WORLD HEALTH ORGANIZATION
EUROPE

Preparing for the Introduction of HPV Vaccine in the WHO European Region

Strategy paper

Vaccine-Preventable Diseases and Immunization Programme

ABSTRACT

HPV is a common infection: over three quarters of sexually active women are estimated to be infected at least once in their lifetimes. Persistent infection with oncogenic HPV types can cause cervical cancer in women and anogenital cancers in both sexes. HPV vaccines have been developed and are being licensed in many countries in the WHO European Region. Policy-makers and programme managers need to take a position on the target groups for vaccination and if and how HPV vaccines will be integrated into existing or new screening programmes in order to guarantee the maximum impact. This document sets out the strategic principles for decision-making and can be used to facilitate the process.

Keywords

PAPILLOMAVIRUS INFECTIONS – prevention and control
PAPILLOMAVIRUS VACCINES – therapeutic use
UTERINE CERVICAL NEOPLASMS – prevention and control
HEALTH POLICY
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Glossary

AIS	adenocarcinoma in situ
ASR	age-standardized rate
CI	confidence interval
CIN	cervical intraepithelial neoplasia
DNA	deoxyribonucleic acid
EMEA	European Medicines Agency
EU	European Union
GAVI	Global Alliance for Vaccines and Immunization
HBV	hepatitis B virus
HPV	human papillomavirus
STI	sexually transmitted infections
UNFPA	United Nations Population Fund
VIA	visual inspection with acetic acid
WHO	World Health Organization

Preface

Purpose

The purpose of this strategy paper is to outline regional strategies for the introduction of HPV vaccines and to provide the Member States of the WHO European Region with the framework and guidelines for evidence-based decision-making.

The paper has been developed by the Vaccine-preventable Diseases and Immunization Programme of the WHO Regional Office for Europe. The objectives of this Programme are to:

- develop strategies and policies for maximizing the use and delivery of vaccines of public health importance;
- support countries in (i) acquiring the necessary skills, competence and infrastructure to implement these policies and strategies through effective planning and management, and (ii) strengthening health and immunization systems and financial sustainability;
- achieve regional and global goals for the control, elimination and eradication of disease.

Background

This strategy paper builds on policy and guidance notes as well as on technical information provided by WHO on the introduction of HPV vaccines.[1] It adapts the current evidence available to the Regional Office, taking into account the diversity of the Region in terms of economic capacity, existing screening programmes and structures, and licensing of the vaccine. The HPV vaccines are in the process of being licensed in many countries in the Region and policy-makers and programme managers are urged to take a position on who should be vaccinated and if and how HPV vaccines will be integrated into existing or new screening programmes in order to guarantee the maximum impact. This paper sets out the strategic principles for decision-making and can be used to facilitate the process.

Target audience

This paper is intended for:

- national immunization programme managers and decision-makers in ministries of health and other relevant ministries and government bodies;
- experts involved in decision-making about the introduction of HPV vaccines in the country such as oncologists, gynaecologists, paediatricians, epidemiologists, infectious disease specialists, specialists in adolescent health, primary practitioners and health economists;

[1] These include: *Preparing for the introduction of HPV vaccines; policy and programme guidance for countries (1)*; *Human papillomavirus and HPV vaccines: technical information for policy-makers and health professionals (2)*; and *Vaccine introduction guidelines (3).*

- technical officers of international and bilateral partner and donor organizations and stakeholders such as WHO, the United Nations Children's Organization, the United Nations Population Fund (UNFPA) and the World Bank;
- other interested institutions, organizations and persons.

It will also be useful for public and private sector health systems and health insurance structures where consideration is being given to the inclusion of HPV vaccines in official formularies or otherwise covering the costs.

Executive summary

Human papillomavirus infection and related diseases

Human papillomavirus (HPV) is a very common infection and more than three quarters of sexually active women are estimated to be infected at least once in their lifetimes. The risk of acquiring HPV infection is highest soon after sexual activity begins. Most of these infections are self-limiting and harmless, but persistent infection with oncogenic HPV types can cause cervical cancer in women. HPV also causes other anogenital cancers (e.g. of the vagina, vulva and penis), head and neck cancers and genital warts in both men and women.

Prevention of cervical cancer

Well-organized cervical cancer screening programmes that achieve high coverage and include effective follow-up and treatment of women with abnormal cytology have been proven to reduce cervical cancer incidence by over 80%. Recently, new options for the control of cervical cancer through primary prevention have become available in the form of prophylactic vaccines against the oncogenic HPV types 16 and 18. Worldwide, HPV 16 and/or 18 are found in nearly 70% of invasive cervical cancers and in approximately 30% of vulvo-vaginal cancers.

With or without vaccines, cervical cancer screening through various methods will continue to be necessary for the foreseeable future and screening recommendations do not need to be changed at the moment.

Current situation in the European Region

Cervical cancer continues to be a public health problem in the European Region, with an estimated 60 000 new cases per year. Although the incidence of cervical cancer and its related mortality have declined in many countries, dramatic differences exist within the Region, with mortality rates in eastern Europe being on average twice as high as rates in western Europe. The lowest incidence is observed in countries such as Finland, where organized cytology-based screening and treatment programmes cover a high proportion of the population, targeting women aged 25–65 years and using five-year screening intervals. But in many European countries there are no organized programmes, or the organized programmes that exist only have low coverage, or screening is carried out opportunistically when women come in for other health care services.

In 2006, the first prophylactic vaccine against HPV 6, 11, 16 and 18 was approved by the European Medicines Agency (EMEA) (Gardasil®, Sanofi Pasteur MSD). By October 2007, this vaccine had been licensed in 38 countries of the Region. A second, bivalent vaccine (Cervarix®, GlaxoSmithKline Biologicals) received a marketing authorization from EMEA in September 2007 and had already licensed in 30 countries in the Region by October 2007. This vaccine protects against HPV 16 and 18.

Technical information about HPV vaccines

Both vaccines are prepared from virus-like particles (VLP) and produced by recombinant technology and are non-infectious. They require three doses and produce a very high immune response which lasts for at least five years after vaccination (longer follow-up data are not available yet). There is some evidence of cross-protection against oncogenic HPV types 31 and 45, which are closely related to types 16 and 18.

Efficacy data are available for both vaccines from phase 2 and phase 3 trials. In these studies, which included women aged 15–26 years, the two prophylactic vaccines have demonstrated at least 90% efficacy in the prevention of persistent HPV 16 and 18 infection and related cervical intraepithelial neoplasia (CIN) grades 2 and 3 in women with no evidence of previous exposure to vaccine-specific types. Follow-up data are available for up to five years. Gardasil® has also demonstrated protection against genital lesions related to HPV 6, 11, 16 and 18, including genital warts and vulvar and vaginal neoplasia. Overall, both vaccines appear to be generally safe and well-tolerated. Bridging studies have demonstrated that the immunogenicity of girls from the age of 9 or 10 years is comparable to or higher than that in the older girls and women who participated in the trials.

As current HPV vaccines are prophylactic vaccines, the greatest impact will be seen by vaccinating girls before they are exposed to HPV, i.e. before they are sexually active. The primary target population for vaccination is, therefore, older girls and young adolescents. Catch-up programmes for older adolescents and young women (for example, up to the age of 26 years) are less cost-effective because in most countries a substantial proportion of women will have already been exposed to HPV, but they could shorten the time before a reduction in precancerous lesions and cancer will be seen in a population. Models suggest that vaccinating boys does not seem to be a cost-effective intervention for the prevention of cervical cancer in women if high coverage of girls is achieved, but may be beneficial to avoid misperceptions and rumours about the vaccine if it were only delivered to girls.

Deciding on the introduction of HPV vaccine at country level

In nearly all upper- and middle-income countries, at least one of the HPV vaccines has been licensed and is being marketed. Key questions remain about how HPV vaccines will influence existing screening programmes, their cost-effectiveness with current or modified screening strategies, methods of reaching adolescent target populations, and how they will compete for funding and priority with other recently introduced infant and childhood vaccines such as rotavirus vaccine.

The overall impact of the HPV vaccines will depend upon their delivery to those populations most in need of them. It is in resource-poor countries, where cervical cancer screening programmes are poor or absent and cervical cancer incidence and mortality highest, that women are in greatest need of primary prevention through HPV vaccines. Yet the high cost of HPV vaccines is an important barrier to widespread access, and the additional cost of including HPV vaccines in national immunization programmes will be important in the decision-making process, although this should not be the sole criterion. The expected costs and benefits will also have to be considered against other (i.e. not vaccine-preventable) health interventions. Some of the major issues to consider will be whether cervical cancer prevention is high enough on the list

of health concerns, how cervical cancer control is to be achieved and what the expected impact of HPV vaccines on the burden of cervical cancer will be.

HPV vaccines raise diverse issues in cancer prevention, in sexual, reproductive, child and adolescent health and in immunizations, thus forcing decision-makers to weigh the benefits and costs of available interventions to prevent HPV-related diseases. It is, therefore, important to include a broad range of experts in the decision-making process. These may include gynaecologists, oncologists, paediatricians, epidemiologists, infectious disease specialists, virologists, primary practitioners, experts in immunization, sexually transmitted diseases (STI), cancer screening, adolescent health and school health, as well as health economists.

A key question is how a strategy of primary prevention through vaccination interacts with a strategy of secondary prevention through screening. Cost-effectiveness studies that take into account national data will help to define the best strategy. In countries with widespread effective cytological screening programmes (such as Denmark, Finland, Iceland, the Netherlands and the United Kingdom), the benefit of adding vaccines to screening programmes will be limited in terms of reducing mortality related to cervical cancer. In these countries, the expected benefits of the vaccine include a reduction in the incidence of cytological abnormalities due to HPV 6, 11, 16 and18. This would result in fewer follow-up examinations, less anxiety for the patients and fewer treatment procedures to be performed, and substantially reduced costs related to follow-up, diagnosis and treatment of cytological abnormalities. Moreover, vaccines will reduce morbidity due to other HPV-induced diseases, such as genital warts (for the quadrivalent vaccine only).

In countries where there are unorganized but functional screening programmes (e.g. Belgium, France and Luxembourg), the introduction of HPV vaccines may provide an opportunity to restructure the target groups for screening and the intervals to make them clinically and economically more effective. The organization of the screening programme is key, with a clear definition of the target population, the introduction of a call/recall system to attain high coverage, quality control and the setting-up of monitoring and evaluation systems. At population level, the benefits and cost-effectiveness of the vaccines will be relatively greater than in countries with organized screening and high coverage, because the current screening programmes are less efficient. Moreover, disparities in cervical cancer mortality could be reduced substantially if widespread vaccination coverage could be achieved in these countries.

In countries with limited or no cytology screening (such as Armenia, Georgia and Kazakhstan), the widespread introduction of HPV vaccine is expected to substantially reduce cervical cancer incidence and mortality compared with the current situation of no screening and no vaccination. The benefits of vaccination will not, however, be observed for decades after vaccination owing to the typically long latent period between initial HPV infection and peak incidence of cervical cancer. In these countries, complementing HPV vaccination with simple non-cytological screening methods, such as visual inspection with acetic acid (VIA) or HPV deoxyribonucleic acid (DNA) testing, could accelerate a reduction in the incidence of cervical cancer in both the non-vaccinated and vaccinated populations.

Funding sources for HPV vaccines will depend on the modalities used to introduce the vaccines into each country. In almost all countries, funding for vaccination comes from both public and private sectors but the degree and mechanisms are very different from one country to another. Low-income countries in the Region may benefit from tiered pricing of the vaccine, and

discussions are under way to obtain access to international financing mechanisms such as the Global Alliance for Vaccines and Immunizations.

Age is the most important factor in defining the female target population for HPV vaccination. This should be based on national data on the age of beginning sexual behaviour and the feasibility of delivering vaccines to children of various ages through schools, health systems or campaigns. Delivery may be enhanced by capitalizing on high rates of school attendance of pre-adolescents and young adolescent girls and on existing school-based vaccination programmes or school-age health campaigns. Some countries may further consider “catch-up” vaccination of older adolescent girls and young women. It is important to educate and train both health providers and the population to ensure that the scope of the HPV vaccines is correctly understood. The critical messages are that HPV vaccines do not protect against all oncogenic types of HPV and have not demonstrated any therapeutic efficacy against disease due to HPV infection present before vaccination. Thus, continued screening will be necessary for optimal cancer prevention.

Monitoring and evaluation of the impact of the vaccines

The impact of immunization with HPV vaccines must be monitored and evaluated through various methods such as type-specific HPV surveillance and, in the longer term, through surveillance of precancerous lesions or cervical cancer morbidity and mortality reported to cancer registries. To assess vaccination coverage in the target population, existing routine methods for monitoring coverage will need to be enhanced to include HPV vaccine. Methods to assess the impact of vaccines on clinically relevant disease endpoints might include surveillance for vaccine-related HPV infection and precancerous lesions or cancers through established or newly developed laboratories or cytology or cancer registries.

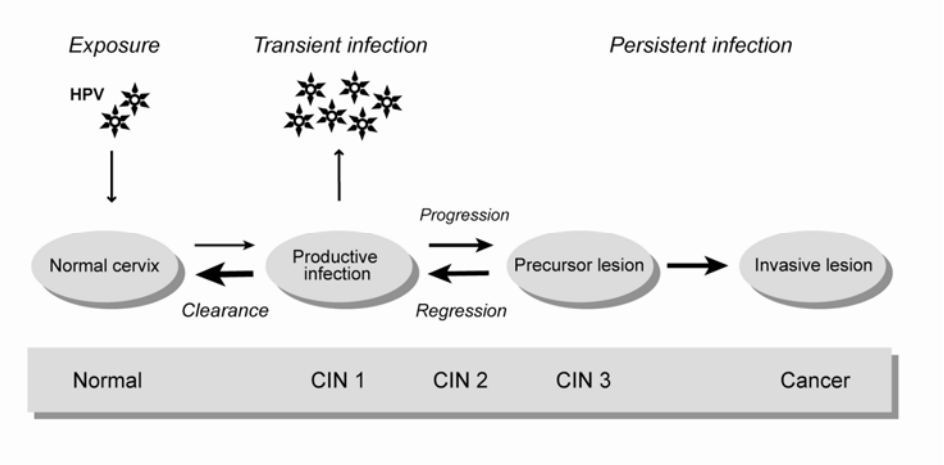
Several indicators can be used to measure the safety of vaccines. In some countries the vaccine manufacturers will carry out post-marketing surveillance. Existing routine reporting and investigation of and response to vaccine-related adverse effects will need to be enhanced to include adverse events following the administration of HPV vaccines. Before broad HPV immunization programmes are established, it would be useful (whenever feasible) to collect background information on the health status of adolescents and young women, including acute, chronic and autoimmune diseases that may first appear in adolescence, which could be analysed to assess whether the HPV vaccines are related to these conditions.

Introduction

HPV infection and related disease

Human papillomavirus is a very common infection and more than three quarters of sexually active women are estimated to become infected at least once in their lifetime. Most initial infections occur shortly after sexual debut. Most of these infections are self-limiting and harmless, but persistent infection with oncogenic types of HPV can cause anogenital cancer in women and men, most commonly cervical cancer. Progression from HPV infection to invasive cancer is usually a slow process, taking 10 to15 years. Pre-invasive cervical lesions are graded from one to three based on histopathological criteria. CIN 1 indicates the presence of active or productive HPV infection; CIN 2 regresses spontaneously in about 40% of cases; CIN 3 has the lowest likelihood of regression and the strongest potential to become invasive (Fig. 1) *(4)*.

Fig. 1. Major steps in cervical carcinogenesis



Adapted from: *Cervix cancer screening (5)*.

HPV also causes other anogenital cancers (e.g. of the vagina, vulva, anus and penis), head and neck cancers and genital warts in both men and women. Of all cancers occurring in both sexes, nearly 4% are attributable to HPV16 and 18 (Table 1) *(6–8)*.

Table 1. Cancers attributable to HPV infection, 2002 (both sexes)

Site	Attributable to HPV (%)	Of which, HPV 16 and/or 18 (%)	Percentage of all cancers
Cervix	100	70	3.18
Penis	40	63	0.06
Vulva, vagina	40	80	0.12
Anus	90	92	0.23
Mouth	3	95	0.07
Oro-pharynx	12	89	0.05
ALL SITES			3.71

Source: Parkin DM, Bray F *(9)*.

Cervical cancer can be controlled through interventions along the continuum of care, including prevention, early detection, diagnosis and treatment and palliative care *(10)*. For the last several

decades, the backbone of cervical cancer control has been secondary prevention through early detection (i.e. screening) and treatment of precancerous lesions.

Secondary prevention of cervical cancer

Well-organized cervical cancer screening programmes that achieve high coverage and include effective follow-up and treatment of women with abnormal cytology have been proven to reduce cervical cancer incidence by more than 80%. Some European countries have been very successful in reducing the burden of cervical cancer through this form of secondary prevention. However, in the many European countries that have not been able to set up or sustain widespread and well-organized programmes or to assure appropriate follow up, cervical cancer continues to be a major public health problem.

The success of screening depends on access and take-up, the quality of screening tests, and the adequacy of follow-up, diagnosis and treatment of the lesions detected. There is strong evidence that organized screening, whereby women are invited for screening, is more effective than opportunistic screening, whereby only those women visiting health services request or are recommended a screening test. Organized screening programmes result in a higher coverage of the target population, improved mechanisms for quality control and monitoring, and data registry.

WHO recommends cytology for large-scale screening programmes, if sufficient resources exist. The recommended target ages and frequency of cervical cancer screening are as follows *(4)*:

- new programmes should start screening women aged 30 years or over and include younger women only when the group at highest risk has been covered; existing organized programmes should not include women under 25 years of age in their target population;
- 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;
- in the group 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 provided the last two previous smears were negative.

The rationale for not screening females aged under 25 years is that invasive cancer is extremely rare below this age, while the presence of transient HPV-induced cytological abnormalities is high. Screening people aged under 25 years may result in considerable overtreatment of lesions that would spontaneously regress. Starting screening at 25 years or later allows programmes to detect those lesions that would be more likely to progress to cancer *(11)*. Screening intervals of three years for women aged 25–49 years and five years for women aged 50–65 years are appropriate as they result in nearly the same reduction in cervical cancer incidence as annual screening at a substantially lower cost and burden on patients and health systems *(12)*.

HPV tests are also increasingly used as screening tools in conjunction with cytology, mainly in women aged 30 years and over. HPV testing is substantially more sensitive than cytology at detecting precancerous lesions of the cervix, but less specific in that it detects transient infections

that have not produced cytological changes. Broad trials are in progress to assess the performance of HPV tests when used as a primary screening tool instead of cytology *(13)*.

Primary prevention of cervical cancer

Changes in sexual behaviour, such as using condoms or delaying first intercourse, offer some protection against HPV. Condoms offer only partial protection against HPV transmission because the virus can exist on body surfaces not covered by the condom and can be transmitted by genital skin-to-skin contact. Despite this, consistent and correct use of condoms has been shown to lead to faster HPV clearance in both men and women, to increase the regression of cervical lesions, and to reduce the risks of genital warts, cervical precancer and cancer *(14–18)*.

Recently, new options have become available for cervical cancer control through primary prevention. In 2006, the first prophylactic vaccine against HPV 6, 11, 16 and 18 was approved by the United States Food and Drug Administration and by EMEA (Gardasil® Sanofi Pasteur MSD). By October 2007, this vaccine had been licensed in more than 80 countries worldwide. A second, bivalent vaccine (Cervarix®, GlaxoSmithKline Biologicals) was approved by EMEA in September 2007, and by October 2007 it had also been licensed in 35 countries worldwide. This vaccine protects against HPV 16 and 18. Worldwide, HPV 6 and 11 are responsible for 90% of genital warts while HPV 16 and/or 18 are found in nearly 70% of invasive cervical cancers and in approximately 30% of vulvo-vaginal cancers (Table 1).

Effect of introducing HPV vaccines on screening programmes

Cervical cancer screening through various methods will continue to be necessary for the foreseeable future, with or without vaccine introduction *(19)*. At present there is insufficient evidence to alter current screening recommendations because it will take decades before a sufficiently large population will derive substantial protection from vaccination.

Non-vaccinated populations who do not benefit from the primary prevention strategy of vaccination need the secondary prevention strategy of screening.

In countries where screening takes place, continued screening for precancerous lesions will also be necessary for the vaccinated females to prevent the roughly 30% of cervical cancers due to HPV types against which the vaccine does not protect, and to prevent cancers from vaccine-related HPV types to which they may have been exposed before vaccination. In addition, the screening of vaccinated populations, at least on a limited sentinel basis, will be valuable to monitor the impact of the vaccine on preventing precancerous lesions due to vaccine-related HPV types.

When offering vaccination, clinicians should stress the need for future screening to detect precancerous lesions from non-vaccine-related types of HPV. It is important to counteract a false sense of security in women who do not always understand that HPV vaccines do not protect against all types of oncogenic HPV infection.

Current situation in the European Region

Burden of disease caused by HPV

Cervical cancer

Although cervical cancer is one of the few cancers that are potentially preventable, it continues to be a public health problem. It is estimated that in the WHO European Region, more than 60 000 women develop invasive cervical cancer every year and almost half of them die from the disease. Dramatic differences exist within countries, with mortality rates in eastern Europe being on average more than twice as high as in the other parts of Europe. The lowest mortality rates (age-standardized rate (ASR) <3) have been observed in Finland, Greece, Italy, Malta, the Netherlands, Spain and Switzerland, whereas very high mortality rates (ASR >9) have been reported in Albania, Romania and Serbia and Montenegro[2] (Table 2) *(20)*.

Other cancers and genital warts

Based on worldwide estimates, 5.17% of cancers from all anatomic sites are attributable to HPV infection and 3.71% are attributable to HPV16 and 18 infection. These HPV types cause high proportions of squamous cell carcinoma of the vulva and vagina, penile cancer, anal cancer and mouth- and oro-pharynx cancer (Table 1). Incidence and mortality rates of these cancers are not available for many countries of the Region. Worldwide figures show ASR of 0.5–1.5 per 100 000 for cancer of the vulva, 0.3–0.7 per 100 000 for cancer of the vagina and less than 1 per 100 000 for penile cancer *(9)*. Based on rough figures from the European Union (EU), 4000 cases of vulvar-vaginal cancer per year and 58 000 cases of precancerous vulvar-vaginal lesions are estimated for the WHO European Region.

Existing data suggest that genital warts, caused mainly by HPV 6 and 11, are a very significant public health problem, being the most common reported STI in Europe. In the United Kingdom, a population-based survey of women and men aged 16–44 years conducted in 2000 found that 3.6% of men and 4.1% of women had been diagnosed with genital warts *(21)*. Less robust data for the population incidence of genital warts exist for the other European countries, but national reports suggest incidence rates similar to those observed in the United Kingdom *(22)*.

Existing cytology screening programmes and policies

There is evidence that screening women aged 35–64 years for cervical cancer precursors by conventional cytology every 3–5 years within high-quality programmes reduces the incidence of invasive cancer by at least 80% among those screened *(5)*.

Several case-control studies, cohort studies and trend analyses in, among others, Finland, other Nordic countries and the United Kingdom have demonstrated that organized screening is more effective and more cost-effective than opportunistic screening, where the initiative for screening has to be taken by the woman herself *(11,23–26)*. Opportunistic or unorganized screening also decreases cervical cancer rates, although to a lesser extent. One of the problems with unorganized screening is that it is more difficult to achieve high coverage and to reach populations at highest risk *(27)*.

[2] Serbia and Montenegro became two separate Member States of WHO in September 2006. In this paper the data refer to the period before 2006 and relate to the then one country of Serbia and Montenegro.

Table 2. Incidence of and mortality from cervical cancer in the European Region[a]

Country	No. of new cases	ASR per 100 000 women	No. of deaths	Mortality ASR per 100 000 women
Albania[b]	389	25.2	146	9.8
Andorra	–	–	–	–
Armenia	380	16.8	130	6.7
Austria	610	10.9	295	4.1
Azerbaijan	345	8.2	113	2.8
Belarus	1 086	13.1	436	5.2
Belgium	667	9.3	326	3.4
Bosnia and Herzegovina[b]	545	21.3	227	8
Bulgaria	979	18.7	506	8
Croatia	431	13.3	209	5
Cyprus	53	11.6	25	5.3
Czech Republic	1 160	16.2	476	5.5
Denmark	439	12.6	230	5
Estonia	156	15.5	74	6.6
Finland	164	4.3	81	1.8
France	4 149	9.8	1 647	3.1
Georgia	580	17.5	225	5.9
Germany	6 133	10.8	2 967	3.8
Greece	578	7.7	239	2.5
Hungary	1 042	15.7	551	6.7
Iceland	13	8.3	10	4.7
Ireland	164	7.2	88	3.5
Israel	160	4.5	82	2.3
Italy	3 418	8.1	1 186	2.2
Kazakhstan	1955	21.6	729	7.9
Kyrgyzstan	522	21.6	186	7.9
Latvia	291	12.9	165	7.4
Lithuania	446	17.5	256	9
Luxembourg	24	8.7	13	3.9
Malta	14	4.8	6	1.6
Moldova	476	18	220	7.8
Monaco	–	–	–	–
Netherlands	753	7.3	307	2.3
Norway	291	10.4	125	3.5
Poland	4 901	18.4	2 278	7.8
Portugal	956	13.5	378	4.5
Romania	3 448	23.9	2 094	13
Russian Federation	12 215	11.9	7 784	6.5
San Marino	–	–	–	–
Serbia and Montenegro	1 816	27.3	815	10.1
Slovakia	654	18.5	242	6.1
Slovenia	207	16.1	79	4.7
Spain	2 103	7.6	739	2.2
Sweden	485	8.2	249	3.1
Switzerland	389	8.3	108	1.7
Tajikistan	232	9.9	70	3.5
The former Yugoslav Republic of Macedonia	167	13.9	99	7.6
Turkey	1364	4.5	726	2.4
Turkmenistan	274	13.5	96	5.2
Ukraine	4 885	14.1	2 578	6.4
United Kingdom	3 181	8.3	1 529	3.1
Uzbekistan	1149	10.7	379	3.9
TOTAL	66 839		32 519	

[a] Standardized rates have been estimated by direct method and the world population as reference.
[b] No data available. Calculated from the averages in neighbouring countries.

Source: Globocan 2002 *(28)*.

Finland and Iceland provide examples of how the incidence of and mortality from cervical cancer can be reduced through the introduction of widespread and high-quality organized screening programmes. The introduction of such programmes in these two countries during the 1960s resulted in a reduction in the world-adjusted cervical cancer incidence rate of 66% and 45%, respectively, over 20 years. Mortality declined by 60% over 20 years and by 82% over 40 years *(25)*. The importance of coverage was also shown in the United Kingdom, where a dramatic reduction in incidence was observed after the introduction of a national call-recall system in 1987, resulting in a two-fold increase in the coverage of women attending the screening programme *(29)*. In the Netherlands, the introduction of organized screening resulted in higher coverage, fewer abnormal cytology results without an increase of interval cancers between two tests, better follow-up of patients with abnormal smears, and limitation of excess smears *(30)*.

The Council of the EU recommended in 2003 that cervical cancer screening should only be offered on a population basis in organized screening programmes, with quality assurance at all levels. They recommended that screening should start by the age of 20–30 years and be repeated every 3–5 years until the age of 60 years *(31)*.

Organized cytological screening programmes are, however, expensive, labour-intensive, and challenging to sustain with adequate quality assurance. Many organized screening programmes in Europe do not reach all women at risk of cervical cancer at appropriate intervals or follow-up for abnormal screening results. Other countries lack organized programmes and only screen opportunistically when women come in for other health care services. Policies for screening as well as the age at and frequency of screening vary between countries.

Eleven countries (Denmark, Finland, Iceland, Ireland, Italy, the Netherlands, Norway, Poland, Slovenia, Sweden and the United Kingdom) have now organized screening, at least at a regional level. In the other countries opportunistic screening is still used. Several countries intend to organize their programmes, including Estonia, Hungary, Latvia, Lithuania and Slovakia. In Finland, Ireland, the Netherlands and the United Kingdom, women are actively invited to be screened. Other countries, such as Denmark, Hungary and Slovenia invite women who do not spontaneously attend screening visits.

The screening interval varies between countries from 1 to 5 years and the starting age for screening varies from 15 to 30 years. As an example, the recommended screening interval is one year in the Czech Republic, Germany and Luxembourg, but five years in Finland, Lithuania and the Netherlands. Luxembourg and Switzerland recommend that screening starts at onset of sexual activity, while Finland, Lithuania and the Netherlands recommend starting at 30 years old, typically many years after onset of sexual activity. Most countries also recommend stopping screening for older women (aged 59–70 years) who have had two consecutive normal smears.

South-east Europe contains the two countries where the burden of cervical cancer has been highest in Europe (Romania and Serbia and Montenegro[3]), as well as countries where the burden is low (e.g. Greece). Although data on characteristics of screening programmes in this region are limited, it is possible that these differences may be due to differences in the prevalence of oncogenic types of HPV and in the coverage and quality of cytology screening programmes *(32)*.

[3] Data prior to September 2006, when Serbia and Montenegro became two countries.

Current status of introduction of HPV vaccines

In September 2006, after a positive opinion by EMEA, the quadrivalent HPV vaccine Gardasil®, was registered for use in the EU (27 countries) to protect against the high-grade dysplasia (precancerous abnormal cell growth) of the cervix or the vulva, cancer of the cervix and genital warts that are caused by HPV infections of types 6, 11, 16 and 18 *(33)*. Since October 2007, this vaccine has also been licensed in other countries of the Region, including Bosnia and Herzegovina, Croatia, Iceland, Israel,[4] Liechtenstein, Norway, the Russian Federation, Serbia, Switzerland, The former Yugoslav Republic of Macedonia and Turkey. In September 2007, the bivalent vaccine Cervarix® received a marketing authorization for all EU countries for the indications of prevention of precancerous cervical lesions (CIN grades 2 and 3) and cervical cancer causally related to HPV types 16 and 18 *(34)*. By October 2007, this vaccine was also registered in Iceland, Kazakhstan and Norway.[5] Owing to regulatory requirements and issues relating to, among other things, importation, distribution and price negotiations, the licensing of a vaccine does not mean that it is in fact marketed in a given country.

In addition, ministries of health or health advisory bodies in several European countries have recommended use of HPV vaccines (Annex 1). There have been slight variations in these recommendations owing to different sexual activity patterns, age-related vaccination patterns, cost-effectiveness, and the priority given to vaccinating older female adolescents and young women or males. Some countries have recommended public sector support for HPV vaccination and secured funding for public sector programmes. In some countries, final policies are under development. For example, in Greece and Slovakia expert advisory committees have recommended including HPV vaccination in the national immunization schedule but no formal decisions have yet been taken by the national authorities. Other countries are carrying out health technology assessments and expect to issue opinions about HPV vaccines within several months.

In September 2007, the bivalent vaccine Cervarix™ received a marketing authorization for all EU countries for the indications of prevention of precancerous cervical lesions (CIN grades 2 and 3) and cervical cancer causally related to HPV types 16 and 18 *(34)*.

HPV vaccines: technical information

Overview

Both the quadrivalent vaccine Gardasil® and the bivalent vaccine Cervarix® are prepared from VLP and produced by recombinant technology. They do not contain any live biological product or DNA, so they are non-infectious *(35,36)*. Table 4 provides a summary of both vaccines.

In the efficacy trials, high-grade cervical lesions (CIN2, CIN3 and adenocarcinoma in situ (AIS)) have been used as an endpoint to establish the efficacy of the vaccines to prevent cervical cancer as a surrogate for invasive cancer itself. As these lesions are recognized as cervical cancer precursors, it would be unethical not to treat them. Moreover, randomized trials with invasive cancer as an endpoint would take several decades before the efficacy could be assessed.

[4] Randall Hyer, Merck and Co, personal communication, October 2007.
[5] Gary Dubin, GlaxoSmithKline, personal communication October 2007.

Table 4. Characteristics of two HPV vaccines and trial populations

Characteristics	Quadrivalent vaccine	Bivalent vaccine
Manufacturer and trade name	Merck, **Gardasil®**	Glaxo Smith Kline, **Cervarix®**
VLP of genotypes	6, 11, 16, 18	16, 18
Substrate	Yeast (*S. cerevisiae*)	Baculovirus expression system
Composition	20 µg HPV 6, 40 µg HPV 11	20 µg HPV 16, 20 µg HPV 18
	40 µg HPV 16 , 20 µg HPV 18	
Adjuvant	Proprietary aluminum hydroxyphosphate sulfate (225ug)	Proprietary aluminum hydroxide (500 µg) plus
	(Merck Aluminium adjuvant)	50 µg 3-deacylated monophosphoryl lipid A (GSK AS04 adjuvant)
Schedule: 3 IM doses of 0.5 ml at	0, 2, 6 months	0, 1, 6 months
Main efficacy trials	Females aged 16–26 years	Females aged 15–25 years
Safety/immunogenicity bridging trials	Females and males 9–15 years	Girls 10–14 years
		Boys 10–18 years
		Women 26–55 years
Other trials in progress or being planned	Efficacy in women 24–45 years	Efficacy in women >25 years
	Concomitant administration with other vaccines	Concomitant administration with other vaccines
	Safety and immunogenicity in HIV-infected people and other immunocompromised groups	Safety and immunogenicity in African populations, including HIV-infected women
	Efficacy trials in men 16–26 years	Comparative immunogenicity studies
	Follow-up of adolescent trials	Phase IV: long-term follow-up
	Phase IV: long term follow-up	Local registration trials
	Alternative dosing schedules	

Adapted from: Cutts et al, 2007 *(37).*

For Gardasil®, data on efficacy are available from phases 2 and 3 double-blind randomized placebo-controlled trials. The phase 2 trial involved over 500 women aged 16–23 years with an initial follow-up of 36 months and an extended follow-up of 5 years *(38–40)*. Efficacy data for the prevention of high-grade lesions are available from a large phase 3 trial including 12 167 women between the ages of 15 and 26 years *(41)*. Forty-four percent of the participants in the study were from European countries including Denmark, Finland, Iceland, Norway, Poland, Sweden and the United Kingdom. The phase 3 trial, to evaluate efficacy in preventing anogenital diseases associated with HPV types 6, 11, 16 and 18, included 5455 women aged 16–24 years *(42)*. Safety and immunogenicity data are derived from the same studies as well as from bridging studies in girls and boys aged 9–15 years *(43,44)*.

The bivalent HPV-16 and HPV-18 VLP vaccine Cervarix® was tested in a phase 2 trial with more than 1000 healthy young women aged 15–25 years, with a follow-up of 27 months *(45)*. Vaccine efficacy and immunogenicity have further been assessed in an extended follow-up period of up to 48 months, involving women from Germany and Poland *(46)*. The interim analysis from a large phase 3 trial has recently been published *(47)*. More than 18 000 women aged 15–25 years from Belgium, Denmark, Finland, Greece, Italy, the Russian Federation and

Spain participated in that trial.[6] Information for other age groups is available from safety and immunogenicity bridging studies in younger girls and boys and older women *(48)*.

Immunogenicity data

Level and duration of antibody response to HPV vaccines

After three doses of either of the HPV vaccines, nearly 100% of women aged 15–26 years naïve to vaccine-related HPV genotypes before vaccination had detectable antibody to the respective HPV genotype after completion of the three-dose vaccination series *(39,45,46)*. The levels are 10–104 times higher than those seen after natural infections with these geneotypes *(48)*. Antibody levels peak at one month after the third dose (i.e. in the seventh month), followed by a decline until the eighteenth month after vaccination. After that, antibody titres stabilize and remain as high as or higher than those seen after natural infection for approximately five years follow-up analysed to date. Longer follow-up data are not available yet *(39,40,46)*. Antibody response to the quadrivalent vaccine has not been affected by race, ethnic origin, concomitant administration of hepatitis B vaccine or use of oral contraceptives. Data on the effects of HIV, severe malnutrition and intercurrent[7] malarial or helminth infections on vaccine immunogenicity are not yet available but research is underway *(2)*.

The antibody levels achieved after vaccination are inversely related to age. Bridging studies also showed high immunogenicity in boys and girls aged 9–15 years, and the antibody levels achieved in this age group are higher than in older people *(42)*. No trials have yet been conducted in children aged under nine years.

The minimum antibody level required for protection and the duration of response is not known because of the high efficacy demonstrated in trials to date. Ongoing follow-up of vaccinated cohorts will help to determine this. This information is crucial to determine if and when booster vaccination may be necessary.

Cross-protection

In preliminary analyses, both vaccines have shown evidence of partial cross-protection against HPV 31 and HPV 45, two oncogenic types that are closely related to HPV 16 and 18. In the extended follow-up of the phase 2 trials of the bivalent vaccine, a significant reduction in incidence of type 45 (efficacy = 94.2%; 95% CI: 63.3–99.9) and type 31 (efficacy =54.5%; 95% CI: 11.5–77.7) was observed *(46)*. For the quadrivalent vaccine, a study of 10 vaccine recipients showed that serum antibodies neutralized the majority of HPV type 45 and type 31 pseudovirions *(49)*. Clinical meaning of this cross-reactivity depends on whether the incidence of CIN caused by HPV types other than HPV 16 and 18 is reduced. Studies on this issue are continuing.

[6] Marc Van Camphenhout, GlaxoSmithKline, personal communication, November 2007.
[7] Occurring at the same time and usually altering the course of another disease.

Effectiveness

In an HPV-naive population

In women with no evidence of previous exposure to vaccine-related HPV types, randomized controlled trials have demonstrated high efficacy in preventing incident and persistent HPV 16 and 18 infections and CIN2/3 related to HPV 16 and 18 in females naïve to these types at baseline who have received the three-dose series, with follow-up data available for four to five years *(38,40,41,45,46,50,51)*. Phase 3 trials of Gardasil® have shown high levels of efficacy in preventing external genital lesions related to HPV 6, 11, 16, 18, including genital warts and vulvar and vaginal neoplasia *(22,51)*.

In the vaccine trials, the primary analyses were conducted among the "according-to-protocol" population, i.e. women aged 15–26 years who received all three doses within one year, did not have evidence of past or current infection with vaccine-related HPV genotypes at baseline, and did not deviate from the protocol. For the bivalent vaccine, data from the combined analysis of the initial phase 2 trial with an extended mean follow-up of 48 months, showed a vaccine efficacy of 96.0% (95% CI: 75.2–99.9) against persistent HPV 16/18 infection and of 100% (95% CI: 42.4–100) for preventing HPV 16 or 18-related CIN1+. In the placebo group, only CIN1 and CIN2 cases were reported, all related to HPV 16 infections *(45,46)*. The interim analysis of the phase 3 trial, with a mean length of follow-up of 14.8 months, showed a vaccine efficacy for the prevention of HPV 16/18-related CIN2+ lesions of 90.4% (97.9% CI: 53.4–99.3) in the population who were seronegative and DNA-negative for the relevant vaccine type at baseline. In the 9258 vaccinated women, 2 cases of CIN2+ associated with HPV 16 or 18 DNA were seen, while 21 were recorded in the control group (n=9267). The two cases in the vaccine group had a co-infection with HPV 58, an oncogenic type that was also detected in the months before CIN diagnosis. In both cases, the vaccine-related HPV types were only detected once *(47)*.

For the quadrivalent vaccine, results from the phase 3 trial with an average follow-up of 36 months showed an efficacy for the prevention of CIN2/3 and AIS lesions related to HPV 16 or 18 of 98% (95% CI: 86–100) in females naïve to these types at baseline. In a population of 10 565 women who underwent randomization, 1 woman in the vaccine group and 42 women in the placebo group received a diagnosis of a CIN2 or 3 or AIS associated with HPV 16, HPV 18, or both. The single case of a precancerous cervical abnormality in the vaccine group was persistently positive for HPV 52, another oncogenic type and had HPV16 DNA detected in one histology specimen before diagnosis of the cervical abnormality *(41)*.

In the phase 3 trial evaluating the efficacy of the vaccine to prevent anogenital disease, 4570 females were followed for vulvar, vaginal or perianal disease. The quadrivalent vaccine was 100% (95% CI: 94–100) effective in preventing vaginal, vulvar, perineal and perianal intraepithelial lesions or warts that were associated with vaccine-type HPV in women naïve to these types at baseline *(42)*.

The phase 3 trial of Gardasil® also evaluated the vaccine efficacy in the total population that was HPV-naïve at enrolment, including those with less than perfect compliance. In this population, vaccine efficacy remained high at 95% (95% CI: 85–99), for prevention of CIN2/3 lesions, AIS, and anogenital diseases of vulvar, vaginal neoplasia and anogenital warts *(41,42)*.

In the general population

A preliminary assessment of the effect of the quadrivalent vaccine on HPV16 or HPV18-related high-grade cervical disease in a general population, with and without pre-existing CIN or HPV infection at baseline, was made through an intention-to-treat analysis of all women who had undergone randomization in the phase 3 trial. The vaccine efficacy was 44% (95% CI: 26–58), with most lesions caused by HPV 16 or 18 infection that had been present before the first vaccine dose. As expected, this prophylactic vaccine did not alter the course of pre-existing infection or lesions related to HPV 16 or 18 *(41).* For the overall prevention of vaccine-type-related external anogenital and vaginal lesions, the quadrivalent vaccine showed an efficacy of 73% (95% CI: 58–83) *(42).*

The intention-to-treat population was also used to evaluate the effect of vaccination with the quadrivalent vaccine on lesions caused by either vaccine- or non-vaccine-related types of HPV. The overall vaccine efficacy for the prevention of any CIN2/3 or AIS was only 17% (95% CI: 1–31); for the prevention of all external anogenital and vaginal lesions it was 34% (95% CI: 15–49) *(41,42).*

Safety

Overall, both vaccines appear to be generally safe and well-tolerated. Common adverse effects included pain, erythema and oedema at the injection site, which occurred significantly more often for vaccine recipients than for placebo recipients in trials of both vaccines. Systemic and serious adverse events, including headaches, fatigue and gastrointestinal symptoms, were reported with equal frequency by vaccine and placebo recipients in both trials and were recorded as mild or moderate in intensity. Only 0.1% of the subjects discontinued due to adverse experiences *(38,45,46,50,51).* Post-marketing surveillance for the quadrivalent vaccine in the United States has demonstrated that syncope and dizziness are among the leading adverse events, resulting in a recommendation by the Advisory Committee on Immunization Practices that vaccine recipients should be observed 15 minutes after vaccination *(52).*

Although pregnant women were excluded from the trials, some women became pregnant during the weeks following vaccination. In the phase 3 trial of the quadrivalent vaccine, 1244 pregnancies in the vaccine group and 1272 in the placebo group were reported. In each group, 3.6% of these women experienced a serious adverse event. There were 15 congenital anomalies in babies born to women in the vaccine group, and 16 in the placebo group. These anomalies were consistent with those generally observed in women aged 16–26 years. Studies in rats have shown no evidence of foetal malformations or other teratogenetic effects *(53).* Bridging studies in boys and girls aged 9–15 years showed the vaccine to be safe in this group for at least 12 months after vaccination *(44).* Clinical trials and post-marketing studies are monitoring safety on a long-term basis.

A study evaluating the safety of the quadrivalent HPV vaccine found no appreciable differences in adverse events when co-administered with recombinant hepatitis B vaccine as compared to administering the two vaccines on different occasions.

Cost-effectiveness

Cost-effectiveness studies have used different types of mathematical model. The accuracy of the results depends on the appropriateness of the assumptions used to build the models and the quality of the data used to develop and validate them. Recently, four studies modelling the cost-effectiveness of HPV vaccination in the United States were reviewed. One dynamic and three static models all suggested that the introduction of an HPV vaccine when administered to girls before the age of 12 years could be cost-effective compared with the current practice of organized cervical cancer screening *(54)*. Three other studies, in which a transmission dynamic model was applied, had similar results *(55–57)*. In Norway, the cost-effectiveness of HPV vaccination, including for types 16/18 in girls aged 12 years, alongside the existing cervical cancer screening programme was compared to a programme of screening alone. A programme of HPV vaccination was evaluated from a Norwegian health sector perspective (assessment of vaccination costs, diagnosis and treatment of cervical cancer and precancers) and from a societal perspective (assessment of losses and gains in productivity associated with cervical cancer mortality and cancer treatment). The economic evaluation suggested that, under several plausible assumptions, the introduction of an HPV 16/18 type vaccination with current screening in Norway may be a cost-effective strategy to reduce the incidence of and mortality from cervical cancer further. However, the estimates were sensitive to both the perspective adopted, and assumptions in the model related to the efficacy, coverage and cost of the vaccine, the discount rate, and the time horizon of the analysis *(58)*.

In countries with established screening programmes, adding HPV vaccines to them may be cost-effective, but this depends on the age screening is started, the screening interval and the management of mildly abnormal and borderline smear results.

The cost-effectiveness of vaccination in resource-poor countries will depend greatly on the price of the vaccine, the costs of achieving high coverage, the feasibility of delivering the three doses to teenagers, and the duration of vaccine-induced immunity. Based on the limited data available, in resource-poor settings the best (and still cost-effective) strategy would consist of vaccination of pre-adolescents followed by two screenings per lifetime between the ages of 35 and 45 years *(59)*. However, more data are needed before firm conclusions can be reached.

Which factors influence costs?

The cost of HPV vaccines is likely to be the major determinant of the cost of a vaccination programme. Delivery costs for HPV vaccines may be higher than for vaccines given to infants if no programmes for delivering health care to pre-adolescents exist and must be established and sustained. Ongoing research will show if different vaccination strategies that would reduce the cost, e.g. using a two-dose schedule or vaccinating children at an earlier age, together with other vaccines (e.g. in infancy or school-entry), are valuable options.

Which factors influence effectiveness?

The benefit from HPV vaccination in a country will depend on the burden of HPV disease attributable to the types against which the vaccines protect or cross-protect, efficacy of the vaccine, achievable vaccine coverage and duration of protection. These factors may differ in different age groups and in populations with a high prevalence of HPV. In general, the most important determinant of overall programme effectiveness will be the coverage of pre-adolescent girls with three doses of HPV vaccine. Although sexually active women will benefit less from

vaccination, as some of them will already have been exposed to the vaccine-related types of HPV, catch-up strategies for older adolescent or young women can accelerate the decline in incidence of invasive disease at population level and result in indirect protection of the population *(41)*. The introduction of HPV vaccines may also affect the effectiveness of screening programmes, which has to be taken into account in countries where HPV vaccines would complement ongoing screening.

The potential gains from vaccinating boys should be considered from a population perspective. Nearly all models evaluating the cost-effectiveness of vaccinating boys to decrease the incidence of cervical cancer have concluded that this is not an attractive strategy if high coverage of females can be achieved *(54,56,57,60)*. If coverage is low, vaccination of boys may play a role in the control of infection, but because vaccination directly protects women significantly more than men, more gains may be derived per girl vaccinated than per boy vaccinated. More long-term field studies of herd immunity are in progress to validate these predictions.

Target group

Primary target group

As current HPV vaccines are prophylactic, the greatest impact will be seen by vaccinating girls before they are exposed to HPV, thus before sexual debut. The target age group for young adolescent girls before sexual debut depends on sexual activity patterns within a given country.

Catch-up population

Catch-up programmes of older females (aged, for example, up to 26 years) are less cost-effective as many women are already sexually active and some have already been exposed to vaccine-related types of HPV before vaccination. Catch-up campaigns, sometimes used at the start of routine vaccination with a new vaccine, may be considered to speed the expected decline in incidence of precancerous cervical lesions in a population, as the latent period between first HPV infection and precancerous lesions is typically a decade or more.

Vaccinating boys

Vaccinating males can provide direct protection against certain HPV-related conditions (including genital warts for the quadrivalent vaccine and anal and penile cancer), but efficacy trials of clinical disease endpoints are still in progress. Vaccinating boys could also offer indirect protection to women by reducing the transmission of HPV. Although this approach does not seem to be cost-effective if a high vaccine coverage of females can be achieved, vaccinating boys may be attractive in some countries, in order to promote gender equity and to prevent rumours that vaccines offered only to females may cause sterility in girls, an ill-founded rumour associated with other vaccines.

Operational data

Costs

In European countries where the HPV vaccines have been licensed, the current price on the private market is at least € 100 per dose for a three-dose schedule. The total cost will be increased by administrative and programmatic costs.

Schedule

The quadrivalent vaccine is given as a series of three 0.5 ml intramuscular injections over a six-month period, with two months between the first and second doses and six months between the first and third doses. The bivalent vaccine is to be given as three intramuscular injections within six months, with a one-month period between the first and second doses and six months between the first and third doses.

Vaccine, presentation

Both vaccines are available in single-dose vials or prefilled syringes.

Storage

The vaccines must be stored refrigerated at 2–8 °C but should not be frozen. They should be protected from light.

Remaining questions

Important issues remaining are the definition of the correlate of protection and the duration of protection. These two issues relate to the need for a booster vaccination. Sustained efficacy for protecting against clinical disease (CIN 2/3) has been demonstrated for phase 3 trials for the quadrivalent vaccine (where average follow-up was three years in published studies) and for the bivalent vaccine (where follow-up time is currently shorter in published studies). Both companies plan follow-up studies to determine the duration of antibody and clinical protection among women enrolled in the phase 3 studies for at least 14 years after the third dose. In the meantime, cost-effectiveness studies that assume protection for 10 or more years or life-long should be interpreted very carefully.

Other remaining questions include:

- the effect on transmission and the potential value of vaccinating boys to achieve herd immunity;
- the long-term impact of vaccination on screening programmes;
- which genotypes to include in second generation vaccines;
- the safety, immunogenicity, efficacy and duration of protection of vaccines delivered with different schedules (e.g. different intervals, two doses);
- potential replacement of other oncogenic HPV types not related to current vaccines;
- the safety, immunogenicity and efficacy of vaccines administered to children aged under nine years.

Deciding on the introduction of the HPV vaccine at country level

Introduction

In nearly all high- and upper-middle income countries in Europe, at least one of the HPV vaccines is licensed and is now marketed in many of them. By November 2007, at least 12 western European countries had issued recommendations for use by national health systems, although funding to implement these recommendations may not yet be secured. Key questions remain about how HPV vaccines will influence existing screening programmes, their cost-effectiveness with given current or modified screening strategies, methods of reaching the adolescent target populations, and how HPV vaccines will compete for funding and priority with other infant and childhood vaccines, including new vaccines such as rotavirus vaccine.

Yet, the overall impact of the HPV vaccines in the Region will depend upon their coverage levels in the populations most in need of them. These populations are often found in resource-poor settings, where cervical cancer screening programmes are poor or absent, and cervical cancer incidence and mortality are highest. The current high cost of HPV vaccines is a major barrier to widespread access until affordable prices can be achieved in all markets. The additional cost of including HPV vaccines in national immunization programmes will also be important in the decision-making process, although it should not be the sole criterion. The expected costs and benefits will also have to be considered against those of other (i.e. not vaccine-preventable) health interventions *(1)*.

Decision-making process

The driving force to consider the introduction of HPV vaccine may come from national immunization cancer control or sexual and reproductive health programmes, international organizations, the academic world, industry, women's health advocates, or women in the community. Because HPV vaccines raise diverse issues regarding cancer prevention, sexual, reproductive, child and adolescent health, and immunizations and force decision-makers to weigh the benefits and costs of available interventions to prevent HPV-related disease, it is useful to consult a broad range of experts for evidence-based analysis and decision-making about the introduction of the HPV vaccine. These may include gynaecologists, oncologists, paediatricians, epidemiologists, virologists, primary practitioners, experts in immunization, STI, cancer screening, adolescent health and school health, as well as health economists. In most countries, recommendations are also formulated by health councils, advisory committees or professional groups such as the colleges of obstetricians and gynaecologists or primary practitioners. Recommendations about the clinical value of the vaccine must then be assessed and put into operation by the organizations responsible for funding health care expenditure, such as government health agencies, insurance companies and donors.

Before deciding to introduce HPV vaccines, decision-makers need to assess several factors. These include policy issues such as the burden of HPV-related disease and the priority to be given to it compared to other health problems, as well as financial issues related to the cost and cost-effectiveness of the vaccine and other vaccine-related factors. Decision-makers should also assess the degree of acceptance of the vaccine by programme staff, clinicians and the young adolescents targeted for vaccine and their parents. In contrast to other new childhood vaccines,

HPV vaccines present unique issues with regard to acceptability because they prevent STI and cancer, which are stigmatized conditions in many communities and may raise concerns about sexual behaviour after vaccination.

Policy issues

Public health priority

Burden of disease caused by HPV

One of the main pieces of evidence in setting national health priorities is the burden of disease that can be prevented by the vaccine. In the case of HPV, this burden is mainly related to invasive cervical cancer and related precancerous lesions and is highly dependent on the coverage and functional aspects of cytological screening programmes. In countries of the European Region where such programmes are absent or have limited coverage or poor performance, the incidence of and mortality from invasive cervical cancer is high (e.g. Albania, Kazakhstan, Romania), in contrast to countries with high-quality and high coverage screening programmes (e.g. Finland, Iceland, the Netherlands, the United Kingdom). In the latter countries the detection of cytological abnormalities and precancerous lesions may be substantial but appropriate follow-up and treatment will prevent most cancers.

Whereas estimates of the incidence of and mortality from cervical cancer are available for most countries in the Region, only a few countries maintain cancer registries that provide the most accurate and up-to-date population-based estimates of incidence and mortality. Population-based data on the prevalence or incidence of precancerous cervical lesions and anogenital warts are scarce, although data from small, non-representative samples are available in many European countries. The WHO/Institut Català d'Oncologia (ICO) HPV and Cervical Cancer Information Centre posted country-specific information on HPV and HPV-related disease, including precancerous lesions, cancer and genital warts on the WHO website in July 2007.[8] These reports, which will be very useful in the decision-making process, will also include available information on screening and immunization practices, factors contributing to cervical cancer and other relevant factors for vaccine introduction decisions *(20)*.

Weighing the prevention of HPV-related disease against other health priorities

Once decision-makers have estimated the burden of HPV-related disease, they need to weigh the value of preventive interventions, including screening programmes and vaccines, against interventions to prevent other diseases, including other vaccine-preventable diseases. These are complex but crucial decisions in the light of the new methods available to screen for cervical cancer (HPV testing and VIA), new and underused infant and childhood vaccines (against pneumococcus, meningococcus, varicella, rotavirus, Hib, hepatitis B) and other major health priorities such as HIV/AIDS, tobacco-related diseases and chronic diseases. One important factor to consider is that some health interventions may yield a rapid return on investment (for example, rotavirus vaccine may prevent infant death within a few months to years of administration) whereas HPV vaccines will yield delayed returns (such as reducing the incidence of precancerous lesions and cancer 10 or more years later).

[8] WHO/ICO Information Centre on Human Papilloma Virus (HPV) and Cervical Cancer, Barcelona, 2008 (www.who.int/hpvcentre, accessed 3 March 2008).

One of the challenges in introducing HPV vaccines will be to include the relevant stakeholders in immunization, sexual and reproductive health and cancer control communities in decision-making *(61)*. Some of the major issues to consider will be whether cervical cancer prevention is high enough on the list of health concerns, how cervical cancer control is to be achieved and what the expected impact of HPV vaccines on the burden of cervical cancer will be.

Is vaccination a valuable strategy to address the problem?

Based on current available epidemiological data, vaccinating all girls with a full three-dose schedule before first sexual activity could prevent up to 70–80% of all invasive cervical cancers and 50% of precancerous lesions needing treatment *(62,63)*. Additional benefits for the prevention of other anogenital and head and neck cancers caused by HPV are also expected, although these cancers are rare. Vaccinating girls before the onset of sexual activity with the quadrivalent vaccine, which includes VLPs specific for HPV 6 and 11 (the most common causes of genital warts), is expected to yield a 90% reduction in the incidence of genital warts.
A key question is how a strategy of primary prevention through vaccination interacts with a strategy of secondary prevention through screening. Cost-effectiveness studies taking into account national data will help to define the best strategy.

In countries with effective and high coverage cytological screening and treatment programmes (such as Denmark, Finland, Iceland, the Netherlands and the United Kingdom), the benefit of adding vaccines to screening programmes will be limited in terms of reducing mortality related to cervical cancer. In these countries, the expected major benefits of vaccine include reductions in: the incidence of borderline or abnormal cytology screening tests and precancerous lesions due to vaccine-related types of HPV that require diagnostic follow-up and/or treatment; complications due to diagnosis and treatment; patient discomfort and anxiety related to screening, follow-up and treatment; and health care costs *(64)*. In countries where HPV vaccines are introduced, it will be necessary to monitor and maintain the quality of cytological screening because widespread vaccination will result in a decline in the prevalence of HPV-related cytological abnormalities and reduce the positive predictive value of cytology *(65)*. Ongoing trials will determine whether HPV DNA tests perform better than cytology as a primary screening tool and if they could be used to screen vaccinated and non-vaccinated populations cost-effectively.

In countries where there are non-organized but functional screening programmes (e.g. Belgium, France and Luxembourg), the introduction of HPV vaccines may afford an opportunity to restructure screening. The organization of the screening programme with a clear definition of the target population, the introduction of a call-recall system to attain high coverage, quality control and the setting-up of monitoring and evaluation systems is key *(4)*. At population level, the benefits and cost-effectiveness of vaccines will be relatively greater than in countries with organized screening and high coverage, because the current screening programmes are less efficient. Moreover, disparities in terms of cervical cancer mortality could be reduced substantially if widespread vaccination coverage could be achieved in these countries *(59)*.

In countries with no or limited cytology screening (such as Armenia, Georgia and Kazakhstan), the widespread introduction of HPV vaccine is expected to substantially reduce the incidence of and mortality from cervical cancer compared to the current situation where there is no screening and no vaccination *(66)*. The benefits of vaccination will not, however, be observed for decades after vaccination due to the typically long latent period between initial HPV infection (usually in adolescence) and peak cervical cancer incidence (usually in people in their 40s and 50s). Such

delayed benefits are similar to those of childhood hepatitis B vaccination that prevents liver cancer and cirrhosis decades later. In such settings, girls and young adolescents could benefit from the primary prevention strategy of HPV vaccination, while older adolescents and women who are sexually active and already likely to have been exposed to HPV could benefit from the secondary prevention strategy of simplified screening programmes that do not depend on regular cytological screening. For example, simple, low-cost visual inspection of the cervix with application of dilute acetic acid or Lugol's iodine (VIA or VILI) has been demonstrated to be an effective screening tool in settings lacking cytological screening. Screening and treatment can take place during a single visit, it can be performed at peripheral health clinics by non-physicians, and it is far less expensive than periodic cytological screening *(4)*. HPV DNA testing is another promising alternative to cytology for primary screening of precancerous lesions, and it is anticipated that rapid HPV tests will become available in the near future at a low cost price *(67)*. Models suggest that screening vaccinated women once in their mid–30s and again in their mid-40s with HPV tests could appreciably enhance the impact and cost-effectiveness of vaccination *(59)*. By complementing HPV vaccination with simple non-cytological screening methods such as VIA or HPV DNA testing, countries lacking cytological screening programmes could accelerate reductions in cervical cancer incidence in both the non-vaccinated and vaccinated populations.

Vaccine efficacy, quality and safety

Both Gardasil® and Cervarix® have been shown to be highly efficacious for the prevention of precancerous lesions related to the HPV types included in the vaccine and to be of high quality. Clinical trials did not show significant differences in serious adverse events by vaccination status. Post-marketing studies are in progress to assess long-term safety.

More detailed information on efficacy, quality and safety has been discussed in the previous section.

Perception of the vaccine

Perceptions of HPV vaccines and of the importance of preventing HPV-related disease among clinicians, patients, parents and the public will influence policy decisions about introduction and acceptability once the vaccines have been introduced. Studies indicate that health care providers, adolescents and parents are generally very interested in HPV vaccination and that they are generally not opposed to a vaccine against an STI, a hypothetical concern before vaccines were marketed *(68–71)*.

In many European countries, HPV vaccines are being actively marketed by pharmaceutical companies through advertising and mass media campaigns that are influencing public awareness. In most countries, HPV vaccines are not funded or reimbursed by public sector health systems, so the publicity campaigns would probably influence vaccine uptake by people who might pay for it through private insurance or out of their own pockets. Such campaigns could also, however, increase pressure for public sector access to the vaccines. It is important that in all countries where HPV vaccines are introduced accurate information about them is disseminated through objective, non-commercial sources. This will allow clinicians and patients to make well-informed decisions and will help to encourage realistic perceptions and discourage misconceptions about the benefits and risks of the vaccine.

Economic and financial issues

Cost of the vaccine and programmes to deliver the vaccine

The current high cost of the HPV vaccines (10 to 1000 times higher than most vaccines in national immunization schedules) is a major barrier to their fast and widespread introduction. Adding HPV vaccines at their current cost to immunization programmes will dramatically increase the costs of the programmes unless prices can be reduced through tiered pricing, subsidies or other measures. Many people expect that the price of HPV vaccines will remain high for some time due to the enormous investment in research and development costs and high cost of manufacturing VLP vaccines. It is possible, however, that the prices may decline over time owing to competition between the two current manufacturers, the transfer of manufacturing technology to middle-income countries, public pressure to increase vaccine access or other factors. Because many European countries do not have a well-established platform to deliver vaccines to older girls and young adolescents (the primary target population for HPV vaccines), the development of a new vaccine delivery programme for this age group will be a major cost in the introduction of the HPV vaccine. Countries that are delivering vaccines to older children and young adolescents through organized programmes in the health sector, schools or national campaigns may wish to explore the costs of adding HPV vaccines to such programmes.

Cost-effectiveness

Cost-effectiveness analyses are important in decision-making as they make it possible to evaluate and compare alternative uses of scarce resources. This approach can help to determine whether investment in HPV vaccines (alone or in combination with screening) achieves greater or lesser health benefits relative to investment in screening alone. For analyses intended to inform resource allocation and health policy decisions, it is not only necessary to compare the cost-effectiveness of different types of intervention, but also of diseases and conditions *(59)*. Details on cost-effectiveness analyses conducted so far have been presented in the previous section. These studies show that in countries with effective screening programmes and limited cancer burden and mortality, the main benefit of HPV vaccines will be the reduction in the number of borderline or abnormal cytology and precancerous lesions associated with vaccine-related types of HPV. Cost-effectiveness will mainly depend on a willingness to initiate screening at a later age, to conduct screening less frequently and to adopt a conservative approach to the follow-up of women with borderline or low-grade abnormal screening results. In countries with no or limited screening, the main benefit will be a reduction in cancer incidence and mortality. In low-resource settings, the cost-effectiveness of introducing the vaccine will depend greatly on its price, the cost associated with achieving high coverage, the cost of delivering three doses of the vaccine to the primary target group, the duration of vaccine-induced immunity and the need for booster doses *(59)*.

These studies give important background information, but countries may want to use country-specific data in the models. In doing so, cost-effectiveness analyses should consider current screening programmes, the impact of current screening if it were streamlined or if new screening technology (e.g. HPV testing) were introduced, the long time horizon before the benefits of intervention become apparent (10–30 years for vaccine, less for screening), and delivery costs with and without other existing child/adolescent vaccine programmes.

Funding

Funding sources for HPV vaccines will depend on the modalities used to introduce the vaccines in the country. In almost all countries, funding for vaccination comes from both the public and the private sector in varying proportions and through different mechanisms. Infant and childhood vaccination is mainly provided free by the government (e.g. the Scandinavian countries and the United Kingdom); although in some countries (e.g. Germany) compulsory or private health insurances pay for the recommended vaccines. In other countries, such as France, vaccines are administered by private practitioners and most of the cost is reimbursed by the government. Adult vaccination in many EU countries is mainly provided through the private sector with patients paying the full cost of the vaccination. In some countries, part of the cost is reimbursed by health insurance, but this does not normally happen within the first couple of years of vaccine introduction *(72)*. In Belgium, France, Germany and the Netherlands, some health insurance plans reimbursed the quadrivalent HPV vaccine within the first year of introduction. In other countries (such as France and Italy), full reimbursement or vaccination free of charge for specific target populations has started.

Countries with limited health resources will have to consider carefully how national and international resources can be mobilized to fund the introduction of HPV vaccine and, if vaccines are introduced, how to identify target populations. For example, if access to vaccine is greatest among populations that are most likely to be periodically screened later in life, the current disparities in the incidence of cervical cancer related to differential access to screening may increase. However, if vaccines are targeted at populations that traditionally have limited access to periodic screening later in life (such as poor, rural or migratory populations) and thus are at increased risk of cancer, the introduction of vaccination could substantially reduce the incidence of precancerous lesions or cancer. This might be accomplished by making free access to vaccination available through public sector health systems.

To improve the availability of important new vaccines in countries with fewer resources, several initiatives have been taken in the field of financing, procurement and alternative routes to the development and production of vaccines.

- Low-income countries might benefit from tiered (or differential) pricing of the vaccine. This is a strategy adopted by vaccine firms in which they sell a vaccine at lower prices to the poorest countries and charge higher prices in middle- and high-income countries. Both GlaxoSmithKline and Merck have stated their commitment to tiered pricing for their HPV vaccines but have not yet announced substantially lower prices, in part because orders for high-volume purchases and price negotiations are just beginning.
- Discussions are also under way to obtain access to international financing mechanisms (e.g. through the Global Alliance for Vaccines and Immunizations – GAVI), which could potentially subsidize the vaccine for low-resource settings until affordable prices are achieved. The GAVI Fund provides funds for strengthening infrastructures, introducing new and underused vaccines, and providing safe injections to the world's 75 poorest countries *(73)*. Armenia, Azerbaijan, Georgia, Kyrgyzstan, Moldova, Ukraine and Uzbekistan are currently eligible for GAVI Phase 2 (which started in 2006), and Georgia is one of the 10 pilot countries selected to receive support in 2007–2008. In GAVI-eligible countries, discussion at national level about resource mobilization should be undertaken in the context of the national immunization programmes' multiyear plans, and should fit within broader health sector planning processes, such as sector-wide approaches and medium-term expenditure frameworks. This is essential to secure long-term governmental

support for the HPV vaccines and to ensure that these vaccines fit within national programmes. In low-income countries, these planning processes can run in tandem with preparing an application to GAVI. National immunization programmes will need the input of sexual and reproductive health and cancer control programmes in preparing applications to GAVI that reflect the multiple dimensions of HPV vaccines *(1)*.

Financial sustainability

Financial sustainability refers to the mobilization of the resources needed to cover the costs of an intervention into the future. If HPV vaccines are totally or partially funded by external donors, decision-makers should pay special attention to the duration of this support and how sustained access to vaccines can be assured once the donors' funding ends. If there are doubts about the sustainability of introducing the new vaccines, decision-makers should consider the benefits and risks of short-term use *(3)*.

Purchase and supply of vaccines

Governments have an important role in financing vaccines. They are responsible for the negotiation of contracts with vaccine manufacturers to obtain reduced prices for the public sector, and they will have to decide the budget to be made available for introducing HPV vaccines and which other funding mechanisms will be used. Principles of equity and access to vaccination have to be taken into account. In many countries, other new vaccines (such as rotavirus) have recently been introduced and may compete for public health care funds.

Once vaccines are licensed and their availability guaranteed, pooled procurement can help to improve access to them and, in some cases, to facilitate differential pricing. For example, purchases pooled by the United Nations Children's Fund (UNICEF) on behalf of low-income countries around the world yield lower prices.

Programmatic issues

Defining the target population for vaccination

When defining the target population for vaccination, decision-makers will need to consider both age and gender. As explained above, targeting older girls and young adolescents aged, for example, 9–12 years, before sexual debut, yields the greatest impact and cost-effectiveness, so this should be the primary target group for vaccination. The definition of the exact age for starting vaccination is important. This should be based on national data on age of sexual behaviour debut and the feasibility of delivering vaccine to children of various ages through schools, health systems or campaigns. Delivery may be enhanced by capitalizing on high rates of school attendance at this age and existing school-based vaccination programmes or school-age health campaigns. Delivery through health systems may capitalize on the extensive immunization experience of clinicians who commonly care for children, such as paediatricians and general practitioners, as well on the strong parental influence on children as regards seeking and deciding about health care.

Some countries may consider "catch-up" vaccination of older adolescent girls and young women, many of whom will already be sexually active. As vaccinating catch-up populations is less cost-effective than vaccinating the primary population, it is important not to divert resources from the primary target population. Mathematical models can help to determine the costs and

benefits of catch-up campaigns; these are likely to depend on the age-specific rates of HPV infection in the country *(2)*.

Currently, HPV vaccines are not licensed for use by boys in most European countries, but if future approved indications include boys, decision-makers should also consider the clinical benefits, costs and cost-effectiveness of vaccinating boys, given the different levels of vaccine coverage of girls.

Reaching target populations

Each country will need to identify the most feasible way to reach older and young adolescent girls before onset of sexual activity.

School-based immunization programmes, either delivered directly through schools or by immunization programmes using schools as venues, are one promising strategy because in Europe, school attendance by older girls and young adolescents is high and in some countries (e.g. Belgium) teenagers and adolescents are already vaccinated at school.

Special vaccine campaigns run by, for example, the Expanded Programme on Immunizations, provide another delivery strategy, although few are now used to reach adolescents. There are adolescent hepatitis B vaccination programmes in more than 15 countries in the Region and it may be possible to co-administer HPV vaccines with other vaccines, especially since data exist demonstrating the safety of co-administration of the quadrivalent vaccine with recombinant hepatitis B vaccines *(52)*. Sexual, reproductive, child and adolescent health programmes are well placed to assist in the development of HPV immunization programmes, given their experience with the delivery of health education and interventions in schools, communities and health care settings. However, many of these programmes have no or limited experience with vaccine delivery, including the complexities of buying the vaccine, maintaining the cold chain, administration and monitoring *(1)*. This highlights the need for collaboration with immunization experts.

HPV vaccines can also be delivered through existing private and public health systems by general practitioners, paediatricians, gynaecologists or other clinicians. These could include family planning clinics that reach many girls before or shortly after sexual debut. Experience with other adolescent vaccines indicates that to reach high coverage levels, programmes organized by health systems or schools that actively invite eligible girls for vaccination will be needed.

Many countries might decide to include older adolescents and young adults in catch-up vaccination campaigns. This group is more difficult to reach than younger girls who attend school. Countries will have to develop new platforms for the delivery of vaccination if they want to achieve high coverage in this population. Service delivery strategies to reach the secondary target population (young sexually active women) will be determined by the resources of the country and programmatic and feasibility considerations. Gynaecologists and general practitioners will probably take the lead in the vaccination of this group by providing the service directly or by referring women to routine vaccination sites.

Education and information

Many studies, including those undertaken in Europe, are largely consistent in their findings that young people of both sexes have limited awareness about HPV and related issues *(68)*. Knowledge of HPV also varies among health care providers, and may be especially limited among paediatricians and primary care providers who traditionally have not provided screening or treatment for cervical cancer or genital warts. However, these clinicians often have extensive experience with the delivery of vaccines. Conversely, gynaecologists who commonly screen for, diagnose and treat precancerous anogenital lesions and cancer are more knowledgeable about HPV and HPV-related disease, but they may lack experience with vaccination and the relevant procedures such as advance purchase, informed consent and storage.

Effective HPV education and training of clinicians are needed to improve their awareness of the benefits and risks of HPV vaccine, the logistics of vaccine delivery and the many new tools available. As an example, the European Cervical Cancer Association's materials (information brochures for patients and clinicians on cervical cancer screening, HPV and abnormal Pap smears) are available in Croatia, the Czech Republic, France, Germany, Greece, Italy, the Netherlands, Serbia, Spain, Sweden, Turkey and the United Kingdom. The Association has distributed information booklets on the prevention of cervical cancer and follow-up of abnormal Pap smears in Croatia, France, Serbia, Spain, Turkey and the United Kingdom. For health professionals, the Association has developed a patient communication tool kit including introductory brochures and information booklets, a guide on how and when to use the brochures and booklets, commonly asked questions with evidence-based answers and further background information.[9] These training materials contain advice about critical messages for clinicians and patients such as that HPV vaccines do not protect against all oncogenic types of HPV or against disease due to HPV infection present before vaccination, and that continued screening, if available, will be necessary after vaccination to reduce the risk of cancer to the maximum.

Delivery issues

The Region can build on its wide experience with administration of vaccines and the existence of expanded vaccination programmes. The Region as a whole has progressed greatly over the last 10 years to achieve sustained high coverage by many infant immunizations: for example, diphtheria, tetanus and pertussis 3 vaccination coverage was 95% in 2004.

Decision-makers considering the introduction of HPV vaccine should consider the logistical issues involved in delivery such as the capacity for cold chain space (which may be large given the current single-dose format and packaging of HPV vaccines), the availability of supplies from manufacturers or through international vaccine procurement agencies, the training of immunization staff, monitoring systems and the impact of co-administration with other vaccines. For both vaccines, studies on the safety, immunogenicity and efficacy of co-administration of quadrivalent HPV vaccine with combined diphtheria, tetanus and pertussis vaccine (with or without polio) and meningococcal conjugate vaccine in adolescents are underway.[10,11]

[9] European Cervical Cancer Association, Lyons, 2006 (http://www.ecca.info/webECCA/en/, accessed 6 March 2008).
[10] Eliav Barr, personal communication, 2007.
[11] Gary Dubin, personal communication, 2007.

Monitoring and evaluation of the impact of vaccination

The monitoring and evaluation of the impact of HPV vaccination will be complex and may require multifaceted strategies. Because invasive cancer can take decades to develop after initial HPV infection and it is not ethical to follow a woman diagnosed with a precancerous lesion until invasive disease develops, many strategies will focus on the impact of vaccination on the incidence of persistent oncogenic HPV infection that is associated with precancerous lesions detected through cytological screening or visual inspection. For example, long-term efficacy trials of HPV vaccine are currently in progress in the Nordic countries. These are designed to detect the impact of vaccination on CIN3+ by 2015–2020, using the Nordic health registry infrastructure *(74,75)*.

Countries that have organized screening programmes could adapt these programmes to monitor the impact of vaccination on precancerous lesions. Countries that use HPV tests as part of their cervical cancer screening or abnormal cytology follow-up could consider surveillance for persistent HPV infection in older women that is associated with precancerous lesions. Countries that have cancer registries should see whether registries that typically conduct surveillance for invasive cancer could be expanded to include surveillance of the incidence of precancerous cervical lesions. Where such programmes do not exist, sentinel surveillance programmes in a limited geographical area may be feasible. In the absence of national data, data from proxy countries where similar programmes exist can be used.

It is clear that, whatever monitoring system will be put in place, coordination with cancer control programmes will be essential to monitor the impact of vaccination and estimate its benefits compared to other interventions, such as screening.

Vaccine uptake and compliance

Process indicators are used to monitor the correct implementation and progress of the programme, with the aim of verifying whether the target population is being adequately vaccinated. These include:

- coverage rate: proportion of the target population that received all three doses;
- drop-out rate: proportion of the target population that received fewer than three doses.

These indicators would need to be added to national immunization information systems, most of which do not have systems for monitoring three-dose vaccines in adolescents.

Surveillance of the disease

Effectiveness of the vaccine

Outcome indicators are used to monitor the effectiveness of the programme. The aim is to verify whether the vaccination reaches its goals of reducing the prevalence of persistent infection with vaccine-related types of HPV, the number of precancerous lesions of the cervix due to vaccine-

related types of HPV and, ultimately, reducing the incidence of and mortality from cervical cancer. Possible indicators include the following.[12]

- *Type-specific HPV prevalence and distribution*. To measure this indicator, type-specific HPV tests are needed. These are not routinely collected but can be obtained by clinical studies in selected sentinel populations of people vaccinated and controls. If HPV tests are not routinely done in a country, laboratories may need to be equipped and staff trained. The WHO HPV Laboratory Network is establishing HPV testing capacity in all regions, including laboratories in Europe, to include the development of standard reagents and operating procedures to standardize HPV test performance.
- *Incidence of precancerous lesions of the cervix*. As noted above, these may be estimated through organized national or sentinel screening programmes. This indicator is most reliable if the coverage, testing methods, age of initial screening and screening intervals remain constant over time. This indicator may, however, be difficult to interpret if the vaccinated populations are initially screened later or less frequently than non-vaccinated populations, as some experts propose to make vaccination a more cost-effective prevention strategy.
- *Ratio of women treated for precancerous lesions per number screened*. This indicator can be used as a proxy for monitoring pre-invasive disease in "screen and treat" programmes that rely on visual inspection methods and do not monitor the incidence of cytological or pathologically-confirmed precancerous lesions. This indicator is, however, highly dependant on the capacity of the system to treat women.
- *Incidence and mortality of invasive cervical cancer*. The monitoring of age-specific incidence and mortality rates of cancer over time allows the effect in vaccinated cohorts to be monitored and compared with non-vaccinated cohorts. These rates can be derived from national cancer registries or, in their absence, from the health information systems and programme monitoring (e.g. cases detected in referral hospitals). Although it may be challenging to establish cancer registries in countries where they currently do not exist, they should be encouraged when resources are available. They are especially valuable for monitoring preventable cancers, such as cervical and tobacco-related cancers, that could decline as a result of cancer prevention interventions.

Monitoring safety and adverse effects following immunization

Countries that introduce the HPV vaccine should actively monitor the results of clinical trials sponsored by industry that continue to monitor vaccine safety, including the long-term Nordic trials that are evaluating the incidence of chronic diseases in vaccine recipients, autoimmune diseases or gynaecological conditions in non-vaccinated populations that may first present in adolescence, such as multiple sclerosis, thyroiditis, diabetes and menstrual problems *(76).*

Other important sources include post-marketing surveillance for adverse events in Europe through the EMEA system. If countries collect background information on the rates of these conditions in the target groups for vaccination (e.g. those aged 9–25 years) before the vaccines are introduced, it will help to distinguish vaccine-related events from events unrelated to

[12] Indicators formulated by experts during the UNFPA/WHO Consultation on Sexual and Reproductive Health Programmes and HPV Vaccines, Montreux, 14–16 March 2006.

vaccination that typically first present at this age. It would also be advantageous for systems to have information on the concurrent administration of vaccines and medications commonly used at this age, including contraceptives, to help distinguish events related to HPV vaccines versus co-administered vaccines or medications.

Although HPV vaccines are not recommended for pregnant women and girls, some will become pregnant during the six-month vaccination period or shortly after vaccination. The safety of vaccinated women who become pregnant is of special concern and is being monitored by the European regulatory agencies. The inclusion of pregnancy status and timing in surveillance systems for adverse events following immunization would allow for the evaluation of safety in pregnancy.

All countries where the vaccine is introduced should establish a system to report vaccine-related adverse effects as an essential part of programme monitoring, if feasible. Such systems should have the capacity to investigate adverse events and communicate any concerns to health care professionals and the public.

Annex 1

RECOMMENDATIONS[a] AND FUNDING STATUS FOR HPV VACCINES AS AT 1 NOVEMBER 2007

Country	Recommendation			Funding	
	Announce-ment date	**Recommend-ing Committee**	**Population targeted**	**Announce-ment date**	**Type of funding**
Austria	20/2/2007	Austrian Supreme Health Board, Vaccination Committee	Girls aged 12 years	–	Government funding for all girls aged 12 years; other populations pay out of pocket.
Belgium	11/5/2007	Superior Health Council	Girls aged 10–13 years. Facultative catch-up vaccination of (virgin) female adolescents and young women aged 14–26 years can be proposed by the physician.	9/1/2007	Partial funding through some health insurance funds, mostly in Flanders. Reimbursement for a generalized catch-up vaccination of children aged 12–15 years including age cohorts for girls.
Denmark[b]	9/10/2007	National Board of Health	Vaccination for all girls aged 12 years. Catch-up for girls aged 13–15 years.	–	Vaccine to be offered through the Childhood Vaccination Programme.
France	9/3/2007	Technical Committee on Vaccinations and Council for Public Health.	Girls aged 14 years. Catch-up for females aged 15–23 years, before or within first year of sexual activity.	17/10/2006	Reimbursement by three private insurances at 65% of cost of the vaccination. Ministry of Health announced integration in reimbursement list by July 2007.
Germany	26/3/2007	Committee on Vaccination at Robert Koch Institute	Girls aged 12–17 years before first sexual intercourse.	Reimbursement by sickness funds started in December 2006. Federal Health Care Committee decision, 22 June 2007. Ministry approval to enter into force expected soon.	Subject to approval of the Ministry of Health and official publication, all preventive vaccinations recommended by the Standing Committee on Vaccination, including HPV vaccines, will be obligatorily reimbursed by the health insurers. Since December 2006, 39 sickness funds have started reimbursements before recommendation (exceptional situation).

Country	Recommendation			Funding	
	Announce-ment date	Recommend-ing Committee	Population targeted	Announce-ment date	Type of funding
					Over 65% (82 million) of the German market within these Gardasil age groups is covered by the sickness funds reimbursing HPV vaccination. On 1 October, in compliance with the publication in the official journal, all sickness funds will have to reimburse HPV vaccination.
Greece	19/10/2007	National Vaccination Committee	Vaccination of girls aged 12–15 years. Catch up for girls aged 15–26 years.		
Italy	11/1/2007	Higher Health Council, Ministry of Health	Girls aged 12 years. Catch-up for females aged 25–26 years. Potential third cohort of females aged 13–24 years.	28/2/2007	The Government will fund Gardasil through a free and proactive vaccination programme for all girls aged 12 years. Local registration and reimbursement for this group. No limitation of prescription by physician. For the population not yet included in the vaccination programme, Gardasil will be available in pharmacies at customers' expense and with a medical prescription.
Liechtenstein				10/7/2007	Vaccination for girls and young women up to 26 years will be obligatorily reimbursed by the health insurers. Reimbursement for women aged over 26 years requires a specific justification by the general practitioner.
Luxembourg	27/2/2007	Superior Hygiene Council	All girls aged 11–12 years. Catch-up for girls aged 13–18 years.	–	–
Netherlands	–	–	–	December 2006	Four private health insurers reimburse Gardasil 100% for 0.5–1 million girls and young women aged 9–26 years and boys aged 9–15 years.
Norway	12/4/2007	The Norwegian Institute of Public Health	All girls aged 11–12 years and catch-up for girls until 16	–	Funding to be decided.

Country	Recommendation			Funding	
	Announce-ment date	Recommend-ing Committee	Population targeted	Announce-ment date	Type of funding
			years. Further vaccination should take place on an individual indication.		
Spain	26/9/2007	Public Health Commission, approved by Inter-territorial Board 11 October.	One cohort of girls aged 11–14 years.	26/9/2007	To be included in the vaccination calendar of the national health system not later than 2010.
Sweden	–	Swedish Pharmaceutical Benefits Board	Vaccination for girls aged 13–17 years.	9/5/2007	Reimbursement of vaccination against cervical cancer for girls aged 13–17 years (private market) (co-payment by parents of more or less 15%).
Switzerland	18/6/2007	Federal Commission for Vaccinations	Girls aged 11–14 years. Catch-up vaccination for girls aged 15–19 years (during 5 years) Vaccination of women aged 20 years and older should be decided on an individual basis.	–	Decision on reimbursement to be taken by end 2007.
United Kingdom	2/7/2007	Joint Committee on Vaccination and Immunization	Girls aged 12–13 years. Catch-up for girls up to 18 years.	2/7/2007	Publicly funded.

Note: The Portuguese recommendation is in preparation. The cohorts for routine vaccination were to be chosen in the group aged 12–16 years by the Vaccine Technical Commission by the end of November.

[a] Apart from the United Kingdom, the recommendations apply to Gardasil, as Cervarix has only recently been marketed and countries have not yet had time to adapt their recommendations.

[b] The Danish recommendation explicitly states that the quadrivalent vaccine should be used to protect also against condyloma.

References

1. Broutet N, Lazdane G. *Preparing for the introduction of HPV vaccines. Policy and programme guidance for countries*, 1st ed. Geneva, World Health Organization, 2006 (WHO/RHR/06.11).
2. Inititative for Vaccine Research. *Human papillomavirus and HPV vaccines. Technical information for policy-makers and health professionals*, 1st ed. Geneva, World Health Organization, 2007 (WHO/IVB/07.05).
3. Expanded Programme on Immunization. *Vaccine. Adding a vaccine to a national immunization programme: decision and implementation*. Geneva, World Health Organization, 2005 (WHO/IVB/05.18, http://www.who.int/vaccines-documents/DocsPDF05/777_screen.pdf, accessed 6 March 2008).
4. *Comprehensive cervical cancer control: a guide to essential practice*, 1st ed. Geneva, World Health Organization, 2006.
5. International Agency for Research on Cancer. *Cervix cancer screening.* Lyons, IARC Press, 2005 (IARC Handbooks of Cancer Prevention. Vol. 10).
6. zur Hausen H. Papillomavirus infections – a major cause of human cancers. *Biochimica et Biophysica Acta*, 1996, 1288(2):55–78.
7. Walboomers JM et al. Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *Journal of Pathology*, 1999, 189(1):12–19.
8. Hobbs CG et al. Human papillomavirus and head and neck cancer: a systematic review and meta-analysis. *Clinical Otolaryngology*, 2006, 31(4):259–266.
9. Parkin DM, Bray F. Chapter 2: The burden of HPV-related cancers. *Vaccine*, 2006, 24(Suppl. 3):S11–S25.
10. *National cancer control programmes*, 1st ed. Geneva, World Health Organization, 2002.
11. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the United Kingdom audit of screening histories. *British Journal of Cancer*, 2003, 89(1):88–93.
12. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. *British Medical Journal*, 1986, 293:659–664.
13. Cuzick J et al. Chapter 10: New dimensions in cervical cancer screening. *Vaccine*, 2006, 24(Suppl. 3):S90–S97.
14. Bleeker MC et al. Penile lesions and human papillomavirus in male sexual partners of women with cervical intraepithelial neoplasia. *Journal of the American Academy of Dermatology*, 2002, 47(3):351–357.
15. Hogewoning CJ et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *International Journal of Cancer*, 2003, 107(5):811–816.
16. Hippelainen MI et al. Clinical course and prognostic factors of human papillomavirus infections in men. *Sexually Transmitted Diseases*, 1994, 21(5):272–279.
17. Manhart LE, Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases*, 2002, 29(11):725–735.
18. Winer RL et al. Condom use and the risk of genital human papillomavirus infection in young women. *New England Journal of Medicine*, 2006, 354(25):2645–2654.
19. Saslow D et al. American Cancer Society Guideline for HPV Vaccine Use to prevent cervical cancer and its precursors. *CA: A Cancer Journal for Clinicians*, 2007, 57(1):6–28.
20. WHO/ICO Information Centre on HPV and Cervical Cancer. *Human papillomavirus and cervical cancer. Europe. Summary report.* Geneva, World Health Organization, 2007.
21. Fenton KA et al. Sexual behaviour in Britain: reported sexually transmitted infections and prevalent genital *Chlamydia trachomatis* infection. *Lancet*, 2001, 358(9296):1851–1854.
22. Lacey CJ, Lowndes CM, Shah KV. Chapter 4: Burden and management of non-cancerous HPV-related conditions: HIV-6/11 disease. *Vaccine*, 2006, 24(Suppl. 3):S35–S41.
23. IARC Working Group on Evaluation of Cervical Cancer Screening Programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its

implication for screening policies. *British Medical Journal (Clinical Research ed.)* 1986, 293(6548):659–664.
24. Lynge E, Madsen M, Engholm G. Effect of organized screening on incidence and mortality of cervical cancer in Denmark. *Cancer Research*, 1989, 49(8):2157–2160.
25. Sigurdsson K. Cervical cancer screening-effectiveness and implications of HPV vaccines in Iceland. *Entre Nous*, 2007, 64:16–18.
26. Nieminen P et al. Organised versus spontaneous pap-smear screening for cervical cancer, a case control study. *International Journal of Cancer*, 1999, 83:55–58.
27. Coleman D et al. European guidelines for quality assurance in cervical cancer screening. *European Journal of Cancer*, 1993, 29A(Suppl. 4):1–38.
28. Cancer incidence, mortality and prevalence worldwide. IARC Globocan CancerBase No. 5, version 2.0. Lyons, IARC Press, 2002 (http://www-dep.iarc.fr/globocan/downloads.htm, accessed 26 March 2008).
29. Quinn M et al. Effect of screening on incidence of and mortality from cancer of cervix in England: evaluation based on routinely collected statistics. *British Journal of Medicine*, 1999, 318(7188):904–908.
30. Rebolj M et al. Monitoring a national cancer prevention program: successful changes in cervical cancer screening in the Netherlands. *International Journal of Cancer*, 2007, 120(4):806–812.
31. Council recommendation of 2 December 2003 on cancer screening (2003/878/EC). *Official Journal of the European Union*, L 327/34, 16 December 2003 (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:327:0034:0038:EN:PDF, accessed 6 March 2008).
32. Arbyn M et al. The burden of cervical cancer in south-east Europe at the beginning of the 21st century. *Collegium Antropologicum*, 2007, 31(Suppl. 2):7–10.
33. *European public assessment report (EPAR). Gardasil*. London, European Medicines Agency, 2006 (EMEA/H/C/703) (http://www.emea.europa.eu/humandocs/PDFs/EPAR/gardasil/070306en1.pdf., accessed 27 February 2008).
34. GlaxoSmithKline. *Cervarix, GSK's cervical cancer vaccine, approved in Europe.* Press release, 24 September 2007 (http://www.gsk.com/media/pressreleases/2007/2007_09_24_GSK1117.htm, accessed 27 February 2008).
35. Zhou J et al. Expression of vaccinia recombinant HPV 16 L1 and L2 ORF proteins in epithelial cells is sufficient for assembly of HPV virion-like particles. *Virology*, 1991, 185(1):251–257.
36. Hagensee ME, Yaegashi N, Galloway DA. Self-assembly of human papillomavirus type 1 capsids by expression of the L1 protein alone or by coexpression of the L1 and the L2 capsid proteins. *Journal of Virology*, 1993, 67(1):315–322.
37. Cutts FT et al. Human papillomavirus and HPV vaccines: a review. *Bulletin of the World Health Organization*, 2007, 85(9):649–732.
38. Villa LL et al. Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial. *The Lancet Oncology*, 2005, 6(5):271–278.
39. Villa LL et al. Immunologic responses following administration of a vaccine targeting human papillomavirus Types 6, 11, 16, and 18. *Vaccine*, 2006, 24(27–28):5571–5583.
40. Villa LL et al. High sustained efficacy of a prophylactic quadrivalent human papillomavirus types 6/11/16/18 L1 virus-like particle vaccine through 5 years of follow-up. *British Journal of Cancer*, 2006, 95(11):1459–1466.
41. The Future II Study Group. Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions. *New England Journal of Medicine*, 2007, 356(19):1915–1927.
42. Garland SM et al. Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases. *New England Journal of Medicine*, 2007, 356(19):1928–1943.
43. Block SL et al. Comparison of the immunogenicity and reactogenicity of a prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in male and female adolescents and young adult women. *Pediatrics*, 2006, 118(5):2135–2145.
44. Reisinger KS et al. Safety and persistent immunogenicity of quadrivalent human papillomavirus types 6, 11, 16, 18 L1 virus-like particle vaccine in preadolescents and adolescents: a randomized controlled trial. *The Pediatric Infectious Disease Journal*, 2007, 26(3):201–209.

45. Harper DM et al. Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial. *Lancet,* 2004, 364(9447):1757–1765.
46. Harper DM et al. Sustained efficacy up to 4.5 years of a bivalent L1 virus-like particle vaccine against human papillomavirus types 16 and 18: follow-up from a randomised control trial. *Lancet,* 2006, 367(9518):1247–1255.
47. Paavonen J et al. Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial. *Lancet,* 2007, 369(9580):2161–2170.
48. Schwarz TF. An AS04-containing HPV 16/18 vaccines for prevention of cervical cancer is immunogenic and well tolerated in women 15–55 years old. *Journal of Clinical Oncology*, 2006, 24(18S):1008 (abstract).
49. Smith JF et al. *Antibodies cross-neutralize pseudovirion infection of vaccine-related HPV types. Prague, 23rd Internation Papillomavirus Conference and Clinical Workshop, 1–7 September 2006* (abstract).
50. Koutsky LA et al. A controlled trial of a human papillomavirus type 16 vaccine. *New England Journal of Medicine,* 2002, 347(21):1645–1651.
51. Mao C et al. Efficacy of human papillomavirus-16 vaccine to prevent cervical intraepithelial neoplasia: a randomized controlled trial. *Obstetrics & Gynecology*, 2006, 107(1):18–27.
52. Markowitz L et al. Quadrivalent human papillomavirus vaccine. *Morbidity and Mortality Weekly Report,* 2007, 56(RR-2).
53. Center for Biologics Evaluation and Research. *Product approval information. Human papillomavirus quadrivalent (types 6, 11, 16, 18) vaccine, recombinant. Gardasil, Merck & Co, Inc.* Rockville MD, U.S. Food and Drug Administration, 2007 (http://www.fda.gov/cber/products/gardasil.htm, accessed 6 March 2008).
54. Newall A et al. Cost-effectiveness analyses of HPV vaccination. *Lancet*, 2007, 7:289–296.
55. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerging Infectious Diseases Journal*, 2007, 13(1):28–41.
56. Barnabas RV et al. Epidemiology of HPV16 and cervical cancer in Finland and the potential impact of vaccination: mathematical modelling analyses. *PLoS Medicine*, 2006, 3(5):e138.
57. French KM et al. Strategies for the introduction of human papillomavirus vaccination: modelling the optimum age- and sex-specific pattern of vaccination in Finland. *International Journal of Gynecology & Obstetrics*, 2006, 94(Suppl. 1):95–105.
58. *Økonomisk evaluering av humant papillomavirus (HPV)-vaksinasjon I Norge [Cost-effectiveness of human papillomavirus (HPV) vaccination in Norway]*. Oslo, Norwegian Knowledge Centre for the Health Services, 2007 (Report No. 12, in English) (http://www.kunnskapssenteret.no/filer/rapport_0712_ HPVdel2.pdf, accessed 6 March 2008).
59. Goldie S. A public health approach to cervical cancer control: considerations of screening and vaccination strategies. *International Journal of Gynecology & Obstetrics*, 2006, 94(Suppl. 1):95–105.
60. Garnett GP et al. Chapter 21: Modelling the impact of HPV vaccines on cervical cancer and screening programmes. *Vaccine,* 2006, 24(Suppl. 3):S178–S186.
61. Kane MA et al. Chapter 15. HPV vaccine use in the developing world. *Vaccine,* 2006, 24(Suppl. 3):S132–S139.
62. Clifford GM et al. Human papillomavirus types in invasive cervical cancer worldwide: a meta-analysis. *British Journal of Cancer*, 2003, 88(1):63–73.
63. Clifford GM et al. Comparison of HPV type distribution in high-grade cervical lesions and cervical cancer: a meta-analysis. *British Journal of Cancer,* 2003, 89(1):101–105.
64. Arbyn M, Dillner J. Review of current knowledge on HPV vaccination: an appendix to the European Guidelines for Quality Assurance in Cervical Cancer Screening. *Journal of Clinical Virology*, 2007, 38(3):189–197.
65. Wright TC et al. Chapter 30: HPV vaccines and screening in the prevention of cervical cancer; conclusions from a 2006 workshop of international experts. *Vaccine,* 2006, 24(Suppl. 3):251–261.
66. Anttila A. Cervical cancer screening is effective. The Finnish experience. *Entre Nous*, 2007, 64:25–27.

67. Rasmussen P. *PATH and Digene partner to bring HPV testing for cervical cancer to developing countries*. Seattle, PATH, 2004 (http://www path org/news/pr-040216 php, accessed 27 February 2008).
68. Zimet GD et al. Chapter 24: Psychosocial aspects of vaccine acceptability. *Vaccine*, 2006, 24(Suppl. 3):201–209.
69. Woodhall SC et al. Anticipated acceptance of HPV vaccination at the baseline of implementation: a survey of parental and adolescent knowledge and attitudes in Finland. *Journal of Adolescent Health*, 2007, 40(5):466–469.
70. Brabin L et al. Future acceptance of adolescent human papillomavirus vaccination: a survey of parental attitudes. *Vaccine*, 2006, 24(16):3087–3094.
71. Brabin L, Roberts SA, Kitchener HC. A semi-qualitative study of attitudes to vaccinating adolescents against human papillomavirus without parental consent. *BMC Public Health*, 2007, 7:20.
72. Wright TC et al. Chapter 14: HPV vaccine introduction in industrialized countries. *Vaccine*, 2006, 24(Suppl. 3):S122–S131.
73. Kaddar M, Lydon P, Levine R. Financial challenges of immunization: a look at GAVI. *Bulletin of the World Health Organization*, 2004, 82(9):697–702.
74. Lehtinen M et al. Enrolment of 22 000 adolescent women to cancer registry follow-up for long-term human papillomavirus vaccine efficacy: guarding against guessing. *International Journal of STD and AIDS*, 2006, 17(8):517–521.
75. Lehtinen M et al. Population-based enrolment of adolescents in a long-term follow-up trial of human papillomavirus vaccine efficacy. *International Journal of STD and AIDS*, 2006, 17(4):237–246.
76. Lehtinen M et al. Chapter 28: Studies to assess the long-term efficacy and effectiveness of HPV vaccination in developed and developing countries. *Vaccine*, 2006, 24 (Suppl. 3):S233–S241.