

Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines

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Assuring Access to Vaccines that Prevent Cervical Cancer

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Abstract

Cervical cancer, a direct consequence of infection with human papillomavirus (HPV), is the most common cause of cancer-related deaths among women in the developing world. Although cervical cancer screening programs have successfully reduced the burden of disease in developed countries, the cost and complexity of these programs have made effective implementation impossible in low-resource settings. Recent United States and European Commission regulatory approval of one of two highly efficacious HPV vaccines, and anticipated approval of the second, has prompted international recognition of some of the difficulties associated with assuring equitable access to these vaccines for populations in greatest need in the near future. Administration of the HPV vaccine necessitates reaching preadolescent and adolescent girls before the peak age of infection, which occurs at the onset of sexual activity, differentiating it from almost all other global vaccine initiatives. In addition, the need is greatest where the disease burden is highest, where the population may be hardest to reach and health systems are weak. Forecasting demand for the vaccine has been hampered by special concerns regarding acceptability; without demand forecasts, costs remain uncertain. This background document summarizes current knowledge about HPV vaccines, avenues for service delivery, and critical information gaps that will inform future efforts to ensure access in the developing world. Educated and informed stakeholders who share goals and objectives can advocate more strongly at the international and national levels.

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1. Introduction

Cervical cancer is a gender-specific disease that disproportionately affects women in the lowest socioeconomic classes throughout the world. A meta-analysis of 57 studies has revealed an estimated 100% increased risk of invasive cervical cancer between high and low social class categories, reflecting the lack of access to screening and treatment services.² In 2004, the 57th World Health Assembly adopted the Global Reproductive Health Strategy of the World Health Organization (WHO), which identified five priority areas for reproductive health, including “combating sexually transmitted infections,” and specifically addressed cervical cancer.³ In 2005, during the 58th World Health Assembly, member states adopted a resolution on cancer prevention and control. The fact that these issues are agreed-on priorities by the 193 WHO member states provides a strong basis for advocacy on behalf of cervical cancer prevention and treatment. Moreover, with the introduction of human papillomavirus (HPV) vaccines, a comprehensive approach to preventing cervical cancer makes it one of the most preventable of all cancer types. HPV vaccines are targeted at preadolescents and

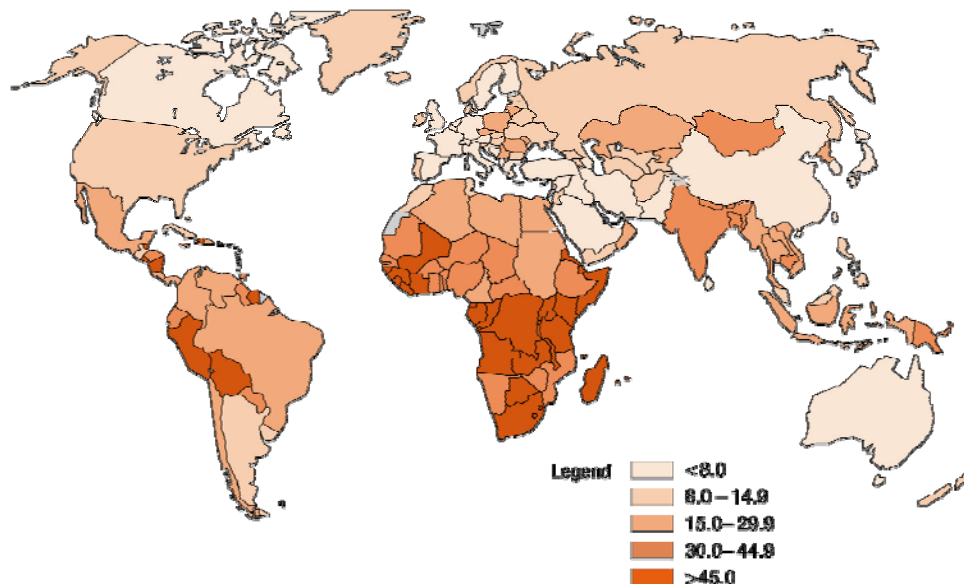
adolescents, making strategies for delivery both a challenge and an opportunity to reach this underserved demographic group with additional priority health messages.

2. Disease Issues

Cervical Cancer: Burden of Disease

Cervical cancer remains the second most common cancer in women worldwide, and the primary cause of cancer-related deaths in women in developing countries.⁴ Eighty percent of all cervical cancer cases (500,000 in 2002) and deaths (274,000 in 2002) occur in developing countries (Figure 1).⁵ Screening programs have successfully reduced disease rates in industrialized countries through cytology-based services that are too complex and expensive for most developing countries to implement. In Latin America, the Caribbean and Eastern Europe, cervical cancer makes a greater contribution to years of life lost (YLL) than obstetrical outcomes or diseases such as tuberculosis or AIDS. An estimated 95% of women in developing countries have never been screened for cervical cancer.

Figure 1: Worldwide Incidence Rates of Cervical Cancer per 100,000 Females (All Ages), Age-Standardized to the WHO Standard Population (2005)⁵



HPV Infection

HPV is a common sexually transmitted infection; a high percentage of all individuals become infected with the virus within 2-5 years of the onset of sexual activity.^{6,7} HPV's link to cervical cancer was first discovered in the 1980s, and it is now recognized as the necessary cause of over 99% of cervical cancers, 90% of anal cancers, 40% of cancers of the external genitalia (vulva, vagina and penis), 12% of cancers of the oropharynx and 3% of mouth cancers.⁸ Over 100 types of HPV have been identified. Of these, HPV types 16 and 18 cause approximately 70% of cervical cancers worldwide. At least 13 other oncogenic types of HPV cause smaller percentages of cancer.⁹ There is some geographic and country-specific variability in terms of which types cause the most cancers, with the exception of HPV 16, which varies minimally across regions. In sub-Saharan Africa and Latin America, HPV 16 and 18 together account for only 65% of invasive cancers. HPV 6 and 11 cause 90-100% of genital warts in men and women. Although these infections can incur psychological morbidity and healthcare costs, they do not cause serious physiological morbidity or mortality. In most studies, the age-specific peak prevalence of HPV infection occurs under the age of 25 and the peak incidence of cervical cancer occurs at age 50.^{9,10} Although 90% of all HPV infections are cleared by the body's immune response, persistent infection beyond 12 months is associated with the development of cancer two to three decades later. This prolonged latent phase allows for screening of the cervix to detect precancerous cellular abnormalities, followed by treatment to prevent disease progression.

Cervical Cancer Screening: Secondary Prevention

Cervical cancer prevention programs to date have been based around Pap smears. Success is dependent upon high rates of coverage of women in the right age group, with repeated, quality-controlled screening. In developed countries, racial and socioeconomic disparities profile cervical cancer cases as women who have never or rarely been screened. Capacity in low-resource settings to implement this complex, high-resource

protocol in entire populations has been scarce. Visual inspection with acetic acid (VIA) and HPV DNA testing can provide alternative screening and management options that are cost-effective^{11,12} and improve efficiency by limiting steps to treatment.¹³ The DNA screening test appears cost-effective, is more objective and less labor-intensive, and has high sensitivity and specificity.¹⁴ Although the current DNA test is too expensive for use in developing countries, lower cost tests are under development. VIA is extremely inexpensive but does require some special training.

3. HPV Vaccines

Vaccines as Primary Prevention

By 2007 two prophylactic vaccines, both highly effective against oncogenic HPV types 16 and 18, should be available in industrialized countries. Between June and October 2006, a quadrivalent HPV vaccine protective against HPV types 6, 11, 16 and 18 (Gardasil[®], Merck) was licensed for use first by the US regulatory authorities and then by the European Commission (EC). EC approval for a bivalent vaccine protective against HPV types 16 and 18 (Cervarix[®], GlaxoSmithKline Biologicals) is expected to follow.^{15,16} Clinical trial data to date suggest a minimum of four to five years' efficacy of close to 100% in preventing persistent infection and precancerous cervical abnormalities (cervical dysplasia) caused by type-specific disease. However, the vaccines are given in a series of three 0.5 ml intramuscular injections over a six month period, and duration of response is only available for the complete series.¹⁷ In addition, women vaccinated with the bivalent vaccine had a 94% reduction in new infections with two other oncogenic HPV types, while those vaccinated with the quadrivalent formulation showed a measurable antibody response to those same additional types, giving evidence of cross-protection.^{17,18} Neither vaccine is designed to be

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curative, and neither contains any live virus. One model suggests that a vaccine with 98% efficacy against HPV-16 and 18 could, within 40 to 50 years, reduce cervical cancer incidence by 51% if all adolescent girls were vaccinated before initiation of sexual activity.¹⁹ The actual impact of the vaccine will be highly dependent on country-specific parameters, including the capacity to deliver current vaccines that require three consecutive doses, cold chain management and a possible booster dose years later.²⁰

Vaccine-Related Knowledge Gaps

Although reported vaccine trial results are extremely promising, there remain evidence gaps that must be filled to help inform service implementation,^{21,22} including the following:

- ***Performance in Africa:*** Both vaccines lack vaccine safety and efficacy data from Africa, and in general from sub-populations immunocompromised by HIV infection and other chronic diseases or causes. Cervical cancer occurs at significantly higher rates in HIV-positive women, and it is an AIDS-defining illness.
- ***Duration of action:*** Data on longevity of immunogenic response persisting at levels several-fold higher than those seen in natural infection extend to almost 5 years post-vaccination to date, with a plateau at 18 months.¹⁷ However, understanding the longer-term duration of immunity could add flexibility, or help reduce dosing schedules, and determine whether a booster is needed.
- ***Data on infants:*** Lack of safety and immunogenicity studies in infants will prevent the vaccine's integration into the WHO's Expanded Program on Immunization (EPI) schedule tailored to childhood vaccination, creating a need for multiple visits to administer vaccines later in life.
- ***Cross-protection:*** Both vaccines provide coverage against the most common HPV types. In early analysis, both the bivalent and the quadrivalent vaccines indicate strong

potential for cross-protection against HPV types 45 and 31 based on incidence of infection or antibody response.^{17,18} Studies are ongoing. HPV types 45 and 31 are together responsible for a further 10% of cervical cancers globally.

- ***Therapeutic effect of current vaccines:*** While current vaccines are highly effective at preventing new infections, it remains unclear whether they will demonstrate any therapeutic impact in women who are already infected with one or more HPV types.²³
- ***Vaccine compatibility:*** Both of the current vaccines ready for market are based on virus-like particles, a new technology. Their stability has not been tested in combination with other vaccines or in populations with compromised immune systems, including people who may be on long-term drug therapy. Bridging studies are needed to address these issues.

4. Critical Issues for Introduction of HPV Vaccines

To make HPV vaccination widely accessible to young adolescent girls, immediate challenges include vaccine cost and procurement, assuring vaccine supply, selection of appropriate age and gender populations to serve, functional delivery systems, and sustained local, national and international commitment.

Cost and Procurement

The delivery costs associated with HPV vaccine include vaccine cost per dose, health system costs for delivery and monitoring, and the often neglected costs of training, i.e., education-, information- and awareness-building. Given the diversity of national budgets and circumstances, estimates of total cost will need to be made at the national level and supported by a variety of funding mechanisms. The countries in greatest need have the greatest degree of dependence on external financing for existing vaccine programs.

External product financing and procurement mechanisms must be considered in the context of

existing mechanisms such as the Global Alliance for Vaccines and Immunization (GAVI), the International Financing Facility for Immunization (IFFIm), the United Nations Children's Fund (UNICEF) and the Pan-American Health Organization (PAHO). GAVI is expected to consider the investment case for HPV vaccines in 2007. National immunization programs in low-income countries rely heavily on UN institutions for guidance during their regulatory review and when setting priorities for vaccine procurement. UN vaccine procurement agencies in turn depend upon the WHO technical assessment group for "prequalification" of each producer of each vaccine before negotiating any purchase. Because global financing mechanisms for a HPV vaccine depend in large part on the cost of the vaccines, financing and procurement-related issues must be accelerated to avoid years of delay in making an HPV vaccine a consideration for most developing countries.

Assuring Vaccine Supply

Manufacturing limitations for HPV vaccines are unclear. Without five-year estimates of purchasing demand, industry is unlikely to invest in building manufacturing capacity, or move towards cost structures that include lower profit margins. A business case for HPV vaccine production and procurement specific to developing countries is needed. Pilot demonstration projects that will both inform industry with demand forecasting and provide models for HPV vaccine introduction to maximize acceptability and access are being implemented in four countries.²⁴

Selecting Appropriate Initial Target Populations for Vaccine

a. Adolescent Girls

Current data indicate that for greatest impact the vaccine will need to be administered to girls prior to onset of sexual activity, beginning at age 10, allowing for "catch-up" strategies aimed at young women up to age 25. Infection with high-risk HPV types is consistently high in almost all adolescent female populations tested. Although pivotal trials for Merck's Gardasil[®] did not

include girls under age 16,²⁵ bridging studies have established immunogenicity in girls and boys as young as age 10,²⁶ and data from GSK's phase III Cervarix[®] trial showed immunogenic responses in girls aged 10 to 14 to be twice as high as in girls and women aged 15 to 25.²⁷

Providing a vaccine "against cancer" to preadolescent girls raises several challenges. Acceptability will require an increased understanding by parents of cervical cancer and the reasons for vaccinating young girls to prevent a disease from occurring decades later. A sobering lesson may be gleaned from past efforts to eradicate poliomyelitis, which have been complicated by misinformation or rumors.²⁸ Although European studies report high acceptability rates for HPV vaccine,^{29,30} there is a clear lack of understanding of cervical cancer causality across class and national lines.

Many young unmarried girls and women face significant challenges because of lack of access to the health care necessary to meet their needs. While neither national immunization programs nor sexual and reproductive health programs are ideally adapted for young adolescent services, a package of health services could be developed to offer girls an HPV vaccine as well as other interventions that would have a broader impact on their reproductive and general health.

b. Boys and Men

HPV prevalence is lower in men than in women, although still frequent; it is unknown whether men clear such infections more quickly or are less likely to be infected.³¹ Although one of the vaccines may be licensed for use in males, modeling studies suggest only a marginal added reduction of disease when coverage is already high in women.³² Financial considerations aside, however, there are other reasons to consider male vaccination.

Gardasil,[®] and probably other later-generation vaccines, will provide protection against genital warts. Although these lesions are not cancer-causing they can cause significant irritation to the genital tissues, thereby increasing vulnerability to infection with HIV.^{33,34}

Both men and women who practice anal receptive sex are at risk of developing anal intraepithelial neoplasia (AIN), the precursor to anal cancer, also strongly linked to HPV infection.³⁵ HIV-positive men with HPV are twice as likely to develop anal cancer than HIV-negative men.³¹

Studies suggest that education and information programs actively designed to inform men about cervical cancer have an impact on their female partners' willingness or ability to access services.³⁶ Ultimately, the involvement of both males and females in vaccination efforts might increase acceptability, both directly and indirectly.

Healthcare Delivery Systems that Reach Populations in Need

a. National Immunization Programs

Despite the successes of the Expanded Program on Immunization (EPI), there are several programmatic challenges in introducing HPV vaccines as part of the EPI in many countries.²¹ It may seem attractive to link HPV vaccine to tetanus toxoid (TT) administration because both are targeted to young adult women, have a schedule requiring three or more doses, and have similar intervals between doses. However, TT vaccine coverage through routine services is only around 50 percent globally, and much of the vaccine is given to parous women, who are much less likely to benefit from vaccination against HPV.²¹ TT is also given to school-age children, but can be given at school entry since the duration of immunity is known. Given the limited data on duration of protection of the HPV vaccines, school entry occurs at too young an age for co-administration.

b. School-Based Vaccination

Where enrollment rates are high, school-based vaccination can be extremely successful in eliminating disease.³⁷ Parents usually trust healthcare recommendations made in a school setting, especially with the endorsement of involved professionals, such as teachers.³⁸ In countries where education is mandatory and/or accessible to all children, laws mandating

vaccination prior to enrollment may increase vaccination rates by as much as fourfold.³⁹ School-based vaccination is cost-efficient, as children are already gathered and accounted for.⁴⁰

However, by age 9, a minority of girls is still in school in many countries.⁴¹ Poor enrollment rates, limited school facilities in rural areas, and migration are obstacles apart from school fees that prevent many girls from remaining in school until the age appropriate for HPV vaccination.⁴²

For countries with low school attendance among girls aged nine and up, the most practical delivery method may be through annual immunization campaigns. However, delivering HPV vaccines through such campaigns would require evaluation of a schedule with a longer interval between 2nd and 3rd doses than has been followed in the trials to date.

c. Sexual and Reproductive Health Services for Adolescents

Sexual and reproductive health (SRH) services, and family planning services in particular, are almost exclusively accessed by women during or following a first pregnancy, motivated by child spacing, rather than before pregnancy to delay early childbearing.⁴³ Young women aged 10–25, and especially unmarried women in that age range, have particular difficulty overcoming social and political barriers in order to access reproductive health services.^{44,45} The time between early childhood and sexual debut defines one of the most difficult cohorts to reach for healthcare.

Adolescent programs are developing user-friendly services that aim to provide counseling on sexual health focusing on the prevention of pregnancy and sexually transmitted infections (STIs), including HIV. The presence of a new intervention, such as an HPV vaccine, could extend the scope of these services and help to integrate other interventions, thereby making them more attractive to young people.

d. Role of Sexual and Reproductive Health Services

Existing SRH programs can play an important strategic role in integrating primary and secondary prevention services. As a sexually transmitted disease that causes cervical cancer, HPV has significant reproductive health implications. Consequently the context of vaccine delivery and the target populations may be different from the traditional EPI milieu. Young women who may have only recently initiated sexual activity, or who are seeking family planning after childbirth, represent a target catch-up population for both primary and secondary prevention, for the following reasons:

- A positive experience with vaccination in this group will be a natural entry point towards the eventual vaccination of adolescents or preadolescents, especially this group's children.
- SRH services provide a broad range of services within a comprehensive approach to sexual and general health.
- SRH initiatives that reach out to older adolescents should address cervical cancer prevention.
- This group is the target of other STI interventions and most VCT/HIV programs.
- Nursing staff caring for this group are motivated towards cervical cancer prevention, and most are already trained in counseling.

A coordinated effort on the part of all stakeholders to consider the implementation of simplified screening and vaccination programs as part of an integrated reproductive health strategy to reach girls and women may be attainable. This requires coordination with and timely inputs from programs with experience in vaccine delivery, sexual and reproductive health and cancer control.

Long Term Commitment: Advocacy, Information and Education

International public health advocacy at the highest level was instrumental in obtaining a commitment by the GAVI Alliance to purchase hepatitis B vaccines, and in devising a ranking scheme to assist donors in their decision-making about financial support.⁴⁶ In the case of cervical cancer prevention, advocacy must come from those who understand the disease and its societal and population-based burden. Surveys of the global environment have indicated that the knowledge levels of female and male patients, health professionals and policy makers regarding HPV and cervical cancer are relatively low.⁴⁷ Cancer and SRH professionals and policy makers can have a unique role in bridging knowledge gaps to assure the generation of strong multisectoral political will.⁴⁸

Since HPV is sexually transmitted, culturally appropriate information must be developed for different regions, countries and/or local communities to avoid a negative reaction against HPV vaccination, particularly in regards to vaccinating young girls. It is also important to acknowledge the risk of a girl-only focus; even if only girls initially receive the vaccine, messaging should be aimed at boys too. Several studies have demonstrated that understanding of vaccine benefits overcomes initial parental caution about the sexually transmitted nature of the infection.⁴⁹

For health professionals, evidence-based, standardized informational materials should be developed or identified. Cancer and SRH communities can play a significant role in nurturing individual champions with a shared set of objectives to advocate for adequate resource allocation nationally and internationally. Comprehensive prevention programs that offer screening and early treatment alongside new vaccine programs could optimize the value of cervical cancer vaccines as a prevention tool and as a tool for promoting adolescent sexual and reproductive health.⁵⁰

5. Conclusion

Cervical cancer is a unique public health challenge. It is gender-specific, caused by a sexually transmitted virus, and its primary and secondary prevention strategies target opposite ends of a wide age spectrum. The natural history of cervical cancer is well studied, and screening programs that identify pre-cancers early have been successful at significantly reducing disease, albeit at significant financial cost. Primary prevention through HPV vaccination will most likely be one of the most remarkable medical advances of this century. Together, secondary prevention through screening and early treatment and primary prevention through early adolescent vaccination could provide a comprehensive strategy for a long-term vision to eliminate cervical cancer. Many stakeholders already understand enough of the associated science and social issues to generate realistic prevention strategies. On a broad scale, next steps for achieving eradication include the following:

- Screening and early treatment programs should be continued and improved through the next several decades to prevent disease in women already infected or those who become infected with oncogenic HPV types not included in current vaccines.
 - Global health policy makers should work together to articulate a long-term vision for disease control on a global scale.
 - International organizations, national governments and private foundations must address, at the highest level, how best to:
 - minimize well-described delays in access to new vaccines in poor countries; and,
 - ensure equity in access.
- New financing mechanisms such as advanced market commitments should be tested for their ability to accelerate global distribution of this and other much-needed medical interventions.⁵¹
 - Information and education efforts should be targeted at not just adolescents, but their parents and the healthcare providers who inform them.
 - Consider HPV vaccine introduction as an opportunity to build a platform for broader general and reproductive health care for young adolescents, who already represent the population at highest risk for neglect in most parts of the world.
 - Consider HPV vaccine introduction as a possible platform for future implementation of an AIDS vaccine, given the probable need to vaccinate the same target population.
 - Policymakers and opinion leaders will need guidance in:
 - acknowledging lessons learned from prior initiatives in vaccine introduction; and,
 - ensuring that this gender-specific disease has the necessary priority on the global public health agenda.

As a foundation for the above objectives, a multisectoral partnership among EPI, cancer control and reproductive health sectors must emerge to engage global stakeholders for advocacy to ensure that the right initiatives are implemented rapidly to prevent this disease that characterizes health inequity today.

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