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An extended cost-effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China

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ABSTRACT

Introduction: Cervical cancer screening and existing health insurance schemes in China fall short of reaching women with prevention and treatment services, especially in rural areas where the disease burden is greatest. We conducted an extended cost-effectiveness analysis (ECEA) to evaluate public financing of HPV vaccination to prevent cervical cancer, adding new dimensions to conventional cost-effectiveness analysis through an explicit inclusion of equity and impact on financial risk protection.

Methods: We synthesized available epidemiological, clinical, and economic data from China using an individual-based Monte Carlo simulation model of cervical cancer to estimate the distribution of deaths averted by income quintile, comparing vaccination plus screening against current practice. We also estimated reductions in cervical cancer incidence, net costs to the government (HPV vaccination costs minus cervical cancer treatment costs averted), and patient cost savings, as well as the incremental government health care costs per death averted.

Results: HPV vaccination is cost-effective across all income groups when the cost is less than US $50 per vaccinated girl. Compared to screening alone, adding preadolescent HPV vaccination followed by cervical cancer screening in adulthood could reduce cancer by 44 percent across all income groups, while providing relatively higher financial protection to the poorest women. The absolute numbers of cervical cancer deaths averted and the financial risk protection from HPV vaccination are highest among women in the lowest quintile; women in the bottom income quintiles received higher benefits than those in the upper wealth quintiles. Patient cost savings represent a large proportion of poor women's average per capita income, reaching 60 percent among women in the bottom income quintile and declining to 15 percent among women in the wealthiest quintile.

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1. Introduction

Cervical cancer is one of the most common diseases affecting women in China. While average national estimates are low, cervical cancer burden may be underestimated, as human papillomavirus (HPV) prevalence is high. Cervical cancer mortality is heterogeneous across geographic settings; and highest among poor women in Gansu, Shanxi, and Shaanxi, the least developed provinces in central and western China.

The low national cervical cancer estimates may be the result of the lack of a nationwide cancer registry. Most registries are located in urban areas, where the socioeconomic status of women is higher and cancer disease burden is likely lower than rural areas [1]. While HPV prevalence has been found to be similar in rural and urban regions, cervical cancer mortality is significantly higher in rural areas. This disproportionate burden is likely attributable to unequal availability and utilization of health services including screening and treatment.

In the absence of a national cervical cancer-screening program in China, screening is opportunistic. From 2009 to 2011, the Chinese government initiated a program to provide free cervical cancer screening for 10 million rural women between 35 and 59 years of age which covered only 7% of women due to shortages

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of gynecologists and cytologists and an overburdened health care system [2,3]. With an estimated 700 million women in China, scaling up preventative services is formidable [4–7].

China's health care system has been evolving to respond to the pervasive unequal access to health services. In 2009, China began to introduce universal health coverage [8], reaching high coverage in urban and rural areas with two government-sponsored schemes. Despite high coverage, reimbursement is limited to inpatient expenses. It is unclear how recent health insurance schemes have impacted women's cervical cancer treatment rates; however, recent studies indicate that services are not reaching poorer women [1,5,9]. This trend is likely to continue until insurance schemes cover outpatient services.

While widespread screening with cytology has dramatically reduced the cervical cancer burden in developed countries, low-resource settings lack the infrastructure and resources to achieve similar cancer reductions. Newer screening technologies that are cheaper, cost-effective and easier to implement than cytology can reduce the cervical cancer burden among Chinese women, protecting them from future costs and consequences of the disease [4,10–13].

HPV vaccination is a promising primary prevention strategy against cervical cancer. Studies indicate that screening women and vaccinating preadolescent girls against HPV is cost-effective in reducing the burden of cervical cancer in China [10,11,14,15]. Vaccination strategies were cost-effective up to US$55 per vaccinated girl, with incremental cost-effectiveness ratios (ICER) of US$2746 per life year saved (LYS) when vaccination was combined with screening once in a lifetime, and up to US$5963 per LYS when combined with screening five times in a lifetime [14]. At, US$25 per vaccinated girl the ICER declines to US$1360 per LYS.

Recent attention to reaching the goal of universal health coverage (UHC) provides strong rationale for exploring mechanisms to expand access to cervical cancer prevention and treatment in China without increasing financial burden of women seeking care [16]. We sought to apply an extended cost-effectiveness analysis (ECEA) methodology [17,18,49] to evaluate public financing of HPV vaccination for cervical cancer prevention. Recent theoretical and empirical work provides guidance in this area; either focused on applications for high-income countries or limited to a few infectious disease conditions in a number of low- and middle-income countries [19–21]. In this application, ECEA adds new dimensions to conventional cost-effectiveness analysis (CEA) through a more explicit treatment of equity and impact on financial risk protection (prevention of medical impoverishment) [17]. Specifically, ECEA can evaluate publicly financed programs by measuring program impact along four main dimensions: (i) health benefits; (ii) household private expenditures averted ("household cost savings"); (iii) financial risk protection provided to households; and (iv) distributional consequences across the wealth strata of country populations. As a result, ECEA enables quantitative inclusion of information on equity and amount of financial risk protection bought per dollar expenditure on health policy, in addition to amount of health bought [17].

Consequently, the distribution of health and financial benefits resulting from interventions—and by extension from the policy instruments that finance them—can be examined to determine whether they are pro-poor. In practice, ECEAs can also be used to examine financial effects of interventions and policies on individuals or families by income group and in aggregate. Health policies and interventions typically involve costs to the public sector and households. Even if an intervention is provided at no cost, users often incur time costs to travel or wait at a health facility; value placed on these costs differs according to income level.

Publicly financed health interventions can help users to avoid future costs; for example, HPV vaccination and cancer screening programs reduce the cervical cancer risk, which might otherwise lead to medical impoverishment (related to expensive medical bills for cancer treatments), devastating health consequences (e.g. death of a mother, which increases the mortality risk for children), or both.

We evaluated the consequences of full public finance of HPV vaccination in China using ECEA methodology. Public finance increases HPV vaccination uptake, leading to important health gains and can reduce household medical expenditures. Finally, public finance can have differential impacts among populations of different income levels. We estimated the level and distribution (across income groups) of the cervical cancer deaths averted; the households' expenditures related to cervical cancer treatment averted and the costs needed to sustain the HPV program; and financial risk protection, using a combination of indicators, detailed below.

2. Methods

2.1. Model

We synthesized available epidemiological, clinical, and economic data from China using a previously described individual-based Monte Carlo simulation model of cervical cancer [23–26]. The model consists of health states representing important clinical stages of disease, including HPV infection, grade of precancerous lesions, and stage of invasive cancer. We evaluate vaccination and screening as a combined strategy in a single cohort, such that preadolescent girls who are vaccinated will eventually also receive screening. Thus, individual girls enter the model at age nine, before sexual debut and free of HPV infection, and they transition between health states throughout their lifetime. Each month, women face a risk of acquiring HPV infection; once infected, they can clear their infection or develop low- or high-grade lesions, categorized as cervical intraepithelial neoplasia, grade 1 (CIN 1) or grade 2,3 (CIN 2,3). Low-grade lesions can regress, and CIN 2,3 can progress to invasive cancer. These transitions are determined by age, HPV type, and type-specific natural immunity after clearance of HPV infections. See appendix Fig. A1 for model schematic cervical cancer can be detected through symptoms or screening, and women with cancer survive according to stage-specific survival rates for local, regional, and metastatic disease.

All women are subject to mortality from competing causes [27]. Our approach was to calibrate the model for cervical cancer burden of the country as a whole. Model parameters were initially established using the best available information on the natural history of HPV infection and cervical carcinogenesis. The model was adapted to the context in China using likelihood-based methods to fit the parameters to epidemiological data. Age-specific cervical cancer estimates were obtained from GLOBOCAN [28]; data on HPV 16 and 18-type distribution in CIN 23 and cervical cancer were from a meta-analysis of primary data from Asia [29]. Baseline natural history parameters were allowed to vary over plausible ranges. We identified sets of parameter values that achieved close fit to the empirical data and conducted the analysis using the parameter set with the maximum likelihood.

2.2. Strategies and assumptions

We simulated screening with cytology and visual inspection with acetic acid (VIA) beginning at age 35 at five-year intervals for a cohort of one million women in each income quintile. We assumed screening frequency progressively increased with income, with women in the lowest two quintiles screened once per lifetime at 21 and 34 percent coverage respectively, those in the next two quintiles screened three times per lifetime at 43 and 47 percent

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coverage, and those in highest screened five times per lifetime at 51 percent coverage. Consistent with assumptions from previous analyses [30,31], cytology was assumed to occur in three visits, initial screening (visit 1), colposcopy and biopsy for screen-positives (visit 2), and treatment of precancerous lesions or invasive cancer (visit 3) with loop electrosurgical excision procedure (LEEP), cold knife conization, simple hysterectomy, or simple radiotherapy, depending on lesion size or cancer stage. VIA screening incorporates same-day screening and treatment for screen positives [32].

Cancer treatment was assumed to be a mixture of different approaches (i.e., cold knife conization, simple hysterectomy, radical hysterectomy, simple radiotherapy, neoadjuvant chemotherapy, and adjuvant chemotherapy), and the distribution of women receiving one treatment versus another varied on urban/rural setting and quintile as a way to capture differential access to cancer treatments. In particular, stage I cancer was assumed to be treated with 90% cold knife and 10% simple hysterectomy for quintiles 1, 2, and 3, and 30% cold knife and 70% simple hysterectomy for quintiles 4 and 5. Stage II cancer was assumed to be treated with 90% simple hysterectomy and 10% radical hysterectomy for quintiles 1, 2, and 3 in urban areas and 100% simple hysterectomy in rural areas and 70% simple and 30% radical hysterectomy for quintiles 4 and 5 in both urban and rural areas. Stage III and IV cancer were assumed to be treated with 80% simple radiotherapy and 20% adjuvant chemotherapy in quintiles 1,2, and 3, and 70% simple radiotherapy, 20% adjuvant chemotherapy and 10 neoadjuvant chemotherapy in quintiles 4 and 5.

Vaccination was assumed to occur before age 12 (prior to sexual debut) with full three-dose adherence and complete and lifelong protection against HPV 16 and 18 infections (with no cross-protection for non 16/18 types). HPV vaccination coverage was assumed at 70 percent coverage based on current immunization rates of over 95% for childhood vaccines and recent evidence on the feasibility of reaching pre-adolescent girls with HPV vaccination using facility, school-based and outreach strategies [33,34]. We used screening coverage estimates by quintile from the WHO Study on Global AGEing and adult health [16]. Because of lack of data on loss to follow-up from treatment by quintile in China, we used variation in treatment seeking rates for non-communicable diseases for patients across the 5 income groups obtained from the WHO Study on global AGEing and adult health (SAGE). We created weights based on this variation adjusted them so the weighted average of loss-to follow-up would be close to 15% per healthcare visit, the percentage traditionally used in the literature [24,35]. Our loss to follow up estimates ranged from 62 percent to 5 percent from lowest to highest quintile, respectively. Recognizing that service utilization and loss to follow up will be influenced by heterogeneity in health system, spatial and socio-economic factors across China's provinces, we conducted a sensitivity analysis on screening coverage and loss to follow-up by quintile. Table 1 summarizes model parameters.

We estimated the reduction in cervical cancer, distribution of deaths averted by income quintile, comparing vaccination plus screening against screening at current coverage. Incremental government costs were equal to HPV vaccination costs minus cervical cancer treatment costs averted and patient cost savings. Financial risks can occur when out-of-pocket household expenditures are substantial and can be considered 'catastrophic', increasing the risk of medical impoverishment. While the definitions and thresholds of catastrophic expenditures vary widely in the literature and in practice ([39–41]), typical measures define catastrophic spending using a threshold for OOP expenditures' share of total household expenditures, ranging from 10% to 40% depending on the setting. Here, we include two simple indicators of financial risk protection using a combination of indicators to measure the protection against financial risk from catastrophic expenses or medical impoverishment, including the number of women who would avoid cervical cancer treatment out-of-pocket expenditures, and the average out-of-pocket expenditures averted as a share of average per capita income, measured by gross domestic product (GDP). All results are presented by income quintile.

Table 1
Summary of the parameters used for modeling the impact and costs of a publicly financed HPV vaccination policy in China.

Parameter	Estimate	Sources
Screening with cytology: frequency[1] and coverage (percent)		
Income quintile (lowest to highest)		
1. Once per lifetime	21	a,b
2. Once per lifetime	34	a,b
3. Three times per lifetime	43	a,b
4. Three times per lifetime	47	a,b
5. Five times per lifetime	51	a,b
Loss to follow up (percent)		
Income quintile (lowest to highest)		
1	62	Assumed
2	40	Assumed
3	22	Assumed
4	13	Assumed
5	5	Assumed
Vaccine characteristics		
Vaccination coverage (percent)	70	Assumed
HPV[2] vaccine price per dose (US$)	13	Assumed
Incremental vaccine program delivery cost per fully immunized girl (US$)	5	Assumed
Vaccine cost per fully immunized girl, including wastage and handling (US$)	46	Assumed
Income and wages		
Gross domestic product per capita (2009 US$)	3749	c
Mean GDP per capita		
Income quintile (lowest to highest)		
1	783	b, c
2	1633	b,c
3	2567	b,c
4	3888	b,c
5	7896	b,c
Mean wage rate		
Income quintile (lowest to highest)		
1	$3	c,d
2	$6	c,d
3	$10	c,d
4	$15	c,d
5	$30	c,d

Sources:
a. Gakidou, Nordhagen, and Obermeyer (2008) [36].
b. World Health Organization (2012) [16].
c. World Health Organization Global Health Observatory [37].
d. Shi and others (2012) [38].
Note:
1. We estimated the frequency of screening at 1× and 5× per lifetime for all income quintiles in sensitivity analysis.
2. HPV = human papillomavirus.

2.3. Costs

Direct medical and non-medical costs were estimated using published cost from two studies in China ([10,27]) expressed in 2009 US$. We assumed an average health-seeking behavior by income quintile and geographic location, where in the lowest three income quintiles rural and urban women were screened at the township (primary health center) and county hospital, respectively, and all women in these lower quintiles received diagnosis and treatment at the county hospital. We assumed that in the highest two income quintiles, rural and urban women were screened and treated at prefecture and provincial level hospitals respectively.

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We then applied a weighted average unit cost for screening, diagnosis, and treatment based on urban and rural population proportions by quintile. To estimate household and government costs consequences, we assumed 35 percent of cancer screening and treatment costs remain privately financed in China [37]. Patient time costs for transportation and waiting were based on time estimates from Shi et al. [27], using an updated national average wage rate in China ranging from US$3 to US$30 per day for the lowest to highest quintile, respectively. The average wage rate is equal to average per capita income divided by 255 workdays per year at 8 h per day [27]. We obtained the GDP from the World Bank and used the Consumer Price Index (CPI) to deflate costs to 2009 US$. Per capita income for each quintile is the proportion of GDP accrued to each income quintile using estimates from the World Bank and PovCalNet, an online poverty analysis tool, divided by the total population per quintile [42].

Commercially available HPV vaccines are not yet approved in China, but vaccines are offered at low prices for public sector programs from the Global Alliance for Vaccines and Immunization (GAVI) at US$5 and from the Pan American Health Organization (PAHO) countries at US$13 [43]. China could likely negotiate lower public sector prices [2], and we assumed a public sector cost of US$46 per fully immunized girl, including the vaccine price (three doses at US$13 per dose), vaccine wastage (2 percent), freight (6 percent), and program administration costs (US$5). Program administration costs are lower than the average incremental costs in recent studies in Sub-Saharan Africa and Latin America, but are likely to reflect economies of scale that are found in more densely populated Asian countries [44]. Annex Tables A2 and A3 summarize cost estimates by quintile.

2.4. Sensitivity analyses

To accommodate the uncertainty around uptake and vaccine delivery costs, we varied the cost per fully immunized girl from US$10 and US$100. We also varied screening frequency, screening coverage and loss to follow up rates. We uniformly increased cancer treatment costs by 50 and 100 percent for all quintiles. Annex Table A4 provides the estimates or ranges used in sensitivity analysis.

3. Results

We found that adding preadolescent HPV vaccination at 70 percent coverage to current screening will yield a 44 percent cancer reduction across all income quintiles (Table 2). While the relative cancer reduction is constant across income groups, the absolute number of cervical cancer deaths averted and the financial risk protection from HPV vaccination are highest among women in the lowest quintile; women in the bottom income quintiles received relatively higher cost benefits compared to the upper wealth quintiles. HPV vaccination averts 15 percent more detected cancer cases and 18 percent more deaths in the lowest compared to the highest quintile. Although in absolute dollars, patient savings were higher in the top income quintile compared to the lowest quintile (US$7,655,200 compared to US$1,636,270), the cost savings from HPV vaccination comprised a larger share of per capita income among women in the bottom income quintiles, ranging from 60 percent among the lowest income quintile to 30 percent among the highest quintile.

At a vaccine cost of US$46 per fully immunized girl and 70% coverage, the incremental cost is approximately US$160 million for a cohort of five million girls. At the relatively low levels of cancer screening and treatment in China, government intervention costs do not vary by wealth strata, since medical savings are offset by the publically financed HPV vaccination costs.

Given China's low reported rates of cervical cancer screening, our results were robust to changes in assumptions about screening frequency, screening coverage, and loss to follow-up (Annex Table A4). As expected, changes in the cost per fully immunized girl do not have an impact on deaths averted, cancer reduction or financial risk protection, assuming that 70 percent coverage is maintained. At US$10 per fully vaccinated girl, the cost per death averted declines to US$2161 for the lowest income quintile to US$2608 among the highest quintile. At US$100 per vaccinated girl, cost per death averted increases to US$24,000 in the lowest income quintile to over US$29,000 in the highest income quintile (Annex Table A5). Universal coverage of the HPV vaccination becomes even more favorable among individuals in lower income quintiles and provides greater relative financial risk protection when treatment costs increased by an additional 50 or 100 percent (Annex Table A6).

4. Discussion

While the HPV vaccine holds great promise for reducing the burden of cervical cancer, it is not yet available in China. Delaying HPV vaccine introduction will result in a lost opportunity to prevent cervical cancer cases and deaths. A national vaccination program of 9–15 year old girls, between 2006 and 2012 could have prevented 381,000 cervical cancer cases and 212,000 related deaths in the coming decades [2]. While it is expected that China could negotiate HPV vaccine prices to cost effective levels of around US $9 to 13 per dose, at least one-third of Chinese women are not willing to pay more than US$3 [45]. A successful program will likely depend on government financing.

We applied an ECEA to evaluate the impact of a publically financed policy for HPV vaccination in China on the distribution of health consequences and financial risk protection across income levels. Results show that preadolescent HPV vaccination added to current practice could reduce cancer by over 40 percent across income groups, while providing relatively higher financial protection to households in the bottom income quintiles. The low screening coverage rates reported for China affect both the government and patient screening and treatment costs, but with differential results. From the governmental perspective, a publically financed HPV vaccination program would increase net costs,

Table 2
Benefits and costs of a publicly financed HPV vaccination policy in China (2009 US$).

Quintile	I	II	III	IV	V
Deaths averted per million women	2877	2854	2667	2604	2362
Government costs per million women (incremental)	$31,417,285	$31,420,191	$31,440,420	$31,446,679	$31,359,970
Government cost per death averted	$10,920	$11,009	$11,789	$12,076	$13,277
Treatment seeking cases of cancer averted per million women	3540	3511	3312	3256	2999
Patient cost savings per million women	$1,633,160	$2,240,688	$2,785,626	$4,417,303	$7,041,335
Savings as a percentage of total income	59	39	33	35	30
Cancer reduction (percent)	44	44	43	43	44

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with little offset from averted cervical-related treatment costs due to the low levels of screening. Although HPV vaccination led to patient cost savings that were small relative to the increase in government costs, all income groups experienced cost savings; importantly, there was a powerful equity effect, with higher financial risk protection in the poorest groups. Patient cost savings represent a large proportion of poor women's average per capita income, reaching 60 percent among women in the bottom income quintile and declining to 15 percent among women living in the wealthiest quintile. We also estimated standard cost-effectiveness ratios (results available from the authors) and found that like previous studies conducted in China, HPV vaccination is cost-effective across all income groups when the cost is less than US $50 per vaccinated girl.

We assumed a cost of US$46 per vaccinated girl, using US$13 per dose, based on the manufacturers' offer price to PAHO for public vaccination programs in Latin America and the Caribbean. The financial cost of vaccinating 70 percent of China's current cohort of 6.6 million 10-year-old girls is US$213 million. This estimate, which accounts for less than 1/2 percent of projected health care spending of US$357 billion in 2011, would have a large financial impact on China's current Expanded Program for Immunization (EPI). The introduction of the HPV vaccine would require a change in policy to publically finance the HPV vaccine, either through current health insurance schemes or through inclusion in the EPI, which provides free childhood vaccines for measles, diphtheria/tetanus/pertussis (DTP), Bacille Calmette Guerin (BCG), polio, and hepatitis B. The EPI manages non-EPI vaccines, such as those for Japanese encephalitis, mumps, and rubella, but patients pay for these vaccines via user fees. A third type of "optional" vaccines, such as hepatitis A, Haemophilus influenza type B (Hib), and rotavirus, are procured and delivered outside of the EPI and paid for by patients without any government subsidy [46].

This analysis has a number of limitations: First, it is an application of the ECEA method using the best available published data from selected provinces, which does not fully capture the heterogeneity in disease burden, health systems, socio-economic development and GDP per capita across China's provinces. Second, the ECEA simulates the costs and impacts of HPV vaccination by income quintile; however, there are limited data on the variation of HPV incidence, mortality rates, loss to follow-up rates for screening, and out-of-pocket health expenses by income category. Third, there is limited information on health service utilization, screening and treatment costs and the impact of mandatory health insurance by prefecture, province and other geographic settings or across wealth strata. Fourth, we estimated women's time using a wage rate derived from a national estimate of per capita GDP income, which may overestimate income in the lowest quintile, where some rural communities are likely to live on $US2.00 per day or less. In addition, we did not include women's transport costs in seeking screening, treatment, or vaccination; these costs are expected to be small components of patient costs based on previous analyses in China. Further, estimates of women's wages do not include work in the informal sector and therefore may be underestimates of true opportunity costs [10,14,27]. Additionally, we do not have information of sexual behavior and HPV prevalence by income quintile. In the absence of such data, we assumed that age-specific HPV prevalence did not vary by quintile, but rather screening coverage and uptake was the main driver of differences in cervical cancer incidence.

An ECEA approach yields new and essential information on a policy's ability to reduce inequity and catastrophic expenses that complements information on value for money from traditional cost-effectiveness analyses. Future applications of this approach will benefit from improved information on public and private health financing, as well as from disaggregated data on disease burden and health service utilization by key socio-economic, demographic, and geographic variables.

A recent editorial recognizing China's cervical cancer burden and its unequal impact among disadvantaged women proposes a semi-mandatory HPV vaccination program in China targeted to low-income, high-risk women living in regions with historically high cervical cancer incidence [47]. Our analysis provides decision makers with the potential distributional consequence and financial risk protection of including cervical cancer in future health care reform investments to provide insight to policy debates in China. An ECEA provides additional evidence beyond effectiveness, costs and cost-effectiveness for selective resource allocation to the populations and provinces most in need in the context of public financing and the strengthening of Chinese health reform.

Previous research has demonstrated that HPV vaccination in China can be cost-effective at a cost of US$50 per vaccinated girl, and a targeted program may even be affordable given China's plans for dramatically increasing health care spending in the near future [44,47]. Ensuring high and uniform HPV vaccine uptake is likely to also contribute to more equitable gains with respect to the reduction of morbidity and mortality from cervical cancer, and it has the potential to protect women in poor households against catastrophic cervical cancer medical expenses.

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Conflict of interest statement: The authors have no conflicts of interest to declare.

Annex.

Fig. A1.
Tables A1–A6.
Figs. A2 and A3.

Defining calibration targets

Calibration targets included type distribution within CIN categories, age-specific cancer incidence, cumulative cancer incidence, and type- and age-specific duration of HPV infections and CIN.

For each calibration target, we determined a point estimate and confidence interval, using the best available data sources. Targets were calculated using 95% confidence intervals of the binomial distribution in STATA/SE 9.0.

Goodness-of-fit

The model outputs using each input parameter set were compared to the calibration targets. Model fit to the targets was evaluated by constructing a goodness-of-fit score. A composite goodness-of-fit score for each parameter set was computed by summing the log likelihood of each model outcome [25]. Goodness-of-fit scores followed a chi square distribution with the number of degrees of freedom equal to the number of targets.

Input parameter acceptance criterion

We determined our best-fitting parameter set as the one with the lowest goodness-of-fit score – the model-generated input parameter whose simulated model outputs were simultaneously closest to all calibration targets.

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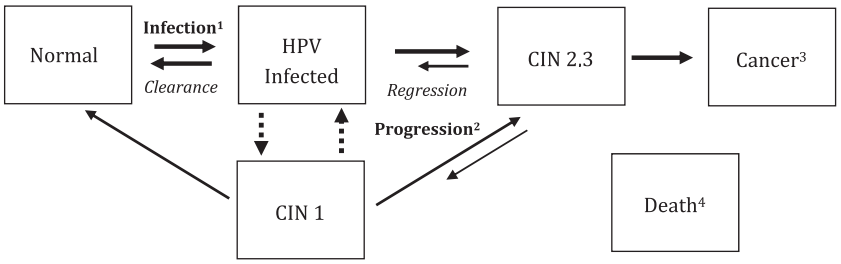

[1] Incidence of infection depends on age, HPV type, prior infection, and type-specific immunity.
[2] Progression of HPV infection and CIN 1 depends on age and HPV type.
[3] Cancer states are stratified by stage (local, regional, distant) and detection status (undetected, symptom-detected, screen-detected).
[4] Death can occur from all-cause mortality from every health state and excess cancer-specific mortality from cancer states.

Fig. A1. Model natural history of cervical cancer pathogenesis.

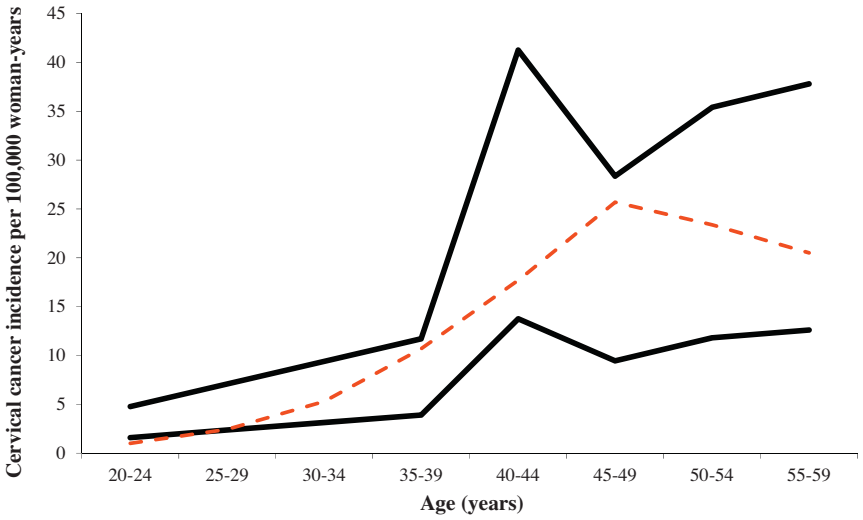

Fig. A2. Calibration results: cervical cancer incidence from best-fitting parameter set, compared with empirical estimates. Black lines depict the 95 percent confidence intervals of age-specific cervical cancer incidence in China [28]. Red dashed line represents the projected incidence of the best-fitting parameter set used in model analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

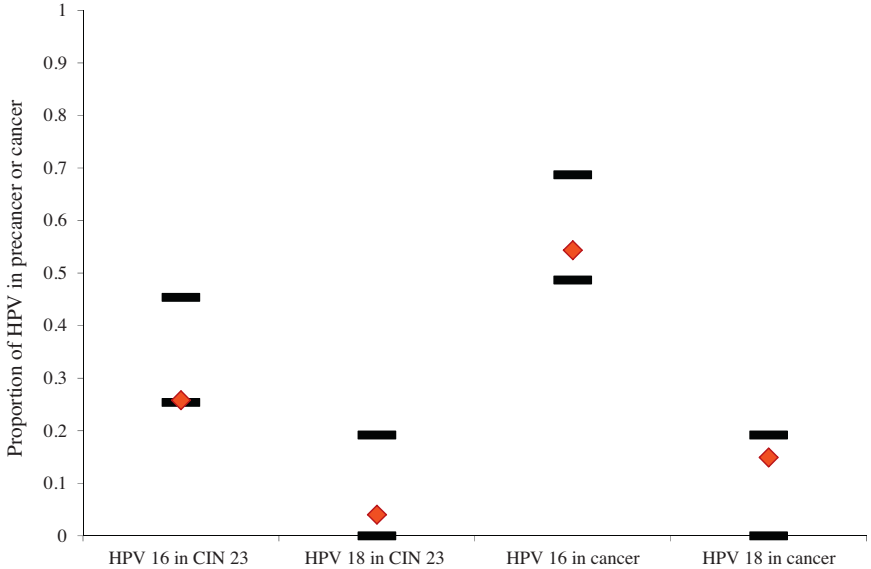

Fig. A3. HPV 16, 18 type distribution from best-fitting parameter set, compared with empirical estimates. Black bars depict the 95 percent confidence intervals of empirical data of HPV 16/18 type distribution in CIN23 and cancer [29]. Red diamonds show the estimates projected by the best fitting parameter set used in modeling analysis. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

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Table A1
Input parameters: baseline ranges.[a]

Variable	Baseline values[b]	Ranges[b]
Progression		
Normal to HPV DNA		
- Low-risk (LR) HPV	0.000100–0.010000	0.1–8
- High-risk other (HR-other) HPV	0.000100–0.010000	0.1–8
- High-risk (HR-16) HPV	0.000100–0.010000	0.1–8
- High-risk 18 (HR-18) HPV	0.000100–0.010000	0.1–6
HPV DNA to CIN 1[c]		
- LR HPV	0.004640–0.005380	0.1–6
- HR-other HPV	0.004780–0.008490	0.1–6
- HR-16 HPV	0.004780–0.008490	0.1–6
- HR-18 HPV	0.004780–0.008490	0.1–6
HPV DNA to CIN 2,3[d]		
- LR HPV	0.000037–0.000778	0–0.1
- HR-other HPV	0.000184–0.003888	0–0.1
- HR-16 HPV	0.000184–0.003888	0.1–1
- HR-18 HPV	0.000184–0.003888	0–0.1
CIN 1 to CIN 2,3		
- LR HPV	0.000037–0.000778	0.1–6
- HR-other HPV	0.000184–0.003888	0.1–6
- HR-16 HPV	0.000184–0.003888	0.1–6
- HR-18 HPV	0.000184–0.003888	0.1–6
CIN 2,3 to local cancer[e]		
- HR-other HPV	0.000015–0.006000	0.5–4
- HR-16 HPV	0.000015–0.006000	0.5–6
- HR-18 HPV	0.000015–0.006000	0.5–6
Local to regional invasive cancer	0.020000	–
Regional to distant invasive cancer	0.025000	–
Regression		
HPV DNA to normal[f]		
- LR HPV	0.030500	3–8
- HR-other HPV	0.030500	3–8
- HR-16 HPV	0.030500	3–8
- HR-18 HPV	0.030500	3–8
CIN 1 to normal[g]		
- LR HPV	0.030500	0.5–6
- HR-other HPV	0.030500	0.5–6
- HR-16 HPV	0.030500	0.5–6
- HR-18 HPV	0.030500	0.5–6
CIN 2,3 to normal[h]		
- LR HPV	0.001410–0.006497	0.5–6
- HR-other HPV	0.001410–0.006497	0.5–6
- HR-16 HPV	0.001410–0.006497	0.5–6
- HR-18 HPV	0.001410–0.006497	0.5–6
Other		
Immunity (HR HPV types only)		
- HR-other HPV	0	0.0–0.5
- HR-16 HPV	0	0.6–1
- HR-18 HPV	0	0.6–1

Source: Goldie and others 2007 [24].

[a] HPV, human papillomavirus; DNA, deoxyribonucleic acid; CIN, cervical intraepithelial neoplasia.

[b] Base case values are monthly probabilities, unless otherwise noted. A hyphenated range reported for a base case value represents age-specific probabilities. Except where noted, the ranges represent multiplier values, which are applied to baseline probabilities during calibration.

[c] Although baseline rates of progression and the range of multipliers were the same among all HR HPV types, the multipliers were allowed to vary independently by type in the parameter searches.

[d] A proportion of women with HPV who progress to CIN 1 transition directly to CIN 2,3.

[e] Infection with high risk HPV is considered a necessary condition for progression to invasive cancer.

[f] We assumed that regression from HPV DNA to normal was equal among types, and therefore the multipliers were held constant among types in the parameter searches.

[g] Although baseline rates of regression and the range of multipliers were the same among all HPV types, the multipliers were allowed to vary independently by type in the parameter searches.

[h] 70% of women with CIN 2,3 regress to normal, 15% to HPV, 15% to CIN 1.

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Table A2
Cost parameters for screening, diagnosis, and treatment, and wage rates by income quintile (2009 US$).

Cost parameter	Quintile 1		Quintile 2		Quintile 3		Quintile 4		Quintile 5	
	Direct medical cost per woman	Woman's time and OOP costs	Direct medical cost per woman	Woman's time and OOP costs	Direct medical cost per woman	Woman's time and OOP costs	Direct medical cost per woman	Woman's time and OOP costs	Direct medical cost per woman	Woman's time and OOP costs
Screening										
Cytology	7.01	2.87	7.01	2.87	7.32	2.87	7.49	2.87	7.96	2.87
VIA	2.24	2.15	2.24	2.15	2.24	2.15	2.24	2.15	2.24	2.15
HPV rapid test	7.33	2.15	7.33	2.15	7.50	2.15	7.59	2.15	7.92	2.15
Diagnosis										
Colposcopy	4.41	2.27	4.41	2.27	4.58	2.27	4.67	2.27	4.93	2.27
Biopsy	5.91		5.91		5.96		5.99		6.06	
Treatment										
LEEP	66.41	166.00	66.41	166.00	68.01	166.00	68.92	166.00	71.43	166.00
Cryotherapy	10.32	2.27	10.32	2.27						
Cold conization	293.15	178.50	293.15	178.50	293.15	178.50	367.54	253.50	367.54	253.50
Simple hysterectomy	409.48	291.00	409.48	291.00	410.60	291.00	446.63	292.00	446.63	292.00
Simple radiotherapy	290.18	252.00	290.18	252.00	292.19	252.00	384.98	252.00	384.98	252.00
Urban share of population (percent)	34 (5)		34 (5)		42 (8)		47 (9)		64 (10)	
Daily wage rate	3.00		6.00		10.00		15.00		31.00	

Sources: Levin and others (2010) [10]; Shi and others (2012) [27].
Note: Rural costs are taken from Shi and others (2012). Costs for urban settings and Beijing are taken from Levin and others (2010). Costs represent a weighted average for urban and rural for each income quintile.
Numbers in parenthesis indicate the percent of women in each quintile assumed to live in or receive care in Beijing.
OOP = out of pocket; LEEP = loop electrosurgical excision procedure; VIA = visual inspection with acetic acid.

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Table A3
Cost parameters for out-of-pocket expenses for direct medical, direct non-medical, and total patient costs by income quintile (2009 US$).

Cost parameter	Quintile 1		Total	Quintile 2		Total	Quintile 3		Total	Quintile 4		Total	Quintile 5		Total
	Direct medical	Direct non-medical		Direct medical	Direct non-medical		Direct medical	Direct non-medical		Direct medical	Direct non-medical		Direct medical	Direct non-medical	
Screening															
Cytology		1.16	1.16	7.01	3.6	10.64	7.32	5.69	13.01	7.49	8.62	16.11	7.96	17.51	25.47
VIA	2.24	1.11	3.35	2.24	2.4	4.66	2.24	3.80	6.04	2.24	5.75	7.99	2.24	11.68	13.92
HPV rapid test	7.33	1.24	7.33	7.33	2.3	9.64	7.50	3.63	11.12	7.59	5.50	13.09	7.92	11.16	19.08
Diagnosis															
Colposcopy	4.41	0.00	4.41	4.41	2.6	7.00	4.58	4.07	8.65	4.67	6.16	10.83	4.93	12.51	17.44
Biopsy	5.91	110.77	5.91	5.91		5.91	5.96		5.96	5.99		5.99	6.06		6.06
Treatment															
LEEP	66.41	110.77	177.17	66.41	194.1	260.52	68.01	285.68	353.69	68.92	415.22	484.13	71.43	808.10	879.53
Cryotherapy	10.32		10.32	10.32	194.1	204.44			0.00			0.00			0.00
Cold conization	293.15	188.17	481.32	293.15		293.15	293.15	382.67	675.81	367.54	811.69	1179.22	367.54	1512.60	1880.13
Simple hysterectomy	409.48	309.35	718.83	409.48	280.8	690.32	410.60	689.95	1100.55	446.63	1007.12	1453.75	446.63	1906.04	2352.67
Simple radiotherapy	290.18	269.68	559.86	290.18	490.7	780.89	292.19	633.49	925.68	384.98	902.93	1287.91	384.98	1720.13	2105.11

Sources: Levin and others (2010) [10]; Shi and others (2012) [27].
Note: LEEP = loop electrosurgical excision procedure; OOP = out of pocket; VIA = visual inspection with acetic acid.
The OOP direct medical costs are 35 percent of total treatment costs shown in annex 16.A1 we assume 35 percent of total treatment costs are privately financed in China (WHO Global Health Observatory). The OOP direct non-medical costs are transport and waiting times for patients. We adjusted transport and waiting times obtained from Shy and others (2012) with new estimates of average wage rates by quintile.

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Table A4
Sensitivity analysis parameter estimates and ranges.

Parameter	Point estimate	Estimate or range	Sources
Screening with cytology: frequency[1] and coverage (percent)			
Income quintile (lowest to highest)			
1. Once per lifetime	21	21–70	a, b
2. Once per lifetime	34	34–70	a, b
3. Three times per lifetime	43	43–70	a, b
4. Three times per lifetime	47	47–70	a, b
5. Five times per lifetime	51	51–70	a, b
Loss to follow up (percent)			
Income quintile (lowest to highest)			
1	62	15, 39	Assumed
2	40	15, 24	Assumed
3	22	15, 22	Assumed
4	13	15, 17	Assumed
5	5	11, 15	Assumed
Vaccine characteristics			
Vaccine cost per fully immunized girl, including wastage and handling (US$)	46	10–100	Assumed

Sources:
a. Gakidou, Nordhagen, and Obermeyer (2008) [37].
b. World Health Organization (2012) [48].
Note:
1. We estimated the frequency of screening at 1× and 5× per lifetime for all income quintiles in sensitivity analysis.
2. HPV = human papillomavirus.

Table A5
Sensitivity analysis, for HPV vaccination costs at US$10, US$46 and US$100 per fully vaccinated girl (US$ 2009).

Quintile	I	II	III	IV	V
HPV vaccination at US$10 per fully vaccinated girl					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$6,217,285	$6,220,191	$6,240,420	$6,246,679	$6,159,970
Gov't cost/death averted	$2161	$2179	$2340	$2399	$2608
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$1,633,160	$2,240,688	$2,785,626	$4,417,303	$7,041,335
Savings as a percentage of income	59%	39%	33%	35%	30%
Cancer reduction	44%	44%	43%	43%	44%
HPV vaccination at US$46 per fully vaccinated girl					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$31,417,285	$31,420,191	$31,440,420	$31,446,679	$31,359,970
Gov't cost/death averted	$10,920	$11,009	$11,789	$12,076	$13,277
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$1,633,160	$2,240,688	$2,785,626	$4,417,303	$7,041,335
Savings as a percentage of income	59%	39%	33%	35%	30%
Cancer reduction	44%	44%	43%	43%	44%
HPV vaccination at US$100 per fully vaccinated girl					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$69,217,285	$69,220,191	$69,240,420	$69,246,679	$69,159,970
Gov't cost/death averted	$24,059	$24,254	$25,962	$26,592	$29,280
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$1,633,160	$2,240,688	$2,785,626	$4,417,303	$7,041,335
Savings as a percentage of income	59%	39%	33%	35%	30%
Cancer reduction	44%	44%	43%	43%	44%

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Table A6
Sensitivity analysis, assuming treatment costs increase by 50% and 100% compared to baseline (US$ 2009).

Quintile	I	II	III	IV	V
Baseline strategy					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$31,417,285	$31,420,191	$31,440,420	$31,446,679	$31,359,970
Gov't cost/death averted	$10,920	$11,009	$11,789	$12,076	$13,277
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$1,633,160	$2,240,688	$2,785,626	$4,417,303	$7,041,335
Savings as a percentage of income	59%	39%	33%	35%	30%
Cancer reduction	44%	44%	43%	43%	44%
Treatment costs increased by 50%					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$31,035,156	$31,057,311	$31,085,113	$31,103,101	$30,939,508
Gov't cost/death averted	$10,787	$10,882	$11,655	$11,944	$13,099
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$1,899,093	$2,506,089	$3,040,532	$4,714,290	$7,310,555
Savings as a percentage of income	69%	44%	36%	37%	31%
Cancer reduction	44%	44%	43%	43%	44%
Treatment costs increased by 100%					
Deaths averted	2877	2854	2667	2604	2362
Government costs (incremental)	$30,647,484	$30,682,085	$30,728,534	$30,760,469	$30,550,290
Gov't cost/death averted	$10,653	$10,751	$11,522	$11,813	$12,934
Treatment-seeking cases of cancer averted	3540	3511	3312	3256	2999
Patient cost savings	$2,165,026	$2,771,490	$3,295,438	$5,011,276	$7,579,775
Savings as a percentage of income	78%	48%	39%	40%	32%
Cancer reduction	44%	44%	43%	43%	44%

Mean cancer reductions and incremental cost-effectiveness ratios by cost per vaccinated girl and availability of screening test.[a]

	Mean cancer reduction (%)	Cost per vaccinated girl[b]					
		I$10	I$25	I$50	I$100	I$150	I$200
Quintile 1							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Cytology once per lifetime	0.12	Dom	Dom	Dom	Dom	Dom	Dom
Vaccination alone	43.94	$513	$1357	$2764	$5578	$8391	$11,205
Vaccination and cytology once per lifetime	44.02	$37,993	$37,993	$37,993	$37,993	$37,993	$37,993
Quintile 2							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Cytology once per lifetime	0.56	Dom	Dom	Dom	$4883	$4883	$4883
Vaccination alone	43.94	$513	$1357	$2764	$5600	$8505	$11,409
Vaccination and cytology once per lifetime	44.11	$17,289	$17,289	$17,289	$17,289	$17,289	$17,289
Quintile 3							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Cytology 3 times per lifetime	4.95	Dom	Dom	Dom	$2766	$2766	$2766
Vaccination alone	43.94	$513	$1357	$2764	$6250	Dom	Dom
Vaccination and cytology 3 times per lifetime	46.21	$6314	$6314	$6314	$6314	$9412	$12,568
Quintile 4							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Cytology 3 times per lifetime	6.51	Dom	Dom	$2575	$2575	$2575	$2575
Vaccination alone	43.94	$513	$1357	$2764	Dom	Dom	Dom
Vaccination and cytology 3 times per lifetime	47.00	$5612	$5612	$5612	$6426	$9672	$12,919
Quintile 5							
Natural history (no screening or vaccination)	–	–	–	–	–	–	–
Cytology 5 times per lifetime	14.63	Dom	Dom	$2323	$2323	$2323	$2323
Vaccination alone	43.94	$513	$1357	$2764	Dom	Dom	Dom
Vaccination and cytology 5 times per lifetime	51.90	$4511	$4511	$4511	$7098	$10,684	$14,270

Costs are expressed in 2009 US dollars.

[a] Values represent incremental cost-effectiveness ratios (the ratio of the mean-costs divided by the mean-effects of best-fitting parameter set) expressed as cost per year of life saved (international dollars per YLS). "Dom" denotes strategies that were either more costly and less effective or less costly and less effective than alternative options, and are thus considered Dom.

[b] Costs per vaccinated girl includes 3 doses of vaccine, wastage, freight and supplies, administration, immunization support, and programmatic costs.

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