to protect against infection and disease due to these types. It is produced using yeast substrate, and contains the adjuvant amorphous aluminium hydroxyphosphate sulphate. It is given as three intramuscular injections at 0, 2 and 6 months.
- Neither vaccine contains thimerosal, preservatives or antibiotics.
- Both vaccines are currently marketed as single dose vials or prefilled syringes.
- Both vaccines require storage and transport in a cold-chain system.

Clinical evaluation and key findings as of September 2008 (Section 3)

Key findings

- Data are publicly available on the safety, immunogenicity, and efficacy of both vaccines in young and older adolescent females and women from large clinical trials conducted in several continents.
- Endpoints of CIN2/3 or AIS have been widely accepted as a proxy for cervical cancer that can be studied ethically in efficacy trials. Trials have also evaluated persistent cervical HPV infection, which is considered necessary for the development of precancers and cancers.
- Among females who, before vaccination, had no evidence of current infection with HPV types related to type-specific VLP antigens (hereafter called vaccine-related types), both vaccines had efficacy of more than 90% against CIN2 or higher grade among females aged 15–26 years who received all three doses; trials showed small variations in efficacy estimates vary by vaccine, type of study, analytic population and duration of follow-up.¹
- Both vaccines appear to provide partial protection against infection, CIN2/3 or AIS due to one or more oncogenic type that is genetically related to HPV 16 or 18.
- Both vaccines induced high levels of serum antibodies against all vaccine-related types in more than 99% of females aged 9–45 years (quadrivalent vaccine) or 10–55 years (bivalent vaccine).
- No clinical efficacy studies have been conducted in females aged less than 15 years due to ethical and practical considerations; immunobridging studies for this age demonstrate higher antibody levels than in older females enrolled in efficacy trials.
- Among females of all ages, both vaccines were generally well tolerated, although injection site pain, redness and swelling were more common in vaccine recipients than in control subjects.
- Both vaccines appear generally safe based on trial data and initial post-marketing surveillance.

¹ This summary of efficacy estimates may reflect results of several analyses. Confidence intervals around all point estimates were narrow and statistically significant, except where confidence intervals are included. Confidence intervals for specific efficacy estimates are given in Section 3.
Detailed results – vaccine immunogenicity and duration of antibody in females (Section 3)

Both vaccines

- The major basis of protection against infection is believed to be neutralizing serum immunoglobulin (IgG) antibody that transudates from capillaries to the genital epithelial mucosa, and binds to viral particles.
- Studies have evaluated immunogenicity in females without current infection with vaccine-related types before vaccination (i.e. HPV DNA negative); subjects were aged 9–45 years for the quadrivalent vaccine trials and 10–55 years for the bivalent vaccine trials. Subanalyses examined subgroups including those with no past HPV exposure (i.e. seronegative and HPV DNA negative at baseline) and subgroups with past, cleared infection (i.e. seropositive and HPV DNA negative at baseline).²
- Both vaccines induce serum antibodies for all vaccine-related types in more than 99% of females after three doses (month 7), and antibody levels for all vaccine-related types are several times higher than those seen after natural infection in all ages.
- Titres peak after the third dose, gradually decline, and level off by 24 months after the first dose; they then remain stable at levels as high as, or higher than, levels seen after natural infection up to 60–64 months after the first dose (quadrivalent vaccine trials have reported follow-up to 5 years, bivalent vaccine trials have reported follow-up to 6.4 years).
- Almost all vaccinees had a substantial immune response to vaccine-related HPV types following dose two. Titers varied only slightly if doses are given slightly earlier or later than recommended.
- Both vaccines induce higher antibody levels in females aged less than 15 years than in older females, and antibody titres decline as the age of vaccine recipient increases to age 55 years.
- The minimum level of protective antibody is not known, because cases of clinical endpoints (i.e. high-grade cervical lesions) in vaccinees have been rare, and antibody levels in these cases were similar to those of cases without clinical endpoints.
- Trials of bivalent and quadrivalent vaccines measured immune response using different assays, precluding direct comparison of immunogenicity. Results of a study sponsored by GSK is comparing the immunogenicity of two vaccines using the same assay are forthcoming.
- Vaccine immunogenicity studies in Africans and in HIV-infected individuals are under way.
- Both manufacturers will study immunogenicity in vaccinees for at least 14 years post-vaccination.

Quadrivalent vaccine

- Compared to other vaccine-related types, a lower proportion of females have sustained detectable antibodies against HPV 18 than against other vaccine-related types, but this has not been associated with reduced efficacy against clinical endpoints.
- Administration of a fourth challenge dose at five years induced a rapid increase in antibody levels, consistent with the presence of vaccine-induced immune memory.
- Age is a significant predictor of antibody titres to HPV 11,16 and 18. Immune response was strong in virtually all trial subjects but varied slightly by race/ethnicity and region. Oral contraceptive use, smoking and co-administration of the vaccine with hepatitis B vaccine and with a licensed diptheria/tetanus/pertussis/poliomyelitis vaccine did not affect immune response.
- In the United States, in an unpublished study in 120 HIV-infected children aged 7–11 years (most of whom used antiretroviral therapy), more than 99% of vaccinated individuals seroconverted. Compared with vaccinated, non-HIV-infected historic controls of similar age,

² Note: HPV seropositivity is a marker of past infection; HPV DNA positivity is a marker of current infection.
HIV-infected children had lower titres for all vaccine-related types, but differences were statistically significantly lower only for HPV 6 and 18.

**Bivalent vaccine**

- Vaccine VLPs combined with AS04 adjuvant in the marketed product induced higher antibody response than the same antigens combined with the GSK aluminium hydroxide adjuvant.
- Antibody responses have not been affected by co-administration of a licensed diphtheria/tetanus/pertussis/inactivated polio vaccine in females aged 10–18 years.
- Up to 24 months after dose 1, levels of HPV 16 and 18 antibodies in cervicovaginal secretions and serum were strongly correlated. Some believe cervical immunity contributes to vaccine efficacy.
- An ongoing trial in the United Republic of Tanzania may be able to evaluate the influence of malaria and helminth infections on vaccine-induced immunity.

**Detailed results – clinical efficacy of HPV vaccines (Section 3)**

- HPV infection per se does not cause signs or symptoms, so HPV-related diseases are relevant trial endpoints. Regulatory and expert groups have recommended using CIN2 or higher grade (CIN2+) or AIS as endpoints for phase III trials, because trials of invasive cervical cancer outcomes would require decades and would not be ethical in settings that screen and treat for precancerous lesions. Some regulatory authorities also recommended evaluating persistent HPV infection as endpoints.
- Most regulatory authorities have allowed immunobridging studies to infer efficacy in children and adolescents who have not yet begun sexual activity and for females aged over 25 years. Efficacy trials have not been conducted in females less than 14 years due to cultural constraints in collecting genital specimens, low risk of HPV exposure at this age, and the long trial duration that would be needed to evaluate vaccine efficacy.
- Phase III trials of both vaccines enrolled females regardless of past or current infection with vaccine-related types to assess efficacy in various groups. Past exposure was defined as positive type-specific HPV serology; current infection was defined as a positive type-specific HPV DNA test.
- It is difficult to directly compare trial results for the quadrivalent vaccine and the bivalent vaccine because the trials differed in many ways: age range and countries of recruitment, control groups, assays to determine baseline infection status and vaccine-induced immune response, outcome definitions, design and analysis of vaccine efficacy studies, timing and duration of follow-up, and extent of published and public domain data.

**Quadrivalent vaccine**

- Published efficacy data for the quadrivalent vaccine are available from two completed randomized phase III trials and long-term follow-up of phase II trials; trials were conducted in 24 countries in Asia, Australia, Europe and North and South America. Vaccine recipients were compared to females receiving placebo containing the same adjuvant. By September 2008, results were presented for the completed phase III trials on persistent infection, abnormal cytology, CIN1–3, AIS, VIN, VaIN and genital warts related to HPV 6, 11, 16 and 18 in females aged 15–26 years, followed for a mean of 3.7 years. Also available are preliminary efficacy data on the combined endpoint of CIN (any grade) and external genital lesions in women aged 24–45 years followed for 2.2 years after the first dose. Section 3 provides details on the analytic populations for the phase III trials of females aged 15–26. In brief, they included:
  - a per-protocol population who were naive (both seronegative and DNA negative) to one or more relevant vaccine-related HPV type, remained DNA negative to relevant types to one month after the third dose, had all three doses and had no major protocol violations; endpoints were ascertained starting 30 days after dose three
an unrestricted susceptible population who were naive to one or more relevant vaccine-related HPV types at baseline (as above); endpoints were ascertained from the day after the first dose, so this population included females who may have had less than three doses; females with protocol violations were also included

an intent-to-treat population who included females who may have had HPV infection with vaccine-related and non-vaccine-related types or cervical neoplasia or abnormal cytology at baseline; endpoints were ascertained starting the day after the first dose, so this population included females who may have had less than three doses as well as females with protocol violations.

Bivalent vaccine

- Published efficacy data for the bivalent vaccine are available for females aged 15–25 years, from interim results of an ongoing phase III trial in the Asia–Pacific region, Europe and Central, North and South America; and from initial and extended follow-up of phase II studies conducted in Brazil and North America. Phase II trials compared vaccine recipients to controls receiving placebo with Al(OH)₃. Phase III trials compared vaccine recipients to females receiving an investigational formulation of a GSK hepatitis A vaccine with the same schedule as the bivalent vaccine. By September 2008, data were published on HPV 16 or 18-related persistent infections, abnormal cytology and CIN2+ in three populations:
  - a total vaccinated cohort from phase III trials (interim results) who were naive (both seronegative and DNA negative) for HPV 16 and/or 18, but may have had prevalent infections with other oncogenic types and may have had normal or low-grade abnormal cytology at baseline; had at least one vaccine dose, and did not have major protocol violations; endpoints were ascertained starting the day after the first dose; analyses of per-protocol and intent-to-treat populations are forthcoming
  - a per-protocol population from phase II trials who were naive (both seronegative and DNA negative) to HPV 16 and 18, and to 12 other oncogenic HPV types at baseline; DNA negative for HPV 16/18 through month 6; denied past abnormal cytology, ablative or excisional cervical treatment, or ongoing wart treatment; received all 3 doses; had no major protocol violations; and had adequate follow-up data
  - an intent-to-treat population from the phase II trials who were identical to the per protocol population (above) except that they had only one dose and may have had major protocol violations.

Vaccine efficacy against persistent infection and disease caused by vaccine-related types in females without evidence of current infection with these types (Section 3)

- Both vaccines provide more than 90% efficacy against persistent infection with vaccine-related HPV types and against CIN2 or higher grades due to HPV 16 and 18 among women aged 15–26 years, who were naive to these HPV types before vaccination, and received all three doses.
- Both vaccines provide high efficacy for several years after the first dose. For the quadrivalent vaccine, efficacy has been sustained to a mean follow-up period of 5 years in phase II trials and a mean follow-up period of 3.7 years in phase III trials, the study endpoint. For the bivalent vaccine, efficacy has been sustained to an average of 6.4 years in phase II trials and 14.8 months in interim results of the phase III trial.
- Among women who had been infected with one vaccine-related type before vaccination and received three vaccine doses, both vaccines have been shown to provide more than 90% efficacy against persistent infection and CIN2 or higher grade due to other vaccine-related types.
- For both vaccines, efficacy is not significantly altered by use of oral contraceptives.
- Both manufacturers plan long-term efficacy studies for at least 14 years after the third dose.
**Quadrivalent vaccine trials have also demonstrated:**
- Efficacy of 90–100% against persistent infection with HPV 6, 11, 16 and 18, depending on the study protocol and HPV type in phase II and III trials of females aged 15–26 years.
- High efficacy against CIN2/3 and AIS due to HPV 16 or 18 in per-protocol populations (≥98%) and unrestricted susceptible populations (≥95%) aged 15–26 years in phase III trials.
- Efficacy of 100% against HPV 6 and/or 11-associated CIN1 in the per-protocol population aged 15–26 years in combined analysis of phase II and III trials.
- Efficacy of 45% against high-grade cervical disease (CIN2/3 or AIS) associated with any HPV type, including non-vaccine-related types, among females aged 15–26 years naive to 14 oncogenic types before vaccination.
- Efficacy of 96% or more against the combined endpoint of CIN1, CIN2/3 and AIS due to HPV 6, 11, 16 or 18 up to a mean of 3.7 years after vaccination among females aged 15–26 years.
- Efficacy of 95–100% in preventing VIN1, VIN2/3, VaIN1 and VaIN2/3 associated with HPV 16/18 or HPV 6, 11, 16 or 18 in per-protocol and unrestricted susceptible populations aged 15–26 years who were naive to relevant vaccine-related types before vaccination.
- Efficacy of 92% against the combined endpoint of CIN (any grade), VIN, VaIN or anogenital warts due to HPV 6, 11, 16 or 18 among females aged 24–45 years who were naive to vaccine-related types before vaccination, based on a mean follow-up of 2.2 years after the first dose.

**Bivalent vaccine trials have also demonstrated:**
- Efficacy of 80–100% against persistent infection with HPV 16 and 18, depending on the study protocol and HPV type in phase II and III trials among females aged 15–25 years.
- Efficacy of 90% against HPV 16/18 associated CIN2 in the total vaccinated cohort, in the interim analyses of the phase III trial. Post-hoc analyses of a subset of females without evidence of infection with HPV 16 and 18 before histologic diagnosis found efficacy against CIN2+ of 100%.
- Efficacy of 100% against HPV 16/18-associated CIN2+ in the per-protocol population of phase II trials who were naive to HPV 16 and 18, and to 12 other oncogenic types at baseline, and were followed for up to 6.4 years.
- Efficacy of 68% against cervical disease due to any HPV type, including non-vaccine-related types, in the per-protocol population of the phase II trials who were naive to HPV 16 and 18, and to 12 other oncogenic types at baseline.
- Efficacy data for VIN and VaIN are not yet available.

**Vaccine efficacy against persistent infection and cervical disease associated with HPV types that are genetically related to vaccine-related HPV types (potential for cross-protection) (Section 3)**
- HPV 16 and 18 are genetically related to other oncogenic types; trials of both vaccines have made preliminary assessments of efficacy against infection and disease due to these types (i.e. potential for cross-protection) but the analytic methods used were not identical.
- The quadrivalent vaccine induced neutralizing antibodies against HPV 31 and 45 in vitro. After an average of 3.7 years of follow-up, vaccine efficacy against the composite endpoint of HPV 31/45-related CIN2/3 and AIS was 59% (95% CI 14% to 82%) among females naive to all 14 HPV types at baseline and 43% (95% CI 12% to 64%) among females naive only to the relevant type at baseline. Efficacy was statistically significant for lesions specifically related to type 31, but not for lesions specifically related to HPV 45. Efficacy was 33% (95% CI 6% to 52%) against CIN2/3 related to any of ten non-vaccine-related oncogenic types.
- The bivalent vaccine induced antibodies against HPV 31 and 45 in more than 80% of vaccine recipients within 50 months after the first dose. Interim results for the total vaccinated cohort in the phase III trial found significant efficacy against 6-month persistent infection with HPV 45 (60%, 97.9% CI 3% to 85%), HPV 52 (32%, 97.9% CI 4% to 52%), and HPV 31 (36%, 97.9% CI 2% to 58%).
CI 0.5% to 60%). Among females seronegative to relevant types at baseline (i.e. no past infection), efficacy against the combined endpoint of 6-month persistent infection with HPV 31/45 was 60% (97.9% CI 21% to 81%) and 41% (97.9% CI 16% to 58%) against the combined endpoint of 6-month persistent infection with any of 5 common oncogenic types (31,33, 45, 52, 58).

**Vaccine efficacy against persistent infection and cervical disease caused by vaccine-related types in females with evidence of current or past infection with the same type before vaccination (Section 3)**

- Although both HPV vaccines are designed to be prophylactic, trials assessed vaccine efficacy among women who were seropositive, HPV DNA positive, or cytologically abnormal at baseline, because some target groups may include such females and vaccination programmes are not expected to screen before vaccination.
- In females, neither vaccine has shown a therapeutic effect against disease due to HPV types with which subjects were infected at baseline (i.e. HPV DNA positive). This illustrates that vaccinating females before first HPV exposure would be most efficacious.
- In one analysis of phase III quadrivalent vaccine trials, efficacy was 100% (95% CI –64% to 100%) against CIN2/3 or AIS among females who were seropositive, but DNA negative to a given vaccine-related type at baseline (so-called “cleared infection”). Investigators concluded that wide confidence bounds precluded conclusive evidence for efficacy on the course of infections present before vaccination. However, later analyses of this group found efficacy against CIN (any grade) of 100% (95% CI 29% to 100%), and against external genital lesions of 100% (40% to 100%).
- Bivalent vaccine trials found that efficacy against HPV 16/18-related CIN2+ lesions was similarly high in the subgroup of females who were seronegative for these types at baseline (90%, 97.9% CI 53% to 99%) and in all females regardless of baseline serostatus (of whom all receiving HPV vaccine were seronegative) (92%, 97.9% CI 60% to 99%).
- Both vaccines appear to boost naturally acquired antibody. Females who were seropositive for vaccine-related HPV types before vaccination had higher type-specific antibody titres than females who were seronegative for vaccine-related HPV types before vaccination.
- In phase III quadrivalent vaccine trials, 27% of females had past or current infection with vaccine-related types at baseline, and these were included in intent-to-treat populations. As expected, efficacy in this population was lower than in per-protocol or unrestricted susceptible populations:
  - 39%-54% for preventing HPV 16/18-related CIN2, CIN3 or AIS (in combined analysis of phase II and phase III trials), and 18% for preventing HPV 16/18-related CIN2/3 or AIS due to HPV of any type, including non-vaccine related types in analyses of phase III trials
  - 71% for preventing VIN2/3 and VaIN2/3-associated with HPV 16/18 (in combined analysis of phase II and phase III trials) and 49% for preventing the combined outcomes of VIN2/3 or VaIN2/3 associated with any HPV type, including non-vaccine related types in phase III trials.
- Results of the intent-to-treat analyses of phase III trials of the bivalent vaccine are pending.

**Efficacy of quadrivalent vaccine in preventing external anogenital warts in females (Section 3)**

- Data on efficacy in preventing external anogenital warts in females are available only for the quadrivalent vaccine because the bivalent vaccine does not contain VLPs for HPV 6 or 11.
- Phase III trials have shown efficacy against warts of 99% or more in the per-protocol population; 96% in the unrestricted susceptible population; and 76% in the intent-to-treat population.

**General vaccine safety in females (Section 3)**

- Neither vaccine contains live biological products or viral DNA, so neither is infectious.
• In June 2007, the WHO Global Advisory Committee on Vaccine Safety concluded that both HPV vaccines are generally safe and well-tolerated, based on 4 or more years of trial data and 1 year of passive, post-marketing surveillance data on the quadrivalent vaccine in the United States.
• In trials of both vaccines (up to 5 years for the quadrivalent vaccine and up to 6.4 years for the bivalent vaccine), serious and systemic adverse events were rare among all ages. Incidence of serious adverse events, medically significant conditions and new-onset chronic conditions or autoimmune disorders was not significantly higher in vaccinated females than in controls.
• None of the rare cases of death among vaccinees was judged to be vaccine related.
• The most commonly reported systemic adverse events were fever, nausea and dizziness (for the quadrivalent vaccine) and fatigue, headache and myalgia (for the bivalent vaccine).
• In trials of both vaccines, vaccinated individuals were more likely to have mild, transient soreness, redness, or swelling at the injection site than recipients of placebo (in trials of both vaccines) or control hepatitis A vaccine (in bivalent vaccine trials only).
• In trials of both vaccines, local and systemic safety profiles of females naive to vaccine-related HPV types before vaccination were similar to those of females who were not naive to these types before vaccination.
• Co-administration of both HPV vaccines with other vaccines was well tolerated: the quadrivalent given with a recombinant hepatitis B vaccine or with a diphtheria/tetanus/pertussis/poliomyelitis vaccine, and the bivalent vaccine given with a diphtheria/tetanus/pertussis/poliomyelitis vaccine.
• Syncope has been reported after receipt of the quadrivalent vaccine through passive, post-marketing surveillance in the United States. However, syncope was not seen in demonstration projects in Peru and Uganda, and was not more common in vaccinees than in placebo recipients in quadrivalent vaccine trials. Syncope is not uncommon among United States adolescents after vaccination, phlebotomy or other invasive procedures.
• In Australia, seven confirmed cases of anaphylactic reactions and instances of mass psychogenic illness were reported during passive post-marketing surveillance after mass school-based quadrivalent HPV vaccination. Reported anaphylaxis rates were low (2.6 per 100 000 doses) but significantly higher than reported anaphylaxis rates for other vaccines delivered in schools. No cases involved shock or serious sequelae. In trials, anaphylactic reactions were not more common in vaccinees than in placebo recipients, and no psychogenic illness was observed.
• Long-term safety is being evaluated in clinical trial extensions, studies in United States health plans, and post-marketing surveillance in Europe (EudraVigilance) (both vaccines), the United States (Vaccine Adverse Event Reporting System) (quadrivalent vaccine), and other countries.

Vaccine safety in pregnant and lactating females (Section 3)
• For both vaccines, studies in rats have shown no evidence of impaired fertility or harm to the fetus.
• Manufacturers of HPV vaccines do not recommend vaccine use in pregnant females.
• Trials of both vaccines excluded pregnant women and actively tried to limit accidental inclusion; nevertheless, several hundred participants inadvertently received vaccines while pregnant. For both vaccines, pregnancy outcomes of vaccinees and control subjects did not differ significantly.
• Neither vaccine has been shown to be causally associated with adverse pregnancy outcomes or adverse fetal or infant outcomes. Rates and types of congenital anomalies among infants of vaccinated females were typical for this maternal age and were judged not to be vaccine related.
• Safety in pregnancy is being monitored in clinical trials of both vaccines in several countries, special studies in some Nordic countries (both vaccines), and pregnancy registries in Europe (both vaccines) and North America (quadrivalent vaccine).
• Among women who received the quadrivalent vaccine while lactating, the few adverse events among infants were judged not to be vaccine related by investigators and safety monitoring boards.
• Data on the safety of the bivalent vaccine in lactating women are not available.

**Vaccine safety in HIV-infected individuals (Section 3)**

• In an unpublished study of HIV-infected children aged 7–11 (most using antiretroviral therapy) in the United States, plasma HIV ribonucleic acid (RNA) and CD4 cell percentage fluctuations were similar in quadrivalent vaccine recipients and placebo recipients.
• Trials of both vaccines are assessing safety in HIV-infected youth and adults in several continents.

**Female sexual and cancer screening behaviour after HPV vaccination (Section 4)**

• There is no evidence that HPV vaccines, or other vaccines, including hepatitis B, influence partner selection, partner number, sexual practices or condom use, but the number of studies is limited.
• Data from other sexual health interventions suggest that sexual disinhibition after HPV vaccination is unlikely. Fear of STI and HIV is not a major motivator of abstinence among virgins in most countries, and it is unlikely that a single vaccine would undermine safe sexual behaviours.
• Quadrivalent vaccine trials have found no evidence of riskier sexual behaviour after vaccination.
• Educational messages that stress that HPV vaccines do not prevent STI other than HPV or do not prevent pregnancy may encourage safe sexual activity.
• Data on the influence of HPV vaccination on future screening behaviour is not currently available, but is being monitored in some high-income countries.
• Educating vaccinees about the importance of future screening, if available, may increase adherence with national screening guidelines.

**HPV vaccine safety, efficacy and immunogenicity in males (Section 3)**

• The safety and immunogenicity of both vaccines in males have been evaluated. Results of a quadrivalent vaccine efficacy trial against anogenital precancers, cancers and anogenital warts are forthcoming.
• In phase III trials, virtually 100% of males aged 9–15 years given the quadrivalent vaccine and 100% of males aged 10–18 given the bivalent vaccine who were naïve to vaccine-related HPV types before vaccination seroconverted to relevant vaccine-related HPV type by month 7.
• For both vaccines, seroconversion rates and antibody levels were non-inferior to females of similar age. The temporal pattern of antibody response up to 24 months after vaccination with the quadrivalent vaccine was similar in males and females.
• For both vaccines, the reactogenicity and safety profiles of males and females were similar.

**HPV vaccine administration (Section 3)**

**HPV vaccine dose and schedule**

• The two marketed HPV vaccines differ in their composition, schedules and indications.
• Data are not available on the safety, immunogenicity or efficacy of the two vaccines when used interchangeably.
• Both vaccines are administered in three doses over 6 months – specifically 0, 2 and 6 months for the quadrivalent vaccine and 0, 1 and 6 months for the bivalent vaccine.
• For both vaccines, minor variations in dosing intervals (< 2 months) do not show major changes in immune response.
• The need for a booster is not established, but will be evaluated as long-term follow-up data accrue.

• Studies are under way to evaluate alternative schedules of both vaccines that may simplify delivery. These include studies of the immunogenicity of alternative 3-dose schedules and the immunogenicity and efficacy of a 2-dose series of the quadrivalent vaccine.

Evaluation before vaccination
• Like all injectable vaccines, both HPV vaccines are contraindicated in individuals with known hypersensitivity to any vaccine components, or with serious bleeding disorders.

• Both manufacturers recommend delaying vaccination in individuals with severe febrile illness.

• HPV serologic or DNA testing or cervical cytology are not recommended before vaccination by manufacturers or countries that recommend HPV vaccines for immunization programmes. Very few girls in the primary target group would be currently infected with all vaccine-related types before vaccination, and thus would not benefit from vaccination. Both vaccines are safe in females with HPV infection before vaccination. Testing before vaccination would be costly and impractical.

• Routine HPV serologic testing after vaccination to assess immune response is not necessary, because the level of protective antibody that confers clinical protection remains unknown.

• Some high-income countries that recommend HPV vaccines for national immunization programmes and address evaluation before vaccination do not advise HIV testing before routine HPV vaccination, because they believe it lacks clear benefit and would be resource intensive.

Co-administration of HPV vaccines with other vaccines
• HPV vaccines are not live vaccines and this may reduce adverse interactions with other vaccines.

• Concurrent administration of the quadrivalent vaccine and a recombinant hepatitis B vaccine and a diphtheria/tetanus/pertussis/polio vaccine (Repevax™) resulted in robust antibody response to all vaccine-related HPV types, no appreciable interference in immune response for either vaccine, and a safety profile similar to that of individuals vaccinated with each vaccine separately. Some immunization experts advise that this HPV vaccine can be administered with the hepatitis B vaccine at the same visit, using separate syringes, or at different anatomic sites, but specific guidance on co-administration with the diphtheria/tetanus/pertussis/poliomyelitis vaccine that is informed by recent study results has not been issued.

• An evaluation of concurrent administration of the bivalent vaccine and a licensed diphtheria/tetanus/pertussis/inactivated poliomyelitis vaccine (Boostrix®-Polio) found that immune response to vaccine antigens was non-inferior to the immune response when each vaccine was administered alone; vaccines were well-tolerated, and no vaccine-related adverse events were reported.

• Studies are under way in the United States to evaluate safety and immunogenicity of the quadrivalent vaccine given with tetanus/diphtheria/pertussis (TdaP) or meningococcal conjugate vaccine and of the bivalent vaccine given with TdaP, meningococcal conjugate or hepatitis A and hepatitis B vaccines.

Possible HPV vaccination target groups and special populations
The primary target group of females (Sections 3-6)
• Because HPV vaccines are most efficacious in females who are naive to vaccine-related types, HPV vaccination is most effective before onset of sexual activity (i.e. before HPV exposure risk).

• The primary vaccine target group will depend on the country’s vaccine licensing indications, estimates of the age of initiation of sexual activity of females, and programmatic considerations.
• Countries that have licensed HPV vaccines have indicated use for females at ages that typically precede onset of sexual activity, as early as age 9 years.
• The primary target age group in most countries that have recommended vaccines for immunization programmes has been within the range of 10–13 years. Specific age ranges have been based on data on age of sexual initiation and feasibility of reaching a given age group through schools, health facilities or community outreach.
• All countries that have recommended HPV vaccination have proposed a routine immunization strategy rather than selective or risk-based strategies. Because risk of HPV infection is high within the first few years after onset of sexual activity, assessing risk factors for HPV acquisition (e.g. number of sexual partners, condom use and smoking) before vaccination accurately and confidentially would be challenging and labour intensive, and might substantially reduce coverage.

Secondary or “catch-up” populations of females (Sections 3–6)
• Models predict that the impact on cancer incidence and mortality and the cost-effectiveness of vaccinating the primary target group (e.g. aged 12 years or less) will be greater than the impact and cost-effectiveness of vaccinating a catch-up population (without vaccinating the primary target population), because older females are more likely to be infected with vaccine-related HPV types before vaccination and will experience lower vaccine efficacy.
• Vaccinating catch-up populations who have not previously been infected with all vaccine-related types might hasten the observable impact of vaccination on cervical cancer, because there is likely to be a shorter interval between vaccination and sexual exposure to vaccine-related HPV types.
• As of January 2008, 13 countries had recommended catch-up vaccination of older adolescent females or young women, to supplement immunization of the primary target group. These decisions were based on programmatic feasibility, affordability, acceptability and cost effectiveness, and assumptions that catch-up strategies would not undermine vaccination of the primary target population.

Males (Sections 3–6)
• If HPV vaccines are efficacious in males, vaccinating males could provide direct benefits against HPV-related penile, perineal, anal and head and neck cancers in males; they could also provide indirect benefits by reducing HPV-related disease in females.
• Some regulatory authorities have registered the quadrivalent vaccine for use in adolescents (gender not specified) or have specifically indicated use in males, on the basis of safety and immunogenicity data in males. However, as of January 2008, only Austria had formally recommended the quadrivalent vaccine for use in boys as part of its national immunization policy, because of anticipated warts prevention benefits. (Clinical efficacy data in males are pending.) The manufacturer of the bivalent vaccine has not sought registration for indications in males.
• The effect of vaccinating males on risk of HPV infection and HPV-related disease in females at a population level is unknown; some studies predict only small levels of this type of herd immunity.
• Some models suggest that, if high vaccination coverage of girls is achieved, vaccinating boys adds little to reducing cervical cancer incidence, even if vaccines are highly efficacious in boys.

Special populations
Pregnant and lactating females (Section 3 and 6)
• Neither HPV vaccine is recommended for use in pregnant females, although trials and passive, post-marketing surveillance have not shown that HPV vaccines cause adverse pregnancy, fetal or neonatal outcomes. Both manufacturers advise that, if pregnant women are inadvertently vaccinated, vaccination be discontinued until completion of the pregnancy.
• Selecting age-specific target populations of females before onset of sexual activity reduces the risk of inadvertently vaccinating pregnant or lactating females.
• Programmes that have offered HPV vaccines to females who may have started sexual activity have attempted to exclude pregnant females by notifying vaccination candidates that vaccines are not recommended in pregnancy or assessing pregnancy status before vaccination (using a verbal report or timing of last menstruation) and then deferring vaccination of pregnant females until pregnancies are completed.
• It is not known whether HPV vaccine antigens or antibodies are excreted in human milk.
• Quadrivalent vaccine trials have identified no causally related adverse events in lactating women or their infants. The manufacturer advises caution when this vaccine is used in lactating women. Some immunization experts advise that lactating women may receive this vaccine because it is non-infectious and no safety concerns have been identified.
• Safety data on the bivalent vaccine in lactating women or their infants are not available. The manufacturer advises use in during lactation only when possible advantages outweigh potential risks.

**Immunocompromised individuals (Sections 3 and 6)**

• Data on the safety, immunogenicity, and efficacy of HPV vaccines in individuals who are immunocompromised due to medications or diseases (e.g. HIV-infection) are limited (see above).
• Selecting target ages for HPV vaccination that precede the onset of sexual activity for most individuals greatly reduces the risk of administering HPV vaccines to HIV-infected individuals.
• Some countries that have recommended inclusion of HPV vaccines in national immunization programmes do not advise deferring the use of HPV vaccines in females whose HIV status is unknown because HPV vaccines are non-infectious; the primary target group for HPV vaccines is girls before onset of sexual activity (i.e. before risk of sexual HIV exposure); potential benefits for HIV-infected females at increased risk of HPV-related disease are great; the burden of HPV-related disease is high; and potential benefits of vaccination outweigh potential risks.
• As yet, there is no programmatic experience of delivering HPV vaccines to large populations who were perinatally or sexually infected with HIV. Results of ongoing studies of the safety and immunogenicity of both HPV vaccines in HIV-infected individuals may inform decisions about vaccine introduction in settings where many vaccination candidates may be HIV infected.
• The influence of later HIV infection on established HPV vaccine-induced immunity is unknown.

**Vaccine delivery issues (Section 5)**

• Unique features of HPV vaccines preclude simple addition to existing vaccine delivery platforms for infants and young children, including Expanded Program on Immunization (EPI) programmes.
• Most countries do not routinely deliver vaccines against any disease to older children and adolescents, especially vaccines with a multi-dose primary series. In many low, middle and high-income countries, only a minority of young people of this age seek preventive care in locations where HPV vaccines could be delivered.
• HPV vaccination programmes are likely to require new approaches to programme design and delivery. New programmes that do not undermine delivery of other vaccines may take time and new resources.
• HPV vaccine introduction may serve as a model for future HIV vaccines for young adolescents.
• Studies and early experience in low, middle and high-income countries indicate that HPV vaccines are highly acceptable to providers, parents and adolescents, especially if these groups
are first educated about safety and efficacy, and vaccines are supported by trusted health authorities.

- Absence of public sector funding or private insurance coverage of HPV vaccines may limit public acceptance and demand.

**HPV vaccination strategies and experience (Section 5)**

- Delivery strategies that prioritize females at highest risk of cervical cancer (e.g. those who later in life may have limited access to screening) will increase the impact of vaccination programmes.
- The impact of vaccination programmes will be maximized by high coverage. This will require delivery methods that are affordable, cost effective, sustainable, and compatible with delivery infrastructure and cold-chain capacity.
- Possible delivery strategies include school-based programmes, child health days, vaccination days or weeks, periodic campaigns for EPI or tetanus vaccines, adolescent health education or health-care providers, community-based sexual and reproductive health programmes (e.g. family planning), special referral and outreach mechanisms, or combinations of these strategies.
- Where a high percentage of the primary target age group attend school, or where the percentage is increasing, early experience indicates that school-based programmes are promising strategies to deliver these multi-dose HPV vaccines.
- School-based strategies have yielded uptake of more than 70% in Australia, Canada, Peru, Uganda and the United Kingdom. If school-based strategies are used, efforts to reach school non-attendees are needed to maximize coverage.
- Methods that streamline or simplify parental consent for vaccinating daughters in schools have increased uptake in Canada, Peru, Uganda and the United Kingdom.
- Pulsed delivery through schools or community campaigns can reduce vaccine wastage and cold-chain requirements at peripheral levels.
- Partnerships of immunization, education and child/adolescent programmes can coordinate vaccine delivery in schools and communities. EPI leadership has proved critical in Peru and Uganda.

**Integrating HPV vaccination with cervical cancer screening (Sections 2, 4 and 5)**

- Vaccination during young adolescence (a primary prevention tool) and screening in mid-life (a secondary prevention tool) can act synergistically to reduce cervical cancer incidence and mortality.
- Screening can detect precancerous lesions due to any oncogenic HPV type in non-vaccinated females, as well as precancerous lesions due to oncogenic types other than HPV 16 and 18 in vaccinated females.
- Because HPV vaccines do not protect against all HPV types that cause cervical cancer, vaccinated females should be encouraged to be screened according to national policies.
- If screening quality and participation are high, vaccination is expected to reduce the incidence and cost of HPV-related disease. However, the health benefits of adding a vaccination programme may be lower than in countries with lower screening coverage, long screening intervals, or suboptimal follow-up and treatment for abnormal screening results, because disease prevented by vaccination would otherwise have been detected by screening and treated.
- Decision making about HPV vaccines may provide an impetus to review the coverage and quality of current screening programmes, or to establish new screening and treatment programmes.
Integrating HPV vaccination with other health interventions (Section 5)

- Vaccine introduction creates opportunities to strengthen services and health systems that reach older children and young adolescents. It can foster new partnerships between programmes in immunization, cancer control, adolescent health, and sexual and reproductive health, to coordinate communication, delivery, financing and monitoring strategies.
- As with many EPI programmes that vaccinate young children, HPV vaccination programmes can be linked to other services, such as other vaccinations, medications (e.g. antihelminths), devices (e.g. bed nets) or education (e.g. life skills, tobacco minimization, nutrition, and sexual and reproductive health).
- When HPV vaccines are offered in the presence of mothers or female guardians, immunization providers can educate adult women about cancer screening if it is locally available.

Health communication and education (Section 5)

- Health communication programmes are essential to acceptance of HPV vaccines by vaccination candidates, parents, health-care providers, school staff, policy makers and the general public.
- Campaigns that have raised public awareness about cervical cancer and have sensitized communities about the benefits of HPV vaccines have increased vaccine uptake in some countries.
- For maximum efficiency and impact, partnerships across programmes of immunization, cancer control, adolescent health, and sexual and reproductive health can provide more comprehensive education about vaccine-preventable diseases, cancer, and sexual and reproductive health.
- HPV and cervical cancer pose complex, sensitive issues that can be challenging to communicate. Messages that are tailored to local communities, cultural norms and specific audience – especially if based on research – are likely to be most effective. Among the most important are the following:
  - HPV is one of the most common viruses infecting humans; it causes virtually all cervical cancers and many other cancers
  - for highest efficacy, both vaccines require three doses, unlike many other adolescent vaccines
  - HPV vaccines are most effective when given before onset of sexual activity
  - both vaccines are safe; mild, transient injection-site soreness and swelling are common
  - there is no evidence that HPV vaccines harm fertility, or cause adverse events in pregnant women or infants, or fetuses of vaccinated females
  - there is no evidence that vaccination increases risky sexual behaviour, HIV, STI or unintended pregnancy; HPV vaccines do not prevent HIV infection or pregnancy
  - vaccinated females should seek screening later in life (if it is available), to protect them from disease due to non-vaccine related HPV types
  - HPV vaccines prevent cancer by preventing a common sexually transmitted virus that causes cancer; whether and how this message is communicated will depend on the age and maturity of the vaccination candidate, family and health-care provider preferences, and cultural norms; stressing that HPV is very common in sexually active persons, even those with few partners, can reduce potential stigma.

Monitoring the impact of vaccination programmes (Section 5)

- During preparation for vaccine introduction, programmes should consider plans to monitor impact of vaccination programmes or to track the monitoring experience of other countries. WHO is developing recommendations for monitoring methods for low, middle and high-income countries.
• Monitoring the impact of HPV vaccination programmes may require new surveillance systems and tests currently available in only a few countries. Large, population-based monitoring may be possible in a few countries, whereas small, sentinel surveillance may be feasible in many countries. Existing systems could be adapted to monitor vaccine coverage and safety in many countries.

• Prevalence of vaccine-related HPV types, and incidence of moderate and high-grade CIN, AIS, invasive cervical cancer (for programmes using either vaccine) and genital warts (for programmes using the quadrivalent vaccine) are possible indicators of programme impact in population-based or sentinel studies. A few countries can evaluate type-specific incidence of cervical lesions and potential replacement of vaccine-related types by other oncogenic HPV types at a population level.

• The WHO HPV Laboratory Network is developing standards for HPV serology and nucleic acid testing, and is supporting laboratories in all regions to implement assays use for monitoring.

• Wide-scale vaccine introduction may influence the effectiveness of current screening programmes using cytology or HPV tests, and performance of screening tests in vaccinated populations should be monitored. As vaccination reduces HPV 16 and 18 prevalence over time in countries with high vaccine coverage, screening programmes for vaccinated women may be able to start later in life, or to screen less frequently than is currently recommended in many countries.

Projected health benefits of HPV vaccination programmes (Section 4)

• The most important benefits of HPV 16/18 vaccination programmes are reducing deaths due to cervical cancer and reducing the pain, suffering, disability and functional and productivity losses due to this cancer. The programmes would reduce the devastating personal, social and economic losses of mid-adult women who provide crucial support to families, communities and economies.

• Because of the strong association between HPV 16/18-related CIN2+ and invasive cancer, models for low, middle and high-income countries predict that vaccinating young adolescent girls will substantially reduce cervical cancer incidence and mortality. Absolute mortality reductions will be greatest in countries without large-scale screening programmes.

• Vaccination is also expected to reduce the incidence of other cancers due to HPV 16 and 18, the incidence of HPV 16/18-related cervical abnormalities detected through screening, and the number of costly diagnostic, follow-up and treatment procedures used to manage these abnormalities.

• Vaccination with the quadrivalent vaccine is expected to reduce the incidence of anogenital warts, low-grade cervical abnormalities due to HPV 6 and 11, and possibly RRP; the number of costly diagnostic and treatment procedures for these conditions; and the associated psychosocial burden.

• Incidence of precancerous lesions and warts are expected to decline much sooner than cancer incidence.

• The benefits of vaccination in a given population depend on vaccine efficacy, achievable coverage, duration of protection, the proportion of disease attributable to vaccine-related HPV types, age-specific rates of infection, the proportion of the target population naive to vaccine-related types before vaccination, degree of cross-protection, potential for herd immunity and type replacement.

• Models project that most cervical cancer deaths prevented by HPV vaccines will be in countries with moderate cervical cancer incidence and large populations.

3 The phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either the bivalent vaccine or the quadrivalent vaccine, because both contain antigens for HPV 16 and HPV 18.
• Models for the Caribbean and Latin American countries have projected that HPV vaccination would avert 27 cervical cancer cases per 1000 girls vaccinated (of which most cases would die). This figure compares to 3 deaths per 1000 children vaccinated against rotavirus and 6.8 deaths per 1000 children vaccinated with the pneumococcal conjugate vaccine.

• The impact of vaccination will be greatest if vaccines are given before sexual activity starts, high vaccine coverage is achieved, and duration of protection lasts at least 10 years. As the age at which females are vaccinated increases, the marginal population benefits of vaccination will decrease.

• In settings where screening is absent or limited, HPV 16/18 vaccination of young adolescent females is expected to reduce cervical cancer incidence and mortality by 35–80%, depending on model assumptions. HPV 16/18 vaccination in all GAVI-eligible countries that scaled up coverage to 70% over 10 years would avert about 2.5 million cancer cases, 1.9 million deaths, the loss of the mother to more than 1.5 million children under 18, and billions of dollars of lost productivity.

• In settings with established screening, the magnitude of cervical cancer reduction will depend on the underlying success of screening programmes. If screening quality and participation are high, the incremental benefits of adding a vaccination programme may be lower than those in countries with lower screening coverage, very long screening intervals, or suboptimal follow-up and treatment of females with abnormal results.

• If vaccine uptake is highest in those who are most likely to be screened later in life, the additional benefits of vaccination will be attenuated; in contrast, high vaccine uptake in young adolescents could reduce the disparities in cancer mortality related to differential screening and treatment.

• The benefits of vaccinating males depend on vaccine efficacy (results of ongoing studies are pending) for HPV-related precancers and cancers (and warts in the case of the quadrivalent vaccine), and other factors. Some models indicate that more benefit is derived per vaccinated female than per vaccinated male, because HPV-related cancers in females, notably cervical cancer, are far more common than HPV-related cancers in males. Models suggest that it is less beneficial (in terms of cervical cancer prevention) to vaccinate boys when female coverage is high than when female coverage is low, but male vaccination can be beneficial when coverage in females is low.

• Ongoing studies in Australia, North America and some European countries will use various outcome indicators to examine the population impact of HPV vaccination in females and males.

Cost-effectiveness of HPV vaccination programmes (Section 4)

• Decisions about vaccine introduction should consider cost effectiveness, cost, affordability and financing. These depend on vaccine price, target populations, cost of new or modified systems to deliver 3-dose adolescent vaccine, availability of external funding, and other factors.

• Several models that estimated the cost effectiveness of different vaccination strategies when used alone or in combination with screening have yielded fairly consistent results. However, some model parameters are uncertain, and there are no standardized methods to express cost-effectiveness ratios or thresholds for cost effectiveness. Cost effectiveness is strongly influenced by assumptions about vaccination costs (including vaccines and delivery systems), the age and size of target populations, vaccine efficacy and duration of protection, achievable coverage, assumptions about herd immunity, and the costs and effectiveness of screening and treatment.

• Models predict that HPV 16/18 vaccination can be cost effective in reducing cervical precancers and cancers in low, middle and high-income countries under certain assumptions. Vaccination cost is a key determinant of cost effectiveness.
• In low and middle-income countries with no or limited screening, models predict that vaccination could be cost effective or cost saving if vaccination costs were substantially lower than current prices in high-income countries. For example, vaccination at a cost per vaccinated girl of IS 10 for three doses, wastage and programmatic costs would cost less than International (I)$ 250 per disability-adjusted life year (DALY) averted in most GAVI-eligible countries; this would be considered very cost effective. At lower prices, vaccination would be cost saving in many GAVI-eligible countries. Vaccination would be cost saving in most Caribbean and Latin American countries at a cost per vaccinated girl of IS 10. For many countries, vaccination would be very cost-effective (as defined by a cost per DALY averted less than per capita GDP) at higher costs. However, the current cost of three doses of HPV vaccine exceeds US$ 300 in high-income countries.

• In low and middle-income countries with no or limited screening, several models predict that vaccination alone will be more effective and cost effective than screening 2–3 times per lifetime. Combining vaccination with screening 2–3 times per lifetime is more effective than vaccination alone, but more costly.

• In high-income countries with established screening programmes, several models predict that HPV 16/18 vaccination at current vaccine costs can be cost effective, especially if screening costs are reduced in the future, either by starting screening of vaccinees later in life or by screening less frequently than is now recommended in many countries. However, if vaccinated females are not screened later in life, cancer incidence and mortality may be greater than if screening continued at current levels, especially if vaccine protection wanes over time.

• Potential benefits of HPV vaccines in preventing vaginal, vulvar, anal, and head and neck cancers (and warts, RRP or cervical abnormalities due to HPV 6 and 11) would increase cost effectiveness, especially where diagnosis, follow-up and treatment of these conditions is costly.

• Savings from averting diagnosis and treatment of warts and precancerous cervical lesions detected through screening would be observed long before savings from averting invasive cancer.

• Most models have found that a strategy of vaccinating females has lower cost-effectiveness ratios than a strategy of vaccinating females and males, especially when female coverage is high. Cost effectiveness ratios improve when wart prevention due to the quadrivalent vaccine is considered.

Cost, affordability, and financing of HPV vaccination (Sections 4 and 5)

• Even strategies that are cost-effective may not be affordable without financial assistance, especially in low- and middle-income countries. For example, at $5 per dose, vaccinating young adolescent females is cost-effective in nearly all Caribbean and Latin American countries (less than $400 per DALY averted), but would require US$ 360 million to vaccinate 70% of just five birth cohorts. Similarly, at $2 per dose, vaccinating young adolescent females is cost-effective in nearly all GAVI-eligible countries (less than $ 200 per DALY averted), but would require $ 1.5 billion to vaccinate 70% of just ten birth cohorts.

• Vaccination programme costs include vaccines, supplies, wastage, cold-chain storage, transport, delivery costs, personnel and training, and monitoring. Delivery of HPV vaccines is likely to be more costly than that for infant vaccines because new or modified systems may be needed. Demonstration projects are estimating delivery costs in some low and middle-income countries.

• HPV vaccines are currently among the most costly vaccines being marketed in private and public sectors in industrialized countries. Current prices (>US$ 300 per series) are far greater than mature prices of other common infant or childhood vaccines that have been marketed for many years.

• HPV vaccination introduction raises critical issues of access and equity. The current high cost of vaccination, especially vaccine price, is a major obstacle to large-scale use in low and middle-income countries, and in some low-income, underserved populations in high-income countries.
without universal health care. If females who are at high risk of cervical cancer due to limited screening later in life are not vaccinated, current inequalities in cancer burden may worsen.

- Most cervical cancer cases occur in low and middle-income countries, especially in GAVI-eligible countries, where about half of cervical cancer cases occur and potential target populations are large. In such countries, vaccine introduction will require major donor funding until mature, affordable prices are achieved.
- Innovative methods are needed to finance HPV vaccination. Efforts are under way to make vaccines more affordable through partnerships between industry and agencies dealing with financing and procurement.
- Global supply and demand in low and middle-income countries are now being forecasted. Marketing and direct-to-consumer advertising of HPV vaccines is widespread in many middle and high-income countries, and may influence private and public sector demand.
- HPV vaccine manufacturers have pledged to offer preferential pricing for the public sectors of low and middle-income countries or for organizations that purchase vaccines for such countries. Middle-income countries that are not GAVI-eligible may be among the first to consider purchase.
- Given industry’s commitment to preferential pricing, vaccine purchasers – for example, the United Nations Children’s Fund (UNICEF) and the Revolving Fund of the WHO Regional Office for the Americas (PAHO) – could purchase HPV vaccine prices at lower prices through large-scale pooled procurement if WHO recommends HPV vaccines for national immunization programmes and prequalifies them for United Nations (UN) procurement.
- GAVI included HPV vaccines in a new investment strategy announced in June 2008 that provides an opportunity to subsidize HPV vaccines in GAVI-eligible countries if WHO recommends them for national immunization programmes and funds are secured.
- As with other vaccines, HPV vaccine prices are expected to decline over time due to product competition, new manufacturers, second generation vaccines and other factors.
- Marketing of second generation vaccines will require at least 10 years, because development timelines are influenced by complex manufacturing processes, patent issues and other factors.

**Decision-making about vaccine introduction (Sections 4, 5 and 6)**

- Governments will need to make careful decisions about the importance of HPV vaccination programmes in the context of competing health priorities, including other new vaccines, other interventions to prevent and control HPV-related disease, the programmatic feasibility of vaccine introduction, vaccine financing and affordability, and other factors.
- Decisions to introduce HPV vaccines should ideally be based on country or region-specific data on the incidence of HPV-related cancers and precancers, mortality from these cancers, and the prevalence of vaccine-related HPV types associated with these conditions. Countries considering the quadrivalent vaccine may also consider data on burden of cervical abnormalities, anogenital warts and RRP due to HPV 6 and 11.
- Many country-specific data are available from WHO. Countries that lack data may estimate burden from other countries with similar demographics, health infrastructure and screening capacity.
- HPV 16 is the most common cause of cervical cancer in all countries in all regions studied, so experts recommend that vaccine introduction decisions should not be delayed while waiting for results of country-specific studies about the association between HPV 16 and cervical cancer.
- Many experts advise that countries should consider licensed HPV vaccines as a prevention option, even if country residents did not participate in trials (i.e. as is the case in African countries), because no appreciable variations in safety, immunogenicity or efficacy have been reported across the regions studied so far, and mechanisms of protection are not expected to vary appreciably by region.
• Models for low, middle and high-income countries have identified vaccination strategies that would substantially reduce HPV-related disease burden and would be cost effective when used alone or in combination with screening later in life. Ideally, country or region-specific analyses of projected impact and cost effectiveness should inform vaccine introduction decisions. Model-based spreadsheet tools that are less complex and data intensive than many published models are being developed to help countries estimate cost effectiveness of possible vaccination strategies.

• Decision making must also consider vaccine affordability and financing sources, the financial and operational impact on immunization delivery systems, current child and adolescent immunization services, and requirements to develop new delivery systems for the primary target population.

• Decisions on vaccine introduction should be made as part of a coordinated strategy to prevent HPV-related disease; the strategy should consider a range of interventions: education and counselling about how to reduce behaviours that increase risk of cervical cancer, screening, and diagnosis and treatment of precancerous lesions and cancer. Vaccine introduction should not undermine or divert funding from other interventions in the country that are proven to reduce HPV-related disease at a population level.

• In settings where both vaccines are licensed and marketed, decisions about specific products should consider unique characteristics. These include different antigens, adjuvants, indications and schedules. Decisions should also consider the extent of publicly available data about vaccine safety, efficacy and immunogenicity, as well as vaccine presentation, price and supply.

• WHO prequalifies vaccines to ensure the quality of vaccines procured by UN agencies for low and middle-income countries. WHO expects to complete dossier review for both vaccines during 2009.

International opinion and policy about HPV vaccines (Section 6)

• Introduction of HPV vaccination is consistent with:
  – the WHO/UNICEF Global Immunization Vision and Strategy (GIVS) to expand immunization programmes beyond infancy and early childhood
  – WHO’s Vaccine-Preventable Disease Categorization Project, which ranked cervical cancer as 1 of 10 “high-priority” diseases, and guided GAVI’s new investment strategy
  – WHO’s Global Reproductive Health Strategy and Global Strategy for the Prevention and Control of Sexually Transmitted Infections
  – Millenium Development Goals to combat disease characterized by socioeconomic inequity, promote gender quality, empower women, and improve maternal health.

• HPV vaccination is endorsed as an important cancer prevention option by:
  – consultations of all six WHO regions during 2007–2008
  – WHO’s Global Cancer Action Plan
  – the International Union Against Cancer
  – more than 1200 organizations, high ranking officials, and health advocates worldwide.

• At WHO regional consultations, strong interest in HPV vaccines was tempered by concerns that vaccines are currently unaffordable for most national immunization programmes, and vaccine introduction must be justified in the face of other important vaccination and health priorities.

• Several Caribbean and Latin American countries have shown interest in HPV vaccines if prices are affordable. PAHO is supporting development of evidence-based decision-making tools and possible Revolving Fund purchase.

• As of September 2008, both vaccines were licensed by more than 76 countries in all regions, and were recommended for use in national immunization programmes in more than 15 industrialized and at least one middle-income country (Mexico).
• All recommendations for vaccine use in national immunization programmes advise vaccination in young adolescent girls of various ages; some also advise catch-up vaccination of older females.
• Only one country (Austria) has recommended use of the quadrivalent vaccine for use in boys (for prevention of warts) but it has not allocated public sector funding for vaccinating males.
• All country recommendations stress continued screening for vaccinated females and non-vaccinated females.

High-priority research that will inform vaccination programmes (Section 5)

• HVAC and other experts have identified several high-priority research topics, most of which are being addressed by ongoing studies. The most important topics include:
  – long-term efficacy and immunogenicity to inform the need for booster dose
  – immunogenicity and efficacy of vaccines delivered using simpler schedules (e.g. 2-doses, alternate 3-dose schedules) or when vaccinees do not adhere to the recommended schedule
  – the minimum protective antibody level (to inform the need for boosters and alternate schedules)
  – safety, immunogenicity and efficacy studies in populations from Africa
  – safety, immunogenicity and efficacy studies in populations with HIV infection or other chronic or recurrent conditions that might influence vaccine immune response
  – safety and immunogenicity of vaccines when given with other vaccines or medicines
  – long-term safety, including rare adverse events and safety in pregnant females
  – safety, immunogenicity and efficacy in males
  – acceptability, effectiveness and cost of delivery strategies in low and middle-income countries
  – impact, cost and cost-effectiveness of vaccination in low and middle-income countries
  – strategies to monitor impact of vaccination programmes (HPV prevalence and related diseases)
  – the impact of vaccination on HPV type replacement and herd immunity
  – influence of vaccination on cervical cancer screening programmes and sexual behaviours
  – operations research on alternative vaccine presentation and storage
  – development of second generation vaccines that offer simpler schedules, fewer doses or alternative routes of administration; broader valency; therapeutic efficacy; manufacturing improvements; less complex storage requirements or cold-chain volume; and lower cost.
Introduction

The Immunization Strategic Advisory Group of Experts (SAGE) is the leading advisory body on immunization matters for the World Health Organization (WHO). Groups of experts in specific diseases provide advice to SAGE. In the case of human papillomavirus (HPV), the relevant group is the HPV Expert Advisory Group (HEAG), which in 2008 was renamed the HPV Vaccine Advisory Committee (HVAC).

In April and November 2007, SAGE asked HEAG to collate and review evidence to inform SAGE’s discussions about recommendations for immunization against disease caused by HPV (1). (See Annex 1). This request is consistent with HEAG/HVAC’s mandate to provide advice that will help WHO and its Member States to:

- reduce the incidence of cervical cancer and related diseases that are caused by HPV but that are preventable by vaccine
- increase safe use of HPV vaccines
- report directly to SAGE about issues to consider when making recommendations about use of HPV vaccines for national immunization programmes.

This background paper summarizes the available evidence (to end of September 2008) about HPV, HPV-related disease and HPV vaccines. Data were collated by staff and consultants to WHO’s Initiative for Vaccine Research (IVR), drawing heavily on a HEAG summary of data available to August 2006 (2). Data were drawn from information in the public domain, including:

- reports of WHO vaccine advisory bodies
- technical or position papers on cervical cancer and HPV vaccines from WHO Regions and Member States
- reports of WHO regional meetings about HPV vaccines
- peer-reviewed publications (including 2007 ePublications)
- abstracts and presentations from scientific meetings
- online reports.

The paper does not include confidential data from national regulatory authorities. For most sections, data to the end of 2007 are given in the main body of the background paper, whereas data from January to end of September 2008 are given in Annex 2.

Several drafts of this paper were reviewed by members of HEAG/HVAC, content experts, and participants of the 2007 HEAG meeting and the 2008 HVAC meeting; the final version was approved by HVAC in September 2008. The paper addresses the two HPV vaccines that have been licensed for use in one or more WHO Member States since 2006. It will be submitted to SAGE before their discussions about HPV vaccine use in national immunization programmes, and its content and organization are designed to expedite drafting of a WHO Position Paper on HPV vaccines, if such a paper were to be requested. The WHO Position Paper would contain essential background information on HPV-related disease and HPV vaccines for Member States. It would emphasize use of vaccines in large-scale public sector immunization programmes and conclude with the current WHO position concerning HPV vaccine use in the global context.
Reference


The pathogens and associated diseases

This section provides some background on human papillomaviruses (HPV) and the diseases associated with these viruses. It describes the structure and mode of infection of HPV, the immune response to genital HPV infection and the natural history of such infection. The section looks at genital infections in terms of mode of transmission, incidence and prevalence by age, and risk factors for acquisition. Finally, it discusses the burden of HPV-related disease and the role of HPV in pre-malignant, malignant and non-malignant disease.

1.1 The viruses

Key points

- HPV are deoxyribonucleic acid (DNA) viruses that are enclosed in a capsid shell comprising major (L1) and minor (L2) structural proteins.
- More than 100 known HPV genotypes infect genital mucosa; of these, at least 13 are classified as “high-risk” because of their oncogenic potential.
- The HPV genes E6 and E7 (where “E” stands for “early”) are associated with cell immortalization and transformation related to carcinogenesis.
- High-risk HPV 16 and 18 are the types most commonly associated with cervical cancer.

HPVs are non-enveloped, double-stranded deoxyribonucleic acid (DNA) viruses in the family Papillomaviridae. They infect epithelial cells of the skin or mucosa. Isolates of HPV are classified as genotypes (i.e. types that are based on the nucleotide sequence of specific regions of the genome) (1,2).

All HPVs have a circular genome enclosed in a capsid shell comprising major (L1) and minor (L2) structural proteins. Purified L1 protein will self-assemble to form empty shells or virus-like particles (VLPs). In addition to coding for the L1 and L2 proteins, the HPV genome encodes several “early” genes (E1–E7) that direct viral transcription and replication, and interact with the human genome. High-risk HPV types have the genes E6 and E7, which are associated with cell immortalization and transformation related to carcinogenesis. Specifically, the E6 and E7 genes code for oncoproteins E6 and E7, which manipulate cell-cycle regulators, induce chromosomal abnormalities and block apoptosis (cell death) (2,3). HPV initially infects the basal layer of human epithelium, causing differentiating epithelial cells – which normally do not divide – to remain in an active cell cycle. The virus then uses the replication machinery of the differentiating cells to amplify the viral genome; this situation can result in thickened or exophytic epithelial lesions. As cells exfoliate from the epithelium, virions are released. When cells become neoplastic (i.e. exhibit abnormal and uncontrolled growth), high-risk viruses may integrate into chromosomes, resulting in cellular immortalization and deregulated proliferation. At this stage, virion production is limited (2,4).

More than 100 HPV genotypes (hereafter referred to as “types”) are known, and they are numbered in order of their discovery. The types that infect the genital mucosa are classified as low or high risk, according to their oncogenic potential. At least 13 high-risk HPV types can cause cervical cancer or are associated with other anogenital and
oropharyngeal cancers – 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66. The HPV types most strongly associated with invasive cervical cancer and other HPV-related cancers are 16 and 18. For invasive cervical cancer, the next most common types include 31, 33 and 45 (Table 1.1). The distribution of HPV types varies between regions, but the dominant oncogenic type in all regions is HPV 16 (5). Infection with low-risk genotypes rarely causes cancer, but it can cause benign or low-grade changes in cervical cells that may be indistinguishable (using cytology or histology examination) from those caused by high-risk HPV genotypes (1,2,5,6).

Table 1.1 Eight most common HPV types associated with invasive cervical cancer in three international studies

<table>
<thead>
<tr>
<th>Order of rank</th>
<th>Study 1a</th>
<th>Study 2b</th>
<th>Study 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>3</td>
<td>45</td>
<td>33</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>31</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>33</td>
<td>31</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>52</td>
<td>58</td>
<td>52</td>
</tr>
<tr>
<td>7</td>
<td>58</td>
<td>52</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>35</td>
<td>58</td>
</tr>
</tbody>
</table>

a 3085 subjects, case–control study, Castle et al. (2005)(7)

b 14 500 subjects, meta-analysis, S de Sanjose, pers. comm., October 2007
c 8785 subjects, meta-analysis, de Sanjose et al. (2007) (8)

1.2 Immunology and natural history of genital HPV infection

Key points

- HPV is a purely mucosal infection; it does not have a bloodstream phase.
- Approximately half of women infected with HPV develop detectable serum antibodies, but these antibodies do not necessarily protect against subsequent infection.
- Innate, adaptive cellular and humoral immune responses help to control HPV infections.
- Median time to seroconversion is approximately 8–12 months after new infection.
- Most infections clear within 1–2 years.
- HPV infections not cleared by the immune system become persistent and can lead to neoplastic changes.

The immediate response to HPV infection is not well understood, for a number of reasons (9):

- HPV infections are restricted to the intra-epithelium layer (although a systemic antibody response to natural infection is seen in many subjects)
- antibody levels are generally low
- genital HPV infections do not promote a vigorous immune response because they are not cytolytic and do not induce local inflammation.

Anogenital and cervical HPV infections are local events in the lower genital tract; thus, site-specific immune responses are believed to help prevent HPV infection and HPV-related disease, particularly for HPV 16 and 18. In particular, the innate immune
response, mediated through specific receptors on dendritic cells and macrophages, may be important in the initial recognition of HPV (10).

Humoral and cellular immune responses against many different products of HPV have been demonstrated, but it is not clear whether these lead to immunity. The best characterized and most type-specific antibodies are those directed against conformational epitopes of the L1 capsid protein assembled as VLPs. However, not all women mount an antibody response to capsid proteins following infection, and only 50–60% of women develop serum antibodies to HPV after natural infection (11). In one study, approximately 55–70% of women with incident infection with HPV 6, 16 or 18 developed antibodies after 18 months (11). Among most newly infected women, the median time to seroconversion is approximately 8–12 months (11-13). The immunologic response to a single HPV type varies between individuals; similarly, the response to different HPV genotypes may be quite heterogeneous (11).

An innate immune response and adaptive cellular and humoral responses appear to control HPV infections and to clear free virus (2,10,14,15). Consequently, most infections in females and males either clear or become undetectable within 1–2 years (16,17). There is little evidence that papillomavirus antibodies provide cross-protection. Antibodies induced by natural infection are believed to be type specific. Papillomavirus antibodies do not appear to provide cross-protection, and those induced by natural infection are believed to be type specific (2). Seroconversion occurs more frequently among women in whom HPV is detected at more than one time point. Antibody titres peak, then decline even when HPV DNA is detected (11). In addition, type-specific antibody usually declines within the first year after infection (11).

The degree of protection and the duration of immunity after natural infection are not well understood. Naturally-acquired infections can evade recognition by the innate immune system and delay activation of the adaptive response, thereby leading to long-term infections. HPV may use several mechanisms to avoid stimulating an immune response:

- HPV E6 and E7 may inhibit signalling by type I interferons, and thus decrease expression of multiple genes that are induced by interferon
- release of HPV occurs in superficial squamous cells; in this location, viral antigens are not readily detected and keratinocytes are not lysed
- HPV may not stimulate dendritic cell activation, migration, antigen processing and presentation, because it does not induce cell death.

Persistent infection with oncogenic HPV genotypes can lead to neoplastic changes that result in low-grade intraepithelial lesions, high-grade cervical intraepithelial neoplasia and, later on, invasive cancer (17-21). Risk of persistence and dysplastic progression is related to type of HPV (and is particularly strong for types 16 and 18), infection with multiple HPV types and high viral load (17,22-27). Changes in the cervical epithelium can be detected by microscopic examination of collected cells using conventional or liquid-based cytology (Papanicolaou (Pap) test). Consequently, women can be screened for cervical cancer using cytology or repeated HPV DNA tests that evaluate persistent infection (see Section 2). Once persistent infection results in precancerous intraepithelial lesions or invasive cancer, these changes can be seen by the naked eye.

An abnormal growth of squamous cells of the cervix, detected by cervical cytology, is classified as either a low-grade squamous intraepithelial lesion (LSIL) or a high-grade squamous intraepithelial lesion (HSIL), depending on the extent of the affected
epithelium and the degree of cellular abnormality. Equivocal changes are called atypical squamous cells of unknown significance. Abnormal cervical biopsy tissue detected by histological examination is classified as cervical intraepithelial neoplasia (CIN), which is graded from CIN1 to CIN3 according to the thickness of the affected epithelium. Most lesions classified as LSIL or CIN1 disappear within a few months without treatment (28). If HPV infection persists, however, it can lead to moderate or severe cervical intraepithelial neoplasia (CIN2 or CIN3), or adenocarcinoma in situ (AIS). These lesions, if untreated, have a high probability of progressing to squamous cell cancer or adenocarcinoma (28). The time between initial HPV infection and development of cervical cancer is usually decades.

1.3 Genital HPV infections

**Key points**

- Genital HPV infections are primarily transmitted by sexual contact, especially penetrative intercourse.
- HPV incidence and prevalence increases with age, as more members of a population initiate sexual activity.
- Regional and socioeconomic variations in the age-specific prevalence of HPV are partly due to variations in sexual behaviours.
- Risk factors for transmission and acquisition of HPV infections include multiple sex partners, lack of condom use, smoking, and coinfection with other sexually transmitted infections (STIs), including human immunodeficiency virus (HIV).

Genital HPV infection is primarily transmitted through sexual intercourse (2,29-31). HPV is transmitted most efficiently by penetrative intercourse, but can also be transmitted by non-penetrative contact, including oral–genital, manual–genital and genital–genital contact (31-36). Risk of incident infection is highest soon after initiation of penetrative intercourse (7,37-39). HPV infection is highly transmissible, and most sexually active men and women will acquire HPV infection at some time in their lives (40). However, only a small proportion will go on to develop HPV-related disease.

Because HPV is sexually transmitted, prevalence peaks in the early 20s, by which time most members of a population have become sexually active. Prevalence then declines with age, because most HPV infection is transient (Figure 1.1) (2). The WHO Information Centre on HPV and Cervical Cancer provides global, regional and country-specific data on HPV prevalence, sexual behaviour, including mean or median age of onset of sexual activity, and number of sexual partners by age and other characteristics (41). In most developed countries, sexual activity begins during the teenage years (41). For example, approximately 24% of females in the United States were sexually active by 15 years of age, 40% by 16 years and 70% by 18 years (42,43). In developing countries, there is considerable variation among adolescent females in terms of premarital sex and age of first sexual activity. In one 10-country study, rates of premarital sex were higher in countries in sub-Saharan African than in countries in Latin America or the Caribbean (44). In many regions, age at first sexual activity has decreased in recent years (45,46), a trend that has implications for programmes that target HPV vaccination to young people before they start sexual activity (47).

**Error! Objects cannot be created from editing field codes.**
In most countries, HPV prevalence is highest among females in their early 20s, by which time most females have initiated sexual activity. Prevalence falls as women age, because incident infections acquired earlier in life spontaneously clear (8). Differences in sexual activity lead to regional and socioeconomic variations in the age-specific prevalence of HPV among cytologically normal women (2,48). In a cross-sectional study of nearly 20,000 women aged 15–74 years, from 15 areas in 4 continents, age-standardized HPV prevalence varied more than 10-fold between populations (49). In some low-income countries (e.g., India, Nigeria and Chad), HPV prevalence was high in all groups aged 15 years or older (49). In the United Kingdom, high-risk HPV prevalence has been shown to be highest in the group aged 20–24 years, and declined with advancing age (50). In Costa Rica, the peak prevalence of HPV infection has been seen in females under 30 years of age. In both Costa Rica and Colombia, smaller peaks have been seen in older women (e.g. over 55 years of age) (51,52). These peaks may be due to age-cohort effects, detection of persistent prevalent HPV infection that increases with age, newly acquired infections or reactivation of latent infections due to the immunologic changes of menopause (7,37,53,54). Data on regional age-specific prevalence can help in determining which groups to target for HPV vaccination, and in designing evaluations of the impact of vaccination (55-57).

Most women who are sexually active will acquire a cervical infection with at least one HPV type during their lifetime. Longitudinal and cross-sectional studies demonstrate that the most consistent predictor of HPV infection in women is the number of lifetime or recent sex partners (2,14,29,40,58-69). In the largest prevalence study, which included more than 11,000 women in four continents, the prevalence of HPV among women with two or more lifetime sexual partners was twice that of women with only one lifetime partner (69). A United States study of women aged 18–25 detected genital HPV infection in 14% of women with one lifetime sex partner, 22% of women with two lifetime sex partners and 32% of women with more than three lifetime partners (62).

Other risk factors for HPV acquisition include having a new sexual partner, concurrent sex partners, short intervals between new sex partners and a male partner with multiple sex partners; another risk factor is smoking (2,31,47,66). Risk of anal HPV infection is about three times higher in women with cervical HPV infection than in women without cervical infection, and the many cases of concurrent cervical and anal infection with the same HPV type indicate a common source of infection (70).

Use of condoms reduces the risk of HPV transmission and the risk of cervical intraepithelial lesions in female sex partners (71,72). However, protection is only partial because condoms do not cover some parts of the body where skin-to-skin transmission of HPV may occur; also, condoms are often used incorrectly or inconsistently over a user’s lifetime (69,73). At least one study has shown that female partners of uncircumcised men have an elevated risk of cervical cancer, which suggests that circumcision may reduce HPV transmission to females (74).

Coinfection with human immunodeficiency virus (HIV) – especially when associated with a compromised immune system – and with Chlamydia trachomatis may increase susceptibility to HPV infection through cervical inflammation, microabrasions or
immunologic mechanisms (2,47,66). Conversely, HPV-infected women are more likely to acquire HIV (after controlling for various sexual behaviors) (75). A recent meta-analysis found that nearly 40% of HIV-infected women with normal cervical cytology were also infected with HPV (76). Concurrent infection with multiple HPV genotypes is more common in women who are HIV-infected (Table 1.2) (77,78). There is little information on the distribution of HPV genotypes in HIV-infected women with cervical cancer (76). However, one Kenyan study found that the proportion of invasive cervical cancer cases associated with HPV 16 or 18 was the same in women with or without HIV, suggesting that HPV vaccines may be effective in HIV-infected women (79). HIV-infected women are at increased risk of cervical cancer, and both HIV-infected women and men are at increased risk of anal cancer caused by HPV (78,80).

### Table 1.2 HPV infection, disease and vaccination issues for HIV-infected individuals

<table>
<thead>
<tr>
<th>Topic</th>
<th>Consideration for HIV-positive individuals compared with HIV-negative individuals</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV acquisition, incidence, prevalence and persistence</td>
<td>Higher incidence of HPV infection of the cervix and anus in women, especially in those with low CD4 T cell counts and those who do not use or adhere to antiretroviral treatment (81-83)</td>
</tr>
<tr>
<td></td>
<td>Higher prevalence of cervical, anal and oral HPV infections in women and men (77,80,81,84)</td>
</tr>
<tr>
<td></td>
<td>Higher risk of persistent HPV infection (including oncogenic types) and, possibly, higher risk of reactivating latent infections in women (77)</td>
</tr>
<tr>
<td>HPV type distribution</td>
<td>HPV 16 and 18 are the most prevalent types detected in cervical precancers and cancers, regardless of HIV infection status (76)</td>
</tr>
<tr>
<td></td>
<td>Among men and women with HPV-related precancers and cancers, infections with multiple types of HPV are more common (76,81,85-87)</td>
</tr>
<tr>
<td></td>
<td>Among those with high-grade cervical precancers, less likely to detect HPV 16, and more likely to detect HPV 11, 18, 33, 51, 53, 58 and 61 (76)</td>
</tr>
<tr>
<td>Cervical neoplasia</td>
<td>Higher risk of cervical precancer (particularly high-grade precancer) in women (77,80,81,88,89)</td>
</tr>
<tr>
<td></td>
<td>Moderately greater incidence of cervical cancer (80,81,83)</td>
</tr>
<tr>
<td></td>
<td>More rapid progression from HPV infection to cervical precancers (90)</td>
</tr>
<tr>
<td>Anal neoplasia</td>
<td>Higher risk of anal precancers and cancers in women and men, including men who have sex with men (80,88,91)</td>
</tr>
<tr>
<td></td>
<td>Higher prevalence of precancer detected within anal and perianal warts (92,93)</td>
</tr>
<tr>
<td>Oropharyngeal neoplasia</td>
<td>Higher incidence of oropharyngeal cancer in women and men (80)</td>
</tr>
<tr>
<td>Warts</td>
<td>Higher incidence and prevalence of anogenital warts in women (94,95)</td>
</tr>
<tr>
<td></td>
<td>Higher prevalence of oropharyngeal warts (96), especially in those with low CD4 T cell counts and those who do not use or adhere to antiretroviral treatment (94,95)</td>
</tr>
</tbody>
</table>

*Potential impact of HPV vaccination*

- Immunogenicity, clinical efficacy and safety data in HIV-infected persons are not yet available, but studies are planned or under way for both vaccines.
- Demonstrated ability to mount humoral immune response to naturally acquired HPV antigens suggests potential for vaccine immunogenicity (80)
- May derive slightly less protection from vaccines due to greater prevalence of infection with multiple oncogenic HPV types (76,80) or blunted immune response (80)
- HPV vaccination before sexual HPV and HIV exposure would maximize protection by reducing risk of HIV–HPV biologic interaction in those receiving vaccine

*a Some of these issues may also be relevant to immunocompromised populations other than HIV-infected persons, including transplant patients, individuals with chronic conditions that affect immune function or those that require immunosuppressive medication (e.g., cancer, renal failure, autoimmunity) in whom data are very limited.

*b Also see above row on anal neoplasia.

Information on risk factors for, and the natural history of, HPV infection in men is more limited than in women. This situation is due to several factors: HPV-related disease is less common in men, sensitive methods for sampling and testing male specimens for genital
HPV DNA have only recently been developed, and study methods have varied substantially (97-100). Recent data from the United States from HIV-negative men who have sex with men showed that the cumulative incidence of anal HPV infection of any type was 61% by 18 months. The type-specific cumulative incidence at 24 months was 17% for HPV 16, 13% for HPV 6, 8% for HPV 18 and 6% for HPV 11 (101). The limited data available, which include longitudinal studies, show that risk factors for anogenital HPV infection in men include lifetime number of sex partners, number of recent sex partners and smoking (100). Some studies suggest that circumcision and condom use protect against penile HPV infection (100,102,103), whereas others found that these factors were not protective (104). Younger age was an important risk factor in one study of anal and penile HPV infection in heterosexual men, whereas anal HPV infections in men who have sex with men are prevalent over a broader age range (101,105).

HPV infection is rarely detected in newborn and healthy young children. Except for rare cases of juvenile onset recurrent respiratory papillomatosis (JORRP), the clinical implications of HPV exposure during the perinatal period and young childhood remain unclear (34-36,106,107). In the United States, oral HPV infections in children aged 2 weeks to 20 years reflect a bimodal age distribution, with peaks in infancy thought to be associated with perinatal transmission, and peaks in late adolescence to initiation of sexual activity (108).

1.4 The burden of HPV-related disease and the role of HPV in development of premalignancy, malignant and non-malignant disease

1.4.1 General considerations

Key points

- HPV-associated diseases include cervical, vaginal, vulvar, penile and anal precancers and cancers, and a subset of head and neck precancers and cancers; anogenital warts; and recurrent respiratory papillomatosis.
- Of the total cancers worldwide thought to be attributable to HPV, more than 90% affect women, and 80% are in developing countries.
- Cervical cancer is the most common HPV-related malignancy worldwide.
- High-risk HPV types 16 and 18 are responsible for the great majority of HPV-related malignant disease.
- Low-risk HPV types 6 and 11 are responsible for the great majority of genital warts and recurrent respiratory papillomatosis.
- Data on the burden of HPV-related disease are available for all regions and many countries (41).

Well established HPV-related malignant diseases include cervical, vaginal, vulvar, penile and anal precancers and cancers, and a subset of head and neck precancers and cancers. High-risk HPV types 16 and 18 are responsible for most of these HPV-related malignant diseases. Non-malignant HPV-related diseases include anogenital warts and recurrent respiratory papillomatosis. Low-risk HPV types 6 and 11 are responsible for most of these conditions. Table 1.3 summarizes the HPV-attributable risk of cancers at different anatomic sites. Of the total estimated HPV-attributable cancers worldwide, more than 90% affect women, and 80% are in developing countries (109).
Table 1.3  Annual number of cases of invasive cancer by anatomic site and by association with HPV type

<table>
<thead>
<tr>
<th>Site</th>
<th>Annual number of cases&lt;sup&gt;a&lt;/sup&gt;</th>
<th>HPV DNA prevalence, %&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Estimated number of cases attributable to HPV types</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HPV 16</td>
<td>HPV 18</td>
</tr>
<tr>
<td>Cervix</td>
<td>492 800</td>
<td>54</td>
<td>16</td>
</tr>
<tr>
<td>Vulva</td>
<td>26 600&lt;sup&gt;b&lt;/sup&gt;</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Vagina</td>
<td>13 300&lt;sup&gt;b&lt;/sup&gt;</td>
<td>57</td>
<td>7</td>
</tr>
<tr>
<td>Anus</td>
<td>30 400</td>
<td>73</td>
<td>5</td>
</tr>
<tr>
<td>Penis</td>
<td>26 300</td>
<td>33</td>
<td>7</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>52 100</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>641 500</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DNA = deoxyribonucleic acid; HPV = human papillomavirus
<sup>b</sup> Source: Adapted from Parkin (2006) (110), assuming a ratio of 2:1 of vulval to vaginal cancer.

1.4.2 Cervical cancer and precancerous lesions

Key points
- Invasive cervical cancer represents the main burden of HPV infection.
- Globally, cervical cancer is the second most common type of cancer among women.
- In 2005, cervical cancer was responsible for more than 260 000 deaths worldwide, approximately 80% of which occurred in developing countries; in these countries, most women with cervical cancer will die from their disease.
- If current trends persist, cervical cancer deaths are expected to rise by nearly 25% in the next 10 years.
- Cervical cancer incidence rates vary at least 20-fold worldwide, with a range of less than 1–50 per 100 000; rates are highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and south-central and south-east Asia.
- More than half of global cases occur in countries eligible for vaccines subsidized by the Global Alliance for Vaccines and Immunization (GAVI), of which about half occur in India alone.
- In Latin America, the Caribbean and Eastern Europe, cervical cancer contributes more to years of life lost (YLL) than tuberculosis, maternal conditions or AIDS.
- Most cervical cancer is diagnosed in women over 40 years. In the absence of vaccination or improvements in screening and treatment, deaths due to cervical cancer are projected to increase by almost 25% over the next 10 years, owing to demographic trends in young women.
- HPV 16 and 18 account for approximately 70% of cervical cancer cases worldwide; HPV 16 has greatest oncogenic potential.

Invasive cervical cancer represents the main burden of HPV infection. Squamous cell carcinoma accounts for most cervical cancers worldwide. In some populations subject to widespread screening, cervical adenocarcinoma can represent up to 25% of cervical
cancers, because screening reduces the incidence of squamous cell carcinoma more than that of adenocarcinoma (109).

Globally, cervical cancer is the second most common type of cancer among women. Regional incidence rates of cervical cancer vary at least 20-fold, with a range of less than 1–50 per 100 000. The lowest rates are in Western Europe and the highest are in parts of Africa, the Americas and Asia (2,109,113). Based on the most recent summary of cancer registry data, published in 2002, cancer incidence was highest in Latin America and the Caribbean, sub-Saharan Africa, Melanesia, and south-central and south-east Asia (Table 1.3 and Figure 1.2) (2,109,113-116). In 2002, 54% of cervical cancer cases were in Global Alliance for Vaccines and Immunization (GAVI) eligible countries (Table 1.4), of which about half were in India alone. The risk of invasive cervical cancer is strongly related to access to screening for precancerous lesions, and most countries with high incidence lack high-quality, organized screening programmes with broad coverage (see Section 2). If current incidence trends continue, incidence of cervical cancer will rise from nearly 500 000 cases per year to an estimated 1 million cases per year in 2050 (114).

Table 1.4 Cervical cancer incidence by country income grouping, 2002

<table>
<thead>
<tr>
<th>Income grouping</th>
<th>Cases</th>
<th>% of global burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lowest income (GAVI eligible)</td>
<td>264 931</td>
<td>54</td>
</tr>
<tr>
<td>Lower middle</td>
<td>112 232</td>
<td>23</td>
</tr>
<tr>
<td>Upper middle</td>
<td>60 223</td>
<td>12</td>
</tr>
<tr>
<td>High</td>
<td>54 402</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>491 788</td>
<td>100</td>
</tr>
</tbody>
</table>

GAVI = Global Alliance for Vaccines and Immunization.
Source: Saxenian and Program for Appropriate Technology in Health (PATH). (2007) (117); 2002 Globocan data, using estimates prepared by PATH.

Figure 1.2  Burden of cervical cancer in the world

Source: WHO (2007) (118)
Cervical cancer was responsible for more than 260,000 deaths in 2005, approximately 80% of which occurred in developing countries. Mortality rates are highest in low-income countries, where most disease is detected at late stage because there is little or no access to screening and effective treatment. In most developing countries, more than 60% of women will die from their disease; survival rates depend on the stage at which cancer was diagnosed and the treatment available (119). If current trends persist, cervical cancer deaths are expected to rise by nearly 25% in the next 10 years, and the proportion of cervical cancer deaths in developing countries is expected to increase to from 80% to 90% by 2020 if current mortality trends continue (114).

In the absence of HPV vaccination or improvements in screening and treatment, deaths due to cervical cancer are projected to rise by almost 25% over the next 10 years as a result of global increases in the number of young women (120). In 2000, cervical cancer resulted in an estimated 2.7 million years of life lost (YLL) (118). In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to YLL than do tuberculosis, maternal conditions or AIDS (121).

In high-income countries that have cytology screening programmes with broad coverage, cervical cancer incidence and mortality are relatively low, but the burden on health systems and the costs of screening and management of precancerous lesions are substantial. In the United States, for example, cytology screening using Pap smears produces about 4.7 million abnormal results each year that require follow-up (122). The diagnosis and follow-up for abnormal screening tests also causes anxiety and lost productivity (123) (See Section 4).

Cervical cancer occurs most commonly in women over 40 years of age (Figure 1.3) (114-116). It therefore strikes mid-adult women in the prime of their lives; these women are working; raising children; caring for spouses, partners and elders; and contributing to the social and economic life of their communities. In some communities most affected by the HIV epidemic, mid-adult women are the only people supporting elders and children. Cervical cancer deaths thus represent both personal tragedies and devastating losses for families, societies and economies (120).

![Figure 1.3 Age-specific cervical cancer incidence](source: Ferlay et al. (2001) (114))
Epidemiological and virological studies estimate that high-risk HPV types cause all cervical cancer cases, making HPV infection the cause of cervical cancer (2,109). The strength of association between high-risk HPV infection and cervical cancer is several fold greater than of the association between smoking and lung cancer, or between hepatitis B and liver cancer (1,124).

Based on data from multicentre studies and large meta-analyses from all regions (although data are sparse for large regions of Africa and Central Asia), HPV 16 and 18 cause approximately 70% of squamous cell cervical cancers and high-grade cervical precancers worldwide (5,7,37,111,125-128). HPV 16 is consistently the type most commonly associated with invasive cervical cancer in all regions, ranging from 52% in cases from Asia to 58% in cases from Europe. HPV 18 is the second most common type in cervical cancer cases globally. Among cervical cancer cases, the combined prevalence of HPV 16/18 is slightly higher in Australia, Europe and North America (74–77%) than in Africa, South and Central America, and Asia (65–70%) (5,111).

Each individual HPV genotype, other than HPV 16 and 18, causes less than 5% of cervical cancer cases. Several major studies, including international studies that used a common DNA assay, found that the six most common high-risk genotypes after HPV 16 and 18 were consistently HPV 31, 33, 35, 45, 52, 58 (Table 1.1) (5,28,37,111,125,126,129). Together, these eight types account for 90% of global cervical cancer cases. The relative importance of HPV 31, 33, 35, 45, 52 and 58 differs by region; for example, HPV 52 and 58 are more prevalent in Asia than elsewhere.

The diversity of HPV types is lower in invasive cancers than it is in cervical specimens of women with normal cytology, low-grade cytologic abnormalities and squamous intraepithelial lesions. Nevertheless, HPV 16 and 18 also cause approximately 70% of AIS and CIN3, and 50% of CIN2 (5,130). Knowledge of the distribution of HPV types in AIS and CIN2/3 cases is needed to estimate the impact of HPV vaccines on precancerous lesions detected by screening. However, intraregional heterogeneity in HPV type distribution in women with low-grade CIN or mild cytologic abnormalities, and in cytologically normal women, is clinically less important because many of these women will not develop invasive cancer (5). Studies are under way in many regions to estimate the distribution of HPV types in cervical precancers and cancer; these studies could provide baseline data for the assessment of vaccine impact.

HPV 16 and 18 cause most cervical adenocarcinomas (131). HPV 18 is relatively more common in adenocarcinoma than in squamous cell cervical cancer, but HPV 16 prevalence remains high in both histologic types (111,125,129,132,133). In the United States, HPV 16 and 18 together account for approximately 68% of squamous cell cancers and 83% of adenocarcinomas (15). Meta-analyses suggest that HPV 18 and the related HPV 45 are relatively more common in adenocarcinoma than in squamous cell carcinoma (126).

Several host characteristics and exogenous agents promote development of squamous cell cervical cancer among HPV-infected women, possibly by influencing HPV persistence, immune response or other factors that influence oncogenic transformation. These factors include age, immunosuppression (e.g. due to HIV infection), multiparity, early age at first delivery, long-term use of hormonal contraceptives and smoking (2,17,134-138). Among women older than 45 years of age, the strongest predictors of HPV persistence appear to be older age, longer time since menopause and use of hormonal replacement therapy (139). Coinfection with C. trachomatis and herpes simplex virus type 2 (HSV-2) promotes HPV persistence (132,140-144). Coinfection with HIV increases persistence of
high-risk HPV genotypes, and progression to precancerous cervical lesions and cancer of the cervix and anus (Table 1.2) (145). Many cofactors for development of cervical adenocarcinoma are similar to those for squamous cell cancer, including long-term use of hormonal contraception, high parity, HSV-2 coinfection and lack of intrauterine device (IUD) use (i.e. IUD use has a protective effect) (2,131,146).

1.4.3 HPV-related non-cervical anogenital cancers and precancers

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvar, vaginal, penile and anal cancers are rare, and age-standardized incidence rates are less than 2 per 100 000.</td>
</tr>
<tr>
<td>Most cases of these cancers occur in adults over 50 years of age.</td>
</tr>
<tr>
<td>HPV is estimated to cause approximately 90% of anal cancer and 40% or more of vulva, vaginal and penile cancers.</td>
</tr>
<tr>
<td>HPV 16 is most commonly detected in non-cervical anogenital cancers, followed by HPV 18, 31 and 33.</td>
</tr>
<tr>
<td>Risk factors for non-cervical anogenital cancers include a large number of lifetime sex partners, immunosupression and smoking.</td>
</tr>
</tbody>
</table>

Vulvar cancer is far less common than cervical cancer, with the global age-standardized incidence rate ranging from 0.5 to 1.5 per 100 000. The highest incidence occurs in Australia, some European countries (specifically Denmark, Italy, Scotland, Spain and United Kingdom), North America, and some African and South American countries (specifically Zimbabwe and Brazil) (109). In a multicountry study, the average age at diagnosis was 69 years (range 49–77 years) and most cases (63%) were of squamous cell type (147). Invasive cancer is preceded by high-grade vulvar intraepithelial neoplasia (VIN2/3), but the natural history of vulvar neoplasia is uncertain (148,149). Warty and basaloid cases, the types most commonly associated with HPV, are diagnosed less frequently than the keratinized type (109). Some studies suggest that the number of treated vulvar carcinoma cases is increasing; and that the age at diagnosis is decreasing (150,151).

Vaginal cancer is less common than both cervical and vulvar cancer (109). Globally, the age-standardized incidence rates for vaginal cancers are estimated to be between 0.3 and 0.7 per 100 000 (109). The average age of diagnosis for women has been estimated to be 59 years (range 45–82 years) (147). High-grade precancerous vaginal intraepithelial neoplasia (VaIN2/3) preceeds invasive cancer, but the natural history of this cancer is not fully understood (152). Vulvar and vaginal cancers have common risk factors, including previous cervical neoplasia, large number of lifetime sex partners, smoking and immunosupression (153).

Anal cancers are predominantly squamous cell carcinomas, but can also be adenocarcinomas, or basaloid and cloacogenic carcinomas. Anal squamous cell carcinomas are more common in women than in men except in some populations with a large proportion of men who have sex with men – a subgroup that has a particularly high prevalence (81,109,154). Global age-standardized incidence rates for anal cancer range from about 0.2 to 2.0 per 100 000. In the United States, the incidence of anal cancer has increased over the last three decades, especially among men (155). Anal intraepithelial neoplasia (AIN) is recognized as a precursor of anal cancer (156). Risk factors for anal
cancer, other than HPV infection, include a high number of lifetime number of sexual partners, male-to-male sex and smoking (109,157).

Globally, cancer of the penis is rare and accounts for less than 0.5% of cancers in men. The estimated age-standardized incidence rate is less than 1 per 100,000 in Western countries. The highest incidence rates have been reported in eastern Southern Africa, southeast Asia, India and Latin America (109). Circumcision appears to hasten clearance of high-risk HPV (158) and reduce risk of penile cancer (109,159).

International studies, including major meta-analyses, have found that HPV is detected in 88–94% of anal cancers, 40–65% of vaginal cancers, 40–90% of vulvar cancers, 40–50% of penile cancers, and more than 50% of high-grade precancerous lesions of these organs (Table 1.3) (109,147,160-162). HPV 16 is by far the most common HPV type detected in non-cervical anogenital cancers, followed by HPV 18, 31 and 33 (109,147,160-164). The International Agency for Research on Cancer (IARC) recently concluded that there was (2):

- sufficient evidence that HPV 16 causes vulvar (basaloid and warty tumours), penile (basaloid and warty tumours), vaginal and anal cancers
- limited evidence that HPV 18 causes vulvar (basaloid and warty tumours), penile (basaloid and warty tumours), vaginal and anal cancers
- limited evidence that HPV 6 and 11 cause verrucous carcinomas of the vulva, penis and anus.

### 1.4.4 Head and neck cancers

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Certain head and neck cancers are associated with HPV infection.</td>
</tr>
<tr>
<td>• Most cases occur in adults over 50 years of age.</td>
</tr>
<tr>
<td>• HPV 16 is most commonly detected in squamous cell carcinomas of the oral cavity, oropharynx and larynx.</td>
</tr>
<tr>
<td>• Cancers of the oral cavity and oropharynx associated with HPV 16 differ from HPV-negative oropharyngeal cancers associated with tobacco and alcohol use.</td>
</tr>
</tbody>
</table>

Global incidence of head and neck cancers varies widely, and this variability is associated with tobacco and alcohol use. In 2002, an estimated 405,000 cases occurred worldwide, with two thirds of these being in developing countries; 211,000 deaths occurred from these cancers (109). Certain head and neck cancers are associated with HPV; these include cancer of the oral cavity, oropharynx and larynx (2). Incidence of these HPV-positive cancers is rising in some countries, possibly due to more oral–genital sex and an increase in the average number of lifetime sex partners (165,166).

Mounting evidence from several studies using different methods to test for HPV has implicated the virus, particularly HPV 18, as an important carcinogen for a subset of cancers of the oral cavity, oropharynx and larynx (oropharyngeal squamous cell carcinomas) (Table 1.3) (2,160). In a recent systematic review of more than 5000 head and neck cancer cases tested for HPV with polymerase chain reaction (PCR) based methods, HPV DNA was present in less than half of oropharyngeal squamous cell carcinomas (35.6%; range 11–100%), oral squamous cell carcinomas (23.5%; range 4–80%) and laryngeal squamous cell carcinomas (24.0%; range 0–100%) (112). HPV 16 was the most common type in squamous cell carcinomas of the oropharynx (86.7%), oral
cavity (68.2%) and larynx (69.2%). HPV 18 was the second most frequent type: found in approximately 3% of oropharyngeal, 34% of oral and 17% of laryngeal squamous cell carcinomas (160). IARC recently concluded that there is (2):

- sufficient evidence to conclude that HPV 16 causes cancer in the oral cavity and oropharynx
- limited evidence that HPV 18 and other HPV types cause cancer in the oral cavity and oropharynx
- limited evidence that HPV 6, 11, 16 and 18 cause laryngeal cancer.

1.4.5 Anogenital warts

Key points

- Anogenital warts are common among sexually active persons.
- Genital warts usually first occur in adolescence or young adulthood, shortly after onset of sexual activity.
- All anogenital warts are caused by HPV, with types 6 and 11 causing 90–100% of these warts.
- A minority of genital wart cases resolve without treatment; recurrence is common.

Genital warts or condyloma acuminatum are highly infectious, and thus are common on the cervix, vagina, vulva or anus in women, and on the penis, scrotum or anus in men. Estimates of the prevalence of anogenital warts vary from 0.24% to 13%, depending on the population’s age distribution and risk of STI (2). Incidence rates for genital warts rise sharply in women aged 15–24 years, and in men aged 20–29 years. Incidence rates peak in 20–29-year-olds in both sexes, and then decline sharply in females but remain high in males up to the age of 40 years (167).

The prevalence of genital warts varies by region, with notably low prevalence in Asia (167-170). A large, population-based study of women aged 18–45 years from four Nordic countries found that approximately 10% of women reported ever having genital warts, and approximately 1% reported having warts in the past year (169). In this same study, the incidence of warts among younger birth cohorts was reported to be increasing in three of the four countries. Similarly, in a recent study of Danish males, 7% reported ever having genital warts and 1% reported having warts in the past year (171). Data from the United States and United Kingdom also suggest that the incidence of genital warts is rising (167,172).

All anogenital warts are caused by HPV (173). Between 90% and 100% of genital warts are caused by HPV 6 and 11 globally, but there may be some geographic or subgroup variability (173-175). Almost 50% of women infected with HPV 6 or 11 will develop genital warts within 12 months of exposure, and 64% within 36 months of exposure (176). The average time taken to develop warts after infection with HPV 6 or 11 is approximately 2–3 months (176). Not everyone infected with HPV 6 or 11 acquires genital warts, and such warts rarely progress to cancer (172). Once genital warts become apparent, only 20–30% of cases resolve without treatment (see Section 2). Recurrence occurs in approximately 30% of cases, regardless of whether clearance initially occurred spontaneously or after treatment (177). Because many warts do not resolve spontaneously and recur, HPV transmission in communities is easily sustained.
Sexual activity with an HPV-infected partner is the primary risk factor for anogenital warts (60). Among men, a high number of sexual partners, older age, smoking, other STIs and anal–manual contact have also been identified as risk factors (171,178). Consistent condom use decreases the risk of genital warts by 60–70%. HIV infection is associated with an increased prevalence of genital warts (Table 1.2). Giant condylomas (Buschke–Löwenstein tumours) have been observed in HIV-infected patients (179).

1.4.6 Recurrent respiratory papillomatosis

### Key points

- Recurrent respiratory papillomatosis (RRP) is rare; global incidence estimates are not available.
- HPV 6 and 11 account for nearly all cases of RRP.
- Juvenile-onset RRP (JORRP) occurs most commonly in children under 4 years of age, resulting from HPV transmission at delivery from a mother infected with HPV 6 or 11, or with genital warts.
- Adult-onset RRP results from sexual contact with infected lesions.

Recurrent respiratory papillomatosis (RRP) is an uncommon, but serious, condition of the upper respiratory tract, particularly the larynx. Although most of the papillomas are benign, some infections descend into the trachea, bronchia and lungs. Papillomas that compromise the airway must be removed surgically and their recurrent nature often requires repeated surgery (see Section 2) (172).

Global estimates of the incidence of JORRP are not available, and the few regional incidence estimates available are imprecise. It has been estimated that 1 in 500 infants born to women with genital warts develop JORRP (180). In Denmark, the incidence of JORRP between 1974 and 1999 was estimated to be 3.5 per 10^6 (181). Incidence estimates from the United States range from 1000 cases per year in a population of more than 250 million (182), to 0.12–2.1 cases per 100 000 children aged less than 18 years (183).

JORRP is predominantly caused by newborn exposure to HPV 6 or 11, or by exposure to genital warts during delivery. A maternal history of genital warts increases risk of JORRP in a newborn more than 200 times (181), and obvious maternal condyloma during pregnancy is a major risk factor for JORRP. However, most children with JORRP are born to women without a history of condyloma during pregnancy, suggesting transmission of asymptomatic maternal HPV 6 and 11. Although HPV is generally transmitted perinatally, the median age of diagnosis is 4 years. HPV detection in fetal laryngeal tissue suggests possible intrauterine HPV transmission (184). Caesarean section provides only partial protection against JORRP (172). In adult-onset RRP (AORRP), infection results from sexual or non-sexual contact with lesions harbouring HPV 6 or 11; these HPV types cause nearly 100% of AORRP (172).

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This section discusses the World Health Organization (WHO) guidelines on prevention and management of cervical cancer and anogenital warts and other guidance on prevention and management of other HPV-related cancers and recurrent respiratory papillomatosis (RRP).

2.1 General considerations

**Key points**

- WHO advises a comprehensive approach to cervical cancer prevention and management; this approach should include affordable and effective primary prevention services, early detection through screening, diagnosis, treatment and palliative care.
- For primary prevention of cervical cancer and anogenital warts, WHO currently recommends reducing sexual exposure to human papillomavirus (HPV) by reducing high-risk sexual behaviours and using condoms.
- WHO currently recommends cytology as the primary screening test for cervical cancer if sufficient resources exist for adequate quality control and follow-up.
- When cytology is not feasible in low-resource settings, WHO currently recommends visual inspection of the cervix as an alternative screening method when accompanied by careful monitoring. If new and well-performing HPV tests become widely accessible, affordable, and sustainable with high quality in the future, they may offer an alternative to cytology in low-resource settings.
- WHO recommends many methods to treat HPV-related cervical precancerous lesions and cancers. Cryotherapy is recommended to treat many precancerous lesions in low-resource settings in low and middle-income countries.
- WHO recommends treating warts with medication applied by patients or providers, or surgery. Widespread access to these therapies is limited in many low and middle-income countries.
- WHO has not issued specific recommendations on prevention or management of other HPV-related cancers or recurrent respiratory papillomatosis.

Screening for human papillomavirus (HPV) infection rather than for HPV-related disease is not warranted because most HPV infection is benign, transient and causes no clinical disease (See Section 1). Likewise, treatment strategies are directed at HPV-associated precancerous lesions detected on screening or clinical disease, not at HPV infection. Accordingly, WHO recommendations have focused on prevention, early detection, diagnosis, and treatment of HPV-related cervical precancers and clinical disease, not on HPV infection.

WHO has issued general guidance on cancer control programmes (1,2), and specific advice on prevention and control of cervical cancer (3). These guidelines advise a comprehensive approach that includes access to affordable and effective services for primary prevention; early detection through screening; diagnosis; treatment; and, for advanced disease, palliative care.
The guidelines stress prevention and screening of cervical cancer, one of the most preventable and treatable forms of cancer if it is detected early and managed effectively. WHO has also issued guidance on prevention, diagnosis and management of genital warts (4). WHO has not issued recommendations on prevention and management of other HPV-related cancers or RRP. WHO recommendations on prevention and management of HPV-related diseases are relevant to the introduction of HPV vaccine because savings in screening and treatment could potentially free resources for prevention strategies, including HPV vaccines.

2.2 Prevention, early detection and treatment of cervical cancer

2.2.1 Prevention

WHO recommends that primary prevention of cervical cancer should include education, awareness raising and other locally appropriate strategies to promote behaviours that reduce risk of HPV exposure (Table 2.1). Such behaviours include delaying onset of sexual activity, reducing the number of sex partners, avoiding sex partners who have multiple partners and using condoms (3). These recommendations are supported by data showing that consistent and correct male condom use hastens HPV clearance in men and women, increases regression of cervical lesions, and reduces risk of cervical precancers and cancer. Condom use also prevents infection with other sexually transmitted infections (STIs), particularly infection with:

- *Chlamydia trachomatis* and herpes simplex virus type 2 (HSV-2), which are possible cofactors for cervical cancer
- human immunodeficiency virus (HIV), which increases the likelihood of acquiring high-risk HPV, persistence of HPV and progression to high-grade cervical precancers.

WHO also recommends seeking prompt treatment for STI symptoms that may facilitate development of cervical cancer, and avoiding or reducing tobacco use, which is a known risk factor for cervical cancer.

2.2.2 Early detection through screening

Cervical cancer prevention programmes should include education (for health-care providers and women) that stresses the benefits of screening, the peak ages of cervical cancer incidence, and the signs and symptoms of precancerous lesions and invasive disease (3). Screening aims to detect precancerous changes, which may lead to cancer if not treated. Screening is only effective if there is a well-organized system for follow-up, diagnosis and treatment.

WHO recommends specific target ages and frequency of cytologic screening (Table 2.1):

- New programmes should start screening women at age 30 or older, and should only screen younger women when the older age groups have been adequately screened. Existing programmes should not screen women less than 25 years of age.
- If a woman can be screened only once in her lifetime, the best age is between 35 and 45 years.
- For women over 50 years, a five-year screening interval is appropriate.
- For women aged 25–49 years, a three-year interval can be considered if resources are available.
- Annual screening is not recommended at any age.
- Screening is not necessary for women over 65 years of age, provided the last two previous smears in mid-life were negative.
Table 2.1  WHO recommendations for prevention and control of cervical cancer and anogenital warts caused by HPV infection

<table>
<thead>
<tr>
<th>Disease</th>
<th>Primary prevention</th>
<th>Early detection and screening</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cervical precancers and cancer (3)</td>
<td>Reduce high-risk sexual behaviours</td>
<td>Periodic screening using:</td>
<td>Precancerous lesions:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cytology (Pap test) for women aged 25+ years, preferably</td>
<td>cyrotherapy, loop electro surgical excision procedure, or surgical</td>
</tr>
<tr>
<td></td>
<td></td>
<td>in organized programmes</td>
<td>excision.</td>
</tr>
<tr>
<td>Condom use</td>
<td></td>
<td>In pilot or carefully monitored settings</td>
<td>“Screen and treat” in low-resource settings using cyrotherapy</td>
</tr>
<tr>
<td>Avoid or reduce tobacco use</td>
<td></td>
<td>periodic screening with:</td>
<td>Cancer: surgery, chemotherpay, radiotherapy, brachytherapy, palliative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HPV DNA tests; or visual inspection of cervix with</td>
<td>care</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acetic acid or Lugol’s iodine</td>
<td></td>
</tr>
<tr>
<td>Seek prompt treatment of sexually</td>
<td></td>
<td>Prompt diagnostic follow-up if screening test abnormal</td>
<td></td>
</tr>
<tr>
<td>transmitted infections</td>
<td></td>
<td>(e.g. colposcopy and biopsy)</td>
<td></td>
</tr>
<tr>
<td>Anogenital warts (4)</td>
<td>Reduce high-risk sexual behaviours</td>
<td>Physical examination of patients that present with anogenital warts</td>
<td>Patient-applied podophyllintoxin or imiquimod; provider-administered</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>podophyllintoxin, trichloracetic acid, cyrotherapy, electrosurgery; or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>surgical excision</td>
</tr>
<tr>
<td>Condom use</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DNA = deoxyribonucleic acid; HPV = human papillomavirus

*a WHO has no specific policies on prevention, control or treatment of HPV-related cancers (other than cervical cancer), or of recurrent respiratory papillomatosis.

Regular cervical cancer screening is especially important for women who are HIV-infected because they are at higher risk of acquiring oncogenic HPV types, and, once infected with HPV, are at higher risk of rapid progression to precancerous lesions and cancer (5).

Cervical cytology, or Papanicolaou (Pap) testing, has been the cornerstone of cervical cancer screening for decades. Most cervical cancer cases and deaths can be prevented through cytologic screening followed by appropriate diagnosis and treatment (6, 7). This has been demonstrated in countries with well-organized screening programmes or extensive opportunistic screening with effective follow-up for patients with abnormal or borderline smears, good quality-control procedures and high coverage.

In most low and middle-income countries, cervical cancer incidence and mortality have not been substantially decreased by cytology screening and early treatment, due to barriers in setting up and sustaining these strategies (6). Such barriers include (8):

- lack of clinical staff to take cervical smears and cytotechnicians and cytologists to read smears
- inadequate coverage or quality of screening programmes, or both
- lack of prompt follow-up for abnormal cytology with diagnosis and treatment.
Other barriers include the need for several health-care visits and multiple procedures, the need to travel long distances to health-care facilities, insufficient personnel with necessary technical skills, lack of specialized equipment, competing health-care priorities, and insufficient health budgets. A 2006 study reported that about 75% of women in developed countries were screened for cervical cancer in the last 5 years, compared to less than 5% in developing countries (6). For example, most countries in Eastern and Southern Africa have a high incidence of cervical cancer, and lack or have limited access to the necessary personnel (e.g. cytotechnicians, pathologists, gynecologists), equipment (e.g. colposcopes) and facilities (e.g. examining rooms equipped for pelvic examinations, cytology and histology laboratories) (6,9). With poor access to screening and follow-up, invasive cancer is often detected too late to be cured (3). These challenges have prompted WHO to propose visual cervical inspection as a potentially more feasible alternative to cytology in low-resource settings, and HPV DNA tests if they become available, feasible and affordable in the future.

Visual inspection involves using illumination to examine the cervix with the naked eye after applying a dilute acetic acid (visual inspection with acetic acid, VIA) or iodine solution (visual inspection with Lugol’s iodine, VILI). Acetowhite or mustard-yellow areas near the squamocolumnar junction of the cervix indicate cervical intraepithelial neoplasia (CIN) (6). Both VIA and VILI are relatively inexpensive, can be carried out by a range of medical personnel, require only modest equipment and widely available consumables, and require no laboratory infrastructure (6). Both methods also give immediate results, making it possible to treat cervical lesions at the same visit. WHO currently recommends visual inspection methods in pilot projects or other closely monitored settings (3). WHO plans to review these recommendations in the future, in response to new data about performance of these screening approaches (10). (See Annex 2 for updated information on this issue.)

In 2005, WHO and International Agency for Research on Cancer (IARC) jointly concluded that there is sufficient evidence that HPV deoxyribonucleic acid (DNA) tests used as primary screening tests can reduce cervical cancer incidence and mortality (11). However, currently available commercial HPV DNA tests require a cervical specimen collected by a health-care provider skilled in internal pelvic examination, specialized specimen transport, and central laboratories with sophisticated processing equipment; also, they are too costly for use in low-resource settings. Consequently, WHO only recommends HPV DNA tests as a primary method of screening in conjunction with cytology or other screening methods for women aged 30 years and older in pilot projects or other closely monitored settings, where sufficient resources exist. Candidate HPV tests that are less expensive, are more rapid, can be performed in peripheral health facilities or use self-collected vaginal specimens are being evaluated in low-resource settings. If these studies demonstrate adequate test performance and cost effectiveness, such tests may be suitable for large screening programmes (12-15). WHO will review its current guidance on HPV tests after reviewing ongoing evaluations of these tests. (See Annex 2 for updated information on this issue.)

Table 2.2 describes performance of currently available screening tests, many of which have been evaluated in Africa, Asia, North and South America, and Europe (16).
Table 2.2 Characteristics of screening tests for secondary prevention

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Conventional cytology</th>
<th>HPV DNA tests</th>
<th>Visual inspection tests</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sensitivity</td>
<td>Specificity</td>
<td>VIA</td>
</tr>
<tr>
<td></td>
<td>Conventional cytology</td>
<td>HPV DNA tests</td>
<td>VIA</td>
</tr>
<tr>
<td></td>
<td>47–62%</td>
<td>66–100%</td>
<td>67–79%</td>
</tr>
<tr>
<td>Specificity (for high-grade lesions and invasive cancer)</td>
<td>60–95%</td>
<td>62–96%</td>
<td>49–86%</td>
</tr>
<tr>
<td>Comments</td>
<td>Assessed over the last 50 years in a wide range of settings in developed and undeveloped countries</td>
<td>Assessed over the last decade in many settings in developed countries and a few developing countries</td>
<td>Assessed over the last decade in many settings in developing countries</td>
</tr>
<tr>
<td>Number of visits required for screening and treatment</td>
<td>Two or more</td>
<td>Two or more</td>
<td>Can be used in a single-visit or see-and-treat approach where outpatient treatment is available</td>
</tr>
</tbody>
</table>

DNA = deoxyribonucleic acid; HPV = human papillomavirus; IARC = International Agency for Research on Cancer; VIA = visual inspection with acetic acid application; VILI = visual inspection with Lugol’s iodine


2.2.3 Treatment and palliative care

Patients with abnormal screening tests should be referred to colposcopy, the examination of the cervix with a magnification device to visualize precancerous lesions before biopsy or treatment. Although colposcopy is used for cancer screening in some regions, WHO recommends colposcopy only for diagnostic purposes, not for primary screening (3).

Cryotherapy, loop electrosurgical excision procedure (LEEP) or cold-knife surgical excision can be used to treat precancerous lesions, depending on the location, extent and characteristics of the lesion; the clinician’s skills; and the equipment available (Table 2.1) (11). Limited data suggest that the therapies available for HPV-related lesions might reduce, but probably not eliminate, infectiousness (17). In low-resource settings, cryotherapy is most commonly used because equipment is less expensive, easier to maintain, and requires less training than other types of ablative or excisional treatment. Nevertheless, cryotherapy is not available in many peripheral health-care settings in many low and middle-income countries, and may require referral to a tertiary care centre (3).

Screen-and-treat strategies allow women with positive screening tests to be promptly treated at the same or next clinic visit. This avoids the delays that may mean loss to follow-up or may preclude treatment. WHO guidance notes two approaches:

- *screen-and-treat* involves immediate cryotherapy of women with positive screening VIA or VILI at the primary health care facility if lesions are suitable for cryotherapy.
- *screen-triage-treat* involves colposcopy of patients with a positive screen (by cytology, VIA, VILI or HPV DNA test) followed by immediate cryotherapy of detected lesions; this approach is intended to minimize the overtreatment associated with the screen-and-treat approach.

The recommendations on using screen-and-treat strategies are supported by several recent longitudinal studies of the safety, feasibility and impact of such strategies in Africa, India and Thailand (10,18,19). For example, the Indian study found that a single-visit screen-
and-treat approach using VIA, colposcopy and cryotherapy, performed by well-trained nurses, significantly reduced cervical cancer incidence and mortality in women aged 30–59 years (10). Modelling studies in India, Kenya, Peru, South Africa and Thailand have estimated that a strategy involving a single one-visit or two-visit screen-and-treat at age 35 would reduce the lifetime risk of cancer by approximately 25–36%, and cost less than 500 international dollars per year of life saved (20). If low-cost, rapid HPV DNA tests currently under development perform well, they may offer another option for the screen-and-treat approach (13).

Invasive cervical cancer can be effectively treated with radical surgery, radiotherapy, brachytherapy and chemotherapy, especially if treatment begins when disease is localized to the cervix or uterus (11). However, many women in low and middle-income countries do not seek treatment until late in the course of their disease, when these treatments may not be effective. Additionally, some treatments are not widely available or affordable. Palliative care, including pain management, is crucial for women in late stages of cervical cancer. WHO recommends that cancer programmes should ensure access to opioid, non-opioid and adjuvant analgesics, particularly oral morphine. However, widespread knowledge of palliative care options, and affordable access to palliative care is limited in many low and middle-income countries (3). In settings where early diagnosis, treatment and palliative care for cervical cancer and other HPV-related cancers are not widely available, many women in the prime of their lives will suffer prolonged, severe pain; debilitating, embarrassing or offensive symptoms such as bleeding, odorous discharge and abdominal masses; and social isolation from family and friends (3).

### 2.3 Prevention and management of other HPV-related cancers

WHO has not issued guidelines on prevention, early detection or treatment of vulvar, vaginal, anal, penile or oropharyngeal precancers related to HPV infection. Reducing the number of sex partners, avoiding partners with multiple partners and using condoms are actions that reduce the risk of HPV exposure of the anogenital organs and oropharynx. Screening for HPV-related cancers of the vagina, vulva, penis, anus and oropharynx is not conducted as part of public health programmes, although those at high risk may be selectively screened using cytology specimens from these sites. Treatments for these cancers include surgery, radiation and chemotherapy (11); these therapies tend to be complex, expensive and debilitating, and are not widely available in low-resource settings (21-24).

### 2.4 Prevention and management of anogenital warts

WHO recommends that primary prevention of cervical cancer should include education, awareness raising and other locally appropriate strategies to reduce high-risk sexual behaviours and promote condom use (Table 2.1) (3). There are no screening tests for anogenital warts. Rather, external warts are diagnosed on careful physical examination—vaginal and cervical warts can be visualized on a pelvic examination with a speculum; internal anal warts can be detected on anoscopy.

People with genital warts who find the warts painful, obstructive, unsightly, disfiguring, embarrassing or shameful generally seek treatment (25). Depending on the anatomic site of the wart and the treatment methods available, WHO recommends treatment with patient-applied podophyllintoxin or imiquimod, provider-administered podophyllin or trichloracetic acid, and removal by cryotherapy, electrosurgery or surgery (Table 2.1) (4). Cervical warts should be managed in conjunction with a provider who can evaluate the patient for cervical dysplasia. Some warts regress spontaneously over several months, but
warts commonly recur despite treatment, and they may require multiple treatments over a lifetime. Large or extensive warts may obstruct the vagina, urethra or anus, and may cause obstructive pregnancy complications; they may also require inpatient treatment. Prompt treatment may reduce the risk of these problems. Although trained staff, equipment, or medications to treat warts are commonly available in industrialized countries, treatment can be burdensome to providers, patients and health systems, and can divert resources from other health interventions (25). In many low and middle-income countries, there is only limited access to trained staff, medication and equipment for treatment of warts.

2.5 Prevention and management of recurrent respiratory papillomatosis

Papillomas of the respiratory tract are benign and rarely fatal. Papillomas often recur (see Section 1). They may spread into the trachea and bronchi, where they may obstruct the airway; occasionally the papillomas become malignant (25). Papillomas may be diagnosed on oropharyngeal examination with confirmation by biopsy, but there is no routine screening test. Surgery is the main therapy for RRP in industrialized countries (11). However, access to surgeons trained in treatment of RRP is limited in many low and middle income countries. Several adjuvant nonsurgical therapies are being evaluated (26). WHO has not issued guidance on prevention, control or treatment of RRP.

References


3 Human papillomavirus vaccines

This section looks in detail at the two types of human papillomavirus (HPV) vaccines, focusing on their composition, mechanism of action, immunogenicity, clinical efficacy, duration of protection and safety. Data on these issues that became available in 2008 are given in Annex 2.

3.1 Characteristics of the two currently licensed HPV vaccines

3.1.1 Composition of vaccines

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>The two currently licensed prophylactic HPV vaccines (bivalent and quadrivalent) are both produced by recombinant technology.</td>
</tr>
<tr>
<td>Purified L1 protein self-assembles to form empty shells or virus-like particles (VLPs) that resemble a virus.</td>
</tr>
<tr>
<td>VLPs do not contain viral genetic material or live biological product, and are therefore not infectious.</td>
</tr>
<tr>
<td>The quadrivalent vaccine contains VLPs for HPV types 6, 11, 16 and 18.</td>
</tr>
<tr>
<td>The quadrivalent vaccine is produced using yeast substrate; amorphous aluminium hydroxyphosphate sulphate is used as the adjuvant.</td>
</tr>
<tr>
<td>The bivalent vaccine contains VLPs for HPV types 16 and 18.</td>
</tr>
<tr>
<td>The bivalent vaccine is produced using a novel baculovirus expression system in Trichoplusia ni cells; AS04 containing monophosphoryl lipid A (MPL) and aluminium is used as the adjuvant.</td>
</tr>
</tbody>
</table>

Currently, two HPV vaccines are licensed and marketed:

- one manufactured by Merck & Co. (known by the brand names Gardasil® or Silgard®), first licensed in 2006 and here referred to as the “quadrivalent vaccine”
- one manufactured by GlaxoSmithKline (known as Cervarix®), first licensed in 2007 and here referred to as the “bivalent vaccine”.

By March 2008, both vaccines were licensed in several countries for use in girls and women. Gardasil® is also licensed for boys in some countries (see Section 6).

Both vaccines are prepared from VLPs produced by recombinant technology (1,2). Purified L1 protein self-assembles to form empty shells that resemble HPV VLPs; these do not contain viral genetic material or live biological product, so they cannot multiply and are not infectious (Table 3.1) (1-3). Both vaccines are designed to be prophylactic (i.e. to prevent infection and consequent disease) rather than to alter the course of existing HPV infection.
Table 3.1  Quadrivalent and bivalent HPV vaccine characteristics

<table>
<thead>
<tr>
<th>Quadrivalent vaccine (licensed in many countries)</th>
<th>Bivalent vaccine (in advanced clinical testing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer and trade name</td>
<td>GlaxoSmithKline; Cervarix®</td>
</tr>
<tr>
<td>Virus-like particles of genotypes</td>
<td></td>
</tr>
<tr>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Substrate</td>
<td></td>
</tr>
<tr>
<td>Saccharomyces cerevisiae (baker’s yeast)</td>
<td>Baculovirus expression system</td>
</tr>
<tr>
<td>Adjuvant</td>
<td></td>
</tr>
<tr>
<td>Proprietary aluminium hydroxyphosphate sulfate (225 µg) (Merck aluminium adjuvant)</td>
<td>Proprietary aluminium hydroxide (500 µg) plus 50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)</td>
</tr>
<tr>
<td>Schedule: 3 doses at intervals of 2 months between doses 1 and 2; 6 months between doses 1 and 3</td>
<td>1 month between doses 1 and 2; 6 months between doses 1 and 3</td>
</tr>
</tbody>
</table>

GSK = GlaxoSmithKline
Source: WHO (2007) (3)

The quadrivalent vaccine contains four VLPs – two related to HPV 16 and 18, which are oncogenic, and two for HPV 6 and 11, which are not oncogenic but cause anogenital warts (4). These four HPV types – HPV 6, 11, 16 and 18 – are referred to as “vaccine-related types”.

The quadrivalent vaccine is produced using the common vaccine expression system of a yeast substrate. It includes a proprietary adjuvant containing amorphous aluminium hydroxyphosphate sulphate (AAHS), which is used in many licensed vaccines (5). Each 0.5 mL dose of the quadrivalent vaccine contains 20 µg of HPV 6 L1 protein (a structural protein of HPV), 40 µg of HPV 11 L1 protein, 40 µg of HPV 16 L1 protein and 20 µg of HPV 18 L1 protein adsorbed onto 225 µg of AAHS. The formulation also includes sodium chloride, L-histidine, polysorbate 80, sodium borate and water, but no thimerosal or antibiotics (4).

The bivalent vaccine contains two VLPs – one related to HPV 16 and one related to HPV 18. It is produced using a novel baculovirus expression system in Trichoplusia ni cells. Each 0.5 mL dose of the bivalent vaccine contains 20 µg of HPV 16 L1 protein and 20 µg of HPV 18 L1 protein adsorbed onto a proprietary AS04 adjuvant system containing 500 µg of aluminium hydroxide and 50 µg of 3-O-desacyl-4′-monophosphoryl lipid A (MPL). AS04 has been used as the adjuvant in Fendrix®, a licensed hepatitis B surface antigen (HBsAg) vaccine, which is used under limited distribution for dialysis patients; it has also been used in a genital herpes simplex virus (HSV) vaccine that is under clinical development (6). Each dose also contains 4.4 mg of sodium chloride, 624 µg of sodium phosphate-monobasic (NaH₂PO₄·2H₂O) and water. The vaccine contains no thimerosal, antibiotics or other preservatives (7).

### 3.1.2 Mechanism of action and immunogenicity

#### General considerations

Data on the immunogenicity, efficacy and safety of HPV VLP vaccines have been derived from studies of a monovalent investigational HPV 16 vaccine (the HPV 16
component of the licensed quadrivalent HPV vaccine) and the licensed quadrivalent vaccine, both of which are manufactured by Merck, and the licensed bivalent vaccine manufactured by GlaxoSmithKline (GSK).

For the quadrivalent vaccine, immunogenicity studies compared vaccinated individuals to those receiving either saline or a placebo containing AAHS (because the type of adjuvant influences the level of immune response). The AAHS-containing placebo included the same dose of AAHS used in the vaccine and the same carrier, but no VLPs (8). The studies included placebo with and without adjuvant, because the type of adjuvant used influences the level of antibody produced by the vaccine and potential immune memory (9).

For the bivalent vaccine, phase II and III trials compared vaccinated females to females receiving either a placebo containing 0.5 mg of aluminium hydroxide (10,11) or a hepatitis A vaccine containing 360 or 720 enzyme-linked immunosorbent assay (ELISA) units of inactivated hepatitis A antigen and 250 or 500 μg of aluminium hydroxide (6,12). In clinical trials, the vaccine containing AS04 produced a stronger immune response targeted to functional neutralising L1 VLP 16 and 18 epitopes that persisted for at least 5.5 years compared to a vaccine in which the same antigens were adjuvanted with the GSK aluminium hydroxide alone (6,13). (See Annex 2 for updated information on this issue.)

The clinical benefits of various antigen–adjuvant combinations are difficult to estimate because the level of immune response required to prevent infection is not known for either vaccine, and studies have used different methods to measure the immunogenicity of the two vaccines.

**Mechanism of action**

**Key points**
- Neutralizing serum immunoglobulin G (IgG) invoked through VLP-based HPV vaccination may be important for protection in humans.
- Neutralizing serum IgG may transudate from capillaries to basal stem cells in the genital epithelial mucosa and bind to viral particles.
- A serologic correlate of protection has not been identified, and the minimum antibody level required for clinical protection is unknown. Therefore, many national regulatory authorities have not accepted immunogenicity comparisons to infer overall efficacy or duration of protection, except in populations in which efficacy studies are not feasible (e.g. young girls and boys).

The mechanism by which HPV vaccines protect against HPV infection and disease has not been fully defined. Animal studies with analogous animal papillomaviruses (rather than HPV) suggest that L1 VLP vaccine efficacy is mediated by humoral and cell-mediated immunity (4,6,14). In studies on dogs, cows and rabbits, immunization with L1 VLPs induced high serum titres of type-specific neutralizing antibodies, which prevented infection after challenge with large amounts of the relevant animal papillomavirus type (15). In humans, the primary mechanism of action of VLP-based vaccines is thought to be transudation of serum neutralizing anti-HPV IgG antibodies from nearby capillaries to the basal stem cells of epithelial mucosa (the obligate target for HPV infection) in sufficiently high concentrations to bind to virus particles (3,14). Protection may also be mediated by exudation of serum IgG onto genital mucosal surfaces after the formation of microabrasions, which induce innate inflammatory responses that facilitate migration of
immune cells to the site of inflammation (16,17). Transudating serum immunoglobulin A (IgA) and neutralizing secretory IgA produced in genital mucosa may also play a role in mucosal immunity.

Many viral vaccines, such as those against hepatitis B, measles and rubella, protect against infections that have a bloodstream phase. Antibody response to natural infection with these viruses is vigorous and sustained, and is a good marker of infection. HPV infection, on the other hand, is a purely mucosal infection without a known bloodstream phase. Only about half of women who are naturally infected with HPV develop detectable serum antibodies, and the antibody response does not necessarily protect against subsequent infection (18-20).

In HPV vaccine trials to date, cases of clinical endpoints in vaccinees have been rare, and have mostly been found in females with antibody levels similar to those in the rest of the vaccinated population. It is not clear whether, to understand vaccine protection, it is valid to compare the immune response induced by vaccine to that induced by natural infection. Thus, a serologic correlate of immunity has not been identified, and the minimum antibody level required for protection by vaccines is not known (3). Immunologic correlates of vaccine protection may be determined during additional follow-up of vaccinated cohorts and through research on the role of cervicovaginal antibodies in mucosal immunity against oncogenic HPV types. In the absence of a serological correlate of protection, some regulatory authorities, including the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMEA), have not accepted comparisons of immunogenicity to infer clinical protection for either vaccine, except in children, where clinical efficacy studies are not feasible. In contrast, other authorities (e.g. in Australia, Mexico and the Philippines) have accepted results of immunobridging studies1 to infer overall efficacy or duration of protection (21).

The lack of a standardized assay to measure HPV antibody titres has hindered both epidemiological studies of HPV infection and comparison of results from different HPV vaccine trials (22). The absolute values of specific serum titres cannot be compared for different HPV types because of differences in values of reference sera and antibody assays. WHO is coordinating work to develop standard assays that will help in monitoring vaccine quality and impact after marketing (23). An immunogenicity comparison of anti-HPV titres induced by the bivalent and quadrivalent vaccines is ongoing (24). The comparison is using a pseudovirion-based neutralization assay unrelated to methods used to produce HPV vaccines made with yeast or insect cells (25). However, interpretation of results is difficult because of a lack of consensus about the correlation between antibodies induced by the different antigens in the two vaccines, and the best immunologic assay for comparative studies (24).

Most studies of the quadrivalent vaccine measured serum IgG antibody to the HPV L1 using a validated competitive Luminex-based immunoassay, which measures one neutralizing epitope for each HPV type (26,27). Although the units for this assay are internally consistent, the geometric mean antibody titres for each type cannot be directly compared (8). Studies of the bivalent vaccine measure serum antibodies to HPV 16 and HPV 18 L1 VLPs using a validated L1 VLP-based ELISA that measures total antibody response (i.e. antibodies binding to conformational epitopes of a type-specific VLP) (10). Recombinant HPV 16 or HPV 18 VLPs were used as coating antigens for antibody

1 An immunobridging study is one that compares the immune response in a group for which data on vaccine efficacy on disease endpoints are not available to the immune response in another group for which such data are available.
detection (11). Additionally, HPV 16 and 18 pseudovirion-based neutralization assays were used to measure functional antibody (10,25,28).

Data are available on immune response up to 60 months after vaccination for the quadrivalent vaccine (Figure 3.1) (29-31), and up to 64 months after the first dose of the bivalent vaccine (10,32) (Figure 3.2). Longer term immunogenicity studies of both vaccines are also under way (see Section 5). The immunogenicity of HPV vaccines when co-administered with other vaccines is addressed in Section 3.2.2 below.

![Figure 3.1](image)

**Figure 3.1** Immune response to three dose primary series and fourth dose of quadrivalent vaccine: Anti-HPV 16 geometric mean titres up to 60 months

Source: Olsson et al (2007) (45)

**Immunogenicity and duration of antibody in persons naive to HPV vaccine-related types**

**Quadrivalent vaccine**

**Key points**

- Phase II and III clinical trials have assessed immunogenicity among females aged 9–26 years and males 9–15 years.
- Almost all vaccinees have an antibody response to relevant vaccine-related HPV types after three doses at month 7.
- Girls and boys aged 9–15 years have higher, statistically non-inferior immune responses than 16–26 year old females.
- Adolescent boys have higher, statistically non-inferior immune responses than adolescent girls.
- Data available up to 60 months after vaccination shows that antibody titres peak after the third dose, gradually decline, and then level off by 24 months after the first dose.
A lower proportion of women have sustained detectable antibodies to HPV 18 than to other vaccine-related HPV types; however, this is not associated with lower efficacy against clinical endpoints.

Intramuscular administration of a fourth challenge dose has resulted in a heightened immune response suggestive of an anamnestic response.

It is unclear whether vaccinated persons experience an anamnestic response after natural mucosal HPV exposure or infection.

Hormonal contraceptive use and smoking have not been shown to modify the immune response to vaccination.

Studies of immunogenicity in HIV-infected persons are under way.

Data on immunogenicity of the quadrivalent vaccine are available from phase II (29,30) and phase III double-blind, randomized, placebo-controlled trials of females aged 15–26 years (33,34), and from immunogenicity studies of females and males aged 9–15 years (Table 3.2) (35,36). (See Annex 2 for updated information on this issue in mid-adult women)

Table 3.2. Quadrivalent and bivalent HPV vaccine immunogenicity and efficacy studiesa

<table>
<thead>
<tr>
<th>Study, vaccine and reference</th>
<th>Protocol number and age range (years)</th>
<th>Study location</th>
<th>Gender</th>
<th>Study endpoints</th>
<th>Population type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase II monovalent HPV 16 vaccine (37)</td>
<td>005 16–23</td>
<td>United States, Europe, Brazil</td>
<td>F</td>
<td>Persistent HPV 16 infection</td>
<td>Women naive to HPV 16 infection</td>
</tr>
<tr>
<td>Phase II monovalent HPV 16 vaccine (38)</td>
<td>16–23</td>
<td>United States</td>
<td>F</td>
<td>CIN2/3 associated with HPV 16</td>
<td>Per-protocol; modified intent to treat</td>
</tr>
<tr>
<td>Phase II quadrivalent vaccine (29)</td>
<td>007 16–23</td>
<td>United States, Europe, Brazil</td>
<td>F</td>
<td>Immunogenicity, seroconversion to HPV 6/11/16/18 after dose 3</td>
<td>Per-protocol</td>
</tr>
<tr>
<td>Phase II quadrivalent vaccine (39)</td>
<td>007 16–23</td>
<td>United States, Europe, Brazil</td>
<td>F</td>
<td>Persistent HPV 6/11/16/18 infections, external genital lesions, cervical disease</td>
<td>Per-protocol</td>
</tr>
<tr>
<td>Phase III quadrivalent vaccine (Future I) (33)</td>
<td>013 16–24</td>
<td>North and South America, Europe, Asia–Pacific region</td>
<td>F</td>
<td>CIN (any grade) or AIS, genital warts, vaginal or vulvar precancerous lesions or cancer associated with HPV 6/11/16/18</td>
<td>Per-protocol; unrestricted susceptible; intent-to-treat populations</td>
</tr>
<tr>
<td>Study, vaccine and reference</td>
<td>Protocol number and age range (years)</td>
<td>Study location</td>
<td>Gender</td>
<td>Study endpoints</td>
<td>Population type</td>
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</tr>
<tr>
<td>Phase III quadrivalent vaccine (Future I) (40)</td>
<td>013 16–26</td>
<td>North and South America, Europe, Asia–Pacific region</td>
<td>F</td>
<td>VIN2/3, ValN2/3 associated with HPV 16/18 VIN (any grade) associated with HPV 6/11/16/18</td>
<td>Per-protocol; unrestricted susceptible; intent-to-treat populations</td>
</tr>
<tr>
<td>Phase III quadrivalent vaccine (Future II) (34,41)</td>
<td>015 16–26</td>
<td>North and South America, Europe, Asia–Pacific region</td>
<td>F</td>
<td>CIN2+ or AIS</td>
<td>Per-protocol; unrestricted susceptible; intent-to-treat populations</td>
</tr>
<tr>
<td>Phase III quadrivalent vaccine (Future II) (42)</td>
<td>013 and 015 15–26</td>
<td>North and South America, Australia, Europe, Asia–Pacific region</td>
<td>F</td>
<td>CIN2+ or AIS, vaginal or vulvar precancer or cancer associated with HPV 6/11/16/18</td>
<td>Included women who were HPV seropositive or DNA positive for vaccine-related HPV types but endpoint analyses examined females naive to relevant HPV type</td>
</tr>
<tr>
<td>Phase III quadrivalent vaccine (43)</td>
<td>24–45</td>
<td>North and South America, Europe, Asia–Pacific region</td>
<td>F</td>
<td>Persistent HPV 6/11/16/18 infections, external genital disease, cervical disease</td>
<td>No history of cervical disease in past 5 years, no history of LEEP, genital warts or hysterectomy</td>
</tr>
<tr>
<td>Quadrivalent vaccine immune-bridging study (36)</td>
<td>9–15</td>
<td>North and South America, Australia, Europe, Asia–Pacific region</td>
<td>F, M</td>
<td>HPV type-specific antibody</td>
<td>Per-protocol; unrestricted susceptible; intent-to-treat populations</td>
</tr>
<tr>
<td>Quadrivalent vaccine immune-bridging study (35)</td>
<td>10–23</td>
<td>North and South America, Australia, Europe, Asia–Pacific region</td>
<td>F, M</td>
<td>Immunogenicity, seroconversion to HPV 6/11/16/18 after dose 3</td>
<td>Immune-bridging study of 10–15 year old girls and boys</td>
</tr>
<tr>
<td>Quadrivalent vaccine co-administration study (44)</td>
<td>013 16–23</td>
<td>North and South America, Europe</td>
<td>F</td>
<td>Immunogenicity to HPV 6/11/16/18</td>
<td>Healthy women with no past abnormal cytology, ≤4 lifetime partners, no prior Hepatitis B infection</td>
</tr>
<tr>
<td>Quadrivalent vaccine extended follow-up study (30)</td>
<td>16–23</td>
<td>United States, Brazil, Finland, Sweden, Norway</td>
<td>F</td>
<td>Immunogenicity, persistent HPV 6/11/16/18 infection, genital warts and CIN</td>
<td></td>
</tr>
<tr>
<td>Study, vaccine and reference</td>
<td>Protocol number and age range (years)</td>
<td>Study location</td>
<td>Gender</td>
<td>Study endpoints</td>
<td>Population type</td>
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<tr>
<td>Quadrivalent vaccine immune memory study (45)</td>
<td>007 16–23</td>
<td>United States, Europe, Brazil</td>
<td>F</td>
<td>Immunogenicity to HPV 6/11/16/18 after dose 3 and 4</td>
<td>Seronegative to relevant HPV type at baseline, DNA negative at baseline through month 60</td>
</tr>
<tr>
<td>Phase II bivalent vaccine (11)</td>
<td>001 15–25</td>
<td>North America, Brazil</td>
<td>F</td>
<td>Persistent HPV 16/18 infection, abnormal cytology, CIN1–2+</td>
<td>Per-protocol; intent-to-treat populations</td>
</tr>
<tr>
<td>Phase II bivalent vaccine (13)</td>
<td>004/005 18–30</td>
<td>United States</td>
<td>F</td>
<td>Immunogenicity to HPV 16/18, vaccine formulations adjuvanted with AS04 or aluminium alone up to 3.5 years after vaccination</td>
<td>Initially seronegative an HPV-negative for HPV-16/18 known to have cytology</td>
</tr>
<tr>
<td>Phase II bivalent vaccine extended follow-up study (10), (28), (46)</td>
<td>001/007 15–25</td>
<td>North America, Brazil</td>
<td>F</td>
<td>Immunogenicity, persistent HPV 16/18 infections, cytological abnormalities, CIN1+, 2+</td>
<td>Per-protocol; intent-to-treat populations</td>
</tr>
<tr>
<td>Phase III bivalent vaccine (47)</td>
<td>001/007 18–25</td>
<td>Costa Rica</td>
<td>F</td>
<td>Rate of HPV 16/18 viral clearance among women after dose 3</td>
<td>HPV DNA positive at baseline</td>
</tr>
<tr>
<td>Phase III bivalent vaccine (PATRiciA) (12)</td>
<td>008 15–25</td>
<td>Asia–Pacific region, Europe, and North and South America</td>
<td>F</td>
<td>Persistent HPV 16/18 infections, cytological abnormalities, CIN1+, 2+. Future analyses to include CIN3 and AIS</td>
<td>Total vaccinated cohort; modified intent-to-treat populations</td>
</tr>
<tr>
<td>Bivalent vaccine immune-bridging study (48)</td>
<td>012 10–25</td>
<td>Europe</td>
<td>F</td>
<td>Immunogenicity, seroconversion to HPV 16/18 after dose 3</td>
<td>Immune-bridging study for adolescent girls age 10–14 years</td>
</tr>
<tr>
<td>Bivalent vaccine immune-bridging study (49)</td>
<td>014 15–55</td>
<td>Europe</td>
<td>F</td>
<td>Immunogenicity, seroconversion to HPV 16/18 after dose 3</td>
<td>Immune-bridging study for women 26–55</td>
</tr>
</tbody>
</table>
AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; DNA = deoxyribonucleic acid; F = females; HPV = human papillomavirus; LEEP = loop electrosurgical excision procedure; M = males; VaIN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia

a For information on sample sizes for various analytic populations, ad-hoc analyses and combined trial analyses consult individual publications.

In all studies to date, more than 99% of vaccinees had an antibody response to the relevant vaccine-related HPV type after the 3-dose series (29,30,33-36). In the unrestricted susceptible population (who were naive to vaccine-related HPV types at baseline but may have not have received all three doses), 5 of 6 vaccinees who developed a genital lesion associated with a vaccine-related HPV type had type-specific antibody titres that were similar to those of the per-protocol susceptible population. This finding suggests that the lesions seen in the vaccinees were due to infection acquired before receipt of the full vaccine series (33).

It is not feasible to study endpoints of precancerous cervical lesions (CIN2/3 or AIS) or cancer in children or young adolescents, because of sociocultural constraints around genital sampling at this age and the long trial duration needed to observe clinical endpoints. Bridging immunogenicity studies have therefore been conducted to determine whether antibody responses of females aged 9–15 years are comparable to those of females aged 16–26 years, for whom clinical endpoint data are available (35). Among boys and girls aged 9–15 years, anti-HPV geometric mean titres (GMTs) one month after dose 3 were not inferior to those of 16–26-year-old females. At month 18, anti-HPV GMTs in females aged 9–15 years was 2–3 times greater than GMTs at month 18 for those aged 16–26 years enrolled in the efficacy trials (8). Additionally, GMT response is greater in younger than in older females, greater in adolescent males than in adolescent females, and greater in study participants from North America than in participants from other regions (50).

Modelling data based on 48 months of follow-up after HPV 16 vaccination suggests that serum levels of anti-HPV 16 will remain detectable for more than 30 years for most vaccinees (51). However, up to the end of 2007, the longest published clinical follow-up data for Gardasil® reported immunogenicity up to 60 months after vaccination among participants in a phase II trial (30). Antibody titres peaked after the third dose, then gradually declined and levelled off by 24 months after dose 1 (Figure 3.1). At 36 months after vaccination, the anti-HPV 16 GMTs of vaccinees were higher than those of placebo recipients who were seropositive to HPV 16 at baseline (29). At the same time point, the anti-HPV 6, 11, and 18 GMTs of vaccinees were similar to those of placebo recipients who were seropositive to HPV 6, 11 or 18 at baseline (29).

These phase II findings are consistent with an analysis of 1512 vaccinees enrolled in immunogenicity substudies of two phase III trials (33,34). At month 24, more than 95% of participants were seropositive for HPV 6, 11 and 16. Lower proportions were seropositive for HPV 18 (68% in Protocol 015 and 74% in Protocol 013). The proportion of women with sustained antibodies to HPV 18 was lower than the proportion of women with sustained antibodies to other vaccine-related HPV types. However, the efficacy for preventing HPV 18-related CIN2/3 or AIS was 100% in the larger trial populations from which these subsets were drawn. In addition, none of the vaccinees who were nominally seronegative at month 24 developed HPV 18-related CIN at that time point or up to 1 year later. These findings highlight the difficulty in correlating anti-HPV levels with vaccine efficacy against clinical endpoints that take months or even years to develop.
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 narrow (1–3 months between doses 1 and 2, and 4–8 months between doses 1 and 3) (30).

Immune memory that is induced after re-exposure to a pathogen is a hallmark of long-term protective efficacy. In an extension of a phase II study (Protocol 007), subjects in the per protocol analysis (seronegative for relevant HPV type at baseline and DNA-negative at day 1 through month 60) who received three vaccine doses and an intramuscular challenge dose of vaccine 4.5 years after dose 3, exhibited a rapid and strong anamnestic response 1 week and 1 month post-challenge (Figure 3.1). In most vaccinees, this response exceeded the anti-HPV GMTs observed at month 60, and they often exceeded the levels observed 1 month after dose 3 (month 7) (45). Anamnestic responses like this are often associated with vaccines that confer long-lasting protection. However, it remains unknown whether immune response after vaccine challenge predicts an anamnestic response after natural, sexual HPV exposure in the genital tract. Such exposure is low level, localized and usually repeated; it may be more efficient at inducing local mucosal immunity than a serologic immune response.

A combined analysis of three phase II and III studies included females aged 9–26 years and males aged 9–15 years in the per-protocol population (i.e. those who received three doses of vaccine, were seronegative for vaccine-related types at baseline, were DNA-negative from enrolment to month 7, and did not have protocol violations). The analysis found that hormonal contraceptive use and smoking were not significantly associated with variations in GMT response for any of the four vaccine-related types. However, race or ethnicity and age were significant predictors of anti-HPV 16 titres; also, titres to both anti-HPV 11 and 18 decreased with increases in body mass index and age (50). Studies of the immunogenicity of the vaccines in HIV-infected individuals are under way (See Section 5).

**Bivalent vaccine**

**Key points**

- Immunogenicity has been assessed in phase II and III clinical trials for females aged 10–55 years.
- Almost all vaccinees developed an antibody response to the relevant vaccine-related HPV type following three doses at month 7, including women aged 26–55 years.
- Among vaccinees aged 15–25 years, virtually all had a strong immune response to vaccine-related HPV types after dose 2 at month 2, but the peak anti-HPV 16/18 and HPV 16/18 neutralizing antibody response occurred after dose 3.
- A heightened immune response has been reported for girls aged 10–14 years compared with females aged 15–25 years.
- Data up to 64 months after vaccination show that, after the third dose, antibody titres decline and then remain stable for 18–24 months thereafter.
- Higher antibody response has been observed for vaccine antigens adjuvanted with AS04 as compared with the same antigens adjuvanted with the GSK aluminium hydroxide adjuvant.

Immunogenicity has been evaluated in phase II and III trials in females aged 10–55 years (Table 3.2, Figure 3.2). Sera were collected at months 0, 7 and 12, and at approximately yearly intervals thereafter; in some studies, sera were also collected after dose 2 (11,52). Interim phase III trial data for a subset of about 2000 females who had antibodies...
measured at 0, 6, 7 and 12 months after baseline found that more than 99.5% of females who were initially seronegative to the corresponding vaccine type and who received all three doses seroconverted to HPV 16 and 18 (12). Peak immune responses for both anti-HPV 16 and anti-HPV 18 were observed after dose 3 (month 7), but serum antibodies were induced as early as after dose 2 (12) (Figure 3.2). Antibody response has also been robust in females both younger and older than the core clinical trial population (aged 15–25). A European study found that, after three doses, girls aged 10–14 years had higher HPV 16 and 18 antibody titres than females aged 15–25 years (48). (See Annex 2 for updated information on this issue.)

Long-term follow-up of phase II trials has shown that antibody levels remain stable for at least 5.5 years in women with no previous HPV exposure (32,46,53). (See Annex 2 for updated information on this issue.) More than 98% of the females remained seropositive for HPV 16 and 18 at each measured time point up to month 64. Similar kinetic profiles were observed for total IgG and neutralizing antibodies in this extended follow-up cohort (28). Mathematical models of antibody kinetics predicted sustained antibody levels for both HPV 16 and 18 (54) for more than 20 years after vaccination. In addition, analysis of approximately 500 healthy women aged 15–55 years who received three vaccine doses and were part of the per-protocol analysis (seronegative for relevant HPV types at baseline) showed that 100% of females remained seropositive 24 months post vaccination. Although GMTs decreased with older age, GMTs in older women were comparable to those found during the plateau phase of the extended follow-up studies (5.5 years) of females vaccinated at age 15–24 (i.e. titres that were associated with clinical protection) (6,49). (See Annex 2 for updated information on this issue.)

Phase II trial results are available for women aged 18–30 years, based on a pseudovirion-based neutralization assay that evaluates functional antibody levels. The results showed that the vaccine formulated with AS04 induced significantly higher antibody responses over 3.5 years compared to the same antigen combined with the GSK aluminium hydroxide adjuvant (13). The immune response measured with the binding ELISA correlates well with the immune response measured using the pseudovirion-based neutralizing assay. Among females who were seronegative and DNA negative for 14 oncogenic HPV types at baseline, the kinetic profiles of total IgG and neutralizing antibodies were similar, with peak response occurring one month after dose 3 and a high, sustained response up to month 64 (28).

Data on serum immune response after a fourth challenge dose are not yet available (see Section 5).

Because HPV exposure occurs at anogenital sites, cervical immunity was evaluated in a subset of 305 women aged 15–55 years enrolled in a phase III study. Up to 24 months after the first vaccine dose, HPV 16 and 18 antibodies measured in cervicovaginal secretions were strongly correlated with serum antibody levels for both HPV 16 and 18 among females of all ages. This is notable if the hypothesis that immunity at the cervix contributes to vaccine efficacy proves true (55).

Annex 2 provides updated information on immunogenicity in males.
Figure 3.2  Immune response to 3-dose primary series of bivalent vaccine: HPV 16 and 18 antibody levels up to 5.5 years

Source: Gall (2007) (46)

Immunogenicity in females with past or current HPV infection at time of vaccination

Key points

- For both bivalent and quadrivalent vaccines, vaccination of females who were seropositive for vaccine-related HPV types before vaccination has induced higher antibody titres than vaccination of females who were seronegative for vaccine-related HPV types before vaccination.
- This situation suggests a boosting of naturally acquired antibody through vaccination.
To assess vaccine immunogenicity and efficacy in females with past or current infection, trials of both vaccines enrolled women regardless of HPV infection status. Seropositive subjects were classified as having evidence of past infection and HPV DNA positive subjects were classified as having acute or chronic infection.

**Quadrivalent vaccine**

In several quadrivalent vaccine trials (Table 3.2), more than 20% of females had evidence of prior exposure to, or ongoing infection with, one or more of the four vaccine-related HPV types. Vaccinated females with evidence of past infection with vaccine-related HPV types at enrolment (positive serology test) had higher titres to the HPV type to which they were seropositive at enrolment than vaccinated females who were seronegative at enrolment, especially after the first dose (29,30). This indicates that vaccination can boost the antibody response initially induced by natural infection (3).

**Bivalent vaccine**

In an interim analysis of a phase III trial (Table 3.2), women initially seropositive for HPV 16 and 18 at baseline had a robust immune response after dose 2 that peaked at month 7, with continued high antibody levels at month 12 (12). These antibody kinetics were similar to those of women who were seronegative for HPV 16 and 18 at baseline and who received three doses of vaccine, again suggesting that vaccine boosts naturally acquired antibody.

**Immune response to oncogenic, genetically related, non-vaccine-related HPV types**

**Key points**

- It has been hypothesized that HPV vaccine may provide cross-protection against non-vaccine-related HPV types, through induction of neutralizing antibodies, which cross-react because of homology between VLPs and common cross-neutralizing epitopes.
- Trials have evaluated the vaccine-induced immune response to several oncogenic HPV types that are genetically related to HPV 16 and 18; types tested include HPV 31, 33, 45, 52 and 58.
- Initial analyses suggest that quadrivalent vaccine can induce neutralizing antibodies against HPV 31 and 45 in vitro, and may be capable of neutralizing these genetically related HPV types.
- Vaccination with the bivalent vaccine has resulted in seropositivity of more than 80% for HPV 31 and 45 within 50 months after the first dose.

**Quadrivalent vaccine**

An in vitro study of sera from a small subset of vaccinated females found that all sera neutralized HPV 18 pseudovirions, and more than half neutralized HPV 31 and 45 pseudovirions. Vaccination induced both HPV 45 cross-neutralizing antibody (based on the pseudovirion assay) and high titres of cross-reactive HPV 45 VLP binding in vitro. The investigators concluded that, in vitro, this vaccine induces an antibody response capable of neutralizing infections with HPV 45, which is closely related to HPV 18, possibly because of common conformational, neutralizing epitopes on VLP surfaces (56,57). Another study detected serum antibodies to HPV 31, 33, 45, 52 and 58 in vaccines (56).

**Bivalent vaccine**

Among a subset of vaccinated females enrolled in a phase II study, 100% were seropositive for both HPV 31 and 45 antibodies at month 7 (post dose 3) as detected by
Seropositivity for both types remained high at 45–50 months after dose 1 (84% for HPV 45, 88% for HPV 31). Titres peaked at month 7, gradually declined and then plateaued in a similar pattern to that seen with HPV 18. Likewise, a strong immune response was observed for HPV 31 up to 56 months after dose 1 that was similar to the immune response for HPV 16. These findings may be due to possible sharing of cross-neutralizing epitopes related to homology between HPV 18 and 45, and between HPV 16 and 31 (18).

### 3.1.3 Clinical efficacy

#### General considerations and trial design

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>Most HPV infections are transient and benign, but persistent infection is associated with development of high-grade CIN and cancer.</td>
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<tr>
<td>Regulatory and expert groups have recommended using histological outcomes of high-grade precancers (CIN2+ and AIS) and invasive cancers as clinical endpoints for phase III trials. They also recommended evaluating persistent HPV infection with a preference for endpoints of infection that persist for 12 rather than 6 months.</td>
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<tr>
<td>Some regulatory authorities have accepted immunobridging data to infer efficacy in young children and adolescents who have not yet begun sexual activity, and in females aged over 25 years.</td>
</tr>
<tr>
<td>Results of phase III efficacy trials have been generated, or are under way, for per-protocol and other less restricted populations, including intent-to-treat populations and total vaccinated cohorts.</td>
</tr>
<tr>
<td>To date, results of phase III quadrivalent vaccine trials have been published for outcomes incident and persistent infections, abnormal cytology, CIN grades 1–3, AIS, VIN, VaIN and genital warts related to HPV 6, 11, 16 or 18, in both per-protocol and intent-to-treat populations.</td>
</tr>
<tr>
<td>To date, results of phase II and interim results of phase III bivalent vaccine trials have been published on outcomes of HPV 16/18-related incident and persistent infections, abnormal cytology, CIN1 and CIN2+. Final results and data on CIN3 from per-protocol and intent-to-treat analyses of trials are expected.</td>
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The efficacy of HPV vaccines against various HPV-related clinical endpoints has been evaluated in several randomized, placebo-controlled clinical trials. The advantages and disadvantages of different endpoints have been reviewed in depth (58). Although the most important benefit of prophylactic HPV vaccines is preventing invasive cervical cancer, phase III trials using this primary endpoint are not feasible or ethical. The care standard in many settings is to screen for and treat CIN2/3 and AIS lesions, to prevent invasive cervical cancer. Moreover, the time between initial HPV infection and the development of invasive cancer can exceed 20 years. In contrast, it usually takes less than 10 years to observe endpoints of high-grade cervical lesions (e.g. CIN1, 2 or 3, or AIS). For these reasons, WHO, the FDA and other regulatory authorities recommend that the primary endpoints of phase III trials should be CIN2/3 and AIS associated with vaccine-related HPV types (58,59). These endpoints have served as the basis for vaccine licensure in many countries (3) (See Section 6). Currently, trial results for the high-grade lesions CIN2/3 and AIS are more plentiful for the quadrivalent than for the bivalent vaccine because the phase III quadrivalent vaccine trials were developed earlier.

Several studies have evaluated persistent vaccine-related HPV type infections because oncogenic viral persistence is strongly associated with the development of CIN2/3 (60-
Infections that persist for at least 12 months are thought to be more clinically relevant than less persistent infections, so continuous detection of viral DNA for at least 12 months is recommended for use in trials (58,59).

Most experts believe that coinfection with multiple HPV types may be common in incident infections, and in low-grade cervical and anogenital lesions. However, the low frequency of multiple HPV types in invasive cancer specimens suggests that most cervical cancer is due to persistent infection with a single HPV type (64). The presence of multiple HPV types in some CIN lesions, and the assumption that HPV types act independently in the causal oncogenic pathway, have prompted researchers to assess persistence of type-specific HPV infection before the CIN diagnosis, to identify a type-specific etiology. However, these ad hoc analyses are not equivalent to analyses of prespecified clinical endpoints, and they are not based on the same consensus about the best analytic approach.

Evaluation of CIN2/3 and AIS is feasible among young women; however, it is not feasible or ethical in children or young adolescents because detection requires cervical sampling. Bridging immunogenicity studies of children and young adolescents are therefore used to estimate efficacy. To establish efficacy in men and in mid adult women (those aged over 25 years), FDA and EMEA have required clinical efficacy studies, which are under way (43,52,59). Authorities in other countries, however, have accepted immunobridging data to infer efficacy among mid adult women (21).

Phase II and III trial design and analytic populations for the two vaccines have some similarities (Table 3.2). For example, trials of both vaccines have been conducted in more than one continent. Phase III trials enrolled females regardless of baseline HPV infection status or cytology results; this allowed the trials to assess vaccine safety and efficacy in a general population that included females who were infected with HPV before vaccination (3,12,41,59). The trials of the two vaccines also differed in several critical aspects – they had different placebos, immunologic assays and analytic populations (12,33,34,40,41). These differences preclude direct comparison of efficacy results for the two vaccines.

Although the trials of both vaccines were conducted in diverse populations drawn from many countries, the benefits to a given population cannot be directly extrapolated from the efficacy results of current vaccine trials. Results from trials of both vaccines indicate that the overall population benefit from vaccinating females 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 types.

For each endpoint, vaccine efficacy and confidence intervals were calculated by comparing the incidence of the endpoint in females who received the vaccine with that in females who received a placebo or control vaccine, where the incidence in vaccinated females equalled the number of cases in vaccinated females/total number of vaccinated females; the incidence in control females equalled the number of cases in control females/total number of control females; and vaccine efficacy equalled (1 – incidence in vaccinated females) / incidence in control females.

**Quadrivalent vaccine efficacy trials**

Several studies defined vaccine efficacy against persistent HPV infection, CIN, AIS, VIN, VaIN and genital warts related to HPV 6, 11, 16 or 18 (Tables 3.2–3.4). All trials evaluated outcomes using prespecified measures of HPV infection, CIN and external genital lesions. Control subjects in phase II and III trials received an AAHS-containing
placebo (33,34). Both phase III studies (Future I and II) were randomized, placebo-controlled double-blind studies. Predefined combinations of data from phase II and III trials of quadrivalent vaccine were also analyzed to increase sample size and improve the precision of point estimates. The resulting dataset included participants from 157 sites in 24 countries in Asia, Australia, Europe and North and South America (40,41). (See Annex 2 for updated information on these trials.)

Future I enrolled 5455 females aged 16–24 years in 62 sites and 16 countries. It assessed endpoints of incidence of genital warts, vulvar or vaginal intraepithelial neoplasia or cancer, and incidence of CIN, AIS or cancer associated with HPV 6/11/16/18. Eligible females were healthy, not pregnant, reported no history of genital warts or abnormal cervical cytology, had four or fewer lifetime sex partners, and agreed to use effective contraception from day 1 to month 7. Future II enrolled 12 167 females aged 15–26 years in 90 sites and 13 countries. The primary composite endpoint was CIN2 or 3, AIS or cervical cancer associated with HPV 16/18. Eligible females were not pregnant, reported no history of abnormal cervical cytology, had four or fewer lifetime sex partners and agreed to use effective contraception from day 1 to month 7.

Published phase III trial results described three different analytic populations (described below) – the per-protocol population, the unrestricted susceptible population and the intention-to-treat general study population.

The per-protocol population was used to assess vaccine efficacy in females naive to vaccine-related HPV types at baseline. It consisted of females who were seronegative and DNA negative for relevant vaccine-related HPV types at baseline, remained DNA negative for the relevant vaccine-related HPV type through one month after the third dose of vaccine or placebo (month 7), received all three doses, had no major protocol violations, and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began 30 days after dose 3.

The unrestricted susceptible population was used to assess vaccine efficacy in females naive to vaccine-related HPV types at baseline under less controlled conditions typical outside formal trials. It consisted of females who were seronegative and DNA negative for relevant vaccine-related HPV types at baseline, may have had major protocol violations (including less than three vaccine doses), and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began after day 1.

The intention-to-treat general study population was used to assess vaccine efficacy in less controlled conditions typical outside of trials. It included sexually active females who may have had past or current HPV infection with vaccine-related HPV types; may have had HPV 6,11,16, or 18 infection or cervical neoplasia before vaccination; had major protocol violations (including less than three doses); or had abnormal cervical cytology at baseline. Endpoint ascertainment began after day 1.

Protocol 019, a study of vaccine efficacy and safety in mid-adult women aged 24–45 years, is under way. It has enrolled women without a history of LEEP, hysterectomy or genital warts; and no cervical biopsy in the last 5 years; nearly all participants are sexually active (Table 3.2) (43). (See Annex 2 for updated information on this trial.)

**Bivalent vaccine efficacy trials**

A phase II trial including 1113 females aged 15–25 years in Brazil and North America evaluated outcomes of incident and persistent infections with HPV 16/18, cytological outcomes – atypical squamous cells of undetermined significance (ASC-US), low-grade
squamous intraepithelial lesion (LSIL), high-grade squamous intraepithelial lesion (HSIL) – and histologically confirmed CIN1, 2 or 3 (Table 3.2) \(^{(10,11)}\). Eligible females were seronegative for HPV 16/18, DNA negative for 14 oncogenic HPV types, reported six or fewer lifetime sexual partners, denied a history of an abnormal Pap test and ablative or excisional cervical treatment, and denied ongoing treatment for external genital warts. In contrast, females eligible for the phase III trials for both vaccines were HPV DNA negative for at least one of the vaccine-related HPV types, although females infected with other oncogenic HPV types may have been enrolled.

In the trial’s extended follow-up, 776 females have been followed for up to 5.5 years to assess efficacy against incident and persistent infections, and CIN2+ related to HPV 16/18, and incident infections with oncogenic HPV types 31, 33, 45, 52 and 58 \(^{(10,46)}\). (See Annex 2 for updated information on this trial.)

This population is considered “unexposed” to HPV so that results estimate the impact of vaccinating a population of females naive to all 14 oncogenic types, including HPV 16 and 18. It serves as the primary population for comparison with other age groups studied in immunobridging studies. The analytic populations from the initial and extension phase of the Phase II studies include the following populations:

- The per-protocol population: females who were HPV 16/18 DNA negative up to the end of month 6, received all three vaccine doses, had no major protocol violations, and had adequate follow-up data.

- The intent-to-treat population: females who were randomized and received at least one dose of either HPV vaccine or placebo.

- The intent-to-treat population for the extended follow-up of this trial used to analyze vaccine efficacy against incident infection with oncogenic HPV types other than HPV 16/18 (i.e. among females who were HPV DNA negative for the relevant type at baseline of the initial study).

A large, phase III trial in over 18 000 females aged 15–25 years (“PATRiciA”, protocol 008) is currently ongoing in the Asia–Pacific region, Central America, Europe, and North and South America (Table 3.2) \(^{(12)}\). Control subjects received an investigational formulation of licensed hepatitis A vaccine with the same vaccination schedule as the HPV vaccine. This trial is designed to evaluate the efficacy against histologically confirmed CIN2+ associated with HPV 16/18, persistent infection with HPV 16, 18 and other oncogenic HPV types (31, 33, 45, 52, 58), cytological outcomes (ASC-US, LSIL, HSIL) related to HPV 16 and 18, and any histological outcomes (Table 3.2). The trial is assessing vaccine efficacy stratified by baseline HPV 16 or 18 serostatus.

A published interim analysis of 18 644 females in this trial described a “total vaccinated cohort” defined as females who, at baseline, reported no more than 6 lifetime sexual partners and no history of colposcopy; were seronegative and DNA negative for HPV 16/18 but may have prevalent infections with other oncogenic HPV types; had normal or low-grade abnormal cytology; received at least one vaccine dose; had endpoint data available; and did not have major protocol violations. Endpoint ascertainment began the day after dose 1. Reported endpoints included CIN2+ (i.e. CIN2, CIN3, AIS and invasive carcinoma), CIN1+ (i.e. CIN1 plus CIN2+ categories), persistent infection with HPV 16 or 18 and other genetically-related, oncogenic HPV types \(^{(12)}\). Future analyses will report on vaccine efficacy against higher grade CIN and AIS in the total vaccinated cohort and in a per-protocol population.
A second phase III trial, Protocol 009, is being conducted in Costa Rica in collaboration with the United States National Cancer Institute. The study is evaluating vaccine efficacy against HPV-16/18 histopathologically-confirmed CIN2+ and other endpoints among 7000 women aged 18–25 years (Table 3.2). This trial will examine prophylactic efficacy in a per-protocol population who received three doses of HPV vaccine or control hepatitis A vaccine, were DNA negative and seronegative to at least one vaccine-related type (HPV 16 or 18) at baseline, and were not lost to follow-up.

**Efficacy in preventing persistent infection with vaccine-related HPV types**

**Efficacy in females naive to vaccine-related HPV types at baseline**

<table>
<thead>
<tr>
<th>Key points</th>
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<tr>
<td>• Phase II and III clinical trial data have demonstrated that, depending on the study protocol and the specific vaccine-related HPV type:</td>
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<tr>
<td>• Results vary by definition of HPV persistence, anatomical sampling method and site (i.e. vaginal versus cervical), study population, number of vaccine doses received and duration of follow-up.</td>
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**Quadrivalent vaccine**

The efficacy of the quadrivalent vaccine and that of an earlier monovalent HPV 16 vaccine against persistent infection was examined in phase II and III trials of females who had no evidence of exposure to or infection with the relevant vaccine-related HPV type (i.e. seronegative and HPV DNA-negative to 1 month after dose 3). Persistent infection was defined as detection of a vaccine-related HPV type by DNA testing at two or more sequential visits at least 6 months apart (with a 1 month visit window). A case of HPV detection at a single visit was included as an endpoint if it was the last visit of record. In the phase II trial, efficacy of the monovalent vaccine against persistent HPV 16 was 94% (95% confidence interval (CI) 88% to 98%) in females receiving all three doses. HPV 16 DNA was detected on the last study visit (without observed persistence) in all seven cases of people with infection who were vaccinated. In analyses defining confirmed persistence as HPV 16 DNA detection on two consecutive visits, efficacy against confirmed persistent HPV 16 infection was 100% (95% CI 96% to 100%).

In a phase II trial of the quadrivalent vaccine efficacy against persistent HPV 6, 11, 16 or 18 infection was 90% (95% CI 71% to 97%) after a mean follow-up period of 2.5 years after dose 3. Among the vaccinated females classified as having persistent infection, three had HPV 16 detected at the last visit (without observed persistence) and one had HPV 18 detected at months 12 and 18, but not at months 24, 30, or 36. Efficacy against confirmed persistent HPV 6, 11, 16 or 18 infections was 89% (95% CI 70% to 97%). In another phase II trial, Protocol 012, efficacy against confirmed persistent infection with HPV 16 or 18 was 99% (95% CI 96% to 100%) based on one case in the vaccine group (Eliav Barr, Merck, pers. comm., 2007).

**Bivalent vaccine**

Phase II trials were designed to measure efficacy against persistent infections with HPV 16 and 18 at 6 and 12 months after the first dose (see eligibility criteria above). Persistent infection was defined as detection of the same vaccine-related HPV type by
DNA testing at intervals of at least 6 months \((10,11)\). Efficacy against persistent infection with HPV 16/18 (where ‘16/18’ represents single or combined infections) was 100% (95% CI 47% to 100%) in the per-protocol population and 95% (95% CI 64% to 99%) in the intent-to-treat population \((11)\). In long-term follow-up to 5.5 years of the per-protocol population, efficacy was 100% against HPV 16/18 infections persisting for 6 months (95% CI 81% to 100%) and 12 months (95% CI 54% to 100%) \((46)\).

The interim analysis of the total vaccinated cohort in the phase III trial reported efficacy against persistent HPV 16/18 of 80% (97.9% CI 70% to 87%) at 6 months and 76% (97.9% CI 48% to 90%) at 12 months. Efficacy against persistent HPV 16 at 6 months was 84% (97.9% CI 74% to 91%), persistent HPV 18 at 6 months was 74% (97.9% CI 49% to 88%), persistent HPV 16 at 12 months was 80% (97.9% CI 48% to 94%), and persistent HPV 18 at 12 months was 66% (97.9% CI < 0% to 94%). A total of 71% of persistent infections were detected at 6 months before all three doses were administered, so efficacy estimates may be conservative \((12)\).

### Efficacy in females with infected with vaccine-related HPV types at baseline

#### Key point
- Among women infected with one or more given vaccine-related HPV types at baseline, there is no evidence that either vaccine prevents persistent infection or cervical lesions due to the vaccine-related types or promotes their clearance (i.e. no evidence that vaccines have a therapeutic benefit).

#### Quadrivalent vaccine
There are no published data on outcomes of persistent infection or clearance of vaccine-related HPV types detected at baseline. However, there are data showing that the quadrivalent vaccine was not efficacious against several clinical endpoints among females who were HPV DNA positive for the relevant HPV type at baseline (see section below on efficacy in preventing cervical disease associated with a given HPV type in females with current or past infection with that same HPV type) \((33)\).

#### Bivalent vaccine
Among females aged 18–25 years in the phase III trial in Costa Rica who were HPV DNA-positive at baseline and received at least two doses of vaccine, there was no evidence that the vaccine induced clearance of HPV 16, 18 or several other oncogenic and nononcogenic HPV types at 6 months (i.e. after dose 2) and 12 months (i.e. after dose 3). The investigators concluded that this vaccine does not provide therapeutic benefit by increasing the rate of clearance of persistent HPV 16/18 infections \((47)\).

### Efficacy against persistent infection with HPV types that are genetically related to vaccine-related HPV types in women naive to those types at baseline

#### Key point
- Preliminary data for both vaccines suggest partial efficacy against persistent infections with two HPV types, 31 and 45, which are genetically related to vaccine-related HPV types.

Trials of both vaccines have evaluated persistent infection of HPV types genetically-related to vaccine-related HPV types – including HPV 31, 33, 45, 52 and 58 – that potentially share cross-neutralizing epitopes with HPV 16 and 18 \((10,12,66)\). Such analyses have been recommended by WHO and some national regulatory authorities \((67)\).
**Quadrivalent vaccine**

Analysis of vaccine impact among a mixed population of females that included both females naive to or infected with HPV 16/18, who received at least one vaccine dose, showed that the proportion with persistent infection was reduced by 20% (95% CI 7% to 31%) for HPV 31/33/45/52/58 and reduced by 31% (95% CI 14% to 45%) for HPV 31/45 (66).

**Bivalent vaccine**

The extended follow-up of the intent-to-treat population in phase II trials found a significantly lower rate of incident infection with type 45 (efficacy 94%, 95% CI 63% to 100%) and type 31 (efficacy 55%, 95% CI 12% to 78%), but not for incidence infection with types 33, 52 and 58. This study did not report data on persistent infection with these five types (10). (See Annex 2 for updated information on this issue.)

An interim analysis of the phase III PATRiciA trial found low but statistically significant efficacy against 6-month persistent infection with HPV 31 (36%, 97.9% CI 0.5% to 60%), HPV 45 (60%, 97.9% CI 3% to 85%), and HPV 52 (32%, 97.9% CI 4% to 52%) in females naive to these types at baseline who received at least one vaccine dose (12). However, an earlier study indicated that efficacy against incident HPV 52 infection may wane (10). Estimates of vaccine efficacy against 12-month persistent infection with HPV types 31, 33, 45, 52 and 58 were not statistically significant (12). (See Annex 2 for updated information on this issue.)

**Efficacy against HPV 16/18-related cervical disease among females naive to vaccine-related HPV type infections at baseline**

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>Both vaccines were more than 90% efficacious in preventing precancerous cervical lesions attributed to vaccine-related types in phase II and III trials of females aged 15–26 years.</td>
</tr>
<tr>
<td>Completed trials of the quadrivalent vaccine have shown:</td>
</tr>
<tr>
<td>- 98% or greater efficacy for preventing CIN2/3 and AIS due to vaccine-related HPV types in per-protocol analyses, and 95% or greater efficacy for preventing these same outcomes in the unrestricted susceptible populations of phase III trials.</td>
</tr>
<tr>
<td>- 100% efficacy for preventing low-grade cervical lesions associated with HPV 6/11 in the per-protocol population of combined phase II and III trials.</td>
</tr>
<tr>
<td>- 46% efficacy for preventing CIN2/3 and AIS associated with any HPV type, including non-vaccine-related types in phase III trials.</td>
</tr>
<tr>
<td>Completed phase II and ongoing phase III trials of the bivalent vaccine have shown:</td>
</tr>
<tr>
<td>- 100% efficacy for preventing CIN1 and CIN2 associated with HPV 16/18 in the per-protocol population of phase II trials.</td>
</tr>
<tr>
<td>- 90% efficacy for preventing CIN1 and CIN2 associated with HPV 16/18 in the prespecified, interim analyses of the total vaccinated cohort of the phase III trial that received at least one vaccine dose.</td>
</tr>
<tr>
<td>- 96% efficacy for preventing CIN1+, and 100% efficacy for preventing CIN2+, in ad hoc analyses of lesions associated with multiple HPV types that considered the pattern of HPV DNA detection before lesion detection in interim analysis of the total vaccinated cohort in the phase III trial.</td>
</tr>
</tbody>
</table>
- 68% efficacy for preventing cervical disease due to any HPV type, including non-vaccine-related types, in the per-protocol population of the extended phase II trial at 5.5 years after the first dose.
- Results for specific outcomes of CIN3 and AIS are not yet available.

**Efficacy in females aged 15–26 years**

**Quadrivalent vaccine**

Efficacy against cervical disease was evaluated in a phase II trial (Protocol 007) and two phase III trials described above (Protocol 013/Future I; Protocol 015/Future II) (33,34) (Tables 3.3 and 3.4). Future II enrolled 12,167 females aged 15–26 years who underwent cytology, genital examinations and cervicovaginal sampling for HPV DNA testing at day 1 and months 7, 12, 24, 36 and 48. Participants with abnormal cytology results were referred to colposcopy using a standard protocol. The primary endpoints were incidence of HPV 16/18-related CIN2, CIN3, AIS or cervical cancer (34). Efficacy against both CIN2 and CIN3 in the per-protocol populations exceeded 96%. As expected, efficacy in the unrestricted susceptible population was slightly lower: 97% against CIN2 and 95% against CIN3. In both the per-protocol and unrestricted susceptible populations, the efficacy for preventing AIS was 100%, but was not statistically significant due to small case number (Tables 3.3 and 3.4).

Future I enrolled females aged 16–24 years who underwent cytology at day 1 and at months 7, 12, 18, 24, 30, 36 and 48; cervicovaginal sampling for HPV DNA testing; genital examinations; colposcopy and cervical biopsies according to protocol. Primary endpoints were CIN, AIS, or cervical cancer related to HPV 6, 11, 16 or 18 (33). After a mean follow-up period of 3 years, efficacy in the per-protocol population was 100% for preventing CIN1, CIN2, CIN3 and AIS, and all estimates were statistically significant. Efficacy in the unrestricted susceptible population was 100% for CIN2, CIN3 and AIS, but slightly lower for CIN1 (97%); all estimates were statistically significant (Table 3.3).

<table>
<thead>
<tr>
<th>Study cohort and clinical endpointsb</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n) Cases (n)</td>
</tr>
<tr>
<td>Per-protocol susceptible populationc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>2241</td>
<td>0</td>
<td>2258</td>
</tr>
<tr>
<td>CIN1</td>
<td>2241</td>
<td>0</td>
<td>2258</td>
</tr>
<tr>
<td>CIN2</td>
<td>2241</td>
<td>0</td>
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</tr>
<tr>
<td>CIN3</td>
<td>2241</td>
<td>0</td>
<td>2258</td>
</tr>
<tr>
<td>AIS</td>
<td>2241</td>
<td>0</td>
<td>2258</td>
</tr>
<tr>
<td>External anogenital and vaginal lesions</td>
<td>2261</td>
<td>0</td>
<td>2279</td>
</tr>
<tr>
<td>Study cohort and clinical endpoints</td>
<td>Vaccine group</td>
<td>Placebo group</td>
<td>Vaccine efficacy (95% CI) (%)</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>--------------</td>
<td>--------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n)</td>
<td>Cases (n)</td>
</tr>
<tr>
<td><strong>Condyloma</strong></td>
<td>2261</td>
<td>0</td>
<td>2279</td>
</tr>
<tr>
<td><strong>VIN1 or ValN1</strong></td>
<td>2261</td>
<td>0</td>
<td>2279</td>
</tr>
<tr>
<td><strong>VIN2/3 or ValN2/3</strong></td>
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<td>2279</td>
</tr>
<tr>
<td><strong>Unrestricted susceptible population</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n)</td>
<td>Cases (n)</td>
</tr>
<tr>
<td><strong>Cervical lesions</strong></td>
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<td>2</td>
<td>(1 HPV 6; 1 HPV 18)e</td>
</tr>
<tr>
<td><strong>CIN1</strong></td>
<td>2667</td>
<td>2</td>
<td>2684</td>
</tr>
<tr>
<td><strong>CIN2</strong></td>
<td>2667</td>
<td>0</td>
<td>2684</td>
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<tr>
<td><strong>CIN3</strong></td>
<td>2667</td>
<td>0</td>
<td>2684</td>
</tr>
<tr>
<td><strong>AIS</strong></td>
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<td>0</td>
<td>2684</td>
</tr>
<tr>
<td><strong>External anogenital and vaginal lesions</strong></td>
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<td>4</td>
<td>(2 HPV 6; 1 HPV 11; 1 HPV 16)e</td>
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<td><strong>Condyloma</strong></td>
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<td>3</td>
<td>2684</td>
</tr>
<tr>
<td><strong>VIN1 or ValN1</strong></td>
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<tr>
<td><strong>Intention-to-treat general study population: lesions associated with HPV vaccine types</strong></td>
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<td></td>
<td></td>
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<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n)</td>
<td>Cases (n)</td>
</tr>
<tr>
<td><strong>Cervical lesions</strong></td>
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<td>(7 HPV 6; 8 HPV 16; 1 HPV 18)e</td>
</tr>
<tr>
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<td>2732</td>
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<td>2732</td>
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<td><strong>CIN3</strong></td>
<td>2723</td>
<td>39</td>
<td>2732</td>
</tr>
<tr>
<td><strong>AIS</strong></td>
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<td>2732</td>
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<tr>
<td><strong>External anogenital and vaginal lesions</strong></td>
<td>2723</td>
<td>28</td>
<td>(20 HPV 6; 2 HPV 11; 6 HPV 16; 1 HPV 18)e</td>
</tr>
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<td>21</td>
<td>2732</td>
</tr>
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### Study cohort and clinical endpoints

<table>
<thead>
<tr>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% CI) (%)</th>
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<tr>
<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n)</td>
</tr>
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<tr>
<td>VIN2/3 or ValN2/3</td>
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</tbody>
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### Intention-to-treat general study population: lesions associated with any HPV type

#### Cervical lesions

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<tr>
<th>Subjects (n)</th>
<th>Cases (n)</th>
<th>Subjects (n)</th>
<th>Cases (n)</th>
<th>Vaccine efficacy (95% CI) (%)</th>
</tr>
</thead>
<tbody>
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<td>VIN1 or ValN1</td>
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<td>344</td>
<td>2732</td>
<td>421</td>
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<td>VIN2/3 or ValN2/3</td>
<td>2723</td>
<td>102</td>
<td>2732</td>
<td>116</td>
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<tr>
<td>CIN1</td>
<td>2723</td>
<td>277</td>
<td>2732</td>
<td>363</td>
</tr>
<tr>
<td>CIN2</td>
<td>2723</td>
<td>79</td>
<td>2732</td>
<td>72</td>
</tr>
<tr>
<td>CIN3</td>
<td>2723</td>
<td>1</td>
<td>2732</td>
<td>6</td>
</tr>
<tr>
<td>AIS</td>
<td>2723</td>
<td>1</td>
<td>2732</td>
<td>6</td>
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</tbody>
</table>

#### External anogenital and vaginal lesions

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Cases (n)</th>
<th>Subjects (n)</th>
<th>Cases (n)</th>
<th>Vaccine efficacy (95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIN1 or ValN1</td>
<td>2723</td>
<td>104</td>
<td>2732</td>
<td>157</td>
</tr>
<tr>
<td>VIN2/3 or ValN2/3</td>
<td>2723</td>
<td>55</td>
<td>2732</td>
<td>111</td>
</tr>
<tr>
<td>Condyloma</td>
<td>2723</td>
<td>45</td>
<td>2732</td>
<td>55</td>
</tr>
</tbody>
</table>

#### Vulvar cancer

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>Cases (n)</th>
<th>Vaccine efficacy (95% CI) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VIN1 or ValN1</td>
<td>2723</td>
<td>1</td>
</tr>
</tbody>
</table>

AIS = adenocarcinoma in situ; CI = confidence interval; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; ValN = vaginal intraepithelial neoplasia; VIN = vulvar intraepithelial neoplasia

Source: Garland et al. (2007) (33)

a This study had an average follow-up of 3 years following the first vaccine dose.
b To be eligible, females had to be aged 16–24 years, healthy, not pregnant, report no history of genital warts or abnormal cervical cytology, have four or fewer lifetime sex partners and commit to using contraception from baseline to the end of month 7.
c The per-protocol susceptible population received all three doses of vaccine or placebo within 12 months; were seronegative and DNA negative for HPV 6, 11, 16 or 18 at baseline; remained DNA negative for the same HPV type (to which they were negative at baseline) through 1 month after the third dose; had no major protocol violations; and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began 1 month after dose 3.
d Unrestricted susceptible population were seronegative and DNA negative for HPV 6, 11, 16 or 18 at baseline but may have had major protocol violations; and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began after day 1.
e HPV types associated with lesion based on DNA testing, assignment of HPV types by lesion grade not provided in publication.
f Intention-to-treat general study population also included females who may have had HPV infection or disease (cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, or vaginal intraepithelial neoplasia) associated with HPV 6, 11, 16 or 18 before vaccination or had major protocol violations. Endpoint ascertainment began after day 1.
g Intention-to-treat general study population was defined the same way as above with the difference that outcomes were assessed regardless of HPV type. Endpoint ascertainment began after day 1.

Prespecified combined analyses of one phase II and the two phase III trials of the quadrivalent vaccine, and one phase II trial of a monovalent HPV 16 vaccine evaluated more than 20 000 females from the Americas, the Asia–Pacific region and Europe. At a mean follow-up of 3 years after the first dose in the per-protocol population, efficacy was high for preventing CIN2 (100%, 95% CI 93% to 100%), CIN3 (98%, 95% CI 89% to 100%), and AIS (100%, 95% CI 31 to 100%), yielding an efficacy of 99% (95% CI 93% to 100%).
to 100%) for the composite endpoint of CIN2/3 or AIS. Efficacy was also high for both HPV 18-related CIN2/3 and AIS (100%, 95% CI 84% to 100%) and HPV 16-related CIN2/3 and AIS (97%, 95% CI 91% to 99%). The latter efficacy estimate was based on one case of CIN3 in a vaccinee who was positive for HPV 52 DNA at baseline and at the time of CIN diagnosis and treatment, and was positive for HPV 16 DNA at time of diagnosis, but not thereafter. In the unrestricted susceptible population that included females who had not received all three doses, efficacy remained high for CIN2 (99%, 95% CI 93% to 100%), CIN3 (97%, 95% CI 90% to 100%) and AIS (100%, 95% CI 55% to 100%), yielding 98% efficacy (95% CI 93% to 100%) for the composite endpoint of CIN2/3 or AIS. These findings suggest that protective antibody may develop before completion of the 3-dose series (41).

In combined per-protocol analyses from three phase II and III trial populations (Protocols 007, 013 and 015), efficacy was 96% (95% CI 89% to 99%) against HPV 6/11/16/18-related CIN1 and 100% (95% CI 87% to 100%) against HPV 6/11-related CIN1 (68, 69). The estimated efficacy against HPV 6/11-related CIN1–3 was also 100% (95% CI 89% to 100%) (69). (See Annex 2 for updated information on this issue.)

Investigators conducted a post-hoc analysis to determine whether this vaccine was efficacious against lesions due to a given vaccine-related HPV type among females who had evidence of past or current infection with other vaccine-related HPV types at baseline. The analysis combined data from two clinical trials (Protocols 013 and 015) on females aged 15–26 years who received at least one dose and had baseline evidence of current or past infection with between one and three of the four vaccine-related HPV types. Females with genital HPV-related disease at baseline or in the past were excluded. Among females who were seropositive or DNA-positive to between one and three vaccine-related types at baseline, efficacy was high against endpoints due to the remaining vaccine-related HPV types: 91% (95% CI 76% to 98%) for HPV 6/11/16/18-related CIN and 100% (95% CI 79% to 100%) for CIN2+ (42).

Investigators analyzed phase III trial data to estimate the impact of vaccination on overall rates of cervical HPV disease, regardless of causal HPV type, in a population naive to vaccine-related HPV type infection before vaccination (e.g. young adolescents or young women before the onset of sexual activity). These analyses comprised about 53% of the overall study population and included participants who at day 1 had no infection with one of 14 oncogenic HPV types (HPV 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58 and 59) and had normal cytology (a surrogate for status of infection with HPV types for which DNA testing is not available). Vaccination reduced the incidence of CIN2/3 or AIS caused by vaccine-related or non-vaccine-related HPV types by 46% (95% CI 24% to 62%). The study also evaluated the impact of vaccination on equivocal or abnormal cytology outcomes that require follow-up with colposcopy and biopsy, cervical treatment with loop electrosurgical excision procedure (LEEP) and external genital lesion treatment. Regardless of causal HPV type, vaccination reduced incidence of ASC-US by 26% (95% CI 12% to 39%), ASC-H by 36% (95% CI 6% to 56%), LSIL by 16% (95% CI 7% to 24%), HSIL by 48% (95% CI 6% to 72%), use of colposcopy with biopsy by 22% (95% CI 12% to 30%), use of LEEP treatment by 40% (95% CI 21% to 55%), and use of biopsy or excision of external genital lesions by 41% (95% CI 19% to 57%). Over a 3-year vaccination period, this impact would be expected to reduce the incidence of each of these outcomes by 5.7 to 30 per 1000 vaccinated females (Eliav Barr, Merck, pers. comm., 2007). (See Annex 2 for updated information on this issue.)
**Bivalent vaccine**

Published analyses of an extension phase of a phase II trial in females aged 15–25 years designed to evaluate incident and persistent infection also reported cytologic abnormalities and CIN endpoints (10,11). Up to 4.5 years after vaccination, vaccine efficacy (95% CIs) was 95.7% (83.5% to 99.5%) for ASC-US or worse outcomes, 92.6% (70.5% to 99.2%) for LSIL or worse outcomes, 100% (42.4% to 100%) for CIN1+, and 100% (–7.7% to 100%) for CIN2+ due to HPV 16 or 18. An unpublished combined analysis of the initial and extension phase of this phase II trial up to 5.5 years had similar findings among females who were seronegative for HPV 16 and 18, and DNA negative for 14 oncogenic HPV types at baseline. In this trial, vaccine efficacy was 100% in preventing HPV-16/18-associated outcomes of ASC-US or worse outcomes (95% CI 85% to 100%), CIN1+ (95% CI 62% to 100%), and CIN2+ (95% CI 33% to 100%). Efficacy against CIN2+ associated with any HPV type was 68% (95% CI 7% to 91%) (46).

In the interim analysis of the phase III study, subjects who were seronegative and DNA negative for HPV 16/18, had normal cytology or low-grade cytologic abnormalities at baseline (month 0), and received at least one vaccine dose, were followed for a mean of 14.8 months (Table 3.4). Efficacy against two prespecified clinical endpoints associated with HPV 16 or 18 was high in females naive to the given type at baseline: CIN1+ (89%, 95% CI 59% to 99%) and CIN2+ (90%, 95% CI 53% to 99%) (12). Of the 23 females, 14 had CIN2+ biopsy or excisional tissue that contained multiple HPV types. For three of these cases, the HPV-16/18 DNA detected in lesions was not detected in any preceding cervical specimens; rather, another oncogenic HPV type was detected in both the lesion and preceding cervical samples.

When analyses excluded females infected with vaccine-related HPV types before histologic diagnosis, efficacy estimates were 96% (97.9% CI 72% to 100%) for CIN1+ and 100% (97.9% CI 74% to 100%) for CIN2+ attributed to HPV 16/18 (12). Based on this ad hoc analysis, efficacy against CIN1+ attributed to HPV 16 was 94% (97.9% CI 54% to 100%) and against CIN1+ attributed to HPV 18 was 100% (97.9% CI 34% to 100%). Similarly, efficacy against CIN2+ attributed to HPV 16 was 100% (97.9% CI 65% to 100%) and efficacy against CIN2+ attributed to HPV 18 was 100% (97.9% CI < 0% to 100%) (157). An additional non-published ad hoc analysis found 100% efficacy (97.9% CI 78% to 100%) against CIN2+ among a mixed population that included mostly females who were seronegative to HPV 16 and 18 at baseline, and some females who were seropositive to these types (70).

In cases where multiple HPV types were detected in biopsies, exploratory, immunohistochemical analysis of the HPV E4 gene or protein expression were used to estimate HPV gene activity in biopsy or excisional tissue, productive infections (associated with CIN1 or a borderline abnormality) or transforming infections (associated with CIN2/3). No HPV 16 or 18 E4 protein was detected in the specimens of two HPV vaccine recipients with CIN2+, suggesting that those two types did not cause the lesions. In contrast, HPV 16 E4 protein was detected in a control patient with CIN2+ and HPV 16 DNA was detected in cytology samples collected before her biopsy (12).
Table 3.4  Vaccine efficacy against outcomes associated with vaccine-related HPV types 16/18 in phase III clinical trial for the bivalent vaccine (PATRiciA) a

<table>
<thead>
<tr>
<th>Study cohort and clinical/select infection endpointsb</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (97.9% CI) (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Subjects</td>
<td>Cases</td>
<td>Subjects</td>
</tr>
<tr>
<td></td>
<td>(n)</td>
<td>(n)</td>
<td>(n)</td>
</tr>
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<td>Modified intent-to-treat populationc</td>
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<td></td>
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<td></td>
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</tbody>
</table>

CI = confidence interval; CIN = cervical intraepithelial neoplasia; DNA = deoxyribonucleic acid; HPV = human papillomavirus
Source: Paavonen et al. (2007) (12)

a This study had an average follow-up of 14.8 months. Prespecified analyses are presented; however additional ad hoc and infection endpoint analyses are available in the publication.

b To be eligible, females had to be aged 15–25 years, healthy, not pregnant, report no history of abnormal cervical cytology, have ≤6 lifetime sexual partners, and commit to using contraception during the vaccination period.

c Modified intent-to-treat study population were seronegative and DNA negative for the corresponding HPV vaccine type at baseline (month zero); had normal or low grade cytology at baseline and received at least one dose of vaccine; and had endpoint data available.

d Type-specific DNA negative at study entry.

Efficacy in mid-adult women

Key point
- Trials of both vaccines are under way to assess efficacy against cervical disease among women over 26 years.

Ongoing trials of women in their mid-20s to mid-50s will estimate the benefits of vaccinating populations of older females of whom many are sexually active and have been infected with HPV (71).
**Quadrivalent vaccine**

A trial of 3819 women from Asia, Europe, Latin America and the United States aged 24–45 years without history of cervical disease in the past 5 years is assessing vaccine efficacy against the combined incidence of persistent HPV 6/11/16/18 infection or external genital or cervical disease related to vaccine-related HPV types (Protocol 019) (43). Eligible women had no history of LEEP, hysterectomy or genital warts, and no cervical biopsy in the past 5 years. Interim analyses have examined a per-protocol population who had received three doses of vaccine or placebo within one year of enrolment, were naive to the relevant HPV type at day 1, and remained free of infection through completion of the injection series. All subjects had initiated sexual activity. After a mean follow-up period of 2.2 years, efficacy against CIN (any grade) or external genital lesions related to HPV 6, 11, 16 and 18 was 92% (95% CI 50% to 100%). Efficacy was high against CIN and external genital lesions related to HPV 16 or 18 (88%, 95% CI 9% to 100%) and HPV 6 or 11 (100%, 95% CI 16% to 100%) (43). (See Annex 2 for updated information on this issue.)

**Bivalent vaccine**

Ongoing efficacy studies are evaluating efficacy against HPV-associated virological and histological outcomes (72).

**Efficacy in preventing cervical disease associated with HPV types that are genetically related to vaccine-related HPV types at baseline**

**Key points**
- Trials have evaluated vaccine efficacy in preventing cervical disease due to HPV types that are genetically related to vaccine types (i.e. the potential for cross-protection).
- Preliminary data suggest that the quadrivalent vaccine may provide partial protection against high-grade CIN caused by some, but not all, genetically related types.

**Quadrivalent vaccine**

Analyses of the placebo arm of two phase III studies (Future I and II) demonstrated that infections with multiple HPV types were common at baseline (~33%). Further, several non-vaccine-related HPV types were detected in incident cases of CIN1–3 in the absence of vaccine-related types, and type detection varied with lesion type (73). HPV infection cross protection was evaluated in subsets of HPV naive subjects from the Future I and II studies. Efficacy was 62% (95% CI 10% to 85%) against CIN2/3 and AIS associated with HPV 31/45, 43% (95% CI 7% to 66%) against CIN2/3 and AIS associated with HPV 31/33/45/52/58, and 38% (95% CI 6% to 10%) against 10 oncogenic non-vaccine-related types. Efficacy was 45% (95% CI 6% to 68%) against any grade of CIN and AIS associated with HPV 31/45 and 33% (95% CI 8% to 52%) against any grade of CIN and AIS associated with HPV 31/33/45/52/58 (66) (74).

Analysis of vaccine impact in a mixed population that included females who were either HPV 16/18 naive or infected with HPV 16 or 18 at baseline and received at least one dose estimated efficacy as follows: 16% (95% CI 2% to 27%) against CIN or AIS associated with HPV 31/33/45/52/58; 14% (95% CI –8% to 31%) against CIN or AIS associated with HPV 31/45; 23% (95% CI 2% to 40%) against CIN or AIS associated with HPV 56, and 48% (95% CI 16% to 68%) against CIN or AIS associated with HPV 59 (66). Long-term population-based studies in the United States and Nordic countries will also evaluate protection against non-vaccine-related HPV types (see Section 5) (75).
**Bivalent vaccine**

Long-term studies in Europe are being planned to evaluate protection against non-vaccine-related HPV types (75,76) (Katherine Taylor, GSK, pers. comm., November 2007) (see Section 5). (See Annex 2 for updated information on this issue.)

**Efficacy in preventing cervical disease associated with a given HPV type in females with current or past infection with that same HPV type**

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Although current HPV vaccines are designed to be prophylactic, trials have also assessed efficacy among females with evidence of past or current HPV infection, or abnormal cytology, at baseline.</td>
</tr>
<tr>
<td>• Neither vaccine has shown a therapeutic effect against disease due to HPV types with which subjects were infected (i.e. DNA positive for) at baseline.</td>
</tr>
<tr>
<td>• Based on phase II and III studies reported through 2007, there was no evidence that either vaccine provides significant protection against CIN or external anogenital disease associated with types for which patients had evidence of past infection that had cleared by baseline; i.e. seropositive but DNA negative. (See Annex 2 for updated information.)</td>
</tr>
</tbody>
</table>

HPV vaccines are designed to be prophylactic (i.e. to prevent infection and consequent disease), not therapeutic. Nevertheless, phase III trials of both vaccines enrolled females regardless of baseline HPV infection status or cytology results to assess vaccine safety, efficacy in a general population that includes persons infected with HPV before vaccination, and the influence of vaccination on infections prevalent at baseline and the course of lesions associated with vaccine-related HPV types (3). Many females with evidence of past infection (seropositive) or current infection (DNA positive) with vaccine-related HPV types were therefore enrolled in phase III trials of both vaccines. Analyses of these cohorts are under way.

**Quadrivalent vaccine**

In combined analyses of data from phase II and III trials, 27% of subjects had evidence of past infection or current infection with at least one of the four vaccine-related HPV types. Among these subjects, 74% had evidence of prior or current infection with only one of the four vaccine HPV types, and were naive (HPV DNA negative and seronegative) to the remaining three types (4). Among participants DNA positive to one or more vaccine-related HPV types, efficacy against disease caused by the remaining vaccine HPV types was high (77).

The impact of vaccination on the course of HPV infection present at baseline was evaluated using data from phase II and III trials (Protocols 005, 007, 013 and 015). Among the 1763 females who were seropositive to a given vaccine-related HPV type, but HPV DNA negative to that type (referred to as “cleared HPV infection”), efficacy was 100% (95% CI –64% to 100%) against CIN2/3 or AIS caused by the type to which the subject showed seropositivity at day 1. Among the 1287 females who were HPV DNA positive but seronegative to a given vaccine-related HPV type, efficacy against CIN2/3 caused by the type to which the subject was HPV DNA positive at day 1 was 31% (95% CI –5% to 55%). Among the 972 females who were both seropositive and HPV DNA positive for a given vaccine-related HPV type (many of whom had precancerous lesions), efficacy against CIN2/3 caused by the type to which they were positive at baseline was 26% (95% CI –76% to 10%). Because of wide confidence intervals, the investigators concluded that there was no clear evidence for vaccine efficacy on the course of
infections present before vaccination, regardless of whether females were seropositive or DNA positive (33,34,41,78). (See Annex 2 for updated information on this issue)

**Bivalent vaccine**

No data are available on the efficacy of this vaccine in preventing CIN due to a given vaccine-related HPV type among females who have evidence of infection with this same type at baseline.

**Efficacy against cervical disease among intent-to-treat populations**

**Key points**

- Analyses of intent-to-treat populations estimate vaccine efficacy in less controlled conditions than trials, because such populations include participants regardless of status of infection with vaccine-related HPV types at baseline and subjects who do not adhere to the full series or schedule.

- In combined phase II and III quadrivalent vaccine trials, efficacy against CIN2 (50%), CIN3 (39%) and AIS (54%) was lower than in per-protocol and unrestricted susceptible populations, because some endpoints were due to HPV 16/18 infections present at baseline.

- Quadrivalent vaccine efficacy against cervical disease associated with any HPV type, including non-vaccine related types, was 18% in phase III trials.

- Analyses of intent-to-treat populations from phase III trials of the bivalent vaccine are pending.

**Quadrivalent vaccine**

To estimate vaccine efficacy under less controlled conditions that might occur outside of trials, phase III studies evaluated intent-to-treat populations that included females who received at least one dose of vaccine and had at least one month of follow-up after the first dose, regardless of baseline serology and HPV DNA test results for vaccine-related HPV types. As expected, efficacy in this population in both phase III trials was less than that in the per-protocol and unrestricted susceptible populations (Tables 3.3 and 3.4). In Future I (34), efficacy in the intent-to-treat population was 57% for HPV 16/18-related CIN2, 45% for HPV 16/18-related CIN3 (both statistically significant) and 28% for HPV 16/18-related AIS (not statistically significant) (Table 3.5). In both the vaccine group and the placebo group, most additional cases identified in this intent-to-treat analysis were attributed to HPV 16 or 18 infections that were present before the first injection. In Future I (33), efficacy in the intent-to-treat population was 62% for CIN1, 30% for CIN2, 12% for CIN3 and 83% for AIS associated with HPV 6/11/16/18, but the only statistically significant result was efficacy for preventing CIN1 (Table 3.3). No cancers associated with vaccine-related HPV types were diagnosed. In the planned combined analysis of phase II and phase III trials of the quadrivalent vaccine, and the phase II trial of a monovalent HPV 16 vaccine, efficacy in the intent-to-treat population was 50% (95% CI 34% to 62%) for HPV 16/18-related CIN2, 39% (95% CI 21% to 53%) for HPV 16/18-related CIN3, and 54% (95% CI 30% to 86%) for HPV 16/18-related AIS. All but one case who received the quadrivalent HPV vaccine occurred in females infected with HPV 16 or 18 before vaccination (41).
Table 3.5 Vaccine efficacy against outcomes associated with vaccine-related HPV types 16/18 in phase III clinical trial for the quadrivalent vaccine (Future II) *

<table>
<thead>
<tr>
<th>Study cohort and clinical endpointsb</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Vaccine efficacy (95% confidence interval) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Subjects (n)</td>
<td>Cases (n)</td>
<td>Subjects (n)</td>
</tr>
<tr>
<td>Per-protocol susceptible populationc</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>5305</td>
<td>1 (1 HPV 16)d</td>
<td>5260</td>
</tr>
<tr>
<td>CIN 2</td>
<td>5305</td>
<td>0</td>
<td>5260</td>
</tr>
<tr>
<td>CIN 3</td>
<td>5305</td>
<td>1</td>
<td>5260</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>5305</td>
<td>0</td>
<td>5260</td>
</tr>
<tr>
<td>Unrestricted susceptible populatione</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>5865</td>
<td>3 (3 HPV 16)d</td>
<td>5863</td>
</tr>
<tr>
<td>CIN 2</td>
<td>5865</td>
<td>1</td>
<td>5863</td>
</tr>
<tr>
<td>CIN 3</td>
<td>5865</td>
<td>2</td>
<td>5863</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>5865</td>
<td>0</td>
<td>5863</td>
</tr>
<tr>
<td>Intention-to-treat general study population: lesions associated with HPV vaccine typesf</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>6087</td>
<td>83 (77 HPV 16; 6 HPV 18)d</td>
<td>6080</td>
</tr>
<tr>
<td>CIN 2</td>
<td>6087</td>
<td>41</td>
<td>6080</td>
</tr>
<tr>
<td>CIN 3</td>
<td>6087</td>
<td>57</td>
<td>6080</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>6087</td>
<td>5</td>
<td>6080</td>
</tr>
<tr>
<td>Intention-to-treat general study population: lesions associated with any HPV typeg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical lesions</td>
<td>6087</td>
<td>219</td>
<td>6080</td>
</tr>
<tr>
<td>CIN 2</td>
<td>6087</td>
<td>149</td>
<td>6080</td>
</tr>
<tr>
<td>CIN 3</td>
<td>6087</td>
<td>127</td>
<td>6080</td>
</tr>
<tr>
<td>Adenocarcinoma in situ</td>
<td>6087</td>
<td>5</td>
<td>6080</td>
</tr>
</tbody>
</table>


*a This study had an average follow-up of 3 years following the first vaccine dose.

*b To be eligible, females had to be aged 15–26 years, pregnant, report no history of abnormal cervical cytology, have ≤4 lifetime sex partners and commit to using contraception from baseline through month 7.

*c Per-protocol susceptible population received all three doses of vaccine or placebo within 12 months; were seronegative and DNA negative for HPV 16 or 18 at baseline; remained DNA negative for the same HPV type (to which they were negative at baseline) through 1 month after the third dose; had no major protocol violations; and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began 1 month after dose 3.

*d HPV types associated with lesion based on DNA testing, assignment of HPV types by lesion grade not provided in publication.

*e Unrestricted susceptible population were seronegative and DNA negative for HPV 16 or 18 at baseline but may have had major protocol violations; and had either normal or abnormal cervical cytology at baseline. Endpoint ascertainment began after day 1.
Prespecified analyses of the phase III trials assessed the impact of the vaccination on HPV-related cervical disease, regardless of causal HPV type, in a population likely to be exposed to one or more vaccine-related HPV types before vaccination (e.g., sexually active female adolescents and young women). These analyses included participants in the intent-to-treat population with at least one follow-up visit. All cases of CIN2/3 or AIS regardless of causal HPV type that occurred after day 1 were included. Vaccination reduced the incidence of CIN2/3 or AIS caused by vaccine or non-vaccine HPV types by 18% (95% CI 7% to 29%) (41). In analyses stratified by type of lesions, population vaccine efficacy was marginally significant for CIN2, but not for CIN3 or AIS (Table 3.4) (41). Although the percent reduction in rates of CIN2/3 or AIS in the vaccine group compared with the placebo group was smaller in this intent-to-treat group than in the HPV-naive population (see above), attributable risk reductions in CIN2/3 or AIS after vaccination of this intent-to-treat populations were similar through the 3-year follow-up period: 8.6 cases prevented per 1000 vaccinated females compared to 9.6 cases prevented per 1000 vaccinated females.

Regional subanalyses of international phase III trials are under way (79,80) (See epub Nov 13 2007). Vaccine efficacy in the Latin American intent-to-treat populations was 51% (95% CI 34% to 65%) for CIN1+, 33% (95% CI 1% to 55%) for CIN2+ and 100% (95% CI < 0% to 100%) for AIS (80) (See epub Nov 13 2007).

**Bivalent vaccine**

Results of the intent-to-treat analyses of the phase III trial are pending (12).

**Efficacy of the quadrivalent vaccine in preventing vaginal and vulvar disease in females**

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Published analyses of vaccine efficacy against vaginal and vulvar disease are available only for the quadrivalent vaccine.</td>
</tr>
<tr>
<td>- Efficacy was 94–100% in preventing VIN2/3 and VaIN2/3 associated with HPV 16/18 or HPV 6/11/16/18 in per-protocol and unrestricted susceptible populations, and 71% for preventing the composite endpoint of VIN2/3 and VaIN2/3 associated with HPV 16/18 in the intent-to-treat population.</td>
</tr>
<tr>
<td>- Efficacy was 49% for preventing the combined outcomes of VIN2/3 or VaIN2/3 associated with any HPV type, including non-vaccine-related types, in intent-to-treat populations used to estimate population impact.</td>
</tr>
</tbody>
</table>

HPV-related vulvar and vaginal cancers are commonly preceded by high-grade precancerous lesions, VIN2/3 and VaIN2/3, respectively. Low-grade vulvar and vaginal abnormalities, VIN1 and VaIN1, also develop but understanding of their natural history is limited.

**Quadrivalent vaccine**

One phase II (Protocol 007) and two phase III studies (Protocols 013 and 015) evaluated vaccine efficacy against external anogenital lesions in females from the Asia–Pacific
region; Europe; and North, Central and South America. Participants in phase III trials were followed for an average of 3 years after their first dose (Table 3.3 and 3.4) (33,40).

In the per-protocol population of Protocol 013, efficacy was 100% (95% CI 49% to 100%) in preventing the combined outcome of VIN1 or VaIN1, and the combined outcome of VIN2/3 or VaIN2/3 related to HPV 6, 11, 16 or 18. In the unrestricted susceptible population, efficacy was 91% for preventing high-grade vulvar or vaginal lesions, and 95% for preventing the composite endpoint of external anogenital lesions (including warts and vulvar lesions) and vaginal lesions. As expected, efficacy was lower in the intent-to-treat population (which included females with HPV infection at baseline) (Table 3.3) (33).

In a combined analyses of three trials, efficacy was 100% for HPV 16/18-related VIN2/3 (95% CI 42% to 100%), VaIN2/3 (95% CI 31% to 100%), or VIN2/3 and VaIN2/3 combined (95% CI 72% to 100%) in the per-protocol population (40). Efficacy was more than 94% for HPV 16/18-related VIN2/3 and VaIN2/3 in the unrestricted susceptible population (40). In combined analysis of HPV 6/11-related disease in the per-protocol population in three phase IIb/III clinical trials (Protocols 007, 013 and 015), vaccine efficacy was 99% (95% CI 96% to 100%) for all external genital lesions (including genital warts and VIN/VaIN1–3) after three years of follow-up (69). In the intent-to-treat populations, efficacy was 62% (95% CI 10% to 85%) against HPV 16 or 18-associated VIN2/3, 82% (95% CI 17% to 98%) against HPV 16 or 18-associated VaIN2/3, and 71% (95% CI 37% to 88%) against the composite endpoint of HPV 16 or 18-associated VIN2/3 or VaIN2/3 (40). In combined, per-protocol analyses of low-grade disease from three phase II and III trials (Protocols 007, 013 and 015), vaccine efficacy was 100% (95% CI 83% to 100%) against HPV 6/11/16/18-related VIN/VaIN1 (68). (See Annex 2 for updated information on this issue.)

Post-hoc combined analyses (Protocols 013 and 015) in females aged 15–26 years who received at least one dose and had baseline evidence of current or past infection with between one and three of the four vaccine-related HPV types showed high efficacy for preventing disease associated with HPV types for which females were seronegative and DNA negative at baseline. Vaccine efficacy was 94% (95% CI 81% to 99%) for HPV 6/11/16/18-related external anogenital and vaginal lesions, 93% (95% CI 79% to 99%) for condyloma, 80% (95% CI < 0% to 100%) for VIN1 or VaIN1, and 100% (95% CI < 0% to 100%) for VIN2/3 or VaIN2/3 (42).

Investigators conducted population impact analyses to examine impact of vaccination on rates of vulvar and vaginal disease due to any HPV type. In the generally HPV-naive population (defined above), vaccination reduced the incidence of VIN2/3 or VaIN2/3 by 76% (95% CI 40% to 92%), regardless of causal HPV type. In the intent-to-treat population (defined above), vaccination reduced the combined rate of VIN2/3 or VaIN2/3 by 49% (95% CI 18% to 69%), regardless of causal HPV type (40).

**Bivalent vaccine**

In the future, it is expected that phase III studies will report outcomes of VIN and VaIN associated with HPV 16 and 18 and a combination of oncogenic types.
Efficacy in preventing external anogenital warts in females

Key points

- Prevention of external anogenital warts in females as an endpoint has been assessed in trials of the quadrivalent vaccine only.
- In phase III trials, efficacy against genital warts was 99–100% in the per-protocol population, 96% in the unrestricted susceptible population and 76% in the intent-to-treat population.

Quadrivalent vaccine

Investigators analysed a per-protocol population of females who were naive to HPV 6 or 11 (or both) at baseline, remained HPV DNA negative up to one month after dose 3 to HPV types to which they were naive at baseline, received all three vaccine doses and had no protocol violations. Efficacy was 100% (95% CI 92% to 100%) against anogenital warts (Table 3.3) (33). In combined per-protocol analyses from three phase II and III trial populations (Protocols 007, 013 and 015), vaccine efficacy was 98.8% (95% CI 95.4% to 99.9%) against HPV 6/11/16/18-related condyloma (68). In the unrestricted susceptible population (females who may not have remained HPV DNA negative up to one month after dose 3 to HPV types to which they were naive at baseline or who may have had protocol violations) and intent-to-treat populations, efficacy was lower (Table 3.3) (33). In analyses that combined results of one phase II (Protocol 007) and two phase III trials (Protocols 013 and 015), efficacy against external anogenital warts related to HPV 6, 11, 16 or 18 in the per-protocol analysis was 99% (95% CI 94% to 100%) (8) and 69% (95% CI 58% to 77%) in the intent-to-treat populations (8). High vaccine efficacy against a combined outcome of CIN (any grade) and external genital lesions (including anogenital warts) was also demonstrated among women aged 24–45 years (see above section on mid-adult women) (43).

Bivalent vaccine

These outcomes are not relevant to this vaccine because it does not contain VLPs for HPV 6 or 11.

Efficacy in preventing HPV-related disease in males

Key point

- Efficacy studies for the quadrivalent vaccine are under way.

Quadrivalent vaccine

Studies of the efficacy against HPV-related anogenital precancers and anogenital warts are underway.

Bivalent vaccine

An immunogenicity study, but not an efficacy study, of this vaccine is underway (See Annex 2 for updated information on this issue.)
3.1.4 Duration of protection against clinical disease

Key points

- Duration of protection is important in determining the appropriate age for vaccination, the need for booster vaccination and the potential impact of vaccination programmes.
- Data are available on duration of vaccine protection for at least 5 years since the onset of phase II trials for both vaccines. (See Annex 2 for updated information.)
- Efficacy against persistent HPV infection and genital disease associated with vaccine-related HPV types has remained high (95–100%) for up to five years for both vaccines.

General considerations

It is not yet known whether seropositivity (according to the thresholds used) correlates with clinical protection. Too few cases of disease associated with vaccine-related HPV types have occurred in vaccinated females to determine whether the small proportion of females who become seronegative are susceptible to disease (3). For both vaccines, data on protection against persistent infection and various clinical endpoints are available for more than 5 years after onset of phase II trials. If antibodies wane, boosters may be needed to maintain protection after onset of sexual activity, possibly 5–15 years after the primary vaccine series, and this would make programme implementation more complex and costly. If protection is long lived, incorporating HPV vaccines into existing childhood vaccination programmes could greatly ease introduction. Duration of protection greatly influences the impact and cost effectiveness of vaccination compared to no intervention or screening programmes (3,81,82). Several studies will evaluate long-term antibody response and vaccine effectiveness against CIN, AIS and cervical cancer for both vaccines (see Section 5) (8,75,78). The licensure of both vaccines raises questions about the ethics of conducting new placebo-controlled trials and underscores the value of long-term follow-up of current trial populations and observational studies (see section on duration of antibody, and Section 5 on monitoring and research).

Quadrivalent vaccine

Trials have demonstrated protection against a composite endpoint of persistent infection and all genital disease up to 5 years after enrolment in a subset of participants of a phase II trial (Protocol 007) (8,83). In a combined analysis of all participants up to the end of year 3 and a subset up to the end of 60 months, the efficacy against vaccine HPV type persistent infection, cervical dysplasia, or genital warts was 96% (95% CI 84% to 100%) and efficacy against vaccine type-related CIN or external genital lesions was 100% (95% CI 12% to 100%) (30). In the subset of subjects followed for 60 months, efficacy remained high without evidence of waning protection. There were no cases of persistent infection among vaccinees between months 36 and 60, while placebo recipients continued to acquire infections (30,45). The population impact of HPV vaccination programs over the course of the next 10–15 years will be evaluated in the Nordic countries (75).

Bivalent vaccine

Trials have demonstrated protection against persistent infection and other clinical endpoints in 776 females followed up to 5.5 years after enrolment in a phase II trial, the longest follow-up period for clinical outcomes to date. At this time point, efficacy against low and high-grade cytological outcomes associated with HPV 16/18 was 100% (see above) (46). Long-term duration of protection will also be assessed in Finland (75,84).
3.1.5 Safety and adverse events

General considerations

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Both vaccines are non-infectious because they do not contain live biological products or viral DNA.</td>
</tr>
<tr>
<td>• In 2007, WHO’s Global Advisory Committee on Vaccine Safety concluded that both vaccines were well tolerated, have good safety profiles, and do not cause adverse reproductive outcomes based on 5–6 years of trial data and early post-marketing passive surveillance data for the quadrivalent vaccine in the United States.</td>
</tr>
<tr>
<td>• Data on longer term safety are limited and will be collected through extended follow-up of clinical trials and post-marketing surveillance for both vaccines.</td>
</tr>
<tr>
<td>• Additional studies of safety in pregnant females and new studies in HIV-infected populations are under way.</td>
</tr>
</tbody>
</table>

Neither HPV vaccine contains any live biological product or viral DNA so they are non-infectious. Both HPV vaccines have been evaluated for local and systemic adverse events during phase II and III trials and post-marketing safety data in the United States are available for the quadrivalent vaccine and will be collected in Europe for both vaccines. (See Annex 2 for updated information on this issue.)

In June 2007, WHO’s Global Advisory Committee on Vaccine Safety reviewed published and unpublished data up to 6 years after the onset of trials for the quadrivalent vaccine, and up to 5.5 years after onset of trials for the bivalent vaccine. The committee concluded that both vaccines are generally well tolerated and have good safety profiles (3,85). This is consistent with a meta-analysis of randomized controlled trials of prophylactic HPV vaccines, which concluded that most reported adverse events are minor and that vaccines do not lead to a significantly higher incidence of adverse events than placebo or control vaccine recipients (86).

For the quadrivalent vaccine, safety data are available from studies of more than 21 000 females from 33 countries and territories. Vaccinees were compared with females receiving placebos containing amorphous aluminium hydroxyphosphate sulfate (AAHS) or saline (33-36,39). Post-marketing surveillance for the quadrivalent vaccine is being conducted in the United States Vaccine Adverse Event Reporting System, sponsored by the Centers for Disease Control and Prevention (CDC) and FDA, CDC’s Vaccine Safety Datalink, and the Nordic Cancer Registry Program (8,78). For the bivalent vaccine, safety data are available from nearly 30 000 females from 40 countries in the Americas, Asia and Europe. Most studies compared vaccinees with controls who received aluminium-containing placebo or a control hepatitis A vaccine (10-12). Post-marketing surveillance is being conducted in the Eudravigilance network in Europe (76,87,88).

Post-marketing surveillance can also evaluate safety in younger girls who were included in bridging immunogenicity studies but not in clinical efficacy trials published to date. It also allows for assessment of incomplete schedules and use outside of approved indications and populations. Neither vaccine is intended for pregnant females, and clinical trials were not designed to address safety in pregnancy or during lactation. Nevertheless, HPV vaccines will be offered to females of reproductive age in some settings (see Section 6) and post-marketing surveillance can evaluate safety in females inadvertently vaccinated during pregnancy or lactation. In the Nordic studies, population-based samples
of sera from vaccine recipients who become pregnant can be used to assess risk of congenital infection (see Section 5).

Reactogenicity and local adverse events

**Key points**

- Recipients of both the quadrivalent and bivalent vaccines have reported more injection-site adverse events (pain, swelling and erythema) than placebo recipients or control females receiving hepatitis A vaccines, regardless of age.
- Incidence of local adverse events does not vary by pre-vaccination HPV infection status.

In phase II trials of both vaccines, completed phase III trials of the quadrivalent vaccine, and an interim analysis of a phase III trial of the bivalent vaccine, pain, erythema and oedema at the injection site were significantly more common in vaccine than placebo recipients (Table 3.6) (3).

### Table 3.6 Vaccine safety in phase II and III clinical trial populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of adverse event (AE)</th>
<th>Vaccine group</th>
<th>Placebo group</th>
<th>Risk difference (95% CI) (%) or P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=272</td>
<td>n=274</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Any etiology</td>
<td>250 (92)</td>
<td>242 (88)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Injection site</td>
<td>234 (86)</td>
<td>212 (77)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>187 (69)</td>
<td>190 (69)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Vaccine associated</td>
<td>243 (89)</td>
<td>225 (82)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Injection site</td>
<td>234 (86)</td>
<td>212 (77)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>104 (38)</td>
<td>90 (33)</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Serious</td>
<td>2 (1)</td>
<td>2 (1)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Phase III (33)</td>
<td>n=2673</td>
<td>n=2672</td>
<td></td>
<td>Risk difference</td>
</tr>
<tr>
<td></td>
<td>Any etiology</td>
<td>2320 (86.8)</td>
<td>2068 (77.4)</td>
<td>9.4 (7.3 to 11.5)</td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>1745 (65.3)</td>
<td>1701 (63.7)</td>
<td>1.6 (–1.0 to 4.2)</td>
</tr>
<tr>
<td>Associated with</td>
<td>Vaccine or placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic</td>
<td>1161 (43.4)</td>
<td>1085 (40.6)</td>
<td>2.8 (0.2 to 5.5)</td>
</tr>
<tr>
<td></td>
<td>Serious</td>
<td>48 (1.8)</td>
<td>45 (1.7)</td>
<td>0.1 (–0.6 to 0.8)</td>
</tr>
<tr>
<td></td>
<td>Vaccine associated</td>
<td>1 (&lt; 0.1)</td>
<td>0 (0)</td>
<td>0 (–0.1 to 0.2)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation because of event</td>
<td>2 (0.1)</td>
<td>3 (0.1)</td>
<td>0 (–0.3 to 0.2)</td>
</tr>
<tr>
<td></td>
<td>Discontinuation because of vaccine associated</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (–0.0 to 0.2)</td>
</tr>
<tr>
<td></td>
<td>Death</td>
<td>2 (0.1)</td>
<td>2 (0.1)</td>
<td>0 (–0.2 to 0.2)</td>
</tr>
<tr>
<td>Study</td>
<td>Type of adverse event (AE)</td>
<td>Vaccine group</td>
<td>Placebo group</td>
<td>Risk difference (95% CI) (%) or P value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Phase III (34) e</td>
<td>n=448</td>
<td>n=447</td>
<td></td>
<td>Risk difference</td>
</tr>
<tr>
<td>Safety cohort f</td>
<td>n  %</td>
<td>n  %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any etiology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>378 84.4</td>
<td>348 77.9</td>
<td>9.4 (7.3 to 11.5)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>372 83.0</td>
<td>339 75.8</td>
<td>7.2 (1.9 to 12.5)</td>
<td></td>
</tr>
<tr>
<td>Systemic</td>
<td>275 61.4</td>
<td>268 60.0</td>
<td>1.4 (–5.0 to 7.8)</td>
<td></td>
</tr>
<tr>
<td>All subjects g</td>
<td>n=6019</td>
<td>n=6031</td>
<td></td>
<td>Risk difference</td>
</tr>
<tr>
<td>Serious</td>
<td>45 0.7</td>
<td>54 0.9</td>
<td>–0.1 (–0.5 to 0.2)</td>
<td></td>
</tr>
<tr>
<td>Vaccine associated</td>
<td>3 &lt; 0.1</td>
<td>2 &lt; 0.1</td>
<td>0 (–0.1 to 0.1)</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>7 0.1</td>
<td>6 0.1</td>
<td>0 (–0.1 to 0.2)</td>
<td></td>
</tr>
<tr>
<td>Serious vaccine associated</td>
<td>0 – 1</td>
<td>1 &lt; 0.1</td>
<td>0 (–0.1 to 0.1)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>7 0.1</td>
<td>5 0.1</td>
<td>0 (–0.1 to 0.2)</td>
<td></td>
</tr>
<tr>
<td>Bivalent</td>
<td>n=531</td>
<td>n=538</td>
<td>p</td>
<td></td>
</tr>
<tr>
<td>Phase II (11) h</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site</td>
<td>499 94.0</td>
<td>472 87.7</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>General symptoms</td>
<td>458 86.3</td>
<td>462 85.9</td>
<td>0.860</td>
<td></td>
</tr>
<tr>
<td>Serious</td>
<td>22 4.0</td>
<td>19 3.5</td>
<td>0.636</td>
<td></td>
</tr>
<tr>
<td>Vaccine associated</td>
<td>0 – 0</td>
<td>0 – 0</td>
<td>– –</td>
<td></td>
</tr>
<tr>
<td>Discontinuation</td>
<td>Non-serious</td>
<td>0 – 3</td>
<td>0.6</td>
<td>0.249</td>
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<td>Serious</td>
<td>1 0.1</td>
<td>0 – 0</td>
<td>0.497</td>
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<tr>
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<td>n=3077</td>
<td>n=3080</td>
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<td>Risk difference</td>
</tr>
<tr>
<td>Safety cohort A i</td>
<td>n  %</td>
<td>n  %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>2786 90.5</td>
<td>2402 78.0</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Redness</td>
<td>1348 43.8</td>
<td>851 27.6</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Swelling</td>
<td>1292 42.0</td>
<td>609 19.8</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>General symptoms</td>
<td>3076 –</td>
<td>3080 –</td>
<td>– –</td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>633 20.6</td>
<td>551 17.9</td>
<td>Not reported</td>
<td></td>
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<tr>
<td>Fatigue</td>
<td>1771 57.6</td>
<td>1652 53.6</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Type of adverse event (AE)</td>
<td>Vaccine group</td>
<td>Placebo group</td>
<td>Risk difference (95% CI) (%) or P value</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>----------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>----------------------------------------</td>
</tr>
<tr>
<td></td>
<td>Fever</td>
<td>381</td>
<td>12.4</td>
<td>337</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal</td>
<td>850</td>
<td>27.6</td>
<td>841</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>1665</td>
<td>54.1</td>
<td>1579</td>
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<td></td>
<td>Myalgia</td>
<td>1606</td>
<td>52.2</td>
<td>1382</td>
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<td></td>
<td>Rash</td>
<td>312</td>
<td>10.1</td>
<td>258</td>
</tr>
<tr>
<td></td>
<td>Urticaria</td>
<td>298</td>
<td>9.7</td>
<td>244</td>
</tr>
<tr>
<td></td>
<td>n=3184</td>
<td>n=3184</td>
<td></td>
<td></td>
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<td>Safety cohort B</td>
<td>Unsolicited symptom</td>
<td>1354</td>
<td>42.5</td>
<td>1389</td>
</tr>
<tr>
<td></td>
<td>n=9319</td>
<td>n=9325</td>
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<td></td>
</tr>
<tr>
<td>All subjects</td>
<td>Serious</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of women</td>
<td>330</td>
<td>3.5</td>
<td>323</td>
</tr>
<tr>
<td></td>
<td>Number of events</td>
<td>389</td>
<td>–</td>
<td>372</td>
</tr>
<tr>
<td></td>
<td>Medically significant</td>
<td>1988</td>
<td>21.3</td>
<td>2030</td>
</tr>
<tr>
<td></td>
<td>condition</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>New onset chronic disease</td>
<td>143</td>
<td>1.5</td>
<td>154</td>
</tr>
<tr>
<td></td>
<td>New onset autoimmune</td>
<td>31</td>
<td>0.3</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**AE = adverse event.**

- **a** Refer to original publications for greater detail on specific adverse events within each general category.
- **b** Source: Villa et al. (2005) (39) Note: safety recorded by: observation for 30 minutes post vaccination; oral temperature recorded daily for 5 days post vaccination; adverse events recorded in diary for 14 days post vaccination.
- **c** ‘n’ refers to the number of subjects reporting events.
- **d** Source: Garland et al. (2007) (33) Note: safety recorded by: observation for 30 minutes post vaccination; oral temperature recorded 4 hours post vaccination and daily for the next 4 days; adverse events reported by vaccine report card for 15 days post vaccination; and all serious adverse events potentially related to a study procedure or vaccination as well as deaths and pregnancy outcomes recorded throughout study.
- **e** Source: The Future II Study Group (2007) (34) Note: safety recorded by: observation for 30 minutes post vaccination; serious adverse events reported 1 to 15 days post vaccination; safety subset of 916 subjects (all subjects at United States centers) were asked to use a report card to list serious non-serious adverse events 1–15 days post vaccination; and all serious adverse events potentially related to a study procedure or vaccination as well as deaths and pregnancy outcomes recorded throughout study.
- **f** The safety cohort included females who completed vaccination report cards from day 1 to 15 after each dose.
- **g** All subjects with safety follow-up data.
- **h** Source: Harper et al. (2004) (11) Note: safety recorded by diary card in the 7 day post vaccination period using a graded scale for symptom intensity; by interview all adverse events within 30 days post vaccination; and serious adverse events and pregnancies were collected throughout the study.
- **i** Source: Paavonen et al. (2007)(12) Note: safety recorded in a subset of women who recorded symptoms within 7 days post vaccination using a graded scale for symptom intensity and symptoms within 30 days post vaccination. All study participants reported serious adverse events, new onset chronic diseases or medically significant conditions and pregnancy outcomes.
- **j** Investigators solicited adverse events within 7 days of vaccination.
- **k** Unsolicited adverse events within 30 days of last vaccination.
**Quadrivalent vaccine**

In all but one trial, participants reported adverse events occurring 14 days after each injection on report cards (40). In the remaining study, a subset completed reports. In the Future II trial in 13 countries, the Future I trial in 16 countries, and a combined analysis from 5 trials of females aged 9–26 years. They consistently found that vaccinees were more likely than placebo recipients to report any injection-site adverse event (84–87% vs 77–78%), especially pain (34,40,89) (Table 3.6). However, nearly all injection-site adverse events were mild to moderate; less than 3% reported severe pain, swelling or erythema (8). A safety study in mid-adult women aged 24–45 years with a mean follow-up of 2.2 years also revealed a similar reactogenicity pattern (43). A post-hoc analysis of the two phase III trials in females with evidence of current or past infection with between one and three of the four vaccine-related HPV types at baseline found that the safety profile did not differ by baseline seropositivity or HPV DNA positivity to the vaccine-related HPV types (42). (See Annex 2 for updated information on this issue.)

**Bivalent vaccine**

An interim analysis of the phase III PATRiciA trial compared more than 9000 HPV vaccine recipients with more than 9000 controls receiving hepatitis A vaccine (12). Injection site events solicited within 7 days of injection were reported more frequently in the HPV vaccine than in the control group (Table 3.6). Few symptoms were graded as severe (< 17% in vaccines vs. < 5% in controls). Most symptoms were transient, with a mean duration of less than 4 days in both groups, and subsequent doses did not induce an increase in local symptoms.

Another unpublished analysis presented to WHO included combined data on more than 29 000 females aged 10–72 years from phase II and III clinical trials, which showed that the vaccine was generally well tolerated (85). Mild adverse events, including local pain, erythema, and swelling, were 10–20% more frequent in vaccinees than in controls who received aluminium-containing placebo (6). An unpublished analysis of the phase III PATRiciA found that among females who had received at least one vaccine dose, the frequency of local (80–84%) and general (64–67%) solicited symptoms did not differ by baseline HPV seropositivity or HPV DNA positivity (70). (See Annex 2 for updated information on this issue.)

**Systemic and serious adverse events and onset of new medical conditions**

<table>
<thead>
<tr>
<th>Key points for both vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Serious adverse events have been rare for both vaccinees and placebo recipients or control subjects in phase II and III trials, and intensity of events was similar by study group.</td>
</tr>
<tr>
<td>• The incidence of medically significant conditions, new onset chronic conditions or autoimmune disorders has been similar in vaccine and placebo recipients or control subjects.</td>
</tr>
<tr>
<td>• None of the rare cases of death among vaccinees were judged to be vaccine related.</td>
</tr>
<tr>
<td>• Newly diagnosed systemic autoimmune disorders were rare (&lt; 1%) and frequency was similar in vaccinees and placebo recipients.</td>
</tr>
<tr>
<td>• To date, the safety profile has not differed by baseline HPV serostatus.</td>
</tr>
</tbody>
</table>
Quadrivalent vaccine

The Future II trial, which included more than 12,000 participants from 13 countries, found that the proportions of females reporting any systemic event of any intensity were similar in vaccine and placebo groups (61.4% vs. 60.0%). Serious adverse events, including death, were rare (< 1%) in both vaccine and placebo groups. Very few (≤ 0.1%) discontinued study participation due to serious events. Among patients who had systemic or serious adverse events, vaccine recipients had nominally more reports of seasonal allergies (risk difference 1.8%, 95% CI 0.3% to 3.7%) and nominally fewer reports of neck pain (risk difference −1.8%, 95% CI −3.7% to −0.3%). Patterns of adverse events were similar for females with and without antibodies to one or more of the vaccine-related HPV types at enrolment (34).

The Future I trial, which included > 5400 participants, analyzed safety data within 15 days of injection, based on report cards. The most common vaccine-related systemic adverse event was low fever, reported slightly more commonly in vaccine than placebo recipients (13.3% vs. 10.3%). Similar but small proportions (≤ 0.1%) of vaccine and placebo recipients reported a serious vaccine-related adverse event, including injection-related events or death. No vaccine or placebo recipients discontinued study participation due to serious vaccine-related adverse events. In addition, the frequency of adverse events among the subset of participants who were seropositive for one or more of the four vaccine-related HPV types at baseline was similar to the frequency among all trial participants (33).

An analysis of serious systemic adverse events in 21,464 females aged 9–26 years and males aged 9–15 years who participated in several trials found that 206 (< 1%) reported a serious systemic adverse events, of which 0.06% were judged by the clinical site investigator to be vaccine related (40). The most frequently reported serious systemic adverse event reported by vaccine compared with placebo recipients were headache (0.03% vs. 0.02%), gastroenteritis (0.03% vs. 0.01%), appendicitis (0.03% vs. 0.01%), pelvic inflammatory disease (0.02% vs. 0.02%) and urinary tract infection (0.02% vs. 0.02%) (3). Few subjects (0.1%) discontinued because of adverse experiences. Of the 18 reported deaths, causes of death did not differ by study group, were consistent with causes expected in general adolescent and adult populations (3), and were not judged to be vaccine-related (40). (See Annex 2 for updated information on this issue.) In the ongoing study of mid-adult women aged 24–45 years, with a mean follow-up of 2.2 years, small and similar proportions of vaccine and placebo recipients have reported serious adverse effects (43).

Less than 1% of vaccine or placebo recipients reported new medical conditions, including those that might indicate a systemic autoimmune disorder, and proportions did not differ by study group: autoimmune thyroiditis, scleroderma/morphea, rheumatoid arthritis, uveitis, arthralgia/arthritis/arthropathy, nephritis/proteinuria and Raynaud’s phenomenon (4).

Vaccine Adverse Event Reporting System (VAERS) data from June 2006 to May 2007, 11 months after United States licensure of this vaccine, included 1763 reports, of which 87% concerned females who received HPV vaccine alone and 3% concerned females who also received the meningococcal vaccine Menactra® (90). The most frequently reported events were dizziness (13%), syncope (10%), injection site pain (10%), nausea (9%), pain and rash (7% each), pyrexia, urticaria and headache (6% each), and loss of consciousness (5%) (90). About half (49%) of events were reported after the first dose. Among the 94 reports of serious events, 42% occurred within one day of vaccination. The most frequent
reported events were vomiting (14%), syncope (12%), pyrexia (11%), nausea (11%) and headache (10%). Of the 11 syncope cases, 7 required hospitalization due to injuries or other serious sequelae (90). VAERS also identified 13 reports of Guillain-Barre syndrome, mostly among 13–16 year olds who had concurrently received Ménactra®, and 3 reports of thrombosis and embolism, all in users of oral contraceptives. Four deaths were reported: one due to myocarditis in a patient with a history of cardiac insufficiency, two due to emboli in users of oral contraceptives, and one due to laboratory-confirmed influenza type B (90). VAERS is currently actively monitoring the following conditions: Guillain-Barre syndrome, seizure, syncope, anaphylaxis, appendicitis, stroke, thrombosis and pulmonary embolism (90). (See Annex 2 for updated information on this issue.)

In Australia, media reports have described mass sociogenic illness involving dizziness and syncope after vaccination of adolescent girls in a confined space (91). (See Annex 2 for updated information on this issue)

**Bivalent vaccine**

Among 3076 HPV vaccine recipients and 3080 controls who received hepatitis A vaccine in the phase III PATRiciA trial, the frequency of some general solicited symptoms within 7 days of injection were slightly higher in HPV vaccinees than in controls: fatigue (57.6% vs. 53.6%), headache (54.1% vs. 51.3%) and myalgia (52.2% vs. 44.9%). Differences in the proportions of groups reporting arthralgia, fever, gastrointestinal symptoms, rash and urticaria were < 5%. More than 95% of these events were rated as “mild” or “moderate”, and did not reduce participants’ willingness to complete the vaccine series. No increase in general symptoms was seen with subsequent doses (12). Among 9319 HPV vaccine recipients and 9325 controls receiving hepatitis A vaccine, less than 4% in each group reported serious adverse events, and there were no differences by study group in the incidence of medically significant conditions or new onset chronic or autoimmune diseases. All five deaths (one in the vaccine group and four in the control group) were judged by investigators to be unrelated to vaccination (12). Unpublished data from this trial among females who had received at least one dose of vaccine found that solicited general adverse events did not differ by infection status with HPV 16 or 18 at baseline, with rates of 67% in females who were HPV 16/18 seronegative and HPV DNA negative, 64% in females who were HPV 16/18 seropositive or HPV DNA positive, and 67% in females who were HPV DNA positive (Gary Dubin, GSK, pers. comm., 2007). (See Annex 2 for updated information on this issue.)

The European post-marketing surveillance system (EudraVigilance) has been monitoring safety of this vaccine since market approval in September 2007, but have not yet identified reports related to this vaccine; safety will also be monitored in Australia (21,87,92) Aleksandra Caric, WHO, pers. comm., March 2008).

**Safety in immunocompromised persons**

**Key point**

- Safety data in immunocompromised persons are not yet available for either vaccine.

There are as yet no data on safety in immunocompromised individuals. Studies of the quadrivalent vaccines are under way among HIV-infected children, women and men in Africa, Brazil and the United States. (See Annex 2 for updated information on this issue) Safety studies of the bivalent vaccine are under way for HIV-infected females in Europe and South Africa (see Section 5). Several countries have issued guidance on HPV vaccine use in immunocompromised individuals (see Section 6). For example, the United States Advisory Committee on Immunization Practices (ACIP) states:
Because quadrivalent HPV vaccine is a non-infectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent (8).

Guidance from Australia notes that data on the bivalent vaccine in immunocompromised persons are not available, and that vaccination may not elicit an adequate immune response (6).

**Safety during pregnancy**

**Key points**

- Neither HPV vaccine is recommended for use during pregnancy.
- Clinical trials excluded pregnant females and actively tried to limit accidental inclusion, but some pregnancies occurred during trials of both vaccines.
- In phase II and III trials of both vaccines, pregnancy outcomes have not differed significantly between vaccinees and placebo recipients.

Regulatory authorities and the recommendations of some countries do not recommend the quadrivalent and bivalent vaccines for use in pregnant females (4-6,8,93-96). Because the target group for vaccination may include females of reproductive age in some settings, it is important to understand the effects of vaccination on pregnancy and infant outcomes. The fact that both HPV vaccines are non-infectious reduces, but does not eliminate, concern that vaccination could harm pregnant females or their fetuses.

Trials of both vaccines excluded females who were pregnant. A pregnancy test was done before each vaccine dose was administered, participants were encouraged to use contraception, and vaccination was discontinued in females found to be pregnant. Nevertheless, some participants became pregnant during the trials and provide the basis for considering safety in pregnancy (12). Safety data also come from animal studies. Based on these data, both vaccines appear to have good safety profiles in pregnancy. Ongoing evaluation of trial participants and post-marketing surveillance will provide additional data (82).

**Quadrivalent vaccine**

The FDA has classified quadrivalent vaccine as Category B2 because animal studies in rats have shown no evidence of impaired fertility or harm to the fetus, but data from well-controlled studies in pregnant women are not available (5,8).

Among participants enrolled in a phase III trial, with pregnancies whose estimated date of conception was within 30 days of vaccination, abnormal outcomes (including congenital anomalies or other medical conditions) occurred among 20% (14/70) of vaccinees and 9% (6/66) of placebo recipients. Congenital anomalies were reported in 47 infants or fetuses of 25 vaccinees and 22 placebo recipients; in 5 cases, these anomalies were related to pregnancies conceived within 30 days of vaccination. An expert panel unaware of vaccination status concluded that the anomalies were diverse and consistent with those seen in offspring of young females. Proportions of vaccinees and placebo recipients reporting spontaneous (21.9% vs. 23.3%) and elective abortions (11.1% vs. 12.5%) were similar (34).

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2 Animal studies have revealed no evidence of harm to the fetus, however, there are no adequate and well-controlled studies in pregnant women.
A combined analysis of both phase III trials compared 1315 vaccinees and 1337 placebo recipients who became pregnant and had known pregnancy outcomes (34). Proportions in the two groups were similar for live births (66% vs. 63%), Caesarean sections (26% vs. 25%), spontaneous abortions (22% vs. 23%), elective abortions (11% vs. 13%) and late fetal deaths (34% vs. 37%). Among pregnancies with outcomes of live birth, or spontaneous abortion or late fetal death, whose estimated date of conception was within 30 days of receipt of vaccine or placebo, rates of spontaneous loss were similar (23.1% vs. 28.3%). Among subjects whose pregnancy went to term, 25.7% of vaccinees and 25.0% of placebo recipients required a Caesarean section. Few pregnant vaccinees or placebo recipients experienced a serious adverse event (3.4% vs. 4.0%).

All countries that have addressed vaccine use during pregnancy as part of recommendations for vaccine use in national immunization programmes to the end of January 2008 indicated that pregnant women should not be vaccinated (see Section 6). For example, if a female is found to be pregnant after initiating the vaccine series, ACIP advises that remaining doses should be delayed until the pregnancy is completed, but that no special interventions are needed (8).

**Bivalent vaccine**

Studies in rats have shown no evidence of impaired fertility or harm to the fetus. The adjuvant substance 3-O-desacyl-4'-monophosphoryl lipid A (MPL) did not cause bacterial mutation or chromosomal damage in in vitro assays, nor genetic damage in rats (6).

An interim analysis of a phase III clinical trial compared 464 HPV vaccine recipients with 452 control subjects receiving hepatitis A vaccine. The two groups had similar proportions of elective termination (19% vs. 21%), spontaneous abortion (15% vs. 12%), normal infants (59% for both groups) and abnormal infants (1% vs. 2%) (12). Among participants who had their last menstrual period within 30 days before, or 45 days after, a vaccine dose, most gave birth to normal infants. Proportions with spontaneous abortion were 11% for the HPV vaccine group, 5.7% for the hepatitis A vaccine group and 13.8% for the aluminium-containing placebo group; these figures compare to a background rate of spontaneous abortion of 13–16%. The effect of the vaccine on fetal, perinatal and postnatal development and survival has not been evaluated in trials (6).

**Safety during lactation**

**Key points**
- Data on the quadrivalent vaccine in lactating females indicate no adverse effects.
- The safety of the bivalent vaccine in lactating females has not been assessed.

**Quadrivalent vaccine**

An interim analysis of a phase III clinical trial compared 500 vaccinees with 495 placebo recipients who were lactating during the vaccination period. A total of 3.4% infants borne to vaccinees experienced a serious adverse event, compared with 1.8% of infants borne to placebo recipients. Of the 23 adverse events among the 17 infants of vaccine recipients, none was judged by investigators to be vaccine related (4,8).

**Bivalent vaccine**

The safety of this vaccine has not been evaluated in lactating females or their infants. Studies in rats suggest a transfer of antibodies to HPV 16 and 18 via breast milk during lactation (6). Based on these data, the manufacturer and some countries have
recommended that the bivalent vaccine should be administered to lactating females only when advantages outweigh the risks (6).

### 3.2 Practical considerations for vaccine administration and delivery

Administration and delivery are addressed below and in Section 5.

#### 3.2.1 Vaccination schedule, dose and administration

<table>
<thead>
<tr>
<th>Schedule</th>
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<tbody>
<tr>
<td><strong>Key points</strong></td>
</tr>
<tr>
<td>• Both vaccines are given as a three-dose series over 6 months.</td>
</tr>
<tr>
<td>• Several organizations provide guidance on alternative schedules.</td>
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<tr>
<td>• The need for boosters has not been established.</td>
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Both vaccines are administered as a three-dose series, and robust data on clinical efficacy are available only after three doses (3). The need for a booster dose has not been established for either vaccine (6,8) but will be evaluated as follow-up data accrue.

**Quadrivalent vaccine**

The quadrivalent vaccine is given at baseline and after 2 and 6 months -- a schedule recommended by all the product circulars in all countries that have licensed the vaccine (4), Eliav Barr, pers. comm., August 2007). The manufacturer recommends a minimum interval between the first and second dose of 4 weeks, and minimum interval between the second and third dose of 12 weeks (4). In trials of females aged 16–26 years, intervals between the first and second dose varied from 6 to 12 weeks, and intervals between second and third dose varied from 12 to 23 weeks, but these variations did not appreciably reduce GMTs after vaccination (8). GMTs for all four type-specific HPV antibodies were higher if the second dose was given earlier than 2 months after the first dose, and lower if given later than 2 months. However, GMTs for all 4 type-specific HPV antibodies were lower if the third dose was given earlier than 105 days after the second dose, and higher if given more than 138 days after the second dose (4). Controlled and observational studies are under way to evaluate the immunogenicity of alternative schedules (see Section 5).

In several countries, vaccine product circulars or recommendations on vaccine use address alternative schedules if doses are delayed (e.g. due to intercurrent illness or scheduling problems). For example, ACIP advises the following:

- if the initial dose was inadequate or the dosing interval shorter than recommended, re-administer the vaccine
- if the schedule is interrupted, dosing should be continued instead of restarting the three-dose series
- if the series is interrupted after the first dose, the second dose should be given as soon as possible and the third dose should follow the second dose by at least 12 weeks
- if the third dose is delayed, it should be given as soon as possible.

In Canada (in Quebec), the proposed public sector immunization program will vaccinate girls at 0 and 2 months, but delay the third dose until about 5 years after the first dose. A
delayed third dose has been used in Canada to deliver three-dose hepatitis B vaccines to adolescents (Randall Hyer, Merck, pers. comm., March 2008).

**Bivalent vaccine**

This vaccine is given at baseline and after 1 and 6 months (6) – a schedule that is recommended by product circulars in all countries that have licensed the vaccine. The manufacturer recommends that, if flexibility in the schedule is necessary, the second dose can be administered between 1 and 2.5 months after the first dose (6). Studies on alternative dosing are under way (Gary Dubin, GSK, pers. comm., August 2007). (See Annex 2 for updated information on this issue.)

**Dose and administration**

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>• Each dose of the quadrivalent or bivalent vaccine is given in a 0.5mL volume by intramuscular injection.</td>
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<tr>
<td>• Both vaccines are available as single-dose vials and pre-filled syringes; dilution is not needed.</td>
</tr>
<tr>
<td>• Both vaccines should be maintained in a cold chain during storage and transport at 2° to 8°C (36–46°F), and should not be frozen.</td>
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Both vaccines are available as a sterile suspension of VLPs for intramuscular injection as single-use glass vials or single use, pre-filled syringes. Dilution is not necessary (3, 4, 6). Both vaccines should be shaken well before administration to maintain the suspension, and should not be used if particulates or discoloration are noted (6, 8).

Both vaccines should be maintained at 2° to 8°C (36° to 46°F) and not frozen (6, 8). Current packaging of both vaccines has a higher per-dose volume than traditional multidose Expanded Programme on Immunization (EPI) vaccines, and this may pose problems for low or middle-income countries, or delivery settings with limited cold-chain capacity at peripheral levels (e.g. schools).

Each of the three doses is 0.5 mL in volume and is given as an intramuscular injection (4, 6). Subcutaneous, intradermal and intravenous administration have not been studied for either vaccine and are not recommended (4, 6).

**Quadrivalent vaccine**

Injection is advised in the deltoid muscle or high anterolateral areas of the thigh (4). When this vaccine is accidentally held at or below 25°C, administration may occur up to 3 days later (Eliav Barr, Merck, pers. comm., 2007). As of mid-2007, reports from over 60 countries where more than 10 million doses of quadrivalent vaccine had been distributed have noted rare problems with the quadrivalent vaccine pre-filled syringe, including 148 reports of medical device complication and 4 reports of device malfunction (Adrian Dana, Merck, pers. comm., June 2007).

**Bivalent vaccine**

Injection is advised in the deltoid muscle (6). The shelf life of this vaccine at 2° to 8°C is three years from date of manufacture. This vaccine is stable when stored at temperatures up to 37° for 1 week, but these storage conditions are not recommended (6).
3.2.2 Co-administration with other vaccines

Key points
- Understanding the safety and immunogenicity of HPV vaccines when co-administered with other vaccines is important where multiple vaccines are given at the same age.
- Concurrent administration of quadrivalent vaccine and the recombinant hepatitis B vaccine resulted in robust GMTs to vaccine-related HPV types, no appreciable interference to the immune response for either vaccine and a safety profile similar to that of individuals vaccinated with a single vaccine.
- Studies of safety and immunogenicity of the quadrivalent vaccine co-administered with vaccines other than hepatitis B, and the bivalent vaccine co-administered with other vaccines, are under way.

General considerations
The primary target population for HPV vaccines is young adolescents, who may receive diphtheria, tetanus, pertussis, meningococcal conjugate vaccine, hepatitis B and rubella or other vaccines at the same age. Understanding the safety and immunogenicity of HPV vaccines when co-administered with other common vaccines is important in settings where multiple vaccines are recommended for young adolescents (82).

Quadrivalent vaccine
In phase III trials of females aged 16–23 years, co-administration of the HPV and hepatitis B vaccines resulted in robust GMTs to HPV 6, 11, 16 and 18, and no significant interference for the immune response for either vaccine, although there was a non-significant reduction in hepatitis B GMT response (44). The safety profile of subjects who received both vaccines was similar to that of subjects who received only one of the vaccines. Studies are under way to evaluate its immunogenicity when administered with other vaccines (see Section 5). (See Annex 2 for updated information on this issue.)

Some countries that have recommended HPV vaccines for national immunization programmes address co-administration. For example, Switzerland recommends the vaccine may be administered concomitantly with hepatitis B vaccine and the diphtheria and tetanus vaccine (dT/dTpa). As a precaution, however, the first HPV dose should not be co-administered with the dT/dTpa vaccine (93). ACIP recommends that the quadrivalent vaccine be administered at the same visit as other age-appropriate vaccines, using separate syringes and different anatomic sites. ACIP notes that administering all indicated vaccines at the same visit increases the likelihood that vaccines are received on schedule (8). According to some experts, the non-infectious nature of this vaccine reduces the risk that it would adversely affect the safety and efficacy of other vaccines (8).

Bivalent vaccine
Co-administration studies with several routinely used adolescent vaccines are under way (see Section 5). (See Annex 2 for updated information on this issue.)
**Co-administration with other medications commonly used by older children, adolescents and young adults**

<table>
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<tr>
<td>• Co-administration of HPV vaccine with other commonly used age-appropriate medications has not been extensively studied.</td>
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<tr>
<td>• Studies of both vaccines show that efficacy is not significantly altered in vaccinees who use hormonal contraceptives.</td>
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HPV vaccine target populations may use medications that could potentially influence vaccine safety or efficacy; these include hormonal contraceptives, antimalarials, antihelminthics and other medications. Little is known about how these medications might influence vaccine-induced immunity or safety. Some national immunization authorities have advised that persons taking immunosuppressive medications may have a reduced immune response to HPV vaccines (see Section 6) (4,6). Post-marketing surveillance in Europe and the United States can potentially evaluate the influence of commonly used contraceptives, but cannot assess the influence of medicines used in developing countries, such as anti-malarials (see Section 5 on monitoring).

**Quadrivalent vaccine**

In studies with more than 13 000 subjects using hormonal contraceptives, vaccine efficacy was similar to that in subjects who did not use such contraceptives (4).

**Bivalent vaccine**

There was no evidence that use of hormonal contraceptives influenced vaccine efficacy among the 60% of trial participants who used hormonal contraceptives (6).

### 3.2.3 Contraindications and precautions

<table>
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<tr>
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<tbody>
<tr>
<td>• Vaccines should not be given to persons with known hypersensitivities to vaccine components.</td>
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<tr>
<td>• Several countries recommend that vaccination should be postponed for individuals who have a recent or current severe febrile illness.</td>
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<tr>
<td>• Due to the occurrence of syncope in some girls after vaccination with the quadrivalent vaccine, ACIP restated their longstanding recommendation that individuals receiving vaccines of any kind should be observed for 15 minutes following vaccination.</td>
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**Contraindications**

**Hypersensitivity to vaccine components**

Vaccine manufacturers, national regulatory authorities and vaccine policy bodies of several countries advise that quadrivalent and bivalent vaccines should not be given to persons with known hypersensitivity to any vaccine component, and that persons showing hypersensitivity after receiving any dose of either vaccine should not receive additional doses (6,8,93-96). The quadrivalent vaccine is manufactured on a *Saccharomyces cerevisiae* yeast substrate (4). VAERS data from the United States indicate that vaccines derived from recombinant yeast pose a minimal risk for anaphylactic reactions in people with a history of allergic reactions to *Saccharomyces cerevisiae* (baker’s yeast) (97). The baculovirus expression system used to produce the bivalent vaccine in *Trichoplusia ni* cells is relatively new, so data on allergic reactions to this component are limited (6).
Acute and chronic illness

Like all injectable vaccines, both HPV vaccines should be deferred or given with caution to people with bleeding disorders (4,76). Several national authorities recommend that individuals with recent or current severe febrile illness should postpone vaccine use (see Section 6) (6,8,93-96). However, vaccine manufacturers do not consider minor acute infections (e.g. low-grade fevers or mild respiratory infections) as contraindications (4,6). As of 2007, there were no data on the use of either vaccine in persons with chronic or recurrent illness, including impaired immune response (see Section 5) (4,6). Immunocompromised individuals may have a blunted immune response to vaccines (4,6).

Precautions for administration

Vaccine policy bodies of several countries advise reviewing the medical history and a clinical examination before administering vaccines, including HPV vaccines (see Section 6). Medical treatment should be readily available in case of rare anaphylactic events after vaccination. Syncope due to a vasovagal or vasodepressor reaction has occurred after vaccination with the quadrivalent vaccine and other vaccines among adolescents and young adults (see above) (98). (See Annex 2 for updated information on this issue). This finding caused ACIP to reinforce their longstanding recommendation to observe individuals vaccinated with any vaccine, including HPV vaccines, for 15 minutes after injection, to reduce risks associated with syncope (8).

3.2.4 Interchangeability of HPV vaccines

There are no safety, immunogenicity, or efficacy data to support the interchangeability of the two HPV vaccines (8,67).

3.2.5 Testing before vaccination

HPV serologic or DNA testing or cytology (Pap test) before vaccination is not recommended by either vaccine manufacturer or by national regulatory authorities. Both vaccines have good safety profiles in females with evidence of past or current infection with vaccine-related types before vaccination; thus, knowledge of infection before vaccination would not be a safety concern. Both vaccines are highly efficacious against CIN2+ associated with HPV types to which females were naive at baseline (12,42). Pre-screening of vaccination candidates would also be costly and complicated.

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Gall S. Substantial impact on precancerous lesions and HPV infections through 5.5 years in women vaccinated with the HPV-16/18 L1 VLP AS04 candidate vaccine. In: *Proceedings of the Annual Meeting of the American Association for Cancer Research*. Los Angeles, USA, 2007.


91 Surveillance of Adverse Events Following Vaccination in the Community (SAEFVIC) Immunization CCRE Infectious Disease Unit; Murdoch Children’s Research Unit; Royal Children’s Hospital Flemington Rd, Parkville 3052, Melbourne, Australia, 2007, 2007. accessed http://www.abc.net.au/worldtoday/content/2007/s1929912.htm).


4 The impact and cost effectiveness of human papillomavirus vaccination programmes

This section considers the impact of human papillomavirus (HPV) vaccination programmes in terms of health benefits and averting costs associated with diseases; it also considers the projected cost effectiveness of possible HPV vaccination strategies. The generic phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either the bivalent or the quadrivalent vaccine, because both vaccines contain virus-like particles (VLPs) for HPV 16 and HPV 18.

4.1 Impact of HPV vaccination programmes on disease prevention and averted costs at a population level

4.1.1 General considerations

**Key points**

- The population impact of vaccination for HPV has been estimated only by controlled trials and modelling. In the future, it will be possible to validate the estimated impact using results of population-based cancer surveillance studies that are ongoing in a few high-income countries.

- The high efficacy of both the bivalent and quadrivalent vaccines in preventing precancerous cervical lesions in females naive to HPV 16 and 18 before vaccination, and the strong association between precancerous lesions and invasive cancer, suggests that vaccination programmes for young adolescent females will reduce incidence of cervical, vaginal, vulvar, anal, and certain head and neck cancers associated with vaccine-related HPV types.

- The high efficacy of the quadrivalent vaccine against genital warts in females naive to HPV 6 and 11 before vaccination suggests that vaccination programmes will reduce incidence of genital warts.

- If ongoing trials in males demonstrate efficacy against anogenital precancers or cancers related to HPV 16 or 18, or against anogenital warts related to HPV 6 or 11 (for the quadrivalent vaccine), male vaccination may reduce incidence of these diseases in males.

- Vaccine impact in a given population will depend on vaccine efficacy in preventing HPV-related diseases, the proportion of these diseases caused by vaccine-related HPV types, the proportion of the target population naive to vaccine-related HPV types, vaccine coverage, duration of protection, potential for cross-protection or type replacement with non-vaccine-related types following vaccination, and the influence of vaccination on cervical cancer screening programmes.

To date, all estimates of the population impact of vaccination have been based on clinical trials and modelling studies, rather than on population-based disease surveillance. Ongoing studies in Australia, some Nordic countries, the United States and other high-income countries will examine the population impact of vaccination on prevalence of vaccine-related HPV types, abnormal cytology, cervical precancers and cancer, using national or regional cytology, histology or cancer registries. However, few low or middle-income countries have this surveillance capacity (see Section 5).
Based on epidemiology, clinical trials and modelling studies, it is expected that HPV 16/18 vaccination will prevent incidence and mortality due to:

- invasive squamous cell cervical cancer and cervical adenocarcinoma related to HPV 16 and 18
- the subset of vaginal cancer and vaginal intraepithelial neoplasia (VaIN), vulvar cancer and vulvar intraepithelial neoplasia (VIN), anal cancer and anal intraepithelial neoplasia (AIN), and head and neck cancers caused by HPV 16 and 18.

Programmes using the quadrivalent vaccine are expected to also reduce incidence of anogenital warts and possibly recurrent respiratory papillomatosis (RRP) due to HPV 6 and 11 (Table 4.1) \(^1\).

If ongoing trials in males demonstrate high vaccine efficacy against anogenital anal precancers or cancers related to HPV 16 or 18, or against anogenital warts related to HPV 6 or 11 (for the quadrivalent vaccine), HPV vaccines may also reduce incidence of these anogenital diseases in males (see Section 5).

The impact of vaccination in a specific population will depend on:

- vaccine efficacy in that population
- the population’s incidence of cervical cancer and other HPV-related diseases
- the proportion of disease caused by vaccine-related HPV types
- the proportion of vaccinated persons naive to vaccine-related types at the time of vaccination
- coverage in the target population and the duration of vaccine protection.

Impact will also depend on the potential for vaccine cross-protection against oncogenic HPV types other than those targeted by vaccines, as suggested by preliminary data from both vaccines (see Section 3), and possible increases in the incidence of disease caused by non-vaccine targeted types (referred to as “type replacement”).

It is not yet known whether vaccine efficacy will be influenced by concurrent illness (e.g. HIV infection or malnutrition), other biologic factors, or co-administered vaccines and medications. Vaccine impact in a population may be influenced both by direct protection of vaccinated persons and indirect protection of non-vaccinated persons resulting from reduced HPV transmission in the community (herd immunity), but the magnitude of indirect benefits is uncertain (2-5). Impact may also vary if vaccination influences coverage and effectiveness of cervical cancer screening, sexual behaviours or condom use.

### 4.1.2 Tools used to estimate the impact and cost effectiveness of vaccination programmes

**Key points**

- Cohort, population dynamic and hybrid models have estimated the benefits and cost effectiveness of HPV vaccination, with and without screening, in various populations.
- These models have considered numerous vaccination strategies, health outcomes, health contexts and cost scenarios using a wide range of data inputs and assumptions. Further modelling using country and region-specific data can refine these estimates.
• Most models have evaluated high-income countries that have cervical cancer screening programmes. Few have evaluated low or middle-income countries, which have the highest cervical cancer burden.

• Few models have incorporated HPV transmission dynamics to assess herd immunity, due to their complexity and data requirements.

• Most model results predict that HPV vaccination will substantially reduce incidence of, and mortality due to, HPV-related disease, particularly cervical cancer. They also predict that, under certain assumptions (including substantially lower vaccine prices), vaccination programmes can be cost effective in low, middle and high-income countries.

As with other areas of public health, decisions about the best strategies to control cervical cancer and other HPV-related disease have to be made despite uncertainty and incomplete information. Decisions about introducing HPV vaccination are particularly complex because of the rapid evolution of our understanding of the natural history of HPV and interactions with screening programmes, which are changing in many countries. Another issue is that vaccines will be introduced in diverse epidemiologic, economic, cultural and political contexts.

Modelling that systematically estimates vaccination impact or cost effectiveness has been extensively used to inform decisions about HPV vaccine introduction. Models can also identify factors that are likely to influence impact and cost effectiveness, guide design of future clinical studies and operational research. Model results contribute to decision making about vaccine introduction that takes into account broader issues including equity, public demand, economic constraints and other factors (6-8).

Three types of models have projected the impact and economic consequences of HPV vaccination – cohort models, population dynamic or transmission models, and hybrid models that use both transmission and stochastic elements.

Each type of model has advantages and disadvantages (2,6,9-12). Models use a wide range of assumptions, calibration approaches, and estimation of unknown parameters – including the natural history of HPV infection – that can strongly influence results (3,6,13-15). Many models have addressed the impact and cost effectiveness of vaccines in settings where cervical cancer screening exists or could be introduced using simple, low-cost methods (e.g. by considering screening as an alternative intervention or examining combined strategies of vaccination and screening). In contrast, most models of infant and childhood vaccines compare vaccination to no intervention.

Current models are limited by uncertainty about some data inputs, and by the difficulty of validating modelled scenarios with real-world data. Also, because of limited data, few HPV vaccine models have addressed the potential impact of herd immunity or have examined non-cervical precancer or cancer outcomes (1,2,4-6,14,16-22). Ongoing HPV transmission studies will help to refine assumptions about herd immunity (23). Data on low and middle-income countries are especially sparse, but work is under way to fill this gap (20,24-26). The results of models vary by country or region, but most have predicted that vaccination will significantly reduce the incidence of cervical cancer in the long term, and can be cost effective in certain scenarios (25-30).
4.1.3 Health impact of HPV vaccines

Impact on precancerous lesions and cancers of the cervix in low and middle-income countries with no or limited screening

Key points

- Cohort models estimate that vaccination against HPV 16/18 (i.e. both 16 and 18) will substantially reduce cervical cancer incidence and mortality. Mortality reductions will be the most important benefit in low and middle-income countries with no or limited screening.

- Vaccine coverage and duration of protection are expected to be the greatest determinants of vaccine impact, assuming vaccine efficacy is high in the target population.

- Models predict that vaccination will reduce lifetime risk of cervical cancer by 35–80%, depending on assumptions related to vaccination and screening programmes.

- Models predict that vaccination against HPV 16/18 in all Global Alliance for Vaccines and Immunization (GAVI)-eligible countries that scaled up coverage from 25% to 70% over 10 years would save the lives of more than one million women.

In countries where screening is absent or limited, and where treatment access is poor, most cases of cervical cancer are brought to medical attention when symptoms are severe, disease is advanced and mortality is high. In these settings, a reduction in cervical cancer deaths will be the most important benefit of vaccination (1). Both cohort and dynamic transmission models for several regions project that vaccinating girls could substantially reduce cervical cancer incidence and mortality compared to the status quo, even if the protection provided by the vaccine were to last for only a moderate length of time (2,5,12,25) (Table 4.1). The most important determinants of programme effectiveness would be coverage of a young female target population with the three-dose series, and duration of protection. The possible need for a fourth booster dose, or use of a 2-dose series, would influence attainable coverage and cost effectiveness (see Section 5). Vaccine effectiveness would decline as age of the target population increases, because more vaccinees will be infected with a vaccine-related HPV type before vaccination. The effectiveness of screening programmes will also strongly influence the impact of vaccination programmes. In turn, vaccination programmes could lead to modifications of screening programmes (see Section 4.1.4, below). (See Annex 2 for updated information on this issue.)

In the Americas, a cohort model using data from Costa Rica estimated that an HPV 16/18 vaccine that prevented 98% of persistent HPV 16 and 18 infection would reduce HPV 16/18-related cervical cancer by about the same percentage (i.e. 98%) and the incidence of cervical cancer due to all oncogenic HPV types by about 51% (31). A study of 33 countries in the Caribbean and Latin America estimated substantial variation in vaccine impact by country, due to differences in age-specific population size, age-specific cancer incidence rate and health infrastructure (26). Seventy percent coverage of girls aged 12 years would reduce cancer incidence by 47–54%, preventing between 1400 and 15 000 cases of cervical cancer in each country’s birth cohort. Over 10 years, vaccination coverage of 25–70% in girls aged 12 years would prevent cervical cancer in half a million women. In Argentina, Brazil, Colombia, Mexico and Peru, adding screening of adult women three times per lifetime to pre-adolescent vaccination would reduce cervical cancer by an additional 20% (26,27,32).
A model of HPV 16/18 vaccination in Brazil estimated that 70% vaccination coverage without screening would reduce the lifetime risk of cervical cancer by an average of 43%, a reduction greater than that projected for screening three times per lifetime without vaccination. However, the most effective strategy was a combination of vaccination and three lifetime screens, which was estimated to reduce risk by 61% (25). Another Brazilian analysis estimated that HPV 16/18 vaccination of girls aged 12 years would reduce cervical cancer cases and deaths by about 61% if vaccines also provided cross-protection against some non-vaccine-related HPV types (33).

In Mexico, a dynamic transmission model estimated the impact of various quadrivalent HPV vaccination strategies in reducing genital warts, and cervical precancers and cancer. Strategies included vaccinating girls aged 12 years, girls and boys aged 12 years, and females or both sexes aged 12–24 years (as a temporary catch-up vaccination). Based on fairly optimistic assumptions about vaccine coverage, efficacy and duration in both genders, the analysis estimated that the most effective strategy was to vaccinate 12-year-old boys and girls, with a temporary catch-up programme for those aged 12–24 years. The model estimated that the incidence of genital warts, and high-grade cervical precancers and cancers due to vaccine-related HPV types, would decline by 87–98% within 50 years of vaccine introduction (20).

In Asia, an individual-based microsimulation model estimated the impact of HPV 16/18 vaccination of adolescent girls in India, a country that accounts for about a quarter of global cervical cancer cases. In this model, vaccination alone reduced cervical cancer incidence by 44%, vaccination combined with screening three times per lifetime reduced cancer incidence by more than 55%, and screening alone reduced incidence by 10–33%, depending on the screening test (30).

A model of HPV 16/18 vaccination of girls in a high-risk, unscreened population in Ho Chi Minh City, Viet Nam predicted an approximately 50% mean reduction in lifetime cancer risk, assuming 100% vaccine efficacy, lifelong protection and 75% coverage. If vaccine protection lasted only 10 years, mean reduction in lifetime cancer risk was 37% (28). Another analysis compared the impact of HPV 16/18 vaccination in Ho Chi Minh City and Hanoi, which have different cancer incidence rates. A combined strategy of vaccinating girls aged 10–12 years at 70% coverage, and screening women three times between ages 30 and 45 years, was estimated to be more effective than vaccination alone or screening alone, and to reduce lifetime cancer risk by 65% in Ho Chi Minh City and 68% in Hanoi (29).

Transmission models adapted to Taiwan estimated the impact of the quadrivalent HPV vaccination of girls aged 12 years and a 5-year catch-up programme for females aged 12–24 years, in combination with current screening practices. All vaccination strategies were estimated to reduce the incidence of HPV 6/11/16/18-related genital warts, cervical intraepithelial neoplasia (CIN) and cervical cancers by more than 70% within 50 years following vaccine introduction. Most early disease reductions were related to disease associated with HPV 6/11 (21).

An analysis of 72 GAVI-eligible countries (i.e. countries with a gross national income (GNI) < US$ 1000 per capita in 2003) used population-based data to estimate the impact of an HPV 16/18 vaccine. With 70% vaccine coverage of young adolescent girls, it was estimated that cancer incidence would decline from 35% in some countries (Ethiopia, Ghana and Nigeria) to more than 50% in others (India, Kenya and Uganda) depending on country-specific cancer incidence, age structure and the proportion of cancers due to HPV 16 and 18. If all GAVI-eligible countries were to implement vaccination that scaled
up coverage from 25% to 70% over 10 consecutive birth cohorts, the lives of more than one million women would be saved (27).

**Impact on precancerous lesions and cancers of the cervix in high-income countries with established screening**

- Models predict that HPV vaccination will reduce incidence of invasive cervical cancer and associated mortality by 20–70%, and substantially reduce morbidity associated with treatment of CIN2/3, adenocarcinoma in situ (AIS), and mild and equivocal cervical abnormalities.
- HPV 16/18 vaccines are expected to have relatively less impact on reducing cervical cancer incidence and mortality in countries with established and effective screening programmes than in countries that lack effective screening programmes.
- Compared to countries without screening, countries with screening are expected to observe a relatively greater impact of vaccination on adenocarcinoma incidence, because adenocarcinomas are less readily detected by screening.
- The impact of vaccination on precancerous lesions will be observed more quickly than that on cancer incidence, which may require 10–30 years to measure.

Models predict that HPV 16/18 vaccines could reduce incidence of invasive cervical cancer and associated mortality by 20–70%; they could also substantially reduce morbidity associated with follow-up and treatment of CIN2/3, AIS and low-grade or equivocal cytology abnormalities (1,31,34-37). The effect of HPV 6/11 vaccination in reducing large numbers of equivocal and low-grade abnormal cytology results may further reduce follow-up, health-care costs and patient anxiety (38,39) (Table 4.1).

In high-income countries, incidence and mortality of invasive cervical cancer has declined dramatically due to organized or opportunistic screening, better detection and management of early precancerous lesions, and access to effective treatment (see Section 2). Against this backdrop, HPV 16/18 vaccination would have relatively less impact on reducing cervical cancer incidence and mortality than it would in countries that lack screening. Settings that can monitor incidence of precancerous lesions through screening programmes should see reductions in the incidence of precancerous cervical lesions due to HPV 16/18 before reductions in cancers related to HPV 16 or 18. Some studies suggest that the quadrivalent vaccination would reduce the incidence of equivocal cervical lesions (ASCUS) and low-grade squamous intraepithelial lesions (LSIL) about 10% more than the bivalent vaccine, because a small proportion of these abnormalities are due to HPV 6 and 11 (10,18,40).

Vaccination is expected to reduce cases of adenocarcinoma (most commonly caused by HPV 16, 18, 31 and 45) even in highly-screened populations, because screening is less effective in detecting adenosquamous and adenocarcinoma than in detecting squamous cell carcinoma (41). Given data that show that HPV 16/18 vaccines may provide partial protection against some oncogenic non-vaccine-related HPV types, such as 31 or 45 (see Section 3), modelling suggests this cross-protection could reduce risk of both squamous cell cancer and adenocarcinoma by an additional 2–20% (42,43).

Published and unpublished models in several regions have estimated impact and have informed the recommendations about HPV 16/18 vaccination in national immunization programmes of several countries (see Section 6) (Table 4.3).
A United States cohort model predicted that vaccinating the full cohort of girls aged 12 years would reduce lifetime risk of cervical cancer by 20–66%, depending on assumptions about vaccine efficacy, duration of protection and screening (12,15,44,45). These models also predict a 21% decrease in low-grade cytologic abnormalities over the lifetime of the vaccinated cohort (45). One United States-based model examined quadrivalent HPV vaccination of girls aged 12 years, plus catch-up vaccination of females aged 12–24 years, after assuming partial cross-protection against five oncogenic HPV types other than 16 and 18. The model projected that vaccination would reduce cases of cervical cancer by 35 000, CIN2/3 by 1.3 million, CIN1 by 349 000 and HPV 6/11-related genital warts by 3 million over 25 years (43). A similar United States-based analysis estimated that, by year 25, vaccination compared to no vaccination would result in an approximate reduction in the cumulative number of HPV 6/11/16/18-related cases of CIN1 by 430 000, CIN2/3 by 1.4 million and cervical cancer by 30 000 (46). In Canada, a model estimated that programmes using HPV 16/18 vaccines would need to vaccinate 4–13 girls to prevent one case of CIN1, 7–18 girls to prevent one case of CIN2 and 279–9080 girls to prevent one case of cervical cancer (34).

In Europe, a French model predicted that HPV 16/18 vaccination combined with the current screening strategy would reduce lifetime risk of cervical cancer by 65%. It would be necessary to vaccinate 47 girls to prevent one case of CIN1, 19 girls to prevent one case of CIN2/3 and 142 girls to prevent one case of cervical cancer (47). In Hungary, a transmission model of the quadrivalent vaccine estimated that vaccinating girls before age 12 years with 85% population coverage, plus 5-year catch-up vaccination for females aged 12–24 years, was the most effective strategy examined, reducing the incidence of HPV 6/11/16/18-related genital warts, CIN2/3 and cervical cancer by more than 70% within fifty years after introduction of vaccination (48).

Influence on cervical disease of vaccinating catch-up populations of older adolescents and young adults

- Because HPV vaccines are prophylactic, the largest impact of vaccination is expected to result from high coverage of young adolescent girls rather than of older age groups.
- HPV vaccine catch-up campaigns could prevent disease due to vaccine-related HPV types in females naive to vaccine-related HPV types.
- Given that the target population for catch-up campaigns would be older than the primary target population of young adolescents, reductions in cervical cancer incidence among catch-up vaccinees are likely to be observed more quickly than incidence reductions among younger vaccinees.
- Some models predict that, as the age of vaccination increases beyond the early 20s, the marginal benefits of vaccination decrease and marginal costs increase.

Catch-up campaigns are often used to rapidly increase coverage at the beginning of new vaccination programmes. HPV vaccine catch-up campaigns could benefit the many older adolescent females and young women who are naive to at least one vaccine-related HPV type. At the population level, the target population age range, and the timing and duration of catch-up programmes would affect their impact and cost effectiveness. Because catch-up populations are older, the cervical precancers and cancer cases averted in previously uninfected women would be realized sooner than for younger cohorts, and these changes could be detected through screening programmes and cancer registries (2,18,38,49).

Several United States models have evaluated the impact of programmes that include catch-up vaccination. One transmission model of HPV 16/18 vaccine evaluated
vaccination of girls aged 10–12 years, and females up to 18, 21 and 26 years. The model found that, as age of vaccination extended beyond 21 years, the marginal benefits decreased and the marginal costs increased. The conclusion was that cost effectiveness would be optimized by achieving high coverage in girls younger than 13 years, and temporary catch-up vaccination of females up to the age of 21 years (38). A United States-based model of vaccination with the bivalent vaccine found that the percent reductions in cervical cancer incidence diminished with successively older upper age of female target population, namely 78% (age 10 years), 72% (age 10–18 years), 66% (age 10–25 years), 61% (age 10–35 years) and 58% (age 10–45 years) (50). These predictions were based on assumptions of 98% efficacy against HPV 16/18, 54% efficacy against HPV 31 and 88% efficacy against HPV 45.

In Europe, one United Kingdom analysis found that vaccinating young adolescent girls would substantially reduce cervical precancer and cancer incidence, but that catch-up vaccination of older females would result in only short-term reductions in these outcomes and no long-term effects (51). A United Kingdom model of the quadivalent vaccine estimated the impact of vaccinating girls aged 12 years together with 2-year catch-up vaccination for females aged 12–14, 12–17 or 12–24 years, in combination with prevailing screening practices. All vaccination strategies reduced the incidence of HPV 6/11/16/18-related genital warts by 89%, CIN1 by 79%, CIN2/3 by 85% and cervical cancers by 86% at year 100 following vaccination (22). A Norwegian model of the quadivalent vaccine found that vaccinating girls before the age of 12 years, plus a 5-year catch-up programme for females aged 12–24 years was the most effective strategy examined, substantially reducing the incidence of HPV 6/11/16/18-related genital warts, CIN and cervical cancer (52). The model assumed coverage of 90%, duration of protection of at least 10 years and unchanged cervical cancer screening. Early reductions in disease and associated costs were primarily attributable to prevention of HPV 6 and 11.

**Impact on cervical diagnostic procedures, results and follow-up**

- HPV 16/18 vaccination is expected to reduce incidence of equivocal or abnormal cytology requiring follow-up (ASC-US, ASC-H and LSIL) or precancerous lesions (high-grade CIN and high-grade squamous intraepithelial lesion, (HSIL)) requiring treatment.

- These reductions will be observed long before reductions in cervical cancer incidence.

In countries that screen for and manage abnormal cytology results, HPV 16/18 vaccination is are expected to reduce incidence of equivocal or abnormal cytology requiring follow-up (ASC-US, ASC-H and LSIL) or precancerous lesions (high-grade CIN and HSIL) requiring treatment. This impact will be observed long before impact on cervical cancer incidence, due to the shorter latency between HPV infection and development of HPV-related cytologic abnormalities. It will reduce the need for diagnostic colposcopies, biopsies and treatment, and will also reduce psychosocial distress and burden to patients, their families and employers, providers and health systems (Table 4.1).

In countries using HPV DNA testing as an adjunct to cytology for primary screening or triage of women with equivocal cytology results, vaccination would substantially reduce the proportion of patients with positive HPV DNA tests. This would allow more conservative management of women with positive HPV DNA tests, reduce colposcopy caseloads, allow longer screening intervals, reduce burden and anxiety for patients, and save health-care resources (2,12,44). The extent of these declines will depend on vaccination coverage. The timing will depend on the interval between vaccination and
initial screening, which may be a decade in countries that would vaccinate girls at ages 10–12 years, but not start screening until girls reach their early 20s (2,18).

One analysis estimated the impact of vaccination with the quadrivalent vaccine on cervical procedures in two populations – women who were naive to 14 common oncogenic HPV types and had normal cytology at baseline, and a general population in which many females may have lacked these characteristics (53). In both populations, vaccination reduced by more than 10% the proportion of women with a cytology diagnosis suggestive of CIN, a colposcopic biopsy, a definitive cervical therapy procedure, a genital biopsy and a definitive genital excision procedure. Model estimates based on 2003–2005 data from family planning clinics in six United States cities predict that, 10 years after HPV 16/18 vaccine introduction, there will be a 7–13% reduction in abnormal cytology results that are due to HPV 16 or 18, and require follow-up (54).

**Impact on non-cervical malignant anogenital disease in females and males**

- HPV 16/18 vaccination is expected to reduce vulvar, vaginal, anal, penile and oropharyngeal cancers related to HPV 16 or 18.
- Most model estimates have relied on assumptions about HPV type detection in non-cervical lesions, because estimates of vaccine efficacy against these lesions have only recently become available.

HPV 16/18 vaccination is expected to reduce cancers of the vagina and vulva related to HPV 16 or 18 (Table 4.1). However, the only published data that have assessed precursors to these endpoints are from quadrivalent vaccine trials (55) (see Section 3). More modelling of these potential vaccine benefits is under way (3,38).

HPV 16/18 vaccination is expected to reduce cancers of the anus, penis and oropharynx related to HPV 16 or 18, but efficacy in reducing these cancers or their precursors has not yet been proven for either vaccine. Models have therefore relied on assumptions about HPV type detection; future trial results may show whether these assumptions are valid.

**Impact of quadrivalent vaccine on genital warts in females and males**

- Programmes using the quadrivalent vaccine are expected to substantially reduce the incidence of genital warts, as well as the associated clinical workload and high recurrent treatment costs.
- Most of the health benefits in the first five years after vaccine introduction would be due to prevention of HPV 6/11.

The quadrivalent vaccine has high efficacy for preventing persistent HPV 6 and 11 infections and genital warts in women; efficacy studies in men are under way (see Sections 3 and 5). In high-income countries where it is common to seek care for warts, vaccination is expected to substantially reduce the incidence of these diseases and the high costs associated with repeated treatment of recurrent lesions, including the workload at sexually transmitted infection (STI) clinics that provide much of the wart-care services (3,22,38,39,46,53,56) (Table 4.1). The impact of quadrivalent vaccination on genital warts would probably be observed relatively soon after high vaccine coverage rates were achieved, because most HPV 6 and 11 infections are acquired within a year after onset of sexual activity, and the latent period between infection and appearance of genital warts is short (57). The impact of quadrivalent vaccination on the burden of HPV 6/11-related
disease, including genital warts, is also being estimated in low, middle and high-income countries, in females and males (18,20,21,47,51,58,59).

Projected estimates of the impact of the quadrivalent HPV vaccine in the United States have shown that most of the health benefits in the first five years after vaccine introduction would be due to prevention of HPV 6/11 (46). If quadrivalent vaccine trials demonstrate efficacy against warts in males, programmes using this vaccine would be expected to directly reduce the incidence of genital warts in males (20). As population prevalence of HPV 6/11 in males declines, this may indirectly reduce the incidence of genital warts in females, and this reduction may be observed more quickly than if programmes vaccinate females only (20) (see below).

Impact of quadrivalent vaccine on recurrent respiratory papillomatosis

- Programmes using the quadrivalent vaccine may reduce incidence of RRP.

The quadrivalent vaccine was highly effective in preventing persistent HPV 6 and 11 infections in women of reproductive age who were naive to these types at baseline (see Section 3). However, studies of the efficacy of quadrivalent vaccine in preventing perinatal HPV transmission or RRP in children born to vaccinated women have not been conducted because of the rarity of juvenile onset RRP (JORRP). The potential impact of quadrivalent vaccination on JORRP, as with the impact on genital warts, would probably be observed relatively soon after high coverage rates were achieved, because most HPV 6 and 11 infection among children is acquired in the birth canal – a few months to years before the child’s lesions appear (58) (Table 4.1). New post-marketing surveillance recently established by Merck & Co. in Australia, Europe and North America (see Section 5) may help to measure actual population impact on RRP.

Impact of vaccinating boys on HPV infection and HPV-related disease in males and females

- Vaccinating males may reduce vaccine-related HPV type infection and HPV-related disease endpoints in males and females, if ongoing trials indicate clinical efficacy in males.
- The added benefits of adding boys to vaccination programme are dependent on gender-specific coverage levels.

The quadrivalent vaccine is highly immunogenic in males, and ongoing studies are evaluating the immunogenicity and/or efficacy of both vaccines to prevent HPV-related disease in males (see Sections 3 and 5). If effective, HPV vaccines could reduce the incidence of penile, anal and oropharyngeal cancer due to HPV 16 and 18. Vaccinating boys with the quadrivalent vaccine may also reduce incidence of genital warts and possibly RRP. Direct benefits in cancer reduction in boys will be less than those in girls, because the prevalence of oncogenic HPV types and the incidence of HPV-related cancers is lower in males (1). Additionally, if HPV vaccines confer herd immunity, vaccinating males may provide indirect benefits to non-vaccinated females and males by reducing HPV transmission in the community. This could increase the impact of either vaccine in populations, depending on gender-specific coverage levels. Long-term studies in Nordic countries will assess this issue (60).

Dynamic transmission models in Australia, Brazil, Finland, the United Kingdom and the United States have assessed the potential impact of vaccinating boys on HPV-related outcomes in boys and girls. Most models have assumed that vaccination would reduce
susceptibility to infection, transmission of infection or perhaps duration of infectiousness, and that sexual mixing patterns, rates of partner change and protective properties of vaccines would influence the prevalence of vaccine-related HPV types. These models have generally found that vaccinating boys in addition to girls only marginally increases vaccination impact on cervical disease endpoints, even assuming high coverage and 10 years of protection in males, and that male vaccination would have a greater impact on reducing the incidence of anogenital warts (2,5,9,10,20,51,61). For example, models predicted that HPV 16 vaccination of boys in Finland at both low (10%) and high (90%) coverage levels had little benefit over vaccinating girls alone (10). If natural immunity wanes after HPV infection, models predict that vaccine impact in preventing warts would increase (62). At low-to-moderate vaccine coverage levels in girls, vaccinating boys at moderate levels may appreciably reduce infections in girls. A United States study estimated that vaccinating both females and males would substantially reduce incidence of warts, and reduce workload in STI clinics by about 10% (63).

4.1.4 Additional impact

Impact of vaccination on the effectiveness and performance of screening programmes to reduce cancer and detect precancerous lesions

- Ideally, investments in vaccination should not erode investment in effective screening programmes for vaccinated or non-vaccinated women. Widespread vaccination will allow vaccinees to safely begin screening at later ages, and to be screened less frequently than is now typical in many high-income countries.
- High coverage of HPV vaccines and resulting declines in HPV 16/18 infections will influence the effectiveness and performance of current cancer screening programmes; for example, reducing the number of false-positive cytology results, the positive predictive value of cytology for CIN3 and cancer, and the specificity of cytology.
- The lower incidence of lesions related to HPV 16 or 18 is expected to reduce the frequency of abnormal lesions reviewed by cytologists and colposcopists, and this may erode diagnostic skills over time.
- If non-type-specific HPV DNA testing becomes a primary cancer screening method, reduced incidence and prevalence of HPV 16/18 infection due to vaccination could decrease the positive predictive value and cost effectiveness of DNA tests, but would be expected to decrease false-negative CIN3 diagnoses.

Vaccine introduction should not compete for investment in screening programmes that have been proven to be effective and cost effective at the population level. In fact, decisions about HPV vaccine introduction can provide an incentive to evaluate screening programmes and, over time, make them more conservative and effective. Lower HPV 16/18 prevalence would result in fewer cytologic abnormalities due to these types. This will allow safe initiation of screening at later ages, or less frequent screening than is currently typical in many industrialized countries (2,64).

Over time, widespread use of HPV vaccines may also influence the performance of cytology as a screening test. The current problem with false-negative cytologic results may decline, but the reduction in precancerous lesions due to HPV 16/18 may reduce the positive predictive value (PPV) of cytology, particularly for CIN3 and cancer (Table 4.1). It could also increase the numbers of false-positive results, assuming constant sensitivity and specificity of cytology, which in turn could increase follow-up costs and anxiety related to these results (65). As the prevalence of both cervical precancers and cancer decreases, the specificity of cytology would also dramatically decrease, irrespective of sensitivity, and this could erode the diagnostic skills of cytologists and colposcopists, who
would see fewer abnormalities (64,65). These effects may not have been seen in
controlled clinical trial settings with strict screening guidelines and quality control
procedures, but they are expected following large-scale vaccine introduction. Some of
these effects are being considered in vaccine impact and cost-effectiveness models
(2,14,15,38).

If commercial HPV DNA tests (which currently do not provide HPV type-specific
results) replace cytology as the primary screening test (see Section 2), this may influence
the choice of screening test to combine with vaccination. For example, one United States
analysis found that HPV 16/18 vaccination programmes were more effective and cost
effective if combined with screening of women over the age of 35 years using HPV DNA
test screening rather than cytology screening (44). Another United States model predicted
that fewer CIN3 diagnoses would be missed if vaccination were combined with DNA
testing than with conventional cytology, but that false-positive results would increase
(66). Widespread HPV 16/18 vaccination could also influence the predictive value of
current HPV DNA tests. If HPV 16 and 18 prevalence declined substantially, the
proportion of true-positive results would drop by approximately two-thirds, while the
predictive value to detect other non-vaccine-related oncogenic types would presumably
remain constant. This would decrease the PPV and cost effectiveness of non-type-specific
HPV DNA tests (65).

Impact of vaccination on subsequent cancer screening behaviour

- It is not known whether HPV vaccination will influence cervical cancer screening
  behaviour of vaccinees later in life.
- Educating vaccinees and their mothers about the need for screening in adulthood to
  protect against disease from all oncogenic HPV types may promote appropriate
  screening behaviour in both vaccinated and non-vaccinated females.
- If vaccine uptake is highest in populations who are most likely to be screened later in
  life, reductions in cervical cancer attributed to vaccination may be less than expected,
  because the disease prevented by vaccination would otherwise have been detected by
  screening, and treated.

It is not known whether HPV vaccination will influence the willingness of vaccinated or
non-vaccinated women to seek screening (Table 4.1). In settings where private sector
HPV vaccination is common, and vaccination is not yet or may never be linked to use of
screening (e.g. the United States), vaccine uptake may be highest among populations that
later in life are likely to be screened. This scenario is quite possible in some industrialized
countries where HPV vaccines are covered by private insurance but not available through
the public sector, and could worsen given the current socioeconomic disparities in
cervical cancer incidence (2,44,67). Under this scenario, the additional benefits of
vaccination would be attenuated because most lesions that would be prevented vaccinated
females would otherwise have been detected by screening. Meanwhile, if non-vaccinated
women are unlikely to be screened, their HPV-related lesions would be likely to progress
to invasive cancer because they would have been missed by screening. Vaccination is
therefore most effective in preventing premature mortality due to cancer if it achieves
high overall coverage, particularly among young adolescents who later in life may not be
screened.

Vaccination provides an opportunity to stress the benefits of screening later in life to
vaccinees or to their mothers, who may already be eligible for screening. However, if
vaccinees are less likely to adhere to screening recommendations because they wrongly
believe that vaccines provide full protection against cervical cancer, cervical cancer incidence could increase, especially if vaccine protection wanes over time or if HPV 16/18 vaccine introduction causes replacement with other oncogenic HPV types (2). One scenario is that vaccinated females may be advised to be screened less frequently (e.g. once each in their 4th and 5th decades) than non-vaccinated females (e.g. once every 3–5 years) to improve the cost effectiveness of screening. This may lead to vaccinees not being adequately screened if they minimize the value of screening or are missed by formal screening invitations. To avoid this scenario, education of vaccinees should stress the need for future screening if screening is available.

Impact of vaccination on subsequent sexual behaviour

- The impact of HPV vaccination on subsequent sexual behaviour is uncertain.
- Data from other sexual education and condom promotion programmes suggest that sexual disinhibition after vaccination is unlikely.
- Counseling and education messages that accompany HPV vaccination could stress sexual risk reduction to prevent HIV, STI and unplanned pregnancy.

Theoretically, HPV vaccination could reduce risky sexual behaviour if vaccinees benefit from education and counseling about sexual risk reduction, awareness of or access to sexual and reproductive health services, and condom promotion, as recommended by several national authorities (see Section 6). Alternatively, sexual disinhibition may occur if vaccinees incorrectly believe that HPV vaccines protect against non-vaccine-related HPV types, HIV, other STIs or pregnancy, and thus engage in riskier sexual behaviour (Table 4.1). However, concerns about sexual disinhibition assume that adolescents delay sexual activity because of fears of HPV infection, although there is no evidence to support this (68). United States studies indicate that fear of an STI, including HIV, is not a major motivator of abstinence among adolescents who are virgins (69). It is also unlikely that a single vaccine would undermine safe sexual behaviour (68). Moreover, evaluations of school-based sex education and condom availability programmes indicate no subsequent increase in sexual behaviour (70). Studies are under way to evaluate the impact of HPV vaccination on subsequent sexual behaviour (see Section 5).

4.2 Cost effectiveness of HPV vaccination programmes

4.2.1 General considerations

- Cost-effectiveness analyses have compared the costs and benefits of a prospective vaccination strategy with other strategies, including no interventions and screening.
- Cost-effective strategies may not be affordable without financial assistance for low and middle-income countries, where health-care budgets are constrained.
- Cost-effectiveness models rely on uncertain assumptions and parameters that may strongly influence results: natural history of type-specific HPV, clinical efficacy, population effectiveness and costs of programmes to reach the target population.
- There is currently no single global standard to express cost-effectiveness ratios or to determine whether a strategy is cost effective.
- Most cost-effectiveness models have assessed the impact and cost effectiveness of HPV 16/18 vaccines in preventing cervical cancer cases and deaths. A few models have estimated the added benefits of preventing precancerous lesions due to HPV 16 or 18, and disease due to HPV 6 or 11.
The major determinants of cost effectiveness are vaccine price and programmatic costs, age of target population, vaccine efficacy, duration of protection, achievable coverage, assumptions about herd immunity and costs of alternative cervical cancer prevention strategies.

Cost-effectiveness analyses can guide vaccine policy decisions by comparing the potential health impact, costs, affordability and feasibility of vaccination with other prevention strategies or no intervention. It must be stressed that strategies deemed cost effective may not be affordable without financial assistance, especially in low-income countries with highly constrained health-care budgets.

Models for high-income countries with screening have typically compared vaccination to existing or alternative screening programmes, whereas models for low and middle-income countries have compared vaccination to no intervention or simplified screening that could be introduced in the future (6) (Table 4.2). Models usually apply a societal perspective, so that all costs and benefits are assessed, regardless of who accrues them. They often present ranges of results because there is no single threshold for decision making, and no international single standard to express cost-effectiveness ratios – commonly used metrics include gross domestic product (GDP), years of life lost (YLL), disability-adjusted life years (DALYs) or quality-adjusted life years (QALYs) (25,71). Evaluations of cost effectiveness of other new childhood vaccines against rotavirus, pneumococcal disease and meningitis A have used the threshold of GDP, where less than the average per capita GDP is considered very cost effective and less than three times the GDP is considered cost effective (71).

Cost-effectiveness analyses of HPV vaccination face several limitations. These include uncertain parameters about the natural history of HPV infections, clinical efficacy of vaccine for certain clinical endpoints, duration of protection, herd immunity and costs (Table 4.2). Several costs are difficult to estimate, especially in low and middle-income countries, where vaccination of adolescents is rare. These include the costs to reach young adolescent target populations, costs of vaccine wasted due to cold-chain problems or incomplete series, and costs for social mobilization and education about HPV vaccines. Vaccination strategies identified as cost effective in one country may not be cost effective in other countries with different burden of disease, HPV type distribution or programme costs (25). Sophisticated models are difficult to develop de novo, and countries seeking cost-effectiveness analyses may find it more feasible to adapt existing models using local data than to develop their own models. Finally, the choice of discount rate matters greatly, given high initial costs and delayed benefits for cancer prevention (6,72).

Cost-effectiveness models have focused on HPV 16/18 vaccines because the greatest benefits of vaccination come from preventing cervical cancer deaths related to HPV 16 or 18 and increasing quality-adjusted life expectancy. This is particularly true in low and middle-income countries where cervical cancer mortality is high (see Section 1). A few models have evaluated the added benefit of the quadrivalent vaccine in preventing HPV 6/11-related disease in high-income countries, where the burden and costs of warts are best characterized.

Several modelling studies have examined cost effectiveness of HPV vaccination in low, middle and high-income countries, but many questions remain and merit evaluation (see Section 5). Models have used different approaches reflecting different vaccination policies, data sources and assumptions (2,4,6,71). The qualitative points of agreement across models show that several factors drive cost effectiveness; these factors include...
vaccine price and associated delivery costs (including wastage), age of target population, achievable coverage, costs of achieving ever higher coverage as programmes scale-up, duration of protection, assumptions about herd immunity, and cost of alternative strategies, such as cancer screening (2).

Achieving high coverage of young-adolescent populations will require new delivery infrastructure and funding in most countries, especially low and middle-income countries that rarely vaccinate young adolescents on a routine basis (73). The feasibility of mobilizing these resources will vary by country (1). Evaluations of delivery in schools, communities and health facilities, and of hybrid strategies using more than one method, are under way or planned in India, Peru, Uganda and Viet Nam (74). Given that public health interventions requiring multiple visits are rarely offered in low and middle-income countries, more operations research is needed to explore options. For example, it may be worthwhile to evaluate whether HPV vaccines can be effectively delivered as part of a package of young-adolescent health services or education, or by distributing vouchers that provide free access to private sector services.

The coverage and impact of prevailing cervical cancer screening will also influence cost effectiveness. Vaccination will be less cost effective if targeted to populations that are routinely screened than if targeted to populations that are not screened (2). Modelling in some countries indicates that, when vaccination coverage is below 50%, the incremental cancer reduction added by screening is appreciable; however, when vaccination coverage exceeds 75%, the incremental benefit of increasing screening coverage is much less (25). Decision makers will therefore need to consider the current and potential coverage rates for vaccination and screening separately, to estimate the best balance of interventions.

Another consistent finding concerns the timing of return on investments in vaccination. Due to differences in latent periods between initial HPV infection and various HPV-related outcomes, models consistently predict that costs related to genital warts, abnormal cytology and follow-up of low-grade lesions would be averted sooner than costs related to the diagnosis and treatment of high-grade lesions and cancer (1).

### 4.2.2 Cost effectiveness of HPV vaccination in preventing cervical disease in low and middle-income countries with no or limited screening

- There are few published cost-effectiveness studies in low and middle-income countries, but new modelling is under way.
- Vaccination cost is one of the most important determinants of cost effectiveness.
- Several models indicate that HPV 16/18 vaccination can be cost effective if the cost per vaccinated girl (including three vaccine doses and programmatic costs) is substantially lower than current costs (i.e. if it is roughly within the range of US$ 5 to US$ 100, depending on country context and model assumptions).

Studies have evaluated cost effectiveness in several low and middle-income regions, but few have been published in peer-reviewed literature (Table 4.3). Results have varied, depending on assumptions used. For example, many studies have assumed that vaccination costs, including vaccine and programmatic costs, would be substantially lower than current industrialized country prices, and many have compared vaccination to screening with conventional cytology or HPV DNA testing. (See Annex 2 for updated information on this issue.)

In the Americas, a microsimulation model in Brazil found that HPV 16/18 vaccination at a cost of International (I)$ 25 vaccinated girl (implying a per dose cost of about I$ 5 plus
programmatic costs) was consistently cost saving compared to no intervention given vaccine coverage levels of 25–90%, but was not cost saving at higher vaccination costs. Combining vaccination at this cost with screening with cytology or HPV DNA testing three times between ages 35 and 45 years was very cost effective compared to no intervention, using the country’s per capita GDP as the threshold for very cost effective interventions (Table 4.3) (5,25,71). If vaccination cost was more than I$ 50, strategies that included vaccination were comparatively less cost effective (25). An analysis in Mexico that assumed a three-dose quadrivalent vaccine cost of US$ 240 (2640 pesos), and vaccine coverage of 70%, predicted that vaccinating girls aged 12 years was cost effective compared to no vaccination (incremental cost-effectiveness ratio (ICER) of US$ 2719) (20). This analysis concluded that vaccination of girls aged 12 years plus temporary catch-up of females aged 12–24 years was more cost-effective (ICER of US$ 3048) than vaccinating girls aged 12 years only.

Recent analyses have estimated the cost effectiveness of HPV 16/18 vaccination in the Caribbean and Latin America using population-based country and regional data (26). At a cost per vaccinated girl of US$ 25 (including programme costs), the cost per DALY was less than the per capita GDP, and was thus considered very cost effective. In Argentina, Brazil, Colombia, Mexico and Peru, adding screening three times per lifetime to vaccination would be cost effective, according to per capita GDP criteria. In the lowest income countries, such as Haiti, the cost per dose of vaccine would need to be US$ 1–2 for vaccination to be cost effective compared to other childhood vaccinations. The study concluded that HPV 16/18 vaccination could be cost effective in almost all countries in the Caribbean and Latin America if prices were substantially lower than they are at present. Two analyses assessed the cost effectiveness of gender-based HPV vaccine strategies in Latin America (see Section 4.2.7) (5,20).

In Asia, a simulation model estimated the cost effectiveness of an HPV 16/18 vaccine in India. Assuming 70% coverage of girls aged 12 years at a cost per vaccinated girl of US$ 10 (including programme costs), vaccination alone was cost saving compared to no intervention. If the cost per vaccinated girl were less than US$ 30, the cost effectiveness ratio associated with screening and vaccination would be consistently less than the per capita GDP, and thus considered very cost effective (71). However, if vaccine cost were similar to current prices in industrialized countries (more than US$ 300 for three dose series), the cost-effectiveness ratio of vaccination would be more than twice the per-capita GDP (30).

In Viet Nam, a model estimated the cost effectiveness of HPV 16/18 vaccination of girls aged 9–11 years in a high-risk, unscreened population in Ho Chi Minh City (see Section 4.1, above). At US$ 5 per vaccinated girl (including programme costs), vaccination was cost saving compared to no vaccination if vaccine efficacy exceeded 90% and protection lasted for at least 20 years. When the cost per vaccinated girl was US$ 150, the cost-effectiveness ratio of vaccination exceeded Viet Nam’s 2005 per capita GDP across a range of values for vaccine efficacy and duration of protection (28). Another analysis from Viet Nam examined the cost effectiveness of HPV 16/18 vaccination alone, screening between ages 30–45 years (either three times per lifetime or every five years), and a combination of these strategies. The most cost-effective strategy (with cost-effectiveness ratios below the per capita GDP) was 5-year screening between ages 30–45 years plus vaccinating girls, assuming a vaccination cost of less than US$ 30 in Hanoi and less than US$ 150 in Ho Chi Minh City. However, at a single, national cost of US$ 50 per vaccinated girl, the most cost-effective strategy would differ by region. This analysis shows that region-specific policies may be useful in countries with major regional variations in cancer incidence, infrastructure and other factors (29).
In GAVI-eligible countries, an analysis of the cost effectiveness of HPV 16/18 vaccination found that, at a cost of US$ 10 per vaccinated girl ($ 2 per dose), vaccination was very cost effective in all countries, using the per capita GDP threshold (71). In countries with high age-standardized cervical cancer incidence rates (> 32/100,000 person-years at risk), ICERs were less than 20–25% of per capita GDP. At higher vaccine costs ($ 5–10 per dose), cost effectiveness varied with underlying incidence, vaccine efficacy and cancer management costs. This study concluded that HPV 16/18 vaccines could be cost effective in the world’s poorest countries if provided at low cost (27).

Additional analyses of the cost effectiveness of HPV 16/18 vaccines in India, Latin America and Caribbean, Viet Nam and GAVI-eligible countries are expected in 2008 and 2009. (Sue Goldie, Harvard University, pers. comm., November 2007).

4.2.3 Cost effectiveness of HPV vaccination in preventing precancerous lesions and cancer of the cervix in high-income countries with screening programmes

- Cost-effectiveness analyses have considered several strategies for vaccination programmes with existing, or potentially modified, screening programmes.
- Vaccination programmes that achieve high coverage in young adolescent girls are expected to greatly reduce costs associated with follow-up and treatment of abnormal screening tests, cancer and genital warts.
- Several studies in industrialized countries have concluded that HPV 16/18 vaccination of young adolescent females is cost effective, especially if screening of vaccinees later in life is modified.

Several published studies from industrialized countries, mostly from the United States, have evaluated the cost effectiveness of HPV 16/18 vaccination or HPV 6/11/16/18 vaccination, compared to current or potentially modified screening programmes (Table 4.3). As in low and middle-income countries, results have been sensitive to age at vaccination, duration of protection and cost of vaccination (17). Results have also been sensitive to assumptions about the age range, coverage, cost and frequency of screening, and the screening test used (conventional or liquid-based cytology, or HPV DNA testing); and more data are being collected to refine model parameters (75). Recently, developed models have considered the influence of cross-protection against non-vaccine-related HPV types (see Section 3), catch-up strategies, vaccination of males and anticipated changes in performance of cytology as a screening test after widespread vaccine introduction (21,22,76,77).

Modelling results from several countries have shown that certain strategies of HPV 16/18 vaccination, combined with some form of screening, can be cost effective at current vaccine prices. However, they are only cost effective if models assume high efficacy, high coverage, duration of protection for at least 10 years, and apply thresholds for cost effectiveness commonly used in high-income countries (e.g. DALY, QALY and ICER) (Table 4.3). Several unpublished country-specific models that have predicted that vaccination can be cost effective were used to support introduction of HPV vaccines into national immunization programmes (see Section 6).

In Europe, models from Italy, the Netherlands and Norway predicted that vaccination with HPV 16/18 vaccines, in combination with current screening practices, would be cost effective compared to screening alone, assuming current vaccine prices and high coverage
(e.g. 80%) of young adolescent girls (35,52,78). Modelling results from several other countries will be available soon.

In the United States and Canada, models have yielded diverse results, depending on model type and assumptions (Table 4.2). For example, one study in the United States found that vaccinating young adolescent girls, combined with conventional cytology every 3–5 years starting at age 25, would yield an ICER of less than US$ 60 000 per QALY gained and was more cost effective than vaccination alone. In contrast, a dynamic transmission model that evaluated a strategy of vaccinating girls before age 12 years, plus a temporary catch-up of females aged 12–24 years, yielded an ICER of US$ 4666 per QALY gained. Models from Canada and the United States (where screening typically begins earlier and is more frequent than in many European countries), and other countries, have consistently predicted that combination programmes will be more cost effective if vaccinees start screening at a later age and are screened less frequently than typical at this time (1,2,12,34,79). This underscores the need to avoid inertia in screening programmes after vaccine introduction. In fact, one Canadian study concluded that, if current screening practices were not modified over time, cancer treatment costs saved through vaccination would be insignificant compared to the costs of vaccination (34).

Most models, especially ones from the United States, have predicted that, in settings where organized or opportunistic screening is widespread, vaccination would reduce costs associated with the follow-up of mild or equivocal cytologic abnormalities and treatment of CIN2/3, AIS and cancer. They also predict that savings from averting follow-up of abnormal screening tests would be observed earlier than savings from cancer diagnosis and treatment (3,80). In the United States, for example, follow-up of abnormal screening tests accounts for more than US$ 3 billion in direct medical costs each year.

An Australian analysis compared a combination strategy including vaccination of girls aged 12 years at 80% coverage and current screening practices, to a strategy of current screening alone. The analysis estimated an ICER of AU$ 51 103 per life year and AU$ 18 735 per QALY, at a cost per vaccinated girl of about AU$ 440 (including administration costs) – values that were considered cost effective. Models that considered herd immunity found vaccination to be more cost effective than models that did not consider herd immunity (AU$ 36 343 per life year and AU$ 13 316 per QALY) (37).

In Israel, where cervical cancer incidence (28/1 000 000) and mortality (11/1 000 000) are low, about 12% of targeted females receive opportunistic cytology screening, and the entire population has access to treatment. A cost-utility analysis compared quadrivalent vaccination to various screening strategies (cytology, HPV DNA testing and VIA) (81). Assuming 95% vaccine coverage of girls aged 12 years, vaccination at the current price of US$ 120 per dose was not cost effective, regardless of assumptions about the need for boosters. Sensitivity analyses estimated that this vaccine would become cost effective if the per-dose price dropped to US$ 97, very cost effective if it dropped to US$ 50 and cost saving if it dropped to US$ 27.

Several models have considered strategies that include catch-up vaccination of older adolescents and young women. For example, a United States dynamic transmission model that compared the cost effectiveness of a quadrivalent vaccine with current cytologic screening practices predicted that vaccinating girls before the age of 12 years, plus a temporary catch-up vaccination of females aged 12–24 years, would yield an ICER of US$ 4666 per QALY gained. The investigators concluded that vaccinating girls and women appeared cost effective compared to other commonly accepted health interventions (18). Another United States model projected that a strategy of vaccination
plus current screening practices was cost effective compared to screening alone (38). As the upper age limit for a temporary catch-up programme extended beyond 21 years, the marginal benefits decreased while the marginal costs increased, yielding a cost that was over US$ 100 000 per year of life saved. Models that have assumed that HPV 16/18 vaccines confer herd immunity predict that herd immunity will improve cost effectiveness of vaccination of young adolescent girls and temporary catch-up vaccination of females up to 24 years of age (82).

A few models have compared the two marketed vaccines. For example, a Canadian model estimated that vaccinating young adolescent girls with HPV 6/11/16/18 or HPV 16/18 vaccines at a cost per vaccinated girl of CAN$ 400 would generate health-provider costs of CAN$ 31 000 per QALY gained to prevent HPV 16/18-related disease and CAN$ 21 000 per QALY gained to prevent HPV 6/11/16/18-related disease (34).

4.2.4 Cost effectiveness for preventing vaginal, vulvar, anal, penile and oropharyngeal precancerous lesions and cancer

- Clinical trials of the quadrivalent vaccine have generated efficacy data for vaginal and vulvar precancerous lesions, but efficacy data for anal, penile or oropharyngeal precancers or cancer are not yet available.
- In high-income settings, vaccination is expected to become more cost effective when models consider prevention of non-cervical precancers and cancers, and resulting savings in diagnosis and treatment.
- In low and middle-income settings, the added benefit of including these endpoints may be minimal because these conditions are often undiagnosed and untreated.

Data on clinical efficacy of the quadrivalent vaccine against precursors of vaginal and vulvar cancer are available for cost-effectiveness models. However, efficacy estimates are currently not available for anal, penile and oropharyngeal precancers or cancers. In high-income countries where treatment of these HPV-related cancers is routinely provided and is costly, the potential costs averted may increase the cost effectiveness of HPV vaccination (3,39). Many experts predict that the benefits of preventing fairly rare non-cervical anogenital cancers are likely to be minimal compared with the benefits of preventing cervical cancers, which are far more common and are addressed by costly screening programmes in many countries (Sue Goldie, Harvard University, pers. comm., November 2007).

4.2.5 Cost effectiveness of the quadrivalent vaccine for preventing genital warts

- In high-income settings, quadrivalent HPV vaccination is expected to reduce costs associated with diagnosis and treatment of genital warts, and these savings are expected to occur sooner than those from averted cervical cancer.
- Cost-effectiveness ratios for HPV vaccination against types 6/11/16/18 are sensitive to values assigned to reductions in QALY due to genital warts, which have been estimated from limited data.

In countries where initial and recurrent treatment of warts is common and costly, vaccination with the quadrivalent vaccine is expected to avert a substantial proportion of the costs associated with these conditions (83,84). A few studies have examined cost effectiveness of the quadrivalent vaccine in preventing HPV-related precancers, cancers and genital warts (Table 4.3). One study reported that total HPV-disease related health-
care costs for HPV-related cancer and warts would be reduced by 26% ($P < 0.001$) over 2.5 years among women receiving the vaccine compared to women receiving placebo (53). Because genital warts develop within a few months to years of HPV exposure, these averted costs would be observed sooner than those associated with averting cervical cancer (3). A recent Canadian study estimated that a diagnosis of new or recurrent warts would reduce the absolute QALY weight by 11.6% (95% CI 7.2% to 15.9%) for females and 8.4% (95% CI 4.4% to 12.5%) for males (85). Modelling in low-income countries has been limited by lack of good data on the costs of wart care (20). Cost-effectiveness analyses are also sensitive to values assigned to the reduction in QALY due to warts. Research is now attempting to reduce these uncertainties (34,86,87).

4.2.6 Cost effectiveness of the quadrivalent vaccine for preventing recurrent respiratory papillomatosis

Because RRP is rare, mass vaccination specifically intended to prevent RRP due to HPV 6, 11, 16 and 18, but not to prevent other disease caused by these HPV types would not be cost effective, despite high treatment costs. However, strategies that consider the benefits of preventing HPV 6/11 infection by the quadrivalent vaccine would be more cost effective if high efficacy against both genital warts and RRP was assumed to be high. Few data on RRP diagnosis and treatment costs are available to inform modelling, especially in low and middle-income countries.

4.2.7 Cost effectiveness of vaccinating males and females compared with females alone

Several models have compared the cost effectiveness of vaccinating females alone versus females and males in middle and high income countries (Table 4.3). A model in Brazil predicted that, although vaccinating boys provided extra benefits to girls, vaccinating boys was always less cost effective than increasing coverage in girls aged 12 years (5). A transmission model in Mexico that examined outcomes for cervical precancers, cancer and warts estimated that vaccinating girls aged 12 years and catch-up vaccination of older females was more cost effective than vaccination of both girls and boys aged 12 years (20).

An Australian model that compared current screening to vaccination of girls aged 12 years at 80% coverage in combination with current screening, and considered herd immunity, found that vaccinating girls alone was more cost effective than vaccinating girls and boys (37). One United States model found that vaccinating girls and boys was more effective than vaccinating girls alone – due to reduced incidence of genital warts (girls only 83% vs. girls and boys 97%) and cervical cancer (girls only 78% vs. girls and boys 91%) – but less cost effective (18). Another model of HPV 16/18 vaccines also found that vaccinating boys in addition to girls aged 12 years would reduce cervical cancer cases by only 2% and was not cost effective ($442,039/QALY compared to vaccinating girls only) (40). A third United States model that examined the cost effectiveness of the quadrivalent vaccine on precancers, cancer and warts in the context of current screening practices predicted that vaccination of girls and boys aged 12 years, plus catch-up vaccination of females and males aged 12–24 years, was the most cost-effective strategy (63).
### Table 4.1 Potential impact of HPV vaccination programmes for females by vaccine type

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Potential health impact</th>
<th>Potential additional impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quadrivalent</td>
<td>Reduce: cancers of cervix, vulva, vagina and anus; HPV-related oropharyngeal cancers; abnormal cervical cytologic and histologic abnormalities requiring follow-up and treatment in females; anogenital warts; recurrent respiratory papillomatosis.</td>
<td>Alter: effectiveness of cervical cancer screening programmes and performance of screening tests; cancer screening behaviour of vaccinees; sexual behaviour of vaccinees.</td>
</tr>
<tr>
<td>Bivalent</td>
<td>Reduce: cancers of cervix, vulva, vagina and anus; HPV-related oropharyngeal cancers; abnormal cervical cytologic and histologic abnormalities requiring follow-up and treatment in females.</td>
<td>Alter: effectiveness of cervical cancer screening programmes and performance of screening tests; cancer screening behaviour of vaccinees; sexual behaviour of vaccinees.</td>
</tr>
</tbody>
</table>

### Table 4.2 Key parameters and assumptions used in models to assess HPV vaccine impact and cost effectiveness

<table>
<thead>
<tr>
<th>Parameters and assumptions</th>
<th>Description of uncertainty</th>
<th>Common assumptions</th>
<th>Possible impact on model findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural history and epidemiology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type-specific immunity following natural infection; potential for reactivation</td>
<td>Level and duration of protection influences choice of susceptible–infected–suscetible–infected–removed model; occurrence unknown.</td>
<td>Assumptions may vary by HPV type; reactivation not taken into account.</td>
<td>Lack of life-long immunity from natural infection increases predicted vaccine impact, which depends on: age of vaccination and prior natural exposure; vaccine efficacy against incident infections among seropositive/DNA-negative individuals; duration of protection.</td>
</tr>
<tr>
<td>HPV type-specific progression between health states</td>
<td>Step-wise progression between infection and clearance, development and regression of lesions and cancer.</td>
<td>Models generally allow for clearance and regression, but allowances for skipping health states may vary.</td>
<td>Flexibility important for model precision, to account for factors such as age and screening.</td>
</tr>
<tr>
<td></td>
<td>Timing between health states</td>
<td>Six-month transitional states often used, and assumptions about rapid progression not always clear.</td>
<td>Assumptions influence estimated time delay in vaccination impact and age-specific vaccination strategies.</td>
</tr>
<tr>
<td></td>
<td>Variability by HPV type</td>
<td>Data for HPV 16/18 available, comparable natural history and model input parameters for other types not available.</td>
<td>Complexities relating to the role of non-HPV 16/18 typically not captured.</td>
</tr>
<tr>
<td>Relationship between HPV types</td>
<td>Interactions between HPV types at the cellular, individual and population level are important due to high level of multiple infections.</td>
<td>Independence and attribution of risk given to vaccine types in multiple-type infections.</td>
<td>Potential to overestimate or underestimate vaccine impact if HPV types not independent.</td>
</tr>
<tr>
<td>Parameters and assumptions</td>
<td>Description of uncertainty</td>
<td>Common assumptions</td>
<td>Possible impact on model findings</td>
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<tr>
<td>----------------------------</td>
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</tr>
<tr>
<td>Type-specific infection incidence by age and gender</td>
<td>Limited differentiation of incident, persistent or reactivated infections in older women</td>
<td>Assume incident infections</td>
<td>Potential to overestimate vaccine impact if infections present before vaccination</td>
</tr>
<tr>
<td></td>
<td>Limited age-specific data in males</td>
<td>Not commonly incorporated into models</td>
<td>Imprecision in transmission models that assess age and gender-specific vaccination strategies</td>
</tr>
<tr>
<td>Variability in natural history of HPV infection and disease by population subgroups</td>
<td>Most natural history data generated from select cohorts; thus, may not be generalizable to populations targeted in models</td>
<td>Generalization from available data, calibration to relevant data when available and use of sensitivity analyses</td>
<td>Inaccurate estimates of vaccine impact for vaccination strategies that include these subgroups (men, older women or immunosuppressed populations)</td>
</tr>
<tr>
<td>HPV transmission dynamics by age and gender</td>
<td>Limited sexual mixing and transmission data (per sex act or partnership, or at the population level) by age, gender (male to female, female to male, male to male or female to female)</td>
<td>Transmission not accounted for, or wide range of transmission probabilities used</td>
<td>Potential herd effects not captured; underestimation of vaccine impact; models may yield imprecise vaccination targeting strategies</td>
</tr>
<tr>
<td>Role of risk factors for HPV acquisition and progression to disease</td>
<td>Detailed understanding and incorporation of identified risk factors into mathematical natural history models</td>
<td>Limited, well-established risk factors may be included, but many risk factors and associations not accounted for in natural history models</td>
<td>Exclusion of important risk factors may influence progression through model-specified health states and result in imprecise results, particularly among subgroups</td>
</tr>
<tr>
<td>Incidence and prevalence of HPV-related disease in low and middle-income countries</td>
<td>Scarce incidence and prevalence data for key health data in situations where primary gynecologic and cervical screening are scarce or registry data is absent</td>
<td>Data used from other regions or countries, or sensitivity analyses conducted (or both)</td>
<td>Imprecise model results</td>
</tr>
<tr>
<td>Natural history of HPV in the development of non-cervical cancers</td>
<td>Role of HPV 16/18 on non-cervical cancers often based on DNA detection in tissue, but natural history data are limited</td>
<td>Models do not routinely account for non-cervical cancer</td>
<td>Potential to underestimate vaccine impact on HPV-related cancers</td>
</tr>
</tbody>
</table>

**Vaccine characteristics**

<p>| Duration of protection | Available data currently extend about five years after vaccination | Life-long protection following primary three-dose series or through booster dose (booster costs not routinely accounted for in models) | Overestimation of vaccination impact on health endpoints; underestimation of costs if booster dose is required but not included in model |
| Clinical efficacy and safety in expanded target populations (older women, males, immunosuppressed) | Studies ongoing or planned for these populations, but published data are not available or not yet incorporated into models | Similar efficacy and safety as reported for females aged 15–26 years | Imprecise model results that likely overestimate vaccine efficacy |</p>
<table>
<thead>
<tr>
<th>Parameters and assumptions</th>
<th>Description of uncertainty</th>
<th>Common assumptions</th>
<th>Possible impact on model findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical efficacy for anal, penile and oropharyngeal HPV-related cancers</td>
<td>No data available</td>
<td>Models generally do not account for anal, penile and oropharyngeal cancers</td>
<td>Potential to underestimate vaccine impact</td>
</tr>
<tr>
<td>Cross-protection</td>
<td>Ad hoc assessments of clinical trial data have indicated that current vaccines may provide some protection against non-vaccine types, but statistical power to assess clinical endpoints has been limited Appropriate statistical methods to assess correlated endpoints and multiple comparisons have not been addressed</td>
<td>Most older models do not account for cross-protection, but several recent models assume broader protection</td>
<td>Accounting for cross-protection may overestimate vaccine impact if formal, statistically powered, analyses do not confirm preliminary findings If substantial cross-protection exists, not accounting for it will underestimate vaccine impact</td>
</tr>
<tr>
<td>Cost data</td>
<td>Cost of primary vaccine series</td>
<td>Pricing in low and middle-income (particularly non-GAVI) countries Potential reduction in developed country pricing in competitive situations</td>
<td>Many models provide a range of vaccine costs to estimate hypothetical cost effectiveness, particularly for lower income settings</td>
</tr>
<tr>
<td>Vaccine administrative and programmatic costs</td>
<td>Start-up costs of new programs aimed at young adolescents Storage, wastage and other practical considerations Integration with existing programmes or co-development with screening programmes</td>
<td>Most models do not account for these costs; others generate an estimated cost per vaccinated individual</td>
<td>Imprecise cost-effectiveness ratios and potential underestimate of vaccine costs may predict more beneficial cost-effectiveness ratios than would actually occur in vaccination programmes</td>
</tr>
<tr>
<td>Cost of screening and treatment</td>
<td>When cervical cancer screening and treatment costs are well documented, there is uncertainty about new screening tools or algorithms that may be used after vaccine introduction Limited data on cervical screening and treatment programme costs in many settings</td>
<td>Most models use country-level data when possible, or generalize from other data sources</td>
<td>Imprecise cost-effectiveness estimates for models that include assessment of screening Potential underestimate of vaccine impact if vaccination prevents non-cervical disease and models do not account for cost savings</td>
</tr>
<tr>
<td>Parameters and assumptions</td>
<td>Description of uncertainty</td>
<td>Common assumptions</td>
<td>Possible impact on model findings</td>
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<tr>
<td>Limited data on genital wart and other non-cervical HPV-related disease diagnosis and treatment costs</td>
<td>Sensitivity analyses are often used to account for uncertainty</td>
<td><strong>Non-medical direct and indirect costs</strong></td>
<td>Limited cost data for transportation, time and care-giver costs due to health-care needs or lost time for work or leisure due to morbidity or mortality</td>
</tr>
<tr>
<td>Lack of consensus on discounting methods (i.e. on discounting benefits and discounting rate, and on whether rate should be constant and similar for both costs and benefits)</td>
<td>Most models use a 3% annual discount rate for both costs and benefits</td>
<td><strong>Discounting</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Programmatic considerations</strong></td>
<td></td>
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</tr>
<tr>
<td>Achievable coverage for primary vaccination series</td>
<td>Partial coverage in population or unequal distribution in population (possibly dependent on age, gender or risk status) Proportion receiving less than three doses</td>
<td>70–100% coverage for entire targeted birth cohort(s)</td>
<td>Overestimate of vaccine impact if actual coverage is lower than assumed</td>
</tr>
<tr>
<td>Variability in age of sexual debut by gender</td>
<td>Vaccination during pre-adolescence or adolescence before sexual debut</td>
<td></td>
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</tr>
<tr>
<td>Potential waning of vaccine protection and increased risk of infection if waning occurs</td>
<td>Life-long protection</td>
<td></td>
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</tr>
<tr>
<td>Limited data available for vaccine effectiveness as opposed to efficacy Use of these data in models as opposed to key efficacy results available to date</td>
<td>Models generally use type-specific efficacy data from per-protocol populations in clinical trial populations</td>
<td><strong>Population level vaccine effectiveness for HPV-related infection and disease</strong></td>
<td>Overestimate of vaccine impact if effectiveness lower than efficacy estimates (as would be expected given lower vaccine efficacy in intent-to-treat populations who received less than 3 doses)</td>
</tr>
<tr>
<td>Characteristics of current cytology or histology tests in many settings Impact of alternative screening methods (e.g. HPV DNA tests and visual inspection with acetic acid) and potential changes following introduction of HPV vaccine</td>
<td>Models often use test characteristic data from the literature or obtain country-specific data</td>
<td><strong>Cervical cancer screening test characteristics and compliance with screening</strong></td>
<td>Model estimates that incorporate screening and vaccination for cervical cancer control may yield imprecise strategies</td>
</tr>
</tbody>
</table>

DNA = deoxyribonucleic acid; GAVI = Global Alliance for Vaccines and Immunization; HPV = human papillomavirus
### Table 4.3(a) Cost-effectiveness of human papillomavirus (HPV) vaccination programmes for girls only: key findings published to end of 2007a

<table>
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</thead>
<tbody>
<tr>
<td>Countryb</td>
<td>Brazil</td>
<td>Israel</td>
<td>Canada</td>
<td>United States</td>
<td>United States</td>
<td>United States</td>
</tr>
<tr>
<td>Model type</td>
<td>State-transition individual-based</td>
<td>State-transition cohort</td>
<td>State-transition cohort</td>
<td>State-transition cohort</td>
<td>State-transition cohort</td>
<td>State-transition cohort</td>
</tr>
<tr>
<td>Health outcomes</td>
<td>Years of life saved (YLS)</td>
<td>Quality-adjusted life years (QALY)</td>
<td>QALY</td>
<td>QALY</td>
<td>YLS</td>
<td>QALY</td>
</tr>
</tbody>
</table>

**Key base-case assumptions**

- **Vaccine HPV type**: 16/18, 6/11/16/18 and 16/18
- **Vaccine efficacy against infections**: 100% against incident infections, 94.3% against persistent infections, 100% against condyloma incidence
- **Vaccination age**: 9–12 years, 12 years
- **Vaccine coverage**: 70%, 95%, 100%
- **Screening coverage and frequency**: 70%, 95%, Age specific coverage of cytology screening programme, 94.8% ever screened
- **Natural type-specific immunity**: Calibrated parameter in the model
- **Duration of vaccine protection**: Life-long, Life-long with booster dose every 10 years until age 62 years, Life-long, Schedule requiring booster dose at 22 years also assessed, Life-long, Schedule requiring booster dose also assessed
- **Cross-protection against other oncogenic HPV types**: No, No, No, No, Indirectly
- **Herd immunity**: No, No, No, No, No

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</thead>
<tbody>
<tr>
<td>Vaccine cost and year</td>
<td>I$ 25 (3-dose primary series), 2000</td>
<td>US$ 120 (per dose), 2007</td>
<td>CAN$ 400 (3-dose primary series) and 167 (booster dose), 2005</td>
<td>US$ 393 (3-dose primary series), 2002</td>
<td>US$ 200 (3-dose primary series), 2001</td>
<td>US$ 300 (3-dose primary series) and 100 (booster dose), 2001</td>
</tr>
<tr>
<td>Non-vaccine interventions</td>
<td>Screening of women age 35 using cytology three times per lifetime, or HPV DNA two times per lifetime (Additional screens at 5-year intervals)</td>
<td>Cytology every 1, 3 or 5 years HPV DNA testing Visual inspection with acetic acid application (VIA) Cytology followed by combined cytology and HPV DNA</td>
<td>Current conventional cytology-based screening</td>
<td>Convention al and liquid-based cytology initiated at different ages, with screening at 1–5-year intervals</td>
<td>Conventional cytology at intervals of 1, 2, 3 and 5 years, beginning between ages 18–30</td>
<td>Current cytology-based screening every 2 years, beginning at age 16</td>
</tr>
<tr>
<td>Main findings</td>
<td>(At cost per vaccinated girl of I$ 25; [per dose cost of I$ 5]), vaccination alone cost saving compared to no intervention Vaccination followed by screening (3 times per lifetime between ages 35 and 45) very cost effective.</td>
<td>At current baseline price, HPV vaccine not cost effective. Vaccination only, or vaccination and Pap screening at 5-year intervals would become cost effective at reduced vaccination costs.</td>
<td>Bivalent and quadrivalent vaccination likely to be cost-effective. Lower cost-effectiveness ratios for quadrivalent vaccine due to QALY gained by preventing genital warts. Vaccination at older ages reduces cost-effectiveness.</td>
<td>Vaccination estimated to be cost-effective compared with current screening practices. Most effective strategy estimated to be vaccination plus screening at 2-year intervals beginning at age 24.</td>
<td>Most effective strategy estimated to be vaccination compared with current screening practices.</td>
<td>Vaccination estimated to be cost effective compared with current screening practices.</td>
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<tr>
<td>Vaccination only (I$ 25), vaccination and 3-visit cytology screening 3 times per lifetime (between ages 35 and 45): I$ 2001.</td>
<td>At vaccination cost (I$ 25), vaccination and 3-visit cytology screening 3 times per lifetime (between ages 35 and 45): I$ 700.</td>
<td></td>
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</tbody>
</table>

CAN$ = Canadian dollar; DNA = deoxyribonucleic acid; HPV = human papillomavirus; I$ = international dollar; LY = life year; QALY = quality-adjusted life year; US$ = United States dollars; VIA = visual inspection with acetic acid application; YLS = years of life saved.

a Studies included in this table were published in English. Many cost-effectiveness analyses summarized in meeting abstracts are not included here but are noted in text (see section on cost effectiveness).
b Data used for model calibration may originate from different locations.
c See primary source for detailed discussion of the sensitivity analyses that modified base case assumptions and influence on study findings.
d Further assumptions used regarding the causative role of vaccine-related HPV types on the development of disease endpoints and population-level vaccine impact.
e Of those ever screened, 70.5% screened in the last year; 12.6% screened in the last 2 years; 4.3% screened in the last 3 years; 3% screened in the last 5 years; 9.6% screened more than 5 years ago.
f Varies across good-fitting parameter sets.
g More frequent booster doses assessed.
h Included only in sensitivity analysis.
i As assessed by assumption that vaccine is efficacious on preventing 70% of oncogenic types.
j As assessed by assumption that vaccine is effective against 13 oncogenic types.
k Included only in sensitivity analysis.
l Includes vaccine, administrative and programmatic costs.
m Includes direct medical costs.
n Includes vaccine and administrative costs.
o Includes vaccine, administrative and programmatic costs, and patient-time costs.
## Table 4.3(b) Cost-effectiveness of human papillomavirus (HPV) vaccination programmes including girls and boys: key findings published to the end of 2007

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Country</strong></td>
<td>Brazil</td>
<td>United States</td>
<td>United States</td>
<td>Mexico</td>
<td>Australia</td>
</tr>
<tr>
<td><strong>Model type</strong></td>
<td>Hybrid (dynamic/ cohort)</td>
<td>Hybrid (dynamic/ cohort)</td>
<td>Dynamic</td>
<td>Dynamic</td>
<td>Hybrid (dynamic/ cohort)</td>
</tr>
<tr>
<td><strong>Health outcomes</strong></td>
<td>Year of life saved (YLS)</td>
<td>Quality adjusted life year (QALY)</td>
<td>QALY</td>
<td>QALY</td>
<td>QALY</td>
</tr>
<tr>
<td><strong>Key base-case assumptions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vaccine HPV type</strong></td>
<td>16/18</td>
<td>16/18</td>
<td>6/11/16/18</td>
<td>6/11/16/18</td>
<td>16/18; non-16/18 oncogenic; types; non-oncogenic types</td>
</tr>
<tr>
<td><strong>Vaccine efficacy against infections</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>100% against incident infections</td>
<td>90% against incident infections</td>
<td>90% against incident infections; 100% against associated disease</td>
<td>90% against incident infections, 98.9% against genital warts; 95.2% against CIN</td>
<td>100% against HPV 16/18 -related cervical intraepithelial neoplasia (CIN)1–3 and cervical cancer</td>
</tr>
<tr>
<td><strong>Vaccination age</strong></td>
<td>12 years</td>
<td>12 years</td>
<td>12 years</td>
<td>12 years</td>
<td>12 years</td>
</tr>
<tr>
<td><strong>Vaccine coverage</strong></td>
<td>70%</td>
<td>70%</td>
<td>70% of 12–year-olds&lt;sup&gt;a&lt;/sup&gt;</td>
<td>70% of 12-year-olds&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Screening coverage and frequency</strong></td>
<td>0–90%</td>
<td>71%</td>
<td>Age-specific coverage of cytology screening&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Age-specific coverage of cytology screening&lt;sup&gt;i&lt;/sup&gt;</td>
<td>5–30% (age dependent)</td>
</tr>
<tr>
<td><strong>Natural type-specific immunity</strong></td>
<td>Calibrated parameter in the model&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Unknown</td>
<td>Life-long</td>
<td>Life-long</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Duration of vaccine protection</strong></td>
<td>Life-long</td>
<td>10 years with booster at age 22 years</td>
<td>Life-long</td>
<td>Life-long</td>
<td>Life-long</td>
</tr>
<tr>
<td><strong>Cross-protection against other oncogenic HPV types</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Herd immunity</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No&lt;sup&gt;i&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Vaccine cost and year</strong></td>
<td>I$ 25–400 (3-dose primary series), 2000&lt;sup&gt;j&lt;/sup&gt;</td>
<td>US$ 300 (3-dose primary series) and 100 (booster dose), 2001</td>
<td>US$ 360 (3-dose primary series), 2005, 2640 pesos (equivalent to ~ US$ 240) (3-dose primary series), 2005, Mexican pesos</td>
<td>AUS$ 115 per dose, 12–31 per dose for administration costs, 2005</td>
<td></td>
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<td>------------------------</td>
<td>------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Non-vaccine</td>
<td>Current cytology-</td>
<td>Current cytology-</td>
<td>Current cytology-</td>
<td>Current cytology-</td>
<td>Current cytology-</td>
</tr>
<tr>
<td>interventions</td>
<td>based screening</td>
<td>based screening</td>
<td>based screening</td>
<td>based screening</td>
<td>based screening every 2</td>
</tr>
<tr>
<td></td>
<td>Screening every 3</td>
<td></td>
<td></td>
<td></td>
<td>years, beginning at age</td>
</tr>
<tr>
<td></td>
<td>years (40%</td>
<td></td>
<td></td>
<td></td>
<td>18–21 years (sensitivity</td>
</tr>
<tr>
<td></td>
<td>coverage)</td>
<td></td>
<td></td>
<td></td>
<td>≥CIN1 80%; specificity</td>
</tr>
</tbody>
</table>

| Main findings      | (At cost per      | Vaccination of girls | Vaccination of girls | Vaccination of girls | Vaccination of girls |
|                    | vaccinated girl   | aged 12 years is     | aged 12 years and    | aged 12 years and     | aged 12 years, in      |
|                    | of I$ 25; [per    | more cost-effective  | females aged 12–24   | females aged 12–24    | addition to cytology    |
|                    | dose cost of I$ 5]| compared with       | is most cost-effective| is most cost-effective| screening, is cost     |
|                    |                   | current screening     | compared with        | compared with         | effective compared to   |
|                    |                   | methods and frequency.| female vaccination   | female vaccination     | screening alone.        |
|                    |                   | Vaccination of girls | strategy.             | strategy.              | Cost effectiveness is   |
|                    |                   | and boys estimated  | Next most cost-       | Next most cost-        | particularly sensitive  |
|                    |                   | to be cost-effective | effective strategy is | effective strategy is  | to duration of vaccine   |
|                    |                   | compared with female | vaccination of girls  | vaccination of girls   | protection and need for |
|                    |                   | vaccination strategy.| aged 12 years plus   | aged 12 years plus    | booster vaccination,    |
|                    |                   |                        | catch-up vaccination  | catch-up vaccination   | vaccine coverage,       |
|                    |                   |                        | of females aged 12–  | of females aged 12–    | efficacy and cost.      |
|                    |                   |                        | 24 years.             | 24 years.              | Vaccinating girls at    |
|                    |                   |                        |                        |                        | age 14–18 years more    |
|                    |                   |                        |                        |                        | cost effective than     |
|                    |                   |                        |                        |                        | vaccinating girls aged  |
|                    |                   |                        |                        |                        | 12 years only, but then  |
|                    |                   |                        |                        |                        | becomes less cost       |
|                    |                   |                        |                        |                        | effective with           |
|                    |                   |                        |                        |                        | increasing age.          |
|                    |                   |                        |                        |                        | Vaccinating boys and    |
|                    |                   |                        |                        |                        | girls may be cost       |
|                    |                   |                        |                        |                        | effective when consider  |
|                    |                   |                        |                        |                        | morbidity from          |
|                    |                   |                        |                        |                        | abnormal cytology        |
|                    |                   |                        |                        |                        | follow-up and treatment,|
|                    |                   |                        |                        |                        | but not when            |
|                    |                   |                        |                        |                        | consider cervical        |
|                    |                   |                        |                        |                        | cancer mortality         |
|                    |                   |                        |                        |                        | only.                    |

Next most cost-effective strategy is vaccination of girls aged 12 years plus catch-up vaccination of females aged 12–24 years.

Vaccination of girls aged 12 years and females aged 12–24 is most cost-effective strategy.

Vaccination of both males and females at age 12–24 years appears cost effective relative to benchmark threshold, based on less than three times the GDP per capita per QALY.

Vaccination of girls aged 12 years, in addition to cytology screening, is cost effective compared to screening alone. Cost effectiveness is particularly sensitive to duration of vaccine protection and need for booster vaccination, vaccine coverage, efficacy and cost. Vaccinating girls at age 14–18 years more cost effective than vaccinating girls aged 12 years only, but then becomes less cost effective with increasing age. Vaccinating boys and girls may be cost effective when consider morbidity from abnormal cytology follow-up and treatment, but not when consider cervical cancer mortality only.
Incremental cost-effectiveness ratio (ICER) per QALY or life year (LY) gained

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At vaccination cost (I$ 25), vaccinating girls only is, cost saving for coverage levels between 25% and 90%.</td>
<td>Vaccination of girls compared with current screening: US$ 14 583. Vaccination of girls and boys compared with girls only: US$ 442 039.</td>
<td>Vaccination of girls aged 12 years compared with current screening: US$ 2964. Vaccination of girls and boys aged 12 years compared with current screening: not cost-effective.</td>
<td>Vaccination of girls aged 12 years compared to no vaccination: 29 905 pesos (US$ 2719). Vaccination of girls aged 12 years and temporary catch-up vaccination of females age 12–24 compared to 12-year old girls: 33 530 pesos (US$ 3048).</td>
<td>Vaccination of girls aged 12 years plus cytology screening compared to screening alone: incremental cost per LY gained US$ 51 103 and US$ 18 735 per QALY.</td>
</tr>
<tr>
<td></td>
<td>At vaccination (I$ 50 to I$ 400), vaccinating girls and boys: I$ 810–136 910 for coverage levels between 25% and 90%.</td>
<td>Vaccination of girls aged 12 years plus catch-up vaccination of females aged 12–24 compared with current screening: US$ 41 803.</td>
<td>Vaccination of girls aged 12 years and temporary catch-up vaccination of females age 12–24: 183 297 pesos (US$ 16 663).</td>
<td>Vaccination of girls and boys aged 12 years and temporary catch-up vaccination of females and males aged 12–24 compared to vaccination of girls and boys aged 12 years and temporary catch-up vaccination of females aged 12–24: 183 717 pesos (US$ 16 702).</td>
<td>Based on a variety of assumptions, vaccinating boys resulted in ICER &gt; US$ 80 000 per LY gained.</td>
</tr>
</tbody>
</table>

AUS$ = Australian dollar; CIN = cervical intraepithelial neoplasia; HPV = human papillomavirus; I$ = international dollar; ICER = incremental cost-effectiveness ratio; LY = life year; QALY = quality adjusted life year; US$ = United States dollar; YLS = years of life saved.

a Studies included in this table were published in English. Many cost-effectiveness analyses summarized in meeting abstracts are not included here but are noted in the text (see section on cost-effectiveness).

b Data used for model calibration may originate from different locations.
c See primary source for detailed discussion of the sensitivity analyses that modified base case assumptions and influence on study findings.

d Further assumptions used regarding the causative role of vaccine-related HPV types on the development of disease endpoints and population-level vaccine impact.

e Increased linearly from 0 to 70% during first 5 years of programme and then remained at 70%.

f Increased linearly from 0 to 50% during first 5 years of programme and then eliminated catch-up programme after 5 years.

g Also assumed 75% of genital warts patients seek care.

h Varies across good-fitting parameter sets.

i Included only in sensitivity analysis.

j Includes vaccine, administrative and programmatic costs.

References


54 Datta DS et al. Modelling the impact of HPV16/18 vaccination on Pap test abnormalities among young women attending family planning clinics in the United States. In: *Proceedings of the*


This section examines the feasibility of introducing human papillomavirus (HPV) vaccines in low, middle and high-income countries. It discusses the types of partnerships and programmes needed to support introduction, and strategies for delivering the vaccine (e.g. in schools, communities or health-care facilities).

Subsequent sections address the acceptability of HPV vaccines to communities, providers, parents and adolescents; the factors that influence this acceptability; and vaccine education and communication at all levels.

Finally, this section looks at other issues that need to be considered when introducing HPV vaccines, such as vaccine affordability and financing, and post-marketing monitoring and research to inform vaccination programmes.

5.1 Partnerships and programmes supporting vaccination

**Key points**

- HPV vaccines present several unique features that require new approaches to designing and delivering programmes.
- Introducing HPV vaccines will require the engagement of stakeholders from programmes on immunization, cancer control, reproductive health, human immunodeficiency virus (HIV) or sexually transmitted infection (STI), child or adolescent health, and education and health communication.
- HPV vaccination will promote the Global Immunization Vision and Strategy (GIVS) of the United Nations Children’s Fund (UNICEF), which aims to expand immunization programmes beyond childhood. It will also promote several Millennium Development Goals (MDGs).

5.1.1 General considerations

HPV vaccine introduction will differ in low, middle and high-income countries, depending on (I):

- overall health priorities
- presence of other control measures for cancer and STIs
- infrastructure to deliver vaccines or other health services to vaccine target populations
- acceptability of vaccines
- other factors.

HPV vaccines present several unique features that require new delivery approaches: the target population differs from the infants and young children that are routinely addressed by national immunization programmes. Also, HPV vaccines prevent disease that would otherwise occur decades after exposure to the pathogen. Furthermore, because HPV is an STI, immunization programmes may be drawn into a sociopolitically charged environment, which can raise potentially sensitive social, cultural and emotional issues about sexuality (I). Additionally, many countries have invested substantially in services for preventing, diagnosing and treating HPV-related disease. These services include health education, condom promotion, cervical cancer screening, and wart diagnosis and
treatment. Ideally, introduction of HPV vaccines should build on this progress where it exists and be integrated with other elements of these prevention and control programmes. The best combination of vaccination, screening and other interventions is determined by country-specific circumstances, and this requires coordination to ensure optimal delivery of interventions across a person’s lifespan.

5.1.2 Role of stakeholders and collaborators

The introduction of HPV vaccines must engage stakeholders from programmes on immunization, cancer control, reproductive health, human immunodeficiency virus (HIV), sexually transmitted infection (STI), child or adolescent health as well as gender rights groups, civil societies and other community groups. Many of these groups have not collaborated in the past. Education departments will be key partners in school-based delivery.

Communicators have been more involved in educating and sensitizing communities about HPV-related disease and vaccines than they have for vaccines involving infants and young children, because the target population for HPV vaccine (adolescents and young adults, and their parents, who may be asked to consent to use of vaccines in their children) are already prime communication markets in most countries. Advertising and messages delivered by the entertainment industry and mass media also provide an effective way to reach this target population. In 2007, global mass-media coverage of HPV vaccines greatly exceeded coverage of any other vaccine (Melinda Henry, WHO, pers. comm., March 2008).

Collaboration across sectors will be crucial in countries with major vaccine introduction in both the private and public-sector health systems. Such collaboration will avoid stand-alone strategies that are difficult to sustain; reduce cost, duplication and waste; improve cost effectiveness; strengthen partnerships between programmes; and promote more consistent education and communication messages. Collaborations can capitalize on unique programme skills and experience. For example, programmes in sexual and reproductive health, adolescent health and HIV reach young and older adolescent females in schools, health facilities and the community. These programmes provide health education; they also advocate for and deliver adolescent-friendly services. Cancer control experts are skilled in estimating the HPV-related cancer burden, and in monitoring the impact of screening (1,2). One example is a multisector collaboration in Europe, which developed a comprehensive control plan for cervical cancer that included HPV vaccines (3). Similarly, Cervical Cancer Action: A Global Coalition to Stop Cervical Cancer is a global partnership of nongovernmental organizations involved in cancer prevention, immunization, reproductive and sexual health, and HIV (4). The partnership also advances MDG 8, which aims to establish global partnerships for development (5).

5.1.3 Relation of HPV vaccination to WHO and United Nations policies

HPV vaccination in older children, adolescents and young adults fosters the aims of UNICEF’s GIVS, UNICEF’s Executive Board and WHO’s World Health Assembly, all of which aim to expand the target age and range of vaccines of immunization programmes (6). HPV vaccination in low and middle-income populations, and low-income populations in high-income countries, could advance several MDGs including:

- MDG 6 (to combat high-impact diseases characterized by socioeconomic inequity) – because cervical cancer is a striking example of such a disease (5)
• MDG 3 (to promote gender equality and empower women) – because vaccination is expected to prevent disability, suffering and death of women from HPV-related cancers.

• MDG 5 (to improve maternal health) – because vaccination will reduce the need to treat HPV-related precancers and cancers that may cause pregnancy complications; the quadrivalent vaccine also prevents genital warts, which may obstruct the birth canal.

5.2 Vaccine-delivery strategies

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Each country will need to consider the delivery strategies, feasibility, level of effort, cost and cost effectiveness of vaccinating target populations.</td>
</tr>
<tr>
<td>Developing new delivery systems will take time and substantial resources. New strategies should not erode other immunization programmes or screening programmes demonstrated to be effective at the population level.</td>
</tr>
<tr>
<td>Delivering a three-dose HPV vaccine will be challenging in all settings; vaccines with simpler schedules would make delivery easier.</td>
</tr>
<tr>
<td>Early vaccination experiences in introducing vaccines in industrialized countries and operations research in developing countries have identified promising delivery strategies.</td>
</tr>
<tr>
<td>School-based vaccination strategies for other vaccines have achieved high coverage in several middle and high-income countries and are being piloted in low-income countries.</td>
</tr>
<tr>
<td>Community health campaigns that now reach the target age group with other vaccines could be adapted to include HPV vaccines.</td>
</tr>
<tr>
<td>Vaccination in health-care facilities, which is the main approach in industrialized countries, allows links to be made with other age-appropriate services and health education.</td>
</tr>
</tbody>
</table>

5.2.1 General considerations

Developing systems to deliver HPV vaccines will take time because most countries, including most industrialized countries, do not routinely vaccinate young adolescents, even though many countries have policies to vaccinate this age group. Delivery will be particularly challenging in developing countries, where health infrastructure is weak and resources are limited. Each country will need to consider the delivery strategies, feasibility, level of effort, cost and cost effectiveness of vaccinating target populations. Operational research is under way to identify single or mixed-mode delivery strategies in many industrialized countries and in a few low and middle-income countries, but more is needed (see section below on evaluating vaccine delivery and alternate schedules).

The greatest benefit of HPV vaccines will be achieved by vaccinating young adolescent girls before the onset of sexual activity (see Section 3). Each country will need to identify the most effective way to reach adolescents before the onset of sexual activity, and this will vary by age of sexual initiation and programmatic opportunities such as school attendance, child-health campaigns and access to affordable primary care. At a population level, vaccinating older adolescent females and young women will have less health impact than vaccinating younger adolescent females because many
older females will already have been infected with vaccine-related HPV types (see Section 4). Nevertheless, many industrialized countries have endorsed catch-up vaccination of older adolescent females and young women, because these strategies may be cost effective, reduce costs of cervical cancer screening and produce an observable effect more quickly than vaccination of younger females. Several countries are exploring methods to reach these groups, particularly methods that do not divert resources from vaccinating the primary target group (7). Vaccine introduction should also not undermine existing screening programmes that have been demonstrated to reduce cervical cancer incidence or mortality at the population level in that country.

Delivering a three-dose HPV vaccine will be challenging, regardless of the target age group or vaccination setting. Delivering boosters (if needed) will be particularly difficult if the target age group vaccinated through schools can no longer be contacted through the school and does not regularly access preventive health care. In many European countries and the United States, experience with hepatitis B vaccines has been informative (9,14-16). For example, while only 11–50% of adolescents attending United States clinics completed a three-dose series of vaccine for hepatitis B virus (14,15), a school-based programme for children aged 11–12 years in Scotland achieved 80% coverage for the full series (17). Barriers to completing a full HPV vaccine series may include lack of knowledge of the need for multiple doses, lack of follow-up or reminder systems, intercurrent illness and scheduling problems. Delivery would be helped by simplified 2-dose schedules, or 6 or 12-month dosing intervals that align with semi-annual or annual vaccination campaigns, school year schedules or routine primary care visits (see section below on evaluating vaccine delivery and alternate schedules).

5.2.2 School-based programmes

Delivering HPV vaccines through schools has great potential in all regions because primary school completion rates among older girls (e.g. aged 8–11 years) are moderate to high and increasing. For example, primary school completion rates among older girls have been approximated as follows:¹

- 51–56% in AFRO
- 79–84% in the WHO Regional Office for the Americas (PAHO) countries outside North America
- 70% in EMRO
- 85% in the WHO Regional Office for Europe outside Western Europe (EURO)
- 68–78% in SEARO
- 91–95% in WPRO.

In China, India and Indonesia, which together represent 38% of the world’s primary school age children, primary school completion rates are 81% (18,19). According to population-weighted estimates pooled across 24 African countries, nearly three quarters of girls aged 10–14 years attend primary school at some point (20). School attendance of this age group is much higher in Western European countries and North America. School-based vaccination that directly involves school health programmes and staff, or simply uses schools as venues, has many advantages (see Table 5.1) (7,21-26).

¹ Estimates are inexact and were calculated using data from cited references.
Table 5.1  Strategies to deliver HPV vaccines to the primary target population

<table>
<thead>
<tr>
<th>School-based programmes</th>
<th>Advantages:</th>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• allow multidose vaccines to be integrated into a single school year</td>
<td>• can present difficulty with obtaining parental consent, which may be challenging or complex</td>
</tr>
<tr>
<td></td>
<td>• are widely accepted and trusted by parents and pupils</td>
<td>• can present difficulty with vaccine payment unless centrally purchased</td>
</tr>
<tr>
<td></td>
<td>• can provide services to older children and adolescents who do not routinely access primary care</td>
<td>• cause additional workload for teachers</td>
</tr>
<tr>
<td></td>
<td>• have relatively low organizational costs</td>
<td>• do not reach out-of-school adolescents</td>
</tr>
<tr>
<td></td>
<td>• provide easy access when enrolment rates of target population areas are high</td>
<td>• have staff that may lack or have only limited experience with medical interventions and consent procedures</td>
</tr>
<tr>
<td></td>
<td>• provide opportunities for group and incremental education about complex topics</td>
<td>• lack or have only limited access to cold-chain storage</td>
</tr>
<tr>
<td></td>
<td>• provide possible links with other health education or services</td>
<td>• require careful planning and logistics to achieve high attendance on vaccination day.</td>
</tr>
<tr>
<td></td>
<td>• reduce time required by parents and pupils.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• are difficult to sustain over time</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• can cause challenges for individual patient follow-up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• can present difficulty with vaccine payment unless centrally purchased</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• cost more for delivery compared to schools and health facilities.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Community-based programmes</th>
<th>Advantages:</th>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• can allow flexible scheduling determined at the local level because of pulsed delivery</td>
<td>• are not used by many older children and adolescents do not seek preventive care, even in industrialized countries</td>
</tr>
<tr>
<td></td>
<td>• can reach adolescents not attending schools or other special populations</td>
<td>• can have difficulty monitoring uptake at population level</td>
</tr>
<tr>
<td></td>
<td>• provide opportunities for mass health education</td>
<td>• have facilities in sexual and reproductive health that serve mainly sexually active females and may be most suitable for catch-up vaccination</td>
</tr>
<tr>
<td></td>
<td>• provide reduced storage requirements at peripheral facilities (advantage for multidose vaccines).</td>
<td>• have internal competition with delivery of other necessary clinical or preventive services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• have limited access to people in many middle-income countries and in most low-income countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lack skilled health-care providers in many low-income countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• may have high organizational costs than other delivery modes.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Health-care facility-based programmes</th>
<th>Advantages:</th>
<th>Disadvantages:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• allow individual patient follow-up and continuing care, including future screening</td>
<td>• are not used by many older children and adolescents do not seek preventive care, even in industrialized countries</td>
</tr>
<tr>
<td></td>
<td>• are accessible to a high proportion of the population in industrialized countries and many middle-income countries</td>
<td>• can have difficulty monitoring uptake at population level</td>
</tr>
<tr>
<td></td>
<td>• have extensive experience and resources with vaccine administration, handling and storage</td>
<td>• have facilities in sexual and reproductive health that serve mainly sexually active females and may be most suitable for catch-up vaccination</td>
</tr>
<tr>
<td></td>
<td>• have personnel who are trusted by parents and children</td>
<td>• have internal competition with delivery of other necessary clinical or preventive services</td>
</tr>
<tr>
<td></td>
<td>• provide opportunities to offer other age-appropriate health services, including other immunizations, and sexual and reproductive health education and services during vaccination visits.</td>
<td>• have limited access to people in many middle-income countries and in most low-income countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• lack skilled health-care providers in many low-income countries</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• may have high organizational costs than other delivery modes.</td>
</tr>
</tbody>
</table>
Many countries have had success with school-based immunization of older children and young adolescents. For example, several European countries and Canada achieved high coverage (70–85%) of hepatitis B vaccine among adolescents through school-based programmes (27-29). Many low and middle-income countries, including Indonesia, Malaysia, Sri Lanka, the Syrian Arab Republic and Tunisia, routinely deliver booster doses to primary or secondary school children for tetanus–diphtheria vaccine, oral polio vaccine, second measles dose or rubella vaccine (30). These programmes could be expanded to include HPV vaccines if target age populations are similar and co-administration of HPV with other vaccines is safe and effective.

Evidence is mounting about the acceptability of HPV vaccination in schools. A study of Chinese mothers reported that most would prefer cervical cancer and HPV vaccine information to be provided by schools or student health counsellors (31). A survey of United Kingdom parents of students aged 11–12 years from a socially and ethnically diverse city found that most favoured delivering information about cervical cancer prevention to young adolescents in schools (32). A Canadian survey of health-care providers found that more than 75% believed parents would prefer HPV vaccines to be given at schools (33).

In spite of their success, school-based vaccination programmes face challenges (see Table 5.1). Out-of-school children will be missed in countries where school attendance decreases at the end of primary school (around age 12 years in many countries) (7). This may prompt some programmes to target girls aged 10–11 years who are more likely to be in school. Also, schools could be used as venues to vaccinate out-of-school adolescents (as antihelminth programmes have shown) or girls in school can be used to notify out-of-school girls (7,34-36). Demonstration projects in Uganda and Viet Nam will be comparing vaccine uptake in programmes with and without efforts to reach out-of-school girls (21). Other challenges include limited experience with medical interventions, the need for consent procedures, lack of vaccine-storage facilities and the need to engage parents to sensitize them about vaccination. Some of these challenges may be overcome by collaborating with experienced immunization programmes.

Several industrialized countries have begun or are planning school-based HPV vaccination programmes. In 2007, an Australian Government-funded programme started vaccinating girls in grade 7 (aged 11–12 years) with a staggered catch-up of girls in grades 8–12 (aged 13–18 years). Local governments coordinated communication with the general public, clinicians and schools. Schools gave general information about HPV and vaccine safety and efficacy to eligible girls to take home to their parents. Parents provided written consent—a process that was more challenging in remote areas. In the first year, about 80% of girls aged 11–12 years were vaccinated (37).

During a pilot project in Manchester in the United Kingdom, schools vaccinated about 70% of targeted students with the first dose. The programme required major staffing from the local health department to oversee written parental consent, confidential exclusion of potentially pregnant girls and scheduling of follow-up doses (Loretta Brabin, University of Manchester, pers. comm., February 2008). (See Annex 2 for updated information on this study.) In September 2008, United Kingdom schools will begin routinely immunizing girls in grade 8 (aged 12–13 years); a catch-up programme for older girls will start in 2009. This programme will be preceded by a major public education campaign to increase the currently limited knowledge about cervical cancer and HPV vaccines (Joanne Yarwood, Department of Health, London, pers. comm., February 2008). Owing to success in school-based hepatitis B programmes, school-based HPV vaccination is being planned in Canada and Belgium using existing infrastructure (38). The phase IV studies
of both the bivalent and quadrivalent vaccines in the Nordic countries will also evaluate uptake of HPV vaccination in schools (39).

In Peru and Uganda, pilot projects are evaluating HPV vaccine delivery in dozens of schools; similar studies are planned in Viet Nam and India (21). (See Annex 2 for updated information on these projects.) The programmes are exploring uptake; optimal age ranges; acceptability in students, parents and teachers; logistic issues; required resources; vaccine wastage; and methods to recall students for second and third doses. Preliminary findings from Peru indicate fairly high acceptability by students, parents and teachers, although formal parental consent procedures have led to some refusals. Viet Nam will be comparing delivery in schools and in health facilities. The Uganda project is comparing school-based delivery during and outside child-health day: approval for school delivery is sought by local leaders and, once a programme is brought to a schools, girls (or their parents) who request vaccination are assumed to have given implicit consent (21). School-based delivery is also being piloted in Nepal among females aged 15–26 years using vaccine subsidized by Australia (40).

A few countries (Greece, Republic of Korea and the United States) require that children in some or all regions receive certain vaccines before starting primary or middle school. These school-entry requirements have dramatically increased vaccine uptake among school-aged children (41-43). However, as of January 2008, only one state passed a school entry law for HPV vaccination, and only after adding liberal provisions for parents to decline vaccination for their daughters (see Section 6) (7,37). Mandatory school entry requirements for HPV vaccines have been opposed by many immunization experts (22,44,45).

5.2.3 Community-based programmes

Community-based vaccination programmes outside schools are another promising option for delivering HPV vaccines (see Table 5.1) (1,46). In some countries, programmes in sexual, reproductive and adolescent health are associated with community-based health and education activities that could teach communities about HPV vaccines or refer adolescents to vaccination sites. The advantages of campaigns are balanced by high cost. However, even campaigns designed to give single booster vaccines can be expensive compared with facility-based delivery or extended outreach, so costs must be balanced with programme effectiveness and acceptability (47).

At least 17 Latin American countries run vaccination weeks either once or twice a year, many of which include rubella vaccines. Some countries, including Argentina and Peru, currently vaccinate adolescents against hepatitis B; this is another multidose vaccine (48). The experience with hepatitis B shows that vaccinating adolescents is feasible and acceptable through mass campaigns (49,50). About 60 countries in Africa and Asia ran child-health days in 2005, and some now deliver vaccine boosters to girls aged 9–14 years (51). For example, Egypt provides tetanus and meningitis vaccines at age 9 years, and Tunisia provides measles–rubella vaccine, tetanus–diphtheria and oral polio vaccine boosters at age 12 year (52). Thailand currently delivers tetanus–diphtheria boosters at age 11–12 years through mobile vaccination teams (Caitlin Wetzel, pers. comm., WHO, March 2008).

Other types of community-based delivery include special outreach to adolescents through community workers or peers who refer vaccination candidates to local health facilities, and continuous delivery of vaccines through mobile vans. Neither of these approaches has been used for large-scale HPV vaccination programmes.
5.2.4 Health-care facility-based programmes

Many countries in all WHO Regions have long delivered vaccines through health-care facilities, and this is the main delivery method in many industrialized countries. Delivering vaccines through health-care facilities has several advantages (see Table 5.1) (53,54).

In spite of the benefits of using health-care facility-based programmes, in many countries only a few young adolescents have preventive or well-care visits where vaccines might be offered. Thus, uptake of preventive services has been slow. Access may be impaired by cost, lack of insurance, embarrassment, concerns about confidentiality and other factors (7,11,12). European countries that have relied mainly on private immunization providers tend to have lower vaccination coverage (35–80%) than countries that have relied on school-based delivery (70–99%) (55).

The following strategies have been used to increase vaccination coverage in health-care facilities, and could be applied to HPV vaccines (22,41-43,56):

- vaccination schedules that allow co-administration with other age-appropriate vaccines
- reminder and recall systems
- routine chart reviews to identify older children and young adolescents eligible for vaccination
- opportunistic vaccination when older children and young adolescents are seen for nonroutine services
- endorsement by influential clinical organizations.

Weak primary care systems and serious shortages of health-care workers make these strategies less promising in many low and middle-income countries. However, a recent study indicates the potential to immunize a substantial portion of adolescents targeted for HPV vaccine in Africa, even in rural areas (57). In four sub-Saharan countries, more than one in five girls aged 12–14 years had received one or more injection of any kind in the past 12 months: 21% in Burkina Faso, 25% in Malawi, 41% in Ghana and 60% in Uganda. Most received injections from doctors or nurses. In all but Burkina Faso, the proportion of girls who had recently received injections of any kind was slightly higher in rural than urban areas (57). A demonstration project in Viet Nam is evaluating HPV vaccine delivery through health-care facilities (21) (see section below on evaluating vaccine delivery).

Many low and middle-income countries provide routine health education, commodities and services for family planning, sexual and reproductive health, or other adolescent health services to older adolescents, including many who are not yet sexually active. Many of these countries also have experience with immunizing adolescents for rubella and tetanus, with health education and cervical cancer screening; such countries may be promising settings for piloting HPV vaccination strategies. Some have proposed offering HPV vaccines to older adolescents and young women when they bring in infants or children for immunization or other health care (2). Although neither bivalent nor quadrivalent HPV vaccine is recommended in pregnant women, antenatal care sites that are widely accessed in most countries could be used to educate women about the benefits of vaccine for girls in the family and community (1). Likewise, women receiving cervical cancer screening will not be a primary target population for HPV vaccines, but screening...
visits provide an opportunity to teach women about cervical cancer prevention and spread the word about HPV vaccines (1).

5.3 **Acceptability of HPV vaccines**

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>• In most countries, acceptability of adolescent vaccines proven to be safe and effective is high among communities, providers, parents and adolescents.</td>
</tr>
<tr>
<td>• Studies of hypothetical or actual introduction of HPV vaccines in low, middle and high-income countries indicate that HPV vaccines are acceptable to providers, parents and adolescents, although data on vaccine delivery in low and middle-income countries are limited.</td>
</tr>
<tr>
<td>• Parent or caregiver attitudes about vaccines are one of the most important determinants of vaccine uptake in children and young adolescents.</td>
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<tr>
<td>• Vaccine acceptability may be influenced by active commercial marketing to consumers and health-care providers in many regions.</td>
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<tr>
<td>• Acceptability in parents and providers is strongly associated with perceptions of vaccine safety and efficacy, and endorsement by trusted authorities.</td>
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<tr>
<td>• Most studies indicate that some parents are concerned that vaccination may increase risky sexual behaviour or harm fertility.</td>
</tr>
<tr>
<td>• Current high costs of the vaccines are expected to deter acceptance, especially if vaccines are not covered by public programmes or insurance plans.</td>
</tr>
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</table>

5.3.1 **General considerations**

HPV vaccines that are accessible, affordable and acceptable are expected to generate high demand and coverage levels. Acceptability of all vaccines is affected by public perception of vaccine safety, which depends on how perceptions of risk of acquiring vaccine-preventable diseases compare with perceptions of risk of vaccine-adverse events. Education and sensitization may be needed to help communities understand the benefits of HPV vaccines because, in most countries, the general public is not aware of the link between HPV infection and disease outcomes. Also, the most serious HPV-related disease, cervical cancer, almost never occurs in young adolescents targeted for vaccination. Awareness of cervical cancer in women may be limited if screening and treatment services are scarce and women with advanced disease are hidden due to stigma. This lack of awareness of the risk of HPV-related disease in many countries may raise public expectations of the safety of HPV vaccines.

While HPV vaccines hold the promise of preventing potentially fatal cancers, they can also raise sensitive issues related to sexuality that may influence acceptability, as well as expectations about parental and vaccinee-informed consent. For example, promoting HPV vaccines as a tool for preventing cancer may yield different acceptance from promoting HPV vaccines as a tool for preventing STIs. Vaccination strategies that target girls only may also raise concerns about special risks to females (e.g. adverse effects on fertility) or gender equity. Most studies of hypothetical or actual HPV vaccine acceptability have been run in industrialized countries (58), and much more information is needed from low and middle-income countries where the economic, sociocultural and logistic context of vaccination can be dramatically different. Cultural and economic considerations make it difficult to extrapolate findings from one country to another (59). (See Annex 2 for updated information on HPV vaccine acceptability.)
5.3.2 Community acceptability

Because both vaccines have been in use for less than 24 months, data on demand and acceptability are limited. Before vaccines were marketed, studies of hypothetical acceptability, mostly in the United States, showed that there was great interest in HPV vaccines. Since HPV vaccines have been marketed in Australia, Europe and the United States, acceptance and demand have been high (37,60). The Program for Appropriate Technology in Health (PATH) is evaluating vaccine acceptability among community leaders, teachers, civil societies, policy-makers, parents and health workers in India, Peru, Uganda and Viet Nam as part of pilot projects of both vaccines. Preliminary results from Peru, Uganda and Viet Nam suggest that communities support vaccination of young adolescent girls once the communities have been informed about the problem of cervical cancer and the safety of HPV vaccines (21). These and other studies have also identified concerns that vaccinating young girls may threaten future fertility (21,61).

Community knowledge, perceptions and acceptability of HPV vaccines may be influenced strongly by marketing. Such marketing has been widespread in industrialized countries (Abigail Shefer, United States Centers for Disease Control and Prevention (CDC), pers. comm., 2007) and is increasing in low and middle-income countries that have licensed HPV vaccines (see Section 6). HPV vaccine manufacturers have sponsored direct-to-consumer vaccine advertising campaigns as well as education about cervical cancer, HPV and HPV vaccines to the general public, immunization providers, policy-makers, insurance companies and funders of public sector immunization programmes (37,62).

5.3.3 Provider acceptability

Studies conducted before and after HPV vaccine introduction indicate that acceptance of HPV vaccines is high among providers in several countries in China, Europe, Mexico and North America – even among providers with limited knowledge of HPV (22,33,63-70). Preliminary data from formative research in Peru and Viet Nam indicate high acceptability among health-care providers (21). These and other studies, many from the United States, have shown that the following factors are associated with intention to recommend vaccines (22,33,65,66):

- knowledge about HPV
- positive attitudes towards vaccination generally
- few perceived barriers to immunization
- clinical experience with young adolescents
- endorsement by influential clinical or public health organizations
- perceived susceptibility of the patient population to HPV infection
- patient cultural considerations such as religion, socioeconomic status and ethnicity
- comfort discussing sexuality with patients
- comfort and competence with immunization procedures
- affordable vaccine cost or reimbursement by insurance plans or public sector programmes
- lack of parental resistance to vaccination (e.g. because of STI prevention)
- parental request for vaccination.
Among United States paediatricians, perceptions about vaccine safety, efficacy, the health impact of vaccination and relevance of HPV vaccines to the clinician’s practice most strongly influenced intentions to recommend HPV vaccines (66).

Some studies show that providers prefer universal vaccination strategies (rather than targeted vaccination strategies) because they understand that risk of HPV acquisition is high in all sexually active adolescents (22). Several studies have indicated that providers prefer vaccinating older rather than younger adolescents – a finding that may be related to reluctance to address sexuality with the youngest adolescent patients (59,65,69). This is concerning because the primary target group for vaccination in most countries is young adolescents (e.g. 10–13 years). One Canadian study found that providers were slightly more likely to recommend HPV vaccines that provided protection against cervical cancer and warts than vaccines that protected against cancer alone (33).

5.3.4 Parental acceptability

Parent or caregiver attitudes about vaccines are the most important determinants of vaccine uptake for minor children, and strongly influence adolescent attitudes about vaccines (71). Research from Australia, Canada, Europe (Finland and the United Kingdom), Israel, Latin America, the United States and Viet Nam has shown high acceptability of HPV vaccines among parents presented with hypothetical scenarios that have different vaccine characteristics. Studies indicate that most parents have limited or no knowledge about HPV, but many would vaccinate their children if they believed vaccines were safe and effective (32,58,72-76).

Early experience with introducing HPV vaccines in Europe and the United States, and in a pilot project in Peru, reveals high acceptability among parents of girls offered HPV vaccines, despite requirements for explicit parental consent (21) and (Loretta Brabin, University of Manchester, pers. comm., April 2008, Abigail Shefer, CDC, pers. comm., April 2008). Nevertheless, evaluations of school-based HPV vaccination in Peru and the United Kingdom that required parental consent have shown some refusals (21,32). In some instances, parents incorrectly believe that HPV vaccination is most appropriate for those who are already sexually active; therefore, campaigns should emphasize that HPV vaccination is most effective when delivered before onset of sexual activity, even though this may generate opposition among a vocal minority (58,77). This situation underscores the fact that many parents have limited information about cervical cancer, HPV and HPV vaccines, and that education is needed to promote fully informed decisions.

Factors that increase acceptability

Several factors are positively associated with parents’ intention to vaccinate their daughters against HPV (32,58,59,68,70,72,78):

- recommendation from a provider, teacher or spiritual leader
- positive perceptions about vaccines generally
- personal experience with STIs, abnormal Pap tests or genital warts
- knowledge of someone with cervical cancer
- desire to protect their child from harm, including the emotional impact of STIs
- belief that HPV-related disease is serious, that their child is susceptible to HPV, that vaccines are effective and safe, and that vaccination will not lead to riskier sexual behaviors.
In general, perceived effectiveness of vaccines in preventing HPV infection was a more important determinant of acceptance than perceived risk of cervical cancer (58). Parents rarely cite fear of injections or vaccine side-effects as reasons to decline vaccinating their daughters (7).

**Factors that decrease acceptability**

Concerns that vaccination might lead to unsafe sex have been associated with disapproval of vaccines in some studies (70,74,79) but not in others (58,63,72). In studies from industrialized countries, only a minority of people believed that HPV vaccines may implicitly condone, and thus increase, adolescent sexual behaviour (58,63,80). These objections were also raised 15 years ago when adolescent vaccination for hepatitis B, another STI, was introduced in many countries, but they have largely been overcome (59,63,67,70). A study from Viet Nam (72) found that mothers and caregivers of adolescent girls favoured vaccinating their daughters, and more than 90% disagreed that their daughter would have sex early if they were vaccinated. Two studies have found potentially higher parental acceptance of vaccines that protect against cervical cancer and anogenital warts, as opposed to cervical cancer alone (74).

It remains unclear whether HPV vaccines targeted to girls only would provoke concerns about adverse effects on fertility, especially in areas where injectable hormonal contraceptives are used widely or where suspicion of western medicine runs deep (21,61). Preliminary data from formative studies in India, Peru and Uganda indicate that some parents worry that vaccination may harm fertility (21).

Currently, HPV vaccines are expensive products in all markets, and cost is likely to have a strong influence on parental acceptability when vaccines are not provided either free or at low cost by public sector programmes or insurance plans. In some countries, costs and lack of insurance reimbursement for vaccines that are far less expensive than HPV vaccines have precluded uptake (58,79,81) and poverty is associated with lower vaccine uptake in many countries (53,82).

**5.3.5 Adolescent acceptability**

Experience in many countries indicates that acceptability of all vaccines by adolescents is usually high if HPV vaccines are endorsed by parents, health-care providers or teachers (21,49) (Abigail Shefer, CDC, pers. comm., 2007). Few studies of HPV vaccine acceptability in adolescents are available, and most were undertaken in the United States. Most adolescents and young adults in the United States have expressed interest in HPV vaccines, especially vaccines that prevent both genital warts and cancer (59). Early concerns that acceptability will be hindered because HPV vaccines prevent STIs have not been realized. A study of Finnish adolescents found that 83% would accept vaccination despite low levels of HPV knowledge (76). A study of prospective clinical trial candidates in Brazil found that 92% cited careful physician consultation as a reason to participate, and 29% cited fear of adverse events as a reason to defer participation (83). Formative research in India, Peru and Uganda has shown that young adolescents understand that HPV vaccines prevent illness, and this notion was associated with vaccine acceptance (21). Acceptability research is also planned in India and Viet Nam (21).

Some studies suggest that decisions about HPV vaccination will be made jointly between parents and their children (32). Joint decisions may raise questions about consent and confidentiality if discussions include sexual activity, but this can be minimized if HPV vaccines are offered well before the onset of sexual activity. When parental consent or confidentiality pose barriers, adolescents in many countries can access sexual or
reproductive health services without consent or knowledge of their parents, and this may include HPV vaccines in some cases (84,85).

5.4 Education and communication

Key points

- Successful vaccine introduction requires informed support from policy decision makers, health-care providers, parents, young people and the public, but knowledge of cervical cancer, HPV and HPV vaccines is limited in these groups.
- Education can promote careful decisions about introducing HPV vaccine and motivate informed uptake of vaccines, correct misinformation and minimize possible stigma about vaccination.
- Potentially complex information about cervical cancer, HPV and HPV vaccines can be distilled into simple, accurate messages for different audiences.
- Many education materials for diverse audiences are available in industrialized countries, but few are available in low and middle-income countries.
- Messages should carefully balance key information requirements with what is culturally acceptable to adolescents, parents and local communities.

5.4.1 General considerations

Successful introduction of any new vaccine requires broad-based support from decision-makers, health professionals, parents, adolescents and the general public (86–88). Educating these groups can promote careful decision-making about introducing HPV vaccines and their informed use (9,89,90). These groups also need a basic understanding of the risks associated with HPV infection and HPV-related disease, the benefits and risks of vaccination and how vaccination may complement other prevention strategies, especially screening.

Education and communication about cervical cancer is challenging for many reasons. In most countries, decision-makers, health-care providers, parents, adolescents and the general public have a low awareness of cervical cancer prevention strategies and HPV vaccines. Information about HPV epidemiology, transmission and natural history, and the relation of HPV to cervical cancer and anogenital warts, is complex. For example, many people are confused by the fact that most sexually active adults will be infected with HPV during their lifetimes, that most HPV infection is transient, and that only a minority of infections result in cancer. The target group age and sex (girls only vs. girls and boys) may vary, depending on HPV vaccine licensing indications in a country (70). The fact that HPV is sexually transmitted and that cervical cancer is a stigmatized condition in many countries raises sensitive issues about sexuality. Messages that promote HPV vaccines as a method to prevent cancer may create different perceptions from messages that promote vaccines as a STI-prevention method. These issues emphasize the importance of developing educational resources appropriate to local culture and audience, including adolescent vaccinees.

Fortunately, many educational print, audiovisual and web-based materials about cervical cancer, HPV and HPV vaccines are available in North America and Europe, and many have translated complex topics into simple, short messages (91–94). Fewer educational materials are linguistically and culturally appropriate for populations with limited health literacy in Africa, Asia, Latin America and the Pacific (70,95,96). Within these Regions, priority should be given to developing materials appropriate for the different needs of
adolescents, parents, health professionals and community leaders. Coordinated efforts of
governments and community-based, public and private organizations, as well as vaccine
manufacturers, will improve the credibility, consistency and clarity of the messages
(70,97).

5.4.2 Educating policy-makers
As part of evidence-based decision-making about introducing HPV vaccines, policy-
makers may make decisions about vaccine licensure, recommendations for use in national
immunization programmes, financing and requirements for post-marketing surveillance
(70). Policy-makers can benefit from understanding basic facts about the burden of HPV-
related diseases, HPV vaccines, other cervical cancer prevention and control options, and
how vaccines and other cancer-control measures might be integrated into a
comprehensive cancer-control strategy (see Table 5.2). Policy-makers in India, Peru,
Uganda and Viet Nam have insisted on such information before discussing vaccine use in
their countries (21). Country-specific data are available for many countries, on (98):

- HPV prevalence and type distribution
- incidence and prevalence of precancerous cervical lesions and cancer
- demographic and sexual characteristics
- immunization and screening programmes.

WHO also provides advice on making decisions about introducing HPV vaccines (1,99). Information that helps to compare the new vaccine with more familiar vaccines or health
interventions can be particularly effective (100).

5.4.3 Educating programme managers
The most successful programmes will introduce HPV vaccines as part of a comprehensive
cervical cancer control strategy that considers education about reducing sexual risk and
promoting condom use, as well as screening, diagnosis, treatment and palliative care
(1,101). In many cases, HPV vaccination programmes will be directed by immunization
programmes with extensive immunization experience. In other cases, programmes may be
directed by adolescent health or cancer-control programmes with limited immunization
experience, so the educational emphasis will vary. Table 5.2 lists some important
messages for programme managers.

5.4.4 Educating immunization providers
Educating immunization providers is critical because provider knowledge about cervical
cancer, HPV and HPV vaccines is limited in most countries. Furthermore, knowledge
motivates providers to vaccinate, and providers are one of the most trusted sources of
vaccine information for parents and the public (7,71,86,102-104). Studies from several
countries indicate that common areas of misunderstanding include the burden of HPV-
related disease; the types of HPV and their health consequences; uncertainty about how
HPV leads to cervical cancer; the management, treatment and prevention of HPV-related
disease; and vaccine characteristics and use (89,90,105-107). Providers may confuse
HPV, HBV (hepatitis B virus), HSV (herpes simplex virus) and HIV (human
immunodeficiency virus) (108).
Table 5.2 Educational topics on HPV vaccines for various audiences

<table>
<thead>
<tr>
<th>General public, parents and adolescents considering vaccination</th>
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<tr>
<td>• Cost and coverage by health systems</td>
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<td>• Health organizations that support HPV vaccination</td>
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<tr>
<td>• Mode of administration, dose number, need to complete the three-dose series on schedule</td>
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<tr>
<td>• Recommended ages and sex for vaccination, including benefits before onset of sexual activity</td>
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<tr>
<td>Serious nature of vaccine-preventable cervical cancer and anogenital warts (for quadrivalent vaccine)</td>
</tr>
<tr>
<td>• Sites where vaccination is provided</td>
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<tr>
<td>• Sources of educational material</td>
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<tr>
<td>• Vaccine benefits, including degree and duration of protection</td>
</tr>
<tr>
<td>• Vaccine limitations (no protection against other STI, or HIV, pregnancy or all cancer-causing HPV types) – safe sexual behaviour and future screening advised</td>
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<tr>
<td>• Vaccine safety (including reproductive safety) and possible side effects</td>
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<th>Immunization providers</th>
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<tr>
<td>• Cost and public-sector reimbursement</td>
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<tr>
<td>• Delivery schedules, including co-administration with other vaccines</td>
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<td>• Deferral of vaccination during pregnancy</td>
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<tr>
<td>• Importance of advising vaccinees to practise safe sex in the future and seek screening later in life (may only be applicable to people who had older vaccines)</td>
</tr>
<tr>
<td>• Recommended ages and sex, including benefits before onset of sexual activity</td>
</tr>
<tr>
<td>• Vaccine efficacy and duration of protection, and uncertainly about the need for a booster</td>
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<tr>
<td>• Vaccination logistics, including cold-chain storage</td>
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<tr>
<td>• Vaccination of special subgroups (e.g. People infected with HIV)</td>
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<tr>
<td>• Vaccine safety and side effects, and how to report adverse events</td>
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<tr>
<th>Programme managers</th>
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<tr>
<td>• Education resources for the community, parents and adolescents</td>
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<tr>
<td>• Monitoring coverage, safety and other programme indicators</td>
</tr>
<tr>
<td>• Role of screening to increase the population impact of vaccination</td>
</tr>
<tr>
<td>• Role of methods to reduce sexual transmission of HPV and prevention resources</td>
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<tr>
<td>• Vaccine delivery strategies and target groups</td>
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<tr>
<td>• Vaccine policies and indications</td>
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<tr>
<td>• Vaccine procurement and financing</td>
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<tr>
<td>• Vaccine storage, transport and security</td>
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<tr>
<th>Policy-makers</th>
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<tr>
<td>• Added impact of screening to vaccination programmes</td>
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<tr>
<td>• Country burden of HPV-related disease</td>
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<tr>
<td>• Estimated time needed to observe declines in HPV-related disease</td>
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<tr>
<td>• Key programme stakeholders and their roles</td>
</tr>
<tr>
<td>• Prevalence of vaccine-related types in women with cervical precancers or cancer</td>
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<tr>
<td>• Potential vaccine impact and cost effectiveness at different coverage levels</td>
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<tr>
<td>• Vaccine cost and financing options</td>
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Educational needs will vary greatly, depending on the provider’s experience with immunization, experience with adolescents, understanding of HPV-related disease and knowledge of prevention and control of HPV-related disease. Providers value materials endorsed by respected health authorities that are brief, relevant to their practices and useful for educating and counselling patients. Materials could include talking points, visual aids and educational brochures. Strategies to help providers talk about sexuality with parents or adolescents may improve the acceptability of HPV vaccines in some settings, but may not always be necessary or appropriate. Table 5.2 lists important messages for immunization providers.
5.4.5 Educating adolescents, parents and the general public

When HPV vaccination is being considered, and certainly after HPV vaccines have been introduced, it is of benefit to educate the general public to generate appropriate vaccine demand, counteract misinformation and avoid exaggerated promises (109,110). Studies from many countries indicate that public knowledge of HPV and cervical cancer is limited and fraught with misunderstanding (75,103,106,111-115). However, accurate, simple information about HPV, cervical cancer and vaccines from respected sources can distinguish truth from myth, dispel rumours and minimize possible stigma about vaccination (70). Given that young adolescents are the primary target group, education through schools, programmes for adolescents and mass media that reach adolescents and their parents will be particularly influential. Messages about vaccination of boys that are consistent with country policy may be needed. Community outreach and mobilization, and activities involving local leaders can have a positive impact when resources or mass media are limited, or where the public may mistrust government or health authorities (86,111). Wherever possible, private and public-sector messages should be coordinated. Targeted information campaigns should focus on populations at highest risk of cervical cancer who may benefit most from vaccines. Before campaigns intended to create vaccine demand are launched, measures should be taken to ensure sufficient stocks, affordable prices and accessible venues (70).

Parents and adolescents who are considering vaccination will need more specific information to inform their decision-making, but which does not cause undue anxiety or offer unrealistic promises (Table 5.2) (67,86,88,103,109,110). Educational messages should take into account the developmental level of children and adolescents. The message that HPV is an STI is less relevant for girls aged 11 (who may not become sexually active for many years) than for girls aged 15 (who may soon start sexual activity). Whenever possible, local research on knowledge and attitudes about HPV vaccines should inform how the message is developed. Educational methods should be suited to the brief time allotted to education in most schools, health facilities and campaigns.

5.5 Vaccine affordability and financing

Key points

- Policy-makers will need to make decisions about vaccine introduction based on projected health impact, feasibility, cost effectiveness, affordability and potential for sustainable financing.
- Introduction and sustainability of HPV vaccination programmes will require financing, but that financing should not erode other important health programmes.
- HPV vaccines are currently among the most expensive vaccines marketed. Both manufacturers, GlaxoSmithKline Inc. (GSK) and Merck, have pledged to offer tiered prices as public-sector programmes make tenders.
- Vaccine price is currently one of the most critical factors influencing vaccine access and potential impact.
- Vaccination costs, including supplies, waste, transport, staffing, programme costs and monitoring, will be substantial if new delivery systems are needed.
- Over the long term, vaccine prices are expected to decline due to tiered pricing, increased demand, competition between products, introduction of new manufacturers and second-generation vaccines.
• High-income countries are currently the most commercially important market for both vaccines, but represent only 11% of the global cervical cancer burden.

• Global Alliance for Vaccines and Immunization (GAVI)-eligible countries had the highest number of cervical cancer cases in 2002; introducing HPV vaccines in these countries will require large external funds because of large target populations and internal budget constraints.

• Delayed introduction of vaccines in developing countries due to financial barriers will increase already dramatic inequities in cervical cancer incidence.

• WHO prequalification\(^2\) of both HPV vaccines is expected during 2009; this may prompt large-scale demand for vaccines procured by United Nations agencies.

5.5.1 General considerations

The introduction and sustainability of an HPV vaccination programme will require new financing, but such financing should not erode other important health programmes (116). Currently, the costs of HPV vaccination programmes are dominated by vaccine price. Several other financing challenges exist: costs of developing infrastructures to deliver three-dose vaccines to young adolescents, the disproportionate burden of cervical cancer in the poorest countries, and the large number of girls eligible for vaccine in high-burden countries.

In many low and middle-income countries, external funding will be essential if HPV vaccines are to be introduced; such support will be needed until the costs of vaccines and delivery systems fall dramatically. These needs come at a time of intense pressure to support other new vaccines and to strengthen systems to deliver established vaccines and other health priorities. Decision-makers in all countries, especially developing countries, must carefully weigh potential investment in HPV vaccines against investments in other new vaccines, cervical cancer screening and other health priorities, as well as the timeline on their return on investment. Countries that now invest heavily in screening, or wish to launch such programmes, should consider vaccine introduction strategies, but need to ensure that these strategies would not undermine current screening programmes in their country that have been shown to reduce cancer burden at the population level.

Key points from an expert review of HPV vaccine financing are summarized in the sections below (47). (See Annex 2 for updated information on affordability, financing and supply issues.)

5.5.2 Vaccine prices in industrialized countries

Currently, industrialized countries are the most important market for both bivalent and quadrivalent vaccines, with approximately 6.5 million girls aged 11 years in the target age range in 2010. Markets will be even larger in countries that also license HPV vaccines for older adolescents and young women or men (47). In the United States, the private sector quadrivalent vaccine price is currently US$ 125.29/dose, or about US$ 376 for the three-dose series, and is priced about the same or higher in other industrialized countries. The United States public-sector Vaccines for Children Program has negotiated a slightly lower price (US$ 100.59/dose), but it remains the most expensive vaccine in this programme (117). HPV vaccines are the most expensive vaccines marketed in several other countries. Even in markets where both vaccines are available (e.g. Australia and some European

\(^2\) Prequalification is a WHO process that assures the safety and quality of vaccines before procurement by United Nations agencies.
High vaccine prices have caused much debate about affordability and cost effectiveness in industrialized countries. For example, the Australian Government initially declined to cover HPV vaccine, but later reversed its decision. The government estimated that funding a four-year school-based programme to vaccinate girls aged 12–13 years and a catch-up population of females up to age 26 years would initially cost US$ 344 million, with recurring annual costs of US$ 40 million (for vaccine alone) (118). The British National Health Service estimates that the cost of their plan to routinely vaccinate girls aged 12–13 years may exceed US$ 200 million (47). Despite high costs, insurers and governments in several high-income countries have agreed to cover vaccine costs (see Section 6).

5.5.3 Vaccine prices in low and middle-income countries

HPV vaccines will have the greatest impact on cancer incidence and mortality in low-income countries with the highest disease burden. In 2002, 54% of cervical cancer cases occurred in the world’s lowest-income countries (GAVI-eligible countries) compared with 23% in lower middle-income countries, 12% in upper middle-income countries, and 11% in high-income countries (see Section 1) (119). Developing countries also have much larger populations of potential vaccinees (e.g. 52.5 million girls aged 11 years in 2010). In 2005, girls aged 11 years comprised 1.22% of populations in the poorest countries, but only 0.59% in industrialized countries. Over the next 20 years, the number of girls of this age will grow in the poorest countries, but decrease in high-income countries (120). Resources therefore need to be mobilized, and the affordability of vaccination increased, to maximize the impact on the global cervical cancer burden (47).

In low and middle-income countries where HPV vaccines are marketed in the private sector, vaccine prices are similar to those in industrialized countries, and prices of about US$ 100/dose are well beyond the reach of public-sector programmes. Both HPV vaccine manufacturers have pledged to provide vaccines at lower prices that are tiered to country income, volumes purchased and length of purchase agreements. GlaxoSmithKline Inc. (GSK) used this type of tiered pricing recently with the rotavirus vaccine, recently purchased by Brazil at $7 per dose, and for pooled vaccine procurement by the WHO Regional Office for the Americas (PAHO) (47). Merck has stated a “no-profit” pricing strategy for HPV vaccines in GAVI-eligible countries. However, neither manufacturer has announced tiered price ranges, because low and middle-income countries or organizations that purchase vaccines for these countries have not issued tenders, and HPV vaccines are not yet prequalified by WHO for United Nations procurement. (See Annex 2 for updated information on this issue.)

Even when tiered pricing becomes available in low and middle-income countries, initial prices may be higher than prices of vaccines used in programs that are part of the Expanded Programme on Immunization (EPI)3 (these six infant and childhood vaccinations all cost less than 25 cents per dose), and of other less commonly used infant and childhood vaccines (most of which cost $3.50 or less per dose) (47). Prices will largely be determined by the size of the global market and the ability of countries to pay for vaccines over time (4). Long-term demand forecasting is under way for low and

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3 EPI is an international effort to increase vaccination in low-income countries.
middle-income countries (21,121). Prices will fall as demand increases and manufacturers are able to increase production capacity. In 2009, WHO is expected to prequalify HPV vaccines for purchase by UN agencies, such as the PAHO Revolving Fund (a regional vaccine procurement mechanism funded largely by country budgets) and UNICEF. This will help access in Latin America and GAVI-eligible countries.

5.5.4 Factors that influence costs of vaccine introduction

HPV vaccination programme costs include the direct cost of vaccine (three doses), vaccine supplies, customs duty or import tax, waste and shipping, insurance, procurement and handling fees, staffing, training, expansion and maintenance of a cold chain, waste management, injection safety, and community sensitization and mobilization campaigns. Monitoring and surveillance to assess vaccine effectiveness and safety also requires investment. Programme costs will be relatively high when new infrastructure is needed to reach young adolescents, especially because most countries do not routinely vaccinate young adolescents with a three-dose vaccine (18,121). Cost will increase substantially if ongoing research indicates that a booster dose is needed. Where cervical cancer screening exists, vaccination programmes may have costs related to integration with screening programmes or monitoring of the impact of vaccination on screening programmes.

Costing tools can help decision-makers estimate affordability of vaccination programmes (18).

Influence of country income

Given the large primary target population for HPV vaccines in most countries, programme costs would be high (47). Even if vaccine prices decrease, delivery costs could make vaccination unaffordable. Programme costs are being refined using field data collected in demonstration projects in India, Peru, Uganda and Viet Nam (21), and experience introducing a new rotavirus vaccine in Brazil and Mexico (47). While it costs nearly US$ 20 to fully immunize a child with the six EPI vaccines, the cost of HPV vaccination alone could be higher. In Brazil, the cost to vaccinate 80% of one cohort of 11-year-old girls (at a theoretical cost of International (I) $ 25 per vaccinated girl) would be nearly IS 33 million (see Table 5.3). Estimates of the cost to vaccinate 80% of girls aged 11 years in six low and middle-income countries (at a cost of US$ 15 per vaccinated girl) ranged from 0.05 to 1.63% of total annual public sector health spending (see Table 5.3). Under the assumption of US$ 15 per vaccinated girl, total annual HPV vaccination costs for all GAVI-eligible countries would eventually reach nearly US$ 400 million per year. This is a massive investment relative to GAVI’s projected spending of US$ 0.9 to 1.0 billion on all 2007 programmes. Of course, HPV vaccination costs would increase substantially with higher vaccine prices or delivery costs, boosters, vaccination of multiple birth cohorts or vaccination of boys.
### Influence of vaccine demand

Vaccine demand will also strongly influence price because, as demand increases and stabilizes, prices tend to fall. Modelling to forecast HPV vaccine demand in public sector programmes in developing countries is under way (Steve Brooke, PATH, pers. comm., April 2008). Early results suggest that demand for HPV vaccines may evolve slowly and possibly erratically over time, for several reasons. Willingness to pay is challenged by competing priorities for other new vaccines, other health interventions and scarce health resources. Manufacturers will not set prices and increase production capacity without knowing demand, yet purchasers and funders will not commit to purchase without knowing vaccine price. Unlike many infant and child vaccines, both the bivalent and quadrivalent HPV vaccines are being heavily marketed to consumers and private health-care providers in low, middle and high-income countries, and this may create demand in the public sector (Sarah Schmitt, WHO, pers. comm., April 2008). As these issues evolve, the PAHO Revolving Fund may consider purchasing HPV vaccines when they are prequalified by WHO (Jon Andrus, WHO, pers. comm., April 2008).

### Influence of supply issues

HPV vaccines also face unique supply issues that may influence price. Lead times to scale-up production capacity for large markets in low and middle-income countries may be substantial, due to complex manufacturing processes and possible competition with supplying industrialized countries. (A detailed report on HPV vaccine production capacity of the two manufacturers is expected in 2008.) Competition is limited by the presence of only two manufacturers that have cross-licensing agreements related to virus-like particle (VLP) antigens (Sarah Schmitt, WHO, pers. comm., April 2008). The two vaccines are not interchangeable due to different components, schedules and properties (122). The introduction of other manufacturers or suppliers of the current HPV vaccines may lower prices, but this may take several years to come into effect, due to patent issues, cross-licensing agreements, requirements for safety and efficacy studies, WHO prequalification and product registration. Over time, stable demand for current vaccines may stimulate investment in second-generation vaccines that may be cheaper to
manufacture or easier to administer, which would greatly benefit developing countries (47). (See Annex 4 for update on supply issues.)

5.5.5 Influence of vaccination programmes on financing decisions

Estimates of the impact and cost effectiveness of vaccination programmes are important to consider when making investment decisions about HPV vaccines (see Section 4). Estimates of the size and timing of declining disease incidence inform the timing of return on investment. HPV vaccines will have a delayed return on investment compared to infant and child vaccines that prevent common childhood infections; this may influence decision-makers who must defend the accountability of new programmes (10,121). Cost–effectiveness models can estimate price ranges at which vaccination would be cost effective, and these can inform price negotiations. For example, studies in Brazil indicate that HPV vaccines would not be cost effective at I$ 100 per three-dose series, but would be cost effective at I$ 25 per series (see Section 4). Decision-makers wish to compare the cost effectiveness of HPV vaccination with that of other well-accepted vaccines, cervical cancer screening or other health interventions. While cost–effectiveness estimates are important in decision-making, other factors may be more important, including affordability, capacity to achieve high coverage with available infrastructure, socioeconomic equity in vaccine access and public demand (123,124).

5.5.6 Influence of competing health priorities on vaccine introduction

In both industrialized and developing countries, HPV vaccines will compete with other new vaccines and interventions for public funds (7,47). Ministries of health and finance, and vaccine regulatory authorities need to prioritize vaccines in terms of disease burden, health impact, cost effectiveness, programme feasibility and sustainable financing. Decision-makers should consider possible synergies as well. For example, introducing several new vaccines could capitalize on common infrastructure, such as cold-chain capacity. Introducing HPV vaccination could also strengthen other health services for adolescents.

Competition between new vaccines

Competition between new vaccines will also prevail at the global level. During 2007–2009, WHO’s prequalification process will review several new vaccines, including HPV vaccines, and this convergence may prolong review times (47). GAVI is reviewing their strategy for financing several new vaccines for low-income countries, including HPV vaccines (Sarah Schmitt, WHO, pers. comm., April 2008). GAVI will consider several factors, including results of the WHO project on prioritization of vaccine-preventable diseases (Craig Shapiro, WHO, pers. comm., November 2007). This project ranked the health, economic and social burden of several vaccine-preventable disease for which vaccines are available or may be available within the next five years. Preliminary results classified diseases as:

- very high priority – malaria and pneumococcal disease
- high priority – HPV, cholera, dengue fever, Japanese encephalitis, meningococcal meningitis (A, C, W135 and Y), rabies, rotavirus, seasonal influenza, typhoid fever and yellow fever
- medium priority – hepatitis A and E, meningococcal meningitis B, mumps, rubella and varicella.

GAVI’s new investment strategy will also consider cost effectiveness, potential for financial sustainability by countries, and added value to investments of other donors (Nina Schwalbe, GAVI, pers. comm., April 2008).
Financing methods

In industrialized countries, some governments directly finance vaccination and procure large volumes of vaccine at public-sector prices (2,7). Vaccine costs are becoming more controversial as the number of recommended vaccines increases; this stresses the capacity of governments to fund immunization even when deemed cost effective. In the United States, the cost of all vaccines (not including administration costs) recommended for children up to 6 years of age in the public sector was US$ 10 in 1975, and estimated to be US$ 1184 in 2007 after considering inflation (7,80,125,126).

Capacity to fund immunization is much lower in low and middle-income countries, where less than 40% of routine vaccine expenditures are now financed by governments. In low-income countries, average public spending on health per capita is US$ 7; it may be even lower in some countries (127). Since 2000, immunization spending in the world’s poorest countries (per capita gross domestic product (GDP) < US$ 1000) has risen from an average of US$ 1.1 billion in 2000 to US$ 2.5 billion in 2005. To increase coverage of existing vaccines and to introduce new vaccines, spending would need to increase to US$ 4 billion (128). Internal immunization funds are more limited in Africa (45%) than in South-East Asia (62%), the Western Pacific (67%), the Eastern Mediterranean (83%) or the Americas (87%) (129). Introducing HPV vaccines would also represent a relatively greater proportion of total public health spending in low and middle-income countries.

For example, if Kenya vaccinated 80% of its 11-year-old girls at a cost per vaccinated girl of US$ 25 (including vaccine and delivery costs), it would cost an additional 3% of all public spending on health; this same immunization cost and coverage would represent only 0.1% of public spending on health in the middle-income country of Brazil. Private sector spending on HPV vaccines is likely to be relatively small in low and middle-income countries, but may raise awareness of vaccines among providers and the public, stimulate broader demand and provide experience with vaccine delivery (47).

These financial realities mean that introducing HPV vaccine in low and middle-income countries would depend heavily on external financing until vaccine prices and programme costs became affordable. For the short term, most countries could not afford HPV vaccination without scaling back on other health services. GAVI is the most important source of external funding for vaccines and immunization infrastructure in the world’s 72 poorest countries, where more than half of new cervical cancer cases occur (see Section 1) (47). Under current GAVI policy, countries where more than 80% of children receive the diphtheria–tetanus–pertussis vaccine (DPT3) are eligible to receive funds for new vaccines, but countries where less than half of children receive DPT3 only receive funds to strengthen immunization services. GAVI’s support for new vaccines is meant to be short term: after five years it is expected that prices will become affordable, and that internal and external sources sustain financing. However, this has not occurred in some cases (47). GAVI also provides cash instead of support for countries that self-procure vaccines included in the GAVI portfolio (Nina Schwalbe, GAVI, pers. comm., May 2008).

GAVI will decide on its new investment strategy at its June 2008 board meeting, and will decide on the timing and types of investments at its board meeting in October 2008 (See Annex 2 for updated information on this issue). A preliminary assessment of programme costs in GAVI-eligible countries is informative. If vaccination cost were US$ 15 per girl, it would require about US$ 180 million to reach 35% of eligible girls in 2016 and US$ 384 million to reach about 75% of eligible girls in 2025 (see Figure 5.1). If GAVI approves HPV vaccines as part of its new investment strategy, countries would need to determine whether HPV vaccines are a priority compared with other, new or underused...
vaccines, whether their co-payment is affordable, and how vaccines might be financed after GAVI financing ends. Discussions about mobilizing resources for HPV vaccines should occur in the context of comprehensive multiyear plans that explain how HPV vaccine introduction might share operational costs with existing immunization, reproductive health or other health programmes.

![Figure 5.1](image)

**Figure 5.1  Full HPV immunization costs for GAVI countries under alternative cost assumptions**

Note: The graph assumes a six-year ramp-up to 80% coverage of a single-year cohort of adolescent girls, and takes into account that some countries are likely to adopt the vaccine sooner than others.

Source: Saxenian and PATH (2007) (47)

Other financing mechanisms may support HPV vaccine introduction for countries that are eligible for GAVI, as well as countries that are not. The sustainability of financing through these mechanisms is critical for programme planning and the final effect. The International Financing Facility for Immunization (IFFIm) is a relatively new mechanism meant to expand GAVI’s available resources (130). Through IFFIm, donors make long-term pledges of financing, and GAVI borrows funds to initiate long-term procurement contracts and front-load immunization financing. Advance market commitments (AMCs) are intended to speed development of new vaccines in developing countries, to increase affordability, stimulate private-sector investment, and scale up vaccine production (47). Under AMCs, donors would subsidize purchase of new vaccines for developing countries that agree to affordable co-financing. After AMC funds are depleted, manufacturers would provide vaccines at predetermined, affordable prices for a certain period. AMCs may be most relevant to new producers of the two current HPV vaccines or second-generation vaccines. Other financing sources include bilateral donors such as Japan;
credits and loans of the World Bank or regional development banks, including sector-wide approaches; poverty-reduction strategy credits; and short-term vaccine donation programmes of manufacturers (1,2,47,131).

5.6 Post-marketing monitoring and research to inform vaccination programmes

### Key points
- Post-marketing monitoring of vaccine effectiveness, safety and population coverage will require new or modified surveillance systems and substantial long-term investment.
- Population-based monitoring may be possible in only a few countries, but small, sentinel surveillance may be feasible in many countries.
- Guidelines for monitoring methods and programme indicators for low, middle and high-income countries are being developed in many countries and at WHO.
- Current safety and efficacy data are available up to at least five years after vaccination, and longer-term studies of duration of antibody and clinical efficacy are under way.
- Data on safety, immunogenicity and efficacy of HPV vaccines in African populations are not yet available, but studies are under way.
- The range of effective delivery strategies remains uncertain, but operations research is exploring several options.
- Additional clinical and epidemiologic studies, economic analyses and programme research are needed to address delivery strategies and evaluate the impact of vaccination programmes; many are under way.

5.6.1 General considerations

In most countries, decisions about vaccine licensure have been based on evidence of short-term safety and efficacy (5–6 years). However, many questions remain that will inform strategies for introducing vaccines and for estimating vaccine impact and cost effectiveness (9). Some will be answered in controlled research studies, while others will be evaluated by post-marketing monitoring and surveillance. (See Annex 2 for updated information on monitoring and research.)

Post-marketing evaluation of vaccine effectiveness is critical to determine the impact of vaccination programmes under real conditions (9,39,132). Monitoring systems are usually developed after initial vaccine introduction; however, they are best planned before introduction and included as a programme cost (7). The most rigorous methods will require new or newly linked surveillance systems to be developed. New approaches are currently being evaluated in a few industrialized countries, and might also be piloted in low and middle-income countries (39,133). While only a few countries will be able to run national or population-based monitoring, many countries may be able to mount small, sentinel studies of the prevalence of vaccine-related HPV types, precancerous cervical lesions or other laboratory-based indicators. General advice on strategies to monitor HPV vaccine safety and effectiveness after licensure are detailed elsewhere (122,134) and (Tiequn Zhou, WHO, pers. comm., 2008). To complement part-marketing monitoring, research can answer many questions about vaccine efficacy, safety, delivery and acceptability. This information will be used to design and implement vaccination programmes.
The following sections summarize high-priority monitoring and research that will inform HPV vaccination programmes. This monitoring and research were identified by the HPV Expert Advisory Group (HEAG) in September 2007 and other experts (9) (see Table 5.4). However, HEAG (and its successor, the HPV Vaccine Advisory Committee) did not indicate that definitive answers to these questions were essential before the WHO Immunization Strategic Advisory Group of Experts (SAGE) discussed recommendations for using HPV vaccines in national immunization programmes.

Table 5.4 Planned monitoring and research topics

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Topic: Immunogenicity, efficacy and safety in trial populations</strong></td>
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<tr>
<td>Long-term duration of antibody and clinical protection and safety in females (12, 39, 123, 133-136)</td>
<td>Bivalent vaccine</td>
<td>Brazil, Finland</td>
<td>Adolescent and young adult females</td>
<td>Periodic updates</td>
<td>Based on long-term follow-up of phase III and IV trials.</td>
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<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>Denmark, Iceland, Norway, Sweden, United States</td>
<td>Adolescent and young adult females</td>
<td>Periodic updates</td>
<td></td>
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<tr>
<td>Immunogenicity and safety in HIV-infected and other special populations (39, 137-142); Jessica Kahn, University of Cincinnati, pers. comm., July 2008)</td>
<td>Bivalent vaccine</td>
<td>South Africa</td>
<td>HIV-infected females</td>
<td>Unknown</td>
<td>Individuals with other immunosuppressive conditions may be included</td>
</tr>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>Brazil, South Africa, United States</td>
<td>HIV-infected children, adolescent and adult females and males; Females with arthritis</td>
<td>2008 (for children), later for other populations</td>
<td></td>
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<tr>
<td>Immunogenicity and safety in low-income countries not included in earlier phase II or III trials (143-146); Randall Hyer, Merck, pers. comm., September 2008)</td>
<td>Bivalent vaccine</td>
<td>India, Senegal, Tanzania</td>
<td>Adolescent and adult females</td>
<td>African studies: 2009+ India: 2008</td>
<td>Studies may be able to assess influence of malaria, helminths and other conditions, but will not enroll HIV-infected patients</td>
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<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>India</td>
<td>Adolescent and adult females</td>
<td>Unknown</td>
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<td>Study</td>
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<td>Study location</td>
<td>Population or database</td>
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<tr>
<td>Safety and immunogenicity in males (12,147,148) (E Barr, Merck, pers. comm., August 2007)</td>
<td>Bivalent vaccine</td>
<td>Finland</td>
<td>Males aged 10–18 years</td>
<td>2008: safety and immunogenicity</td>
<td></td>
</tr>
<tr>
<td>Immunogenicity, efficacy and safety in adult women (12,39,149) (E Barr, Merck, pers. comm.)</td>
<td>Bivalent vaccine</td>
<td>United States, Europe</td>
<td>Women aged 25–55 years</td>
<td>2010</td>
<td>Will analyze efficacy in females with past HPV infection</td>
</tr>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>United States</td>
<td>Women aged 25–45 years</td>
<td>Data on persistent infection, CIN (any grade) and external genital lesions presented in 2007; 2010+ for data on higher grade lesions.</td>
<td></td>
</tr>
<tr>
<td>Immunogenicity and/or efficacy of alternate 3-dose schedules and 2-dose series in adolescent and adult females (38, 159) (Jan Agosti, Bill and Melinda Gates Foundation, pers. comm., July 2008)</td>
<td>Bivalent vaccine</td>
<td>EU countries to examine delayed 3rd dose</td>
<td>Females aged 15–25 years</td>
<td>Unknown</td>
<td>Studies of quadrivalent vaccine will complement non-controlled observational studies of females who missed third dose in United States (L Markowitz, CDC, pers. comm., August 2007).</td>
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<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>Canada – 2-dose immunogenicity</td>
<td>Adolescent females</td>
<td>Canada: 2009+ India: 2012+ Viet Nam: late 2010</td>
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<td></td>
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<td>India –2-dose immunogenicity and efficacy</td>
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<td></td>
<td></td>
<td>Viet Nam – immunogenicity of alternate 3-dose schedules</td>
<td>(0, 3, 9 month, 0, 6, 12 month, and 1,12, 24 month)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparative immunogenicity and bivalent vaccines in females (150)</td>
<td>Bivalent and quadrivalent vaccines</td>
<td>United States</td>
<td>Females aged 18–45 years</td>
<td>Preliminary data in 2008</td>
<td>Being conducted by GSK</td>
</tr>
</tbody>
</table>

**Topic: Safety during post-marketing period, including safety in women inadvertently vaccinated during pregnancy**

<p>| Passive safety surveillance (12,13,39,133,151) | Bivalent vaccine | Many countries, including EU | Vaccinated individuals | Periodic updates | Will use government and industry-sponsored systems. |</p>
<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
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<tr>
<td>Quadrivalent vaccine</td>
<td></td>
<td>Many countries including Australia, Canada, EU, and United States</td>
<td>Vaccinated individuals</td>
<td>Periodic updates</td>
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<td>Active safety surveillance</td>
<td>Bivalent vaccine</td>
<td>Scotland</td>
<td>Young adolescent females and women</td>
<td>Unknown</td>
<td>Will complement passive surveillance; rare conditions and safety in females inadvertently exposed during pregnancy.</td>
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<tr>
<td>(12,133,151)</td>
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<td>(Randall Hyer, Merck, pers.</td>
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<td>comm., September 2008)</td>
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<td>Quadrivalent vaccine</td>
<td></td>
<td>Canada, Denmark, Iceland, France, Norway, Sweden, United States</td>
<td>Populations tracked by Nordic cancer registries, enrolled in US health plans, or special pregnancy registries (Canada, France, United States)</td>
<td>2009+</td>
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**Topic: Co-administration with other vaccines**

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<th>Population or database</th>
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<tr>
<td>Safety and immunogenicity</td>
<td>Bivalent vaccine</td>
<td>United States and Europe</td>
<td>Adolescent females receiving other vaccines</td>
<td>2008 for dTap-IVP; later for hepatitis B, hepatitis A/B, and meningococcal vaccines</td>
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<td>when administered with other</td>
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<td>vaccines (12,151,154-158)</td>
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<tr>
<td>Quadrivalent vaccine</td>
<td></td>
<td>United States</td>
<td>Adolescent females and males receiving other vaccines</td>
<td>2008 for tetanus/diphtheria/pertussis/polioymyelitis vaccine; 2009 for TdaP and meningococcal vaccine; hepatitis B data published in 2007</td>
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## Study Vaccines addressed Study location Population or database Date data expected to become public Comments

### Topic: Population-level impact and effectiveness of vaccination programmes

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<tr>
<td>Long-term duration of clinical protection against CIN 2/3 and cervical cancer (10+ years), cross-protection, and type replacement (9,12,39,151) (Suzanne Garland, University of Melbourne, Australia, pers. comm., January 2008)</td>
<td>Bivalent vaccine</td>
<td>Finland</td>
<td>Adolescent females</td>
<td>2012 or later</td>
<td>Includes community randomized trials and special studies of females vaccinated in schools and health facilities. Finland study to explore herd immunity</td>
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<td></td>
<td>Quadrivalent vaccines</td>
<td>Australia, Denmark, Iceland, Norway, Sweden</td>
<td>Adolescent females</td>
<td>2012 or later</td>
<td></td>
</tr>
<tr>
<td>Protection against genital warts (133,151) (Joakim Dillner, Lund University, Sweden, pers. comm., July 2008)</td>
<td>Quadrivalent vaccine</td>
<td>Sweden and United States</td>
<td>Individuals attending STI clinics and health facilities</td>
<td>Unknown</td>
<td>Not relevant to bivalent vaccine</td>
</tr>
</tbody>
</table>

### Topic: Vaccine delivery, acceptability and coverage

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coverage, acceptability, feasibility, vaccination costs, and mobilization and education needs (21) (Loretta Brabin, University of Manchester, pers. comm., February 2008)</td>
<td>Bivalent vaccine</td>
<td>United Kingdom, Uganda</td>
<td>Adolescent females</td>
<td>2009–2011</td>
<td>Will examine school, health facility and community-based delivery strategies</td>
</tr>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>India, Peru, Viet Nam</td>
<td>Adolescent females</td>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>Coverage using alternative vaccine schedules (21,38,159)</td>
<td>Quadrivalent vaccine</td>
<td>Viet Nam: alternate 3-dose schedules; Canada: 2-dose schedule</td>
<td>Adolescent females vaccinated in schools or health facilities</td>
<td>Viet Nam: late 2010; Canada: 2009–2010</td>
<td>3-dose schedules: 0, 3, 9 month, 0, 6, 12 month, and 1,12, 24 months</td>
</tr>
<tr>
<td>Population coverage estimates (151-153,160)</td>
<td>Bivalent vaccine</td>
<td>Australia, several European countries</td>
<td>Vaccinated individuals</td>
<td>2008+</td>
<td>Based on national registries and surveys; data on Australian and European school programmes available first</td>
</tr>
<tr>
<td>Study</td>
<td>Vaccines addressed</td>
<td>Study location</td>
<td>Population or database</td>
<td>Date data expected to become public</td>
<td>Comments</td>
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</tr>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>Australia, several European countries, United States</td>
<td>Vaccinated individuals</td>
<td>2008+</td>
<td></td>
</tr>
</tbody>
</table>

**Topic: Sexual behaviour after vaccination**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>Denmark, Iceland, Norway, Sweden, United States</td>
<td>Adolescent and adult females, including American females who acquired HIV through sexual exposure</td>
<td>Unknown</td>
<td>Will include participants of population-based and longitudinal surveys, STI clinic studies; and clinical trials</td>
</tr>
</tbody>
</table>

**Topic: Screening behaviour and effectiveness of screening programmes after vaccination**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Quadrivalent vaccine</td>
<td>United States</td>
<td>National Ambulatory Health Care Database</td>
<td>Unknown</td>
<td>Will assess vaccine impact on utilization of screening, diagnosis, and treatment of cervical cancer</td>
</tr>
</tbody>
</table>

**Topic: Impact on disease prevention and cost-effectiveness of vaccination strategies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Generic HPV 16/18 vaccines and quadrivalent vaccine, specifically</td>
<td>Using data from Asia, GAVI-eligible countries, others, India, Latin America and Caribbean, Western and Central Europe, North America.</td>
<td>Hypothetical cohorts of primary target populations (with and without catch-up vaccination)</td>
<td>2008: Data on Latin America and Caribbean, Asia, GAVI-eligible countries, Europe and North America; other data unknown</td>
<td>Assess alternative sex and age-based vaccination strategies with or without screening. Studies of quadrivalent vaccine include HPV 6/11-related benefits and costs</td>
</tr>
</tbody>
</table>

**Topic: Burden of HPV-related disease due to vaccine-related types**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Not applicable</td>
<td>Selected parts of African, Asian, Eastern Mediterranean and Eastern European regions</td>
<td>Females with high grade CIN or cancer, including HIV-infected females (in some regions)</td>
<td>2008+</td>
<td>Includes populations with no or limited data on HPV type distribution in cervical precancers and cancers</td>
</tr>
</tbody>
</table>

**Topic: Second generation vaccines**

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccines addressed</th>
<th>Study location</th>
<th>Population or database</th>
<th>Date data expected to become public</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candidate vaccines</td>
<td>Preclinical studies in China, Europe, India, and North America</td>
<td>Females</td>
<td>Unknown</td>
<td>Attributes include different antigens, broader valency, mucosal delivery, new manufacture methods, and therapeutic vaccines</td>
</tr>
</tbody>
</table>
5.6.2 Monitoring after introducing HPV vaccine

Monitoring the population coverage of HPV vaccines

**Key points**
- Levels of vaccine coverage should be monitored through routine national surveillance or special surveys.
- Several coverage surveys from Europe and the United States are planned.

Levels of vaccine coverage are typically measured through routine national immunization programme surveillance using vaccine registries or sero-epidemiological surveys (1,134). National HPV vaccine registries are established or being planned in Australia, many European countries, the United States and other countries (151,152,160). In the United States, HPV vaccine coverage is being evaluated through national surveys of adolescents and parents, sentinel surveillance in six states, and a national survey of provider-reported information on adolescent vaccination (151). WHO measures vaccine coverage including the number of doses completed annually in all Member States through administrative data from service providers and cluster surveys collected by the EPI and UNICEF (170). Future surveys may include questions about plans to introduce HPV vaccines.

Monitoring vaccine safety

**Key points**
- Passive and active post-marketing safety assessments are ongoing or planned for both bivalent and quadrivalent vaccines in several industrialized countries.
- Potential modulating factors investigated include pregnancy, co-administration with other vaccines, and medications.
- Capacity for safety evaluations is greatest in industrialized countries with existing infrastructure and funding.
- Post-marketing assessment of safety in women inadvertently given vaccines during pregnancy is important because data from clinical trials are limited.

Post-marketing surveillance is passive and non-systematic, but it is a valuable method for assessing safety after widespread vaccine use that is less controlled than in clinical trial conditions. Post-marketing safety surveillance for the quadrivalent vaccine is currently occurring through existing drug and vaccine surveillance systems or special vaccine registries in several countries, including the Vaccine Adverse Event Reporting System (VAERS) in the United States, the Eudravigilance system in Europe, state-based surveillance systems in Australia, and vaccine registries in Belgium and Nordic countries (39,133,151-153). VAERS allows surveillance of safety in people who received HPV vaccines together with the tetanus/diphtheria/acellular pertussis (Tdap) vaccine and Sanofi Pasteur's meningococcal (groups A, C, Y and W-135) conjugate vaccine (MCV4), two vaccines that are commonly administered to adolescents in the United States (133). Post-marketing safety surveillance for the bivalent vaccine is occurring in several
countries, including the Eudravigilance system in Europe and state-based surveillance systems in Australia (12) (Suzanne Garland, University of Melbourne, Australia, pers. comm., January 2007).

Countries that lack post-marketing safety surveillance or that cannot mount special safety studies may use the experience of countries with these resources (1). In 2007, the Global Advisory Committee on Vaccine Safety (GACVS) concluded that recommendations about improving post-marketing safety surveillance should be directed primarily to industrialized countries with adequate infrastructure and funding (171) and (Dina Pfeifer, WHO, pers. comm., June 2007). These recommendations encouraged safety registries in other countries, but advised that developing countries with a high burden of cervical cancer need not do this if that would complicate HPV vaccine introduction. They also advised that protocols to analyse post-marketing surveillance data be made publicly available to help countries considering new safety surveillance. GACVS also cautioned that safety surveillance would be challenged by limited data on baseline occurrence in the general population of conditions that commonly present during adolescence (e.g. autoimmune conditions) (172).

Active safety surveillance is also under way. The CDC sponsors the Vaccine Safety Datalink, which is a network of managed care organizations in six sites. The datalink is evaluating the safety of the quadrivalent vaccine alone or when co-administered with TdaP or MCV4. As of May 2007, this system started tracking people who together had received nearly 70 000 doses of quadrivalent vaccine. The system has the ability to track serious outcomes, such as Guillain–Barre syndrome, seizure, syncope, anaphylaxis, appendicitis, stroke, thrombosis and pulmonary embolism (133,151). The Nordic Cancer Registry programme will be used for long-term evaluations of general safety, including major chronic diseases (39). For the bivalent vaccine, GSK has proposed a safety study in Scotland that would follow approximately 100 000 vaccinated females for several safety issues, including autoimmune diseases and adverse pregnancy outcomes (12).

Post-marketing surveillance for pregnancy outcomes after vaccination is important to expand on the limited safety data from clinical trials (1). Nordic trials will evaluate adverse pregnancy outcomes (39). The quadrivalent vaccine in pregnancy will also be monitored through special registries in Canada, France, several Nordic countries, and the United States; and the Vaccine Safety Datalink in the United States (133,151). The bivalent vaccine will be evaluated in Eudravigilance and other country registries. Special safety evaluations are also planned in Finland and Scotland (12). If this vaccine were to be licensed in the United States, GSK would implement a special pregnancy registry, as Merck has done.

**Monitoring the duration of antibody and clinical protection**

**Key points**

- Knowing the duration of vaccine protection is vital for making decisions about target age groups and the need for booster doses, and estimating vaccine impact, cost effectiveness and programme cost.
- Long-term follow-up of phase II trials indicates that antibody titres remain high for at least 5 years after vaccination, but it remains unknown whether immunity wanes over time, or whether waning immunity reduces clinical protection.
- Results of long-term immunogenicity and clinical efficacy studies will be available in 5 years or more.
Understanding the duration of vaccine protection is critical because the risk of HPV exposure can occur many decades after vaccination. The need for boosters is uncertain for three reasons: the level of protective antibody is unknown, the duration of antibody and clinical protection is currently limited to 5–6 years after vaccination, and it is uncertain whether natural exposure to vaccine-related HPV types induces a protective immune response in vaccinated people (134) (see Section 3). WHO therefore recommends long-term follow-up of antibody levels of vaccinated cohorts for at least 10 years, including characterizing immune status and type-specific antibody levels in any “breakthrough” cases (122). WHO also recommends measuring immune responses to doses given after the primary series is completed.

Both GSK and Merck plan to evaluate immune response and clinical efficacy at least 14 years after the primary vaccine series as part of long-term follow up of phase III trials and immunobridging studies of adolescents aged 9–15 years (12,39,123,134,135,136,173). An anamnestic response to a fourth vaccine dose has been demonstrated for the quadrivalent vaccine, suggesting that boosters may augment the antibody (174). Phase III clinical trials will evaluate the immune response to a fourth dose of the bivalent vaccine (Kathleen Vanderdael, GSK, pers. comm., November 2007). Countries that set up HPV vaccine registries can also evaluate antibodies over time, and this is planned in Nordic countries and the United States among others (12,39,134,136).

Other countries are considering special serosurveys: these would be facilitated by developing surrogate markers of clinical protection, such as standardized criteria for serological assays being developed by the WHO HPV Laboratory Network (134).

**Monitoring the impact on cervical cytologic abnormalities and cervical cancers**

**Key points**

- Monitoring the incidence of HPV type-specific cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3) may serve as an early measure of vaccine impact, because measuring vaccine impact on cervical cancer incidence and deaths is expected to take 10–30 years from vaccine introduction.

- Linked immunization, cytology, histology and cancer registries could provide the infrastructure to assess vaccine impact on cervical abnormalities and cancer.

Surveillance for precancerous cervical lesions and cancer is needed to determine whether the most important benefits of HPV vaccines are realized (134). Unlike many other vaccines, HPV vaccines generate cancer prevention benefits decades after vaccination because the latent period between initial HPV infection and cancer is 10–30 years (134). Monitoring cancer outcomes will therefore require long-term studies. Because the latency from HPV 16/18 infection to cervical precursor is 1–5 years, as opposed to decades for cancer, decreases in the incidence of cervical intraepithelial neoplasia grades 2 and 3 (CIN2/3) due to associated with vaccine-related types will provide an early estimate of vaccine impact (134).

Monitoring cancer prevalence may require cytology and histology registries to be linked with vaccine and cancer registries; it may also require the use of standardized, type-specific HPV deoxyribonucleic acid (DNA) tests that are not yet commercially available. The WHO Global Laboratory Network and other laboratories are developing standardized assays (134,175); however, type-specific assays are also needed to evaluate cross-protection and type replacement in populations with either HPV-related cytologic abnormalities or CIN (134). Because most HPV infection is benign and transient, studies that assess the status of HPV infection in females with neoplastic changes are more
clinically relevant than studies of HPV infection status in general populations or in women with normal cytology. HPV detection methods that distinguish oncogenic types that are merely present from types that drive neoplastic process would also be valuable; however, consensus on an ideal testing methodology has not been reached (Tiequn Zhou, WHO, pers. comm., February 2008).

In the Nordic countries, phase III studies that are double-blind, controlled and population-based will evaluate the efficiency of the bivalent and quadrivalent vaccines. These studies will be extended to assess population impact on CIN3 and higher-grade disease (see Table 5.4). In the United States, cancer registry studies will monitor the impact of HPV vaccination on invasive cancer. The Vaccine Safety Datalink project and special studies will monitor vaccine impact on CIN2/3 incidence (151). Australia plans to monitor the impact of the quadrivalent vaccine programme on precancerous lesions and cervical cancer (Suzanne Garland, University of Melbourne, Australia, pers. comm., September 2007). In the many locales where cancer registries are absent or of poor quality, evaluating the experience of other countries with better registries may be informative (1).

**Monitoring the impact of quadrivalent vaccine on genital warts**

<table>
<thead>
<tr>
<th><strong>Key points</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreases in the incidence of anogenital warts are expected to be an early indicator of quadrivalent vaccine effectiveness, given the usually short latency from exposure to HPV 6 and 11 and wart onset.</td>
</tr>
<tr>
<td>• However, genital wart surveillance will be challenging, given the lack of routine registries in most countries and limited knowledge of the pre-vaccination wart burden in all regions.</td>
</tr>
</tbody>
</table>

The impact of quadrivalent vaccine on warts will be observed before the impact on cancer (1,134) because the interval between exposure and obvious condyloma is 3–12 months (134). Monitoring genital warts may therefore allow for early assessment of quadrivalent vaccine impact (1). If declines are not seen, it may indicate that HPV vaccines are less effective than expected, or that there is (134):

- insufficient population coverage
- insufficient understanding of the at-risk period for exposure or detection
- HPV type replacement
- waning immunity
- inadequate vaccine quality.

Wart surveillance is challenging because surveillance systems are rare, and the epidemiology and public health burden of condylomas are poorly characterized. In the United Kingdom, England and Wales implemented a genital wart registry in the 1970s (134) and new studies are planned in Sweden and the United States to monitor genital warts in STI clinics and administrative health care databases (133,151) (Joakim Dillner, Lund University, Sweden, pers. comm., July 2008).
Monitoring the impact on HPV infections, type replacement and herd immunity

**Key points**

- HPV type-specific prevalence and incidence in females without cytological abnormalities may serve as early measures of vaccine impact.
- HPV incidence and prevalence data may provide preliminary evidence of vaccine effectiveness, cross-protection and type replacement.

HPV prevalence and incidence in females without cytologic abnormalities may serve as early measures of vaccine impact because both prevalence and incidence of vaccine-related HPV types are expected to decline after vaccine introduction (133). If HPV vaccination programmes do not reduce the incidence of vaccine-related HPV types, they will not result in adequate cancer control decades later (134). Such assessments will require country-level type-specific HPV epidemiology data and good estimates of targeted population and coverage level. Population-based HPV prevalence studies can also evaluate potential type replacement. If vaccine-related HPV types are replaced by other oncogenic HPV types, this could dampen the impact of vaccination (134).

Some experts have proposed evaluating the prevalence of vaccine-related HPV types through sentinel sampling of sexually active teens, particularly subgroups with multiple partners who seek sexual health services. In these populations, HPV incidence is high and it may be possible to measure the effect of vaccination programmes fairly rapidly (134). A forthcoming phase IV study in Nordic countries will measure the reduction in HPV prevalence in maternity patients several years after school-based vaccination of adolescents using the quadrivalent vaccine (39). In the United States, HPV type-specific prevalence is monitored using self-collected vaginal swabs from participants in a national household health survey that began in 2002 (151). For the bivalent vaccine, large studies of HPV prevalence and possible type replacement and herd immunity have begun in Finland and are planned for Scotland (12).

Virologic surveillance could potentially use HPV DNA tests, investigational rapid HPV tests intended for low-resource settings or molecular markers under development (1,128). However, HPV prevalence monitoring is currently hampered by a lack of commercial tests specific for HPV 16 and 18. Also, lack of international standards for HPV serology, DNA detection, laboratory reagents and quality-assurance procedures results in significant variations in test performance (161). The WHO HPV Laboratory Network is developing international standards for HPV antibodies and HPV DNA tests that could be used by laboratories in all regions (134,176). Access to affordable, HPV type-specific tests will improve surveillance options in low-resource settings, but the rapid HPV DNA test under development is not specific for vaccine-related HPV types (177).

Monitoring the impact on cervical cancer screening programmes

**Key points**

- Post-marketing assessment of the influence of HPV vaccination on the performance, cost and cost effectiveness of screening programmes is needed.
- Studies on the use of screening by vaccinated females are needed in settings where screening is available.

In countries with extensive cytology screening, HPV vaccination is expected to reduce the number of abnormal cytologic results caused by vaccine-related HPV types and the burden associated with following up these abnormalities (see Section 4). This will
probably reduce the cost of screening programmes and the burden to women and health systems. However, monitoring is needed to evaluate the impact of vaccination on screening and follow-up resource needs (see Section 4) (9,133). Given the complexity of these issues, monitoring that is paired with formal economic evaluation to compare various prevention strategies will be useful (9,10,178). In the United States, a national study of ambulatory visits for abnormal cytology tests will provide a baseline against which to measure future effects of HPV vaccination and DNA testing on health care use (151,162).

Although all industrialized countries that have recommended HPV vaccines for national immunization programmes stress the need for ongoing screening, it remains uncertain whether vaccinated females will follow the prevailing recommendations on when to start screening and screening frequency (9). Therefore, studies are needed to assess the impact of vaccination on future screening behaviours. These studies can inform models assessing the interaction of vaccination and screening on vaccine impact and cost effectiveness.

**Monitoring the impact on sexual behaviour, sexually transmitted disease and unplanned pregnancy**

**Key points**

- More information is needed on how vaccination affects the timing of sexual debut, partner selection, sexual practices, condom use and rates of STIs, HIV or unplanned pregnancies in diverse cultures with different behavioural norms.
- The impact of HPV vaccination on the use of health services for STIs, HIV and reproductive health merits evaluation.

Education and counselling provided at the time of HPV vaccination should emphasize the value of safe sexual activity. This could reduce risky sexual behaviours and incidence of STIs and HIV in vaccinees, or improve access to education and counselling about condoms, family planning and reducing sexual risk. Several countries have stressed these educational messages in their recommendations for vaccine use in immunization programmes (see Section 6). Alternatively, if HPV vaccination causes sexual disinhibition because vaccinees incorrectly assume that HPV vaccines protect against other STIs, HIV or pregnancy, vaccination may result in increased incidence of HIV and STIs or unplanned pregnancies. Although research suggests this may not be a problem (see Section 4), many questions remain about how vaccination might influence subsequent sexual behaviour, the timing of sexual activity debut, partner selection and condom use. In the United States, several studies are planned to evaluate the behavioural consequences of vaccination, including a population-based survey of adolescents and young adults, a special school-based project and a longitudinal survey of adolescents (9). Studies in some European countries and the United States are currently assessing the effect of HPV vaccination programmes on the use of STI prevention and treatment in STI clinics and gynaecological offices (see Section 6). It is important to expand this research by assessing the impact of vaccination on sexual behaviours under diverse sociocultural contexts with different sexual behaviour norms in all regions.

**5.6.3 High-priority research to inform vaccination programmes**

**Estimating the burden of disease from vaccine-related HPV types**

**Key points**

- HPV-related disease burden estimates should inform decisions about introducing HPV vaccines.
• Estimates of cervical cancer burden are refined in many countries but lacking in others, especially low-income countries.
• Estimates of HPV-related disease in HIV-infected populations and anogenital warts in all populations are limited worldwide.

Ideally, countries should make decisions about introducing HPV vaccines based on estimates of the burden of cervical cancer and other HPV-related diseases. Disease burden estimates are also needed as a baseline against which to measure the impact of vaccination programmes. Data from many countries are already available (98,179). New studies are measuring cervical cancer burden in many low and middle-income countries, including in HIV-infected populations. Studies of the global burden of other HPV-related cancers and anogenital warts that often do not come to attention of health systems remain challenging.

**Estimating vaccine efficacy and safety in selected populations**

**Key point**
- Data are needed on vaccine efficacy and safety among people who are immunocompromised or have chronic conditions that may influence immunological response. These data will be particularly important in low-income countries where these conditions are prevalent.

Cervical cancer rates tend to be highest in countries with high rates of HIV infection, acquired immunodeficiency syndrome, malnutrition, tuberculosis, anaemia, helminth diseases and other chronic conditions that alter immune response. The safety and efficacy of HPV vaccines may differ in the presence of these conditions, and because of genetic, environmental and behavioural factors. Little is known about HPV vaccine safety and efficacy in people using HIV antiretrovirals, other chronic medications or co-administered vaccines. Trials of both bivalent and quadrivalent vaccines in HIV-infected children and adults are in progress in several regions (see Table 5.4) (39,137-142). However, the effects of severe malnutrition and intercurrent malarial or helminth infection on immune response to HPV vaccines are currently not the primary focus of any study (123). Long-term follow-up studies in the Nordic countries will evaluate the impact of other host factors on the risk of acquiring vaccine and non-vaccine HPV types after vaccination with the bivalent vaccine (9). To extend data on co-administration of the quadrivalent vaccine with hepatitis B vaccine, studies in the United States are evaluating the safety and efficacy of the quadrivalent vaccine when administered with TdaP and meningococcal conjugate vaccine (123,158,180). Studies in Europe and the United States are evaluating the safety and immunogenicity of the bivalent vaccine when co-administered with several vaccines (see Table 5.4) (12,154-157).

**Estimating vaccine efficacy, immunogenicity and safety in selected regions**

**Key points**
- Data on HPV vaccine immunogenicity, efficacy and safety from Africa and the Eastern Mediterranean Region are not yet available for either the bivalent or the quadrivalent vaccine.
- A comparative study of the safety, reactogenicity and short-term immunogenicity of the bivalent and quadrivalent vaccines in females aged 18–45 years is under way in the United States.
Trials of both bivalent and quadrivalent HPV vaccines were run in several continents but did not include participants from Africa, where cervical cancer incidence is high, or the Eastern Mediterranean Region, where incidence is much lower. Vaccine safety and efficacy may vary if the either prevalence of vaccine-related types or cofactors for HPV carcinogenesis vary by region. However, analyses to date show that HPV 16 is the dominant HPV type in all countries, and that there are no differences in HPV vaccine safety or efficacy by region (see Sections 1 and 3). The safety and immunogenicity of both vaccines are being studied in India and African countries, and the efficacy of the quadrivalent vaccine is being studied in India (see Table 5.4) (143,144) (Randall Hyer, Merck, pers. comm., September 2008).

GSK has launched a comparative study of the safety, reactogenicity and short-term immunogenicity (over 24 months) of the bivalent and quadrivalent vaccines in females aged 18–45 years in the United States. Immunogenicity will be measured using the pseudoviron neutralization assay (see Section 3) (150).

### Estimating vaccine efficacy in females who have initiated sexual activity

#### Key points
- Vaccine efficacy in females who have begun sexual activity and may already be infected with vaccine-related HPV types is uncertain, but is likely to be lower than efficacy in females before sexual debut.
- Vaccine efficacy in these females will determine the impact and cost effectiveness of vaccinating older, sexually active catch-up populations.

The potential benefit of vaccines depends on the timing of HPV acquisition, the duration and strength of natural immunity to protect against reinfection, and the extent to which latent infection may be reactivated (see Section 3). Women who successfully clear HPV infections may be protected from reinfection without vaccination; alternatively, vaccination may give them fundamental or increased protection. If natural immunity provides substantial protection, vaccination programmes risk diverting vaccine to females who do not need protection and neglecting HPV-naive people at the highest risk of cancer (9). These questions relate to the impact of catch-up programmes of older adolescents and women who may be sexually active. Long-term efficacy studies of both vaccines evaluate immunogenicity and efficacy in older adolescent and adult females who are sexually active, including those who are not infected with all vaccine-related types before vaccination, are currently infected at the time of vaccination (i.e. HPV DNA-positive) or have past infections that have cleared by the time of vaccination (HPV DNA-negative, HPV-seropositive) (see Table 5.4) (12,39,149).

### Estimating vaccine efficacy and safety in males

#### Key points
- Data on safety and clinical efficacy for males are not published for either vaccine.
- Published data are available only for the immunogenicity of the quadrivalent vaccine in males.
- Additional studies are needed to estimate the impact and cost effectiveness of vaccination to directly benefit males and indirectly benefit females.

The quadrivalent vaccine is highly immunogenic in boys aged 9–15 years, (181) but immunogenicity data for males vaccinated with the bivalent vaccine are not yet available. Data on clinical efficacy in preventing the combined endpoint of penile/perineal/perianal
precancer and cancer, and anogenital warts associated with HPV 6,11, 16 or 18 in males are forthcoming (see Table 5.4). These studies have been challenged by evolving methodology for HPV detection in males. HPV detection differs according to the anogenital sampling site (181,182). Agreement on the optimal anogenital sampling sites for HPV DNA testing will be useful in ongoing studies of immunogenicity of the bivalent vaccine, and of immunogenicity and efficacy of the quadrivalent vaccine (147,148).

Future clinical efficacy data in males will also inform models of the impact and cost effectiveness of vaccinating males to prevent HPV-associated neoplasia. Where the quadrivalent vaccine is considered, data will inform how to prevent anogenital warts (9). Data are also needed on the effectiveness of vaccinating males to prevent transmitting the disease to both female and male sexual partners (133). Given that HPV-related disease affects females disproportionately, decisions about whether to vaccinate females only, or to vaccinate both females and males, have relied on comparing female-only strategies with different coverage levels from strategies involving males and females, as well as studies of the acceptability and feasibility of sex-specific vaccination strategies (see Section 4).

Estimating vaccine acceptability and education about HPV vaccines

<table>
<thead>
<tr>
<th>Key points</th>
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<tbody>
<tr>
<td>• Considerable data from industrialized countries indicate that HPV vaccines are acceptable to providers, teachers, parents and girls, but few data are available from low and middle-income countries.</td>
</tr>
<tr>
<td>• Because acceptability is influenced by sociocultural context and delivery methods, acceptability studies are needed in more varied populations of adolescents and parents where vaccines are or will be marketed, and in populations with a high disease burden.</td>
</tr>
<tr>
<td>• More research on adolescent, parent and provider acceptance of HPV vaccination is needed in girls aged 9–12 years (the usual primary target population) and in boys.</td>
</tr>
</tbody>
</table>

Most of the published research on vaccine acceptability comes from industrialized countries, and much is based on hypothetical opinions rather than use (see Section 5.3). However, evidence is mounting for acceptance in public and private-sector health systems and a few school-based programmes in several countries. Far less is known about vaccine acceptability in low and middle-income countries and among medically marginalized populations in high-income countries. Because some countries have licensed the quadrivalent vaccine for use in both females and males, research is needed to assess acceptability in boys, impact on uptake in girls, and the benefits or drawbacks of vaccinating boys, including education of boys, parents, and communities.

Ongoing research and evaluations of pilot projects are assessing acceptability and uptake in both developed and developing countries (see Table 5.4). These projects are examining opinions about logistic issues, consent procedures, how presenting HPV vaccines as a cancer vaccine versus an STI vaccine might influence acceptability and other issues (9,21) (Loretta Brabin, University of Manchester, pers. comm., February 2008). Studies done before vaccines are marketed are useful to guide development of education and information materials. Whenever possible, educational messages and materials should be tested and evaluated for their effectiveness. The WHO HPV Vaccine Global Community, a global online forum about opinions and experience with HPV vaccines, plans to provide technical assistance to investigators and programmes who want to study vaccine acceptability or develop education programmes (see http://www.hpv-vaccines.net).
Evaluating vaccine delivery and alternative schedules

Key points
- Programme evaluations and operations research are under way to identify delivery options for low, middle and high-income countries, and the costs of delivery.
- Research is needed on alternative schedules that would be simpler or easier to integrate with ongoing immunization programmes.
- Operations research is needed on alternative vaccine presentation and storage.

Operations research is under way to identify optimal strategies to reach the primary target group of young adolescents. This population is rarely targeted for routine immunization and has low rates of health service use in industrialized and developing countries (9) (see Table 5.4). The research compares vaccine delivery through health facilities, schools or community venues, as well as through mixed delivery modes (see Section 5.2). Work is also under way to assess facilitators and barriers to delivering the full three-dose series, including methods and costs to remind and recall girls for second and third doses, and methods of motivating providers, parents and vaccinees to complete the series (9). Drop-outs after the first dose may waste HPV vaccine if at least two doses are needed for significant protection, and the extent of wastage has a major impact on costs of vaccination programmes for a relatively expensive vaccine.

As the data on the association between immunogenicity and disease protection grow, several studies are exploring immunogenicity as a surrogate measure of efficacy. A study in Viet Nam is currently evaluating alternative delivery schedules of the quadrivalent vaccine at 0, 3 and 9 months; 0, 6 and 12 months; and 0, 12 and 24 months (21). This study will compare immune response with that of trial participants vaccinated at 0, 2 and 6 months as a surrogate for clinical efficacy. This study will help estimate immunogenicity in real conditions, where individual doses are sometimes delayed or missed due to intercurrent illness or scheduling difficulties (9). If longer dosing intervals induce a strong immune response and do not reduce long-term immunity, these schedules may be easier to synchronize with other child-health days once or twice a year, other services offered on that schedule, or school calendars. If clinical efficacy were high after only two doses of vaccine, vaccination costs would be lower and administration would be simpler. Three Canadian provinces are studying the immunogenicity of two doses of the quadrivalent vaccine among girls aged 9–13 years (within the country’s primary target age range), compared with the immunogenicity of three doses among females aged 16–26 years. Quadrivalent vaccine trials found that immunogenicity of two doses among 10–15-year-olds was equivalent to three doses among 16–26-year-olds for three of the four vaccine-related HPV types, but the Canadian study will provide a direct comparison with a younger age-group (38). A study of immunogenicity and efficacy of two doses of the quadrivalent vaccine is planned in India (Jan Agosti, Bill and Melinda Gates Foundation, pers. comm., July 2008).

Observational studies in the United States will evaluate immunogenicity in girls who do not follow the recommended schedule of the quadrivalent vaccine (Lauri Markowitz, pers. comm., August 2007; Jessica Kahn, University of Cincinnati, pers. comm., May 2008). In Quebec, the proposed public sector immunization programme will vaccinate girls at 0 and 2 months, but delay the third dose until about 5 years after the first dose. Clinical and operational issues may be evaluated (Randall Hyer, Merck, pers. comm., March 2008). If HPV vaccines provide protection for a long time (including lifelong duration), they could potentially be co-administered with other vaccines given to young
children, using existing delivery infrastructure. However, there are currently no studies of vaccine safety, immunogenicity or efficacy in children younger than 9 years.

Currently, both vaccines are available as single-use pre-filled syringes or vials that may be too bulky or costly for many settings. Research is needed on packaging options that require less cold-chain space, multidose vials, vaccine vial monitors, vaccine use beyond the cold chain and methods to optimize vaccine stability.

Trade-offs between potential waste, cost and volume should be evaluated.

**Measuring the impact and cost effectiveness of vaccination on HPV infection and outcomes**

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most models have evaluated industrialized countries with screening programmes. More studies are needed in low and middle-income countries with either no or limited screening.</td>
</tr>
<tr>
<td>Models have estimated the impact of HPV vaccines in a variety of settings, but additional field-based data on costs and delivery issues are needed to refine these models.</td>
</tr>
<tr>
<td>Models of the impact of HPV vaccines are also needed to assess vaccine-introduction strategies in the context of alternative screening strategies, including the use of new screening tests.</td>
</tr>
<tr>
<td>Models should be refined with new estimates of the duration of vaccine protection, vaccine delivery costs and other crucial determinants of impact and cost effectiveness.</td>
</tr>
</tbody>
</table>

In settings where cervical cancer screening is established, monitoring the impact and cost effectiveness of HPV vaccines must be evaluated against alternatives of screening programmes or combinations of vaccination and screening (9,183-185). However, questions remain about the most effective and cost-effective combinations of vaccination and screening for various age cohorts (9,186). While models have examined many scenarios in high-income countries (10,18,183,187), information is limited in low and middle-income countries. Moreover, modelling using field-based data is needed to help decision-making, especially in countries with a high disease burden (188). Models should also consider new low-resource screening methods, such as visual cervical inspection, and rapid HPV tests if they become available (189). Models must also be updated with new data on duration of protection, efficacy in individuals infected with HPV before vaccination, cross-protection against non-vaccine-related HPV types, herd immunity, type replacement, efficacy in males, delivery costs and actual vaccine prices.

**Evaluating second-generation vaccines**

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second-generation HPV vaccines may offer alternative administration routes, broader valency, therapeutic effects, easier manufacture or different storage requirements.</td>
</tr>
<tr>
<td>Identifying surrogate markers of protection would help future vaccine studies by simplifying and shortening clinical trials.</td>
</tr>
</tbody>
</table>

HPV VLP-based vaccines that require three doses are complicated and expensive to manufacture, distribute and deliver. Efforts to understand the immunological mechanisms of current HPV vaccines may identify surrogate markers of protection that could be used to evaluate new vaccine candidates (9). Improvements in antigens, valency,
manufacturing, stability and delivery systems could influence vaccine efficacy, ease of delivery, acceptability, manufacturing costs and affordability (9). Second-generation vaccines might include various attributes (9,167-169):

- subdermal, intradermal, mucosal and needle-free delivery
- single-dose delivery using live vectors
- increased valency
- better therapeutic effects
- chimeric particles based on expanded viral proteins
- simplified manufacturing processes.

Several second-generation vaccines are being developed, including candidates that are being evaluated in China and India. These vaccines will be targeted for markets in developing countries (167,168).

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29 Shapiro, C. WHO and adolescent immunization expanded programme on immunization, Viral Hepatitis Prevention Board Meeting, Ljubljana, Slovenia, 15–16 March, 2007.


41 Morita JY, Ramirez E, Trick WE. Effect of a school-entry vaccination requirement on racial and ethnic disparities in hepatitis B immunization coverage levels among public school students. Pediatrics, 2008, 121(3):e547–e552.


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6 Opinion and policies on HPV vaccines throughout the world

This section describes conclusions of World Health Organization (WHO) regional consultations on cervical cancer prevention and human papillomavirus (HPV) vaccines convened through May 2008, information on licensure status of HPV vaccines, recommendations of countries to include HPV vaccines in national immunization programmes, and an update on the status of WHO prequalification of HPV vaccines. Unlike other sections, this section includes selected information from 2008 that were available to WHO staff. See Annex 2 for additional 2008 information on this issue, including the summary of the WHO Regional Office for Africa (AFRO) regional meeting.

6.1 Summaries of WHO regional consultations about cervical cancer prevention and HPV vaccines

<table>
<thead>
<tr>
<th>Key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>All five of the six regional consultations that had convened by May 2008 concluded that:</td>
</tr>
<tr>
<td>• cervical cancer places a high burden on women, their families and communities</td>
</tr>
<tr>
<td>• access to high-quality cytology screening, treatment and palliative care is limited in low and middle-income countries in these regions</td>
</tr>
<tr>
<td>• regions are enthusiastic about the potential of HPV vaccines</td>
</tr>
<tr>
<td>• current costs of vaccine and delivery systems are prohibitive for low and middle-income countries with highest cancer burdens, and vaccine introduction in these countries would not be affordable without financial assistance or substantially lower costs</td>
</tr>
<tr>
<td>• few low and middle-income countries in these regions have routine delivery systems for adolescent vaccines, but school-based programmes appear promising</td>
</tr>
<tr>
<td>• investments in HPV vaccines must be justified in the face of other vaccination and health priorities.</td>
</tr>
</tbody>
</table>

All consultations recommended that, whenever feasible, countries should:

• introduce HPV vaccines as part of a comprehensive cervical cancer prevention and control programme that includes prevention, screening and treatment

• assess status of existing cervical cancer prevention and control programmes, including new screening technologies suitable for low-resource settings such as visual cervical inspection

• develop cancer-prevention priorities and plans by coordinating bodies of stakeholders in programmes related to immunization, cancer control, adolescent health, and sexual and reproductive health

• raise public awareness about cervical cancer burden, and prevention and control strategies, using communication campaigns.

By May 2008, WHO had carried out numerous consultations on cervical cancer prevention and human papillomavirus (HPV) vaccines. The consultations encompassed the WHO Regional Office for South-East Asia (SEARO), the WHO Regional Office for
the Western Pacific (WPRO), the WHO Regional Office for Europe (EURO), the WHO Regional Office for the Americas (PAHO) (Central and South America), and the WHO Regional Office for the Eastern Mediterranean region (EMRO). Consultation with the WHO Regional Office for Africa (AFRO) is scheduled for September 2008. See Annex 2 for updated information on the AFRO consultation.

These consultations provided information on the status of cervical cancer burden in the region, as well as prevention and control activities, and updated participants on HPV vaccines. The consultations discussed the need to:

- address and improve gaps in current screening and treatment programmes by assessing human resource capacity, infrastructure, training systems, programme effectiveness, policies and surveillance systems
- develop comprehensive cervical cancer programmes that include primary prevention (education about reducing sexual risk, condom promotion), secondary prevention (screening and diagnosing precancerous lesions), treatment, palliative care and public education
- apply evidence-based decision making about HPV vaccine introduction
- consider new screening methods suitable for low-resource settings, such as visual inspection with acetic acid application (VIA) (see Section 2)
- define a national coordinating body of stakeholders from programs on immunization, cancer control, adolescent health and sexual and reproductive health
- establish surveillance systems to monitor disease burden and the impact of cervical cancer prevention programmes.

Several conclusions about HPV vaccines that were common to all consultations are listed in the Key Points above. Additional issues are noted in the region-specific summaries below.

### 6.1.1 Bi-regional consultation in South-East Asia and the Western Pacific

The WPRO/SEARO Bi-regional Meeting was held in Thailand in April 2007. The meeting included representatives from programmes in immunization, cancer control, and sexual and reproductive health of 17 countries, including India, where approximately 25% of global cervical cancer cases occur. Most women in these regions do not have access to cytology-based screening or subsequent treatment for precancerous lesions (I).

In addition to the common points noted above, the consultation concluded that:

- the challenges of vaccine affordability, access and acceptance will take time to resolve and will probably require partnerships with donors (e.g. the Global Alliance for Vaccines and Immunization – GAVI)
- information is needed on long-term effectiveness of vaccines and acceptability among clients and health professionals, especially because HPV is sexually transmitted
- major investment in cervical cancer prevention may be questioned when other health problems, particularly maternal mortality, may be of higher priority.

The consultation recommended that countries should:

- strengthen current screening and treatment programmes (including pilot testing screening methods suitable for low-resource settings) while waiting for more affordable HPV vaccines
• consider vaccine introduction initially as a pilot when vaccines are affordable or are supported by donors
• evaluate potential costs and cost effectiveness of screening and vaccination
• establish surveillance to monitor HPV-related disease burden and the impact of vaccination programmes as part of vaccine introduction
• seek political commitment and community mobilization to ensure sustainable funding and continued demand for prevention services
• integrate cervical cancer prevention services into other reproductive health or primary-care services to ensure sustainability.

6.1.2 Consultation in Europe

A EURO Regional Consultation was held in Denmark in May 2007. The consultation included representatives of government programmes in immunization, cancer control, and sexual and reproductive health from 45 countries. Most of the high-income, western European countries represented at the meeting have established cervical cancer control programmes, including screening, but few have organized screening programmes with high coverage. Some of these countries have issued recommendations about HPV vaccine use for national programmes, or reimburse vaccination through public funds or insurance plans (see Section 6.3). The low and middle-income countries represented at the meeting have less developed cervical cancer programmes, and screening coverage tends to be low, especially outside cities. Some of these countries have licensed HPV vaccines and have started discussions about introducing HPV vaccines (2).

In addition to the common points above, the consultation recommended that countries:
• prepare for evidence-based decision-making about HPV vaccine introduction, with the help of WHO guidance and technical information
• support national regulatory authorities considering licensure of HPV vaccines and seeking assistance from WHO as needed (3)
• review global, regional or country-specific data on HPV-related burden of disease, epidemiology and risk factors (4), and HPV vaccine efficacy, safety, impact and cost effectiveness, as relevant to country context (5)
• explore how HPV vaccine might complement and be integrated into existing cancer-prevention services, including screening
• develop strategies and materials for accurate, non-biased information, education and communication to educate policy makers, health-care providers, patients, parents and the public about HPV vaccines
• assess the cost of licensed HPV vaccines and potential funding mechanisms for the public sector (Global Alliance for Vaccines and Immunization (GAVI) for the few eligible countries in this region; other sources for more affluent countries)
• assess the potential to monitor vaccine impact and safety of marketed HPV vaccines.

6.1.3 Consultation in the Eastern Mediterranean Region

An EMRO Regional Consultation was held in Morocco in March 2008. The consultation was attended by representatives from programmes on immunization, cervical cancer control, and sexual and reproductive health from nine low, middle and high-income countries that contain most of this region’s population. The countries were Egypt, Iran, Morocco, Oman, Pakistan, Sudan, Syria, Tunisia and Saudi Arabia. This diverse region
includes low-income countries where screening is rare due to lack of clinical and laboratory resources, as well as high-income countries where screening is well established (6).

In addition to the common points above, the consultation produced several conclusions:

- screening, treatment and HPV vaccination should form the basis of all national comprehensive cervical cancer prevention and control programmes
- simplified methods are needed to assess cost effectiveness of primary and secondary prevention methods (including screening, vaccination and combined strategies), to inform programme policy
- HPV vaccination will not protect against all oncogenic HPV types, so vaccinated and non-vaccinated women should continue to be screened if effective screening is available
- before making the decision to introduce the vaccine, countries should assess the burden of HPV-related disease and possible ways to deliver the HPV vaccine
- school-based programmes can facilitate vaccination, but will depend on high rates of enrolment of the target age group
- support for HPV vaccine introduction at affordable prices is needed for middle-income countries; this can be achieved by tiered pricing, bulk procurement, revolving funds, sharing costs with vaccinees, private financing or technology transfer that produces cheaper vaccines
- countries should initially offer HPV vaccines on an optional basis through the private sector in countries where the vaccines are licensed and use is consistent with national immunization policies
- surveillance systems to measure burden of cervical cancer and precancers should be established to assess vaccine impact in the future
- advocacy for HPV vaccines should stress cancer prevention to avoid the stigma associated with sexually transmitted infections.

6.1.4 Consultation in the Americas

The PAHO Regional Consultation was held in Mexico in May 2008. It included representatives from government programmes in immunization, cancer control, and sexual and reproductive health from 21 countries of the Americas. In addition to the common points above, the consultation issued a Declaration Towards Comprehensive Cervical Cancer Prevention and Control (7) which stated that:

- cervical cancer is one of the most common causes of death among women in Latin America and the Caribbean; about 33 000 deaths occur per year and, if this trend continues, the number of deaths will double by 2030
- cervical cancer primarily affects vulnerable, poor and indigenous populations
- HPV vaccines offer great hope to prevent cervical cancer; the current high cost is the main barrier to use
- countries should work together and with PAHO’s Revolving Fund to obtain affordable HPV vaccine prices so that all countries in the region can add these vaccines to their national immunization programs as soon as possible
• mechanisms and negotiating processes with high-level financing stakeholders at the national level are needed to support sustainable vaccination programs and other services to prevent and control cervical cancer

• HPV vaccination should not replace screening, diagnosis or treatment; instead, it should offer an opportunity to strengthen education, prevention, screening, diagnostics and treatment for cervical cancer

• programmes in immunization, prevention, control, and adolescent and reproductive health should promote an integrated approach to strengthening the prevention and control of cervical cancer

• decisions on whether to introduce a HPV vaccine should be based on the diverse technical, programmatic and operational criteria of individual countries, taking into account the need to strengthen the cold chain, epidemiological surveillance systems, and the laboratory networks.

The consultation recognized that much work needs to be done at the national level to make sure that countries in the region are fully engaged in making decisions that are evidence based. Work also needs to be done to secure affordable vaccines, strengthen delivery infrastructure for the young adolescent target group, and analyse the cost effectiveness of introducing vaccines (Andreas Ullrich, WHO, pers. comm., May 2008, final meeting report pending).

In 2006, PAHO also rated HPV vaccines as a “definite priority” for introducing new vaccines, together with rotavirus and pneumococcal vaccines. The PAHO Directing Council recommended that the PAHO Revolving Fund be used to procure HPV vaccines. In June 2007, a regional strategy for cervical cancer prevention and control was presented to the PAHO Executive Committee. It urged countries with cancer burdens to introduce HPV vaccines in the public sector, and recommended that equitable access to affordable vaccines is a priority. The PAHO Executive Committee did not endorse this strategy, largely because current high vaccine prices preclude introduction (Jon Andrus, PAHO, pers. comm., May 2008).

6.1.5 Consultation in Africa

The AFRO Regional Consultation will be held in Burkina Faso in September 2008. (See Annex 2 for updated information on this meeting.)

The December 2007 meeting of the African Task Force on Immunization recommended that WHO, AFRO and partners develop innovative mechanisms to reduce the costs of HPV vaccines and help countries to introduce them more quickly (Robin Biellik, PATH, pers. comm., January 2008). Support for increasing access to HPV vaccines in Africa was evident at two regional meetings: the African Organization for Research and Training in Cancer in South Africa in 2007 (8) and the first “Stop Cervical Cancer in Africa” Conference in Nigeria in July 2007 (Scott Wittet, PATH, pers. comm., September 2007). HPV vaccine access was also the focus of the second “Stop Cervical Cancer in Africa” Conference, which was subtitled “Accelerating access to HPV vaccines” and was held in Uganda in July 2008 (sponsored by the Princess Nikki Breast Cancer Foundation).

HPV vaccines were also highlighted at the African Vaccine Regulatory Forum in Burkina Faso in September 2007, to support the several national regulatory authorities who have, or will soon, review dossiers on HPV vaccines (Liliana Chocarro, WHO, pers. comm., September 2007).
### 6.2 Current vaccine licensure status

**Key points**
- To the end of March 2008, each vaccine was licensed in more than 40 countries in all regions.
- All countries have approved indications for both vaccines for use in girls.
- Some countries have approved indications for both vaccines for use in adolescent and adult women.
- Some countries have approved indications for the quadrivalent vaccine for use in boys.

The quadrivalent vaccine was the first HPV vaccine to be licensed; this occurred in Gabon in March 2006 (Randall Hyer, Merck & Co, pers. comm., April 2008). By the end of March 2008, the vaccine was licensed in more than 90 countries. (See Annex 2 for updated information.) Cervarix was first licensed in Australia in April 2007 (9) and was licensed in more than 40 countries by March 2008 (Robin Biellik, PATH, pers. comm., March 2008) (see Table 6.1). National regulatory authorities of many other countries are now considering dossiers for one or both vaccines. A licensed vaccine may not necessarily be marketed in a given country due to requirements related to importation, distribution and regulation, or to price negotiations.

In some countries, including those in the European Union, the approved indications for HPV vaccines do not specify the sex or age range of vaccine recipient, effectively allowing use in all patients. Of the indications that specify patient age and sex, all countries have approved indications for both vaccines for girls, and some countries have approved indications for women. Some countries have approved the quadrivalent vaccine for use in males. GSK has not sought registration of the bivalent vaccine for males. In some countries, the approved indication specifies that the vaccine should be used according to official recommendations; however, in some cases the recommendation is more restrictive (e.g. girls only) than the approved indication (e.g. approved indications for women or boys or approved indication does not specify patient age or sex) (see Table 6.1).
<table>
<thead>
<tr>
<th>WHO region</th>
<th>Quadriivalent vaccine</th>
<th>Bivalent vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>Central African Republic, Chad, Democratic Republic of the Congo, Equatorial Guinea, Ethiopia, Gabon, Kenya, Mauritania, Mauritius, Togo, Uganda</td>
<td>Kenya, South Africa, United Republic of Tanzania</td>
</tr>
<tr>
<td>Americas</td>
<td>Argentina, Aruba, Bahamas, Barbados, Bermuda, Brazil, Canada, Cayman Islands, Chile, Colombia, Costa Rica, Curaçao, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Jamaica, Mexico, Nicaragua, Peru, Puerto Rico, Trinidad and Tobago, Uruguay, United States</td>
<td>Brazil, Mexico, Peru, Uruguay</td>
</tr>
<tr>
<td>Europe</td>
<td>European Union (27 countries), Belarus, Bosnia, Bulgaria, Croatia, Iceland, Cyprus, Israel, Liechtenstein, Macedonia, Malta, Montenegro, Norway, Romania, Russia, Serbia, Switzerland, Turkey</td>
<td>European Union (27 countries), Iceland, Israel, Kazakhstan, Moldova, Ukraine</td>
</tr>
<tr>
<td>Eastern Mediterranean</td>
<td>Bahrain, Egypt, Jordan, Morocco, Saudi Arabia, United Arab Emirates</td>
<td>Saudi Arabia, United Arab Emirates</td>
</tr>
<tr>
<td>South-East Asia</td>
<td>Indonesia, Thailand</td>
<td></td>
</tr>
<tr>
<td>Western Pacific</td>
<td>Australia, Hong Kong SAR, Macao SAR, Malaysia, New Zealand, Philippines, Singapore, South Korea, Thailand, Taiwan</td>
<td>Australia, Hong Kong SAR, Philippines</td>
</tr>
</tbody>
</table>

SAR = Special Administrative Region
A licensed vaccine may not necessarily be marketed in a given country due to requirements related to importation, distribution and regulation, or to price negotiations.

* Some countries have not specified the patient sex or age for the approved indications. Of those that have, all countries have approved indications for young adolescent girls and some have also approved indications for older adolescent females, women, boys or men.
6.3 Country recommendations about HPV vaccine use in national immunization programmes

Key points

- By the end of January 2008, 15 countries – 12 European countries, Australia, Canada and the United States – had recommended or funded use of at least one vaccine for national and regional immunization programs.
- All 15 countries are industrialized, have well-established (but costly) screening programs and relatively low cervical cancer burdens.
- The rationale for recommendations has included the high burden of cervical cancer or precancers, vaccine safety, efficacy in preventing HPV-related cancer and warts (for the quadrivalent vaccine), cost effectiveness and capacity to vaccinate using existing infrastructure.
- In the one country, France, where the recommendation was amended after both vaccines were licensed and vaccines were similarly priced, the recommendation noted a preference for the quadrivalent vaccine due to benefits in preventing warts and other conditions caused by HPV 6 and 11.
- All recommendations advise that girls should be the primary target population although the specific age range targeted varies within the range of 9 and 17 years.
- Most recommendations advise vaccinating “catch-up” populations of older females (specific ages are within the range of 13–26 years), stressing the benefits to those who may not yet be infected with all vaccine-related HPV types.
- To the end of January 2008, only one of the 15 countries (Austria) advised vaccinating boys, citing benefits for wart prevention.
- Most recommendations specifically advise against vaccinating pregnant women.
- A few recommendations specify delivery venues, including school-based programmes.
- Several recommendations advise monitoring vaccine coverage, safety and public health impact.
- Several recommendations advise high priority research that can inform programme operations.
- Most recommendations and related funding decisions support public funding to vaccinate at least part of the primary target and catch-up populations; none have endorsed funding vaccination of boys.
- All recommendations stress continued screening of both vaccinated and non-vaccinated women.
- Since January 2008, a few countries have finalized or are finalizing recommendations on vaccine use.

As of January 2008, government bodies in 15 high-income countries – 12 European countries, Australia, Canada and the United States – had issued formal recommendations about large-scale HPV vaccine use in national health systems, immunization programmes or public sector health systems, and some had approved funding for HPV vaccination in public sector programmes (10-26) (see Table 6.2). One country, Liechtenstein, approved funding for HPV vaccination through the national health insurance programme, but did not issue a formal recommendation on vaccine use (11) (Kornelia Vallaster, Ministry of Health, pers. comm., January 2008).(See Annex 2 for updated information.)
All 15 countries have well-developed health systems, national immunization policies or programmes, organized or opportunistic cervical cancer screening programs with moderate or high population coverage (more than 50% of eligible women), and substantially lower burdens of cervical cancer than low or middle-income countries with limited or no screening (4). New Zealand, and several countries in western and eastern Europe are in advanced discussions about recommendations for vaccine use, and are expected to issue formal recommendations in 2008 or 2009 (27,28).

In addition to country recommendations, several international, national or regional nongovernmental organizations – including public health and clinical organizations, health advocacy groups and patient organizations – have issued recommendations about HPV vaccine use, which are largely consistent with these country recommendations (29-32).

Most country recommendations were issued in the first half of 2007 (before the bivalent vaccine was widely registered), so all but three recommendations or funding proposals pertain only to the quadrivalent vaccine. The United Kingdom recommendation, issued shortly before Cervarix® was approved by the European Medicines Agency (EMEA), pertained to HPV 16/181 vaccines generically. However, the United Kingdom Joint Committee on Vaccination and Immunisation noted that the choice of vaccine to be purchased by the National Health Service will be primarily determined by cost effectiveness, which is highly dependent on the negotiated vaccine cost. If both vaccines were offered at similar prices, the committee would recommend the quadrivalent vaccine because it also prevents warts (33).

Greece and Portugal issued recommendations after the September 2007 EMEA decision to license Cervarix®. Vaccine product choices are being evaluated as part of funding discussions (14,34,35) A Kyrlesi, Greek Ministry of Health, pers. comm., 4 March 2008). After Cervarix® was licensed by EMEA, France amended its recommendation to indicate preference for Gardasil/Silgard® because of expected benefits against genital warts, cervical intraepithelial neoplasia (CIN) and vulvar precancers, and a larger body of published clinical efficacy data (15). Because many countries have now licensed both vaccines, some are reviewing recommendations in light of product choice.

The recommendations from the 15 countries, and the recommendations of nongovernment organizations, reflect a high degree of consensus on clinical benefits and delivery issues. The primary rationale for recommendations includes the safety and efficacy of HPV vaccines, the expected reduction in incidence of cervical precancers and invasive cervical cancer, and — in the case of the quadrivalent vaccine — the expected reduction in anogenital warts. All recommendations have defined primary target populations of girls before sexual debut. This is usually defined using country-specific data on the mean age of sexual debut, because routinely assessing sexual history in girls is difficult and unreliable. Recommended ages range from a low of 9 years (Canada) to a high of 17 years (Germany). All recommendations propose vaccinating girls under 15 years (see Table 6.2), an age group for which vaccine trials of both vaccines assessed only immunogenicity and not clinical efficacy against CIN. Thirteen countries have recommended “catch-up” vaccination for older female adolescents or young women, because of the anticipated benefit in preventing HPV-related disease due to types to which vaccinees had not yet been exposed, cost effectiveness, delivery considerations and other factors.

1 The phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either the bivalent vaccine or the quadrivalent vaccine, because both contain antigens for HPV 16 and HPV 18.
### Table 6.2 Summary of prevailing recommendations and assessments through January 2008a

<table>
<thead>
<tr>
<th>Recommendation for or assessment of</th>
<th>Prevailing recommendation or assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary target population</strong></td>
<td>Females, age range 9–17 years</td>
</tr>
<tr>
<td></td>
<td>Twelve countries include ages ≤ 12 years</td>
</tr>
<tr>
<td></td>
<td>Six countries include ages ≥ 14 years</td>
</tr>
<tr>
<td>Rationale: HPV prevalence is high; persistent infection causes cervical cancer; vaccines most efficacious before sexual debut; better immunologic response at this age.</td>
<td></td>
</tr>
<tr>
<td><strong>Catch-up population</strong></td>
<td>Thirteen countries recommend catch-up vaccination</td>
</tr>
<tr>
<td>Rationale: females without prior infection by vaccine-related HPV types will benefit</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccinating males</strong></td>
<td>Thirteen countries do not address or recommend vaccinating males</td>
</tr>
<tr>
<td>Rationale: lack of data on vaccines efficacy in males</td>
<td></td>
</tr>
<tr>
<td><strong>Safety and efficacy of vaccines</strong></td>
<td>Five countries discuss possible adverse events</td>
</tr>
<tr>
<td></td>
<td>None recommend vaccinating pregnant women</td>
</tr>
<tr>
<td><strong>Financing mechanism</strong></td>
<td>Eleven countries fund vaccination for at least part of primary target population through national or regional programs</td>
</tr>
<tr>
<td></td>
<td>Seven out of 13 countries that advise catch-up vaccination fund vaccination for at least part of the catch-up population</td>
</tr>
<tr>
<td><strong>Delivery strategy</strong></td>
<td>Five countries address co-administration with other vaccines</td>
</tr>
<tr>
<td></td>
<td>Five countries note specific delivery sites, including schools or clinicians</td>
</tr>
<tr>
<td><strong>Monitoring and evaluation</strong></td>
<td>Eight countries advise monitoring vaccine coverage, adverse events, public health impact, and impact on screening programmes</td>
</tr>
<tr>
<td><strong>Integration of vaccination with cervical cancer screening programs</strong></td>
<td>All countries recommended continued cancer screening for vaccinated and non-vaccinated women</td>
</tr>
<tr>
<td></td>
<td>Three countries note screening programmes may change in future</td>
</tr>
<tr>
<td><strong>Recommendations for future research to guide vaccination programmes</strong></td>
<td>Eight countries advise research on duration of protection and possible need for booster, efficacy, tolerance and/or cross-protection against non-vaccine related types</td>
</tr>
<tr>
<td></td>
<td>Five countries advise research on HPV prevalence, disease burden and/or cervical cancer screening programmes</td>
</tr>
<tr>
<td></td>
<td>A few countries advise research on vaccine efficacy in older women and men, co-administration with other vaccines, safety in pregnancy, HPV type replacement, cost effectiveness of vaccination strategies, and the impact of vaccination on screening programmes</td>
</tr>
</tbody>
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a Recommendations through January 2008 come from 15 countries: 14 that advise use of HPV vaccines in national immunization programmes (Australia, Austria, Belgium, Canada, France, Germany, Greece, Italy, Luxembourg, Portugal, Spain, Switzerland, United Kingdom and United States), and one (Liechtenstein) that approved funding for HPV vaccination but had not issued a specific recommendation for use.

Sources: (10-26).

Some of the recommendations note the potential benefits of the quadrivalent vaccine for males, but only Austria has formally recommended quadrivalent vaccine use for males because of the potential benefits for preventing warts. The country has not endorsed public sector funding of this vaccine for boys (17) and (Pierre Van Damme, WHO Collaborating Centre for Vaccine Evaluation, pers. comm., April 2008). As data become
available on the efficacy of vaccinating males to prevent HPV-related disease in males and females, more countries may debate recommendations about vaccinating males for direct or indirect benefits.

Many recommendations have considered cost-effectiveness analyses, citing national or regional data, and addressed financing. As of January 2008, 11 country recommendations proposed free HPV vaccination for at least part of the primary target population. Seven of the 13 countries that recommended catch-up vaccination proposed funding for at least part of that cohort. Four recommendations specifically addressed vaccine-delivery strategies, including school-based strategies or clinician delivery (see Table 6.2). Some countries recommended informed-consent procedures, or patient or parent education messages, but none advised mandatory vaccination. In the United States, several states proposed legislation requiring HPV vaccination before school entry but, as of February 2008, only the State of Virginia passed a law mandating HPV vaccination for girls entering sixth grade (aged approximately 11–12 years) after full consideration of parents’ rights to decline vaccination of their daughters (36).

Eight countries had recommendations that proposed monitoring the public health impact of vaccines in their country or in other countries, including vaccine coverage; vaccine efficacy; duration of protection and need for boosters; safety and adverse events, including safety in pregnancy; vaccine impact on HPV prevalence, cervical precancers, invasive cancer and anogenital warts; and HPV type replacement in populations.

A few recommendations proposed using or creating vaccine registries linked with existing cytology or cancer registries. Recommendations of at least 10 countries advised research to monitor vaccine efficacy in older women, men and immunocompromised people; tolerance and safety; cross-protection against other oncogenic HPV types; and cost effectiveness (see Table 6.2).

All country recommendations stressed that both vaccinated and non-vaccinated women should continue to be screened (Table 6.2). France and Italy specifically recommended information campaigns to educate women and health-care providers about the efficacy of a combined strategy of screening and vaccination. Some countries and the European Centre for Disease Prevention and Control (ECDC) have indicated the need to improve the effectiveness of screening programs after introducing HPV vaccines (37).

6.4 Status of WHO prequalification of HPV vaccines

By the end of 2007 (third quarter for quadrivalent vaccine, fourth quarter for bivalent vaccine), manufacturers of both vaccines had submitted dossiers to WHO for prequalification review. The review process is intended to assure vaccine quality before the vaccine is purchased by United Nations vaccine procurement agencies, such as the PAHO Revolving Fund or the United Nations International Children’s Emergency Fund. Quality and clinical assessments for both vaccines are under way. Both vaccines are currently available as vials and pre-filled syringes, but the prequalification process is currently only considering one-dose vials because pre-filled syringes are too costly for low-income countries, and auto-disabling syringes are readily available. Prequalification assessments are usually completed within 18 months from submission of a dossier (See Annex 2 for updated information.)
References


This section details candidate recommendations for use of HPV vaccines in national immunization programmes proposed by the World Health Organization (WHO) human papillomavirus (HPV) Vaccine Advisory Committee (HVAC) as of September 2008. The recommendations concern the two prophylactic HPV 16/18 vaccines (i.e. bivalent and quadrivalent) that are licensed and marketed in several regions. The bivalent vaccine, Cervarix®, is indicated for prevention of precancers and cancer of the cervix caused by HPV 16 and 18. The quadrivalent vaccine, Gardasil® or Silgard®, is indicated for prevention of precancers and cancer of the cervix caused by HPV 16 and 18, and anogenital warts caused by HPV 6 and 11. Hereafter, the phrases “HPV 16/18 vaccines” and “HPV 16/18 vaccination” indicate vaccination with either vaccine because both vaccines contain antigens for HPV 16 and HPV 18.

7.1 Overall recommendation

Routine HPV 16/18 vaccination should be included in immunization programmes of all countries where prevention of cervical cancer and other HPV-related diseases is a public health priority, vaccine introduction is programmatically feasible and sustainable financing can be secured. If cost-effective analyses may guide a country’s health decisions, countries should consider the cost-effectiveness of possible vaccination strategies in their country or region, when feasible.

7.2 Detailed recommendations

7.2.1 Target populations

The primary target population should be young adolescent girls. Because vaccination is most efficacious in girls who have not become sexually active and are naive to HPV 16/18, programmes should determine the primary target age group based on data on the age of sexual initiation and/or the feasibility of reaching young adolescent girls through schools or health-care facilities, or through community-based methods. In most countries, this group would include girls within the age range of 10–13 years.

Catch-up strategies for older adolescent females and young women are recommended to supplement routine vaccination of young adolescent females. However, such programmes are only recommended if they are feasible, affordable and cost-effective, and do not divert resources from vaccination of the primary target population or from existing cervical cancer screening programmes that have been demonstrated to be effective in reducing cervical cancer incidence or mortality at a population level.

1 The phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either the bivalent vaccine or the quadrivalent vaccine, because both contain antigens for HPV 16 and HPV 18.
Vaccinating males is not recommended because data on the efficacy against persistent HPV 16/18 infections, HPV 16/18-related precancers or cancers, or anogenital warts are not yet available for either vaccine. Most models also indicate that vaccinating males is not cost effective, except when coverage among young adolescent females is low.

### 7.2.2 Special populations

HPV 16/18 vaccines are not recommended for pregnant females. HPV 16/18 vaccines have not been causally associated with adverse pregnancy, fetal, or neonatal outcomes, but data on safety among females who were inadvertently vaccinated during pregnancy are limited. Selecting target ages for HPV vaccination that precede the onset of sexual activity will reduce the risk of inadvertently vaccinating pregnant females.

The quadrivalent HPV vaccine may be administered to lactating females, because there are data demonstrating safety in lactating females. The bivalent vaccine is not recommended for lactating females because safety data in lactating females are currently not available.

Data on the safety and immunogenicity of HPV vaccines in individuals who are immunocompromised due to medications or diseases (e.g. HIV infection) are currently very limited. However, more data will be available after completion of ongoing studies of safety and efficacy of both vaccines in immunocompromised HIV-infected adolescents and adults in several continents. Selecting target ages for HPV vaccination that precede the onset of sexual activity minimizes the risk of administering HPV vaccines to human immunodeficiency virus (HIV)-infected individuals. HPV vaccination of young adolescent females with unknown HIV infection status who have not initiated sexual activity is expected to be beneficial; it should not be deferred because of concerns about potential adverse events, because the potential benefits of vaccination outweigh the potential risks. However, vaccine immunogenicity and efficacy in HIV-infected individuals may be less than that in HIV-uninfected individuals. HIV testing before routine HPV vaccination is not advised because it lacks clear benefit and would be resource intensive.

### Alternative wording of above paragraph

Data on the safety and immunogenicity of HPV vaccines in individuals who are immunocompromised due to medications or diseases (e.g. HIV infection) are currently very limited. However, more data will be available after completion of ongoing studies of safety and efficacy of both vaccines in immunocompromised HIV-infected adolescents and adults in several continents. The introduction of HPV immunization to girls with unknown HIV serostatus who have not begun sexual activity is expected to be beneficial because (a) HPV vaccines are non-infectious, (b) the target group for HPV vaccines is girls before onset of sexual activity (and thus before risk of HIV exposure), (c) the potential benefits of HPV vaccines for HIV-infected females at increased risk of HPV-related disease are great, and (d) the burden of HPV-related disease in HIV-infected females is high. However, vaccine immunogenicity and efficacy in HIV-infected individuals may be less than that in individuals who are not HIV infected. Countries considering vaccinating girls who are known to be perinatally infected with HIV but have not begun sexual activity, or older adolescent or adult females who may already be HIV-infected through sexual exposure, may prefer to wait for results of safety and efficacy studies before deciding to introduce vaccination for these populations.
7.2.3 Vaccine administration

Both vaccines should be administered according to manufacturer specifications, schedules and advice on interrupted schedules; that is, three doses over 6 months (0, 2 and 6 months for the quadrivalent vaccine; and at 0, 1, and 6 months for the bivalent vaccine).

Clinical efficacy trials for both vaccines demonstrate that protection lasts for at least 5 years. The need for a booster vaccination has not been established.

Vaccinees should receive all three doses with the same product, because the two products have different characteristics, components and indications. Also, data are lacking on the safety, immunogenicity or efficacy of the two vaccines when used interchangeably.

Studies show that the following combinations of co-administration are safe and do not appreciably impair the immune response to any antigen: the quadrivalent vaccine with a recombinant hepatitis B vaccine; the quadrivalent vaccine with a diphtheria/tetanus/pertussis/poliomyelitis vaccine, and the bivalent vaccine with a diphtheria/tetanus/pertussis/inactivated poliomyelitis vaccine. Both HPV vaccines are non-infectious and can be co-administered with other non-live vaccines. Administering all vaccines together at a single visit increases the likelihood that vaccines will be received on schedule. Guidance should be updated as results of ongoing co-administration studies become available.

**Alternative wording of above paragraph**

Both HPV vaccines are non-infectious. Studies show that the following combinations of co-administration are safe and do not appreciably impair the immune response to any antigen; the quadrivalent vaccine with a recombinant hepatitis B vaccine; the quadrivalent vaccine with a diphtheria/tetanus/pertussis/poliomyelitis vaccine; and the bivalent vaccine with a diphtheria/tetanus/pertussis/inactivated poliomyelitis vaccine. HPV vaccines should only be administered with other vaccines at the same visit if studies have shown that co-administration is safe and does not appreciably impair the immune response to antigens of either vaccine. Administering all vaccines together at a single visit increases the likelihood that vaccines will be received on schedule. Guidance should be updated as results of ongoing co-administration studies become available.

7.2.4 Vaccine product choice

All manufacturers of HPV vaccines that supply United Nations (UN) procurement agencies and are subject to WHO prequalification should comply with WHO requirements for production, quality control and tender specification.

In settings where both vaccines are approved and marketed, decisions about use of specific and sometimes unique vaccine products should consider:

- approved indications for disease prevention (i.e. HPV 16/18-related cervical precancers and cancer, and HPV 6/11-related anogenital warts) and target populations (e.g. young adolescent girls, older adolescent girls, women and males)
- the extent and quality of data that is available to decision makers concerning vaccine safety, immunogenicity, efficacy, reactogenicity and safety in special populations that may be eligible for vaccination (e.g. females of reproductive age, lactating females and HIV-infected females), duration of HPV 16/18 antibody and clinical protection, and efficacy against cervical disease due to HPV types closely related to HPV 16/18. The extent and quality of data in the public domain on the two vaccines differs.
• unique product characteristics (e.g. price, supply characteristics and cold-chain requirements related to package volume).

7.2.5 Vaccine delivery strategies
Several vaccine delivery strategies are possible, including school-based programmes, pulsed delivery through child health days, vaccination days, periodic campaigns, routine provision through health facilities, or combination strategies. Countries should use delivery methods that are compatible with delivery infrastructure and cold-chain capacity; are affordable, cost-effective and sustainable; and achieve the highest coverage. Priority should be given to delivery strategies that ensure inclusion of females at highest risk of cervical cancer (i.e. those who later in life may have limited access to screening).

7.2.6 Integration of vaccination with other interventions
Whenever possible, HPV 16/18 vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related diseases. Such a strategy should include education about how to reduce behaviours that increase risk of these diseases, cervical cancer screening, and diagnosis and treatment of precancerous lesions and cancer. HPV vaccine introduction should not undermine or divert funding from existing programmes that have been proven to reduce HPV-related disease at a population level.

HPV vaccination is a primary prevention tool; it does not eliminate the need for screening, which (if available) is a secondary prevention tool. Whenever possible, vaccinated females should be screened later in life to prevent cancer caused by HPV types other than 16 and 18, as these other types may cause up to 30% of cervical cancer cases.

7.2.7 Monitoring HPV vaccination programmes
After large-scale introduction of HPV vaccine, all countries should measure coverage by age and district, preferably through routine immunization monitoring systems. As with the introduction of any new vaccine, countries should conduct surveillance to identify possible, rare unexpected adverse events through existing passive reporting systems or new sentinel studies, or should track the experience of other countries using these methods. Whenever possible, countries should monitor the impact of HPV vaccination on the prevalence of vaccine-related HPV types, the incidence of cervical abnormalities and high-grade precancerous lesions, and the incidence and mortality of invasive cancer. Programmes using the quadrivalent vaccine should also monitor the impact of vaccination on anogenital wart incidence, where feasible.

7.2.8 Patient, parent and community education
It is recommended to use educational messages and, if necessary, informed consent methods, that are tailored to the local cultural context and information needs of different audiences — vaccination candidates, parents or guardians of vaccination candidates, educators, community leaders and health-care providers.

Educational messages should stress that HPV vaccines are intended to prevent cancer; they are not therapeutic or curative; are most effective when given before onset of sexual activity; require three doses for full protection; are not intended for pregnant females; and will not prevent HIV, other sexually transmitted infections or pregnancy. Messages should also stress that vaccinees should seek cervical cancer screening later in life, if it is available. Programmes using the quadrivalent vaccine may note benefits related to wart prevention.
Annex 1: Statements about HPV vaccines by WHO immunization committees to end of 2007

This annex provides statements about human papillomavirus (HPV) vaccines made by World Health Organization (WHO) immunization committees.

A1.1 Meeting of the Strategic Advisory Group of Experts (immunization), April 2007

The Immunization Strategic Advisory Group of Experts (SAGE) on immunization reports to the Director-General of WHO on issues ranging from vaccine research and development to immunization delivery. Its scope extends beyond childhood immunization to include all vaccine-preventable diseases. SAGE met on 17–18 April 2007 in Geneva, Switzerland. This section summarises the conclusions and recommendations from this meeting, which are reproduced verbatim.

In terms of human papilloma virus (HPV) vaccines, SAGE was updated on:

- the global burden of cervical cancer and the relationship of HPV to cervical cancer and genital warts
- data on the safety, efficacy and immunogenicity of the quadrivalent HPV vaccine (types 6, 11, 16 and 18) now licensed in more than 70 countries, and of the bivalent vaccine (types 16 and 18) submitted for licensure in several countries
- ongoing research on vaccine safety and efficacy, including alternative schedules, delivery costs and vaccine acceptability
- vaccine cost effectiveness and vaccine delivery options for young adolescents through school-based programmes, CHDs [child health days — these are special days used to delivery health interventions, including vaccines] or vaccination weeks, including delivering HPV vaccine with other vaccines and health interventions
- the feasibility and acceptability of vaccine delivery overall and in subpopulations, such as pregnant women and people infected by HIV
- the potential of monitoring vaccination through screening programmes
- ongoing and planned WHO regional consultations on vaccine introduction.

SAGE concluded from clinical trial evidence that introducing vaccines is likely to bring great benefits worldwide, particularly to those developing countries where cervical cancer is a major cause of death, and screening programmes are limited or absent. Vaccines may also provide important benefits in countries with screening programmes. Although data from clinical trials on vaccine safety and efficacy are convincing, data on the duration of protection after five years will not be available until ongoing trials extend follow-up. Developing appropriate, effective strategies to deliver vaccine to young pre-adolescents is challenging but crucial, given the high incidence of HPV infection in sexually active young adults.
From a programmatic perspective, SAGE noted that:

- introduction of hepatitis B vaccine in Asia and Africa has demonstrated strong public demand for anticancer vaccines
- introduction of HPV vaccine could accelerate the Global Immunization Vision and Strategy (GIVS) to expand adolescent vaccination
- successful young-adolescent school-based campaigns and vaccination weeks in Latin America and Asia could expand to include HPV vaccines and inform adolescent immunization in other regions
- introduction of HPV vaccine will require strong political as well as information, education and communication, and commitment
- introduction of HPV vaccine should be coordinated with school health programmes and should provide opportunities to educate young people about pregnancy and prevention of sexually transmitted infections, including HIV
- WHO could collaborate with the International Labour Organization to better reach working adolescents
- strategies to monitor vaccine impact on precancerous lesions and on cervical and other HPV-related cancers are required, but would require development in many countries.

SAGE noted that the current high price of vaccines is a major barrier to their introduction. In this respect, the willingness of industry to share data and to accelerate affordability and access are encouraging. Demand and supply must be matched to meet the needs of developing countries and financing capacity. Technology transfer that allows vaccine manufacturing in developing countries may help lower prices and improve access. WHO should monitor candidate vaccines suitable for manufacture in developing countries, and simplified schedules that could increase future vaccine uptake.

SAGE acknowledged the ongoing work by a number of agencies to inform and support developing countries as they consider HPV vaccine introduction. The committee recommended that the WHO Secretariat, potentially assisted by SAGE members, accelerate the regional consultation process to assess political will, acceptability and feasibility, and introduction challenges and opportunities. Moreover, SAGE requested that regional technical consultative groups (TCGs) be involved in these activities. The Immunization, Vaccines and Biologicals’s (IVB’s) HPV Vaccine Advisory Committee, in collaboration with WHO’s experts from relevant departments, should review evidence for a future WHO HPV vaccine position paper, and identify outstanding questions about safety, efficacy and delivery, with a view to presenting this to SAGE for future consideration.

SAGE urged the completion of ongoing research in:

- HIV-infected people
- prolonged (including yearly) intervals between doses
- demonstration projects on delivery methods
- cost-effectiveness studies of vaccinating young adolescents and older, “catch-up” populations in low- and medium-income countries.

SAGE also urged new research on the feasibility and effectiveness of simplified schedules, such as 2-dose schedules or dosing for infants and young children, to assess
initial and sustained immunogenicity. The committee called for a plan be developed to mobilize resources to introduce vaccines in developing countries. It recommended that decision makers at all levels should collaborate closely with immunization, cancer, child, adolescent and reproductive health programmes and interventions to ensure that vaccine introduction is integrated into comprehensive cervical cancer control programmes that include screening.

A1.2 Meeting of the Global Advisory Committee on Vaccine Safety, June 2007

The Global Advisory Committee on Vaccine Safety (GACVS) is an expert clinical and scientific advisory body. It was established by WHO to deal with vaccine safety issues of potential global importance independently from WHO and with scientific rigour. GACVS held its 16th meeting in Geneva, Switzerland, on 12–13 June 2007 (2).

This section summarises HPV vaccine issues that were considered during the meeting, which are reproduced verbatim.

At the request of the WHO Immunization Strategic Advisory Group of Experts (SAGE), the committee reviewed the safety of human papillomavirus (HPV) vaccines.

The committee reviewed evidence of the safety of both the quadrivalent HPV vaccine (marketed as Gardasil®) and the bivalent HPV vaccine (marketed as Cervarix®). The review included data from pre-licensure randomized controlled trials and post-licensure surveillance reports from the two vaccine manufacturers, as well as from the European Medicines Agency, the United States Food and Drug Administration (FDA) and the United States Centers for Disease Control and Prevention (CDC).

The evidence on the safety of HPV vaccines is reassuring. The reviewed data covered local and systemic events in short-term and long-term events up to six years after vaccination, including pregnancy events. A common observation was the occurrence of injection site reaction and muscle pain. During campaigns to vaccinate adolescent vaccine campaigns, some mass sociogenic illnesses, such as post-vaccination dizziness and syncope, have been reported. These events have been prevented by observing adolescents for 15 minutes after vaccination and encouraging good hydration. No concerns with the safety profile were identified.

As with the introduction of any new vaccine, surveillance is important for identifying possible, rare, unexpected adverse effects, especially because good-quality information on the rates of a variety of diseases before widespread vaccine introduction is generally lacking in the target age group for HPV vaccination (i.e. 9–26 years). Also, careful surveillance for specific adverse effects during pregnancy will be important, because the target group includes females of reproductive age.

The committee was advised of studies that are planned, mostly in developed countries, to monitor adverse effects of HPV vaccination. The committee recommended that the protocols for these studies be made available to the public to encourage similar studies in other locations, including developing countries. National registers of all those vaccinated would allow adverse effects to be evaluated, particularly long-term events and the effectiveness of the HPV vaccine. Some countries are already planning to set up these registries, and other countries should be encouraged to do the same.
A1.3 Meeting of the Immunization Strategic Advisory Group of Experts, November 2007

SAGE met in November 2007 (3). This section summarises the main issues that were considered during the meeting, which are reproduced verbatim.

The World Health Organization’s (WHO’s) Immunization Strategic Advisory Group of Experts (SAGE) was provided with reports from the Global Advisory Committee on Vaccine Safety (GACVS), WHO’s Expert Committee on Biological Standardization, and the Advisory Committee of WHO’s Initiative for Vaccine Research. SAGE was also presented with a report of the September 2007 meeting of the human papillomavirus (HPV) Expert Advisory Group (HEAG). SAGE had requested that the group review the evidence to be included in a WHO position paper on HPV vaccines and identify outstanding questions on vaccine performance and delivery. The Chair summarized HEAG’s accomplishments.

There was a strong consensus that evidence is now sufficient to draft recommendations on the use of HPV vaccine for consideration by SAGE. WHO’s first consultations in the regions of the Americas, Europe and South-East Asia have shown there is great interest in HPV vaccines, but concerns about affordability, access and the development of delivery systems for pre-adolescents remain. The 60th World Health Assembly (WHA60), held in 2007, noted the Executive Board’s reports referred to in WHA60(12). These reports refer to the progress report, Cancer prevention and control (Resolution WHA58.22): cervical cancer, which recommended:

- integrating HPV vaccines into existing programmes for immunization, cancer control, and reproductive and adolescent health
- improving affordability and sustainable financing in the context of financing existing screening programmes
- using opportunities offered by HPV vaccination programmes to strengthen other pre-adolescent health interventions.

In June 2007, GACVS concluded that the safety data are reassuring. SAGE concluded that it should discuss HPV vaccines as soon as possible after receiving a detailed background paper.

References


Annex 2: Selected data relevant to decision-making about HPV vaccine introduction published or presented from January to the end of September 2008

This information supplements information to the end of 2007 that is summarized in Sections 1–6 of this background paper. For each topic, the related section in the background paper is noted.

Most 2008 data were reviewed at the July 2008 meeting of the Human Papillomavirus (HPV) Vaccine Advisory Committee (HVAC), World Health Organization (WHO), Geneva, Switzerland, or by individual HVAC members during July to September 2008. This summary does not list all data on HPV vaccines published or presented in 2008.

A2.1 Epidemiology of genital HPV and burden of HPV-related diseases (Section 1)

Two studies of human immunodeficiency virus (HIV)-infected females in Africa have shown that HPV 16 infection is the most common type in South Africa and one of the most common types in females aged 12–24 years in Uganda. The cumulative incidence of HPV 16 and HPV 18 in Uganda was estimated to be 50% by age 21 years (Denny et al., 2008; Banura et al., 2008).

One study suggests that uncircumcized men have an increased risk of acquiring infection with oncogenic HPV types (Hernandez et al., 2008).

The incidence of HPV-related vulvar, vaginal and anal cancer is rising in some regions and subpopulations (Giuliano et al., 2008).

HPV has been detected in breast milk of HPV-infected mothers. It is not known whether HPV vaccine antigens or antibodies are excreted in human milk (Sarkola et al., 2008).

A2.2 Limitations of current cervical cancer screening strategies (Section 2)

A global review of screening from population-based surveys found that, on average, 19% of women aged 25–64 years in 30 of the more affluent developing countries reported ever having had a Papanicolaou (Pap) test, compared with 63% in 27 developed countries. However, these estimates did not assess follow-up or treatment for abnormal Pap tests, which is a major problem in many developing countries. Screening rates were lowest in women who had low incomes or were older than 45 years. In many developing countries, most women had never had a pelvic examination, which is required for screening (Gakidou, Nordhagen & Obermeyer, 2008).

Recent studies in several developing countries have found that visual inspection of the cervix is a fairly sensitive cancer screening tool. Screen-and-treat strategies involving visual inspection and immediate cryotherapy for visible lesions under conditions of high quality assurance have significantly reduced cancer incidence and mortality in one trial in India. However, it is challenging to maintain the quality of visual inspection and
cryotherapy; this raises questions about long-term sustainability of these methods (Cuzick et al., 2008).

A rapid point-of-care HPV deoxyribonucleic acid (DNA) test that could be used for screening in low-resource settings was evaluated in rural China. This test had high sensitivity (90%) and specificity (84%) for detecting cervical intraepithelial neoplasia (CIN)2+, only slightly lower than the sensitivity and specificity of the most widely used, non-rapid and costly commercial HPV DNA test. Additional field evaluations are planned in India, Nicaragua and Uganda (Qiao et al., 2008).

A2.3 Clinical efficacy and immunogenicity of bivalent vaccine (Section 3)

A2.3.1 Efficacy against CIN2+ through 6.4 years after vaccination

Phase II trials extended to 6.4 years after the first dose evaluated 776 females aged 15–25 years who were naive to 14 oncogenic types before vaccination. Among those who received all three doses, efficacy against 12-month persistent infection was 100% (95% confidence interval (CI) 82% to 100%). Among those who received at least one dose, efficacy against HPV 16/18-related CIN2+ was 100% (95% CI 51.3% to 100%) and efficacy against CIN2+ due to any HPV type (including types other than 16 and 18) was 72% (95% CI 21% to 92%). Titres to HPV 16 and 18 at 6.4 years remained high, and were similar to levels at 24 months after vaccination. Antibody responses varied slightly when vaccines were given either slightly earlier or later than recommended (Harper et al., 2008; Wheeler et al., 2008; Laurence de Moerlooze, GSK, pers. comm., September 2008).

A2.3.2 Efficacy against infection with non-vaccine-related types

Phase II trials extended to 6.4 years after the first dose evaluated females aged 15–25 years who were naive to 14 oncogenic types before vaccination. Efficacy was moderate for preventing incident infection with HPV 45 (78%; 95% CI 39% to 93%) and HPV 31 (60%; 95% CI 21% to 81%) (Descamps et al., 2008).

In the total vaccinated cohort in the ongoing phase III trial, vaccine efficacy against infection lasting 6 months or more varied by HPV type: HPV 45 was 60% (97.9% CI 3% to 85%), HPV 31 was 36% (97.9% CI 0.5% to 60%) and HPV 52 was 32% (97.9% CI 4% to 52%). Efficacy against type-specific infection lasting 6 months or more was calculated for the subset of females seronegative to relevant types at baseline (indicating no past infection): 60% (97.9% CI 21% to 81%) against the combined endpoint of HPV 31/45 infection 41 (97.9% CI 16% to 58%) against the combined endpoint of infection with any of five common oncogenic types (31,33, 45, 52 and 58) (Jenkins et al., 2008).

A2.3.3 Immune response

Minor variations in timing of the second dose did not appreciably influence immune response (Laurence de Moerlooze, GSK, pers. comm., September 2008).

Immunobridging studies in girls aged 10–14 years, negative to HPV 16 and 18 at baseline, found that all girls seroconverted to HPV 16 and 18 at month 7; more than 99% were seropositive at month 24; geometric mean titres (GMTs) were four to eight-fold higher than those in vaccinated females aged 15–25 years; and no adverse vaccine-related reactions were reported (Pedersen et al., 2008).
Among 666 females aged 26–55 years in Germany and Poland, all vaccinees seroconverted to HPV 16 and 18. GMTs for HPV 16 and 18 were slightly lower than those among females aged 15–25 years, but remained well above levels induced by natural infection with these HPV types (Dubin, 2008).

Among 181 males aged 10–18 years who were seronegative to HPV before HPV vaccination, 100% seroconverted to HPV 16 and 18 at month 2 and remained seropositive at month 7. Seroconversion rates and GMTs were non-inferior to those of females aged 15–25 years enrolled in efficacy trials. The reactogenicity profile among males was similar to that among females (Lehtinen et al., 2008).

### A2.4 Clinical efficacy and immunogenicity of quadrivalent vaccine (Section 3)

#### A2.4.1 Efficacy against CIN2/3 and AIS

Combined data were analyzed from phase II and phase III trials of more than 20 000 females aged 15–26 years naive to the relevant HPV type, who were followed for a mean period of 44 months. Efficacy was very high efficacy against HPV 6/11/16/18-related CIN2/3 (98%; 95% CI 93% to 100%), adenocarcinoma in situ (AIS) (100%; 95% CI 31% to 100%), vulvar intraepithelial neoplasia (VIN) 2/3 or vaginal intraepithelial neoplasia (VaIN) 2/3 (100%, 95% CI 83% to 100%) and genital warts (99%; 95% CI 96% to 100%) (Haupt, 2008).

#### A2.4.2 Efficacy against CIN, VIN, VaIN and warts in mid-adult women

A phase III trial evaluated women aged 24–45 years who were HPV DNA negative to vaccine-related types (regardless of serostatus), and had no history of loop electrosurgical excision procedure (LEEP), cervical biopsy in the last 5 years, hysterectomy or genital warts. After 2.2 years, vaccine efficacy was 92% (95% CI 50% to 100%) against a combined endpoint of CIN (any grade) and external genital lesions (VIN, VaIN or warts) caused by HPV 6,11,16 or 18. Efficacy was also high against HPV 16/18-related cytology of atypical squamous cells of undetermined significance (ASCUS)\(^1\) or higher (94%; 95% CI 63% to 100%) or low-grade squamous intraepithelial lesion (LSIL) or higher (100%; 95% CI 61% to 100%). The safety profile in these women was similar to that of younger females (Haupt, 2008).

Among females without evidence of past infection by vaccine-related HPV types before vaccination, efficacy was also high against any grade of CIN (95%; 95% CI 92% to 97%) and external genital lesions (VIN, VaIN or warts) (96%; 95% CI 94% to 98%) caused by HPV 6,11,16 or 18. Estimated efficacy ranges were much broader among females who were seropositive but DNA negative for vaccine-related types before vaccination (indicating past, cleared infection): CIN of any grade (100%; 95% CI 29% to 100%) and external genital lesions (VIN, VaIN or warts) (100%; 95% CI 40% to 100%) caused by HPV 6,11,16 or 18. Efficacy against HPV 16/18-related CIN2/3 or AIS was 98% (95% CI 94% to 100%) (Haupt, 2008; Ferris(b), 2008).

#### A2.4.3 Efficacy against HPV 18 related CIN2/3 or AIS after one dose

Efficacy against HPV 18-related CIN2/3 or AIS was high among females aged 16–26 years who were naive to HPV 18 at baseline and received either three doses (100%;

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\(^1\) Category may also include those in which high-grade intraepithelial lesions (ASC-H) cannot be excluded.
A2.4.4 Efficacy against equivocal or low-grade abnormal cytology

Vaccination reduced the incidence of HPV 16/18-related cytology of ASCUS, LSIL or higher grade abnormality by 93% (95% CI 85–97%) among females aged 16–23 years who were negative to 14 oncogenic types and had normal cytology at baseline (Ault(b), 2008).

A2.4.5 Reductions in cervical procedures among vaccinees

Analysis of combined data from phase II and phase III trials found that among females aged 16–26 years who were naive to 14 oncogenic types before vaccination, vaccinees had fewer cervical procedures than placebo recipients: 19% fewer colposcopies, 22% fewer biopsies and 42% fewer definitive therapies. Among females in the intent-to-treat population who may have either received only one dose or had HPV infection or abnormal cytology at baseline, vaccinees had fewer procedures than placebo recipients: 12% fewer colposcopies, 13% fewer biopsies and 24% fewer definitive therapies (Gold, 2008).

A2.4.6 Immune response

Of 120 HIV-infected children aged 7–11 years in the United States, most of whom were using antiretroviral therapy, more than 99.5% seroconverted to HPV 16 and 18 (Weinberg, Song & Handelsman, 2008). GMTs for all four HPV types were lower for HIV-infected children than non-HIV-infected historical controls of similar age, but differences were statistically significant only for HPV 6 and 18. Plasma HIV ribonucleic acid (RNA) and CD4 cell per cent fluctuations were similar in vaccinees and placebo recipients. The profile of local adverse events in vaccinees did not differ by HIV infection status (Weinberg et al., 2008).

More than 95% of women age 24–45 years seroconverted to each vaccine-related HPV type. Compared to GMTs 7 months after the first dose for females aged 16–23 years, females aged 35–45 years had lower GMTs for all HPV types and females aged 24–34 years had lower GMTs for all types except HPV 16 (Ferris(a), 2008).

A2.5 Reactogenicity and safety of bivalent vaccine (Section 3)

A2.5.1 Safety data through 6.4 years after vaccination

In an extension of phase II trials through 6.4 years, recipients of this vaccine and the placebo aluminium hydroxide (Al(OH)₃) had similar rates of serious adverse events (< 11%) and new onset chronic disease (< 6%). Similarly, a pooled analysis of safety from phase II and phase III trials found no difference in the percentage of unsolicited medically significant adverse events, new onset autoimmune diseases or adverse pregnancy outcomes among females who were vaccinated with HPV vaccine, were vaccinated with hepatitis A vaccine or received Al(OH)₃ placebo.

Proportions of the study participants reporting miscarriage, abnormal infants or premature births were comparable between HPV vaccine recipients and the control group (Descamps et al., 2008).
A2.5.2 Safety data in girls and mid-adult women

Analysis of solicited local symptoms in girls aged 10–14 years found that more than 20% experienced pain, redness or swelling at the injection site. These were higher rates than in females vaccinated with hepatitis A vaccine. However, few symptoms were severe (Pedersen et al., 2007).

In a trial of women aged 26–55 years, HPV vaccine recipients were more likely to have injection-site symptoms than participants receiving hepatitis A vaccine, but most were mild. Rates of new onset chronic disease and serious adverse events were comparable, and were similar to those of females aged 15–25 years (Dubin, 2008).

A2.6 Reactogenicity and safety of quadrivalent vaccine (Section 3)

A2.6.1 Safety data from more than 20 000 trial participants

Pooled analyses of safety data from more than 20 000 participants of phase II and phase III studies found that vaccinees were significantly more likely to have injection site erythema, pain or swelling than subjects receiving placebos of either saline or adjuvant. There were no significant differences in incidence of reported systemic adverse events and new medical conditions, including autoimmune conditions. There were no vaccine-related deaths. Of the more than 4200 pregnancies, rates of pregnancy, spontaneous abortion or late fetal death, adverse pregnancy outcomes and infant congenital anomalies were comparable between vaccinees and placebo recipients (Garland, 2008; Reisinger, 2008).

A2.6.2 Passive postmarketing surveillance data

More postmarketing surveillance data are available for the quadrivalent vaccine than for the bivalent vaccine, because the quadrivalent vaccine has been marketed longer in most countries with established postmarketing surveillance systems. Also, the bivalent vaccine is not monitored by the Vaccine Adverse Event Reporting System (VAERS), because it is not licensed in the United States.

In passive, post-marketing surveillance in the United States to the end of June 2008, less than 6% of more than 7800 reports noted serious side effects – about half the average rate for vaccines monitored by this system. No deaths were attributed to vaccination, and the number of cases of Guillain-Barré syndrome were within the range expected by chance alone. Syncope was the most commonly reported symptom among more than 7500 reports. Syncope is noted among United States adolescents after vaccination, phlebotomy or other invasive procedures. Syncope was not more common in vaccinees than placebo recipients in trials and has not been observed in HPV vaccine demonstration projects in Peru and Uganda. Surveillance reports prompted the United States Advisory Committee on Immunization Practices (ACIP) to restate longstanding advice that persons be observed for 15 minutes after receiving any vaccine (Centers for Disease Control and Prevention, VAERS; Sutherland et al., 2008).

Rare cases of lymphadenopathies after HPV vaccination have been reported by VAERS and published case reports. This condition rarely occurs after use of many other non-HPV vaccines. One case of unilateral cervical and supraclavicular lymphadenopathy was attributed to vaccination (VAERS; Studdiford et al., 2008).

A few cases of brachial plexus injuries and neuritis have been reported by VAERS after distribution of more than 20 million doses of the quadrivalent vaccine. One case report of brachial plexus neuritis following quadrivalent vaccination has been published in Europe.
These conditions have rarely been reported after vaccination with other vaccines (VAERS; Debeer et al., 2008).

Other adverse reactions were experienced by five females aged 16–26 years who presented with either multifocal or atypical demyelinating syndromes within 21 days of receipt of quadrivalent vaccine. Four were ultimately diagnosed with multiple sclerosis, and three had neurological dysfunction before vaccination. Symptoms resolved either spontaneously or after steroid treatment in all five. The diagnosing physicians concluded that no definite conclusions could be made about the causes of these events because this age group has about twice the risk of developing multiple sclerosis than Australian females overall. Because some cases were atypical, physicians advised future studies to explore possible associations between multiple sclerosis and HPV vaccination (Sutton et al., 2008).

In Australia, seven confirmed cases of anaphylactic reactions were reported during passive postmarketing surveillance following school-based vaccination with the quadrivalent vaccine. Reported anaphylaxis rates were significantly higher than reported anaphylaxis rates for other vaccines delivered in schools. However, overall rates were low (2.6 per 100 000 doses), no cases involved anaphylactic shock and all were managed with no serious sequelae. These reports did not result in programme changes. In trials, anaphylactic reactions were not more common in vaccinees than placebo recipients (Brotherton et al., 2008).

A2.6.3 Pregnancy registry data

Of more than 1200 pregnant women who inadvertently received the quadrivalent HPV vaccine and were enrolled in a multinational pregnancy registry for the United States, Canada and France, congenital anomalies were rare and were consistent with those seen in the same maternal age range (Garland, 2008).

A2.7 Co-administration of HPV vaccines with other vaccines (Section 3)

Co-administration of the bivalent vaccine with a licensed diphtheria–tetanus–pertussis–inactivated poliomyelitis vaccine (Boostrix®–Polio, GlaxoSmithKline Inc. (GSK Biologicals)) to females aged 10–18 years resulted in more than 96% seroconversion to all antigens at month 1, including more than 99% seroconversion to HPV 16 and 18. Co-administration was well-tolerated and no vaccine-related serious adverse events were reported (Schwarz et al., 2008).

Co-administration of the quadrivalent vaccine with a diphtheria–tetanus–pertussis–poliomyelitis vaccine (REPEVAX™) in females and males aged 11–17 years did not interfere with the immune response of either vaccine. More than 99.7% of recipients seroconverted to all antigens. Co-administration was well-tolerated and no vaccine-related adverse events were reported (Protocol 024 Investigators, 2008).
A2.8 Impact, cost-effectiveness and cost of HPV vaccination in low and middle-income countries\(^2\) (Section 4)

A2.8.1 Model characteristics

Empirically-calibrated models have been developed to estimate the impact of HPV 16/18 vaccination\(^3\) in several middle and low-income countries including Argentina, Brazil, China, Chile, Colombia, India, Mexico, Peru, Thailand and Viet Nam. Simple population-based models have been used to estimate the impact of HPV 16/18 vaccination in 72 Global Alliance for Vaccines and Immunization (GAVI)-eligible countries (considered as a group and as individual countries, see below) and 33 Latin American and Caribbean countries (considered as a group and as individual countries, see below). Some of these simple models have been validated against more complex models. Modelling methods are consistent with WHO recommendations. These models assume vaccination of girls with three doses before age 13 and hypothetical costs per vaccinated female that include vaccine, wastage and delivery costs. Some of these hypothetical costs may be affordable for a given country but require vaccine prices that are about 100-fold lower than current costs in most high-income countries.

Several models have estimated the impact and cost-effectiveness of vaccination with or without screening methods suitable for low-income countries. It can be misleading to directly compare quantitative results of models due to differences in model type, assumptions and uncertainty in parameters. However, most models predict that in low and middle-income countries with either no or limited screening, vaccination alone with at least 70% coverage will avert more cases of cervical cancer than will screening alone for one to three times per lifetime. Vaccination plus screening two to three times per lifetime is more effective than vaccination alone, but more costly.

Less complex, less data-intensive population-level models that capture the main dimensions of more complex research models, use accessible epidemiological data from countries or regions, and spreadsheet-based analysis have been developed (Sue Goldie, Harvard University, pers. comm., July 2008). If standardized assumptions are used, these models project similar outcomes for adolescent vaccination to those of more complex models in several Latin American, Asian and GAVI-eligible countries. Countries can use such simple population-level models to estimate avertable disease burden and cost-effectiveness of vaccination strategies, and inform decisions around vaccine introduction (Lee & Irwin, 2008).

A2.8.2 Asia

In India, models predict that vaccination alone would reduce lifetime risk of cancer by about 44%, compared with only screening twice per lifetime, which would reduce risk by about 24%. Vaccinating 70% of five birth cohorts at age 12 would prevent more than 600 000 deaths and about 3 million disability-adjusted life years (DALYs) from cancer. At a cost per vaccinated girl of International (I)$ 50 (assuming a per-dose cost of I$ 12.25), such a 5-year programme would cost nearly I$2 billion (Diaz et al., 2008; Goldie(b) et al., 2008).

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\(^2\) Several studies about impact, cost-effectiveness and cost of vaccination programmes in high-income countries published in 2008 are not included here because they are less relevant to the WHO Immunization Strategic Advisory Group of Experts than studies from low- and middle-income countries.

\(^3\) The phrases “HPV 16/18 vaccination” and “HPV 16/18 vaccines” refer to either vaccine as both vaccines contain HPV 16 and HPV 18 antigens.
In China, models predict that vaccinating 70% of five birth cohorts at age 12 would prevent more than 100,000 deaths and the loss of more than 280,000 DALYs from cancer. At a cost per vaccinated girl of US$ 50 (assuming a per-dose cost of US$ 12.25), such a 5-year programme would cost about US$ 1.5 billion (Goldie(b) et al., 2008).

In Thailand, a cost–benefit analysis found that vaccination was not cost effective compared to the current strategy of screening women aged 35–60 years with cytology every 5 years. The analysis assumed that vaccination would cost purchasing power parity (PPP) \(^4\) US$ 1145.05 and that vaccine efficacy was 79% with lifelong protection. The incremental cost–effectiveness ratio of PPP US$ 24,343 per life year saved, compared to the alternative of screening women above 35-years-old, was not favourable compared to the GDP of PPP US$ 8138. The analysis concluded that the HPV vaccine should be introduced to the public health benefit package only when vaccination costs were reduced to the point where incremental cost–effectiveness ratios were below an agreed threshold and the programme was affordable. (International Health Policy Program Thailand and Health Intervention and Technology Assessment Program, 2008).

### A2.8.3 Latin America and the Caribbean

In most of 33 Latin American and Caribbean countries, population-based models predict that lifetime cancer risk would be reduced by about 40% (Goldie(a) et al., 2008; Lee & Irwin, 2008). However, the size of the risk would depend on underlying HPV incidence, proportion of disease attributable to HPV 16/18 and population age structure. Several outcomes were projected by modelling.

- More than 1 million cases of cervical cancer would be prevented by vaccinating 10 consecutive birth cohorts of young adolescent girls. Most preventable deaths would occur in countries with moderate cancer incidence and large populations.
- At a cost per vaccinated girl of US$ 25 (US$ 5 per dose), the cost of vaccination per DALY saved is less than US$ 400. At a cost per vaccinated girl of US$ 10 (US$ 2 per dose), vaccination is cost-saving in 26 of 33 countries. This compares with a cost of US$ 300–11,700 per DALY saved for rotavirus in eight Latin American countries and US$ 110 per DALY saved for pneumococcal vaccination in GAVI-eligible countries.
- Seventy percent vaccination coverage of five birth cohorts would avert about 300,000 deaths. Such a 5-year programme would cost about US$ 811 million assuming a per-dose vaccine cost of US$ 12.25 or US$ 360 million assuming a cost of US$ 5 per dose. A hypothetical ten-year vaccination campaign in these 33 countries would prevent an estimated 27 cases of cervical cancer and 16 deaths per 1000 vaccinated girls. This projection compares to 3–4 deaths per 1000 children vaccinated for rotavirus and 6.8 deaths per 1000 children vaccinated with the pneumococcal conjugate vaccine.

In Mexico, an analysis using a public-sector perspective concluded that the cost-effectiveness of vaccination (at 181 pesos \(\sim\) US$ 17 per dose) was equal to that of screening with cytology and commercial HPV DNA tests. It concluded that vaccine introduction should be considered at such prices (Gutierrez-Delgado et al., 2008).

In Brazil, models project that vaccination alone would reduce lifetime risk of cervical cancer by 36–53% compared with screening alone twice per lifetime with HPV tests.

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\(^4\) PPP = purchasing power parity, a concept underlying the international dollar (IS), a hypothetical currency unit that assigns the same purchasing power that a US dollar had in the United States within a given period.
which would reduce risk of cervical cancer by 12–22% depending on the screening test. At a cost per vaccinated girl of IS 25, vaccination alone would be a cost saving; at a cost of IS 50, vaccination would cost IS 300 per year of life saved (YLS), considered very cost-effective using the threshold of gross domestic product (GDP). Screening vaccinated girls later in life would be more costly than vaccination alone, but more effective. Vaccination plus three lifetime screenings would reduce lifetime cancer risk by 47–67%, and cost IS 700 per DALY saved assuming a cost per vaccinated girl of IS 25 (Lee & Irwin, 2008).

A2.8.4 GAVI-eligible countries

A ten-year vaccination programme was modelled in 72 GAVI-eligible countries (Goldie(c) et al., 2008). Several outcomes were projected.

- An average of 70% coverage would avert 2.5 million cervical cancer cases and 1.9 million deaths, or about 14 deaths per 1000 vaccinated girls. Such a programme would also prevent the loss of a mother from cervical cancer by more than 1.5 million children under 18 years and billions of US dollars of lost productivity costs.

- Vaccination would avert more deaths in countries with moderate cervical cancer incidence and large populations than in countries with higher cervical cancer incidence. More than half of the averted cases and deaths would occur in the WHO South-East Asia Region and more than a quarter would be averted in the WHO African Region, partly due to the large populations of some countries in these regions.

- Vaccination at a cost per vaccinated girl of IS 10 for three doses, waste and programme costs would be less than IS 250 per DALY saved in most GAVI-eligible countries. In all 36 GAVI-eligible countries in Africa, vaccination would be either cost-saving or cost less than IS 250 per DALY saved at a cost per vaccinated girl of IS 5. At a cost per vaccinated girl of IS 10, the cost–effectiveness ratio of adolescent vaccination would be less than the GDP per capita for all 36 of these countries, a value considered very cost-effective.

- At a cost per vaccinated girl of IS 10 (a per-dose cost of IS 2), a ten-year programme that achieved 70% coverage would cost nearly US$ 1 billion.

A2.9 HPV vaccine financing (Section 5)

In June 2008, GAVI announced that it would consider HPV vaccines in its new investment strategy. This would allow GAVI to subsidize HPV vaccines in GAVI-eligible countries if WHO recommended HPV vaccines for use in national immunization programmes, WHO prequalified HPV vaccines for United Nations (UN) procurement, and GAVI secured donor funds. GAVI’s decision was informed by the WHO Vaccine-Preventable Diseases Categorization Project, which ranked several diseases that could be prevented by either new or forthcoming vaccines according to their health, economic and social burdens. Cervical cancer, along with several other diseases were ranked as “high priorities” compared with malaria and pneumococcal disease that were ranked as “very high priorities” (GAVI Investment Strategy; Vaccine-Preventable Disease Categorization Project).

In April 2008, WHO convened agencies that may be involved in HPV vaccine procurement, purchase or supply forecasting for UN agencies in the future: GAVI, United Nations Children’s Fund (UNICEF), Pan American Health Organization (PAHO), United Nations Population Fund (UNFPA), Program for Appropriate Technology in Health (PATH) and International AIDS Vaccine Initiative (IAVI). Participants at this meeting
recommended continuing interagency collaboration, extending decision-making and HPV vaccine programme costing tools to low and middle-income countries, forecasting vaccine demand in the 10 largest potential vaccine adopters, and assessing industry production capacity for low and middle-income country markets (Schmitt, 2008). Various mechanisms now being used to support introduction of other new vaccines are being explored as possible mechanisms for HPV vaccines in low and middle-income countries (Andrus et al., 2008).

A2.10 HPV vaccine demand, supply and prices (Section 5)

The vaccine target population in developing countries (52.5 million) far exceeds the target population in industrialized countries (6.5 million). The current strong demand for HPV vaccines in high-income countries, despite high price, may affect the supply and price in low and middle-income countries. Middle-income countries that are not GAVI-eligible may be among the first to consider vaccine purchase if prices are affordable and financing is sustainable. Global demand for vaccines could be strongly influenced by demand by countries with large populations such as India. Accurate forecasting of potential introduction dates for these countries is needed. Marketing and direct-to-consumer advertising of HPV vaccines, unlike many other vaccines, is widespread in many countries and may influence private and public-sector demand (Schmitt, 2008).

Analysis by PATH and Applied Strategies of projected vaccine demand through 2025 suggests that both GSK and Merck have bulk vaccine capacities that could supply a large portion of global demand. However, the manufacturers may need to increase capacity for vial filling and finishing for product presentations that are acceptable to developing country markets (Schmitt, 2008).

Merck and GSK are expected to be the only suppliers of a WHO-prequalified vaccine until at least 2015. No major competition in vaccine prices has been noted in private sector markets. Private market price competition is unlikely in the short term due to strong demand and early phase of introduction. Royalties and patent agreements between the manufacturers may also influence price competition (Schmitt, 2008).

Both manufacturers have pledged preferential pricing for public sector markets based on a country’s ability to pay. For example, Mexico has reported starting negotiations at prices that are less than half that of private sector prices in industrialized countries (Martinez-Montanez OG, Uribe Zuniga PU, Lazcano Ponce E). Merck has indicated that a “non-profit” price for lowest-income countries could be within the range of US$ 5–15 per dose (Schmitt, 2008).

WHO is expected to complete a review the prequalification dossiers for each HPV vaccine during 2009. Prequalification will consider only vials with vial monitors, because the glass prefilled syringes without autodisable features marketed in developed countries are too costly and are inappropriate for public-sector immunization programmes in low-income countries. WHO is currently reviewing proposals for both vaccines in one-dose vials. Multiple-dose vials may be delayed because neither marketed HPV vaccine contains preservatives (Schmitt, 2008).

A2.11 HPV vaccine acceptability and delivery (Section 5)

Early studies in low, middle and high-income countries indicate that HPV vaccines are highly acceptable to providers, parents and adolescents. Acceptability is increased if groups are first educated about safety and efficacy, are informed that vaccines and
vaccination are endorsed by trusted health authorities, and are provided with messages that primarily stress that vaccines prevent cancer (as opposed to messages that primarily stress that vaccines prevent a common STI) (Brabin et al., 2008; Lee & Irwin, 2008; Lenselink et al., 2008; Wong, 2008).

Campaigns that have raised public awareness about cervical cancer and have sensitized communities about vaccine benefits have increased vaccine uptake in low, middle and high-income countries (Garland et al., 2008; Lee & Irwin, 2008).

### A2.11.1 High-income countries

The first school-based HPV vaccine delivery programmes in high-income countries, all of which required written parental consent, have achieved fairly high coverage: in several Australian states, nearly 80% completed three doses; in four Canadian provinces, 50–85% completed three doses; and in a demonstration project in Manchester, United Kingdom, 71% received the first dose and 69% the second. These programmes have used various methods to educate youth and parents, obtain consent and exclude girls who may be pregnant. The main reasons that parents refused were lack of information about the vaccine, including long-term safety. Maintaining vaccination schedules has also been challenging (Brabin et al., 2008; Shefer et al., 2008; M Appleton, Canadian Coalition for Immunization Awareness and Promotion, pers. comm., June 2008).

### A2.11.2 Low and middle-income countries

Formative research and demonstration projects on HPV vaccine delivery have found that, in India, Peru, Uganda and Viet Nam, youth, parents, decision-makers and community members had positive attitudes about HPV vaccination after information was provided. Some concerns were not specific to HPV vaccines (injection-site pain, long-term effectiveness and safety) and some concerns were specific to HPV vaccines (cost and belief that request for informed consent implied vaccine was experimental). Few people expressed concerns that HPV vaccines would impair fertility or lead to sexual disinhibition.

In all four countries schools could be used to reach the primary target group but would require creating new linkages with the education sector, strengthening the peripheral cold-chain capacity, training health workers, creating new youth and parent education materials, sensitizing the community and detailed planning with schools. Vaccination was best directed by Expanded Programme on Immunization (EPI) programmes, but required linkages with other governmental and non-governmental stakeholders in health and education, from central to peripheral levels.

In rural and urban Peru, the first year of vaccination with the licensed quadrivalent vaccine in nearly 100 schools achieved 57–61% coverage of all three doses. A detailed, active parental consent process led to some refusals when parents misunderstood that the consent request implied that the vaccine was experimental.

Ninety-five per cent of girls who received the first dose completed all three doses. Active follow-up to ensure series completion did not substantially increase three-dose coverage rates. The second year of vaccination that scaled up to more than 750 schools and used more streamlined, standard parental approval methods achieved coverage of 83% for the first dose. Wastage and cold-chain problems were rare.

In one Ugandan district with 64% three-dose diphtheria–polio–tetanus vaccine coverage in 2005, coverage of the first HPV vaccine dose was an average of 92% in more than 100 schools in participating communities. The programme had strong support from
leaders and communities, required 4–6 months of community sensitization and detailed planning and EPI leadership that collaborated with other health and education sectors.

Data on vaccination programme costs are being collected in Peru, Uganda and other countries to determine if they are within the range assumed by cost-effectiveness models. Some models have assumed programme costs that are up to US$ 2 per targeted person. These costs account for about 20% of total vaccination costs, and are higher than programme costs of EPI vaccines.

WHO is developing a protocol to evaluate HPV vaccine uptake when delivered alone compared with vaccine uptake when delivered with other evidence-based interventions for young adolescent females. The protocol will assess the potential to integrate HPV vaccines with other age-appropriate health services (Lee & Irwin, 2008).

A2.12 Monitoring the impact of HPV vaccination programmes (Section 5)

The WHO HPV Laboratory Network was created to support laboratory-based monitoring of the impact of HPV vaccination programmes. As of January 2008, two global reference laboratories and seven regional reference laboratories have been established. The network will provide expertise on sampling and testing of sentinel or population-based studies of HPV prevalence using either nucleic acid testing or serology. To monitor programme impact using large numbers of specimens in an internationally comparable manner it will be necessary to standardize and validate sampling methods for HPV DNA testing; improve high-throughput sample extraction, HPV detection and HPV typing; and assess reproducibility of HPV assays (WHO HPV Laboratory Network, 2008).

Monitoring aims to assess duration of vaccine protection and population-level impact of vaccination on HPV prevalence, precancerous cervical lesions and cancer; HPV type replacement; and herd immunity. In the five Nordic countries, monitoring will rely on linkages of recently established HPV vaccination registries and cancer, pathology and biobank registries. Sweden also has a pilot project in STI clinics to assess the early impact of vaccination with the quadrivalent vaccine on genital wart incidence (Lee & Irwin, 2008).

A2.13 Policies and opinions about HPV vaccines throughout the world (Section 6)

A2.13.1 HPV vaccine licensure

As of September 2008, each HPV vaccine was licensed for prevention of cervical precancers and cancer in at least one country in each WHO Region, the bivalent vaccine in 71 countries and the quadrivalent in 105 countries. At least one country, the United States, has specifically licensed the quadrivalent vaccine for prevention of vaginal and vulvar precancers and cancer. Due to importation, distribution and regulatory requirements, as well as price negotiations, a licensed vaccine may not be marketed in a given country. Several countries have now licensed both vaccines and this may allow product choice when procuring vaccines for national immunization programmes (United States Food and Drug Administration, 2008; Robin Biellik, PATH, pers. comm., July 2008).

Both vaccines are licensed for use in females; the lower and upper age limits vary by country. Some regulatory authorities have registered the quadrivalent vaccine for use in “adolescents” (gender not specified) or specifically for males. GSK has not sought registration of the bivalent vaccine for males.
Registration trials of both vaccines have been completed in India, a country requirement before vaccine licensure (V Tsu, PATH, pers. comm., 2008). India contributes a large proportion of global cervical cancer cases, including about half of cases in GAVI-eligible countries.

A2.13.2 Recommendations to include HPV vaccines in national immunization programmes

By September 2008, vaccines were recommended for use in national immunization programmes in more than 15 high-income countries and at least one middle-income country, Mexico. All recommendations advised vaccinating in girls of various ages; some also recommended catch-up vaccination of older females (Koulova et al., 2008).

Only Austria recommended use of the quadrivalent vaccine for use in boys for preventing warts, but it has not allocated public-sector funding for vaccinating males.

The European Centre for Disease Prevention and Control issued guidance on use of HPV vaccines to guide HPV vaccine introduction in the European Union, which includes some middle-income countries (Hamers, 2008).

The Thailand Ministry of Public Health decided not to recommend a national programme of HPV vaccination in August 2008, partly because a national cost–utility analysis predicted that vaccination would not be cost-effective compared to the current strategy of cytology screening every 5 years of women aged 35–60 years. Section A2.9 provides more details. (International Health Policy Program Thailand and Health Intervention and Technology Assessment Program, 2008).

The WHO HPV Vaccine Advisory Group unanimously concluded in July 2008 that evidence was sufficient for the WHO Immunization Strategic Advisory Group (SAGE) to discuss recommendations about use of HPV vaccine in national immunization programmes.

A2.13.3 Endorsement of HPV vaccines as a cancer prevention option by WHO regions

As of September 2008, HPV vaccination was specifically endorsed as one effective option for cervical cancer prevention by consultations of all six WHO regions during 2007–2008 (See Section 6 for summaries of all regional consultations and WHO AFRO, 2008). In September 2008, the WHO Regional Office for Africa (AFRO) Regional Consultation on Cervical Cancer Prevention convened representatives from immunization, cancer control and reproductive health programmes from 22 countries. Ninety-five per cent of women in sub-Saharan Africa have never had a Pap test and mortality rates from cervical cancer are rising. The consultation recognized that a combination of vaccination, screening and treatment can control cervical cancer in the region, but acknowledged that current high vaccine cost and the lack of established systems that either routinely vaccinate young adolescents or monitor HPV vaccination programmes in many countries pose major challenges to vaccine introduction. Delegates recommended that WHO, UNFPA, UNICEF, GAVI, PATH and other organizations should continue discussions with industry to promote HPV vaccine prices that are affordable to public-sector programmes in Africa. They also recommended that WHO-HQ and WHO-AFRO provide guidelines for evidence-based decision-making about vaccine introduction, write operational guidelines for national programmes introducing HPV vaccines and provide technical support to monitor the safety and impact of HPV vaccines in Africa (WHO AFRO, 2008).
A2.13.4 Opinions about HPV vaccines at WHO and other international organizations

WHO and the International Union Against Cancer have endorsed HPV vaccines as one effective cancer prevention option (WHO, Cancer Action Plan, 2008; (International Union Against Cancer, 2008). Also, the 2008 World Health Assembly approved the WHO Executive Board Resolution to facilitate research and development of safe and effective vaccines against poverty-related and neglected diseases of which cervical cancer is an example (WHO Executive Board, 2008). The Assembly also supported the WHO report noncommunicable disease prevention that called for studying approaches to increase access to HPV vaccines (WHO, Prevention and Control of Noncommunicable Diseases, 2008).

A policy analysis concluded that cervical cancer prevention programmes, including those that include HPV vaccination, would advance several Millennium Development Goals (Wittet & Tsu, 2008).

By September 2008, Cervical Cancer Action, a global coalition to stop cervical cancer, received more than 100 official statements, editorials and letters from government and health officials, health professionals and consultations that support cervical cancer prevention, including HPV vaccination. More than 1200 people have signed a Global Call to Action for Cervical Cancer Prevention that includes HPV vaccination as one strategy (Cervical Cancer Action; Lee & Irwin, 2008).

In June 2008, the HPV Vaccine Global Community of Practice, an independent, web-based knowledge gateway began to gather opinions and experience about HPV vaccines throughout the world. The first online videoconference and discussions included more than 400 members from 80 countries, revealed strong interest in HPV vaccine but raised concerns about the current high price of HPV vaccines and questions about how to most effectively integrate screening and vaccination programmes (HPV Vaccine Global Community of Practice; Lee & Irwin, 2008).

Reference list


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WHO AFRO. Recommendations from the Ouagadougou Regional Consultative Meeting on Cervical Cancer Prevention and Control, September 2008 (website pending).


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<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tbody>
<tr>
<td>ASCUS</td>
<td>Atypical squamous cells of undetermined significance (category may also include those in which high-grade intraepithelial lesions (ASC-H) cannot be excluded).</td>
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<tr>
<td>Boostrix&lt;sup&gt;R&lt;/sup&gt; – Polio</td>
<td>GlaxoSmithKline Biological’s licensed diphtheria, tetanus, pertussis, inactivated poliomyelitis vaccine.</td>
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<tr>
<td>Cervarix®</td>
<td>GlaxoSmithKline Inc.’s HPV 16/18 prophylactic vaccine-like particle-based vaccine.</td>
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<tr>
<td>Cold chain</td>
<td>A temperature-controlled supply chain (e.g. for vaccines, sera and medications).</td>
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<tr>
<td>DTP, dTaP, dTpa, DPT3</td>
<td>Types of diphtheria/tetanus/pertussis vaccines.</td>
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<tr>
<td>Gardasil®</td>
<td>Merck &amp; Co.’s HPV 6/11/16/18 prophylactic vaccine-like particle-based vaccine (also marketed as Silgard®).</td>
</tr>
<tr>
<td>Herd immunity</td>
<td>Indirect protection of non-vaccinated persons resulting from reduced pathogen transmission in the community.</td>
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<td>High-risk HPV</td>
<td>Human papillomavirus types with high oncogenic potential.</td>
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<tr>
<td>Immunobridging study</td>
<td>A study that compares the immune response in a group for which data on vaccine efficacy on disease endpoints are not available to the immune response in another group for which such data are available.</td>
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<tr>
<td>REPEVAX™</td>
<td>Sanofi Pasteur MSD’s diphtheria, tetanus, pertussis and poliomyelitis vaccine.</td>
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<tr>
<td>Silgard®</td>
<td>Merck &amp; Co.’s HPV 6/11/16/18 prophylactic vaccine-like particle-based vaccine (also marketed as Gardasil®).</td>
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<tr>
<td>TdaP</td>
<td>Type of tetanus/diphtheria/pertussis vaccine.</td>
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<tr>
<td>Type replacement</td>
<td>Increases in the incidence or prevalence of types of a pathogen that are not targeted by vaccines against other types of that pathogen.</td>
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<td>Types of HPV for which type-specific virus-like particles serve as vaccine antigens.</td>
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