HPV Vaccine Adoption in Developing Countries:
Cost and Financing Issues

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To request additional print copies of this working paper or other information from IAVI or PATH please contact:

Publications Unit
International AIDS Vaccine Initiative
110 William Street, 27th Floor
New York, NY 10038 USA
Tel: + 1.212.847.1111
Fax: + 1.212. 847.1112
Email: pubs@iavi.org
Web: www.iavi.org

Cervical Cancer Prevention Programs
PATH
1455 NW Leary Way
Seattle, WA 98107 USA
Tel: + 1.206.285.3500
Fax: + 1.206.285.6619
Email: info@path.org
Web: www.path.org

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HPV Vaccine Adoption in Developing Countries: Cost and Financing Issues

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

i

ACRONYMS & ABBREVIATIONS

AMC	advance market commitment		**IDA**	International Development Association
BCG	Bacillus Calmette-Guérin		**IFFIm**	International Finance Facility for Immunisation
CDC	Centers for Disease Control and Prevention		**MMR**	measles, mumps, and rubella
CIN	cervical intraepithelial neoplasia		**MR**	measles-rubella
DALY	disability-adjusted life year		**NGO**	nongovernmental organization
DT	diphtheria and tetanus toxoid		**OPV**	oral polio vaccine
DTP	diphtheria, tetanus, and pertussis		**PAHO**	Pan American Health Organization
EMEA	European Medicines Agency		**PPP**	purchasing power parity
EPI	Expanded Programme on Immunizations		**QALY**	quality-adjusted life year
FDA	Food and Drug Administration		**SAGE**	Strategic Advisory Group of Experts
GDP	gross domestic product		**SIL**	squamous intraepithelial lesions
GNI	gross national income		**TT**	tetanus toxoid
GSK	GlaxoSmithKline Biologicals		**UN**	United Nations
HepB	hepatitis B		**UNICEF**	United Nations Children's Fund
Hib	Haemophilus influenzae type b		**USAID**	United States Agency for International Development
HPV	human papillomavirus		**WHO**	World Health Organization
I$	international dollar		**YLS**	years of life saved
IBRD	International Bank for Reconstruction and Development			

EXECUTIVE SUMMARY

Cervical cancer is the second most common cancer in women worldwide, with approximately 492,000 new cases in 2002. About 89% of these occur in developing countries, largely because of the difficulty and cost of providing cervical cancer screening and treatment in resource-poor settings. New, highly efficacious vaccines against the strains of the human papillomavirus (HPV) responsible for 70% of cervical cancer cases have recently come on the market. These two vaccines offer tremendous potential health benefits, with the largest potential gains in reducing cervical cancer deaths in developing countries. As long as the prices of these vaccines are not too high, their use is likely to be cost-effective in most settings.

There are, however, challenges to successfully reaching the primary target population – preadolescent girls – with a three-dose vaccine schedule in developing countries. Delivery mechanisms need to be created or strengthened to reach this population, using approaches such as school-based programs, immunization campaigns, and clinic-based programs, among others. Stakeholders will need to be mobilized and educated, and political support for the vaccine must be fostered. Further, logistical challenges in the cold chain and storage systems will need to be addressed.

Financing the vaccine and mobilizing resources to support new delivery mechanisms will constitute some of the most significant challenges to achieving widespread HPV vaccination in the developing world. Manufacturers have pledged to offer lower prices for developing countries, but even at a reduced, "tiered" price the HPV vaccine is likely to be much more expensive for developing countries than traditional Expanded Program on Immunization (EPI) vaccines and possibly more expensive than the newer and still underused vaccines such as Haemophilus influenzae type b (Hib). Delivery costs will also be significant, since the preadolescent target group does not have regular contact with the health system, and the vaccine storage cold chain and transportation may have to be expanded.

Country decision makers will need to weigh the value of HPV vaccines against other national health priorities, against other vaccines entering the market, and, for some countries, against expanding coverage of existing vaccines. Factors to take into consideration include impact, affordability, programmatic feasibility, cost effectiveness, and financial sustainability. In addition, they will have to consider how to improve pre-cancer screening of older women while protecting the younger generation with the HPV vaccine.

The GAVI Alliance, a public-private partnership dedicated to ensuring that all children worldwide have equal access to vaccines, could be a major source of external financing for HPV vaccination in the poorest countries, if the vaccine is deemed eligible by the GAVI Board. Middle-income countries that are not GAVI-eligible will need to rely on domestic resources and other sources of external assistance to introduce HPV vaccines.

The potential HPV target population in developing countries dwarfs that of industrialized countries. There will be an estimated 52.5 million 11-year-old girls in developing countries in 2010, compared to 6.5 million in industrialized countries. Strong indications of likely domestic and external funding, as well as country political commitment to use the vaccine, could help give manufacturers the assurances necessary to scale-up production to meet developing country demand. With these cost and financing obstacles resolved, developing countries would be able to build robust programs to immunize adolescents and thus dramatically reduce the incidence of cervical cancer.

I   INTRODUCTION

Cervical cancer is the second most common cancer in women worldwide. The majority of cases occur in developing countries, where cervical cancer is the primary cause of cancer-related deaths in women (Ferlay et al. 2002).

Virtually all cases of cervical cancer are caused by human papillomavirus (HPV) infection (see Box 1, pg. 5), which is transmitted primarily through sexual intercourse. The recently licensed bivalent and quadrivalent HPV vaccines could substantially reduce cervical cancer incidence and mortality in low- and middle-income countries over the long term, if high levels of coverage can be reached. For example, a recent study estimated that HPV vaccination of 70% of girls before age 12 in Brazil, combined with screening three times per lifetime between the ages 35 to 45, would prevent 100,000 cases of invasive cervical cancer over a five-year period and would reduce the lifetime risk of cervical cancer by 61% (Goldie et al. 2007). To achieve these benefits, girls will have to be reached at a young age, before they become sexually active, and screening programs, which currently benefit only a tiny fraction of the women who need them, will also need to be developed. Even without screening, vaccination could reduce lifetime risk of cervical cancer by 43%, according to the Brazil study.

Achieving widespread vaccination coverage of young adolescent girls in developing countries in the next 5 to 10 years will require a concerted global effort, given social, logistical, and financial challenges. For instance, reaching high coverage will require addressing social and cultural perceptions about the HPV vaccine, improving systems for providing health care to adolescents, strengthening the vaccine cold chain, and improving transportation. The challenge is compounded by the need to deliver three doses of the vaccine over an interval of six months. Innovative delivery strategies to reach young adolescent girls are currently being investigated, building on existing immunization programs and looking for integration opportunities with other health priorities (PATH 2007).

Financial obstacles are another blockade given that HPV vaccines, like most new vaccines, will be expensive compared to the traditional childhood vaccines widely utilized in low- and middle-income countries. Moreover, the target group for HPV vaccination, young adolescent girls, makes up a larger proportion of the population in developing countries than in the industrialized world, although this is also true of the infants reached by the well-established childhood immunization programs. This demographic phenomenon, combined with highly constrained health budgets, suggests that the countries that need the largest quantity of the HPV vaccine will be the least likely to afford it.

This paper looks at a subset of challenges related to cost and financing requirements for HPV vaccine adoption in developing countries. It examines the cervical cancer burden in developing countries, characteristics of HPV vaccines, delivery challenges, likely cost and cost effectiveness of HPV vaccination in low- and middle-income countries, financial needs at the national level and across low-income countries as a group, and possible mechanisms for meeting these needs.

2   CERVICAL CANCER: DISEASE BURDEN AND ITS CAUSES

In 2005, over 500,000 new cases and almost 260,000 female deaths were attributed to cervical cancer (WHO 2006). The cumulative risk of developing cervical cancer before age 65 is approximately 1.5% in developing countries, compared to 0.8% in industrialized countries. The risk of dying from cervical cancer is also substantially higher in developing countries, where it represents about 15% of all female cancers (Ferlay et al. 2002). HPV vaccines therefore have enormous potential to make a difference in the lives of women and their families in low-income countries. This increased risk of dying from cervical cancer exists in part because few women in developing countries have access to the screening and treatment services that have greatly reduced cervical cancer deaths in the industrialized world over the past four decades (IARC 2004). About 75% of women in industrialized countries have been screened for cervical cancer in the previous five years, compared to less than 5% in developing countries (Denny et al. 2006). Cervical cancer screening programs were introduced in much of Europe, North America, and Australia/New Zealand in the 1960s and 1970s. Before these programs were established, the incidence of cervical cancer was similar to levels in developing countries today (IARC 2004).

Table 1. Distribution of New Cervical Cancer Cases by Country Income Grouping, 2002

GAVI-eligible countries[A]	264,931	54%
Lower middle income	112,232	23%
Upper middle income	60,223	12%
High income	54,402	11%
TOTAL	**491,788**	**100%**

[A] India accounts for an estimated 132,082 of these cases.
   Source: 2002 Globocan data, estimates prepared by PATH.

Box I. HPV Viruses

HPV stands for human papillomavirus and is generally used to refer to a group of over 100 related viruses. Within this group, HPV viruses are numbered and referred to as HPV types. About 60 HPV types cause warts (papillomas) on nongenital skin. The remaining approximately 40 HPV types are mucosal HPV types (also called genital HPV types) that affect the anal and genital area. These types can be divided into low-risk and high-risk types. Genital warts are most often caused by HPV-6 and HPV-11. These are considered low-risk types because they rarely develop into cancer. High-risk HPV types include HPV-16, HPV-18, HPV-31, HPV-39, HPV-45, HPV-51, HPV 52, HPV-58, and others.

HPV and cervical cancer

Most genital HPV infections are eliminated or suppressed by the body. When this does not happen, the virus can cause cervical cells to change and become pre-cancerous. Pre-cancerous cell changes are referred to either as high-grade squamous intraepithelial lesions (SIL) or CIN2 and CIN3 (cervical intraepithelial neoplasia). This condition can return to normal. However, most of CIN3 is believed to progress to cancer over a period of about 10 years if not treated.

While there are several high-risk HPV types that cause cervical cancer, HPV-16 and HPV-18 are believed to cause most cases—about 70%. This concentration appears to be somewhat higher in developed countries (72-77%) compared to developing countries (65-72%). Eight types (HPV-16, HPV-18, HPV-45, HPV-31, HPV-33, HPV-52, HPV-58, and HPV-35) account for 90% of cervical cancer (Clifford et al. 2006). While studies show some variation in HPV-type distribution across countries, HPV-16 and HPV-18 are the leading causes in all regions, and the same top eight types are the most frequent across countries.

HPV and other cancers

Cervical cancer is the most common cancer related to HPV, although several less common cancers are also related. More than 40% of cancers of the vulva are HPV-related, and about 80% of squamous cell anal cancers are caused by HPV types 16 or 18. Penile, vaginal, urethral, tongue, and tonsil cancers have been associated with high-risk HPV types.

HPV and other diseases

HPV types 6 and 11 are related to juvenile respiratory papillomatosis in infants and children. This can cause respiratory problems and, more rarely, progress to cancer of the larynx.

Anogenital warts, as mentioned above, are also related to HPV. Over 90% are believed to be caused by HPV types 6 and 11.

Source: American Cancer Society

3   HPV VACCINES

3.1   Current Vaccines

Currently, there are two HPV vaccines on the market. Merck has developed a quadrivalent vaccine that protects against HPV types 6, 11, 16, and 18 (HPV types 16 and 18 cause approximately 70% of cervical cancers, while HPV types 6 and 11 cause approximately 90% of genital warts — see Box 1). This vaccine, marketed as Gardasil®, was approved by the U.S. Food and Drug Administration (FDA) in June 2006, and by the European Medicines Agency (EMEA) in September 2006, for use in females 9 to 26 years of age. It was approved in Australia for females aged 9 to 26 years and for boys aged 9 to 15. It has subsequently been approved in over 80 countries. GlaxoSmithKline Biologicals' (GSK) bivalent vaccine, Cervarix®, which protects against HPV types 16 and 18, was approved in its first major market, Australia, in May 2007 for girls and women aged 10 to 45. The EMEA granted marketing authorization for Cervarix® in September 2007. GSK filed for FDA approval in March 2007 and the company expects to bring the vaccine to market in the United States in 2008. As of September 2007, Cervarix® was licensed in the European Union, Australia, and Kenya. Both vaccines have been shown to be close to 100% effective in preventing precancerous lesions of the cervix due to HPV types 16 and 18 over the time period studied (approximately 5 to 5.5 years) in women not yet infected with those HPV types. Both vaccines have also shown some cross-protection against two additional cancer-causing HPV types: 31 and 45. In January 2007, GSK announced plans for a clinical trial to directly compare the immune responses of Gardasil® and Cervarix®. Both firms have invested and continue to invest heavily in clinical trials and post-approval marketing studies. They are likely to compete over time on the basis of product characteristics and possibly price.

3.2   Second-Generation Vaccines

A second-generation of HPV vaccines could offer one or more improvements over current vaccines in terms of price, efficacy, ease of delivery, and the like. For example, they could be cheaper—the Merck and GSK HPV vaccines are relatively expensive to manufacture, as they are produced in eukaryotic cell culture and require extensive purification (Shiller et al. 2006). They could protect against additional HPV types. They could be lyophilized to a powder that could be reconstituted at the point of delivery (thus eliminating the need for the cold chain), require only one or two doses, and be targeted to childhood vaccination schedules instead of young adolescents. John Schiller and Denise Nardelli-Haefliger describe an ideal HPV vaccine as one that would "be inexpensive to manufacture and distribute, protect against all oncogenic types after a single vaccination, and act therapeutically and prophylactically" (Shiller et al. 2006). While no second-generation vaccine will meet all these criteria, some under development could result in significant improvements over current vaccines. None are expected to reach market in the next five to seven years, however.

This paper focuses on cost and financing issues of introducing and scaling up the distribution of the two current vaccines over the next 5 to 15 years, recognizing that success with these vaccines will help speed up research and development on second-generation vaccines. The more solid the market is for HPV vaccines in developing countries, the more companies will be willing to invest in new and improved vaccines.

4 COST AND FINANCING ISSUES WITH THE CURRENT HPV VACCINES

4.1 Setting Priorities: HPV Vaccines in the Context of Other New Vaccines

The HPV vaccines are not the only new vaccines for diseases prevalent in developing countries. There are also new vaccines for Japanese Encephalitis (manufactured by Chengdu, Intercell, and Acambix), pneumococcal infections (Wyeth, GSK), and rotavirus (GSK, Merck, Bharat), as well as several somewhat older vaccines that have not yet been broadly adopted in developing countries. While some of these vaccines will be of interest to a relatively small number of countries (for example, Japanese Encephalitis vaccines), others are of great interest to many countries, and they will need to review and set priorities for incorporation into their immunization programs.

At the global level, after a major new vaccine has been licensed by a WHO-recognized regulatory authority, it is reviewed by the World Health Organization's (WHO) Strategic Advisory Group of Experts (SAGE). If the vaccine is endorsed by SAGE, and the vaccine manufacturer applies to WHO for prequalification, then WHO also goes through a process to prequalify the vaccine for procurement purposes. Both the United Nations Children's Fund (UNICEF) and the Pan American Health Organization's (PAHO) Revolving Fund require that vaccines have WHO prequalification before they will procure them. There will likely be bunching problems in the SAGE and prequalification processes over the period 2007 to 2009 from this unprecedented number of new vaccines coming through the pipeline for review. This could slow down the review of the new HPV vaccines. SAGE started to review HPV vaccines at its April 2007 meeting (WHO 2007). A decision on recommendation will likely be made in 2008. Just as global agencies are expected to struggle with the large number of new vaccines to review, so too will regulatory authorities and policymakers in developing countries. At the country level, policymakers will need to prioritize vaccines in terms of programmatic feasibility, cost, and health impact, as well as other considerations, and regulatory authorities will have to review these new products. In addition to considering HPV vaccines in the context of other new vaccines, many countries also have to make choices about scaling up coverage of traditional childhood vaccines or coverage of newer, underutilized vaccines. These decisions could have implications for HPV vaccination program costs, as costs may be partly offset by national efforts to expand the cold chain to accommodate other new vaccines.

4.2 Delivery Strategies

Countries are likely to experiment with a variety of delivery strategies to reach young adolescent girls. These are likely to include school-based programs, vaccination during established health days or other community outreach activities, and campaigns to reach young people. The Bill & Melinda Gates Foundation has granted US$ 27.8 million to PATH to help four countries—India, Peru, Uganda, and Viet Nam—generate evidence about the introduction of HPV vaccines. These experiences will be documented to help other countries and donors make informed decisions about delivery strategies, program costs, and cost effectiveness. Several middle-income countries are likely to be early adopters of HPV vaccines. In Latin America, for example, Brazil and Mexico tend to be early adopters of new vaccines and could pioneer approaches to HPV vaccine introduction that other countries could learn from.

4.2.1 Contracting Out

Some countries may wish to experiment with contracting nongovernmental organizations (NGOs) or other providers to deliver the vaccine, either to complement public sector outreach or instead of developing public sector capacity. Countries could test whether this mode of delivery achieves greater coverage and/or lower costs. If contracting out is explored, performance incentives could be considered. Haiti has experimented with contracting NGOs to deliver immunizations, among other services, and has used performance bonuses successfully (Eichler et al. 2006).

4.2.2 Private Clinics

Another important delivery strategy could be to use the private sector to meet some demand through private clinics (with private financing). While not likely to play a major role in achieving coverage goals, the private sector could play an important role in generating knowledge and experience with the vaccine amongst health professionals and the community at large. In Viet Nam, a study of private willingness-to-pay for the typhoid vaccine found significant demand at prices from US$ 2.30 to US$ 4.80 per vaccine. The researchers concluded that there is potential to sell the typhoid vaccine through the private sector, or by charging fees in the public sector, in order to expand coverage, given highly constrained public resources (Canh et al. 2006).

4.3 Pricing

4.3.1 HPV Vaccine Price for Industrialized Countries

Merck's entry price for its quadrivalent vaccine in industrialized countries is high relative to other vaccines. Merck has priced its vaccine at US$ 120/dose, or US$ 360 for the three-dose series, for the U.S. market, and at similar (if not higher) levels in other industrialized countries. The reduced price for the Centers for Disease Control and Prevention (CDC) Vaccines for Children Program is US$ 97/dose. This makes Gardasil® the most expensive vaccine on the CDC's list for the Vaccines for Children Program (CDC 2007). GSK has not announced a price yet for its bivalent vaccine in the United States, but it launched its vaccine in the UK at the same private prescription price as Gardasil®, or GB£ 240 (US$ 490) for the three-dose series.

While there has been debate over the affordability and cost effectiveness of the vaccine in industrialized countries, as of February 2007 insurers and governments in at least 11 countries had decided to pay for the vaccine. The Australian Government initially rejected the funding of Gardasil® but then reversed its decision following negotiations with the supplier, which included a price reduction and a risk-sharing arrangement in the event that booster shots would be required. It estimates that a four-year program of vaccinating girls 12 to 13 years of age and a catch-up population of girls and women 13 to 26 years of age will cost US$ 344 million. An ongoing program will then cost about US$ 40 million a year (for the vaccines alone) (Australian Government 2006). The vaccine will be provided free to girls through schools and to females 18 to 26 years of age from their general practitioner. The negotiated public sector price is not public, but the unsubsidized private sector price in Australia is A$ 460 or about US$ 425 for the three-dose series.

In October 2007, the British National Health Service announced the inclusion of HPV vaccines in routine immunizations for girls 12 to 13 years of age, starting in September 2008. There will also

be a two-year catch-up campaign starting in the fall of 2009 for girls up to 18 years of age. The government estimates that the routine program could cost up to GB£ 100 million a year (US$ 208 million), depending on the eventual price negotiated during the procurement process with the vaccine manufacturers (UK Government 2007).

Competition between GSK and Merck could drive down the price of HPV vaccines in industrialized countries, although the firms may prefer to compete on the basis of product characteristics. For both companies, industrialized countries represent the most important market for their vaccines. There will be approximately 6.5 million 11-year-old girls in industrialized countries in 2010. If the market includes older females for "catch-up" purposes and some males as well, it promises substantial revenues for the companies even at somewhat lower prices.

4.3.2 HPV Vaccine Price for Developing Countries

The largest group of girls that could benefit from an HPV vaccine is in developing countries, however. Compared to the 6.6 million 11-year-old girls in industrialized countries in 2010, there will be an estimated 52 million girls that age in developing countries (see Table 2) (United Nations Secretariat 2004). This large cohort does not, however, translate into a larger market because of budget constraints in developing countries. Price is likely to be one of the most challenging obstacles to HPV vaccination in the developing world. Both GSK and Merck have pledged to offer reduced prices to developing countries for their HPV vaccines and are likely to use multi-level pricing so that the public sector in the poorest countries receives the lowest price. In addition, pooled procurement by PAHO's Revolving Fund and UNICEF has played a crucial role in making vaccines available to developing countries at affordable prices and is likely to be important in the case of HPV vaccines as well.

Table 2. Population Dynamics and the Target Population for HPV Vaccine

(A) TOTAL POPULATION OF FEMALES AGED 11 (2005) AND PROJECTED 2010-2025 BY INCOME GROUPING (MILLIONS)			
	MORE DEVELOPED COUNTRIES	LESS DEVELOPED COUNTRIES	LEAST DEVELOPED COUNTRIES (SUBSET OF LESS DEVELOPED)
2005	7.12	51.59	9.30
2010	6.59	51.53	10.01
2015	6.58	52.00	11.04
2020	6.63	53.65	12.10
2025	6.56	55.37	13.16
(B) FEMALES AGED 11 AS A SHARE OF THE TOTAL POPULATION IN 2015			
2015	0.53%	0.87%	1.16%

Source: United Nations Secretariat, Population Division of the Department of Economic and Social Affairs

Even with tiered pricing, HPV vaccines may turn out to be expensive for developing countries, certainly compared with the traditional EPI vaccines, which cost pennies a dose (see Table 3). HPV vaccines could be similar in price or more costly than the "underused" vaccines such as the diphtheria, tetanus, pertussis; hepatitis B; Haemophilus influenzae type b combination vaccine (DTP-HepB+Hib), which UNICEF procures at US$ 3.50 per dose; and GSK's Rotarix vaccine for rotavirus, which was prequalified by WHO in February 2007. As of March 2007 a price had not yet been negotiated with UNICEF for the rotavirus vaccine, but Brazil, as an early adopter, has already started purchasing it independently at about US$ 7 per dose for the two-dose series.

Table 3. Prices of Traditional EPI Vaccines, Newer Vaccines, and Rotarix, 2007 (USD)

VACCINE	UNICEF WEIGHTED AVERAGE PRICE PER DOSE	DOSES PER VIAL
1. TRADITIONAL EPI VACCINES		
DTPw	.21	10
BCG	.08	20
Measles	.19	10
TT	.07	10
DT	.10	10
OPV	.16	10
2. UNDERUSED VACCINES		
DTP-HepB-Hib	3.50	2
Hib lyophilized	3.40	1
HepB recombinant	.21	10
Yellow Fever	.65	5
MMR Urabe strain lyophilized	1.42	10
MR	.48	10
Meningitis A&C	.50	50
NEW VACCINES, NO UNICEF-NEGOTIATED PRICE YET	**BRAZILIAN GOVERNMENT PRICE**	
Rotarix (GSK)	$7.00 per dose for two dose series	

Sources: UNICEF Supply Division for UNICEF prices; price for Rotarix from Jane Parry, New Vaccines to Boost Child Care in Developing Countries, Bulletin of the WHO, Vol. 85, No. 6, June 2007.

Whatever the short-term price, prices for HPV vaccines will almost certainly fall over the long term as more suppliers enter the market, demand grows and stabilizes, and patents expire. Alternate suppliers using the Merck and GSK technology (virus-like particles based on the L1 protein) will likely not 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 it takes for HPV vaccines to drop in price and reach large-scale production and adoption are critical.

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[1] Shanta Biotechnics in Hyderabad, India, is working to develop a vaccine based on the L2 protein, which may protect 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 NCI in 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, L (2006) "Coming Soon: Cervical Cancer Vaccines, and an Array of Public Health Issues," *Journal of the National Cancer Institute*, Vol 98, No. 7; 432-34.)

4.3.3 Other HPV Vaccination Costs

Vaccine cost per dose is just one component of what the introduction of HPV vaccines will cost countries. In addition, vaccine wastage,[2] freight, insurance, UNICEF's 6% procurement fee (if the vaccines are procured through UNICEF), and all the nonvaccine programmatic and delivery costs must be considered. Since HPV vaccines require cold storage, investments to expand the cold chain will probably be required. Most importantly, the target group, young adolescent girls, is not routinely reached with other vaccines. The programmatic cost of reaching girls with an HPV vaccine is likely to depend on the selected delivery strategy as well as on the current capacity of the immunization system. It will be important to coordinate the introduction of the HPV vaccine with other efforts to strengthen the immunization system—either to increase coverage of the traditional six vaccines targeted by EPI or to introduce other new or underutilized vaccines. New strategies will need to be integrated with existing immunization services, school health programs, or community outreach activities to deliver not one but three doses to these girls over a six-month period.

Additional program costs are difficult to estimate, as few programs exist for this target group. But insights can be gleaned from the economic analysis of existing childhood immunization programs in the developing world. A literature review presented in Disease Control Priorities for Developing Countries found that the population-weighted mean cost per fully immunized child in 27 developing countries was about US\$ 17, with a range from US\$ 3 to US\$ 31 (Jamison et al. 2006).[3] Costs varied by delivery strategy, with the lowest cost for extended outreach services (US\$ 6), followed by routine facility-based strategies (US\$ 14). Campaigns (US\$ 27) and mobile strategies (US\$ 26) had the highest costs. Costs also varied considerably by region, given variation in labor costs and in delivery strategies. Costs were estimated to be lowest in East Asia and the Pacific (US\$ 13) and sub-Saharan Africa (US\$ 14). Costs were highest in Europe and Central Asia at US\$ 24 per fully immunized child. The vaccine cost as a proportion of the total cost of the EPI strategy can range from 8% for mobile strategies to 29% for extended outreach strategies.

4.4   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 beneficial use of scarce resources. Cost-effectiveness models have been used to compare the net cost of HPV vaccination with the potential benefits, expressed as years of life saved (YLS) or quality-adjusted life years (QALYs). Models can be used to better understand the epidemiological and economic implications of vaccinating young adolescent girls, vaccinating older females in catch-up campaigns, including boys in vaccination programs, and adjusting screening programs, where they exist, once HPV vaccination is introduced and certain coverage rates are achieved.

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[2] Vaccines are wasted due to temperature damage, contamination during reconstitution, expiration, multi-dose 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] A fully immunized child has received the EPI cluster antigens—one dose of Bacillus Calmette-Guérin, three doses each of polio and DTP (a combination of diphtheria, tetanus, and pertussis) vaccines, and one dose of measles—children who have been partially immunized do not qualify. The costs include labor, vaccines, supplies, transportation, communication, training, maintenance, and overhead, including annualized value of equipment, vehicles, and building space.

The setting matters greatly to cost-effectiveness analyses. In developing countries, where access to cervical cancer screening and treatment is generally limited, HPV vaccination could substantially reduce cervical cancer deaths and morbidity. In contrast, screening tends to be widespread in industrialized countries, so reductions in cervical cancer morbidity and mortality will be far smaller, but HPV vaccination promises large savings in medical costs. The potential cost savings include reductions from follow-up for cervical lesions, treatment of CIN2+ and cancer, and possible reductions in screening frequency and increases in the age of initiation of screening. There have been nine published studies on the cost effectiveness of HPV vaccination, five on the U.S., one on Canada, one on Australia, and two on Brazil (Goldie et al. 2007; Elbasha et al. 2007; Goldie et al. 2004; Taira et al. 2004; Sanders et al. 2003; Kulasingam et al. 2003; Kim et al. 2007; Brisson et al. 2007; Kulasingam et al. 2007). These are summarized in Appendix 1, pg. 27. More studies in both industrialized and developing country settings are expected to be published in the coming years. Studies to date have used two types of models: dynamic transmission models and cohort models. Dynamic models estimate herd immunity effects (the indirect benefits to people other than those who receive a vaccine) and can thus be used to explore the value of vaccinating boys along with girls. Cohort models could underestimate the cost effectiveness of vaccination because they do not capture the indirect benefits as well as the direct benefits of vaccination.

The nine models summarized in Appendix 1 all make assumptions about vaccination costs, vaccine efficacy, coverage rates, duration of protection, screening, diagnosis and treatment costs, and stage-specific cancer rates. All studies estimate reductions in cancer incidence and incremental cost-effectiveness ratios, using YLS or QALYs, and all but the Australian study use a 3% discount rate for costs and benefits.[4] Most of the models look at how incremental cost effectiveness and cervical cancer risks change with the introduction of vaccination along with adjustments to the starting age of screening and screening intervals.

Key findings:

- The incremental cost-effectiveness ratio of HPV vaccination of girls in industrialized countries ranged from US$ 2,964 per QALY (Elbasha et al. 2007) to US$ 44,889 per YLS (Kulasingam et al. 2003). The estimates for Australia and Canada fell between these ranges, at US$ 17,372 per QALY for Australia and US$ 22,000 to US$ 33,000 per QALY for Canada. Although the various models are not exactly comparable because of differences in cost and benefit calculations, and in some cases in approaches, all arrive at estimates implying that HPV vaccination would be cost-effective by conventional standards.

- The lowest estimate of US$ 2,694 per QALY in the Elbasha et al. study is, in part, because the team used a dynamic transmission model that included direct as well as indirect benefits, and because it included averting genital warts as a benefit as well as CIN and cervical cancer (this study looks at the quadrivalent vaccine).

- The discount rate matters a great deal to the results, since the benefits of HPV vaccination occur only many years after the costs are incurred. For Australia, the estimate of US$ 17,372 per QALY is with a 5% discount rate, as mandated for health technology assessments in Australia. If a 3% discount rate is used, as in the other models, the cost per QALY falls to US$ 7,806.

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[4] The Australian study uses a 5% discount rate because this rate is mandated in Australia for health technology assessments (Kulasingam et al. 2007).

- The Brazil models used a large range of estimates for the cost per vaccinated individual, given the high uncertainty of vaccine prices for developing countries. The Goldie et al. Brazil study found that vaccination of young girls dominated screening if the cost per vaccinated girl was I\$ 50 (international dollars) or less (that is, vaccination is both more effective and less expensive). At a cost of I\$ 50, the cost-effectiveness ratio was about I\$ 300 per YLS with a reduction of about 43% in the lifetime risk of cancer—implying a very cost-effective intervention. At vaccine costs above I\$ 75, vaccination plus screening dominated vaccination alone. Combined vaccination and screening at costs of I\$ 75, 100, and 450 per vaccinated girl resulted in cost-effectiveness ratios of about I\$ 1,100, 1,700, and 9,600 per YLS compared to screening alone. (For comparison purposes, Brazil's gross domestic product (GDP) per capita was about US\$ 4,800 in 2005 and its GDP per capita, estimated in current international dollars, was I\$ 9,500 for that same year [IMF 2007]).

- Cost-effectiveness analyses can help decision makers determine how to optimally combine cervical cancer screening with HPV vaccination. For example, in the United States, a cost-effective approach would be to combine HPV vaccination with screening starting at age 25, conducted every three years (Goldie et al. 2004).

- The three dynamic transmission models (Elbasha et al. 2007; Kim et al. 2007; Taira et al. 2004) compared vaccinating girls to vaccinating both girls and boys, a key issue for decision makers. Taira et al. found that vaccinating 70% of girls in the U.S. would reduce cervical cancer cases by 61.8% at a cost of US\$ 14,583 per QALY. Adding boys further reduces cervical cancer cases by 2.2% at an incremental cost effectiveness of US\$ 442,039 per QALY. Under these assumptions, female vaccination is cost-effective, but including males is not, unless coverage of females is low (on the order of 30% or less). In Brazil, 75% coverage of young adolescent girls (vaccinated before age 12) would reduce cervical cancer risk by 63% (Kim et al. 2007). Adding 75% of young adolescent boys (vaccinated before age 12) would reduce cancer risk by an additional 4%. Assuming the cost per vaccinated individual was I\$ 50, vaccinating 75% of girls cost less than I\$ 200 per YLS. Vaccinating girls and boys cost I\$ 2,180 per YLS at this coverage level. Moreover, at any level of coverage there is more to be gained from expanding coverage of girls than from adding boys — an important conclusion for resource-constrained settings. The third model, focusing on the U.S., differed from the other two in considering catch-up campaigns for girls and boys aged 12-24 and in including benefits from reduction in genital warts from the quadrivalent vaccine (Elbasha et al. 2007). This study also found that male vaccination becomes less cost effective as female coverage rates increase. It found that vaccinating a one-year cohort of girls only at 75% coverage cost US\$ 2,964 per QALY. Vaccinating this cohort plus a catch-up population of girls aged 12-24 cost US\$ 4,666 per QALY. Cohort vaccination of girls and boys plus catch-up campaigns for girls and boys aged 12-24 cost US\$ 45,056 per QALY.

4.4.1 HPV, Pneumococcal, and Rotavirus Vaccine Cost Effectiveness Comparison

GAVI has already approved an initial investment of US\$ 200 million for pneumococcal conjugate and rotavirus vaccines based on investment cases for these vaccines. Table 4 compares the incremental cost-effectiveness ratios for pneumococcal vaccine and rotavirus vaccine that were included in their GAVI investment cases to HPV vaccine cost-effectiveness estimates for Brazil. Even though HPV vaccine benefits accrue only after a long lag, all three vaccines provide excellent value for money under similar assumptions about price per dose. If pneumococcal vaccine cost US\$ 5 per dose, the incremental cost-effectiveness ratio was estimated at about US\$ 100 per

disability-adjusted life year (DALY). At US$ 6 per dose for rotavirus vaccine, calculations were similar at about US$ 100 per DALY. The estimates from Goldie et al. (2007) for Brazil note that if the vaccine cost I$ 5 per dose, so that the cost per vaccinated girl were about I$ 25, the vaccine would be cost saving, and if the cost per vaccinated girl were I$ 50, the cost effectiveness was about I$ 300 per YLS—still cost-effective for most countries, using the comparison of cost-effectiveness ratio and GDP per capita. The studies assume much lower delivery costs for pneumococcal and rotavirus vaccines, given that they can be folded into childhood vaccine schedules. Note that all the studies used a 3% discount rate for costs and benefits.

Table 4. Comparison of Cost Effectiveness and Disease Impact across HPV, Pneumococcal Conjugate, and Rotavirus Vaccine

	HPV VACCINE	PNEUMOCOCCAL CONJUGATE VACCINE	ROTAVIRUS VACCINE
RESEARCH STUDY	Goldie, S et al. Cost-effectiveness of HPV 16, 18 Vaccination in Brazil, *Vaccine* 25 (2007) 6257-6270.	Sinha, A et al. Cost-effectiveness of Pneumococcal Conjugate Vaccination in the Prevention of Child Mortality: An International Economic Analysis, *Lancet* 369 (February 3, 2007) 389-396.	Emory University Study as reported in "Accelerating the Introduction of Rotavirus Vaccines into GAVI-eligible Countries: Investment Case for GAVI Secretariat," October 2006.
Countries	Brazil	72 GAVI-eligible countries	72 GAVI-eligible countries
Incremental Cost-effectiveness Ratio	If cost per vaccinated girl was I$ 25 (assuming a cost of I$ 5 per dose), the vaccine was cost- saving. If cost per vaccinated girl was I$ 50, cost effectiveness was I$ 300 per YLS.	I$ 100 per DALY at cost estimate of I$ 5 per dose.	US$ 100 per DALY (from US$ 65 to US$ 360 per DALY averted, depending on region) at US$ 6 per dose. At US$ 1 per dose, US$ 15 per DALY.
Health Outcome	Lifetime risk of cervical cancer reduced by 43%.	262,000 deaths averted per year in children aged 3-29 months.	3.4 lives saved per 1,000 vaccinated over the period 2007-2025.
Assumptions	70% vaccination coverage of adolescent girls. Girls receive the full three doses before age 12. 100% efficacy against HPV 16 and 18. Lifelong immunity. 3% discount rate, I$.	Each country's most recent DTP3 coverage rates used to estimate pneumococcal vaccine coverage. 77% efficacy against invasive infection. Deaths reduced by up to 7.4 deaths per 1,000 children (from trial in Gambia), depending on infant mortality rate. 3% discount rate, 2000 I$.	90% coverage. Vaccine efficacy: 85% against severe disease resulting in hospitalization or mortality. 70% for other rotavirus illness. Efficacy is reduced by half if only one dose is received. 3% discount rate, 2002 USD.

4.5 Financing

4.5.1 Domestic Sources of Financing

Public Spending. Public spending on health varies enormously by country income group, and this has implications for the affordability of HPV vaccines. Table 5 presents data on public spending on health for 2005 by income and region. These data indicate that public spending was approximately US$ 7 per capita on health in 2005 in low-income countries. This figure rises to about US$ 53 per capita in lower middle-income countries, US$ 240 per capita in upper middle-income countries, and US$ 2,366 per capita in high-income countries. Table 5 also presents these same data by region (regions are defined here to only include developing countries). Public spending on health per capita is lowest in South Asia at US$ 6 per capita, followed by US$ 22 per capita in sub-Saharan Africa, US$ 28 per capita in East Asia and Pacific, US$ 63 per capita in Middle East and North Africa, US$ 173 per capita in Latin America and the Caribbean, and US$ 213 per capita in Europe and Central Asia.

Table 5 also shows that total spending on health (both public and private) as a share of GDP is lowest for low-income countries (4.6%), rising steadily as income grows to 10.7% for high-income countries. As income grows, the share of spending on health that is public also increases.

Table 5. 2005 Health Expenditures by Income and Regional Country Groupings

	TOTAL HEALTH SPENDING AS PERCENT OF GDP	PERCENT OF HEALTH SPENDING PUBLIC	PERCENT OF HEALTH SPENDING PRIVATE	PUBLIC SPENDING ON HEALTH AS SHARE OF TOTAL GOVERNMENT SPENDING (%)	TOTAL HEALTH SPENDING USD PER CAPITA	PUBLIC SPENDING ON HEALTH USD PER CAPITA
BY INCOME GROUPING						
Low Income	4.6	27.6	72.3	4.9	27	7
Lower Middle Income	5.1	44.2	55.7	9.9	109	53
Upper Middle Income	6.7	58.6	41.4	11.4	408	240
High Income	10.7	65.5	34.5	16.4	3,928	2,366
BY REGION (DEVELOPING COUNTRIES ONLY)						
East Asia and Pacific	4.3	38.2	61.8	8.7	69	28
Europe and Central Asia	6.6	63.2	36.8	10.5	313	213
Latin America and the Caribbean	7.5	53.0	47.0	14.2	331	173
Middle East and North Africa	5.8	50.6	49.4	8.3	123	63
South Asia	4.5	19.9	80.1	3.3	31	6
Sub-Saharan Africa	5.2	44.3	55.7	8.7	51	22

Source: Health expenditure data from WHO, National Health Accounts website. Country groupings per World Bank classification. Regional and income groups are population-weighted. Per capita figures are calculated using exchange rates (not purchasing power parity (PPP) dollars).

Low-income countries have significant dependence on external financing for their immunization programs. WHO/UNICEF data show that in low-income countries only about 35% of expenditures on routine immunization came from internal public funds (excluding external assistance) in 2004. For all developing countries (both low- and middle-income), spending from internal public funds was highest for the Americas in 2004, at 89% of total costs. It was lowest for Africa at 45%. The Eastern Mediterranean, Southeast Asia, and Western Pacific Regions reported 83, 62, and 67%, respectively (Table 6) (WHO 2004).

Table 6. Percentage of Routine Vaccine Expenditures Financed by National Governments by Region

WHO REGION (NUMBER OF COUNTRIES REPORTING)	2004[A]
Africa (40)	45
Americas (34)	89
Eastern Mediterranean (21)	83
European (44)	83
Southeast Asia (10)	62
Western Pacific (26)	67

[A]Internal public funds. WHO and UNICEF Joint Reporting Forms.
Source: WHO, Analysis of Vaccine Financing Indicators.

The HPV vaccine will be difficult for low-income countries to finance over the short to medium term without external assistance. Many middle-income countries will also find it difficult to finance. The poorest countries, with the least ability to pay, have the largest number of young adolescent girls as a share of their total population (Table 2, pg 9). 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. Table 7 shows how the costs of HPV vaccination[5] would compare with total public spending on health for several countries, under different vaccination cost scenarios (US$ 10, 15, and 25 per vaccinated girl). For example, if it cost US$ 25 in Kenya to vaccinate a girl against HPV (including both vaccine and delivery costs), reaching 80% of 11-year-old girls would cost an additional 3% of all public spending on health. If the cost were much lower, at US$ 10 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 a more modest 0.1% of total public spending on health to vaccinate 80% of 11-year-old girls, if the costs per vaccinated girl were US$ 25.

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[5] The cost of vaccination refers to total costs (vaccine and delivery costs) regardless of source of finance (who pays).

16

Table 7. Costs of Reaching 80% of 11-year-old Girls with HPV Vaccine in Several Countries, under Different Vaccination Cost Scenarios (vaccination costs include cost of vaccine and all other delivery and programmatic costs)

		IF COST PER VACCINATED GIRL WERE:		
BRAZIL		**US$ 10**	**US$ 15**	**US$ 25**
Number of Girls Aged 11, 2005	1,630,400			
Number of Girls Vaccinated with 80% Coverage	1,304,320			
Total Population, 2005	186,405,000			
Public Spending per capita, 2005	$204			
Total HPV Vaccination Costs		13,043,200	19,564,800	32,608,000
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**0.03%**	**0.05%**	**0.09%**
CAMBODIA				
Number of Girls Aged 11, 2005	170,600			
Number of Girls Vaccinated with 80% Coverage	136,480			
Total Population, 2005	14,071,000			
Public Spending per capita, 2005	$7			
Total HPV Vaccination Costs		1,364,800	2,047,200	3,412,000
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**1.39%**	**2.08%**	**3.46%**
INDIA				
Number of Girls Aged 11, 2005	10,444,200			
Number of Girls Vaccinated with 80% Coverage	8,355,360			
Total Population, 2005	1,103,371,000			
Public Spending per capita, 2005	$6			
Total HPV Vaccination Costs		83,553,600	125,330,400	208,884,000
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**1.26%**	**1.89%**	**3.16%**
INDONESIA				
Number of Girls Aged 11, 2005	2,047,600			
Number of Girls Vaccinated with 80% Coverage	1,638,080			
Total Population, 2005	222,781,000			
Public Spending per capita, 2005	$12			
Total HPV Vaccination Costs		16,380,800	24,571,200	40,952,000
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**0.61%**	**0.92%**	**1.53%**
KENYA				
Number of Girls Aged 11, 2005	419,000			
Number of Girls Vaccinated with 80% Coverage	335,200			
Total Population, 2005	34,256,000			
Public Spending per capita, 2005	$9			
Total HPV Vaccination Costs		3,352,000	5,028,000	8,380,000
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**1.09%**	**1.63%**	**2.72%**
ZAMBIA				
Number of Girls Aged 11, 2005	**157,800**			
Number of Girls Vaccinated with 80% Coverage	**126,240**			
Total Population, 2005	**11,668,000**			
Public Spending per capita, 2005	**$18**			
Total HPV Vaccination Costs		**1,262,400**	**1,893,600**	**3,156,000**
VACCINATION COSTS AS SHARE OF PUBLIC SPENDING ON HEALTH		**0.60%**	**0.90%**	**1.50%**

4.5.2 External Financing

The GAVI Alliance. The most important source of external funding for vaccines in low-income countries is the GAVI Alliance. Given the concentration of cervical cancer in GAVI countries (about 54% of the world's annual new cases of cervical cancer occur in GAVI countries), the GAVI Alliance could play a pivotal role in accelerating the adoption of HPV vaccines by the countries that need them most—provided GAVI approves this vaccine for financing and countries choose to apply for and use GAVI funds in this way. The GAVI Alliance is a partnership of governments, international organizations, philanthropists, research institutions, and the private sector 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. Currently there are 72 countries eligible for GAVI support (Table 8). China was included in GAVI's first phase of support, but is no longer eligible because its per capita income level is now beyond the threshold for eligibility. India is one of the GAVI-eligible countries but, as a large country, has a cap on its support of US$ 100 million through 2010. This is important for HPV vaccine adoption, given that India accounts for 27% of global cervical cancer cases, and about half of the total cases in GAVI-eligible countries.

Table 8. GAVI-eligible Countries *(countries with GNI per capita < $1,000 as of December 2006)*

Afghanistan	Cuba	Lao PDR	São Tomé
Angola	Djibouti	Lesotho	Senegal
Armenia	Eritrea	Liberia	Sierra Leone
Azerbaijan	Ethiopia	Madagascar	Solomon Islands
Bangladesh	Gambia	Malawi	Somalia
Benin	Georgia	Mali	Sri Lanka
Bhutan	Ghana	Mauritania	Sudan
Bolivia	Guinea	Moldova	Tajikistan
Burkina Faso	Guinea-Bissau	Mongolia	Tanzania
Burundi	Guyana	Mozambique	Timor Leste
Cambodia	Haiti	Myanmar	Togo
Cameroon	Honduras	Nepal	Uganda
Central African Republic	India	Nicaragua	Ukraine
Chad	Indonesia	Niger	Uzbekistan
Comoros	Kenya	Nigeria	Viet Nam
Congo, Democratic Republic	Kiribati	Pakistan	Yemen
Congo, Republic	Korea, DPR	Papua New Guinea	Zambia
Côte d'Ivoire	Kyrgyz Republic	Rwanda	Zimbabwe

Source: www.gavialliance.org

18

Phase I Financing. Under GAVI's Phase I financing, countries were required to submit applications for funding and meet several requirements, such as developing a multiyear 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. Countries where more than 80% of children receive DTP3 receive new vaccines (HepB, Hib and yellow fever vaccines). Countries where less than half of children are immunized with DTP3 can receive funds to strengthen services.

As of the end of 2006, about US$ 2.2 billion had been committed by GAVI to countries. The bulk of funding is for vaccine purchase, followed by immunization services support and injection safety support. These commitments are notional amounts, as each year the country estimates are recalculated with revised immunization targets. For new vaccines, GAVI's support has been intended to be time-limited, generally for a period of five years. Over that time, it was hoped that vaccine prices would fall and national governments and donors would be able to shoulder the responsibility of continued financing. In fact, prices have declined for some of the new vaccines but risen for others. For example, the price for the DTP-HepB vaccine has fallen significantly over the period 2002 to 2007, but prices for DTP-Hib and DTP-HepB-Hib have risen. The Hib and HepB Procurement Reference Group Report to the GAVI Board in March 2007 concluded that GAVI's expectations of strong price declines over the period were unrealistic. It also concluded that prices can decline but the process requires more time, and the presence of multiple suppliers is essential, not only to price declines but also to vaccine security (GAVI 2007).

Phase II Support and Country Co-pays. Phase II financing support is starting in 2006/2007 and running through 2015. The GAVI Alliance has changed its financing policies for Phase II support based in part on what it has learned from the Phase I experience. GAVI will not only consider new vaccines but existing underused vaccines not currently purchased by GAVI (for example rubella, cholera, and influenza). It will use the investment case framework to consider vaccines for financing. Countries will be required to co-finance vaccine purchase, through co-pays that would be related to the country category (poorest, intermediate, least poor, and fragile).[6] Poorest countries are asked to pay US$ 0.20 for the first vaccine and US$ 0.15 for the second and third vaccines. The intermediate group is asked to pay US$ 0.30 for the first vaccine and US$ 0.15 for the second and third. The least poor grouping is asked to pay US$ 0.30 for the first vaccine, and US$ 0.15 for the second and third vaccines, with an annual increase in their co-pays of 15%. The fragile group is asked to pay US$ 0.10 for the first vaccine, and US$ 0.15 for the second and third. Other donors may help countries cover the cost of the co-pays. In 2010, GAVI intends to evaluate this policy, but it has indicated that co-financing levels will increase, and country groupings may change.

The first investment cases presented under this new framework were for rotavirus and pneumococcal vaccines. In November 2006, the GAVI Alliance announced that it had approved an initial round of US$ 200 million to support newly licensed vaccines against rotavirus and pneumococcal infections.

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[6] The poorest group includes Myanmar, Ethiopia, Malawi, Guinea-Bissau, Rwanda, Niger, Nepal, Uganda, Gambia, Madagascar, Mozambique, Tanzania, Togo, Guinea, Cambodia, Mali, São Tomé and Principe, Burkina Faso, Chad, Lao PDR, Bangladesh, Zambia, Benin, Mauritania, Solomon Islands, Yemen Rep., Comoros, Senegal, Bhutan, and Lesotho. The Intermediate group includes Cuba, Korea DR, Tajikistan, Zimbabwe, Kyrgyz Republic, Ghana, Uzbekistan, Kenya, Nigeria, Viet Nam, Papua New Guinea, Mongolia, Pakistan, India, Moldova, and Nicaragua. The Least Poor group includes Bolivia, Cameroon, Guyana, Djibouti, Kiribati, Sri Lanka, Honduras, Azerbaijan, Indonesia, and Georgia. The Fragile group includes Angola, Afghanistan, Burundi, Central African Republic, Congo Rep., Côte d'Ivoire, Democratic Republic of Congo, Eritrea, Haiti, Liberia, Sierra Leone, Somalia, Sudan, and Timor Leste.

HPV and the GAVI Alliance. Should HPV vaccines become eligible for GAVI support after submission and review of an investment case, this would turn out to be an important financing option for the 72 GAVI-eligible countries. However, in the interim, GAVI's new window for health systems strengthening could be used to help facilitate the delivery of HPV vaccines. Some countries are now applying for this support. If GAVI approves the HPV vaccine for funding, countries will need to consider the priority of HPV versus other existing and new vaccines, whether the co-pay is affordable in the short term (with or without donor assistance for the co-pay), and if the vaccine will be affordable once GAVI financing ends.

IFFIm: More Support to the GAVI Alliance. The International Finance Facility for Immunisation (IFFIm) is a new mechanism that is expanding GAVI's available resources even more. The IFFIm was officially launched on September 9, 2005, with a goal of US$ 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 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.

Advance Market Commitments. Advance market commitments (AMCs) are another possible source of external finance for HPV vaccine, if not for the current vaccines, then possibly for second-generation vaccines. AMCs are intended to speed up the development of new vaccines and help ensure affordable pricing for developing countries. Under an AMC, donors subsidize the purchase of a new vaccine when it is developed to certain standards and is demanded by developing countries. With the AMC subsidizing the bulk of the price, countries then contribute with an affordable co-pay. Once AMC funds are depleted, manufacturers are required to supply the vaccine at a predetermined low price for the remaining agreed time period, with certain exit conditions. The donor commitment would provide an incentive for private sector investment, innovation, and production scale-up.

HPV vaccines were one of the six vaccines considered for a pilot AMC (PATH et al. 2006). The main arguments for including HPV vaccines as "late stage" vaccines are that an AMC would result in large-scale capacity increases and lower pricing years sooner than would be normally expected. In the end, pneumococcal disease was chosen as the first target of the initiative. There is one pneumococcal vaccine licensed for use in children under two and many candidate vaccines. For developing countries, new pneumococcal vaccines that add more serotypes are the urgent priority. The AMC was launched formally on February 9, 2007, with US$ 1.5 billion in commitments (Italy $635 m; UK $485 m; Canada $200 m; Russia $80 m; Norway $50 m; and the Bill & Melinda Gates Foundation $50 m). Should the pneumococcal pilot be successful, the lessons might be applicable to HPV vaccines—either for scaling up production of the current vaccines for developing countries, or for accelerating the development of second-generation vaccines with more characteristics of the "ideal" HPV vaccine, as mentioned earlier.

Bilateral Donors. While many donors are channeling support to immunization through GAVI, IFFIm, and AMCs, some continue to provide support directly to countries. The Japanese Government is the largest single source of bilateral support for immunization. It, and other countries, could also be a source of support for HPV vaccine adoption in several low- and middle-income countries.

Multilateral Banks. The World Bank and the four regional development banks could also be a source of support for HPV vaccine introduction. This support could be provided through traditional lending, perhaps focused on helping countries pay for the start-up phase for HPV vaccination, if a case for long-run sustainability could be made. The International Bank for Reconstruction and Development (IBRD) and the International Development Association (IDA) "buy downs," which allow IBRD loans and IDA credits to be converted to grants under certain conditions, might also be used to support HPV vaccination. The World Bank has supported these instruments on a case-by-case basis for activities that contribute substantial global or regional public goods (for example, polio eradication). The World Bank has indicated some interest in exploring IBRD and IDA "buy downs" for activities with high social returns that are undervalued at the country level. HPV vaccination may qualify.

*Donation Programs.* Pharmaceutical donation programs will also be used as a way to facilitate faster adoption and access to HPV vaccines in the short-term. Through the Gardasil® Access Program, Merck will donate three million doses of Gardasil® to fully vaccinate one million people over five years in GAVI-eligible countries and low-resource parts of non-GAVI countries. A primary purpose of the program is to pilot, refine, and replicate successful models for HPV vaccine delivery in these settings. In addition, Merck and GSK have agreed to donate HPV vaccine for use in the introduction demonstration projects PATH is supporting in Uganda, Viet Nam, India, and Peru. While these donation programs do not constitute long-term sustainable initiatives, they may prove helpful in the initial rollout phase for HPV vaccines by encouraging increased national government and international donor support for the vaccine.

4.5.3 Global Estimates of HPV Vaccination Costs in GAVI-eligible Countries

Batson et al. developed an optimistic demand estimate for HPV uptake in GAVI-eligible countries over the period 2010 to 2030. They grouped countries into four categories: early adopters, starting in 2011, mid adopters, starting in 2014; late adopters, starting in 2018; and a set of countries unlikely to adopt at all because of low disease burden (Batson et al. 2006). This study assumed that there would be a linear six-year ramp-up to eventual coverage rates of 80%. Furthermore, it assumed that the vaccine would be used only for a single year cohort of young adolescent girls, with no catch-up vaccination. Figure 1 presents the vaccine doses required under this scenario, which would reach 36 million doses annually by 2016 and 77 million annually by 2025. The total costs for GAVI countries associated with this level of HPV immunization are presented in Figure 2, under alternative scenarios of vaccination cost (vaccination cost refers to all program delivery costs, including vaccines, transport, communication, labor, and others). If the vaccination costs were, on average, US$ 15 per girl, the costs in 2016 would be about US$ 180 million, reaching US$ 384 million in 2025. If the vaccination costs were, on average, US$ 25 per girl, the costs would be about US$ 300 million in 2016, reaching US$ 641 million in 2025. If coverage is assumed to ramp up over 10 years rather than 6, 22 million doses would be required for GAVI-eligible countries by 2016 and, at US$ 15 per girl, total costs would be US$ 108 million.

These rough estimates are intended to illustrate the approximate magnitude of vaccine quantity and financing that could be required under rather optimistic assumptions about uptake. Note that one of the simplifications made in this exercise is that cost is assumed to stay constant as coverage increases. Average costs will vary as the marginal costs change (up or down) with expanding coverage. Programs typically have initially high start-up costs, with average costs falling as coverage expands. At some point, average costs will increase as marginal costs go up when programs try to include more difficult-to-reach groups.

Figure 1. Potential HPV Vaccine Adoption Uptake for GAVI-eligible Countries, Six-Year Ramp-Up to 80% Coverage
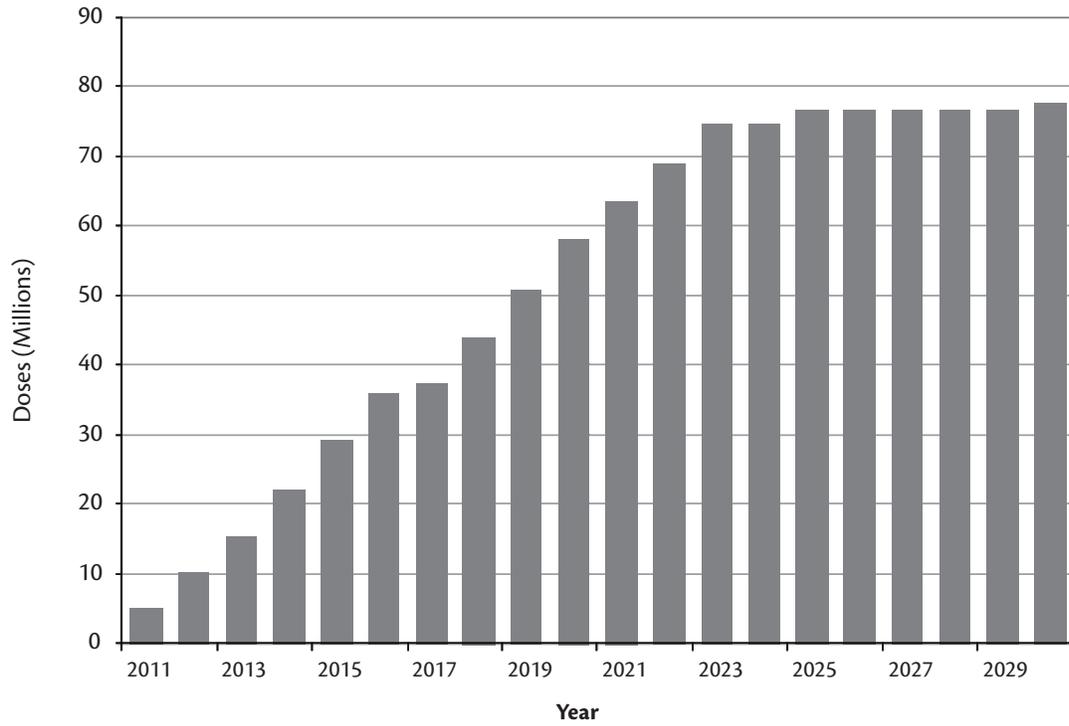
Figure 2. Full HPV Immunization Costs for GAVI Countries under Alternative Cost Assumptions, Six-Year Ramp-Up to 80% Coverage.
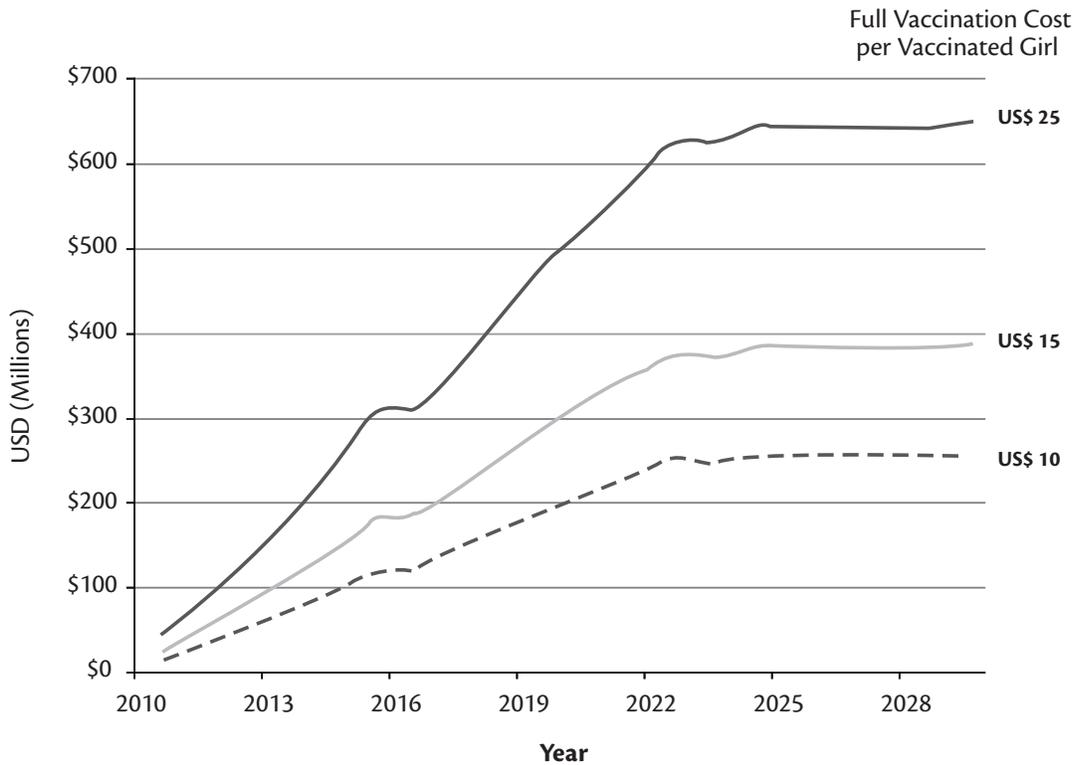
4.6   Scaling up Production Capacity for HPV Vaccines

Lead times for constructing new vaccine manufacturing plants are significant. Merck has been stockpiling its vaccine, but production capacity and stockpile information are not publicly available. GSK has been taking similar steps. Both companies have indicated that, with a firm commitment on purchasing for developing countries, they would be ready to build a second plant to produce large quantities of the HPV vaccine. Companies will do demand forecasting of developing country markets before investing in scaling up for these 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 of external funding commitments from the GAVI Alliance or other organizations as well as indications from middle-income countries that they are prepared to finance HPV vaccines.

5   CONCLUSIONS

HPV vaccines could greatly reduce cervical cancer morbidity and mortality in developing countries, but social, political, economic, and logistical challenges must be addressed in order for these benefits to be realized. Cost and financial issues include:

- Determining the price that manufacturers will charge in developing countries, which will greatly influence the cost effectiveness of HPV vaccination in these countries as well as the affordability of HPV vaccine purchase and delivery.

- Convincing finance and health ministries of the vaccine's programmatic feasibility, financial sustainability, and value relative to competing demands for resources. Country-level cost-effectiveness studies need to be supported and disseminated widely, making an effective case that HPV vaccination can be a wise investment even though the benefits accrue well into the future.

- Ensuring considerable assistance to low-income countries from GAVI or other sources to finance HPV vaccine introduction, at least until prices fall to sustainable levels. Obtaining this support will, in turn, require presenting a clear and compelling investment case to GAVI and individual donors for extending financing to HPV vaccines.

- Assuring manufacturers that demand will materialize and financing is secured so that they will scale up production to meet developing country needs.

- Signaling to manufacturers that it is worthwhile to invest in improved second-generation HPV vaccines which, over the longer run, could contribute substantially to increasing coverage of HPV immunization in developing countries. Second-generation vaccines could be superior to the existing ones on a number of dimensions, including price, efficacy, and ease of delivery.

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APPENDIX 1. KEY FINDINGS FROM NINE PUBLISHED COUNTRY ECONOMIC ANALYSES OF HPV VACCINATION

COUNTRY, RESEARCH ARTICLE, AND TYPE OF MODEL	VACCINE AND SCREENING ASSUMPTIONS	DISCOUNT RATE AND COSTS	MAIN OUTCOMES MEASURED	KEY RESULTS
Brazil Kim, JJ., Andres-Bek, B. and Goldie, SJ. (2007). The Value of Including Boys in an HPV Vaccination Programme: a Cost-effectiveness Analysis in a Low-Resource Setting. *British Journal of Cancer* 97: 1322-1328. Dynamic Transmission Model.	Coverage varied from 0-90% in girls alone versus 0-90% in boys and girls. Assumed vaccine efficacy 100% against HPV 16/18. Lifelong immunity.	3% discount rate. International dollars. Varied cost per vaccinated girl/boy from I$ 25 to I$ 400.	Incremental cost effectiveness (using YLS).	At 75% coverage, vaccinating girls alone resulted in a reduction in lifetime cancer risk of 45%, with a cost per YLS ranging from nothing (cost saving) if cost is I$ 25 per vaccinated individual, to I$ 130 per YLS if cost is I$ 50 per vaccinated individual, to I$ 740 if cost I$ 100 per vaccinated individual, to I$ 3,940 per YLS if cost is I$ 400 per vaccinated individual. Adding boys to this level of coverage (now 75% coverage of both girls and boys) brings the reduction in lifetime cancer risk to 57%. Using the same ranges in costs per vaccinated individual, the cost per YLS for girls and boys together ranges from I$ 2,440 (at I$ 25 per vaccinated individual) to I$ 18,820 (at I$ 400 per vaccinated individual). One key conclusion was that efforts to increase the coverage of girls made more sense in terms of cost effectiveness than increasing coverage of boys.
Australia Kulasingam, SL. et al. (2007). A Cost-effectiveness Analysis of Adding a Human Papillomavirus Vaccine to the Australian National Cervical Cancer Screening Program. *Sexual Health* 4: 165-175. Cohort Model	80% coverage of 12-year-old girls. Vaccine efficacy 100% against HPV-16/18. Lifetime immunity.	5% discount rate "as required for health technology assessment in Australia" but 3% used in sensitivity analysis. Australian dollars Cost of vaccine alone A$ 115 (US$ 107) per dose for 3 doses. Administration cost A$ 12 per dose for school administration, and A$ 31 per dose for G.P. administration.	Incremental cost effectiveness (using QALYs).	Compared to a program of screening alone, vaccination of 12-year-old girls with screening costs A$ 18,735 (US$ 17,372) per QALY and reduces the lifetime risk of cancer by almost 50%. If a 3% discount rate for costs and benefits is used instead of the 5% discount rate used for health technology assessment in Australia, the cost per QALY falls to A$ 8,419 (US$ 7,806).

COUNTRY, RESEARCH ARTICLE, AND TYPE OF MODEL	VACCINE AND SCREENING ASSUMPTIONS	DISCOUNT RATE AND COSTS	MAIN OUTCOMES MEASURED	KEY RESULTS
Canada Brisson, M. et al. (2007). The Potential Cost-effectiveness of Prophylactic Human Papillomavirus Vaccines in Canada. *Vaccine* 25: 5399-5408. Cohort Model	Vaccination of 100,000 girls aged 12. Lifelong immunity. Bivalent and quadrivalent vaccines both modeled. Vaccine efficacy is 95% against HPV-6/11/16/18 for the quadrivalent vaccine and 95% effective against HPV-16/18 for the bivalent vaccine. No change in existing screening practice and compliance.	3% discount rate. Canadian dollars Cost of both quadrivalent and bivalent vaccines assumed to be C$ 400 per course, including vaccine and administration.	Incremental cost-effectiveness ratios (using QALYs). Note QALY losses stem from diagnosis with genital warts, CIN, or cervical cancer.	Using the cost-effectiveness threshold of C$ 40,000 (US$ 42,000) per QALY gained as cost-effective, HPV vaccination is cost-effective under a wide range of scenarios. Bivalent vaccine has cost per QALY gained of C$ 31,000 (US$ 33,000). Quadrivalent vaccine has cost per QALY gained of C$ 21,000 (US$ 22,000) because of the additional impact from averting genital warts.
Brazil Goldie, SJ. et al. (2007). Cost-effectiveness of HPV 16, 18 Vaccination in Brazil. *Vaccine* 25: 6257-6270. Cohort Model	70% vaccination coverage of adolescent girls. Girls receive the full 3 doses before age 12. 100% efficacy against HPV 16 and 18. Lifelong immunity. Screening 70% women over age 30 with HPV DNA testing or cytology 3X per lifetime, 15% lost to follow up per visit.	3% discount rate International dollars Cost per vaccinated woman ranged from I$ 25 to I$ 450 (of this, vaccine cost alone ranges from I$ 6 to 390).	Incremental cost-effectiveness ratios (using YLS), cancer incidence reduction.	Vaccination alone dominates screening if cost per vaccinated woman was less than or equal to I$ 50. When cost per vaccinated woman was I$ 50, cost effectiveness was I$ 300 per YLS for vaccination alone. This strategy reduces the lifetime risk of cancer by about 43%. At all vaccine costs above I$ 75, vaccination plus screening dominated vaccination alone. Combined vaccination and screening at I$ 75, 100, and 450 per vaccinated woman results in I$ 1,100, 1,700, and 9,600 per YLS.

COUNTRY, RESEARCH ARTICLE, AND TYPE OF MODEL	VACCINE AND SCREENING ASSUMPTIONS	DISCOUNT RATE AND COSTS	MAIN OUTCOMES MEASURED	KEY RESULTS
USA Elbasha, EH., Dasbach, EJ., Insinga, RP. (2007). Model for Assessing Human Papillomavirus Vaccination Strategies. *Emerging Infectious Diseases.* 13 (1): 28-41. Hybrid Cohort/dynamic transmission model	Examined routine vaccination of: -girls by age 12 -girls and boys by age 12 -girls by age 12 and catch-up vaccination for females ages 12-24 -girls and boys by age 12 and catch-up vaccination for ages 12-24 for females and males Assumed lifelong protection from the vaccine. Assumed 100% protection against HPV6/11 or 16/18. Assumed that coverage reached 70% of 12 year olds with the 3-dose vaccine, after increasing from 0 at program initiation to 70% at five years.	3% discount rate 2005 U.S. dollars Vaccination costs (vaccine and administration): US$ 360	Incremental cost-effectiveness ratios (measured in QALYs), cervical cancer incidence reduction, genital warts incidence reduction.	Vaccinating 12-year-old girls and catch-up vaccination of females aged 12-24 resulted in a cost-effectiveness ratio of US$ 4,666 per QALY. Vaccinating 12-year-old girls and boys and catch-up vaccination of females and males aged 12-24 resulted in a cost-effectiveness ratio of US$ 45,056 per QALY. As in the Taira, AV et al. (2004) study (see below), vaccination of boys was more cost-effective the lower the coverage of girls. However, this study found that vaccinating males and females (at high levels of coverage) would be cost-effective. At lower coverage levels of females, vaccination of boys and men becomes more cost effective relative to vaccinating boys when coverage levels of females are higher.
USA Goldie, SJ. et al. (2004). Projected Clinical Benefits and Cost-effectiveness of a Human Papillomavirus 16/18 Vaccine. *Journal of the National Cancer Institute* 96: 604-615. Cohort Model	100% vaccination coverage of adolescent girls at age 12, with the full 3 doses. 70-100% efficacy against HPV 16 and 18. Lifelong immunity. 100% screening coverage. Screening intervals of 1-5 years with conventional and liquid-based cytology initiated at 18, 21, 25, 30, or 35 years. (Coverage assumptions vary in the sensitivity analyses).	3% discount rate. 2002 U.S. dollars Vaccination costs (3 doses): US$ 393 (includes US$ 300 for vaccine, as well as US$ 77 for costs of 3 brief clinic visits, surveillance, and education, and US$ 16 patient time costs).	Incremental cost-effectiveness ratios (using [QALY]), cancer incidence reduction costs.	At 100% efficacy, the incremental cost-effectiveness ratio was estimated at US$ 20,600 per QALY in the context of current screening. Comparing vaccination combined with type of cytologic screening showed that the most effective strategy with an incremental cost-effectiveness ratio of under US$ 60,000 per QALY was one that combined vaccination at age 12 with conventional cytologic screening starting at age 25, repeating every 3 years. This approach cut the lifetime risk of cervical cancer by an estimated 94% over no intervention.

COUNTRY, RESEARCH ARTICLE, AND TYPE OF MODEL	VACCINE AND SCREENING ASSUMPTIONS	DISCOUNT RATE AND COSTS	MAIN OUTCOMES MEASURED	KEY RESULTS
USA Taira, AV. et al. (2004). Evaluating Human Papillomavirus Vaccination Programs. *Emerging Infectious Diseases* 10 (11): 1915-1923. Dynamic Transmission Model	70% vaccination coverage of 12-year-old girls with 3 doses. Boosters required every 10 years. 90% vaccine efficacy against HPV16/18.	3% discount rate U.S. dollars Initial vaccine cost: US$ 300 Booster: US$ 100	Incremental cost-effectiveness ratios (measured in QALYs), cancer incidence reduction.	Base case (vaccination of 12-year-old girls) results in an estimated cost-effectiveness ratio of US$ 14,583 per QALY and a 62% reduction in cervical cancer over a lifetime. Including boys would add an additional .21 QALY per woman at an incremental cost-effectiveness ratio of US$ 442,039/QALY. Vaccinating girls was found to be cost-effective at all levels of coverage. Vaccinating boys only becomes cost-effective at low levels of female coverage.
USA Sanders, GD. and Taira, AV. (2003). Cost-effectiveness of a potential vaccine for human papillomavirus. *Emerging Infectious Diseases* 9 (1): 37-48. Cohort Model	70% vaccination coverage of 12-year-old girls. 75% vaccine efficacy (against high-risk HPV types). Booster required every 10 years.	3% discount rate 2001 U.S. dollars Initial vaccine costs: US$ 300 Booster shot: US$ 100	Incremental cost-effectiveness ratios (measured in QALYs), cancer incidence reduction.	Vaccination is estimated to have an incremental cost-effectiveness ratio of US$ 22,755 per QALY.
USA Kulasingam, SL. and Meyers, ER. (2003). Potential health and economic impact of adding a human papillomavirus vaccine to screening programs. *JAMA* 190 (6): 781-789. Cohort Model	Vaccine targeted to 70% of oncogenic HPV types, with an efficacy of 90%. Vaccine efficacy constant for 10 years and then assumed to decrease to zero. 100% of 12-year-old girls vaccinated once (with a 3-series vaccine). Compared vaccination only, conventional cytology-based screening only, and vaccination followed by cytology screening.	3% discount rate U.S. dollars Vaccine costs: US$ 200. Booster cost: US$ 200.	Incremental cost-effectiveness ratios (measured in YLS, sensitivity analysis with QALYs), cancer incidence reduction.	With US$ 50,000 per life year saved as a threshold, vaccination plus screening at two-year intervals starting at aged 24 appeared to be the best strategy, with an 83% reduction in cancer incidence and a cost of US$ 44,889 per life year saved.