HPV vaccination: the promise & problems

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Four-fifths of the cervical cancer burden in the world is experienced in developing countries. HPV genotypes 16 and 18 account for 70 per cent of cervical cancers and currently available vaccines targeting these two types confer a high degree of protection against HPV 16/18 infection and related cervical precancerous lesions. However, widespread implementation of HPV vaccination programs are challenged by the unaffordable high costs of the vaccines and the lack of effective vaccine delivery platforms for sexually naïve girls. Other unresolved issues include long-term protection, cross-protection against HPV types not included in the vaccine and whether booster doses will be needed. Sensitivities associated with a vaccine preventing a sexually transmitted infection in girls, lack of awareness, public demand and political will, lack of coordination between cancer control, sexual and reproductive health and vaccine delivery services are additional challenges. Reduced costs, simple vaccine regimes and strengthening vaccine delivery platforms for adolescents should eventually facilitate HPV vaccine introduction in developing countries.

Key words Cervical cancer - challenges - effectiveness - prevention - vaccination

Introduction

Cervical cancer is an important public health problem, especially affecting socio-economically disadvantaged women in many low-resource countries where high rates are observed due to lack of effective screening programs. There is more than eight-fold difference between the highest and lowest incidence rates of cervical cancer worldwide. In many countries in sub-Saharan Africa, Central and South America, South and South-East Asia, age-standardized incidence rates of cervix cancer exceed 25 per 100,000. Rates are lower than 7 per 100,000 women in middle-eastern countries and are lower than 10 per 100,000 in most developed countries. Estimated age-adjusted cervical cancer mortality rates range between 3-8 per 100,000 women in developed countries, while exceed 10 per 100,000 women in most developing countries, with rates exceeding 25 per 100,000 in East African countries.

Of the estimated 10.9 million new cancer cases (5.8 million in men and 5.1 million in women) in the world around 2002, cervical cancer accounted for 493,000 cases; of the estimated 6.7 million total cancer deaths (3.8 million in men and 2.9 million in women) it accounted for 273,000 deaths. More than 80 per cent of the estimated global burden is experienced in countries of South and South-East Asia, sub-Saharan Africa, and South and Central America. It is striking that one third of cervical cancer burden in the world is experienced in South Asia. In many low resource
countries, cervical cancer is still the most common cancer in women, where women at the highest risk of death have the least access to screening, early diagnosis and treatment. Thus, prevention of cervical cancer assumes great importance in these countries. While cytology screening has contributed to a substantial decline in developed countries over the last 5 decades, cervical cancer still remains the largest single cause of years of life lost to cancer in many low-resource countries, with devastating effects on the well-being of families and society at large, due to lack of effective screening and other prevention measures.

The fact that cervical neoplasia are caused by persistent infection with one or more of the 15 high-risk human papillomavirus (HPV) genotypes[^4][^5], and cervical cancer is essentially a rare long-term outcome of this common infection of the cervical surface epithelium, has opened up new avenues such as vaccination for preventing cervical cancer. In the context of eventual widespread HPV vaccination in sexually naïve girls, screening guidelines must adapt in order to retain efficiency and cost-effectiveness. The prospects and challenges for cervical cancer prevention HPV vaccination in developing countries is briefly discussed in this paper.

**Persistent HPV infection and cervical neoplasia**

The fact that cervical cancer is caused by persistent infection by one or more of the high-risk oncogenic HPV types provides the exciting opportunity for prevention through vaccination. In a meta-analysis involving 14,595 cases of invasive cervical cancer, 87 per cent contained one or more of the oncogenic HPV genotypes that cause cervical cancer and the frequency of HPV in cervical cancer specimens ranged from 86 to 94 per cent by different regions of the world[^6] (Table). HPV 16 was the most common type (ranging from 52% in Asia to 58% in Europe) and HPV 18 was the second most common (ranging from 13% in South/Central America to 22% in North America). Overall HPV 16/18 frequency in cervical cancer specimens was 70 per cent and varied from 65 per cent in South/Central America to 76 per cent in North America (Table). The other common HPV types in cervical cancer were the same in each continent, namely HPV 31, 33, 35, 45, 52 and 58. HPV types other than these 8 accounted individually for less than 2 per cent of cervical cancer cases from any continent.

Overall HPV prevalence in high-grade cervical intraepithelial neoplasia (CIN 2 and 3) was 85 per cent, ranging from 78 per cent in Asia to 88 per cent in Europe. HPV 16 was the predominant type in CIN 2-3 varying from 34 per cent in Asia to 52 per cent in Europe and the combined HPV 16 and 18 prevalence was 52% (Table)[^6]. The 8 most common HPV types in CIN 2-3 were largely similar to those in cervical cancer, but for a noticeable absence of HPV 45.

**Prevention by vaccination**

The currently available and evaluated HPV vaccines target preventing infection by HPV types 16 and 18. HPV vaccines are prepared from virus-like particles (VLPs) produced by recombinant technology and are given as three 0.5 ml intramuscular injections over a six-month period. Recent results indicate that HPV vaccines are highly immunogenic inducing high levels of serum antibodies in almost all vaccinated women, and have conferred a high degree of protection against HPV-16/18 infection and thus the associated precancerous cervical lesions in fully vaccinated

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**Table.** Prevalence of human papillomavirus (HPV) type 16/18 among women with invasive cervical cancer and with high-grade cervical intraepithelial lesions (CIN)[^6]

<table>
<thead>
<tr>
<th>Regions</th>
<th>Invasive cervical cancer (14595 cases)</th>
<th>CIN 2 and 3 lesions (7094 cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any HPV</td>
<td>HPV 16</td>
</tr>
<tr>
<td>Africa</td>
<td>93.9</td>
<td>54.5</td>
</tr>
<tr>
<td>Asia</td>
<td>85.9</td>
<td>52.0</td>
</tr>
<tr>
<td>Europe</td>
<td>85.7</td>
<td>58.1</td>
</tr>
<tr>
<td>North America</td>
<td>86.9</td>
<td>54.2</td>
</tr>
<tr>
<td>South/Central America</td>
<td>91.1</td>
<td>52.4</td>
</tr>
<tr>
<td>Oceania</td>
<td>88.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Total</td>
<td>87.3</td>
<td>54.4</td>
</tr>
</tbody>
</table>

Source: Ref 6
women. These vaccines have demonstrated a high-safety profile as well. A quadrivalent (HPV 6/11/16/18) vaccine, evaluated in 27,000 women in 33 countries, has proved to be effective in preventing more than 99 per cent of persistent infections and CIN grades 2 and 3 caused by HPV types 16 and 18. A bivalent vaccine targeting HPV types 16 and 18 evaluated in a clinical trial involving 18,700 women aged 15-25 yr was found to have similar efficacy. The remarkably consistent finding that a regimen of three intramuscular injections of HPV vaccines offer HPV-naïve women a very high-level of protection from infections and CIN associated with the HPV types included in the vaccine has opened up a vast potential to reduce cervical cancer burden.

In many countries, HPV vaccination is now recommended for girls aged 11 to 15 yr. “Catch-up” vaccination of girls and women aged 16 to 26 yr who have not been previously vaccinated or who have missed a vaccination is also recommended, as women within this age group have the highest prevalence of HPV infection. Some propose that vaccination can still benefit women over the age of 26 yr who have not been previously exposed to HPV 16, or 18 and those who may have new sexual partners in the future.

Cross protection

The available data on whether natural HPV infection infers cross protection against other related strains from the same species are equivocal. There appears to be a reduced risk of contracting the same strain of HPV following HPV infection. However, natural infection with HPV does not confer group-specific immune protection or general protection from re-infection with genital HPV mucosal types. Recent studies conducted with HPV vaccines show data on cross-protection against related HPV strains. *In vitro* experiments with serum from recipients of the quadrivalent HPV vaccine (HPV-6/8/16/18) show neutralization of HPV 45 pseudovirions. Cross-protection following vaccination of women with three doses of bivalent HPV vaccine (HPV-16/18) demonstrated that, over a period of up to 4.5 years, long-term vaccine efficacy was observed for HPV-16 and -18, and vaccine efficacy was also observed against incident infection with HPV-31 and -45. In a large study involving some 18,700 women aged 15 to 25 yr vaccinated with the bivalent HPV vaccine (HPV-16/18), cross-protection was observed against persistent infections with HPV-45, -31 and -52, and, at 12 months, modest protection was demonstrated against persistent infections with 12 combined oncogenic HPV types. Although prolonged follow-up will be required to establish the extent of protection against infection by oncogenic types of HPV not included in the vaccine, the emerging preliminary data on this aspect of cross-protection against related oncogenic types (including HPV types 31, 33, 35, 45, 52 and 58) are encouraging.

Challenges for HPV vaccination

There are several challenges and uncertainties that need to be resolved before HPV vaccination can be widely implemented in low-resource countries, despite the fact that it is an important emerging option for cervical cancer prevention, and the currently available evidence support the introduction of HPV vaccines. The challenges include: current high costs of the available vaccines, feasibility, acceptability, logistics of vaccine delivery (in view of the need for three doses spread over 6 months, improved strategies and vaccine platforms to reach out to pre- or early-adolescent girls), long-term immunogenicity and efficacy in preventing cervical neoplasia, cross-protection against HPV infections not targeted by the vaccine antigens and the efficacy of different and the need for more logistically feasible dose regimes in inducing and maintaining immunogenicity and long-term protection against cervical neoplasia. These issues are critical for adequate support for a global acceptance and momentum for the introduction of HPV vaccines in public health services.

In many developing countries after licensure, new vaccines are often only available in the private sector for those who can afford them and their availability through the public health services is usually delayed for several years even decades. This was the case for vaccines such as hepatitis B and Hib. The availability of newer and effective vaccines on the private market promotes, and eventually facilitates, the demand for its introduction in the public sector, as it may prove educative for physicians, decision makers, and the public about the availability and benefits of these new products. Vaccines purchased and prescribed to individuals through the private sector in countries also contribute to the overall coverage and these are usually supported by out of pocket payments or by private insurance schemes.

The high cost is a very major barrier for the widespread use of HPV vaccine. One dose of HPV vaccine currently costs more than 100 USD in many developed and developing countries. It is impossible for the public health sector to consider implementing HPV vaccine at this price level, given the fact the
early. In areas where the rate of school enrolment to be in school than boys as they often leave school later adolescence may be low; girls may be less likely many of the poorer countries, school attendance during infancy). A comprehensive vaccination delivery infrastructure for adolescent vaccines is either poorly developed or non-existent in many developing countries. In developing countries, schools are often used as a focus for adolescent vaccination; however, in many of the poorer countries, school attendance during later adolescence may be low; girls may be less likely to be in school than boys as they often leave school early. In areas where the rate of school enrolment among girls is low, community-based efforts to reach girls outside school must be evaluated. Thus, new systems will be needed to reach young adolescents in many settings and achieving wide HPV vaccination coverage among preadolescent and adolescent girls by integration of HPV vaccines into existing vaccine platforms will require additional vertical inputs in resource-poor settings.

Many developing countries have few resources to devote to introducing new vaccines and several new vaccines against major killers of children such as pneumococcal pneumonia, rotaviral diarrhea, Japanese encephalitis, and meningococcal meningitis will compete for these limited resources. The impact of these vaccines against infections that kill children will be evaluated vis-a-vis the HPV vaccine. A major challenge in the introduction of HPV vaccine in developing countries will be the bringing-together of the immunization, reproductive health and cancer control communities to engage in rational decision-making to select new vaccines among these potentially competing priorities.

A vaccine targeting women, and associated with a sexually transmitted infection, may generate rumours that it is a plot to sterilize girls and young women. This misunderstanding may be further potentiated in environments characterized by the mistrust of governmental health care initiatives. The general lack of awareness on the relationship between HPV infection and cervical cancer may further complicate the scenario. Lack of demand for HPV vaccine, socio-cultural sensitivities regarding HPV infection and the promotion of HPV vaccine may lead to inadequate political will and lack of public support. HPV vaccine should be promoted as cervical cancer prevention vaccine for better acceptance rather than a vaccine for a sexually transmitted infection. If it is promoted as a vaccine for the prevention of a sexually transmitted disease, controversies and difficulties may arise in some settings with a polemic on moral issues and the possibility of increased promiscuity.

In countries with limited resources and health care infra-structure, coverage for re-vaccination programmes is often lower than those requiring a single shot of the vaccine. For instance the coverage for the first dose of polio vaccine or triple vaccine is substantially higher than that for three doses in many developing countries. Thus, the current regime of three doses of HPV vaccine spread across three months for
those aged above 9 yr brings in difficulties to achieve high coverage. It is not known yet whether fewer than three doses of vaccination can provide adequate protection against infection and CIN; this question needs to be addressed in order to reduce costs and make its delivery more feasible and complete.

Conclusion

HPV-related morbidity and mortality from cervical cancer primarily occurs in the developing world where, unfortunately, access to vaccines, in particular expensive newer vaccines, is more limited than in the industrialized world. In order to save women’s lives, developing countries should explore local production options, price negotiation, and secure financing. Much effort, political will, and resources will be needed to avoid the tragedy of delaying the benefits of HPV vaccine to women in low- and medium-resource countries. The affordability of vaccines and future evidence base for issues related to long-term immunogenicity, cross-protection, dose regimes and ultimate reduction in the burden of disease following immunization are critical for the early introduction of HPV vaccination.

References


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