

Stop Cervical Cancer: Accelerating Global Access to HPV Vaccines

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HPV Vaccines: Costs and Financing

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Abstract

The purpose of this paper is to review the major cost and financing challenges for the introduction of human papillomavirus (HPV) vaccines in developing countries and to present possible next steps for addressing those challenges. HPV vaccine prices will be much more expensive for developing countries than traditional Expanded Program on Immunization (EPI) vaccines and likely to be more expensive than the “newer” vaccines such as Hib and Hep B. There will also be significant non-vaccine delivery costs since reaching the target group, preadolescents, with three doses of the vaccine will require innovative delivery approaches. The poorest countries, with the least ability to pay, have the largest cohorts of preadolescent girls as a share of their total population. Decision makers will need to weigh the priority for HPV vaccines against other health priorities, as well as against other vaccines entering the market. In doing so, they will consider, among other factors, costs, cost-effectiveness, programmatic feasibility, and financial sustainability. The Global Alliance for Vaccines and Immunization (GAVI) could be a major source of external assistance for HPV vaccines if approved for eligibility by the GAVI Board. Preparation of a clear and compelling GAVI HPV investment case is critical. A strong investment argument for HPV vaccines will also need to be made at the country level. Middle-income countries that are not GAVI-eligible will need to look much more to domestic resources and to other sources of external assistance to introduce HPV vaccines. Strong signals of external assistance and country commitment will give manufacturers the assurance that they can scale up production to meet developing country requirements.

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1. Introduction

The potential benefits from the new human papillomavirus (HPV) vaccines are enormous for developing countries, given that cervical cancer is the primary cause of cancer-related deaths in women. But the challenges of financing and delivering these vaccines are large. GlaxoSmithKline (GSK) and Merck have not yet announced prices for developing countries. Although both companies have pledged to sell the vaccines at discounted prices in these markets, their vaccines are likely to be significantly more expensive than traditional Expanded Program on Immunization (EPI) vaccines over the short to medium term. Ministries of health and finance in developing countries face tight resource constraints. Some countries still need to increase coverage of traditional vaccines, and many more countries are grappling with financing coverage of the newer “underused” vaccines, such as Hib. Furthermore, several other new and important vaccines are expected to come to market in the next 5-7 years that will also compete for limited resources. In addition to the HPV vaccine costs, the additional non-vaccine delivery costs would also need to be financed. HPV vaccines cannot be easily folded into existing EPI delivery mechanisms because the target population is older (most commonly, girls before reaching puberty). Countries will take different approaches but at present the delivery costs are unknown.

External resources will help, especially for the poorest countries. The Global Alliance for Vaccines and Immunization (GAVI) is expected to consider the investment case for HPV vaccines in late 2007, and, if the vaccine becomes eligible for GAVI support, this would become a financing option for the 72 GAVI-eligible countries. Upcoming innovative financing mechanisms such as the International Financing Facility for Immunization (IFFIm) and Advanced Market Commitments (AMCs) could, possibly, help too if they cover HPV vaccine.

Countries that are not GAVI-eligible will necessarily need to look much more to domestic resources and to other sources of external assistance to finance HPV vaccination. Ultimately, at the national level, the decision on

whether or not to incorporate HPV vaccines into national programs, and when, will hinge on many factors, including, but not limited to burden of disease, cost-effectiveness, cost, financing source and the sustainability of financing.

2. Main issues

a. Pricing

Vaccine Price

Price is likely to be the main obstacle to HPV vaccination in the developing world. The HPV vaccines are likely to be expensive for developed countries and to remain that way until off patent. For the U.S. market, Merck’s entry price for its HPV vaccine is \$120/dose, or \$360 for the series (this price may fall when the GSK vaccine is approved). No industrialized country price has been announced for the GSK vaccine, which was submitted to the European Union’s European Agency for the Evaluation of Medicinal Products (EMA) in March 2006 and is targeted for submission to the United States Food and Drug Administration (FDA) by end-2006. Both GSK and Merck have pledged to offer lowered prices to developing countries for their HPV vaccines and are likely to use multi-level pricing so that the poorest countries (possibly those that are GAVI-eligible) receive the lowest price. Even with tiered pricing, the HPV vaccines are likely to be expensive for developing countries. They are likely to be many times more expensive than traditional EPI vaccines, which are pennies a dose (Table 1 presents 2006 UNICEF prices for traditional EPI vaccines). They could well be more expensive than the “underused” vaccines such as DTP-hepB-Hib which UNICEF offers at \$3.65 per dose. GSK’s Rotarix vaccine for rotavirus is not yet WHO prequalified, but Brazil, as an early adopter, has already started purchasing it at about \$7.50 per dose for the 2 dose series.

The long term price for HPV vaccines will certainly fall from whatever the short term price will be as more suppliers enter the market and demand becomes more stable and high volume. Alternate suppliers based on the Merck and GSK technology (using virus-like particles based on the

L1 protein of HPV types 16 and 18) will likely not begin to enter the market until 2015 or later. Other technologies are under investigation.¹ Clearly, given the disease burden from cervical cancer in developing countries, efforts to shorten the time frame that it typically takes for a HPV vaccines to drop in price and reach large scale production and adoption are critical.

Table 1. Pricing Comparison of Traditional EPI Vaccines, Newer Vaccines and Rotarix, 2006 (US\$)		
Vaccine	UNICEF Weighted Average Price Per Dose	Doses Per Vial
1. Traditional EPI Vaccines		
DTPw	\$0.177	10
BCG	\$0.08	20
Measles	\$0.17	10
TT	\$0.067	10
DT	\$0.091	10
OPV	\$0.157	10
2. Underused Vaccines		
DTP-hepB-Hib	\$3.65	2
Hib monovalent	\$2.65	1
hepB monoval	\$0.23	10
Yellow fever	\$0.60	5
MMR Urabe strain lyophilized	\$1.35	10
MR	\$0.488	10
Meningitis A&C	\$0.411	50
New Vaccines not yet Prequalified with WHO		
Rotarix (GSK)	Brazilian Government Price \$7.50	

Other costs

Vaccine cost per dose is just one component of what the introduction of HPV will cost to countries. In addition, vaccine wastage², freight, insurance, UNICEF’s procurement fee (if procured through UNICEF), and all the non-

vaccine delivery costs must be considered. Investments to expand the cold chain may be required. A variety of delivery strategies will likely be experimented with and adapted, depending on the country, to successfully reach the age group required. These include school-based and clinic-based strategies, and campaigns to reach young people. The Gates-funded PATH project will generate much useful experience and information on these issues. Some countries may wish to experiment with contracting NGOs or other providers to deliver the vaccine in order to see if that delivery mode can achieve greater coverage and/or lower costs. If contracting out is explored, payment for performance incentives could be considered.

b. Other Vaccines in the Pipeline

In addition to the Merck and GSK HPV vaccines, one or more vaccines for Japanese encephalitis, malaria, meningococcal-A, pneumococcal, and rotavirus are expected to come to market in the next five to seven years. These vaccines are of great interest to many countries. There will likely be bunching problems in the WHO prequalification process from this large number of new vaccines (see the background paper on regulatory issues). At the country level, policy makers will need to prioritize across the vaccines in terms of programmatic feasibility, cost, and health impact, as well as other considerations. Information on disease burden and cost-effectiveness could help country decision makers and donors weigh these options.

c. Cost-Effectiveness

Decision makers will be concerned not only with the affordability of HPV vaccination, but also with its cost-effectiveness. Cost-effectiveness is a tool to identify the most effective use of scarce resources. Cost-effectiveness models are used to compare the net cost of HPV vaccination with the potential benefits (often expressed as years of life saved or years of disability-adjusted life saved).

The setting matters. In developing countries, where access to cervical cancer screening and treatment is generally low, the benefits of

vaccination are dominated by the potential reduction in cervical cancer morbidity and deaths. The setting can change, over time, as developing countries strengthen screening and treatment programs.

In developed countries, where screening tends to be widespread, reductions in cervical cancer morbidity and deaths will be far smaller but there will be large cost savings from reductions in medical costs (follow-up to cervical lesions, treatment of CIN 2+ and cancer, and possibility adjustments to screening frequency).

There have been four published studies to date on the cost-effectiveness of adding an HPV vaccine to screening programs in the United States.³ Similar models are being applied to developing country settings. Goldie and others are comparing the cost-effectiveness of vaccination, screening (varying methods and intervals), and combined vaccination/screening. The models use assumptions about vaccination costs, costs of screening, diagnosis and treatment, and stage-specific cancer data. The researchers have found that in Tanzania, for example, a combined approach of vaccinating young girls with a single screening of older women is likely to be cost-effective.⁴ More generally, researchers have found that there are vaccination and screening strategies for women in developing countries with cost-effectiveness on par with other well accepted public health interventions under the assumptions used (for example, that the vaccine would cost less than \$25 per vaccinated woman). Although there are direct benefits to men from HPV vaccines (e.g. anal cancers, genital warts), researchers have also found that cost-effectiveness of vaccinating men is much less than women alone.

The key drivers on the costs side include vaccine price and non-vaccine delivery costs. On the benefits side, key drivers include ability to achieve widespread coverage in preadolescent girls (including the ability to deliver the three doses), the duration of vaccine protection, and the existence and effectiveness of cervical cancer screening programs. More specific information on cost-effectiveness results in specific developing countries will be of great value in providing insights for priority-setting and program design. Findings from the Bill & Melinda Gates Foundation-funded PATH research and demonstration project will be important. To be most useful, results will need to be disseminated widely and in a timely way.

d. Financing

Domestic Sources of Financing

Public Spending

Public spending on health in 2002 was approximately \$8 per capita in low-income countries and \$49 per capita in middle-income countries, compared with \$1,924 in high-income countries (see Table 2). Low-income countries have significant dependence on external financing for their immunization programs. WHO/UNICEF joint reporting forms from countries indicated that public funding from internal public funds (excluding external assistance) for routine immunization was only about 35% for low-income countries in 2004. For all countries (both low- and middle-income), spending from internal public funds was highest for the Americas in 2004, at 87% of total costs. It was lowest for Africa at 45%. The Eastern Mediterranean,

Table 2. Health Spending Per Capita in Low-, Middle-, and High-Income Countries, 2002 (US\$)

Table 2 Health	Spending Per Capita in,	Low, Middle-, and High	Income Countries, 2002 (US\$)
Countries	Total Spending on Health Per Capita	Public Spending	Private Spending
Low-income	\$26	\$8 (29%)	\$18
Middle-income	\$103	\$49 (48%)	\$54
High-income	\$3,054	\$1,924 (63%)	\$1,130

Southeast Asia, and Western Pacific Regions reported 83, 62 and 67%, respectively.⁵

While there is certainly scope for creating more “fiscal space”⁶ for key health interventions over the long term, public spending on health will be highly constrained over the short to medium term for almost all low-income countries. The HPV vaccine will be difficult for countries to finance without external assistance. Table 3 shows how the costs of HPV vaccination would compare with total public spending on health for several countries, under different vaccination cost scenarios (\$8, \$10, \$15, and \$25 per vaccinated girl). For example, if it costs \$25 in Kenya to vaccinate a girl against HPV (including vaccine and non-vaccine delivery costs), and if 80% of 11 year-old girls were reached, it would cost an additional 3% of all public spending on health. If the cost were much lower, at \$8 per vaccinated girl, it would cost an additional 1% of total public spending on health - much less - but still a sizable amount, considering competing priorities and the small margins that countries have for reallocation in the short term from their own resources. For middle-income countries like Brazil, with much higher public spending on health per capita, it would cost an additional 0.2% of total public spending on health to vaccinate 80% of 11 year-old girls, if the costs per vaccinated girl were \$25. The poorest countries, with the least ability to pay, have the largest cohorts of preadolescent girls as a share of their total population. Low prices and external assistance will be needed to make the vaccine accessible for low-income countries, and low prices will also be important for middle-income countries.

Private Spending

There is likely to be some private sector demand for HPV vaccines independent of whether the public sector has started to supply the vaccine, especially in middle- and upper-middle- income countries. While private spending will play a modest role in contributing to coverage rates, the private sector can be significant in stimulating broader demand and raising awareness among the medical community and the population. It can also give the health community early experience with the vaccine.

External Financing

The GAVI Alliance

The most important source of external funding for vaccines is the GAVI Alliance. The GAVI Alliance is a partnership of governments, international organizations, philanthropists, research institutions and the private sector. GAVI was launched in 2000 with the goal of strengthening and expanding immunization services in the poorest countries. Countries with less than US\$1,000 per capita annual GDP are eligible for support. Countries must submit applications for funding and meet several requirements, such as developing a multi-year plan outlining how immunization services will be improved and mechanisms for sustainable financing. The type of support provided depends on the country’s immunization program. For example, countries where more than 80% of children receive DPT3 can receive new vaccines (hepatitis B, Hib and yellow fever vaccines). Countries where less than half of children are immunized with DPT3 can receive funds to strengthen services. About \$1.477 billion has been committed by GAVI to countries through December 2005. Of this, about 23% is for immunization services support, 8% for injection safety support, and 69% for new and underused vaccines. The \$1.477 billion is a notional amount, as each year the country estimates are recalculated with revised immunization targets. Donor contributions to GAVI totaled \$1.7 billion through the end of December 2005. Firm commitments for the period 2006-15 will bring total contributions and commitments to about \$3.3 billion.

International Financing Facility for Immunization (IFFIm): More Support to the GAVI Alliance

The IFFIm is a new mechanism that should expand GAVI’s available resources even more. The IFFIm was officially launched on September 9, 2005 with a goal of \$4 billion in pledges. Under the IFFIm, donors make long term pledges of financing. On the basis of those pledges, GAVI will borrow from financial markets to enter into long-term procurement contracts and to also

Table 3. Costs of Reaching 80% of 11-Year Old Girls with HPV Vaccine in Several Countries Under Different Vaccination Cost Scenarios (US\$)				
	Assumed Cost per Vaccinated Girl			
	\$8	\$10	\$15	\$25
Brazil				
Number of girls vaccinated with 80% coverage	1,304,320			
Estimated public spending per capita, 2005*	\$96			
Total HPV vaccination costs	\$10,434,560	\$13,043,200	\$19,564,800	\$32,608,000
HPV Vaccination Costs as Share of Public Spending on Health	0.06%	0.07%	0.11%	0.18%
Cambodia				
Number of girls vaccinated with 80% coverage	136,480			
Estimated public spending per capita, 2005*	\$6			
Total vaccination costs	\$1,091,840	\$1,364,800	\$2,047,200	\$3,412,000
HPV Vaccination Costs as Share of Public Spending on Health	1.29%	1.62%	2.42%	4.04%
India				
Number of girls vaccinated with 80% coverage	8,355,360			
Estimated public spending per capita, 2005*	\$7			
Total vaccination costs	\$66,842,880	\$83,553,600	\$125,330,400	\$208,884,000
HPV Vaccination Costs as Share of Public Spending on Health	0.87%	1.08%	1.62%	2.70%
Indonesia				
Number of girls vaccinated with 80% coverage	1,638,080			
Estimated public spending per capita, 2005*	\$11			
Total vaccination costs	\$13,104,640	\$16,380,800	\$24,571,200	\$40,952,000
HPV Vaccination Costs as Share of Public Spending on Health	0.53%	0.67%	1.00%	1.67%
Kenya				
Number of girls vaccinated with 80% coverage	335,200			
Estimated public spending per capita, 2005*	\$8			
Total vaccination costs	\$2,681,600	\$3,352,000	\$5,028,000	\$8,380,000
HPV Vaccination Costs as Share of Public Spending on Health	0.98%	1.22%	1.83%	3.06%
Zambia				
Number of girls vaccinated with 80% coverage	126,240			
Estimated public spending per capita, 2005*	\$11			
Total vaccination costs	\$1,009,920	\$1,262,400	\$1,893,600	\$3,156,000
HPV Vaccination Costs as Share of Public Spending on Health	0.79%	0.98%	1.48%	2.46%

*Estimated public spending per capita, 2005 assumed to be the same in real terms as public spending per capita in 2003. Population estimates from UN Population Division. Health spending estimates from WHO.

front-load financing for vaccination programs. GAVI will handle the operational work of the IFFIm, and IFFIm monies will be channeled to GAVI-eligible countries.

HPV and the GAVI Alliance

The GAVI Board is expected to approve a process for soliciting new vaccines and new investment cases at its meeting in November 2006. GAVI is

expected to consider the investment case for HPV vaccines in late 2007. Should HPV vaccines be approved for GAVI funding, GAVI-eligible countries would then need to apply for the funding. However, in the interim, GAVI's new window for health systems strengthening could be used to help facilitate the delivery of HPV vaccines, should countries wish to use it for this. Countries are applying now for this support.

HPV Vaccines and Advanced Market Commitment

In considering possible sources of external financing, AMCs should also be mentioned. The AMC concept is that donors would commit to subsidize the purchase of a new vaccine when it is developed to certain standards and is demanded by developing countries. The donor commitment would provide an incentive for private sector investment and innovation. AMCs would speed up the development of new vaccines needed in developing countries, and ensure that they are priced affordably for developing countries. HPV vaccines were included as one of the six vaccines for consideration in the AMC Pilot.⁷ The main arguments for including HPV vaccines as "late stage" vaccines are that the AMC would result in large-scale capacity increases and lower pricing many years sooner than would normally be expected. AMCs were discussed at the recent G8 Summit in July 2006. Italy, Canada, the United Kingdom, the United States, and Russia expressed continued support for the AMC in annexes to the G8 communiqué. Some non-G8 countries will likely join in with these five countries to take the AMC pilot forward. Canada has already pledged \$100 million Canadian towards a pilot for pneumococcal vaccine. While pneumococcal vaccine appears to be the first selected for the pilot, it is possible that HPV vaccines could still enter at a later stage.

e. Scaling up Production Capacity for HPV Vaccines

Lead times for constructing new vaccine manufacturing plants are significant. Merck has been stockpiling its vaccines but production capacity and stockpile information are not publicly available. GSK is working on validation

for its new HPV vaccine plant in Belgium and at this point is just producing for its clinical trials. GSK indicated that, with a firm commitment on purchasing for developing countries, it would be ready to build a second plant to produce its HPV vaccine. Companies will do demand forecasting of developing country markets before investing in scaling up for developing country markets. In order to help manufacturers gain the confidence to invest in expanded production capacity to go beyond meeting the demand of high-income countries, companies will need strong signals both of external funding commitments from the GAVI Alliance or other organizations, as well as indications from countries that they will seek this financing for HPV vaccines.

3. Possible Next Steps

- Develop a clear and compelling HPV vaccine investment case for GAVI consideration in 2007, based on wide expert consultation and stakeholder buy-in.
- Support and accelerate cost-effectiveness studies in a variety of developing country settings, backed up by rapid and widespread collection of vaccine delivery cost data/estimates and completion of HPV vaccine demand/uptake scenarios.
- Disseminate cost-effectiveness and affordability analyses widely to decision-makers, taking into account resource constraints and competing priorities including other vaccines likely to come to market in the next 3-10 years.
- Explore how the GAVI Health Systems Strengthening Support window might be used to facilitate HPV vaccine introduction
- Monitor the first AMC pilot as it is implemented and engage in AMC discussions with donors and technical experts to test the opportunity for HPV vaccine to be a pilot of a "late stage" vaccine.

4. Issues for Discussion by Meeting Participants

- How can manufacturers be incentivized to offer the lowest and most affordable prices for poor countries?
- How can demand uncertainties be reduced so vaccine manufacturers will scale up production for developing countries and feel confident about higher expected volumes, which can also have a downward effect on prices? What might be done to help companies with demand forecasting?
- How might the economic “investment case” for HPV vaccines best be made for national-level decision makers? While HPV vaccines are likely to be cost-effective at certain price points, ministries of health face many competing priorities. HPV vaccines have a long term, not short term, pay-off. (If a country only vaccinates 11-12 year olds, it will be 20 years or so before the initial impact is felt on cervical cancer.) What will this mean for ministers of health struggling with day-to-day problems?
- What needs to be done to advocate to donors for HPV vaccine financing support? What are the compelling arguments, and what type of financing schemes and volumes should be proposed to them?

5. Conclusions

- HPV vaccines could make a tremendous impact in reducing cervical cancer deaths in developing countries. But the important cost and financing issues need to be addressed for this to be achieved.
- Manufacturers need to be assured that demand is there and financing is secured in order to scale up demand to meet developing country markets.
- At the country level, ministries of finance and health need to be convinced of the vaccine’s importance relative to competing demands, of

its programmatic feasibility, and that financing is sustainable. Country-level cost-effectiveness studies need to be supported and disseminated widely and in a timely way. Making an effective case that HPV vaccination can be a wise investment, even though the benefits accrue well into the future, will be important.

- At the global level, a clear and compelling investment case needs to be made to GAVI and individual donors for financing to be extended for HPV vaccines. In the interim, the GAVI-supported new Health Systems Strengthening Support window might be a possible avenue to facilitate HPV vaccine introduction.

References

- ¹ Shanta Biotechnics in Hyderabad, India, is working to develop a vaccine based on the L2 protein. It is hoped that this would offer cross-protection against multiple HPV types. Another approach under development is to use a live bacterial vector to produce L1 virus-like particles. This product would be an oral vaccine, not requiring cold storage. Production costs are expected to be low. Indian Immunologicals Ltd., also in Hyderabad, is working on this approach and is planning trials in early 2007. The product is still several years away from major clinical studies. Both companies are working with researchers at United States National Cancer Institute (NCI) in the National Institute of Health (NIH) on these approaches, with the hope of bringing a successful product to market as soon as possible to increase affordability to developing countries (McNeil. Coming Soon: Cervical Cancer Vaccines, and an Array of Public Health Issues, Journal of the National Cancer Institute, Vol 98, No. 7; 432-34.)
- ² Vaccines are wasted due to temperature damage, contamination during reconstitution, expiry date reached, multidose vials opened to vaccinate fewer people than the vial size, and other reasons. Because of this, procurement requirements can be 10 to 60% higher than the number of doses actually used.
- ³ Sanders GD, Taira AV. *Emerg Infect Dis.* 2003; 1:37-48; Kulasingam SL, Meyers ER. *JAMA.* 2003; 290: 781-789; Goldie SJ et al. *J Natl Cancer Inst.* 2004; 8: 604-615; Taira AV et al. *Emerg Infect Dis.* 2004; 10: 1915-1923. These studies used varying assumptions about vaccine efficacy and costs, duration of immunity, screening intervals, and the like. The models can provide useful insights into the question of whether to vaccinate girls or, girls and boys, and how best to adjust screening programs after vaccine introduction. They can also be fine-tuned as better data emerge on the duration of efficacy of the vaccines.
- ⁴ WHO, Report of the Consultation on Human Papillomavirus Vaccines, Geneva, April 2005.
- ⁵ WHO, Analysis of Vaccine Financing Indicators.
- ⁶ Peter Heller defines fiscal space as “availability of budgetary room that allows a government to provide resources for a desired purpose without any prejudice to the sustainability of a government’s financial position” in “Understanding Fiscal Space”, Peter Heller, IMF Policy Discussion Paper, March 2005.
- ⁷ Potential Advanced Market Commitment (AMC) Investment, Vaccine-Preventable Disease Information for Expert Committee: HPV Vaccines, Prepare by PATH and WHO for the World Bank and GAVI, February 21, 2006