

Chapter 15: HPV vaccine use in the developing world

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Abstract

Human papillomavirus (HPV)-related morbidity and mortality from cervical cancer primarily occurs in the developing world, where, unfortunately, access to vaccines in general, and expensive newer vaccines in particular, is often more limited than in the industrialized world. In addition, secondary prevention methods such as HPV screening, Pap testing, or visual inspection are uncommon in the developing world. The HPV vaccine will be first introduced into the industrialized countries and it will then, over the course of time, become used in the developing countries. HPV vaccine should be introduced in the framework of comprehensive cervical cancer control, and offers an opportunity to bring together a wide range of constituents who have not to date worked closely on vaccination. Ultimately, the decision of whether and when a vaccine will be introduced will depend on individual countries. To prepare for decisions on HPV vaccine use, the sexual and reproductive health (SRH; including adolescent health), immunization, and cancer control communities need to work together to analyze the appropriate data and build international and national consensus. The timeframe for other newer vaccines, such as hepatitis B and Hib, has been measured in decades, and the challenge to the public sector is to greatly shorten the time needed to make HPV vaccines available and affordable for the developing world, where their impact will be greatest.

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1. Introduction

The discovery, development, and testing of the second vaccine against a major human cancer, namely HPV vaccine, is a major breakthrough in modern preventive medicine. The impact of this important new vaccine will be realized only if and when it is effectively delivered to the populations that need it. In the industrialized world, while the cost will be high, this vaccine will be affordable and welcomed by most health workers, adolescents, and parents. In the poorer countries in

the developing world, however, it has taken two decades for new vaccines to become available in the public sector. While the vaccine may soon be available in the private sector in some of these countries, major reductions in the morbidity and mortality of cervical cancer will only come about when HPV vaccine is used “routinely” in public health programs that deliver vaccines to all adolescents and other appropriate target groups. For this to happen, partnerships between the sexual and reproductive health (SRH), immunization, adolescent health, and cancer control communities must be forged. The SRH community understands first hand the impact of HPV infection and cervical cancer, and must become a powerful and effective advocate for the use of this vaccine together with the pediatric and public health communities that have been the traditional advocates for vaccination.

The women at highest risk of death from cervical cancer live in the developing world, where it is the leading

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cause of cancer mortality in women in most countries [1]. Unlike women in industrialized countries, who have access to screening and treatment that have greatly reduced cervical cancer deaths, most women in the developing world will never be screened, and adequate treatment for cervical cancer is largely unavailable. Thus, the women at highest risk of death from cervical cancer have the least access to secondary prevention and the greatest need for primary prevention through HPV vaccine.

Current HPV vaccines protect against subtypes 16 and 18, which cause the majority, but not all of cervical cancer [2]. These vaccines are prophylactic, not therapeutic, therefore, current screening programs will need to continue so that secondary prevention may be offered to women who may already be infected or who will be un-immunized and infected in the future. It must also be kept in mind that it will take decades to measure a major reduction in cervical cancer mortality because of the long incubation period of the disease. However, as soon as the vaccine is delivered, women are protected from HPV infection with the included serotypes and are no longer at risk of cervical cancer from those types as long as immunity lasts.

In this chapter, we will first describe immunization programs and past experience with the introduction of new vaccines in the developing world, and then discuss critical issues concerning the introduction of HPV vaccine as part of comprehensive cervical cancer control programs.

2. How immunization works in the developing world

All countries have a National Immunization Program (NIP) that delivers vaccines, funded by the government (and sometimes donors), to eligible children and often to adolescents and selected adults. The great majority of children in both the industrialized and developing worlds receive their vaccines through NIPs. Many countries (industrialized and developing) also have a private sector market that provides vaccines to individuals and families with private insurance coverage or to those who choose to pay for the vaccines themselves. Policies and strategies for NIPs in developing countries are determined nationally, but are strongly influenced by policies of the World Health Organization (WHO) Expanded Programme on Immunization (EPI). The EPI began in 1974 with six antigens, but now includes at least eight antigens in its globally recommended schedule (bacille Calmette-Guerin (BCG) against tuberculosis, oral polio vaccine (OPV), diphtheria–tetanus–pertussis (DTP), hepatitis B (HBV), and measles vaccines in the infant immunization schedule, and tetanus–toxoid (TT) containing vaccines for women of child-bearing age) [3].

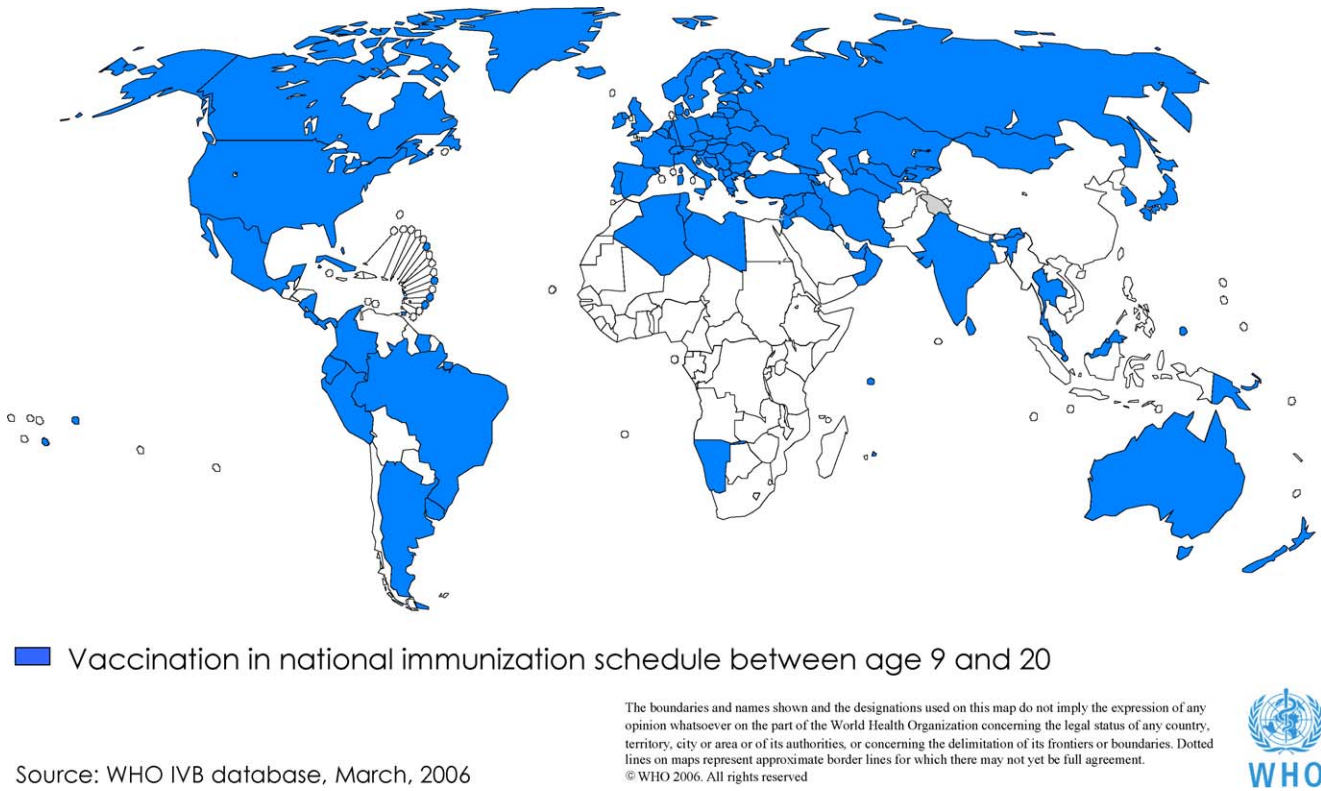
In addition to these eight antigens, the WHO's Scientific Advisory Group of Experts (SAGE) recently recommended global implementation of *Haemophilus influenzae* type B vaccine unless robust epidemiological evidence exists of low disease burden, lack of benefit, or overwhelming impedi-

ments to implementation [4]. Countries with a demonstrated burden of congenital rubella syndrome are encouraged to include rubella vaccine, and vaccines such as yellow fever and Japanese encephalitis vaccines are used in appropriate regions. By the end of 2004, 153 (82%) countries had included HBV vaccine and global coverage was estimated as 48% of infants in the world [5].

Following the primary immunization series in infancy, some countries give booster doses according to the epidemiological patterns of diseases in a particular country, the level of health service infrastructure and resources, and the relative priority of boosters compared to introduction of new vaccines into the primary vaccination schedule. Fig. 1 shows the number of countries reporting administration of booster doses in preschoolers and to persons aged 9–20 years in their routine national immunization schedule in 2004 [6]. The most commonly used vaccine in this age group is a booster of tetanus–diphtheria (with or without pertussis) vaccine, which provides long-lasting immunity to these infections. The inclusion of boosters broadly follows the level of economic development of countries and regions; therefore, few countries in Africa currently include boosters in their NIPs.

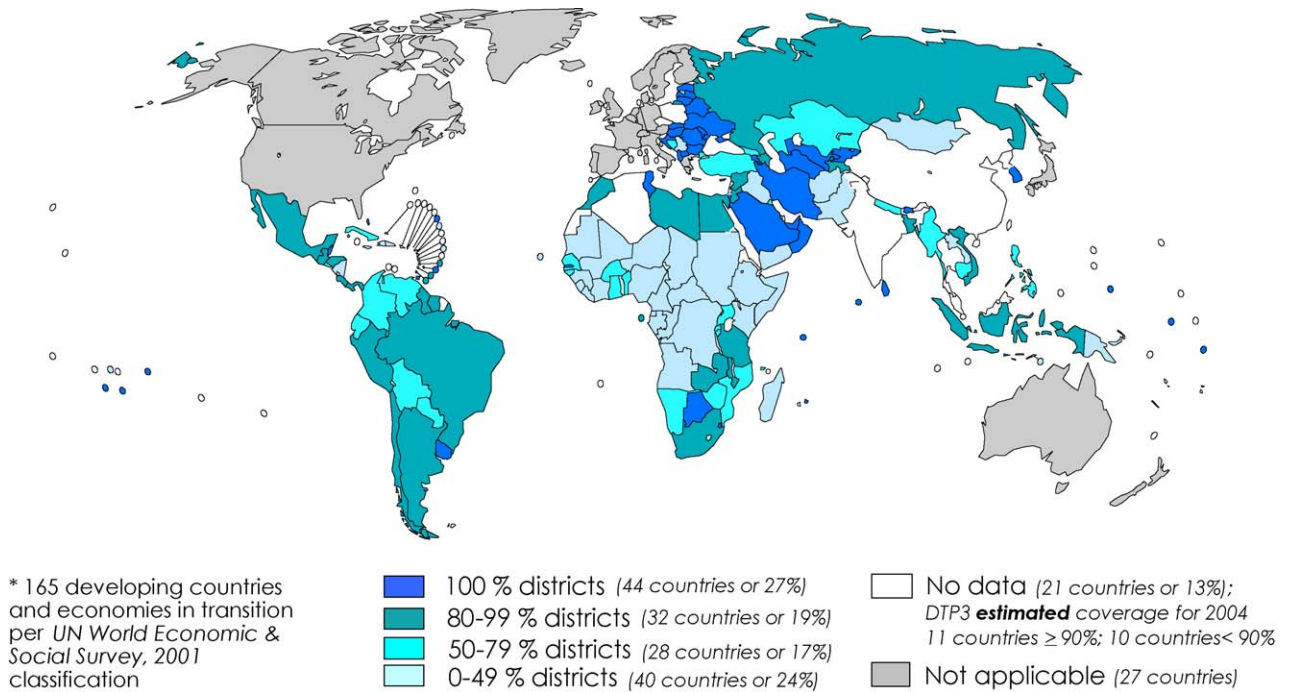
Delivery sites for vaccination range from fixed sites to mobile teams. Fixed sites include health centres and health posts that offer a range of primary healthcare (PHC) activities including immunization, growth monitoring and nutrition, family planning, antenatal care, basic treatment of common childhood illnesses, etc. Utilization is higher when sites are easily accessible, have minimal administrative barriers, and also provide good quality curative care and an adequate supply of essential drugs. In areas progressively further from a health facility, regular outreach services from the nearest health facility or district centre, or mobile teams (which involve a stay of at least one night in a distant village) are used. Typically, vaccination is available daily in large fixed health facilities, especially those in urban areas, but only once a week or once a month in smaller fixed facilities and outreach sites [7].

In addition to routine vaccination through the PHC system, mass campaigns are used globally to achieve herd immunity for polio eradication (two national immunization campaigns of children under 5 years each year for several years), measles elimination (in which all children from 9 months to 15 years of age receive a dose in one initial catch-up campaign, followed after 3–5 years by follow-up campaigns targeting children under five) [8], and rubella elimination, in which women only, or women and men up to 30 or 35 years of age are immunized with rubella or measles–rubella vaccine [9]. For maternal and neonatal tetanus elimination, campaigns are used as strategies to reach women in “high-risk” districts, where the incidence of neonatal tetanus is above the target of 1 per 1000 live births. Three rounds of immunization of all women of childbearing age with TT or Td are implemented as “supplementary immunization activities” (SIAs), in addition to ongoing vaccination of pregnant women. Over 200 million women have been targeted through these SIAs for TT [10].



Source: WHO IVB database, March, 2006

Fig. 1. Countries with vaccination in national immunization schedule between 9 and 20 years, 2004.



Source: WHO/UNICEF estimates and WHO/IVB database, 2005
192 WHO Member States. Data as of September 2005

Fig. 2. “Developing” countries with % of districts achieving at least 80% diphtheria-tetanus-pertussis (DTP3) vaccine coverage (2004).

In most countries, the EPI has reached very high coverage of infants through a wide range of strategies. Overall, about 75% of the children in the world receive basic immunization services, and campaigns such as polio and measles reach more than 90% of the children in the world. Nonetheless, there is wide variation in coverage within the developing world and even within countries (see Fig. 2). Some developing countries have excellent programs and higher immunization coverage than some industrialized countries, while other countries, particularly in Central Africa, barely manage to immunize 40% of their children and have not been able to introduce newer vaccines.

3. Past experience with the introduction of new vaccines in developing countries

In developing countries, expensive newer vaccines are often available to those that can afford them on the private sector market long before they are available from the public sector. The availability of newer vaccines on the private market is important, since it educates physicians, decision makers, and the public about the availability and benefits of these new products and creates demand to make them available in the public sector.

Historically, people in the developing world have had to wait decades before new vaccines become available to their NIPs. HBV vaccine was licensed in 1981 in industrialized countries, but it took 10–15 years before the vaccine was used in public health programs in wealthier developing countries, and over 20 years before children in the poorest developing countries had widespread access to the vaccine [11]. Hib vaccine has been used in industrialized countries for two decades, virtually eliminating Hib meningitis, but most developing countries have yet to introduce it. Much attention has been paid over the last few years on new ways to give people in the developing world access to newer vaccines sooner.

NIPs in many developing countries have few resources to devote to introducing new vaccines and there are many new vaccines available or soon to be available that will compete for these limited resources. New vaccines against major killers of children such as pneumococcal pneumonia, rotaviral diarrhea, Japanese encephalitis, and meningococcal meningitis are available and, since they kill children, the impact of vaccines against these infections will be seen long before that of HPV vaccine. One of the challenges in the introduction of HPV vaccine will be the bringing-together of the immunization (traditionally pediatric) community and the SRH and cancer control communities to engage in rational decision-making to select new vaccines among these potentially competing priorities.

The public health community is currently working on issues such as financing, procurement, and alternative pathways to vaccine development and production to shorten the time gap between the availability of important new vaccines in the industrialized and developing worlds. Much effort,

political will, and money will be needed to avoid the tragedy of delaying the benefits of HPV vaccine to many cohorts of women in the developing world.

4. Who will deliver HPV vaccine in the developing world?

A major issue is whether countries will use the established immunization networks that deliver vaccines to infants, children, and pregnant women (and run campaigns) or use networks of SRH services such as family planning, pre- and post-natal care, or a mixture of systems. It may be possible to empower the immunization system and/or the SRH system to take the primary responsibility for delivery of HPV vaccines. These are usually administratively separate except at the PHC level and sometimes the level of a Department of Family and Community Health that embraces both systems. Different countries may choose to empower different systems, or use a combination of both, and this could be an area explored by demonstration projects.

Immunization service delivery is the most successful public health system in the world and the infrastructure of trained staff, cold chain and logistics, clinics and outreach services, and information systems is a resource that could be utilized to deliver HPV vaccine. Experience in vaccinating school-age children, however, is more mixed than that of infant vaccination, although most industrialized and middle-income countries have policies of vaccinating school children (Fig. 1). In many of the poorer countries, however, school attendance during later adolescence may be low, girls may be less likely to be in school than boys, and the poor who need the vaccine most are most likely not to be in school. There are reports of using schools as vaccination sites during measles campaigns in Africa and successfully using school children to bring non-school attendees to the vaccination site (Grabowsky, personal communication, 2005), and this could be built upon and evaluated in demonstration projects. Another strategy that should be explored is the possibility of immunizing female caregivers (mothers, grandmothers, older sisters, or aunts) when they bring in children for immunization.

Developing programs for adolescents or school children represents a challenge that needs addressing in the near future, and HPV vaccines can be used as the entry point. Such programs may eventually offer countries a second major opportunity to deliver a package of vaccination, as well as other interventions like nutritional supplements, health promotion, and provision of sex education for adolescents and reproductive health information [12]. These packages can be tailored to country-specific needs and will set the stage for potential future addition of new vaccines against HIV or TB.

The immunization system will need to be substantially enlarged to reach large numbers of adolescents and women of child-bearing age outside of pre-natal services, especially in low-income countries, and the time is ripe to develop

expanded systems for the adolescent age group. The Global Immunization Vision and Strategy of the WHO and United Nations Children's Fund (UNICEF) has declared introducing new vaccines and technologies and integrating immunization and other linked interventions in the health systems context as two of the major goals for the next decade [13]. The SAGE gives strong support for the integration of vaccination as part of strengthening school and adolescent health services [14], and the WHO Department of Child and Adolescent Health and UNICEF have both indicated a strong commitment to work with EPI and other partners to achieve this. Adolescent health programs aim to develop adolescent-friendly services that promote healthy lifestyles and provide counseling on sexual and reproductive health. HPV vaccine is seen by some as providing a new incentive both for the expansion of adolescent health services and for their uptake by young persons in a wide range of settings.

SRH services are another potential entry point for HPV vaccines. Although SRH services may include adolescent health services, in many countries these services currently reach few women before marriage and pregnancy. Because SRH programs play an important role in cervical cancer screening, they need to be closely involved with the development and implementation of comprehensive cervical cancer prevention programs that include HPV immunization [14]. Although the primary target group for HPV vaccination is likely to be young adolescent girls before sexual debut, who are generally too young for family planning, pre-natal care, or cervical cancer screening services, SRH services could provide important contacts for education and advocacy for HPV vaccination. Some countries may elect to vaccinate older adolescents and young women (and eventually perhaps also men) in addition to the primary target group. SRH services can also help to develop strategies to advocate for vaccination of the daughters when mothers attend services for antenatal care, family planning, cervical cancer screening, or other reasons. SRH programs should mobilize and create partnerships to build support for, and contribute to, cervical cancer and HPV vaccine programs.

5. How do countries decide which new vaccines they will use?

Each country decides which vaccines to fund and use in the public sector, and on the target groups for that vaccine. Ultimately, the decision is a political one and is often heavily driven by economic realities. Many countries have an advisory body consisting of respected academics and clinicians as well as public health experts, economists, regulatory experts, ethicists, etc., who make recommendations to the government on which vaccines to use and how to use them. Important inputs need to be considered (Table 1).

Different groups of decision makers are involved in ensuring that vaccines contribute effectively and efficiently to the disease control efforts of a country. Decisions must be made

Table 1

Important considerations for decision makers

Local epidemiology and burden of disease
Successful demonstration projects in the country or region
Global and regional WHO recommendations
The position of GAVI, UNICEF, and bilateral donors
Economic modeling of cost-effectiveness and impact
Level of knowledge about the disease and the vaccine in the medical community, the public, and the media
Cost of the vaccine
The "affordability" of the vaccine to the country
Competing priorities for immunization resources
The behavior of other countries in the region and the world
The strength of internal advocacy for introduction of the vaccine into the public sector
The success of the vaccine in the private sector
Influence of vaccine producers

about the goals of the vaccination program, and technical guidelines must be established regarding vaccine use, including selection of the optimal schedule and recommendations regarding contraindications to vaccines. Appropriate technology must be utilized for vaccine storage (the "cold chain"), injections, and waste disposal, and appropriate strategies must be selected for delivery of vaccines. National inter-agency coordinating committees (ICCs), which should include all key government departments and ministries (e.g., health, education, and finance), international partners, civil society organizations (CSOs), and the private sector can provide a key mechanism to facilitate coordinated planning, financing, political and technical support, and capacity building for comprehensive immunization programs. It will be important to include representation from obstetrics and gynecological professional societies on these advisory boards as key advocates for HPV vaccine introduction.

Recently, the WHO has developed guidelines to assist countries in deciding whether to introduce a new vaccine, and which product to use [15]. Criteria for assessing the NIP readiness for new vaccine introduction are summarized in Table 2.

6. Determining the correct target groups for developing countries

The strategies and target groups chosen for delivering vaccines are country-specific and there may be significant differences between regions and countries at different levels of economic development. Economic modeling will be an important input to this discussion, but the realities in the field must take precedent. For example, if modeling predicts that immunizing only adolescent women will be the most cost-effective strategy but this is not practically achievable in a particular country, other more achievable strategies must be developed if real impact is to be achieved.

Possible target groups include:

- adolescent/young adult women;

Table 2
Vaccine introduction guidelines

Criteria for assessing the National Immunization Program (NIP) readiness for new vaccine introduction

- (1) Obtaining full benefit from existing vaccines
 - An immunization multi-year plan and annual work plans are in place, with regular updating of policies
 - Immunization coverage reflects satisfactory access and limited drop out. Each NIP should set its own coverage targets in the multi-year-plan (MYP) considering the regional targets and global targets in the Global Immunization Vision and Strategy (GIVS)
 - Specific objectives are met or well under way for already existing vaccines. For example, timely (i.e. within 24 h) coverage with HepB birth dose is achieved where relevant, catch-up measles vaccination has been conducted, or two-dose measles strategy has been established
- (2) Financially sustainable programme
 - The NIP is able to mobilize and use resources for existing programme strategies with secure current and future financing
 - MYPs include a budget linked with the national health budget to secure vaccine supply and other costs
 - There is a capacity to expand the programme without threatening financial sustainability
- (3) Functional cold chain
 - National cold-chain policy and vaccine management systems include an updated cold-chain inventory as well as plans for the maintenance and replacement of equipment
 - The cold chain has adequate volume capacity and performance for existing vaccines at all levels
 - Cold space is able to meet any additional demands of the new vaccine, with an adequate spare capacity to meet campaign or unforeseen needs
- (4) Well managed vaccine stock
 - There are 2–5-year forecasts for all existing vaccines (including planned/likely campaigns) and the new vaccines, including the transition period when existing vaccines are being replaced
 - There is effective monitoring of wastage for all vaccines, with acceptable levels of wastage compared to coverage
 - Vaccine stock-outs at national or sub-national levels are infrequent
- (5) Safe immunizations and monitoring of adverse events
 - All vaccines are given with auto-disable (AD) syringes
 - Proper diluents and reconstitution methods are used for lyophilized vaccines
 - There is capacity to procure, distribute and dispose of additional injection materials for new vaccine
 - There is capacity to investigate and respond to adverse events following immunization
- (6) High quality disease surveillance
 - There is timely, reliable and comprehensive surveillance for major vaccine-preventable diseases
 - There is surveillance with pre-introduction baseline data to monitor impact of new vaccine

Adding a vaccine to a national immunization program: decision and implementation, WHO/IVB/05.18.

- adolescent/young adult women and men;
- adolescent/young adult women and female children;
- adolescent/young adult women and men and children of both sexes.

Important possible benefits from male immunization include significantly reducing or eliminating transmission of the virus in the population, thereby protecting the unimmunized, and the benefits from preventing HPV disease in males, which is not insignificant [16]. In models conducted to date, the impact of including men in a vaccination program varies according to the coverage achievable among women (see Chapter 21). The efficacy of the HPV vaccine in males has not yet been established. In certain populations where female-only immunization may be problematic, however, immunizing both sexes may be more culturally and politically acceptable.

In the longer term, there is considerable programmatic interest in the potential to vaccinate children during routine EPI sessions because the infrastructure is already in place to reach 75% of children. The advantage of immunizing children could include achieving much higher coverage at a lower cost, using reduced doses of vaccine (cheaper), even if a booster dose is needed at adolescence, and combin-

ing with other interventions through existing health delivery programs. However, there have been no trials conducted in children under 9 years of age, so further data on the immunogenicity, persistence of immunity, safety, compatibility with other vaccines, and acceptability of vaccinating children will be needed before HPV vaccine can be recommended for children.

7. The role of the Global Alliance for Vaccines and Immunization (GAVI)

The Global Alliance for Vaccines and Immunization (now named the GAVI Alliance) was established in 1999 as an alliance of countries and major partners that support immunization globally. The GAVI Fund, now with projected income of over US\$ 5 billion, helps to finance GAVI assistance to the 75 poorest developing countries by providing funds for infrastructure strengthening, introduction of new and underutilized vaccines, and provision of safe injections [17]. GAVI is also a forum where national governments, bilateral donors, international agencies, technical agencies, civil society, and industry can try to harmonize and coordinate their individual efforts to improve immunization in the developing

world. GAVI has already had major impacts on introduction of hepatitis B vaccine and safe injections in more than 40 countries, improvements in immunization coverage, financing, information systems, and infrastructure.

GAVI is encouraging the development of “investment cases” for all new vaccines proposed to be included in immunization programs in developing countries using standard guidelines [18]. This will help countries and the international immunization community to compare the burden of disease, impact, and cost-effectiveness of investments in new vaccines, and HPV vaccine will be one of these. It is essential that the HPV community begins to engage with GAVI to educate the partners on the benefits of this vaccine and work together on financing and advocacy issues. At a national level, vaccine introduction should work through national development and health-sector planning processes, such as sector wide approaches and poverty reduction strategy credits, to ensure budgetary support for the HPV vaccine program (including support to SRH, cancer control, EPI). Securing support from international financial mechanisms (such as GAVI) is a first-order priority, even as discussions take place in priority countries on developing national-level financial mechanisms

8. Cultural issues

Gender-specific immunization may be culturally difficult because a number of immunization programs have been damaged by rumors that vaccination is a plot to sterilize girls and young women. A vaccine targeted primarily to females and associated with a sexually transmitted infection may exacerbate these rumors. The impact of these rumors should not be underestimated. Even for polio immunization of young infants, rumors have seriously impeded the polio eradication program in countries as diverse as Nigeria and India, with global implications [19]. In Mexico, the Philippines, and Uganda, rumors that TT immunization was actually a trial for an anti-fertility vaccine became widespread and were difficult to manage for a number of years [20]. The importance of appropriate information and communication to effectively address these issues is to be emphasized at all levels.

The acceptability of this vaccine may be questioned by religious fundamentalists, who argue that giving a vaccine against an STI will “give permission” for their children to become sexually promiscuous [21]. Others will argue that “their” children will not have sex before marriage, so do not need the vaccine. It should be pointed out that even women who are virgins at marriage are often infected by their husbands. Some of these issues were faced with introduction of HBV vaccine in some countries, but in developing countries most hepatitis B transmission occurs in the perinatal period and early childhood, and thus HBV vaccine is administered in infancy, so these issues were of little relevance at the global level. The HIV/AIDS community has great expe-

rience in dealing with cultural issues involving sexuality, and will be very helpful in designing materials and training health workers to discuss these issues on a country-specific basis.

Anti-vaccine groups are active in many countries and have done significant damage to immunization programs in both industrialized and developing countries [22]. While these groups vary widely in their composition, they are very sophisticated in their use of the Internet and the media, and anti-vaccine ideas spread globally. Some of these groups have web sites designed to look like official sites [23]. It is important that groups and individuals educating and advocating for the use of HPV vaccines have training on how to address these issues with the public, the media, and government decision makers. Reliable information on the facts, and experience of how other anti-vaccine rumors were handled, should be available on easily accessed web sites [24].

9. Role of developing country manufacturers

As the vaccines used in the industrialized and developing world diverge, most of the vaccines used in developing country immunization programs now come from producers in the developing world. Private and public sector producers in countries such as India, China, Indonesia, and Brazil make most of the traditional EPI vaccines used in the world. Hepatitis B vaccine production in South Korea was a major factor in bringing the price of this vaccine to affordable levels in the developing world [11]. About one third of the world’s population lives in India, China, and Indonesia, where vaccines used in the public sector come primarily from local producers. While China and Indonesia now use Hepatitis B vaccine routinely in the public sector, India still does not provide this nationally.

The current HPV vaccines are made by pharmaceutical companies in industrialized countries who will first introduce the vaccine at relatively high prices in the industrialized world and private-sector markets in developing countries. There is discussion about early introduction of HPV vaccines into public sector markets in developing countries at lower prices, but this will depend on demand and financial commitment from the public sector. These companies are also discussing local production options with developing country government and private producers, but whether this will result in affordable local production is unknown. The intellectual property (IP) situation with regard to independent production in the developing world is unclear (important IP is held by public sector entities), and it would be useful to prepare IP “maps” to help local producers decide if development of locally produced HPV vaccines is an attractive option for them. Alternative ways to make HPV vaccines that do not use current virus-like particle (VLP) technologies are also being explored, but they represent technologies at a very different stage of development and therefore have many years of research and development ahead of them [25].

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FC: Consultant (GlaxoSmithKline)

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