SUMMARY 1

Global Cervical Cancer Prevention

Health and Economic Benefits of HPV Vaccination and Screening

Summary of Prior Work

Sue J. Goldie[1], Steven Sweet[1]

Affiliations:
1 Center for Health Decision Science, Harvard School of Public Health, Harvard University, Boston, Massachusetts, USA.

Corresponding author: ssweet@hsph.harvard.edu

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This summary document provides an overview of prior work that was conducted to evaluate the impact and cost-effectiveness of different cervical cancer prevention and treatment strategies. Several prior publications listed in the reference section provide greater detail. However, since we provided extracted estimates for the *Lancet* Commission on Investing in Health from this work, we provide a brief summary for readers.

INTRODUCTION

As the leading cancer killer of women in developing countries, cervical cancer accounts for more than a quarter million deaths each year, but can be prevented by vaccination against human papillomavirus (HPV). The GAVI Alliance endeavors to reduce the historical time lag associated with new vaccine introduction in developing countries by funding immunization programs in the world's poorest countries. In late 2008, the GAVI Alliance prioritized support for HPV vaccines. Since then, with dramatic price reduction agreements to as low as $4.50 per dose, GAVI now provides two application pathways for countries to pursue HPV vaccination (http://www.gavialliance.org/support/nvs/human-papillomavirus-vaccine-support/). The analyses described in this brief report were conducted over the last several years largely to support the evidence base to make HPV vaccines available to the poorest adolescent girls in the world, as well as rapid HPV DNA testing for screening women over age 30 2-3 times per lifetime.

OBJECTIVE

To comparatively assess the health and economic outcomes associated with alternative cervical cancer control strategies in low and low-middle income countries (e.g., HPV vaccination of pre-adolescents; screening of older women 1-5 times per lifetime; and combined programs of vaccination followed by screening later in life). We simulate the epidemiology of cervical cancer with a sophisticated microsimulation stochastic model that is empirically calibrated to country-specific data in 23 countries, to conduct vaccine and screening analyses. Additionally, in countries with limited epidemiological data, we utilize an Excel-based companion model of more than 140 countries worldwide, focused on estimating vaccine benefit, financial projections, and scenario analysis.

ANALYTIC APPROACH

Rigorous studies addressing specific knowledge gaps – from epidemiologic studies of cancer incidence to clinical trials of vaccine efficacy – have contributed to what has become a substantial evidence base to support programs for cervical cancer control. Synthesizing this evidence to catalyze global strategic action requires a distinct effort drawing upon a broader range of multi-dimensional policy tools.

For example, what is the projected impact and cost-effectiveness of alternatives to conventional cytology, such as HPV DNA testing? How can we implement screening with fewer technical and infrastructure requirements? How will countries overcome the logistical barriers associated with delivering a 3-dose vaccine during early adolescence? Is there a combined strategy of screening and vaccination that is likely to be cost-effective, or will countries need to choose between the two?

Consider just a few of the factors that will influence decisions about optimal strategies for screening –

- relative performance and costs of different screening tests;
- effectiveness of different treatment options;
- effective strategies that target appropriate age groups at specific intervals;
- acceptability, availability, and accessibility of screening programs;
- programmatic resources, such as health infrastructure and workforce capacity.

Consider just a few of the factors that will influence decisions about introducing the HPV vaccine –

- type-specific incidence of HPV, type-specific distribution of cervical cancer;

- vaccine efficacy, cost, and duration of immunity;
- acceptability, availability, and achievable coverage;
- programmatic resources, such as delivery mechanisms and cold chain capacity.

No clinical trial or single longitudinal cohort study will be able to consider all of these factors; in fact, just predicting the population-level impact of cervical cancer prevention is challenging as the time course from infection to disease spans several decades and most data are based on intermediate endpoints. Computer-based mathematical models can provide a useful tool with which synthesize data in an internally-consistent and epidemiologically plausible way. In the HPV-related cervical cancer arena, models have been used in the context of different research objectives, ranging from projecting type-specific HPV prevalence patterns with vaccination to evaluating the cost-effectiveness of screening and vaccination in different world regions; accordingly, they have differed in their design and structure, accommodation of transmission dynamics, inclusion of multiple HPV types, and use of empiric calibration.

The insights we summarize are from those model-based studies conducted with a decision analytic perspective – that is, with the primary purpose of guiding decision making in the real-world context of uncertainty. A decision analytic approach provides a way to integrate different types of information into a logical conceptual framework, extrapolate costs and effects beyond the time horizon of a single clinical study, and compare strategies targeting different points in the disease course. By linking the knowledge gained from empirical studies to real-world situations, these analyses can provide estimates of the benefits (e.g., avertable disease burden, cancers prevented, lives saved), economic costs (i.e., net resources required to implement the program), value (i.e., cost-effectiveness), and financial costs (i.e., affordability) of different strategic choices about cervical cancer prevention.

Evidence-informed guidance is needed at several junctures of the policy process, and the information needs for different decision-makers and stakeholders vary considerably. For example, vaccine financing actors (e.g., GAVI Alliance) require estimates of lives saved and cost requirements of different adoption scenarios in GAVI-eligible countries; on the other hand, individual countries need contextualized information based on local data, as they compare the value of cervical cancer prevention with other competing priorities and explore the relative feasibility and sustainability of different options.

General insights about the value of HPV vaccination and new screening strategies are reasonably concordant across most model-based analyses. We summarize the most robust of these insights below, and provide specific examples from studies conducted for the primary purpose of guiding real-time decision making. Documentation of the methods, tools, and assumptions used for the latter may be found in previous publications. We organize the findings according to their relevancy to a specific ‘decision’ and target population. For example,

- For women who are 30 years of age and older, what is the best strategy to prevent deaths from cervical cancer? Should we screen once, twice or three times per lifetime? Which screening test? What screening algorithm?
- For girls who are 12 years of age and younger, or not yet sexually-active, what is the best way to prevent deaths from cervical cancer? Should we vaccinate now? Should we just wait and screen them as adults? Should we vaccinate now and then also plan to screen them as adults?

OVERVIEW OF MODEL-BASED ANALYSES

We have conducted HPV vaccine analyses in 128 countries (including the 72 GAVI countries and the 33 LAC countries) using our excel-based companion model; these have focused on estimating vaccine benefit in terms of cases and deaths averted, YLS and DALYs, and cost per DALY, as well as financial projections and scenario analysis. Vaccine delivery scenarios include population coverage at a country level, year of introduction, and cost of vaccine doses. In addition, more than 25 analyses and published papers look at screening and vaccination, alone and in combination. An additional 25 analyses target just screening questions.

Overview of HPV Models (Harvard Team)

- **Individual-based micro-simulation model** [26 countries]
- **Dynamic transmission model** [5 countries]
- **Models including non-cervical HPV-related outcomes** [U.S.]
- **Excel-based population-level model** [128 countries]
- **Integer programming model** [3 regions, 1 country]
- **Country-contextualization tools** [Latin America/Caribbean]

Our more sophisticated microsimulation stochastic model that is empirically calibrated to country-specific data has been used to conduct vaccine and screening analyses in 23 countries (vaccination of pre-adolescents, screening of older women 1-5 times per lifetime beginning between ages 30 and 35, and combined programs of vaccine followed by screening later in life). The microsimulation model simulates the natural history of HPV and cervical carcinogenesis, accommodates multiple HPV types, can reflect cross protection and can be linked to a dynamic model to capture herd immunity. It can also be used to assess any vaccine or screening strategy combination. Because we are empirically calibrating this model to country-specific data, and it is run as Monte Carlo simulation, it is time and data intensive. The application of this model to 70 plus GAVI countries would not be feasible given data limitations, resources, and time constraints. (in addition, to model financial and forecasting analyses with this large a number of countries and vary start year, ramp up speed, maximum coverage achieved, and changes in coverage over time, a simpler model is more suitable. We use a variety of other model types for specific kinds of analyses as shown on the right.

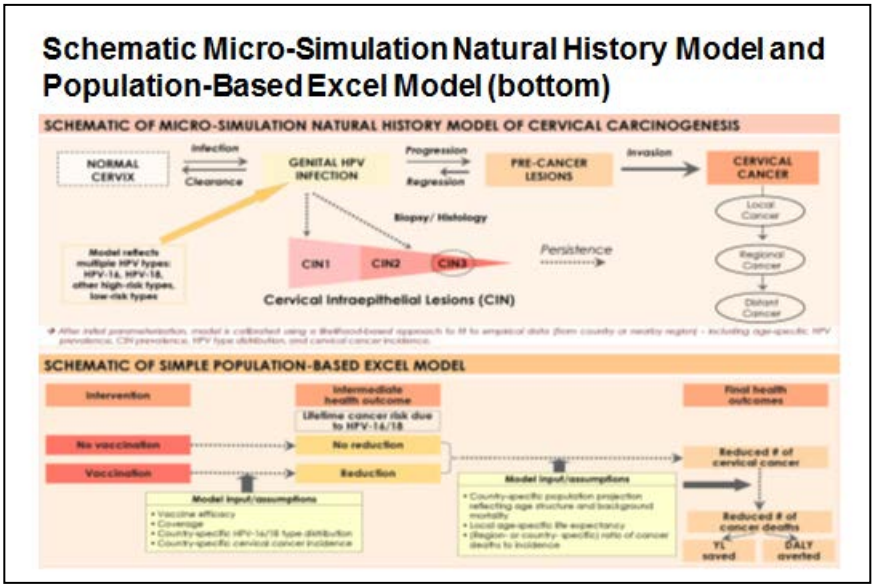
Spectrum of Analyses (Harvard Team)

- **Comprehensive policy analyses**
  - synthesize evidence to date, identify promising approaches, most influential factors
- **Special target groups**
  - vaccinating boys, older women, delivery of adolescent package
- **Country contextualization**
  - adapting analyses to local situations, technical capacity building
- **Methodological work**
  - model simulation, empirical calibration
- **Rapid response to time-sensitive policy questions**
  - global benefits, cost-effectiveness, financing, demand, forecast (e.g., SAGE, GAVI)

Many of the analyses summarized here were driven by the need for information by those making immunization policy recommendations (e.g., World Health Organization, WHO), financing coordination mechanisms (e.g., GAVI Alliance), and potential donors.

POPULATION-BASED COMPANION MODEL (Excerpts taken from various publications listed below)

Overview



The companion population-based model is a flexible tool that has been developed to reflect the main features of HPV vaccines, and to project the potential impact (health and economic consequences) of HPV vaccination at the population level in settings where data are very limited (Goldie 2008a,b). The model is constructed as a static cohort simulation model based on a structure similar to a simple decision tree, and is programmed using Microsoft® Excel and Visual Basic for Applications, 6.3 (Microsoft Corporation, Redmond, WA). The model tracks a cohort of girls at a target age (e.g., 9 years) through their lifetimes, comparing health and cost outcomes with and without HPV vaccination programs. Unlike our more complex empirically-calibrated micro-simulation models (Goldie 2007, Kim 2007, Diaz 2008, Kim 2008, Diaz 2010, Sharma 2012, Campos 2011), the companion model does not fully simulate the natural history of HPV infection and cervical carcinogenesis. Instead, based on simplifying assumptions (i.e., duration and stage distribution of, and mortality from, cervical cancer), which rely on insights from analyses performed with the micro-simulation model, and using the best available data on local age-specific incidence of cervical cancer and HPV 16,18 type distribution, and assumed vaccine efficacy and coverage, the model estimates reduction in cervical cancer risk at different ages. By applying this reduction to country-specific, age-structured population prospects incorporating background mortality (UN 2009), the model calculates averted cervical cancer cases and deaths, and transforms them into aggregated population health outcomes, years of life saved (YLS) and disability-adjusted life years (DALYs) averted. DALYs are calculated using the standard approach by the Global Burden of Disease (GBD) study (Murray 1996) although they are not age-weighted. The model also combines vaccination program costs and direct medical treatment costs associated with cervical cancer over the course of the simulation, and generates short-term financial costs, long-term economic outcomes (e.g., lifetime costs), and incremental costs (expressed in 2005 international dollars) per DALY averted.

The companion model captures the burden of HPV infection by estimating the number of cervical cancer cases caused by HPV infection based on epidemiological data obtained from various sources. In the absence of vaccination, women may develop HPV infections and cervical cancer based on the epidemiologic estimates specific to each country. We assume that age-specific cervical cancer incidence, average age of sexual debut, and the level of other risk factors remain constant over the time horizon of the model. We assume that girls are fully immunized with 3 doses. We assume that girls effectively immunized against HPV16/18 can be infected with non-16/18 type HPV (e.g., no cross-protection is assumed), and vaccine-induced immunity is lifelong. All assumptions are varied in sensitivity analyses.

Previous impact findings

Previous publications have applied the HPV Excel companion model to 72 GAVI-eligible countries, 25 countries in Asia, and 33 countries in Latin America and the Caribbean (Goldie 2008a, 2008b, 2008c), estimating averted cervical cancer cases and deaths, disability-adjusted years of life (DALYs) averted and incremental cost-effectiveness ratios (I$/DALY averted) associated with HPV 16,18 vaccination of young adolescent girls. In addition to vaccine coverage and efficacy, relative and absolute cancer reduction depended on underlying incidence, proportion attributable to HPV types 16 and 18, population age-structure and competing mortality. For the GAVI-eligible countries, at 70% vaccination coverage, mean reduction in the lifetime risk of cancer was below 40% in some countries (e.g., Nigeria, Ghana) and above 50% in others (e.g., India, Uganda, Kenya). Taking into account country-specific assumptions (per capita GNI, DPT3 coverage, percentage of girls who are enrolled in fifth grade) for the year of introduction, percent coverage achieved in the first year, and years to maximum coverage, a 10-year modeled scenario prevented the future deaths of ~2 million women vaccinated as adolescents. We concluded that provided high coverage of young adolescent girls is feasible, and vaccine costs are lowered, HPV 16,18 vaccination could be very cost-effective even in the poorest countries, and provide comparable value for resources to other new vaccines such as rotavirus.

In the regions of Latin America and the Caribbean and Asia and the Pacific, absolute reduction in lifetime risk of cancer also varied between countries: at 70% vaccination coverage, cancer reduction ranged from 40% in Mexico and 49% in Cambodia to more than 50% in Argentina and 57% in Indonesia. Of the 22 GAVI-Alliance eligible countries in the Asia/Pacific region, India, Bangladesh, Vietnam and Indonesia accounted for 87% of the total DALYs averted. In Latin America and the Caribbean, countries with the highest risk of cancer (age-standardized rate > 33.6) accounted for only 34% of deaths averted with vaccination, highlighting why a regional universal vaccination approach will be most effective in reducing the overall global burden.

To provide early insight into the comparative impact of HPV and rotavirus vaccination in resource-poor settings, we also developed a similar static model of rotavirus vaccination and in a preliminary analysis estimated affordability, cost-effectiveness, and distributional equity for the two vaccines (Kim 2011). With 70% coverage of a single-age cohort of infants and pre-adolescent girls, the lives saved with rotavirus (~274,000) and HPV vaccines (~286,000) are similar, although the timing of averted mortality differs; rotavirus-attributable deaths occur in close proximity to infection, while HPV-related cancer deaths occur largely after age 30. Deaths averted per 1000 vaccinated are 5.2 (rotavirus) and 12.6 (HPV). Disability-adjusted life years (DALYs) averted were ~7.15 million (rotavirus) and ~1.30 million (HPV), reflecting the greater influence of discounting on the latter, given the lagtime between vaccination and averted cancer. In most countries (68 for rotavirus and 66 for HPV, at the cost of I$25 per vaccinated individual) the incremental cost per DALY averted was lower than each country's GDP per capita. Financial resources required for vaccination with rotavirus are higher than with HPV since both genders are vaccinated. While life-saving benefits of rotavirus and HPV vaccines will be realized at different times, the number of lives saved over each target populations' lifetimes will be similar.

Description of current model

As of 2013, the HPV Excel model can be applied to more than 140 countries within various geographic regions (e.g., Latin America and Caribbean, sub-Saharan Africa, Middle East/Northern Africa), economic classifications (eligible for financing from the GAVI Alliance; classified as low- or middle-income by the

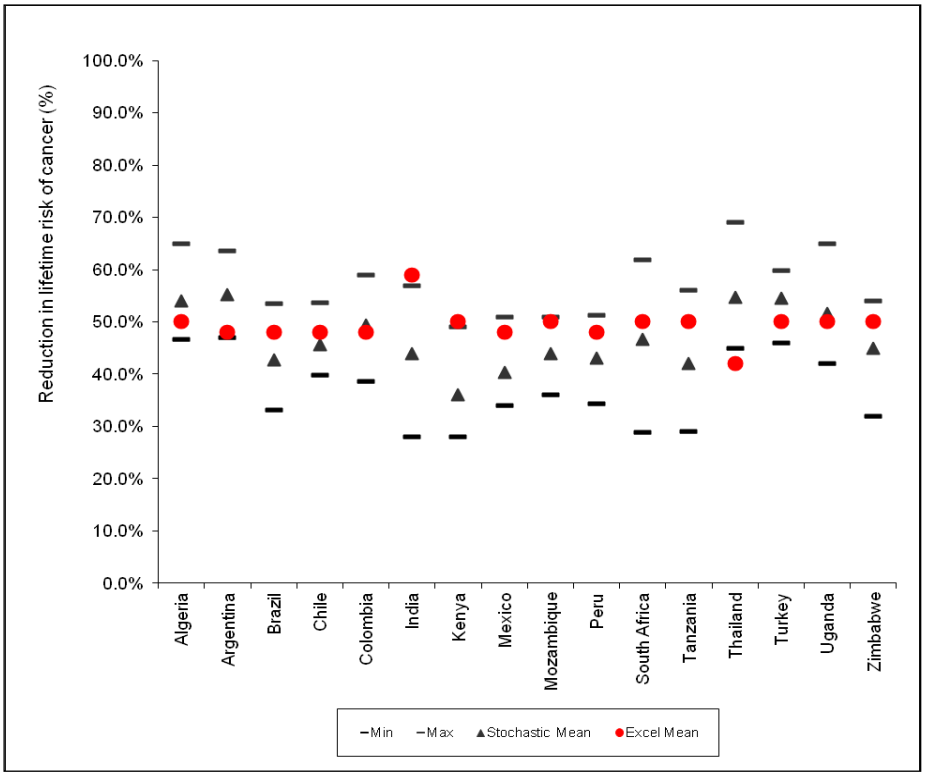
World Bank on July 1, 2011), and cancer incidence groups (e.g., age-standardized rate (ASR) of <5 = low; 5-15 = mid-low; 15-25 = medium; 25-35 = mid-high; >35 = high per Globocan 2008 [Ferlay 2010]).

COMPARATIVE VALIDATION: COMPANION MODEL AND STOCHASTIC MODELS

Overview of stochastic models

We have previously described a series of cervical cancer models that include an individual-based stochastic model to simulate cervical carcinogenesis associated with all high-risk HPV types and a dynamic model to simulate sexual transmission of HPV-16 and -18 infections between males and females (Goldie 2007, Kim 2007a, Kim 2007b, Diaz 2008, Kim 2008, Diaz 2010, Sharma 2012, Campos 2011). A likelihood-based approach is used to calibrate these models to empirical data, including age- and type-specific HPV prevalence, age-specific prevalence of cervical lesions, HPV type distribution within women with normal cytology, cancer precursors and cervical cancer, and age-specific incidence of cervical cancer. Our empirically calibrated models include countries in Asia (India, Thailand, and Vietnam – Hanoi and Ho Chi Minh City), Africa (Zimbabwe, Tanzania, Nigeria, Kenya, Uganda, Mozambique, South Africa), Latin America and the Caribbean (Brazil, Argentina, Chile, Colombia, Costa Rica, Mexico, Peru), and the Middle East/North Africa (Lebanon, Algeria, Turkey).

Comparative validation



To ensure the validity of simplifying assumptions identified for the companion population-based model we compared results to our micro-simulation models when subject to those same assumptions. The figure at right presents the results of a comparison exercise assuming vaccination coverage of 70%. For each country, an upper and lower bound of reduction in lifetime cancer risk is denoted by horizontal bars as well as an expected mean (denoted by a black triangle) projected using the micro-simulation model, and the corresponding mean reduction generated by the companion population-based model (denoted with a red circle). While the mean reduction in lifetime risk of cancer varies reflecting epidemiological differences in the proportion of HPV 16- and 18-related cancer, the average reduction in cancer predicted with the Excel-based companion model falls within these bounds.

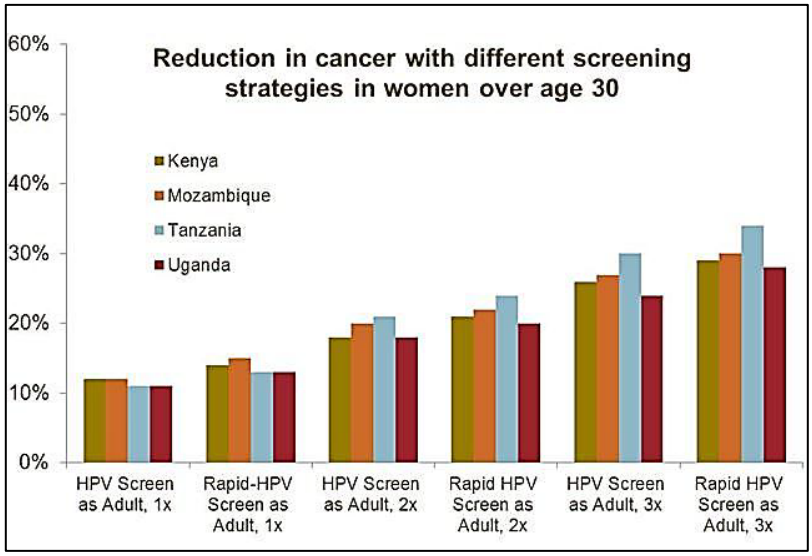
Prevention strategies

We consider various strategies including HPV vaccination of pre-adolescents; screening of women 1-5 times per lifetime beginning between ages 30 and 35 using cervical cytology, HPV DNA testing, and/or visual inspection with acetic acid (VIA); and combined programs of vaccine followed by screening later in life.

RESULTS

What is the expected reduction in cervical cancer with new screening strategies?

In resource-poor settings, cancer deaths can be reduced by approximately one third with three screenings per lifetime using alternatives to cytology. For example, in 5 East African countries (Campos 2011), assuming 70% coverage, and an attrition rate of 15%, screening three times per lifetime with one-visit rapid HPV DNA testing (at ages 35, 40, and 45) reduced cancer incidence by 27%-34%. The projected reduction in the lifetime risk of cervical cancer for each country with different screening strategies is shown in the figure on the right.



What general insights have emerged from model-based studies about screening?

- Screening needs to be targeted to the correct ages (after age 30) and screening all women at least 2-3 times per lifetime should be prioritized over screening a small proportion of women more frequently.

- The choice between screening tests (e.g., HPV, VIA) is most sensitive to the ability to link screening and treatment in fewer visits, the resources required, and test sensitivity.

- All things being equal, screening with HPV testing 2-3 times between ages 30-45 is the most effective and cost-effective screening strategy, compared with no screening or current low levels of screening with cytology. The recently available rapid HPV test allows for screening and treatment in 1-2 visits, improving cost-effectiveness.

- Cervical cancer mortality reduction is most sensitive to quality of screening, coverage rates, and minimizing loss to follow-up of women with positive results. Cost-effectiveness may be substantially influenced most by nonmedical costs (time and transportation).

What is the expected reduction in cervical cancer with HPV 16,18 vaccination of adolescent girls?

In countries without screening, vaccinating 70% of adolescent girls is expected to cut the average lifetime cancer risk in half. Country-specific estimates of cervical cancer reduction are influenced by local cancer incidence rates and the HPV 16 and 18-attributable fraction. For example, assuming 70%

coverage, the reduction in lifetime cancer risk varies from 40% in Nigeria, Ghana, and Chile to more than 50% in India, Uganda, and Argentina (Goldie 2008a,b,c)

Should HPV 16,18 vaccination be initially targeted to countries with the highest cancer rates?

Among the 72 GAVI-eligible or formerly eligible countries, those with the highest incidence rates represent less than 25% of averted deaths. The greatest number of preventable deaths is expected in countries with moderate cervical cancer incidence and large populations. For example, 41%of averted deaths would be expected in India alone (Goldie 2008).

How many deaths are prevented per 1000 vaccinated?

Considering the GAVI-eligible countries, 13 cervical cancer deaths expected to be averted per 1,000 girls vaccinated, and among the poorest countries in Africa, 17 deaths per 1,000 vaccinated. In comparison, rotavirus vaccination is expected to avert 3 deaths per 1,000 children vaccinated (Kim 2011).

How many lives would be saved by vaccinating 10 consecutive cohorts of 12-year-old girls?

With 70% coverage, approximately 3 million future deaths would be prevented in the 72 GAVI-eligible countries. The addition of the non-GAVI eligible countries in the Latin American and Caribbean region, as well as China and Thailand, would prevent almost 1 million additional future deaths (Goldie 2008 a,b,c).

Impact and cost-effectiveness of 70% coverage HPV vaccination in girls younger than age 13

	Vaccinate Girls Now	*Vaccinate Girls Now*	
Vaccine $5/dose	Alone	Followed by Screening with HPV in 20 Years	
	3 doses prior to sexual debut	*2-3x per lifetime between age 35-45*	
		2x/lifetime	3x/lifetime
India	44%	58%	63%
Kenya	36%	49%	55%
Mozambique	44%	56%	61%
Tanzania	42%	56%	61%
Uganda	44%	56%	60%

Color Code Key	GDP per capita, %	Interpretation
	<.5x	Very Cost-Effective
	.5 - 1x	Very Cost-Effective
	1x - 2x	Cost-Effective
	2x - 3x	Cost-Effective
	> 3x	Lower Value

Would vaccination of adolescent girls against HPV 16, 18 be cost-effective?

Provided the cost is less than $25 per fully vaccinated girl (~$5 per dose), inclusive of three doses, administration, FOB, wastage, vaccine support and program delivery costs), vaccination is *more cost-effective* than screening once or twice per lifetime. At costs between $10 and $25 per fully vaccinated girl (~$2-5 per dose), vaccination is expected to be *very cost-effective* in all 72 countries using the criterion of a cost-effectiveness ratio below the per capita GDP (Goldie 2008).

How much additional benefit would be gained by screening previously vaccinated girls after they reach age 30?

Screening previously vaccinated girls three times per lifetime (e.g., ages 35, 40 and 45) is expected to provide an additional 20-25% mortality reduction. While more costly than vaccination alone, this strategy is still cost-effective (e.g., good value for resources invested) according to the commonly used heuristic of a CE ratio less than three times the per capita GDP.

How does the HPV 16, 18 vaccine compare to other new vaccines?

While life-saving benefits of rotavirus and HPV vaccines will be realized at different times, the number of lives saved over each target populations' lifetimes will be similar. Provided costs are between $10 and

$25 per fully vaccinated girl (~$2-5 per dose), adolescent HPV vaccine provides comparable value (i.e., similar cost-effectiveness ratios) to other new vaccines (Kim 2011).

Are other benefits expected from cervical cancer prevention efforts?

A ten-year vaccination program at 70% coverage in GAVI-eligible countries would prevent the loss of a mother to cervical cancer for approximately 10 million children; between 1.5 and 2.9 million of these children would be under the age of 18. . In addition, an adolescent immunization program, possibly school-based, could serve to provide a platform for delivering other adolescent health services. Opportunities for strengthening health systems can be created through the establishment of new mechanisms for vaccine delivery, screening services and surveillance of impact. Finally, saving women's lives contributes to the health and education of children, strengthens families and communities, and translates more broadly to poverty reduction (Goldie 2008).

What assumptions influenced the estimated health benefits and cost-effectiveness of vaccination?

Influential uncertainties include the duration of immunity, efficacy in settings with high HIV prevalence, and magnitude of herd immunity. Estimated finance requirements and cost-effectiveness are influenced by vaccine price and programmatic costs (e.g., delivery and vaccine support). Compared with childhood vaccines, cost-effectiveness of HPV vaccination is disproportionately influenced by discounting because future cervical cancer deaths prevented occur decades after vaccination costs are paid, while in vaccinated children (e.g., rotavirus) health and economic outcomes are in close temporal proximity.

As we have reported in all studies, the synergies between vaccination and screening allow for a greater benefit than with either alone, but equally important – *both young and older women benefit.* In addition, since there is uncertainty in both the projected vaccination impact *and* projected screening benefit, the magnitude of uncertainty in the projected benefit of both together is reduced.

Country	Cancer reduction: spectrum of analyses conducted with multiple models (Goldie 2008, Diaz 2008, Kim 2008, Campos 2011)				
	Vaccination Excel companion model 100% coverage	Vaccination Excel companion model 70% coverage	Vaccination Microsimulation model 70% coverage	Screening 2x/lifetime Microsimulation model 70% coverage	Screen 3x/lifetime + Vaccination Microsimulation model 70% coverage
India	73.9%	51.7%	44% (28-57%)	21% - 54%	57%
Kenya	79.2%	55.4%	36% (28-49%)	18% - 52%	49%
Mozambique	78.7%	55.1%	44% (36-51%)	19%	55%
Tanzania	72.5%	50.8%	42% (29-56%)	21% - 39.5%	54% - 68%
Uganda	76.7%	53.7%	44% (37-55%)	20%	56%
Vietnam	70.6%	49.4%	51%*	20.4% - 33.3*	59.3% - 68.2%
Zimbabwe	76.3%	53.4%	45% (32-54%)	21%	57%

India	Lower bound screening: 70% coverage for screen, vax; 1-visit VIA or 3-visit cyto; screen + vax: 2-visit HPV Upper bound screening: 100% coverage for screen, 1-visit HPV Excel model: 100% coverage: 205,501 cases & 164,401 deaths averted; 70% coverage: 143,851 cases & 115,081 deaths averted
Kenya	Lower bound screening: 70% for screen, vax; 15% attrition rate; 2-visit HPV; screen + vax: 1-visit HPV Upper bound screening: 100% coverage for screening, 1-visit HPV Excel model: 100% coverage: 8,805 cases & 7,044 deaths; 70% coverage: 6,164 cases & 4,931 deaths averted
Mozambique	Lower bound screening: 70% coverage for screen, vax; 15% attrition rate; 1-visit HPV; screen + vax: 2-visit HPV Excel model: 100% coverage: 3,759 cases & 3,007 deaths averted; 70% coverage: 2,631 cases averted & 2,105 deaths averted
Tanzania	Lower bound screening: 70% coverage for screen, vax; 15% attrition rate; 2-visit HPV; screen + vax: 2-visit HPV Upper bound screening: 100% coverage for screening; 1-visit HPV Excel model: 100% coverage: 21,222 cases & 16,977 deaths averted; 70% coverage: 14,855 cases & 11,884 deaths averted
Uganda	Lower bound screening: 70% coverage for screen, vax; 15% attrition rate; 1-visit HPV; screen + vax: 1-visit HPV Excel model: 100% coverage: 11,602 cases & 9,282 deaths averted; 70% coverage: 8,121 cases & 6,497 deaths averted
Vietnam	Lower bound screening: 70% coverage for screen, vax; screen + vax: cyto 3x/lifetime in HCMC Upper bound screening: HPV 3x/lifetime in Hanoi Excel model: 100% coverage: 12,801 cases & 10,240 deaths averted; 70% coverage: 8,960 cases & 7,168 deaths averted *national average = 51% reduction; ~33%-65% (Hanoi), 39%-61% (HCMC)
Zimbabwe	Lower bound screening: 70% coverage for screen, vax; 15% attrition rate;1-visit HPV; screen + vax: 1-visit HPV Excel model: 100% coverage: 4,032 cases & 3,266 deaths averted; 70% coverage: 2,822 cases & 2,258 deaths averted

Eastern Africa: Kenya, Mozambique, Tanzania, Uganda

Provided (a) the cost per vaccinated girl was equal to, or below I$10, vaccination was less than I$500 per YLS, and was more effective and had lower cost-effectiveness ratios than screening alone; and (b) provided the cost per vaccinated girl was equal to, or below I$25, vaccination was less than each country's per capita GDP, and was more effective and had more attractive cost-effectiveness ratios than screening alone. If vaccination is not available because a woman is over the age of 30 and therefore eligible only for screening, or because the price per dose exceeds $5-8, or because global support and financing for the vaccine is not available for countries, then screening with a rapid HPV DNA test, allowing for a one-visit or two-visit strategy, applied three times per lifetime between ages 30 and 50, would be cost-effective in all four countries (Campos 2011).

Synergies - Vaccination and Screening

Strategies that utilize both adolescent vaccination and screening of women between 30 and 45, assuming equivalent coverage rates, are generally more effective than either approach alone, but their cost-effectiveness is sensitive to vaccine price. While the cost-effectiveness ratios of adding enhanced screening of adult women to vaccination of pre-adolescent girls are higher, these strategies provide greater benefits, and in all analyses we identify strategies that would be considered cost-effective.

Thailand

A combined strategy of pre-adolescent vaccination (at 80% coverage) and HPV DNA testing five times per lifetime, starting at age 35 years, had a cost-effectiveness ratio less than the GDP per capita (I$8100), provided the cost per vaccinated girl was I$200 or less. At vaccine costs of up to I$50, strategies combining pre-adolescent vaccination with screening using a one-visit VIA two, three, or five times per lifetime were <I$3000 per YLS; the combined strategy of vaccination and HPV DNA testing five times per lifetime yielded the highest cancer reductions, costing I$6380 per YLS. Using a lower threshold of 100 000 baht (approximately I$3340), vaccination combined with VIA screening five times per lifetime would be the most effective strategy, provided the cost per vaccinated girl was <I$50; at higher vaccine costs, screening alone with HPV testing five times per lifetime would be optimal (Sharma 2012).

Brazil

When the cost per vaccinated girl was I$25, vaccination plus screening at ages 35, 40, and 45 ranged from I$200 to I$700 per YLS depending on the choice of screening test (e.g., 3-visit cytology or 2-visit HPV DNA testing); these cost-effectiveness ratios are less than Brazil's per capita GDP. A combined vaccination and screening strategy, at I$75, I$100, and I$450 per vaccinated girl, using 2-visit HPV DNA testing was I$1,100, I$1,700, and I$9,600 per YLS, respectively, compared to screening alone. A combination strategy of adolescent vaccination followed by screening women three times per lifetime would be deemed cost-effective as long as vaccine costs were less than I$ 100 per woman vaccinated (Goldie 2007).

Peru

Enhanced screening in adult women combined with pre-adolescent vaccination had incremental cost-effectiveness ratios lower than per capita GDP – and would be considered cost-effective. Even at a cost per vaccinated girl of $72.48 ($20 per dose), the cost of pre-adolescent vaccination added to the current standard screening was approximately $1,300 per YLS. (Kim 2007).

Argentina, Chile, Colombia, Mexico

As the cost per vaccinated girl exceeds I$100, vaccination plus screening (at ages 35, 40 and 45) dominates vaccination alone. For example, in Mexico, a combined vaccination and screening strategy, at I$75, I$100, and I$360 per vaccinated girl, using 2-visit HPV DNA testing is I$1,530, I$1,780, and I$7,070 per YLS, respectively, compared to the next best strategy (Goldie 2008).

Eastern Africa: Kenya, Mozambique, Tanzania, Uganda

If the cost per vaccinated girl was between I$10 and I$25, vaccination followed by HPV DNA testing would be cost-effective. For vaccine costs at or below I$25 per vaccinated girl, preadolescent vaccination followed by screening with one-visit HPV DNA testing at age 35 was associated with a cost per YLS ranging from I$740 (Tanzania) to I$2090 (Kenya). At I$200 per vaccinated girl, adolescent vaccination followed by screening with one-visit HPV DNA testing at age 35 was associated with a cost per YLS ranging from I$5610 (Tanzania, Uganda) to I$15,000 (Kenya) – beyond the per capita GDPs for the individual countries (Campos 2011).

India

Assuming 70% coverage, at a cost per vaccinated girl of I$10, pre-adolescent vaccination followed by screening three times per lifetime using either VIA or HPV DNA testing, would be considered cost-effective. Vaccination and screening three times per lifetime with VIA was I$290 per YLS. As the cost per vaccinated girl exceeded I$10, vaccination alone was no longer more efficient than screening alone, yet combined strategies remained cost-effective: the incremental cost-effectiveness ratio for preadolescent vaccination followed by screening in adulthood three times per lifetime varied from I$340 per YLS at I$20 per vaccinated girl, to I$1920 per YLS at I$75 per vaccinated girl. At a vaccine price per dose of approximately $100, vaccination was dominated by screening alone, with vaccination combined with single-visit VIA exceeding $7000 per YLS (Diaz 2008).

Vietnam

Assuming 70% coverage, only when the cost per vaccinated girl was low (i.e., <I$25) was vaccination combined with screening (three times per lifetime or every 5 years with either cytology or HPV DNA testing) favored in both regions (e.g., Hanoi in the North and Ho Chi Minh City in the South); at high costs per vaccinated girl (i.e., >I$100), screening alone was most cost-effective. In Hanoi, at a cost of I$10 or I$25 per vaccinated girl, vaccination combined with screening every 5 years ranged from I$1250 to I$2180 per YLS (with cytology) to I$6620 per YLS (with HPV DNA testing). Results in the South followed a similar trend, but because of its higher cancer risk, cost-effectiveness ratios were more attractive than in the North. When using the per capita GDP (I$2000) threshold, the optimal strategy in the North at a cost of I$10 per vaccinated girl was combined vaccination and cytology screening every 5 years; at I$25 per vaccinated girl or higher, strategies involving vaccination were no longer optimal, and cytology screening alone every 5 years was most cost-effective. In the South, the cost at which the optimal strategies shifted away from vaccination was much higher; provided the cost per vaccinated girl was less than I$100, combined vaccination and HPV DNA testing every 5 years was the optimal strategy, while above I$100, HPV DNA testing every 5 years without vaccination was the most cost-effective strategy. At a lower cost-effectiveness threshold (50% per capita GDP), strategies including vaccination were no longer attractive between I$25 and I$50 per vaccinated girl (Kim 2008).

SUMMARY

Total avertable burden with either vaccination or screening depends on the effectiveness of the intervention, the quality of delivery and coverage achieved with the intervention, and the size of the population that will benefit. Pre-adolescent HPV vaccination at high coverage is more effective than an individual strategy of cervical cancer screening of adult women once or twice per lifetime. If the cost of vaccination is less than $25 per fully vaccinated girl (~$5 per dose), inclusive of three doses, administration, FOB, wastage, and vaccine support and program delivery costs), then, for GAVI eligible (or formerly eligible) countries, pre-adolescent HPV vaccination is more cost-effective than an individual strategy of cervical cancer screening of adult women once or twice per lifetime. There is a synergistic role for both screening and vaccination in global cervical cancer prevention, yielding a greater benefit than with either alone, although cost-effectiveness is affected by the relative cost of delivering and paying for the vaccine, and the comparative benefits achieved with screening. Finally, while there is uncertainty in the projected impact of both vaccination and screening, the magnitude of uncertainty in the projected benefit of both strategies together is reduced.

Future directions

Ongoing research can enhance our analyses by refining estimates of vaccine efficacy, the need for and cost of booster doses, and the feasibility of vaccinating girls who are sexually naive. Incorporating data on financial requirements necessary for social mobilization and an education campaign for a new vaccine (e.g., PATH demonstration projects; Gardasil Access Program), allows economic evaluations of alternative modes of vaccine delivery and strategic approaches to scaling-up. Still unknown are the comparative costs of different vaccine formulations, such as a reduced number of required doses, or whether vaccination could be given at an earlier age with other vaccines (e.g., at school entry).

Policy implications

Given the efforts to leverage new resources for immunization through global vaccine financing initiatives, these results provide a contextual basis for immediate HPV vaccination, especially of the poorest women in developing countries. Vaccines are considered cost-effective health interventions yet policy-makers wishing to introduce a new vaccination program face multiple challenges: financial constraints, difficult choices among the range of vaccines available (e.g., rotavirus, pneumoccocal, HPV), and multiple competing priorities (e.g., new vaccine introduction versus existing immunization programs versus scale-up efforts). Decision makers must consider neglected outcomes alongside the challenges of financing HPV vaccine introduction. A delay in HPV vaccine introduction by GAVI may in turn affect other donor support for HPV vaccine introduction and will certainly result in lost lives.

HPV vaccination is recommended for girls ages 9 to 12, representing both a new population for vaccination and an opportunity to reach girls prior to sexual activity, thereby improving sexual and reproductive health. Beyond the reduction in cervical cancer, HPV vaccination offers a chance to provide other services targeted to adolescents, such as HIV prevention efforts, tetanus immunization, etc. Additionally, HPV vaccination could serve as a catalyst for integration between reproductive health and cancer control activities to achieve a reduction in cervical cancer. In this way, this research contributes to fulfillment of UN Millennium Development Goal #5, to improve maternal health, by preventing unnecessary deaths among women.

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