Preparing for the introduction of HPV vaccines: policy and programme guidance for countries

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Contents

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– Reproductive Health and Research (RHR)
– Immunization, Vaccines and Biologicals (IVB)
– Child and Adolescent Health and Development (CAH)
– Chronic Diseases and Health Promotion (CHP)
– Health Policy, Development and Services (HDS)
– Ethics, Trade, Human Rights and Health Law (ETH)

Introduction

This guidance note is based on a UNFPA/WHO Technical Consultation on HPV Vaccines and Sexual and Reproductive Health Programmes, held in March 2006 in Montreux, Switzerland. It is intended to alert a broad array of stakeholders – in sexual and reproductive health, immunization, child and adolescent health, and cancer control programmes – to some of the key issues surrounding the upcoming introduction of HPV vaccines against cervical cancer. In particular, it highlights the contributions that national immunization programmes, sexual and reproductive health programmes, and cancer control programmes can make in preparing for national introduction of the vaccines in the context of the Global Immunization Vision and Strategy.

Cervical cancer and HPV infection

Cancer of the cervix is the second most common cancer in women worldwide, with about 500 000 new cases and 250 000 deaths each year. Almost 80% of cases occur in low-income countries, where cervical cancer is the most common cancer in women.

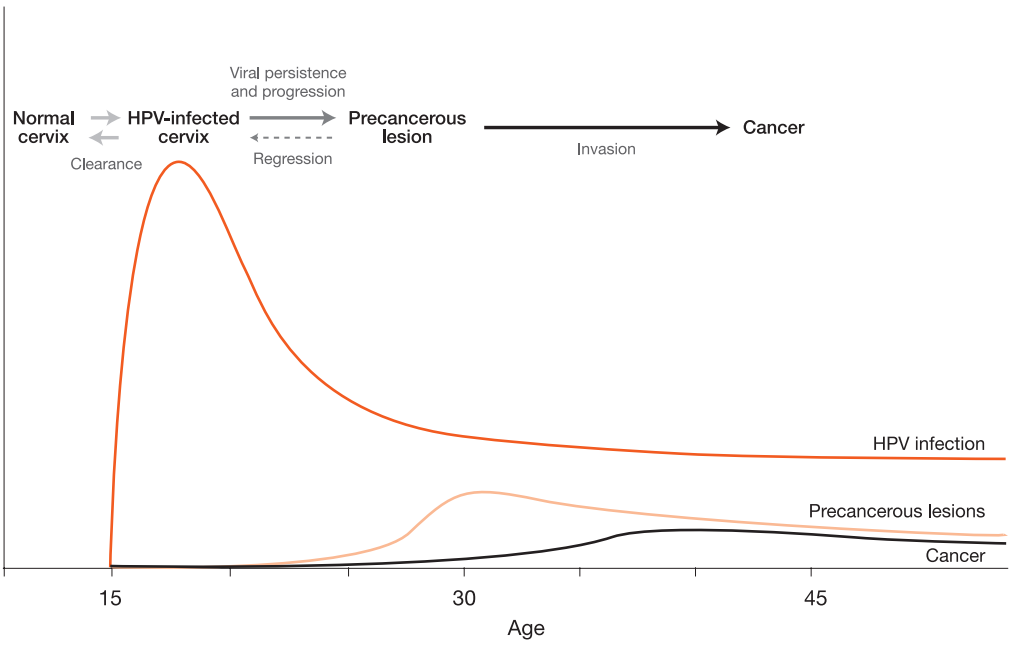
Virtually all cervical cancer cases (99%) are linked to genital infection with human papillomavirus (HPV), which is the most common viral infection of the reproductive tract. There are 40 different genotypes of HPV that can infect the genital area of men and women, including the skin of the penis, the vulva (the area outside the vagina), and anus, and the lining of the vagina, cervix, and rectum. Two "high-risk" genotypes (HPV 16 and 18) are responsible for the majority of HPV-related cancers of the cervix, vulva, vagina, anus and penis worldwide. Two "low-risk" genotypes (HPV 6 and 11) cause a substantial proportion of low-grade cervical dysplasia (i.e. cell abnormalities) detected in screening programmes and more than 90% of genital warts. The peak incidence of HPV infection generally occurs between the ages of 16 and 20 years. HPV infection usually resolves spontaneously, but it may persist, and precancerous cervical lesions may follow. If untreated, these may progress to cervical cancer over a period of 20–30 years. During the period of persistent HPV infection, precancerous changes may be detected in the cervix; early detection of these changes is an effective strategy for prevention of cervical cancer (Figure 1).

A comprehensive approach to prevention and control of cervical cancer encompasses interventions along the continuum of care, from primary prevention to early detection, treatment and palliative care. In high-income countries, deaths from cervical cancer have been greatly reduced through wide coverage of cytology-based screening programmes, which allow early detection and treatment of precancerous lesions. Progress has been made in developing a simplified approach to early detection of precancerous lesions, for use in low-income countries, through visual inspection of the cervix. Studies have shown that this approach has the potential to reduce cervical cancer in low-resource settings, since it can be implemented by mid-level personnel and does not need laboratory services or highly trained staff. Screening and treatment, where necessary, can be done at a single visit, using visual inspection with acetic acid (VIA) and cryotherapy. However, the impact of this approach on cervical cancer incidence and mortality still needs

World Health Assembly resolution on prevention and control of cancer

A resolution on cancer prevention and control, in the context of WHO's intensified action against cancer, was adopted by WHO Member States during the 58th World Health Assembly in 2005 (Resolution WHA58.22). This resolution emphasizes that the control of cervical cancer will contribute to the attainment of international development goals and targets related to reproductive health, and urges Member States to pay attention in their cancer control planning to cancers for which avoidable exposure is a factor, particularly exposure to certain infectious agents. It also requests the Director-General, "to promote research on development of an effective vaccine against cervical cancer."

Figure 1. Prevalence of HPV infection, precancerous lesions and cervical cancer by age of women



Source: Schiffman M, Castle PE. The promise of global cervical-cancer prevention. *New England Journal of Medicine*, 2005, 353(20): 2101–2103. (© 2005 Massachusetts Medical Society. Adapted with permission.)

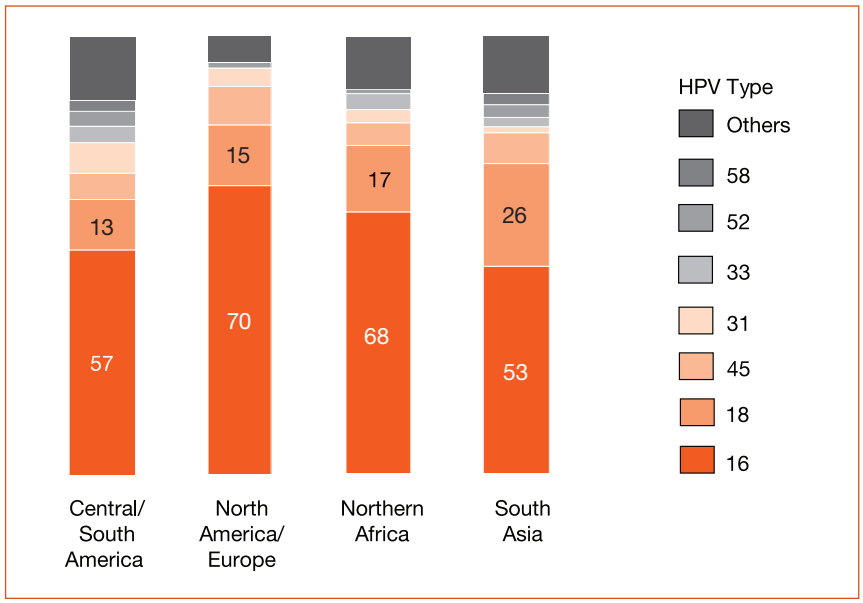
to be documented. Even if cervical cancer is only detected at early invasive stages, it can be treated through surgery or radiotherapy, which have a high cure rate.

Vaccines against HPV

HPV vaccines contain the major capsid L1 proteins, which self-assemble into virus-like particles (VLP) resembling HPV. These particles do not contain viral genetic material and thus are unable to multiply, which means they are non-infectious. Two prophylactic HPV vaccines have shown excellent efficacy against persistent HPV infection and related cervical lesions among HPV-naive women (i.e. women who have never been exposed to the virus) aged 16–24 years, in proof-of-principle studies.

Both vaccines target HPV types 16 and 18, which are responsible for 70% of cervical cancer cases worldwide. In addition, one vaccine also targets HPV types 6 and 11, which cause low-grade cervical abnormalities and the vast majority of genital warts. Results from large studies of the HPV vaccines, with about 2–5 years of follow-up, showed almost 100% protection against cervical cancer

Figure 2. Prevalence (%) of different HPV types among women with cancer, by region



Source of data: Muñoz N et al. Against which human papillomavirus type shall we vaccinate and screen? The international perspective. *International Journal of Cancer*, 2004, 111:278–285.

precursor lesions related to the vaccine genotypes. For the quadrivalent vaccine, protection against genital warts was 95–99%. However, because of the heterogeneity of HPV genotypes in different parts of the world (Figure 2), the impact of the two candidate vaccines may vary across regions. Nevertheless, the vaccines are expected to prevent cervical cancer in 70% of HPV-naive women.[1]

Follow-up of the women involved in the large Phase III multicentre clinical trials is continuing, combined with bridging immunogenicity and safety studies, to answer outstanding questions about both candidate vaccines. Among the points under study, the following are particularly relevant for programmes and service delivery strategies: long-term efficacy; duration of immunogenicity and hence the need for boosters; and immunogenicity, safety and efficacy in specific populations, such as pregnant women and immunocompromised patients.

For more technical information on the two HPV vaccines, please visit the following web site: <http://www.who.int/vaccine_research/documents/816%20%20HPV%20meeting.pdf>.

Target populations for HPV immunization

In defining the target population for immunization, a key consideration is that HPV infection is sexually transmitted and is usually acquired within the first few years following sexual debut. Ideally, therefore, the vaccine should be administered before sexual debut, i.e. before any risk of exposure to HPV.

Current indications suggest that, initially, the HPV vaccines will be licensed for use in girls and women aged 9–26 years. Vaccination has been shown to result in high seroconversion rates in all age groups studied, but bridging immunogenicity studies for both vaccines have demonstrated higher immunogenicity in young adolescents than in women over 15 years. The target age range will be specified in national licensing standards, and appropriate service delivery strategies will need to be developed to reach the primary target population (young age cohort). In addition, strategies may be needed to provide “catch-up” vaccination for secondary populations (see section on Service delivery, page 13).

[1] Two prophylactic vaccines, both highly effective against oncogenic HPV types 16 and 18, are expected be available in developed countries by 2006–2007. GlaxoSmithKline Biologicals’ Cervarix® is expected to complete Phase III testing in 2007. Merck’s Gardasil® also includes protection against HPV types 6 and 11. At the time of writing, an application for registration of Gardasil has been filed in a number of countries, including the USA and several European countries; approval is expected in 2006. Cervarix is expected to be registered in Europe soon after, and an application filed in the USA by the end of 2006.

Other populations may potentially benefit from HPV vaccines, but more clinical data are needed before licensing guidelines can be expanded. These populations include:

- *Males*. Potentially, both vaccines could provide direct benefit by preventing HPV16/18-related anogenital cancers. Although vaccinating males could theoretically reduce transmission of HPV to females, preliminary results of modelling studies in Finland suggest that, in settings with high vaccination coverage of the female population, the additional benefit in terms of cervical cancer reduction – over and above that resulting from vaccinating women alone – is marginal. However, modelling studies of the benefit of male vaccination where vaccination rates in females are moderate are still continuing.
- *Younger age groups (<9 years)*. Vaccination of younger age groups may be more easily incorporated into existing national immunization programmes than vaccination of older groups (9–26 years). No vaccination trials have yet been conducted in children less than 9 years old.
- *HIV-infected persons*. The efficacy and safety of the vaccine in HIV-infected individuals are currently unknown. Trials among HIV-infected women are still in progress.
- *Pregnant women*. The safety of the vaccine in pregnant women is currently unknown.

Trials are also under way to evaluate the effects of vaccine administration to women older than 25 years, and those who have, or have previously had, infection with HPV 16 or 18. The cost-effectiveness of including these groups in vaccination programmes is not known.

Innovative features of HPV vaccines

The Global Reproductive Health Strategy (*Reproductive health strategy to accelerate progress towards the attainment of international development goals and targets*, Geneva, World Health Organization, 2005), adopted by WHO Member States in 2004 (World Health Assembly Resolution WHA57.12), identified five essential components of sexual and reproductive health: improving antenatal, delivery, postpartum and newborn care; providing high-quality services for family planning, including infertility services; eliminating unsafe abortion; combating sexually transmitted infections, including HIV, reproductive tract infections, cervical cancer and other gynaecological morbidities; and promoting sexual health. The Strategy also states that, "*because of the close links between different aspects of reproductive and sexual health, interventions in one area are likely to have a positive impact on others. It is crucial for countries to strengthen existing services and use them as entry points for new interventions, looking for maximum synergy.*"

HPV vaccines have the potential to strengthen interactions among different health services and to provide a new way of preventing a common cancer on a very large scale, as well as reducing the more widespread burden of genital dysplasia and warts. Some of the key features of the vaccines are discussed below.

A unique opportunity

Vaccines against HPV have several features that require special consideration. Their use requires new approaches to programme delivery; the target population is different from that usually addressed by national immunization programmes; multiple stakeholders need to be involved in advocacy and social communication; and the best combination of vaccination and screening for cervical cancer programmes remains unclear. For the first time, sexual and reproductive health communities will be working with a vaccine directed against a sexually transmitted infection that is linked to a fairly common genital cancer, raising issues quite distinct from experience with other vaccines, such as those against rubella and tetanus.

The HPV vaccines will bring national immunization programmes to the sociopolitically charged environment of sexual health, sexuality and sexually transmitted infections among young adolescent girls and possibly boys. Other challenges will be associated with broadening the scope of the Expanded Programme on Immunization (EPI) from its predominant focus on infant and childhood conditions to encompass older age groups.[2]

[2] Although most Expanded Programmes on Immunization now include hepatitis B vaccine, which prevents related liver cancer, this vaccine is given to infants because most infections in developing countries occur in early childhood. Hence, direct links with existing cancer control programmes were not a prerequisite for the introduction of hepatitis B vaccine.

UNICEF/WHO Global Immunization Vision and Strategy (GIVS)

A new vision for immunization, the Global Immunization Vision and Strategy (GIVS) developed by WHO and UNICEF, has been endorsed by the 58th World Health Assembly. GIVS is striving for a world in 2015 in which:

- immunization is highly valued
- every child, adolescent and adult has equal access to immunization as provided for in their national schedule
- more people are protected against more diseases
- immunization and related interventions are sustained in conditions of diverse social values, changing demographics and economies, and evolving diseases
- immunization is seen as crucial for the wider strengthening of health systems and a major element of efforts to attain the Millennium Development Goals
- vaccines are put to best use in improving health and security globally
- solidarity among the global community guarantees equitable access for all people to the vaccines they need.

This expansion is envisioned in the Global Immunization Vision and Strategy (GIVS), which has been developed jointly by WHO and the United Nations Children's Fund (UNICEF), and was adopted by the World Health Assembly in 2005,[3] and which seeks to expand the scope of EPI into other settings and to other age groups than infants. National cancer control programmes will also face difficult decisions regarding the priority they give to primary prevention (vaccination), secondary prevention (screening and treatment of precancers), cancer treatment, and palliative care and where to start in settings where very little is currently done to prevent and control cervical cancer.

Experience with the introduction of HPV vaccines may serve as a model for an eventual vaccine against human immunodeficiency virus (HIV); cervical cancer prevention and care among immunocompromised women are also of interest to the HIV community. This fits within the New York Call to Commitment on linking HIV and sexual and reproductive health, and addresses the need to place HPV vaccines higher on the rights-based agenda. There is a key role for the HIV activist community in the introduction of HPV vaccines.

[3] Global Immunization Vision and Strategy: <http://www.who.int/immunization/givs/en/index.html>.

HPV vaccines may also serve as an important additional interface and entry point to the operationalization of the "WHO global strategy for the prevention and control of sexually transmitted infections: 2006–2015", that was approved by the 59th World Health Assembly, in May 2006. While the provision of HPV vaccines constitutes a significant endeavour in preventing HPV infection and cervical cancer, it offers an additional opportunity to strengthen prevention measures against sexually transmitted infections by educating adolescents to delay sexual debut and to use condoms.

These various interests and the potential for innovation provide many unprecedented opportunities. Moreover, successful introduction of an HPV vaccine will depend on the creation of strong and effective partnerships with these programmes.

An expensive product

Although the price of HPV vaccines for developing countries is not yet known, it is likely to be substantially higher than the traditional EPI vaccines, at least initially, even with differential pricing between developed- and developing-country markets. Discussions are under way to obtain access to international financing mechanisms (e.g. through the Global Alliance for Vaccines and Immunization – GAVI), which could potentially subsidize the vaccine for low-resource settings until mature, affordable prices are achieved. The additional cost of including HPV vaccines in national immunization programmes will be important in the decision-making processes, but should not be the sole criterion. The indirect benefits of vaccination should also be considered (see section on Advocacy, information and communication, page 10). When preparing to introduce the HPV vaccine, advocacy will be important to influence policy- and decision-making, inform public opinion, correct misperceptions, and mobilize resources. Introduction in the private sector is likely to target affluent groups, beginning in high- and middle-income countries, and to proceed independently of public-sector decisions. There is therefore a risk that the introduction of the vaccine will increase health inequities in the population. To avoid this, strong public–private partnerships will be needed in all settings.

Introduction challenges

The service delivery strategy and promotion of HPV vaccines will need to be based on country-specific considerations of what is affordable, feasible and culturally acceptable. Vaccinating young girls against cancer, and other genital diseases, caused by a sexually transmitted infection may be a sensitive issue in some countries and cultural settings. It will be essential to avoid a harmful backlash against sexual and reproductive health and adolescent health programmes (see section on Advocacy, information and communication, page 10), and to ensure that complementary messages about delay of sexual debut, condom use, HIV risk reduction, and cervical cancer screening and treatment are clearly articulated and evaluated during the introduction process. National cervical cancer control strategies will need to be updated to incorporate the new vaccines. It is hoped that the interest generated by the HPV vaccine will act as a stimulus to

the establishment of cervical cancer screening and treatment services in settings where progress has so far been limited.

HPV vaccination has the potential to build synergy among immunization, cancer control and sexual and reproductive health programmes (including for adolescents). In this regard, the immunization encounter with health-care personnel constitutes an opportunity to encourage responsible behaviour among adolescents.

Not business as usual

The unique features and characteristics of the HPV vaccines mean that all the concerned programmes in each country will be challenged to find new ways of working together. Moreover, as mentioned above, public programmes will need to act in concert with the private sector.

At international level, partnerships need to be established now to try to reduce the usual lag time between formal registration and availability of health-care products in developed countries and establishment of a negotiated price and adequate production capacity to supply developing countries.

Advocacy, information and communication

Developing advocacy, information and communication programmes related to HPV vaccination, for multiple stakeholders and audiences, presents specific challenges and opportunities. One challenge is to produce a balanced and informative public education and communication programme about HPV, cervical cancer, and other HPV-related cancers and diseases, and to explain the benefits and limitations of the vaccines. Managing expectations and addressing the concerns of different stakeholders may also be challenging. Policy guidance will be needed on: how the HPV vaccines relate to existing programmes; how to develop complementary messages for HPV vaccines, sexual and reproductive health and HIV activities; and how to develop programmes that balance the roles and responsibilities of different actors who may not have collaborated extensively in the past.

The opportunities are intimately related to the challenges. The maximum potential of the vaccines can be realized only if they are presented as part of a multipronged strategy aimed at preventing cervical cancer deaths and promoting sexual and reproductive health. Introducing the vaccines in this way provides opportunities for collaboration between stakeholders and service providers working in different fields, such as national immunization programmes, family support, HIV prevention, sexual and reproductive health, women's health, cancer control, and adolescent life skills and wellbeing.

One of the first basic considerations is how to present these new vaccines. While each country will need to consider its particular sociocultural and religious contexts, the key messages are as follows:

- HPV has been demonstrated to be the cause of more than 99% of cases of cervical cancer and is involved in other cancers and diseases.
- HPV is one of the most common viruses infecting humans. It is sexually transmitted and highly infectious – its rate of transmission is several orders of magnitude greater than that of some other sexually transmitted organisms, such as HIV. It affects a high proportion of sexually active women and men, usually very soon after sexual debut. HPV infection is, however, not necessarily an indicator of sexual practice or promiscuity; transmission does not require full penetrative intercourse or many partners.
- Most HPV infections have no signs or symptoms, and most infected people are unaware that they are infected; yet they can transmit the virus to a sex partner.
- Prophylactic HPV vaccines have a high efficacy among HPV-naive women aged 16–26 years, and are expected to prevent up to 70% of cervical cancers among vaccinated women.
- HPV vaccines are likely to have maximum impact if they are administered before sexual debut.
- HPV vaccines may also protect against vulvar and vaginal cancers, and one of the vaccines may also prevent genital warts.
- HPV vaccines protect against selected HPV genotypes and do not protect against other STIs, including HIV.
- A proportion of cervical cancer cases (about 30%) cannot be prevented by vaccination with the current HPV vaccines; screening pro-

grammes will therefore need to be maintained and women should be encouraged to continue to come for screening.

The presentation of this information in clear and non-confusing health messages that take into account the sociocultural norms of each community will be challenging for every country. In particular, since HPV is sexually transmitted, care must be taken not to provoke a negative reaction against HPV vaccination, or sexual and reproductive health services, particularly if young adolescents are to be vaccinated. It is also important to avoid focusing too much on girls, even if it is only girls who receive the vaccine; appropriate messages have to target boys too. Several studies have demonstrated that an understanding of the benefits of the vaccine can overcome initial parental caution related to the sexually transmitted nature of the infection.

It will also be important to develop strategies to explain clearly what the vaccine can and cannot do, thus pre-emptively addressing public perceptions of the partial effectiveness of the product (since it does not protect against all HPV types, and may not prevent cancer in all of the women who have already been infected with the HPV types included in the vaccine).

The vaccine is a tangible product, which can complement the information services on lifestyle and behaviour that are customarily provided to young people.

Action points

Key actions related to advocacy, information and communication include the following:

- Interaction between those responsible for advocacy, service delivery and stewardship is important, especially to generate the evidence and country-specific information (e.g. on cervical cancer burden, HPV strains circulating in the country, age of sexual debut) needed to support policy and programmes (see section on Stewardship and financing, page 17).
- A communication strategy on cervical cancer control in general, and the HPV vaccines in particular, should target key stakeholders and decision-makers, as well as health-care professionals, women and the community. The messages should be aligned with national decision-making processes and the stages of the vaccine introduction programme.
- Health promotion strategies related to the introduction of HPV vaccines should be based on country-specific considerations, as well as on the needs and perspectives of community members.
- Materials published by the United Nations Population Fund (UNFPA), WHO and other key agencies should be adapted by countries for use at national level.
- National programmes will need to define messages for each of the key audiences to be reached as outlined below.
- **National policy-makers, programme managers and service providers.** Messages aimed at this group include: the burden of cervical cancer that the HPV vaccines will address; the

benefits that their introduction will bring to the national immunization programme, sexual and reproductive health programme, cancer control programme, and child and adolescent health programme; how the planning and operations of existing clinical and programme interventions will be coordinated, including cervical cancer screening using direct visual inspection of the cervix after application of acetic acid (VIA), HPV testing, cytology, etc.; how partnerships between programmes, and with the private sector, can be formed and managed; why screening will continue to be important once the vaccine is being used; expectations from the vaccine and the programme that delivers it, and how impact will be measured in the short, medium and long term; and who will pay for the programme-related costs of introduction.

- Adolescents and families. Information aimed at adolescents and families should include: what HPV is, the link between HPV and cancer, and why it is important to be vaccinated; why girls of a certain age are targeted; the roles and relevance of the vaccine for boys, older girls, and adult women; the role of parents; and basic information about the vaccine, including its benefits, safety profile and limitations.
- Civil society organizations, professional associations and special interest advocacy groups. Messages targeted at these groups should include: what the vaccine is for; its safety and side-effects, with a clear history of testing and data; why the HPV vaccine is being offered to the specified target population; why this targeting is not a stigma or a presumption of sexual activity; what is unknown about the vaccine, such as its use in HIV-infected women, in pregnant women and in women who receive less than a full course of immunization; why HPV vaccine is important, both in general and to specific groups, such as family support groups, cancer advocacy groups, organizations dealing with acquired immunodeficiency syndrome (AIDS), sports and youth groups, and faith-based groups; which health-care providers will be able to obtain the vaccines and at what cost; how individual providers will be trained, compensated, supported, etc. in introducing the vaccine into their clinics or practices; and whether health insurance (tax-based or social insurance schemes) will cover the cost of the vaccination.

- Delivery of HPV vaccines to girls before or around the time of sexual debut offers a unique opportunity to address other needs of this hard-to-reach segment of the population. Therefore, HPV vaccines should be used as a mechanism for strengthening existing programmes and initiatives targeting adolescent girls and boys, such as school-based programmes providing education on sexual and reproductive health, nutrition and diet, tobacco and HIV/AIDS prevention.

Service delivery

Reaching target populations

The vaccine licences will probably establish an age range of 9–26 years for the target population. This age range will need to be subdivided into two categories: the primary group and the catch-up group.

Primary target population

This will most likely be girls aged 9–13 years, the intention being to reach them prior to sexual debut. Each country will need to identify the most convenient and effective way of reaching adolescents before they are likely to have begun their sexual life.

If the new vaccine is to be introduced within an existing school-based immunization programme, information on the proportion of 9–13-year-old girls attending school will be important. The coverage of the primary target population by school-based programmes will be limited in countries where a large proportion of girls leave school early in adolescence. EPI campaigns provide another service delivery strategy. However, such campaigns commonly target infants and children under five years of age, making the addition of an HPV vaccine quite challenging. Including an HPV vaccine in tetanus vaccination efforts may be considered. Experience in the Americas with both tetanus and rubella vaccines shows that vaccination of adolescents and adults is feasible through mass campaigns and that vaccination against these two infections is acceptable. Sexual and reproductive health programmes are well positioned to assist in the development of school- and EPI-based HPV immunization programmes, given their experience with healthy lifestyles programmes for schools and information, education and communication (IEC) strategies for sensitive issues.

Non-school-based service delivery strategies and involvement of community-based health professionals will be required to reach adolescents who do not attend school. In many countries, adolescent sexual and reproductive health programmes have considerable experience with community-based health and education activities. These programmes aim to provide counselling on sexuality and sexual health, with a focus on delaying sexual debut and preventing pregnancy and STIs, including HIV. They could therefore be used to deliver key messages related to HPV vaccines and, in some settings, to deliver the vaccine itself. However, these programmes usually have limited service delivery experience – most commonly distribution of condoms and education on safer sex practices – and generally reach young people older than 10–13 years. It may be difficult to extend the national vaccine cold chain to provide the HPV vaccine as part of community-based adolescent programmes. In addition, the staff of these programmes may not have the skills needed to deliver vaccination services. Nevertheless, out-of-school youth programmes may be effective in increasing awareness about HPV immunization and in promoting referral to either public-sector or private providers. Innovative referral mechanisms could possibly be explored, e.g. distributing vouchers for obtaining the vaccine. Such a strategy would require education of health-care professionals in youth programmes on the benefits and target groups of HPV vaccination, as well as incentives for imple-

mentation. Some of these initiatives would require close links with education services. Civil society and community-based health and welfare initiatives working with adolescents can play an important role in reaching out-of-school youth.

The secondary target population

This is the "catch-up" group comprising young women aged 14–26 years who have not been previously vaccinated against HPV. Vaccinating this group may considerably increase the speed of impact on the disease, and thus potentially the effectiveness of HPV vaccination. However, the service delivery strategy, and the level of effort put into reaching this population will be determined by the resources of the country and by programmatic and feasibility considerations. More data are still needed on the cost-effectiveness of vaccination of this population, and of young men, for the prevention of cervical and other anogenital cancers. Vaccinating catch-up populations is likely to have a more limited health impact than vaccinating the primary population, and it is important not to divert resources from the primary target cohort.

Increasing the reach of services

Sexual and reproductive health services can contribute to information dissemination and increase vaccine coverage by transmitting messages to women older than 26 years, who come for cervical cancer screening, about the need for HPV immunization of their children, other young female family members and other girls in their community. These women can be involved in sensitizing the communities in which they live and influencing local opinion leaders. Women who attend STI or HIV services, particularly for voluntary counselling and testing or prevention of mother-to-child transmission of HIV, can also be given information on cervical cancer, HPV vaccines and cancer screening services, and can be referred to those services.

The HPV vaccine licence will establish an upper, as well as a lower, age limit for the target population. Thus, attention will need to be given to ensuring that comprehensive cervical cancer screening, diagnosis and treatment are available to respond to the health-care needs of older women. Women and girls given HPV vaccine will need to be screened at the time recommended by the national cervical screening programme, i.e. generally some 10–15 later for women vaccinated in early adolescence. Likewise, women considered too old for vaccination, or who are likely to have already been exposed to HPV, should be screened according to national guidelines.

An overarching consideration is the importance of delivering HPV vaccine as part of comprehensive, rights-based and evidence-informed health services. Stand-alone vaccine delivery strategies should be avoided and partnership between different programmes should be strengthened.

Partnerships between programmes

Programme approaches will need to be planned and organized, making the most cost-efficient use of existing or, where necessary, strengthened services. HPV vaccine delivery should be built on

structures already in place at the national level, for example, the vaccine cold chain infrastructure. This will maximize cost-efficiency and avoid wastage and duplication, which countries can ill afford. While it is likely that, in many countries, the national immunization programme will take the lead in introducing the HPV vaccine, partnerships will be needed with sexual and reproductive health services, as well as adolescent health, cancer control and HIV/AIDS programmes. Close working links should also be developed with the education services, family support groups and other actors that reach the primary or secondary catch-up populations, as well as women in general. These include civil society organizations, community-based health and welfare initiatives, and the private sector. Delivery of the new HPV vaccines provides multiple opportunities for innovative programming and new partnerships.

Monitoring and evaluation

Although the construction of an effective monitoring and evaluation system is a "downstream" activity, it is important during the preparatory stage to consider how to assess process and impact. Process indicators will have to be measured through routine national immunization programme surveillance. The impact on genital warts (with the quadrivalent vaccine) or on abnormalities detected on screening – such as cervical intraepithelial neoplasia (CIN) I or II – is likely to be observed sooner than the impact on cervical cancer. Monitoring these outcomes in pilot studies may be useful for early assessment of vaccine impact and potential breakthrough cases. Data from these pilot studies could be used to develop protocols for disease surveillance. In addition, systems for monitoring adverse events should endeavour to capture HIV status and pregnancies, since there are as yet no data on the use of the vaccines in HIV-infected subjects and, while the data on pregnancy so far are reassuring, further monitoring is warranted.

The long-term impact of HPV vaccination on incidence of, or mortality from, cervical cancer and other HPV-related cancers will not be observed until at least 10 years, and more probably 30 years, after introduction. Where cancer registers exist, it will be important to include data on precancerous cervical lesions, which can be used as a proxy for invasive cancer for monitoring purposes. Where cancer registries do not exist or are of poor quality, countries are advised to monitor vaccine coverage and the outcomes of postmarketing surveillance in other countries. In the future, such surveillance may best be achieved using molecular markers for HPV infection, provided that appropriate tests are available and affordable. In particular, the reporting of adverse events will be important; this will require the cooperation of the private sector.

Action points

National programmes will need to undertake the following actions:

- Develop links between the many different implementing stakeholders.
- Define the primary target population, taking into account the most convenient access points, and the earliest age of sexual debut.

- Address sociocultural barriers to vaccination of young adolescents.
- Determine school attendance rates for the 9–13-year age group.
- Update national cervical cancer control strategies to incorporate the new HPV vaccines.
- Plan a service delivery strategy for HPV vaccines:
  - Base service delivery for the introduction of the HPV vaccine on country-specific considerations of what is feasible and culturally acceptable, as well as the needs and perspectives of community members.
  - Expand the scope of EPI services into other settings and to other age groups than infants.
  - Work with school-based immunization programmes and EPI services to develop messages consistent with those provided by national cervical cancer control programmes, adolescent sexual and reproductive health services and HIV prevention programmes.
  - Incorporate information about HPV vaccines and referral in community-based programmes on adolescent sexual and reproductive health.
  - Develop IEC messages for sexual and reproductive health clients, explaining the benefits of HPV vaccines for young people, and of cervical cancer screening for older women.
  - Train health-care professionals to recommend or administer HPV vaccination to all unvaccinated individuals in the target population whom they encounter.
- Develop a comprehensive approach to cervical cancer prevention:
  - Ensure access to secondary prevention programmes based on screening and treatment of precancerous lesions, using cytology, VIA or HPV testing, depending on availability of funding and national decisions.
  - Put in place treatment options and appropriate referral mechanisms for patients with invasive cancer.
  - Provide HPV vaccine as appropriate.
  - Monitor vaccine effectiveness.
  - Educate and sensitize health professionals regarding primary prevention.
- Determine key process and outcome indicators for monitoring and evaluation.

Stewardship and financing

The mobilization of resources for strengthening the health system and purchasing HPV vaccines, both internationally and within national health budgets, must be a high priority. Financing for the introduction of HPV vaccine will need to be approached as part of an overall strategy involving a number of partners, both globally and within individual countries, and be part of a general scaling-up of resources to strengthen health systems. Some of the necessary financing decisions will be made at global forums, or at levels within government higher than the national programme manager. These decisions will be of vital importance to the eventual introduction of the HPV vaccine, and policy-makers and programme managers should follow developments closely during the preparatory phase.

Depending on the service delivery strategy selected for the introduction programme, different institutional policies and oversight actions will need to be addressed. Sexual and reproductive health programmes are particularly well placed to advise and assist in these policy decisions, given their familiarity with adolescent health, STIs and cervical cancer control.

In all settings, governments will be challenged to decide on the relative importance of the HPV vaccine for national programmes, because of its cost and competing priorities (including other vaccines that are in the pipeline). Some of the decisions about introducing an HPV vaccine can be guided by lessons learned from countries' experiences with introducing other vaccines, notably the hepatitis B vaccine. Pharmaceutical companies may be lukewarm about investing in licence application procedures in settings where the market is small or uncertain. Managers of sexual and reproductive health programmes will need to be prepared to discuss these and other issues during the preparatory phase, drawing on professional associations and advocacy groups on cervical cancer for the evidence needed to inform policy decisions. Basic epidemiological information will be required to demonstrate the health-care need and potential impact of HPV vaccines in the short term (impact on early disease and screening) and long term (impact on cancer and on women and family productivity). Demand-forecasting models will need to be generated at country level, to guide fiscal and programme planning analyses. Furthermore, key stakeholders will need to be engaged to ensure that the benefits of introducing the HPV vaccine not captured in health and cost analyses are nevertheless given consideration in national policy decision-making processes.

Securing international funding commitments for HPV vaccines, for example through GAVI, the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO) Revolving Fund, is critically important for two reasons. First, it will convince the vaccine manufacturers to invest in expanding production capacity to ensure sufficient supplies of the new vaccines for markets other than high- or middle-income countries. Second, it will help secure a negotiated price for low-resource settings, which will be essential given the expected high private-sector price of the HPV vaccines. The availability of funding for the HPV vaccines might also act as a stimulus for action by national stakeholders in low-resource settings. In the absence of external funding, attention will need to be focused

on marshalling public-sector resources to cover the cost of the vaccines or on managing donated supplies. In some settings, it will be necessary to work with the private sector on a purely commercial introduction of the HPV vaccine (most likely into the upper-end markets of middle-income countries).

Discussions at national level about resource mobilization should be undertaken in the context of the national immunization programme's multiyear plans, and should fit within broader health sector planning processes, such as sector-wide approaches (SWAps) and medium-term expenditure frameworks. This is essential both to secure long-term governmental support for the HPV vaccines and to ensure that they fit within national programmes (i.e. are not an "off-budget" activity). In low-income countries, these planning processes can be engaged in tandem with preparing an application to GAVI, particularly as resources from GAVI Phase 2 financing windows are available for financing of New Vaccines (Vaccine window) and for Health Systems Strengthening (HSS window). National immunization programmes will need the input of sexual and reproductive health programmes and cancer control programmes in preparing applications for HSS that reflect the multiple dimensions of HPV vaccines.

In settings where there is limited public-sector programme support, but the commercial market is viable enough for a purely private-sector introduction programme, there is a different set of considerations that will require government oversight. These centre principally on establishing different models of public-private partnership and ensuring consistency with national sexual and reproductive health, immunization, and cancer control programmes. In middle- and low-income countries, governments can insist on beneficial post-licensing actions, including, for example, private-sector reporting of adverse events, postmarketing surveillance, and package inserts containing appropriate messages for both providers and consumers.

Action points

In the area of stewardship and financing, the following actions will need to be undertaken.

- A broad range of stakeholders should be involved in developing a strategy for a comprehensive and workable introduction of HPV vaccines. A national HPV vaccine working group should be established in each country to set up coordination mechanisms between health programmes, civil society and private sector. This could be a subgroup of the inter-agency coordinating committee of the immunization programme, with representation from sexual and reproductive health, cancer control, HIV, and youth programmes, as well as local experts on HPV and cervical cancer.

- Models should be developed at country level to forecast demand and to estimate the financing and coverage needed – of women only or of both sexes – to have an impact on disease at the population level. The business case should be developed, both for public funds and for potential private partners, based on up-to-date projections of the burden of cervical and other anogenital cancers (incidence, prevalence,

hospitalization rates and mortality) and data on the prevalence of different HPV types, savings produced by vaccination, and overall impact on budget.

- National sexual and reproductive health programmes should participate in preparing an application for funds to GAVI, particularly by:
  - contributing to the health sector analysis needed in any request to GAVI;
  - providing inputs to the comprehensive multiyear plans on the financial implications of introducing HPV, as well as different scenarios of financial sustainability.
- Countries not eligible for GAVI support can ask for technical assistance from WHO and UNFPA, for fund-raising and programme planning.

Epilogue

Ultimately, the decision on whether and when to introduce an HPV vaccine will depend on national policy in each country. An overarching consideration is the importance of positioning the HPV vaccine within a comprehensive, integrated service delivery structure. Because this vaccine "fits" in several different programmes, effective partnerships will be key to any successful introduction programme. Moreover, before implementing large-scale HPV vaccines programmes, especially in developing countries, several knowledge gaps will need to be bridged. Also, comprehensive guidelines and protocols for the delivery of HPV vaccines will need to be developed and disseminated to serve the implementation of the recommended action points included in this document.

The HPV vaccine addresses a critical public health need, and is one element of a comprehensive cervical cancer control strategy. Ensuring universal access to cervical cancer prevention, screening and treatment services will be the key to reducing the burden of cervical cancer worldwide. There are critical issues of equity associated with the introduction of these new vaccines which must be addressed. If due attention is not given to reaching poorer women, the new vaccine risks increasing health inequities, rather than contributing to the realization of the goal of universal access to sexual and reproductive health care.

Note added in proof

On June 8, 2006, the United States Food and Drug Administration (FDA) approved a license application for the Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine (Gardasil®). This vaccine is intended for use in girls and women aged 9–26 years for the prevention of the following diseases caused by the human papillomavirus (HPV) types 6, 11, 16, and 18:

- cervical cancer
- genital warts (condyloma acuminata)

and for the following precancerous or dysplastic lesions:

- cervical adenocarcinoma in situ (AIS)
- cervical intraepithelial neoplasia (CIN) grade 2 and grade 3
- vulvar intraepithelial neoplasia (VIN) grade 2 and grade 3
- vaginal intraepithelial neoplasia (VaIN) grade 2 and grade 3
- cervical intraepithelial neoplasia (CIN) grade 1.

For additional information, please see the FDA web site: **http://www.fda.gov/cber/products/hpvmer060806.htm**

Additional resources

UNFPA	http://www.unfpa.org/
WHO	http://www.who.int/en/
	http://www.who.int/reproductive-health
	http://www.who.int/cancer/en/
	http://www.who.int/reproductive-health/pages_resources/listing_cancer.en.html
GIVS	http://www.who.int/immunization/givs/en/index.html
GAVI	http://www.gavialliance.org/