Mathematical Models of Cervical Cancer Prevention in the Asia Pacific Region

Sue J. Goldie, Mireia Diaz, Sun-Young Kim, Carol E. Levin, Hoang Van Minh, Jane J. Kim

Program in Health Decision Science, Department of Health Policy and Management, Harvard School of Public Health, Boston, MA, USA
Unit of Infections and Cancer (UNIC), Cancer Epidemiology Research Program (CERP), Catalan Institute of Oncology, L’Hospitalet de Llobregat, Barcelona, Spain
PATH, Seattle, WA, USA
Health Economics Department, Hanoi Medical University, No 1, Ton That Tung, Dong Da, Hanoi, Vietnam

Keywords:
- Mathematical model
- HPV
- Cost-effectiveness
- Asia Pacific

Using population-based and epidemiologic data for 25 countries in Asia (22 GAVI-Alliance eligible countries, Thailand, China and Japan), a model-based approach was used to estimate averted cervical cancer cases and deaths, disability-adjusted life years (DALYs) and incremental cost-effectiveness ratios ($/DALY averted) for vaccination of young adolescent girls against human papillomavirus (HPV) types 16 and 18. Absolute reduction in lifetime cancer risk varied between countries, depending on incidence, proportion attributable to HPV-16 and -18, and population age-structure; for example, with 70% coverage, cancer reduction was 57% in Indonesia, whereas in Cambodia, it was 49%. Screening of women over age 30 three times per lifetime, after vaccinating them as pre-adolescents, is expected to provide an additional 20% to 30% mortality reduction. Of the 22 GAVI-Alliance eligible countries, India, Bangladesh, Vietnam and Indonesia account for 87% of the total DALYs averted. Assuming a cost per vaccinated girl of $10 ($2 per dose), the cost per DALY averted is less than $250 in 18 of 22 countries. Assuming a cost per vaccinated girl of $25, the cost per DALY averted is $1,360 in China compared with $250 in Thailand, reflecting the greater number of girls that need to be vaccinated to prevent a death from cervical cancer in China. Vaccine price has an even greater effect on predicted affordability. For the 22 GAVI Alliance-eligible countries, vaccinating 5 consecutive birth cohorts at 70% coverage would cost over US $500 million versus almost US $1.3 billion at per dose costs of $2 and $5, respectively. Including China and Thailand would add US $251 million to US $1.4 billion at per dose prices of $2 and $12.25, respectively. In the countries we assessed, vaccination of young adolescent girls against HPV-16 and -18 could be very cost-effective if the cost per vaccinated girl is less than $10–$25; for it to be affordable, however, even with financing assistance, vaccine prices may need to be even lower.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Over 250,000 incident cases of cervical cancer [1] occur in the Asia Pacific region each year, accounting for more than half of the world’s burden. With more than one billion women over the age of 15 [2] and epidemiological differences between and within countries, the region presents a challenge for cervical cancer prevention efforts. For example, age standardized incidence rates (ASR) of cervical cancer range from 2.4 per 100,000 person-years at risk (PYR) in Jiashan, China to 28.9 in Chiang Mai, Thailand. Within India, age-adjusted incidence rates range from 9.4 in Trivandrum to 28.0 per 100,000 PYR in Chennai [3]. Similar to cancer incidence, there is variation in the prevalence of human papillomavirus (HPV) [4]. For example, in Vietnam, based on a population-based random sample of married women, HPV prevalence was five times higher in Ho Chi Minh City (10.9%) in the South of the country, than in the Northern capital of Hanoi (2.0%) [5]. While the majority of cancers are attributable to HPV types 16 and 18, types 58 and 52 are more prevalent among cancer cases in Asia and the Pacific than in other regions of the world [6].

While cervical cancer screening has been implemented in some of the wealthier countries in the Asia Pacific region (Australia, Japan, New Zealand, Singapore, and South Korea), most poor countries have been unable to sustain a scaled-up cytology-based program that relies on repeated screening at frequent intervals, multiple follow-up clinic visits for women with abnormal cytology (e.g., for screening, diagnostic testing, and treatment), and sophisticated laboratory requirements [7]. That being said, there have been efforts in this region to make cervical cancer prevention possible. For example, although the long-term impact on cancer incidence is not yet known, a population-based screening program in Ho Chi Minh City and a pilot screening project in Hanoi, have demonstrated...
the ability to introduce cytology screening within the context of a five-year program, starting at age 30 [8]. In India, alternatives such as HPV DNA testing and visual inspection with acetic acid (VIA) have been demonstrated to be acceptable and promising approaches when embedded in a screening protocol that requires fewer visits and simpler treatment protocols that can be delivered by nurses [9–12]. These strategies, less dependent on existing health system infrastructure and more closely linking screening and treatment, are expected to be cost-effective [13].

With the availability of vaccines against HPV types 16 and 18, there are new opportunities for primary prevention to add to ongoing efforts to identify feasible secondary prevention strategies. However, the decision for any country to add a new vaccine to national immunization programs requires careful assessment of the relative value of the vaccine compared with alternative uses of resources (i.e., cost-effectiveness) and its affordability (i.e., budgetary impact). Decision makers will need to consider (1) the expected avertable burden with current HPV vaccines given regional variation in HPV types and different levels of cervical cancer risk; (2) the likelihood of cultural acceptability of a vaccine against a sexually-transmitted infection; and (3) the relative feasibility of achieving coverage in young adolescent girls. Country-specific decisions will likely be complicated further by variation in factors such as public health capacity (e.g., adequate health personnel, functional health system), non–health sector infrastructure such as paved roads, and the proportion of the population in rural and/or hard-to-reach areas (Table 1) [14,15,16].

Predicting the future effectiveness of a public health prevention program is challenging, particularly when the course from infection to disease spans multiple decades, when new technologies are built upon existing interventions and when resource constraints limit the range of reasonable choices [16,17]. By systematically synthesizing the available health and economic information, the use of models in a decision analytic framework can provide early insight into what strategies are most promising and are likely to be cost-effective and affordable [16–18]. Recent published reviews have identified those elements of modeling and cost-effectiveness analysis most relevant to cervical cancer control evaluation [16–20]. This article presents information available from analyses assessing the cost-effectiveness of pre-adolescent HPV-16/18 vaccination in select countries in Asia.

### 2. Methods

#### 2.1. Analytic overview

A model-based approach was used to synthesize the available evidence and estimate averted cases of invasive cancer, cancer deaths, disability-adjusted life years (DALYs) averted and incremental cost-effectiveness ratios (ICERs) averted for HPV-16/18 vaccination of young adolescent girls under different cost, coverage and vaccine efficacy assumptions. For selected countries (e.g., India and Vietnam), adequate epidemiological data were available to empirically calibrate a complex natural history model of HPV and cervical cancer using previously published methods [21–24], and the cost-effectiveness of strategies including both vaccination and screening was evaluated. For countries without the extensive data required for a complex model (i.e., China, Thailand, Japan and 22 GAVI-eligible countries in Asia), a simple Excel-based model was developed to generate health and economic outcomes of pre-adolescent vaccination at the population level.

Consistent with recommended guidelines for economic evaluation, a societal perspective is adopted and future costs and benefits are discounted by 3% annually [14,25–27]. Costs are presented in 2005 international dollars (I$) for the cost-effectiveness analysis to allow for broad comparison across countries, while projections of financial resource requirements are also presented in local currency and US dollars. The performance of alternative strategies is described using incremental cost-effectiveness ratios, defined as the additional cost of a specific strategy, divided by its additional benefit, compared with the next best strategy. Sensitivity analyses assess how uncertain parameters and assumptions might influence results.

#### 2.2. Empirically calibrated models

A series of models has been previously described [21–24] including an individual-based stochastic model of cervical carcinogenesis that includes all high-risk HPV types and a dynamic model of sexual transmission of HPV-16 and -18 infections between males and females [21,23,24]. A likelihood-based approach was used to calibrate these models to country-specific empirical data, such as age-specific prevalence of HPV, age-specific incidence of cervical cancer, and HPV type distribution in women with cancer precursors and cervical cancer. Good-fitting sets of parameters were identified based on a formal comparison of the quality of model fit to empirical data. This process determined the sample of parameter sets ultimately used in country-specific analyses.

Details of the model parameterization process, including the calibration methods, can be found in previous publications [21–24]. The epidemiological data used to establish calibration targets and their 95% confidence intervals, and selected good-fitting parameter sets are provided in the Appendix. Fig. 1 shows examples of model output from a sample of good-fitting parameter sets com-
Fig. 1. Model calibration: Cervical cancer incidence and HPV type distribution in cancer in India and Vietnam. (Upper Panel) Cervical cancer incidence in India. Shown are selected model outputs for India from good-fitting parameter sets compared with the 95% confidence intervals of empirical data for age-specific cancer incidence rates [3]. Bold orange lines represent the 95% confidence intervals of the empirical data. See Appendix for additional results and data sources. (Middle Panel) Cervical cancer incidence in Vietnam. Shown are selected model outputs for Hanoi, Vietnam from good-fitting parameter sets compared with the 95% confidence intervals of empirical data for age-specific cancer incidence rates [3]. Bold orange lines represent the 95% confidence intervals of the empirical data. See Appendix for additional results. (Lower Panel) HPV type distribution in cancer in Vietnam and India. Shown are selected model outputs for India and Vietnam (Hanoi) from good-fitting parameter sets compared with the 95% confidence intervals of empirical data type for distribution of HPV within cancer [6,29–34]. Bold orange lines represent the upper and lower bound of the empirical data. See Appendix for additional details.
pared with the 95% confidence intervals of empirical data, including age-specific cancer incidence rates from the International Agency for Research on Cancer [3] for India (Upper Panel) and for Hanoi, Vietnam (Middle Panel); and type-distribution of HPV in cancer based on published data [6,28–32] (Lower Panel). Additional results of the calibration exercises are available in the Appendix.

In this article, selected results are generated from three models empirically calibrated to Southeastern India, North Vietnam, and South Vietnam [33–35]. These models are able to simulate both vaccination of young adolescent girls and screening of adult women, and are used to project health and economic outcomes associated with strategies that include one or both interventions. To explicitly incorporate the effect of parameter uncertainty, cost-effectiveness analyses are conducted with a subset of good-fitting parameter sets for each country. Results are reported as a mean and range of outcomes, while incremental cost-effectiveness ratios are reported as the ratio of the difference in mean costs divided by the difference in mean effects of one strategy compared with the next best strategy across the good-fitting parameter sets.

The following assumptions pertain to the strategies assessed: (1) vaccination occurs prior to sexual debut (between ages 9 and 12 years), and successful completion of three doses is assumed to provide full, life-long protection against HPV-16 and -18 infections; (2) vaccinated recipients continue to be susceptible to infection with other high-risk HPV types not included in the vaccine; and (3) screening strategies may differ by the initial screening test (cervical cytology, HPV DNA testing, or visual inspection), frequency (once, twice, or three times per lifetime), targeted ages (ages 35, 40, or 45), and number of visits required to receive initial test results, undergo diagnostic confirmation, and be treated if appropriate. The initial screening visit occurs between ages 30 and 35, and additional screenings occur at 5-year intervals. Additional assumptions related to screening protocols have been previously published [13,21].

2.3. Simple Excel-based model

The Excel-based model was developed as a companion to the complex empirically calibrated micro-simulation model described above, to serve as a simple tool to project the main features of the potential impact of HPV vaccines at the population level in settings where data are limited. The model is constructed as a static cohort simulation model based on a structure similar to a simple decision tree (Appendix), and is programmed using Microsoft® Excel and Visual Basic for Applications, 6.3 (Microsoft Corporation, Redmond, WA). A cohort of girls is tracked starting at a target age (9 years) through their lifetimes, comparing health and cost outcomes with and without HPV vaccination programs. Unlike a more complex empirically calibrated model, this simple model does not fully simulate the natural history of HPV infection and cervical cancer. Instead, the Excel-based model relies on several simplifying assumptions (e.g., duration of disease, stage distribution of cancer, ratio of mortality to incidence), which are based on insights from analyses performed with the micro-simulation model.

Using the best available data on age-specific incidence of cervical cancer and HPV-16/18 type distribution in cancer, and assumed vaccine efficacy and vaccination coverage, the model estimates reduction in cervical cancer risk at different ages. By applying the reductions to country-specific, age-structured populations incorporating background mortality [2,36], the Excel-based model further calculates cases of averted cervical cancer and cancer deaths, and transforms them into final forms of health outcomes, years of life saved (YLS) and DALYs averted. DALYs are calculated using the standard approach by the Global Burden of Disease (GBD) study [37] but are not age-weighted. The model tracks program costs and direct medical treatment costs over the course of the simulation. The main final outcome measure is incremental costs (expressed in 2005 I$) per DALY averted.

For analyses included in this article, the model is applied to 22 GAVI-eligible countries (3 countries in Central Asia, 2 countries in Eastern Asia, 7 countries in Southern Asia, 4 countries in Western Asia, 6 countries in South-eastern Asia), as well as Japan and China, both in Eastern Asia, and Thailand in Southeastern Asia. Selected assumptions for China, Japan and Thailand include: (1) the average mean duration of time between development of invasive cancer and death is 6 years (varied from 2–10 years); (2) cancer stage-distribution in an unscreened population is 30% local and 70% regional and distant; and (3) ratio of mortality to incidence approximates 60% (varied from 40%–90%). For the 22 GAVI-eligible countries the ratio of mortality to incidence is assumed to be worse (80%, range 60%–90%), and cancers detected on the basis of symptoms in an unscreened population are at regional and distant stages.

Vaccination strategies assume three doses are required, and are distinguished by age of vaccination, coverage level, and vaccine efficacy. The base case assumes 70% coverage to estimate the potential avertable burden without making assumptions about the differential operational capacity to deliver the vaccine. Lower coverage rates are evaluated in sensitivity analyses and are also reported elsewhere [38]. For analyses conducted with the Excel-based model, screening is not considered. Alternatives to these assumptions are examined in sensitivity analysis.

Age-specific cervical cancer incidence rates are provided in the Appendix. Cervical cancer incidence data were hierarchically ranked such that data from national registries in Cancer Incidence in Five Continents (CI5C) [3] were used if available, followed by estimates from Globocan [1]. If more than one registry was available from a country, a pooled estimate was used. The proportion of cancer attributable to HPV-16 and -18 was estimated using studies included in a published meta-analysis [32] and adjusted when data were not available for cases with multiple HPV types (Appendix). When country-specific information was not available, HPV type distribution data from countries within the same region were pooled. Demographic estimates for age-specific population size (in 1-year intervals) and age-specific life expectancy (grouped in 5-year intervals) were from United Nation’s (UN) World Population Prospects 2004 and 2006 data and 2004 World Health Organization (WHO) life tables, respectively [2,36,39].

2.4. Cost estimation

Since the HPV vaccine price for resource-poor countries is not yet known, nor are the programmatic or delivery costs, a composite value is defined as the ‘cost per vaccinated girl’ and includes vaccine costs, wastage of vaccine and supplies, freight and supplies, administration, immunization support and programmatic costs [14,40–43]. Analyses are conducted using a total cost per vaccinated girl (I$) of $5, $10, $25, $50, $75, $100, $200, $300, and $360, which implies a cost per dose (US $) of $0.55, $2, $5, $12.25, $19.50, $26.75, $54.25, $83.23, and $98, respectively. For example, for a composite cost of $150 per vaccinated girl, an approximate breakdown of component costs would include: (1) three doses of vaccine at US $2.00 each; (2) wastage of US $0.90; (3) freight and supplies of US $0.59; (4) vaccine administration of $0.50; and (5) immunization support and programmatic costs of $82.00.

Other costs are based on published studies and previously described approximation methods, which leverage available data in select countries and extrapolate to other countries based on per capita Gross Domestic Product (GDP) and other indicators [21,44].
Mean reductions in lifetime risk of cancer predicted with two models. The mean reduction (thick grey line) in lifetime risk of cervical cancer with HPV-16/18 vaccination of 70% of a 12-year-old birth cohort of girls generated using empirically calibrated models for Southeastern India and North and South Vietnam. The range (orange rectangles) represents the minimum and maximum reductions achieved for each strategy using the micro-simulation model. The stars indicate the average reduction predicted with the Excel-based companion model.

For the selected countries in which screening strategies are analyzed, screening, diagnosis and treatment costs are categorized into direct medical costs (e.g., staff, supplies, equipment, and specimen transport), women’s time costs (time spent traveling, waiting and receiving care), transportation costs and programmatic costs. Time estimates for various clinical services, for the number and type of follow-up visits and for hospitalization days are based on previously published assumptions [13,21]. Additional detail on cost assumptions are provided in the Appendix.

3. Results

3.1. Comparative validation: North Vietnam, South Vietnam, and Southeastern India

Shown in Fig. 2 are the comparative results generated using models for Hanoi and Ho Chi Minh City, Vietnam, and Southeastern India, assuming a vaccination coverage rate in young adolescent girls of 70%. While the expected mean reduction in lifetime risk of cancer varies between countries, reflecting epidemiological differences in the proportion of HPV-16- and -18-related cancer, the average reduction in cancer predicted with the Excel-based model falls within the bounds for each site. Similarly, the cost-effectiveness ratios generated using both models for pre-adolescent vaccination alone differ by less than 5% (data not shown).

3.2. Cost-effectiveness results for empirically calibrated models of North and South Vietnam, and Southeastern India

Results are shown in Table 2 for selected analyses in which the cost per vaccinated girl is varied in North (Hanoi) and South (Ho Chi Minh City) Vietnam, and Southeastern India. With vaccination of young adolescent girls alone, the mean reduction in lifetime risk of cancer ranges from 44% in India to 51% in Vietnam. Adding a program of screening adult women three times per lifetime to pre-adolescent vaccination provides mean reductions in cancer incidence ranging from 56% (India) to 68% (Vietnam) (data not shown).

For North and South Vietnam, results are shown in Table 2 (upper section) for screening adult women with 3-visit cytology every 5 years, vaccination of young adolescent girls alone, and preadolescent vaccination plus screening using two-visit HPV DNA testing every 5 years. Assuming 70% coverage, screening alone ranges from $20 per YLS in Ho Chi Minh City to $370 per YLS in Hanoi, reflecting the higher burden of disease in the former location. In Hanoi, at vaccine costs exceeding $10 per vaccinated girl, vaccination alone is dominated, and at $50 per vaccinated girl, vaccination plus screening is $5,840 per YLS. As vaccine costs increase, the incremental cost-effectiveness ratios for pre-adolescent vaccination plus screening increase dramatically when compared to screening alone: at a cost (US $98 per dose) nearing the current price of the vaccine, the cost per YLS exceeds $35,000. In Ho Chi Minh City, a similar pattern emerges, however all cost-effectiveness ratios are more attractive. At $10 per vaccinated girl, vaccination alone is $30 per YLS and vaccination followed by screening is $240 per YLS. At a cost of nearly US $100 per dose, the cost of the combined strategy per YLS is $7,500.

For India, results are shown in Table 2 (lower section) for strategies that include vaccination of young adolescent girls and screening of adult women three times per lifetime with either VIA or rapid HPV DNA testing, assuming 70% coverage. The two screening tests are considered independently. First, assuming VIA is the only screening test that is feasible, pre-adolescent vaccination alone is cost-saving at a cost of US $2 per dose and pre-adolescent vaccination plus screening of adult women with VIA three times per lifetime is $290 per YLS. A second analysis assumes point of care rapid HPV DNA testing is the only feasible screening strategy, and the incremental ratio for screening and pre-adolescent vaccination is $710 per YLS. According to a cost-effectiveness threshold of per capita GDP, these would both be considered very cost-effective. In both analyses, at US $2 per dose ($10 per vaccinated girl), screening alone is never as cost-effective as pre-adolescent vaccination alone; in contrast, at vaccine costs over US $5 per dose ($25 per vaccinated girl), pre-adolescent vaccination alone is no longer cost-effective. Additional results are available in forthcoming publications [33–35,45,46].

3.3. Sensitivity analysis for empirically calibrated models

Previous analyses, including those in Vietnam and India, have shown that the comparative performance of different cer-
<table>
<thead>
<tr>
<th>Country</th>
<th>Strategy Description</th>
<th>Cost per Vaccinated Girl (US$)</th>
<th>ICERs (US$/YLS)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vietnam</td>
<td>$10 (US $2 per dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$50 (US $12.25 per dose)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>$360 (US $98 per dose)</td>
<td></td>
</tr>
<tr>
<td>Hanoi</td>
<td>Screening alone with 3-visit cytology (adult women, every 5 years)</td>
<td>$10 (US $2 per dose)</td>
<td>370</td>
</tr>
<tr>
<td></td>
<td>Vaccination alone (girls vaccinated with three doses before age 12)</td>
<td>$10 (US $2 per dose)</td>
<td>1,200</td>
</tr>
<tr>
<td></td>
<td>Vaccination (by age 12) and screening with 2-visit HPV DNA testing (every 5 years)</td>
<td>$10 (US $2 per dose)</td>
<td>2,540</td>
</tr>
<tr>
<td>Ho Chi Minh City</td>
<td>Screening alone with 3-visit cytology (adult women, every 5 years)</td>
<td>$10 (US $2 per dose)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Vaccination alone (girls vaccinated with three doses by age 12)</td>
<td>$10 (US $2 per dose)</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Vaccination (by age 12) and screening with 2-visit HPV DNA testing (every 5 years)</td>
<td>$10 (US $2 per dose)</td>
<td>240</td>
</tr>
<tr>
<td>India</td>
<td>Southeastern India, Visual inspection with acetic acid (VIA)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Screening alone with 1-visit VIA (3 × per lifetime at ages 35, 40 and 45)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Vaccination alone (girls vaccinated with three doses before age 12)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Vaccination (by age 12) and screening with 1-visit VIA (3 × per lifetime at ages 35, 40 and 45)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Southeastern India, Rapid HPV DNA test</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Screening alone with 1-visit rapid HPV DNA (3 × per lifetime at ages 35, 40 and 45)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Vaccination alone (girls vaccinated with three doses before age 12)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
<tr>
<td></td>
<td>Vaccination (by age 12) and screening with 1-visit rapid HPV DNA (3 × per lifetime at ages 35, 40 and 45)</td>
<td>$10 (US $2 per dose)</td>
<td>dominated c</td>
</tr>
</tbody>
</table>

Notes:
- **C/S:** Cost-saving; **ICER:** Incremental cost-effectiveness ratio; **YLS:** Year of life saved. All strategies assume 70% coverage, and screening alone is compared to no cervical cancer prevention program.
- **b** ICERs represent the difference in mean costs divided by the difference in mean effects of one strategy compared to the next most costly strategy among non-dominated strategies across good-fitting parameter sets. The cost per vaccinated individual is assumed to include the cost of three doses, wastage, delivery, and programmatic components. Vaccination strategies assume three doses before age 12; vaccine has 100% efficacy against infection with types 16 and 18, and provides lifelong immunity. Screening strategies include 3-visit cytology testing, 2-visit HPV DNA testing, 1-visit VIA testing, or 1-visit HPV DNA testing with a rapid HPV DNA test. Details of each strategy are available elsewhere [13]. HPV DNA tests are assumed to differ by virtue of when results are available, with the rapid HPV DNA test allowing for 1 visit instead of 2 visits; both are assumed to have a baseline specificity of 0.84 and sensitivity of 0.90, and would only be considered feasible if available for $10.30 as previously assumed [13].
- **c** These strategies are either more costly and less effective, or less costly and less cost-effective, than alternative options, and are thus considered (strongly or weakly) dominated.
vical cancer prevention strategies depends on several factors [13,16,21,24,33–35]. For vaccination, the performance of different strategies, in terms of their relative effectiveness (i.e., reduction in incidence and mortality), is influenced by 1) the ability to achieve widespread coverage in young adolescent girls; 2) vaccine efficacy; and 3) the duration of vaccine protection. Kim J et al. [35] explored the influence of varying assumptions about vaccine efficacy and duration of vaccine-induced protection, on clinical and economic outcomes in a high-risk, unscreened region of Vietnam (Ho Chi Minh City). Varying vaccine efficacy (70% to 100%) and duration of protection (10 years to lifelong), the reduction in lifetime cancer risk and cost-effectiveness of vaccinating pre-sexually-active adolescent girls was projected at different levels of cost (I$5–I$150 per vaccinated girl) and vaccine uptake (25% and 75%). Assuming 100% efficacy, lifelong protection, and 75% uptake (coverage) the mean reduction in lifetime cancer risk was 50%; with vaccine-induced immunity of only 10 years, expected mean cancer reduction fell to 37%. With both waning immunity at 10 years and 70% efficacy, expected mean cancer reduction was only 25%. At I$5 per vaccinated girl (per dose cost of US $0.55), pre-adolescent vaccination was cost saving compared to no vaccination, provided efficacy was greater than 90% and lasted for more than 20 years. When the cost per vaccinated girl was doubled to I$10 (per dose cost of US $2), pre-adolescent vaccination exceeded I$100 per YLS when efficacy was less than 100% or duration was less than 10 years. When the cost per vaccinated girl was I$150 (per dose cost of US $40), pre-adolescent vaccination exceeded Vietnam’s 2005 per capita GDP (I$3,000).

As previously reported, the mean reduction in cervical cancer mortality with HPV vaccination, predicted by models, is influenced by uncertain assumptions [13,16,21,24]. For example, the benefits of vaccination might be greater than that reported in baseline analyses if currently available HPV-16/18 vaccines partially protect against other HPV types, if there are significant herd immunity effects, and if the vaccine reduces other HPV-16/18-associated cancers. The benefits could be lower than expected (at least in certain settings) if girls are vaccinated after sexual debut, if efficacy is lower in human immunodeficiency virus (HIV)-infected adolescents, and if there is an increase in prevalence of non-vaccine-targeted HPV types, and their associated pre-cancer and cancer. Cost-effectiveness results are slightly less favorable if the costs associated with invasive cervical cancer are reduced by 50% or if boosters are required for lifelong immunity.

While studies have been done to describe the relative sensitivity and specificity of HPV DNA testing, conventional cytology and VIA, the real world choice about which screening modality to implement is most influenced by the ability to conduct high quality screening, reliably follow-up abnormal results and deliver prompt treatment, and achieve high coverage in women above age 30. While an important advantage to HPV DNA testing is the negative predictive value (i.e., the probability of no disease given the screening test is negative), which allows for longer intervals between screening tests, VIA is currently less costly and provides immediate results, allowing for screening and treatment to conceivably occur in the same visit. With plausible changes in relative costs and test performance and the ability to obtain a same-day test result, the use of “rapid” HPV DNA testing could be equally attractive to VIA in terms of relative costs and cost-effectiveness. For some countries, cytology screening might be favorable if the test sensitivity is increased, costs are reduced, and a two-visit strategy without diagnostic confirmation is possible. Most importantly, regardless of specific test choice, analyses to date provide strong support for screening adult women one to three times per lifetime in addition to pre-adolescent vaccination.

3.4. Cost-effectiveness results (incremental cost per DALY averted) for the companion Excel-based model in 22 GAVI-eligible countries

Table 3 presents estimates of health outcomes and cost-effectiveness of HPV-16/18 vaccination of young adolescent girls (compared to no vaccination) for 22 GAVI-eligible countries, in terms of reduction in lifetime risk of cancer, DALYs averted (discounted at 3%) and incremental cost-effectiveness ratios (additional cost per DALY averted, expressed in 2005 I$). The number of avertable DALYs depended on a country’s population structure and size as well as epidemiological factors (cancer incidence and the proportion of cancer attributable to types 16 and 18). Countries with moderate cervical cancer incidence and large populations had more DALYs averted than those with high incidence and smaller populations. For example, at 70% coverage of a single birth cohort, approximately 10,900 DALYS were averted in Cambodia (ASR of 38.7) compared to nearly 80,000 in Indonesia (ASR of 15.7); four countries in the region – India, Bangladesh, Vietnam and Indonesia – accounted for about 87% of the total DALYs averted.

In Table 3, incremental cost-effectiveness ratios (I$ per DALY averted) are shown for three costs per vaccinated girl (I$10, I$25 and I$50, which correspond to a vaccine cost per dose (US $) of $2, $5 and $12.25, respectively). Assuming a cost of I$10 per vaccinated girl (US $2 per dose), the cost per DALY averted ranged from I$30 (India) to I$340 (Afghanistan); for 18 out of 22 countries, the cost per DALY averted was less than I$250. The cost-effectiveness estimates increased substantially with escalating vaccine prices.

3.5. Sensitivity analyses for the companion Excel-based model

Fig. 3 shows the influence of changing selected variables on cost-effectiveness, using India as an example. Analytic assumptions necessary for simplifying the model, such as duration of cancer prior to death and proportion of effectively treated cancer, were less influential on cost-effectiveness results than the discount rate and vaccine costs.

3.6. Cost-effectiveness and affordability for the companion Excel-based model

Fig. 4 (Upper Panel) collectively presents both projected incremental cost-effectiveness ratios and financial requirements for pre-adolescent HPV-16/18 vaccination programs in the 22 GAVI-eligible countries in Asia for per dose costs (US $) of $2, $5 and $12.25 (corresponding to I$10, I$25 and I$50 per vaccinated girl, respectively). According to the standard suggested by the Commission on Macroeconomics [47], which considers any intervention with an incremental cost-effectiveness ratio less than a country’s per capita GDP very cost-effective, the range of the incremental cost-effectiveness ratios shown in the figure suggests that pre-adolescent HPV vaccination programs would be considered very cost-effective. To provide insight into the impact of vaccination costs on affordability, for just 5 consecutive cohorts of girls, the financial requirements (US $) for pre-adolescent vaccination vary from over $500 million at US $2 per dose (I$10 per vaccinated girl) to over $3 billion at US $12.25 per dose (I$50 per vaccinated girl).

Fig. 4 (Lower Panel) presents the financial costs (US $) required to vaccinate 70% of 5 consecutive birth cohorts in India versus China, for per dose costs ranging from US $2 (I$10 per vaccinated girl) to US $83.25 (I$300 per vaccinated girl). At a per dose cost of US $26.75 (I$100 per vaccinated girl) costs for vaccinating 5 consecutive birth cohorts in China and India range between US $2.8 and US $
Table 3
Cost-effectiveness analysis of HPV-16/18 vaccination in 22 GAVI-eligible countries

<table>
<thead>
<tr>
<th>Country (cancer incidence ASR)</th>
<th>Reduction in lifetime risk of cancer (%)</th>
<th>DALYs averted</th>
<th>ICER ($/DALY averted)</th>
<th>ICER ($/DALY averted)</th>
<th>ICER ($/DALY averted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>I$10 per vaccinated girl</td>
<td>I$25 per vaccinated girl</td>
</tr>
<tr>
<td><strong>EMR Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yemen (8.0)</td>
<td>49.1</td>
<td>3,783</td>
<td>510</td>
<td>1,380</td>
<td>2,830</td>
</tr>
<tr>
<td>Afghanistan (6.9)</td>
<td>51.2</td>
<td>5,338</td>
<td>540</td>
<td>1,410</td>
<td>2,840</td>
</tr>
<tr>
<td>Pakistan (6.5)</td>
<td>51.2</td>
<td>21,801</td>
<td>500</td>
<td>1,430</td>
<td>2,970</td>
</tr>
<tr>
<td><strong>EUR Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyrgyzstan (21.6)</td>
<td>51.2</td>
<td>2,658</td>
<td>70</td>
<td>280</td>
<td>630</td>
</tr>
<tr>
<td>Georgia (17.5)</td>
<td>49.1</td>
<td>1,168</td>
<td>90</td>
<td>310</td>
<td>690</td>
</tr>
<tr>
<td>Armenia (16.8)</td>
<td>49.1</td>
<td>785</td>
<td>70</td>
<td>310</td>
<td>720</td>
</tr>
<tr>
<td>Uzbekistan (10.7)</td>
<td>51.2</td>
<td>7,460</td>
<td>200</td>
<td>590</td>
<td>1,240</td>
</tr>
<tr>
<td>Tajikistan (9.9)</td>
<td>51.2</td>
<td>1,938</td>
<td>260</td>
<td>710</td>
<td>1,450</td>
</tr>
<tr>
<td>Azerbaijan (8.2)</td>
<td>49.1</td>
<td>1,424</td>
<td>230</td>
<td>720</td>
<td>1,530</td>
</tr>
<tr>
<td><strong>WPR Region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cambodia (38.7)</td>
<td>49.4</td>
<td>10,872</td>
<td>50</td>
<td>210</td>
<td>470</td>
</tr>
<tr>
<td>Viet Nam</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hanoi (5.81)</td>
<td>49.4</td>
<td>10,884</td>
<td>450</td>
<td>1,200</td>
<td>2,450</td>
</tr>
<tr>
<td>Ho Chi Minh City (23.06)</td>
<td>49.4</td>
<td>43,686</td>
<td>70</td>
<td>250</td>
<td>570</td>
</tr>
<tr>
<td>Mongolia (18.0)</td>
<td>43.6</td>
<td>866</td>
<td>160</td>
<td>470</td>
<td>970</td>
</tr>
<tr>
<td>Lao PDR (36.8)</td>
<td>49.4</td>
<td>2,435</td>
<td>180</td>
<td>520</td>
<td>1,070</td>
</tr>
<tr>
<td><strong>SEAR region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India (30.7)</td>
<td>51.7</td>
<td>531,789</td>
<td>30</td>
<td>250</td>
<td>630</td>
</tr>
<tr>
<td>Bangladesh (27.6)</td>
<td>51.2</td>
<td>90,193</td>
<td>50</td>
<td>240</td>
<td>560</td>
</tr>
<tr>
<td>Bhutan (26.4)</td>
<td>51.2</td>
<td>1,457</td>
<td>60</td>
<td>250</td>
<td>570</td>
</tr>
<tr>
<td>Nepal (26.4)</td>
<td>51.2</td>
<td>18,235</td>
<td>70</td>
<td>270</td>
<td>600</td>
</tr>
<tr>
<td>Myanmar (24.6)</td>
<td>49.4</td>
<td>24,008</td>
<td>40</td>
<td>260</td>
<td>610</td>
</tr>
<tr>
<td>Korea, DR (17.2)</td>
<td>43.6</td>
<td>6,548</td>
<td>120</td>
<td>420</td>
<td>910</td>
</tr>
<tr>
<td>Sri Lanka (17.2)</td>
<td>51.2</td>
<td>5,878</td>
<td>80</td>
<td>370</td>
<td>850</td>
</tr>
<tr>
<td>Indonesia (15.7)</td>
<td>56.7</td>
<td>79,675</td>
<td>90</td>
<td>360</td>
<td>810</td>
</tr>
<tr>
<td>Timor Leste c</td>
<td>49.4</td>
<td>403</td>
<td>140</td>
<td>410</td>
<td>860</td>
</tr>
</tbody>
</table>

a ASR: Age standardised incidence rates (per 100,000 person-years at risk); DALY: Disability-adjusted life year; EMR: Eastern Mediterranean Region; EUR: European Region; ICER: Incremental cost-effectiveness ratio; I$: International dollars; SEAR: South-East Asian Region; WPR: Western Pacific Region. Incremental cost-effectiveness ratios are for a strategy of vaccinating 70% of a single birth cohort of 9-year-old girls in 2007 with a 100% effective vaccine at a cost of I$10, I$25, and I$50 (approximately US $2, $5 and 12.25 per dose) per vaccinated girl, compared to no vaccination. See Methods for further details.

b Estimates for ASR of cancer incidence are from GLOBOCAN [1], except in India and Vietnam where data were used from Cancer Incidence in Five Continents [3]. Estimates are provided to describe general comparative risk, but for the model we hierarchically ranked sources such that data from national registries in Cancer Incidence on Five Continents (CI5C) [3] were used if available, followed by estimates from Globocan [1]. See Methods and Appendix for details.

c Data not available.

Fig. 3. Selected results of sensitivity analyses (using companion Excel-based model, India). Using a representative example of India, shown is the impact of several one-way sensitivity analyses on the incremental cost-effectiveness ratio (I$/DALY averted, base case I$29 per DALY averted; dotted orange vertical line) for a cost per vaccinated girl of I$10. Orange horizontal bars represent the influence of changing variables and assumptions on the incremental cost-effectiveness ratio. DALY: Disability-adjusted life year; I$: International dollars.
Fig. 4. Cost-effectiveness and affordability, and financial costs to vaccinate 70% of 5 consecutive birth cohorts in India versus China.
(Upper Panel) Cost-effectiveness and affordability. Shown are the incremental cost-effectiveness ratios (cost I$ per DALY averted) associated with pre-adolescent vaccination alone, and the average financial costs (US$) for the 22 GAVI-eligible countries in Asia at prices costs per dose (US$) of $2, $5, and $12.25, corresponding to I$10, I$25, I$50 per vaccinated girl, respectively.
(Lower Panel) Financial costs to vaccinate 70% of 5 consecutive birth cohorts in India versus China. Shown are the financial costs required to vaccinate 70% of 5 consecutive birth cohorts in India versus China, for per dose prices costs (US$) ranging from $2 (I$10 per vaccinated girl) to $83.25 (I$300 per vaccinated girl). In India, there are 15 deaths averted per 1,000 vaccinated girls; in contrast, in China, there are just 5 averted per 1,000 vaccinated. DALY: Disability-adjusted life year; I$: International dollars.

$3.6 billion each. The difference in the magnitude of health benefits reflects, in large part, the difference in rates of cancer, while the difference in financial costs reflects the difference in population size (e.g., number of girls necessary to vaccinate). In India, there are 15 deaths averted per 1,000 vaccinated girls; in contrast, in China, there are just 5 averted per 1,000 vaccinated.

3.7. Cost-effectiveness results (incremental cost per DALY averted) for the companion Excel-based model in China, Thailand and Japan

Table 4 shows the incremental cost-effectiveness ratios (I$/DALY averted) for pre-adolescent HPV-16/18 vaccination (compared to no vaccination) for China, Thailand and Japan. Of these three countries, China accounts for the greatest number of DALYs averted (97,575) despite the relatively low ASR. The incremental cost-effectiveness ratios are shown assuming a cost per vaccinated girl (I$) of $25, $100, $300 and $430. At a cost per vaccinated girl of I$25, the cost per DALY averted is I$1,360 in China compared with I$250 in Thailand and I$430 in Japan, reflecting the greater number of girls that need to be vaccinated to prevent a death from cervical cancer in China than in the other two countries. For all three countries, ratios increase substantially as the cost of vaccination increases.

Using results from these three countries, the cost-effectiveness ratio is calculated using lifetime costs and benefits discounted at an annual rate of 3% (base case), and 6% (sensitivity analysis).
Incremental cost-effectiveness ratios calculated using lifetime costs and benefits discounted at 6% per annum (sensitivity analysis) are approximately 5- to 7-fold higher than those calculated using a discount rate of 3% (base case) (e.g., for China, costs per DALY averted are I$1,360 at 3% versus I$7,080 at 6% and a cost per vaccinated girl of I$25).

To illustrate the sensitivity of the cost-effectiveness ratio to the timing of benefits relative to the timing of costs, we also show ratios in which only the costs are discounted. For example, at I$100 per vaccinated girl, with standard discounting of costs and benefits (at 3% per year), the cost-effectiveness ratio is I$5,960 in China, I$1,550 in Thailand and I$2,690 in Japan; without discounting benefits, these would be reduced by over 80%. This feature may justify also presenting the health consequences of pre-adolescent HPV-16/18 vaccination in terms of undiscounted benefits, such as the number of cases and deaths averted (irrespective of when those cases or deaths would be prevented) per 1,000 girls vaccinated.

Assuming a vaccination coverage rate of 70% of young adolescent girls, the number of future cancer deaths averted by HPV-16/18 vaccination of 10 consecutive birth cohorts in the 22 GAVI-eligible countries and Japan, China and Thailand, is approximately 2.2 million; of these, approximately 89% would be averted in the GAVI-eligible countries. Averted deaths from cervical cancer averaged 13 per 1,000 vaccinated girls in the GAVI-eligible countries, 15 per 1,000 India, 11 per 1,000 in Thailand, 5 per 1,000 in China and 0.7 per 1,000 in Japan.

4. Other published data

Published studies that have assessed the cost-effectiveness of HPV vaccination in Australia and Israel are included in Kim J et al. [48].

5. Discussion

A model-based approach was used to synthesize available evidence and generate estimates for health and economic outcomes associated with HPV-16/18 vaccination of young adolescent girls. This article focused on 22 GAVI-eligible countries (with eligibility defined as Gross National Income per capita below US $1,000 in 2003), and included China, Thailand and Japan as representative examples of countries in the region with varying burden, population size and socioeconomic resources. In order to generate preliminary estimates expeditiously, results were presented from two countries in which adequate data were available to calibrate a complex micro-simulation model (Southeastern India and Vietnam), and a simple Excel-based model was used to assess the cost-effectiveness of pre-adolescent vaccination in countries with more limited data.

With pre-adolescent vaccination, relative and absolute cancer reduction varied between countries in Asia, and depended on underlying incidence, proportion of disease attributable to HPV types 16 and 18, population age-structure and age-specific competing mortality. For example, in Indonesia, the mean reduction in lifetime risk of cancer with 70% coverage was 57%, whereas in Cambodia, it was 49%. At lower coverage rates, the overall reduction in cancer deaths was lower, although adding screening in women over age 30, two to three times per lifetime, was synergistic with vaccination of young adolescent girls, as it reduced the risk of cervical cancer attributable to non-vaccine-targeted HPV types as well as types 16 and 18.

In countries such as India and Vietnam, in which both pre-adolescent vaccination and screening of adult women were evaluated, there was a 20 to 30% increased mortality reduction when screening three times per lifetime was added to vaccination of young adolescent girls. Analyses comparing the relative cost-effectiveness of alternative screening modalities, while beyond the scope of this article, are reported elsewhere [13,18] and new studies are likely to be available in the near future [33–35]. Countries will need to assess their own situations to decide which screening test will be most feasible, most sustainable and amenable to quality control, and will have the greatest likelihood of successful scale-up. For countries able to implement both vaccination of young adolescent girls and screening of adult women, a strategy worthy of future study is one that uses HPV DNA testing as the screening test modality, and that capitalizes on test information at the individual level for clinical decision making and at the population level for surveillance.

Vaccination of young adolescent girls has the potential to be a very cost-effective intervention to prevent cervical cancer. Assuming a cost per vaccinated girl of I$10 (US $2 per dose), the cost per DALY averted was less than I$250 for 18 out of 22 GAVI-eligible countries in this region; for the 8 countries with ASR greater than 20, the cost per DALY averted was less than I$100. The most influential factor on cost-effectiveness was the cost of vaccinating young adolescent girls with a three-dose vaccine. For example, at current vaccine prices (US $120 per dose), the cost per DALY averted exceeds I$5,000 in the majority of countries analyzed (data not shown). In

<table>
<thead>
<tr>
<th>Country</th>
<th>Cost per vaccinated girl</th>
<th>3% discounting</th>
<th>6% discounting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Costs and benefits</td>
<td>Costs only</td>
<td>Costs and benefits</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Costs only</td>
</tr>
<tr>
<td>China</td>
<td>I$1,360</td>
<td>240</td>
<td>7,080</td>
</tr>
<tr>
<td>Thailand</td>
<td>I$25</td>
<td>50</td>
<td>1,650</td>
</tr>
<tr>
<td>Japan</td>
<td>I$430</td>
<td>70</td>
<td>3,120</td>
</tr>
<tr>
<td>China</td>
<td>I$5,960</td>
<td>1,050</td>
<td>28,920</td>
</tr>
<tr>
<td>Thailand</td>
<td>I$100</td>
<td>310</td>
<td>7,370</td>
</tr>
<tr>
<td>Japan</td>
<td>I$2,690</td>
<td>450</td>
<td>13,790</td>
</tr>
<tr>
<td>China</td>
<td>I$18,220</td>
<td>3,210</td>
<td>87,170</td>
</tr>
<tr>
<td>Thailand</td>
<td>I$300</td>
<td>1,000</td>
<td>22,620</td>
</tr>
<tr>
<td>Japan</td>
<td>I$7,470</td>
<td>1,450</td>
<td>32,530</td>
</tr>
<tr>
<td>China</td>
<td>I$6,190</td>
<td>1,000</td>
<td>22,620</td>
</tr>
<tr>
<td>Japan</td>
<td>I$12,640</td>
<td>2,120</td>
<td>60,760</td>
</tr>
</tbody>
</table>

DALY: Disability-adjusted life year; I$: International dollars.
Cancer incidence (age standardized incidence rates, ASR, per 100,000 person-years at risk): China: 6.8; Thailand: 19.8; Japan: 8.0 [1].
DALYs averted for a campaign that vaccinates 70% of a single birth cohort in each country are as follows: China: 97,575; Thailand: 16,885; Japan: 13,486.
contrast, at a cost per vaccinated girl of $5 (US $0.55 per dose), the vaccine is cost saving in more than 25% of the 22 poorest countries (data not shown). There is uncertainty both in the price of the HPV vaccine for these countries and the programmatic costs associated with vaccination of young girls. While there are estimates for some of the general costs associated with supplies and administration, freight into the country and vaccine support for childhood immunization programs, the costs associated with social mobilization, new campaigns and education – all necessary with this particular pre-adolescent vaccine – are yet to be determined. Further, there are formidable data gaps for the absolute costs of delivery, as well as costs associated with wastage, across and within countries in the Asia Pacific region. These may be quite important, in that depending on the eventual price per dose, the implications of wastage rates above 10% may be substantial. Although wastage may be lower with single-dose vials, these are generally more expensive than multi-dose vials. Vials with 10 or more doses tend to be cheaper, but are substantially more troublesome for managing wastage in routine delivery settings.

Guidelines for economic evaluations recommend discounting future costs and benefits to their present values to reflect inherent uncertainty about the future and preferences for timing of consumption [14,25–27]. In contrast to a rotavirus vaccine targeting children, for example, where the costs and benefits are in close temporal proximity, the benefits of vaccinating young adolescent girls against HPV are realized decades after the costs are paid. While adhering to recommended guidelines for the formal cost-effectiveness analysis, it may be useful for analysts to present a range of results in additional formats. For example, per 1,000 girls vaccinated, the averted deaths from cervical cancer averaged 13 in the 22 GAVI-eligible countries, 15 in India, 11 in Thailand and 5 in China. This compares quite favorably to 3 deaths per 1,000 children vaccinated for rotavirus [49]. Also important to consider are the factors not included in these cost-effectiveness analyses because they are difficult to measure and monetize (e.g., impact on the household and the welfare of children who lose their mothers). For women in particular, this may grossly underestimate the benefits of a health intervention.

Both the financial costs and the cost-effectiveness profile of an HPV vaccine will need to be favorable as it is inevitable that this vaccine will compete for dollars earmarked for existing immunization programs, initiatives for scale-up and other new vaccines. At vaccine costs (US $) of $2 and $5 per dose, pre-adolescent vaccination was unarguably cost-effective, according to a sole requirement of a ratio less than the per capita GDP; at higher costs, the vaccine is not likely to have a favorable cost-effectiveness profile compared with other well accepted vaccines, and this may be a much more important “real world threshold” for decisions about introduction. While a cost-effectiveness analysis provides information on value for money, it is not equivalent to providing information on affordability [50]. Considerations of affordability acknowledge that there is a real-world budget constraint, and that a lack of available funds may require the cost per vaccinated girl to be lower than implied when judged solely on the attribute of cost-effectiveness. Considering just the 22 GAVI-eligible countries, financial requirements in US dollars for vaccinating 5 consecutive birth cohorts at 70% coverage would be over $500 million, almost $1.3 billion and over $3 billion at per dose prices (US $) of $2, $5 and $12.25, respectively. Including China and Thailand would add (US $) $251 million, $623 million and $1.4 billion at the same per dose costs.

The analyses in this article are subject to several limitations that motivate our emphasis on the main qualitative results and themes we find to be robust even when accounting for uncertainty. Unlike our detailed micro-simulation model [21,23,24] that accommodates screening as well as vaccination, includes HPV types not targeted by the vaccine, allows for empiric calibration to multiple epidemiological targets, and accommodates transmission dynamics, the Excel-based static model does not include these features. Accordingly, for analyses conducted with only the latter model, there is not capacity to incorporate uncertainties with respect to the natural history of HPV, such as the extent of type-specific immunity following natural infection. For example, while the mean cancer reduction in lifetime risk of cancer in Ho Chi Minh City, Vietnam is 49% using both models, a range of 38% to 61% is produced by conducting analyses with good-fitting parameter sets using the empirically calibrated micro-simulation model, providing more comprehensive insight into the potential impact of parameter uncertainty. In addition, the empirically calibrated micro-simulation model requires extensive data; therefore, the projections using this model reflect the specific regions in the country from which those data were obtained. For example, the Excel-based model predicts a mean reduction in the lifetime risk of cancer in India of 52%; however, based on the micro-simulation model calibrated to data in Southeastern India, the mean reduction was 44% (range, 28%–57%). While there are different limitations associated with each model, this exercise reveals the value of using multiple models to gain insight into the economic and health outcomes expected with vaccination against HPV-16 and –18.

The vaccine-preventable cervical cancer burden in each country is a product of several factors, including the underlying cervical cancer incidence, the proportion of cancer attributable to HPV-16 and –18, and vaccine efficacy. While the limitations of available epidemiological data relevant to the first two factors are reviewed in other articles of this monograph, it is important to emphasize that assumptions used in the models for vaccine efficacy are uncertain. Vaccine efficacy may be lower than assumed in the base case analyses if older girls are vaccinated who may have been infected previously with type 16 or 18; if there is less robust vaccine-induced immunity in individuals with other diseases, such as HIV; or if there is waning of vaccine-induced immunity in the period when women are still at risk for new HPV infections. On the other hand, benefits attributable to the vaccine may be higher if there is cross-protection against non-HPV-16/18 type infection; if herd immunity benefits to unvaccinated individuals augment population-level benefits beyond predictions based solely on coverage rates; and if other non-cervical HPV-16/18-related cancers and diseases are prevented. These are all important and uncertain issues for which empirical data are needed.

Finally, our cost estimates are largely based on indirect methods and at best are crude approximations. The evidence gaps with respect to the costs associated with vaccination of young adolescent girls, coupled with the heterogeneity between and within countries in this region of the world, highlight several priorities for country-specific costing studies. These include economic evaluations of alternative modes of delivery, assessment of the costs associated with scale-up, and studies to identify economies of scale with other programs directed at this age group (e.g., educational interventions for HIV prevention). In addition to financial support to subsidize the cost of vaccine purchase, operational research will be needed to develop new avenues to reach young adolescent girls. If a two-dose schedule could be used, or if vaccination could be given at an earlier age with other vaccines (e.g., at school entry), delivery costs might be reduced. Country-specific economic studies using standardized cost instruments are a high priority. There is also a need for local data on the costs associated with implementing newer screening strategies that are delivered only two or three times per lifetime, costs associated with combined screening and surveillance efforts, and costs of improving quality and efficiency in countries already engaged in screening activities.
Disclosed potential conflicts of interest

None of the authors has disclosed potential conflict of interest.

Acknowledgments

The authors gratefully acknowledge the Global HPV and Cervical Cancer Modeling Team.

The analyses included in this chapter were supported by the Bill and Melinda Gates Foundation (30505) (Principal Investigator: Sue J Goldie), who had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; or preparation, review, or approval of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.vaccine.2008.06.018.

References


