Cervical cancer, human papillomavirus (HPV), and HPV vaccines

Key points for policy-makers and health professionals
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Every year, almost 500,000 women develop cervical cancer and 274,000 die from the disease. Cervical cancer is caused by certain types of human papillomavirus (HPV) and is the most common cancer affecting women in developing countries.

Until recently, cytology-based screening programmes (using Pap smears) were the main tool to prevent cervical cancer. Well-organized programmes to detect and treat precancerous abnormalities and the early stages of cancer prevent up to 80% of cervical cancers in developed countries. However, effective screening programmes have been difficult to implement in low-resource settings. This is one reason why cervical cancer mortality rates are much higher in the developing world.

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

As of January 2008, two HPV vaccines have been approved for use in many countries. Clinical trial results show that both vaccines are safe and very effective (when given to females with no past infection by vaccine-related HPV types) in preventing infection with the two types (HPV 16 and 18) that cause most cervical cancer and precancerous cervical lesions.

HPV vaccines address a critical public health need, and will be an important element of a comprehensive cervical cancer control strategy. Ensuring universal access to HPV vaccination, screening and treatment services will be key to reducing the burden of cervical cancer worldwide. Furthermore, introducing HPV vaccines may provide a platform for the introduction of vaccines against the human immunodeficiency virus (HIV) in the future, given the probable need to vaccinate the same target population of older children and adolescents.

This booklet summarizes and updates the World Health Organization document “Human papillomavirus and HPV vaccine: technical information for policy-makers and health professionals” and the WHO/UNFPA guidance note “Preparing for the introduction of HPV vaccines—policy and programme guidance for countries.” They are available at www.who.int/reproductive-health/publications/stis_rtis.htm.

**HPV and cancer**

- HPVs are a family of viruses that are extremely common worldwide.
- They are deoxyribonucleic acid (DNA) viruses that infect skin or mucosal cells.
- There are more than 100 types of HPV.
- At least 13 of these types are oncogenic (cancer-causing).
- HPV is estimated to cause
  - 100% of cervical cancer cases,
  - 90% of anal cancer cases,
  - 40% of cases of cancers of the external genitalia (vulva, vagina and penis),
  - at least 12% of oropharyngeal cancer cases, and
  - at least 3% of oral cancer cases.
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- HPV types 16 and 18 cause approximately 70% of all cervical cancers worldwide.
- Cervical cancer is the leading cause of cancer death of adult women in the developing world and the second most common cancer among women worldwide.
- Almost 500,000 cases of cervical cancer and 274,000 cervical cancer deaths occurred in 2002.
- About 80% of cervical cancer deaths occur in developing countries.
- Non-oncogenic types of HPV (especially types 6 and 11) can cause genital warts and respiratory papillomatosis. Although these conditions very rarely result in death, they may cause significant morbidity and can incur substantial health-care costs, especially in industrialized countries.

### Age-specific cervical cancer mortality rates per 100,000 women

<table>
<thead>
<tr>
<th>Age</th>
<th>Less developed countries</th>
<th>More developed countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 45–54</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>Age 55–64</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Age 65+</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

Source: Globocan 2002 (WHO/IARC)

Many more women die of cervical cancer in the developing world than in wealthier countries. In the industrialized world, effective screening programmes help to identify pre-cancerous lesions at stages when they can easily be treated. But lack of screening programmes in poorer countries means that the disease is not identified until symptoms develop. Prospects for treatment of such late-stage disease may be poor, resulting in higher mortality. For this reason, vaccination before exposure to oncogenic HPV types is particularly important.
HPV transmission

- HPV infection is very common; most women and men will be infected some time in their lives.
- HPV is sexually transmitted, but penetrative sex is not required for transmission: skin-to-skin genital (e.g., penile-vulvar) contact is a well-recognized mode of transmission.
- HPV is highly transmissible, with peak incidence soon after the onset of sexual activity.
- HPV infections usually clear within a few months, and about 90% clear within two years. A small proportion of infections persist and can progress to cancer.

HPV vaccine characteristics

- Two HPV vaccines are now licensed for use in many countries.
- Both vaccines are prepared from virus-like particles (VLPs) produced by recombinant technology. They do not contain any live biological product or DNA, so they are not infectious.
- The bivalent vaccine contains VLPs for HPV types 16 and 18. The quadrivalent vaccine contains VLPs for four HPV types 6, 11, 16, and 18.
- Both vaccines are given in a series of three 0.5-mL intramuscular injections over six months.
- Both vaccines are currently available only in single-dose format.
- Both vaccines require storage and transport in a cold-chain system.

Efficacy

- Both vaccines are designed to prevent HPV infection and are not intended to treat women with past or current infection with vaccine-related HPV types.
- Both vaccines have been evaluated in adolescent and young adult females in large clinical trials conducted in several continents.
Published analyses restricted to females who had not been infected with vaccine-related HPV types before vaccination have shown that:

- both vaccines induce high levels of serum antibodies against the HPV types 16 and 18 in virtually all vaccinated persons;
- the quadrivalent vaccine had an efficacy of more than 96% in preventing high-grade, precancerous lesions of the cervix, vagina and vulva and genital warts arising from HPV types 6, 11, 16 or 18 in completed phase 3 clinical trials;
- the bivalent vaccine has an efficacy of more than 90% in preventing high-grade cervical lesions arising from HPV types 16 and 18 in interim results of phase 3 clinical trials and an efficacy of more than 75% in preventing persistent infection with HPV 16 or 18;
- although the duration of protection is not yet known, there is evidence of protection for at least six years after vaccination for both vaccines. Studies of both vaccines are evaluating longer term efficacy.

Recent studies indicate that both vaccines may provide partial protection against other oncogenic HPV types that are genetically related to HPV 16 and 18, such as evidence of partial protection against new infections by or development of neutralizing antibodies against these genetically related types. Ongoing studies will evaluate impact on precancerous cervical lesions due to these genetically-related types.

Data on the efficacy of the vaccines in preventing disease in males are not yet available.

Factors associated with HPV persistence and the development of cervical cancer

- Immune suppression*
- Multiparity
- Early age at first delivery
- Long-term use of hormonal contraceptives
- Cigarette smoking
- Infection with other sexually transmitted diseases (e.g., Chlamydia trachomatis and Herpes simplex virus type 2)

* HIV-infected individuals are at higher risk of HPV infection and persistence and are infected by a broader range of HPV types.
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Safety

- Both vaccines appear generally safe and well tolerated based on available data from trials and post-marketing surveillance.
- In June 2007, the WHO Global Advisory Committee on Vaccine Safety judged both vaccines to have good safety profiles and identified no major safety concerns.
- In clinical trials of both vaccines, vaccinated persons were not significantly more likely to have serious or systematic adverse events than placebo recipients.
- However, vaccinated persons were more likely to have mild, transient soreness, redness or swelling at the injection site than placebo recipients.
- Reports of fainting immediately after HPV vaccination have been noted in some countries, and this prompted health authorities in some countries to reinforce long-standing recommendations to observe all vaccinated persons for 15 minutes after vaccination.
- Neither vaccine is intended for use in pregnant women. Although clinical trials excluded pregnant women, some women became pregnant during the studies. Rates and types of congenital abnormalities were consistent with those generally observed at this maternal age and were not judged to be vaccine-related. Data on safety in pregnant women are being further evaluated as part of post-marketing surveillance in the USA and Europe.

HPV vaccine delivery strategies

- Because HPV is sexually transmitted and is usually acquired within the first few years after onset of sexual activity, HPV vaccination is most effective for girls and young women before they begin having sex. Countries that have licensed HPV vaccines have advised use for girls at ages that typically precede onset of sexual activity.
- Candidates for HPV vaccination can be divided into two subgroups: the primary target group for routine vaccination (girls before sexual activity starts, defined by many countries as ages 9–13 years) and a secondary target group for “catch-up” campaigns (defined in many countries as girls and women aged 14 to 26 years who have not been previously vaccinated against HPV).
• The impact on cancer incidence and mortality of vaccinating the primary target group is expected to be greater than vaccinating the “catch-up” group because younger girls are less likely to be infected with vaccine-related HPV types before vaccination.

• Vaccination of “catch-up” populations who have not been infected with at least one vaccine-related type before vaccination might hasten the observable impact of vaccines on cervical cancer because the interval between vaccination and sexual exposure to vaccine-related HPV types will likely be shorter than for younger vaccinated girls.

• Results of some mathematical models of HPV transmission suggest that if high vaccine coverage of girls can be achieved, little additional reduction in cervical cancer is gained by vaccinating boys even if vaccines have high clinical efficacy in boys.

• Because very few girls who are the primary target group for vaccination are likely to be infected with all vaccine-related HPV types before vaccination, there is no need to test for HPV infection before offering vaccine.

• Most developing countries do not routinely vaccinate older children and adolescents against other diseases, so new systems will have to be created to reach these populations with HPV vaccines. The systems may offer many positive opportunities for impacting adolescent health. Data from ongoing projects in Africa, Asia, and Latin America are evaluating various vaccine delivery strategies.

• Because HPV vaccines do not protect against all types of HPV that cause cervical cancer, vaccinated persons may become infected with HPV types against which vaccines do not offer protection. For this reason, vaccinated persons should be encouraged to be screened for cervical cancer later in life according to national policies.

### Possible vaccine delivery mechanisms

- School-based immunization programmes
- EPI (Expanded Programme on Immunization) campaigns
- Tetanus vaccination campaigns
- Adolescent-friendly health programmes
- Community-based sexual and reproductive health programmes (e.g., family planning)
- Special referral and outreach mechanisms
Communication and partnerships

- Health communication programmes are essential to ensure acceptance of HPV vaccination by patients, parents, health care providers, health policy-makers and the general public.
- For maximum efficiency and impact, partnerships across immunization, cancer-control, adolescent health and sexual and reproductive health sectors are needed to introduce HPV vaccines as part of comprehensive programmes to prevent cancer, warts, sexually transmitted infections and vaccine-preventable diseases.
- Communicating about HPV and cervical cancer is challenging. Programmes must consciously and carefully deal with several complex issues including:
  - most adolescent vaccines used in immunization programmes are single-dose boosters, so it is important to explain a three-dose HPV vaccine to providers, parents and vaccinees;
  - HPV vaccines prevent cancer by preventing a common sexually transmitted infection that causes cancer. The extent to which these benefits are emphasized will depend on the age and maturity level of the person offered vaccine, family and health care providers’ preferences and cultural norms;
  - thoughtful communication that stresses that HPV infection is extremely common in sexually active females and males, even those with few sex partners, may reduce potential stigma about vaccination;
  - because HPV vaccines will be given to older girls and female adolescents, both vaccine candidates and their parents can be counselled about vaccination. This provides opportunities to address sexual health and life skills, and encourage cervical cancer screening of mothers of girls offered vaccine.
Potential impact and cost-effectiveness of HPV vaccination

- In settings with established cervical cancer screening programmes, modelling suggests that, in many countries under certain assumptions, HPV vaccination can reduce cervical cancer mortality, the incidence of cervical cancer, and the incidence of abnormal Pap tests and precancerous cervical lesions that require costly medical follow-up in many countries.
- Models also predict that, under certain assumptions, vaccination can also be cost-effective in the long term when added to current screening programmes, especially when screening costs are offset by starting screening at later ages than is now typically the case or by reducing the frequency of screening. However, if vaccinated females are not screened later in life, cervical cancer incidence and mortality may be greater than if screening continued, especially if vaccine protection wanes over time.
- Models also predict that, under certain assumptions, vaccination can be cost-effective in some low- and middle-income countries with no or limited screening. Ongoing modelling in many regions will guide vaccine introduction decisions.
- The impact of HPV vaccination will depend on the age-specific incidence rate of vaccine related types in a specific population.
- Savings resulting from improved screening and HPV vaccination will depend on the actual costs in a given country. Savings for outcomes such as follow-up of abnormal screening test results and prevention of genital warts (for persons vaccinated with the quadrivalent vaccine) will occur before savings related to preventing cancer.
Financing

- Introduction of HPV vaccines raises critical issues of equity. If girls and young women in both developed and developing countries who are at high risk of cervical cancer (largely because of limited access to screening later in life) are not able to access HPV vaccines, current inequalities in cervical cancer burden may worsen.
- Financing for HPV vaccination programmes requires involvement of global partners, individual countries, and communities. Governments will need to make careful decisions about the importance of these programmes in the context of competing health priorities, including other new vaccines.
- Large-volume vaccine purchasers such as GAVI, UNICEF, and PAHO may be able to negotiate lower prices for low-resource countries as they have for other vaccines. They can also promote scale up of vaccine manufacture to ensure adequate global supply.
- Differential pricing between developing and developed countries is anticipated, but the initial price of HPV vaccines for public sector programmes in developing countries is not yet known.

Unresolved research questions

- The safety and efficacy of HPV vaccines are now being evaluated in Africa and in populations with high HIV prevalence but results are not yet available.
- Studies of vaccine efficacy in boys are also ongoing.
- The minimum protective antibody level produced by HPV vaccines is not known. This information will be important to determine the duration of vaccine protection, the need for boosters, and the efficacy of simpler schedules such as a two-dose series.
- If a two-dose series could be used, or vaccination could be given at an earlier age when other childhood vaccines are given (e.g., at school entry or during infancy), costs of vaccine and delivery could be reduced. Evaluations of two-dose regimens in older girls are underway.
• The impact of HPV vaccine introduction on developing world health systems is not yet known, but is being evaluated by ongoing operational research in several countries.

• Acceptability of HPV vaccines likely will vary by country and by groups of patients, parents, providers and policy makers. HPV vaccine acceptability is being studied in high-, middle- and low income countries.

• The impact and cost-effectiveness of HPV vaccination in many low- and middle income countries, in “catch-up” target populations and in boys need further evaluation. This will require mathematical modelling using country- and region-specific data on HPV epidemiology, the natural history and transmission of HPV infection, the mechanism and duration of protection of HPV vaccines, and the costs and effectiveness of various delivery strategies.

• Strategies to monitor the long-term safety and impact of vaccines on incidence of HPV-related disease must be developed. In some cases, this may require unique linkages with cytology and cancer registries.

Conclusions

New HPV vaccines create opportunities to greatly reduce cervical cancer rates. In countries where effective cervical cancer screening programmes exist, screening should continue to prevent cancer in both nonvaccinated women and vaccinated women to provide protection from oncogenic HPV types for which HPV vaccines do not offer protection. As HPV vaccines are introduced, adaptation of prevention and screening programmes may become possible because of declines in disease incidence due to vaccination.

Given that HPV vaccines and delivery costs likely will be higher than for routinely recommended infant vaccines, innovative methods will be needed to finance HPV vaccine introduction. This is especially true in low- and middle income countries where primary health care systems rarely provide preventive care to older children and adolescents.
The introduction of HPV vaccines creates opportunities to strengthen health systems—particularly those that reach older children and young adolescents—and such opportunities may be realized by establishing new partnerships between immunization, cancer control, adolescent health, and sexual and reproductive health programmes. Together, these programmes can promote comprehensive vaccine information and communication, delivery, financing, and monitoring strategies that prevent deaths from cervical cancer and promote women’s health.

**Cervical Cancer Prevention - Action Points**

- Raise awareness about cervical cancer among a wide range of audiences, including key stakeholders, health care professionals, women and the community.
- Generate needed evidence to guide programme design and answer unresolved questions, including determining the best strategies to reach girls with vaccine.
- Develop comprehensive approaches to cervical cancer prevention that effectively integrate screening, treatment of precancerous lesions, and immunization.
- Base cervical cancer advocacy and prevention strategies on country-specific considerations.
- Update national cancer control strategies to consider the option of HPV vaccines.
- Develop new systems to vaccinate young adolescent girls and use the systems to reach out to both girls and boys with other health services and education on sexual and reproductive health, nutrition and diet, tobacco and drugs, and HIV/AIDS.
- Train health care workers to effectively interact with and serve young adolescents.
- Carefully monitor and evaluate programmes.
- Work with a broad range of stakeholders, including GAVI, to develop strategies for long-term financing of cervical cancer prevention.
- Negotiate differential vaccine pricing for middle- and low-income countries and advocate for production capacity adequate to supply all countries.