Projections up to 2100 and a budget optimisation strategy towards cervical cancer elimination in China: a modelling study

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Summary

Background **The incidence of cervical cancer in China is increasing rapidly. We aimed to forecast the age-standardised incidence of cervical cancer in China up to 2100, and to determine the optimal strategy to eliminate cervical cancer under different budget scenarios.**

Methods **In our modelling study, we developed an adapted and calibrated hybrid model to estimate the incidence of cervical cancer in urban and rural China until 2100. All 1·15 billion Chinese women living or projected to live during 2015–2100, under the projected trends in ageing, urbanisation, and sexual activity were considered. We assessed several scenarios of budget constraints (a current budget [2012–18], twice the current budget, and no budget constraints), implementation of human papillomavirus vaccination (with different target populations and coverage), and cervical cancer screening characteristics (with different target ages, screening intervals, and coverage). We used a budget optimisation process to select the best available combinations of vaccination and screening. The primary outcomes were the annual incidence of cervical cancer in 2015–2100, and the year of elimination (the first year in which the incidence was expected to be lower than four new cases per 100 000 women).**

Findings **Under the current strategy, by 2100, the age-standardised incidence of cervical cancer is projected to increase to three times the incidence in 2015. However, if China adopts an optimal strategy under the current budget from 2020 onwards (namely, introducing vaccination of 95% coverage for girls aged 12 years, and expanding coverage of once in a lifetime screening for women aged 45 years of 90% in urban areas and 33% in rural areas), the annual age-standardised incidence of cervical cancer is predicted to decrease to fewer than four new cases per 100 000 women (ie, elimination) by 2072 (95% CI 2070–74) in urban China and 2074 (2072–76) in rural China. If the current budget were doubled from 2020 onwards, elimination would be achieved by 2063 (2059–66) in urban China and 2069 (2066–71) in rural China. The earliest possible year of cervical cancer elimination would be 2057 (2053–60) in urban China and 2060 (2057–63) in rural China, if vaccination coverage for girls aged 12 years and coverage of screening at 5-year intervals for women aged 35–64 years was maximised, with no budgetary restrictions.**

Interpretation **Cervical cancer incidence in China will continue to increase under current cervical cancer prevention strategies. However, under our budget optimisation strategy from 2020 onwards, cervical cancer could be eliminated as a public health problem by the early 2070s. Elimination could be achieved by the late 2050s by increasing the budget towards vaccination against human papillomavirus and cervical cancer screening.**

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Introduction

In May, 2018, WHO made a global call for action towards the elimination of cervical cancer.[1] A modelling study[2] projected that cervical cancer could be considered to be eliminated as a public health problem (incidence of less than four new cases per 100 000 women per year) in Australia within the next decade. This promising timeframe was a result of the combined effects of a low incidence of cervical cancer, high coverage of human papillomavirus (HPV) vaccination, and a high uptake of screening in Australia. However, in China, population-wide cervical cancer screening has only been available since 2009, and it was only in 2016 that the HPV vaccine was approved.[3] Furthermore, the population coverage of cervical cancer screening is only 21·4%, and coverage of HPV vaccination is poor because the vaccine is yet to be introduced to the national immunisation programme.[3,4] As such, the elimination of cervical cancer in China will take greater efforts and a longer time to achieve than elimination in Australia. In our modelling study, we aimed to develop an adapted and calibrated model for China, to forecast cervical cancer incidence up to 2100 and to assess budget optimisation strategies for eliminating cervical cancer.

Research in context

Evidence before this study

We searched PubMed, Google Scholar, and China National Knowledge Infrastructure, without language restrictions, for studies published before April 28, 2019, with the search terms "cervical cancer", "timing OR timeline OR timeframe", and "elimination". The search was restricted to studies that reported the timeframe of cervical cancer elimination. We identified two modelling studies. One study estimated that cervical cancer would likely be eliminated in the next decade in Australia. Another global study estimated that China would eliminate cervical cancer by 2060–65 by adopting a rapid scale-up scenario, but this study used several simplified assumptions and failed to integrate budget constraints and societal transitions. Although the Chinese Government has assigned substantial funding for cervical cancer prevention since 2009, the incidence of cervical cancer is increasing rapidly in China. Few studies have evaluated the effects of cancer prevention strategies in China and, to our knowledge, no study has determined the optimal strategy for elimination of cervical cancer worldwide.

Added value of this study

Given ageing, urbanisation and sexual activity trends, the incidence of cervical cancer in China is predicted to triple from 2015 to 2100 if the current strategy remains unchanged. As such, neither urban nor rural China are likely to achieve an incidence of fewer than four new cases per 100 000 women by the end of this century. Our estimates highlight that, even without increasing the relevant budget, China can eliminate cervical cancer by optimising the cervical cancer prevention strategy. For example, if China adopts an optimal and tailored strategy from 2020 onwards (namely, introducing vaccination for girls aged 12 years and expanding population coverage of screening by adopting a wide screening interval for women), cervical cancer elimination can be achieved in China in the early 2070s, with no increase to the budget. However, elimination could be achieved in the late 2050s by increasing the cervical cancer prevention budget in China.

Implications of all the available evidence

China has made efforts to reduce the burden of cervical cancer with the initiation of a health-care reform in 2009. Our findings suggest that, although the current strategies of cervical cancer prevention will benefit Chinese women, policy makers should give priority to the effective implementation of high-coverage HPV vaccination and cervical screening in both urban and rural areas. By optimising use of the budget, elimination of cervical cancer can be achieved in China with no budgetary increase, resulting in more than 5 million cervical cancer cases being averted by the end of the century. However, the current budget is insufficient, and more investment should be directed towards cervical cancer prevention, particularly to cervical cancer screening being targeted towards unvaccinated women.

Methods

Overview

In this modelling study, we assessed the effect of several HPV vaccination and cervical cancer screening scenarios on cervical cancer elimination in China. For these scenarios, we considered all 1·15 billion women projected to live in China between 2015 and 2100, including 171 birth cohorts born between 1930 and 2100, to obtain estimates of the annual incidence of cervical cancer. Elimination was defined as the first year when the age-standardised annual incidence decreased to fewer than four new cases per 100 000 women.[2] We stratified all populations projected to live between 2015 and 2100 by year of birth (from 1930 to 2100), sex (male or female), age (by year of age from 0 to 84 years, or ≥85 years), area (urban or rural), and sexual activity (high [individuals with several lifetime sexual partners, low [individuals with one lifetime sexual partner], and none). We incorporated 14 HPV strains (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), which are high-risk for the development of cervical cancer and its precursor lesions, into our analyses. The intervention for cervical cancer prevention includes bivalent HPV vaccination and cervical cancer screening. The primary outcomes were the annual incidence of cervical cancer in 2015–2100 and the year of cervical cancer elimination.

See Online for appendix

Model

Hybrid models have been used worldwide in cervical cancer modelling studies.[5,6] For our analysis, we developed a Chinese adapted and calibrated hybrid model to estimate the prevalence of high-risk HPV and the incidence of cervical cancer. Briefly, this model consisted of a deter-ministic age-structured compartmental dynamic model and an individual-based stochastic Monte Carlo simulation model. The model structure and equations are shown in the appendix (pp 2–10). We used the deterministic model to simulate the sexual trans-mission of HPV infections between men and women, whereas we used the stochastic model to simulate the natural history of cervical cancer and to obtain the number of cervical cancer cases asso-ciated with HPV infections. Each individual was entered into the model at their age in 2014 or the year of their birth, if after 2014 and, within the model, they were randomly allocated to a new state, based on the transition proba-bilities. Individuals were transitioned between states representing no current or previous infection or vaccine (in which they were considered susceptible to infections); immunity (including infection-acquired immunity and vaccine-acquired immunity); infection; development of cervical intraepithelial neoplasia (CIN) grade 1, CIN2, or CIN3 disease (representing mild, moderate, and severe dysplasia); effective detection and treatment; and cervical cancer likely to cause death or to extend until the simulation end point. Neonates are assumed to be in the uninfected state at birth, and all-cause mortality was present in all states. We assumed that individuals with CIN3 do not recover naturally, and that infection-acquired immunity will wane over time, whereas vaccine-acquired immunity will be lifelong. If HPV vaccination is available, individuals aged 12 years were considered to be vaccinated at predefined coverages in the dynamic model. Cervical cancer screening fits in the natural history model where individuals are randomly assigned to screening. This two-stage hybrid model was concatenated by the force of infection—ie, the age-specific HPV incidence from the deterministic model served as inputs to the stochastic model.

The sexual mixing matrices for every stratum were calculated by use of partner acquisition rates and assortativity of age, area, and sexual activity.[7] Partner acquisition rates were adjusted to maintain the number of male–female sexual partnerships (appendix p 6).[6] We used the Gaussian kernel to model age assortativity because its shape conforms with the patterns observed from sexual activity surveys[6] and age distribution of legitimate sexual partners from marriage registration data.[8] We simulated the force of infections and prevalence for every high-risk HPV strain separately, because of the potential variations on transmission probability between sexual pairs and the substantial differences in vaccine efficacy for each high-risk HPV type. However, in the individual-based stochastic model, we combined the high-risk types other than HPV16 and HPV18 into the non-vaccine group because evidence suggests that the probability of disease progression is much higher with HPV16 and HPV18 infections than with other high-risk HPV types.[9] We modelled co-infections among the HPV16, HPV18, and non-vaccine groups by assuming that disease progression of a given co-infection is dominated by the most aggressive HPV type, whereas type-specific clearance is unaffected by co-infections.

We calibrated our model in a two-stage calibration process. By searching the best fit parameters, we reran the model for a scenario in which the current strategy was maintained, assuming a constant urbanisation rate and sexual activity until the predicted age-specific HPV prevalence and cervical cancer incidence in 2015–2100 were consistent with those in 2014. We used the 2015 birth cohort for the budget optimisation process, to assess which combination of HPV vaccination and cervical cancer screening strategies was the best-available approach to minimise cervical cancer incidence, given the budget constraints (appendix pp 11–16). This cohort was chosen because it is the only cohort likely to live for the entire period of 2015–2100 and, thus, it should be considered a suitable illustration of transformation between the cohort approach and the population approach.

Inputs and assumptions

We used parameters that we obtained from open-source publications or government-released online datasets (appendix pp 18–25). Briefly, we extracted natural history parameters of cervical cancer from literature reviews and demographic data, which we obtained from national statistical databases and publications. We extracted the projected fertility rate of women aged 15–49 years and urbanisation data from the UN Population Division. We extracted the proportion of residents with several sexual partners from a national representative longitudinal study,[10] we extracted the prevalence of high-risk HPV infections from our pooled study[11] in China, and we inferred the efficacy of the bivalent HPV vaccine against 12 months of persistent infection from the PATRICIA trial.[12] We based the sensitivities of screening by cytology, the careHPV test, or a PCR-based HPV test in China on our pooled study.[13,14] Finally, we estimated the population coverage of screening in urban and rural China from a nationally representative survey.[4,15]

For **fertility and urbanisation data from the UN Population Division** see https://population.un.org/

Degree of urbanisation and the proportion of the population with high sexual activity (those with several lifetime sexual partners) have been projected to substantially increase in upcoming decades on the basis of patterns from 2000 to 2015. We assumed that these trends of increasing numbers of people reporting high sexual activity will continue by the year when the values reach the maximum achievable targets, then they will maintain a constant value until 2100. The patterns in sexual activity in China were projected with historical data from the USA as a reference, and the delay in timing of these patterns was determined by use of the Human Development Index.[16] For example, we assumed the proportion of individuals with high sexual activity in China between 2040 and 2045 to be the same as that in the USA between 2005 and 2010, because the predicted Human Development Index in China is equal to the actual Human Development Index values in the USA in these years.[16]

The information on the cost of cervical cancer screening was primarily collected by a microcosting survey[17] in 2008–09, and a Delphi panel was done in 2013, to confirm, validate, and modify the estimates.[18] In October, 2018, we did a panel review involving experts from all seven administrative regions of China (namely, north, northeast, east, central, south, southwest, and northwest China; appendix p 34), to ascertain the average costs of cervical cancer screening and the proportion of women who comply with routine cervical screening in urban and rural China. After validation with data from national and local cervical cancer screening programmes (CCSP),[19,20] we estimated the cost of per screening at US$9·93 in urban areas and $7·21 in rural areas. Marriage registration data from China indicated that women tend to seek male partners older than them, with a mean age gap of about 2 years.[8] As such, the mean age gap between male partners and an age-specific female cohort was set at 2 years in sexual mixing matrices.

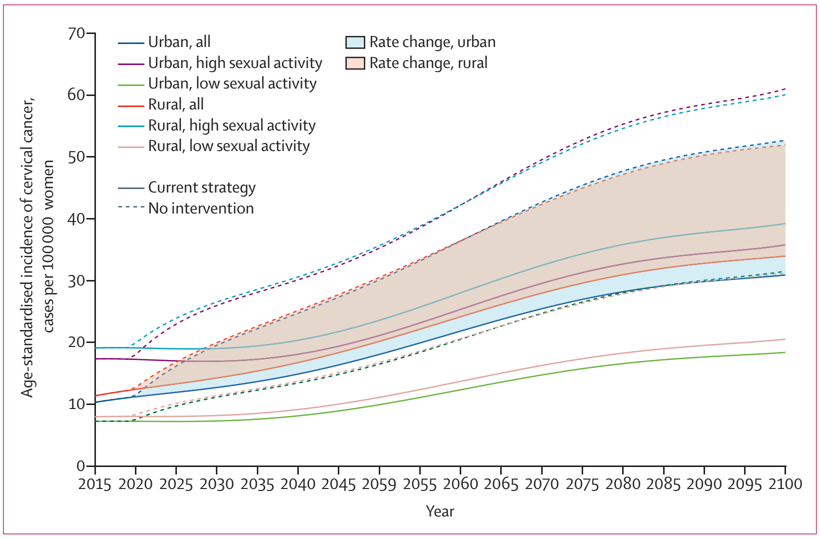

Figure 1: **Age-standardised annual incidence of cervical cancer in China between 2015 and 2100, under the assumptions of continuing the current strategies for HPV vaccination and cervical cancer screening and of no interventions**

No intervention is an assumed scenario in which screening and vaccination are stopped from 2020 onwards. HPV=human papillomavirus.

The expensive prices and restricted supplies of HPV vaccine, particularly for the quadrivalent and nonavalent vaccines, are a substantial obstacle for vaccine roll-out in China.[3] Because domestic bivalent HPV vaccine was the most likely vaccine (rather than the quadrivalent and nonavalent vaccines) to be approved by the National Medical Products Administration of China in 2019, the bivalent HPV vaccine was considered the most likely to be adopted by the national immunisation programme from 2020 onwards.[3,21] However, the cost to the Chinese national immunisation programme would be much lower than the commercial price, which is about \$84·7 per dose.[3] We assumed the cost of the Government-delivered bivalent HPV vaccine would be the same as that enabled by Gavi, the Vaccine Alliance, namely \$4·6 per dose.[21,22] Additionally, the cost of administration of vaccination is \$3·33 per dose.[23] The available budget (ie, the current budget in the model, defined as that between 2012 and 2018) towards cervical cancer prevention in China comprises the national and local financial expenditure of rural and urban CCSPs. We estimated the annual budgets towards cervical cancer prevention are \$78·1 million in rural China and \$132·6 million in urban China, giving a total budget of about \$210·7 million per year (appendix pp 12–13).

Alternative scenarios

The assumed current strategy is that the CCSP will continue to screen women aged 35–64 years in urban and rural China, with 3-year coverages of 26·6% in urban areas and 19·3% in rural areas, and a negligible coverage of HPV vaccination because it has not been introduced to the national immunisation programme.[3,4,15] We considered nine major alternative scenarios for HPV vaccination and cervical cancer screening in China from 2020 to 2100 (appendix p 11). Population coverage of every major alternative scenario was varied from 0% to maximum achievable coverage by 0·01%. As such, we evaluated approximately 1·2 billion cervical cancer prevention strategies that encompassed all possible combinations of alternative scenarios of budget constraints (the current budget, twice the current budget, and no budget constraints), screening (different target ages, screening intervals, and coverage), and vaccination (different target populations and coverage).

Data from China's Expanded Programme on Immunization suggested that hepatitis B vaccine coverage is about 95% in China because the vaccine is free to children aged 14 years or younger.[24] The Government has set the cervical cancer screening target at 80% coverage.[25] As such, we assumed the maximum achievable coverage of a two-dose HPV vaccine regimen would be 95% and that maximum achievable coverage of cervical cancer screening would be 90%.

Sensitivity analysis

We did univariate sensitivity analysis by varying key parameters in the model to quantify their effects on the predicted year of elimination. Variables altered in the sensitivity analyses comprised the projected trends in fertility rate, urbanisation, and sexual activity; the price and efficacy of the vaccine; the cost and sensitivity of screening; the maximum achievable coverages of vaccination and screening; compliance to routine cervical screening; cross-protection from vaccination; variations in the total budget for cervical cancer prevention; and the inclusion of boys in the HPV vaccination schedule.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The estimated age-standardised annual incidences of cervical cancer in China between 2015 and 2100, under the current strategy and with no intervention, are shown in figure 1. Under the current strategy, by 2100, the age-standardised incidence of cervical cancer is projected to increase to three times the incidence in 2015. With no interventions, the incidence is projected to increase to five times that in 2015 by 2100.

The optimal strategy for cervical cancer prevention from 2020 onwards was evaluated through different combinations of HPV vaccination and cervical cancer screening according to budget (table 1). The optimal strategy (of all available strategies) under the current budget (2012–18) would comprise 95% coverage of the vaccine in girls aged 12 years in urban and rural areas,

	HPV vaccination for girls		Cervical cancer screening			Additional notes
	Coverage (%)	Proportion of budget (%)	Coverage (%)	Proportion of budget (%)	Age at screening, years	
Urban						
Current budget (vaccination for girls only)	95%	57%	90%	43%	45	Also screening 27% of women aged 35 years
Current budget (consistent strategy in urban and rural China)	95%	69%*	80%	31%*	45	··
200% of current budget	95%	29%	65%	71%	35–64, every 5 years	··
Maximum coverage of vaccination and screening (assumed strategy)	95%	22%	90%	78%	35–64, every 5 years	2·55 times the current budget
Current budget (vaccination for boys, if best available strategy)	95%	57%	90%	33%	45	In sensitivity analysis: vaccination of 16% of boys, accounting for 10% of the budget
110% of current budget	95%	52%	72%	48%	35 and 50	In sensitivity analysis
90% of current budget	95%	63%	89%	37%	45	In sensitivity analysis
150% of vaccine price	95%	74%	72%	26%	45	In sensitivity analysis
50% of vaccine price	95%	41%	81%	60%	35 and 50	In sensitivity analysis
120% of screening cost	95%	57%	90%	43%	45	In sensitivity analysis: also screening 7% of women aged 35 years
80% of screening cost	95%	57%	73%	43%	35 and 50	In sensitivity analysis
Achievable vaccination coverage set at 85%	85%	51%	90%	49%	45	In sensitivity analysis: also screening 43% of women aged 35 years
Achievable screening coverage set at 80%	95%	57%	80%	43%	45	In sensitivity analysis: also screening 37% of women aged 35 years
Rural						
Current budget (vaccination for girls only)	95%	87%	33%	13%	45	··
Current budget (consistent strategy in urban and rural China)	95%	69%*	80%	31%*	45	··
200% of current budget	95%	43%	90%	57%	35–64, every 10 years	Also screening 10% of women aged 50 years
Maximum coverage of vaccination and screening (assumed strategy)	95%	28%	90%	72%	35–64, every 5 years	3·05 times the current budget
Current budget (vaccination for boys, if best available strategy)	95%	87%	33%	13%	45	In sensitivity analysis: vaccination of no boys
110% of current budget	95%	79%	57%	21%	45	In sensitivity analysis
90% of current budget	95%	96%	8%	4%	45	In sensitivity analysis
150% of vaccine price	85%	100%	0	0	··	In sensitivity analysis
50% of vaccine price	95%	62%	90%	38%	45	In sensitivity analysis: also screening 5% of women aged 35 years
120% of screening cost	95%	87%	27%	13%	45	In sensitivity analysis
80% of screening cost	95%	87%	41%	13%	45	In sensitivity analysis
Achievable vaccination coverage is 85%	85%	78%	55%	22%	45	In sensitivity analysis
Achievable screening coverage is 80%	95%	87%	33%	13%	45	In sensitivity analysis

The achievable coverage of vaccination was set at 95% and of screening was set at 90%. The current budget is that between 2012 and 2018. For sensitivity analyses, the achievable coverage of vaccination was set at 85% and screening was set at 80%. HPV=human papillomavirus. ··=not applicable. *Proportion of national total budget (combined budget of urban and rural areas).

Table 1: **Budget optimisation strategies of HPV vaccination and cervical cancer screening in urban and rural China**

and coverage of once in a lifetime screening for women aged 45 years of 90% in urban areas and 33% in rural areas. Under the optimal strategy for the current budget, the annual age-standardised incidence of cervical cancer is likely to decrease to fewer than four new cases per 100 000 women (ie, elimination) by 2072 (95% CI 2070–74) in urban China and 2074 (2072–76) in rural China (figure 2A). If a consistent budget optimisation strategy was adopted across urban and rural China (table 1), elimination would likely be achieved in 2072 (2070–74) in urban China and 2073 (2071–75) in rural China (figure 2B).

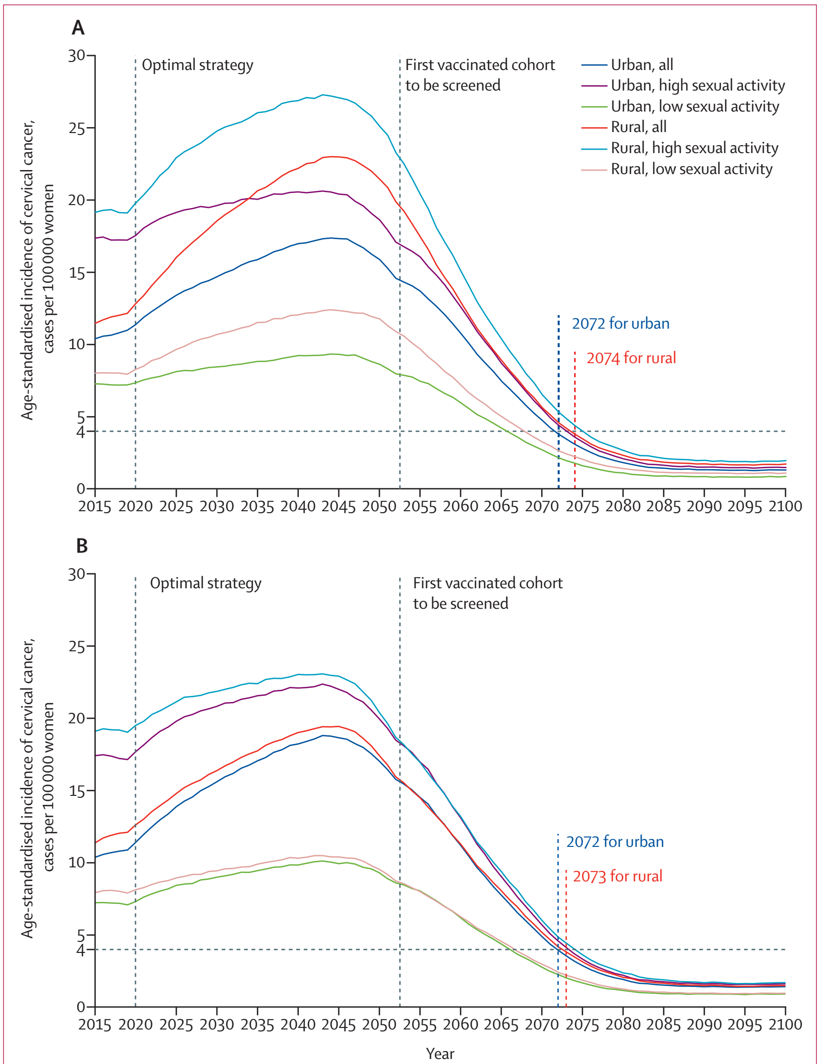

***Figure 2:* Age-standardised annual incidence of cervical cancer in China between 2015 and 2100, for budget optimisation strategies under the current budget (2012–18)**

(A) Data are reflective of the current split of the budget between urban and rural China (because they receive unequal proportions of the budget). (B) Under the assumption that urban China would receive a consistent budget to rural China.

The optimal strategies and speed of achieving elimination varied with budget (table 1) and elimination would therefore be achieved sooner by increasing the budget. For example, our model predicts that if the current budget were doubled from 2020 onwards, elimination would be achieved by 2063 (95% CI 2059–66) in urban China and 2069 (2066–71) in rural China (figure 3A). The earliest possible year of cervical cancer elimination was estimated to be 2057 (2053–60) in urban China and 2060 (2057–63) in rural China, providing that vaccination coverage for girls aged 12 years and coverage of screening at 5-year intervals for women aged 35–64 years were maximised, with no budgetary restrictions (figure 3B). Maximising screening and vaccination coverage would require corresponding budgets to be expanded to 2·55 times the current budget for urban areas and 3·05 times the current budget for rural areas. Under this maximum assumption but assuming that cervical cancer screening for vaccinated women was discontinued, elimination would be achieved in 2062 (2058–68) in urban China and 2066 (2062–72) in rural China (figure 3C).

Notably, although about 5·69 million cases of cervical cancer would be further averted by 2020–2100 by adopting the optimal strategies under the current budget (with vaccination for girls only), the estimated number of cases of cervical cancer with this optimal strategy under the constraints of the current budget are higher than those for the current strategy in 2020–49, particularly in 2020–29 (table 2). This finding is because the optimal strategy under the restricted current budget prioritises vaccination above screening. By expanding the budget to enable maximum coverage of screening and vaccination, 2·88 million cases of cervical cancer could be further averted by 2049.

The findings of our analysis were sensitive to our assumptions regarding cross-protection and the efficacy of the HPV vaccine (figure 4). However, varying assumptions about screening, demographic characteristics, and the total budget had little effect on the predicted year of elimination. Our baseline estimates of the year of cervical cancer elimination were 2072 in urban China and 2074 in rural China, but our sensitivity analysis indicates that the elimination year could vary from 2070 to 2074 in urban areas and 2072 to 2076 in rural areas.

Discussion

In this modelling study, we estimate that if the current coverage of vaccination and screening in China are maintained, under projected ageing, urbanisation, and sexual activity trends, the annual incidence of cervical cancer will continue to increase and the incidence will triple by 2100. However, if China adopts the optimal cervical cancer prevention strategy—namely, introducing vaccination for girls aged 12 years and expanding population coverage of once in a lifetime cervical cancer screening for women—from 2020 onwards, under the current budget, the annual incidence of cervical cancer in China is likely to decrease to fewer than four new cases per 100 000 women by 2072 (95% CI 2070–74) in urban China and 2074 (2072–76) in rural China. We predict that elimination would be achieved much earlier by increasing the budget. If the budget were doubled from 2020 onwards, we project elimination by 2063 (2061–65) in urban China and 2069 (2067–71) in rural China. The earliest we estimate elimination could be achieved would be 2057 (2053–60) in urban China and 2060 (2057–63) in rural China, if the corresponding budgets were increased to 2·55 times the current budget in urban areas and 3·05 times the current budget for rural areas.

There are several strengths to our analysis. To our knowledge, this is the first study incorporating a dynamic transmission model, an individual-based stochastic model, and a budget optimisation process to estimate the timeframe for elimination of cervical cancer in China. We used a deterministic dynamic transmission model rather than a static model to capture herd immunity from HPV vaccination. However, a deterministic dynamic transmission model always results in the same output, with the same set of parameter values and initial conditions, because the interactions between the uncertainties of several parameters cannot be measured.[26] By contrast, a grafted stochastic model produces different outputs every time the model is run, because it accounts for randomness. Assumptions on population coverage of vaccination and screening that do not consider the available budget and constraints of resources seem less convincing to policy makers and stakeholders and can thus have a lesser impact on policy, particularly in low-income and middle-income countries (LMICs). Our study provides an optimised strategy with no budget increase and under the constraints of accessibility of populations and resources, which makes our strategy more feasible and applicable than the assumed scenarios in a response to the WHO call to eliminate cervical cancer.

Model-projected trends in cervical cancer incidence were generally based on the long-term and successive data from cancer registries.[27] In China, only a few cancer registries can provide 20-year successive estimates of cancer incidence.[28] Further, the restricted population from these few cancer registries does not represent the total general population of China.[28] Notably, a substantial decrease in mortality from cervical cancer was reported in China[29] from 1973–75 to 2004–05, whereas the incidence of and mortality from cervical cancer has increased since 2005.[30] This temporal pattern of mortality from and incidence of cervical cancer in China might link to several determinants, such as the changes in the age of the population, urbanisation, and sexual activity. As such, we systematically assessed the temporal trends in cervical cancer incidence by considering the rapid changes to society and sexual behaviour being reported in China.

Our findings should be interpreted in consideration of the study's limitations. As with any modelling study, the results that we present are dependent on the assumptions made. For example, the proportion of women complying to routine cervical screening was estimated by an expert panel review, and they are therefore subjective. Progression and regression estimates in the natural history of cervical cancer were primarily determined from the

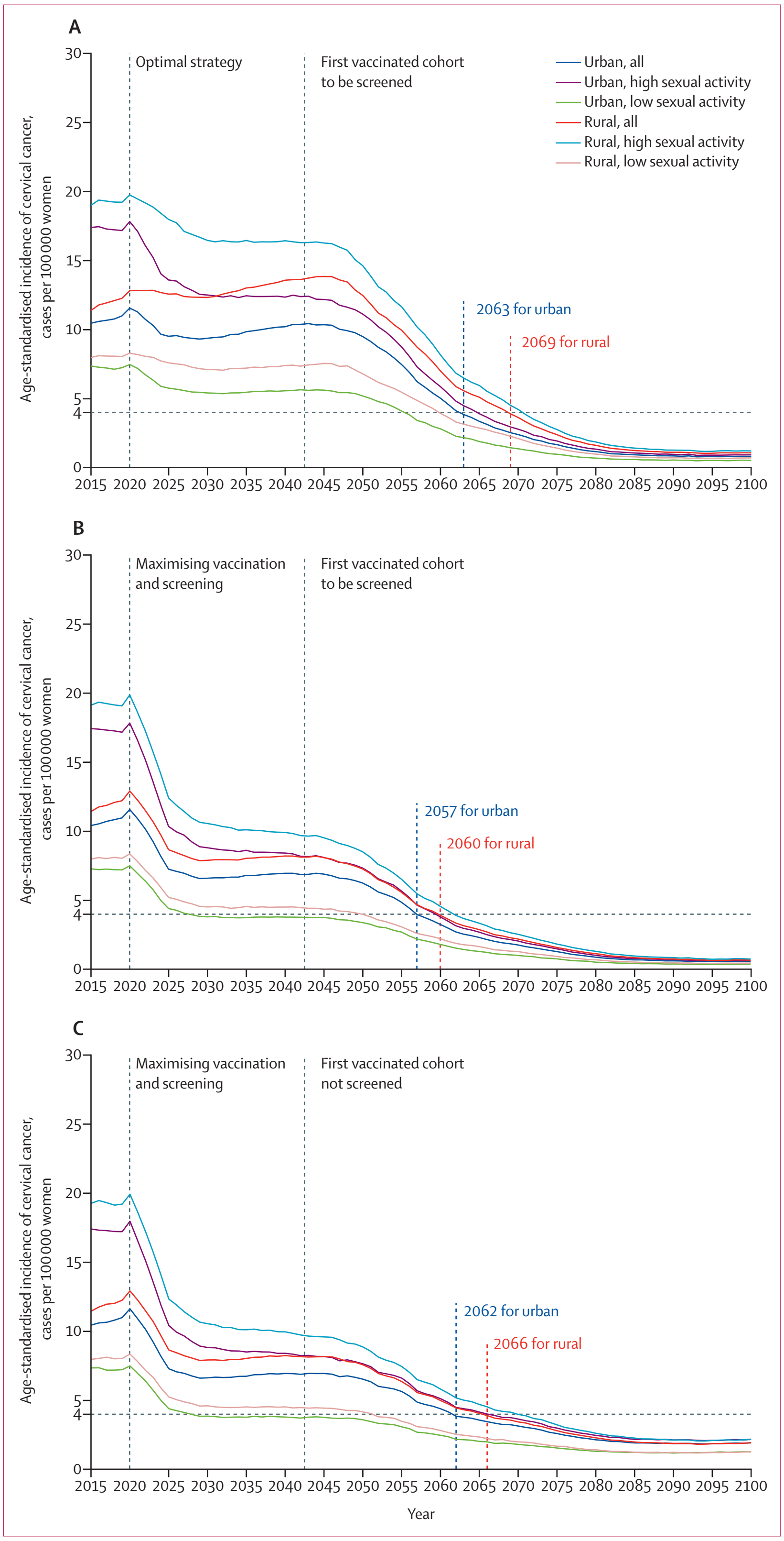

Figure 3: **Age-standardised annual incidence of cervical cancer in China between 2015 and 2100, for strategies under an increased budget**
Assuming 200% of current (2012–18) budget, then optimising vaccination and screening coverage (A); no budget constraints, thereby maximising vaccination and screening coverage (B); or no budget constraints, but discontinuing screening for vaccinated women (C).

	Total cases of cervical cancer				Cases of cervical cancer averted			
	2020–29	2030–49	2050–2100	2020–2100	2020–29	2030–49	2050–2100	2020–2100
Urban								
No intervention	1138	3892	12 240	17 270	..	..	..	..
Current strategy	871	2365	7265	10 501	267	1527	4975	6769
Optimal strategy under current budget	990	2781	2479	6250	148	1111	9761	11 020
Optimal strategy under current budget (consistent across urban and rural areas)	1018	2940	2573	6531	120	952	9667	10 739
Optimal strategy under 200% of current budget	714	1599	1370	3683	424	2293	10 870	13 587
Maximum coverage of vaccination and screening	577	1103	1033	2713	561	2789	11 207	14 557
Maximum coverage of vaccination and screening, and no screening for vaccinated women	577	1107	1353	3037	561	2785	10 887	14 233
Rural								
No intervention	546	1122	3807	5475	..	..	..	..
Current strategy	458	779	2525	3762	88	343	1282	1713
Optimal strategy under current budget	531	998	797	2326	15	124	3010	3149
Optimal strategy under current budget (consistent across urban and rural areas)	508	878	706	2092	38	244	3101	3383
Optimal strategy under 200% of current budget	428	639	500	1567	118	483	3307	3908
Maximum coverage of vaccination and screening	332	404	324	1060	214	718	3483	4415
Maximum coverage of vaccination and screening, and no screening for vaccinated women	332	406	416	1154	214	716	3391	4321

No intervention is an assumed scenario that both screening and vaccination are stopped from 2020 onwards in China. This scenario serves as a reference point, to assess the effectiveness of all other strategies.

Table 2: **Estimated total cervical cancer cases and cases averted for different strategies in China (thousands)**

global medical literature, which might not account for variations between populations. We assumed high effectiveness of the vaccine at two doses in those aged 12 years, and a lifetime duration of protection, which is supported by evidence suggesting that the duration of vaccine protection is likely to be at least 20 years or, potentially, lifelong.[6] The budget optimisation process we used was dependent on a single birth cohort, rather than the whole population, to generate an integrated and applicable strategy for 2015–2100. Although individuals born in 2015 can be considered the most representative cohort for the transformation of the cohort and population approaches, it is likely that the optimal strategy would be different when optimising the budget for the whole population than for a single cohort. The major limitation of our use of optimal strategies under budget constraints is that the optimisation strategy is the best-available combination from the perspective of the whole population or the whole period of investigation whereas, from the individual perspective, some women would not benefit from the optimisation strategy because of the constraints of the restricted budget. The possible solution for this dilemma is increased investment or reduced cost of interventions.

China has substantially improved efforts to improve cervical cancer screening. However, cervical cancer screening coverage in China remains low relative to that of other countries, and further expansion of the CCSP will be needed. Our estimates suggest that population coverage of screening is more important than the frequency of screening, and the once in a lifetime screening at age 45 years might be the best available strategy, given the insufficient budget. The optimal age at which to screen is driven from the distinctive age-specific prevalence of CIN2 (or more severe CIN) and high-risk HPV in Chinese women.[11] Because the HPV vaccine was only approved in China in 2016, vaccination coverage is low.[3] The absence of an HPV vaccination programme and the potential benefits of HPV vaccination highlight the importance of introducing the HPV vaccine into the Chinese national immunisation programme. This *Escherichia coli*-produced vaccine is efficacious against high-grade genital lesions and persistent infection in Chinese women.[21] The easy scale-up and low manufacturing cost of the manufacturing process is promising for inclusion within the Chinese national immunisation programme. In accordance with our estimates, an increased budget could provide a substantial intermediate benefit (2·88 million cervical cancer cases would be further averted by 2049) before elimination in the long-term, particularly through cervical cancer screenings targeted at unvaccinated women in 2020–49. From this perspective, a cost-effectiveness analysis that compares quality-adjusted life-years might be worthwhile. Intermediate-term goals might be more consistent with the timescales of policy makers, but might delay elimination.

A 2019 study by Michaela Hall and colleagues[2] estimated that the age-standardised annual incidence of cervical cancer will decrease to fewer than four new cases per 100 000 women in Australia by 2028 (range 2021–35), and cervical cancer-related mortality will decrease to less than one death per 100 000 women by 2034 (2025–47). This outcome means that Australia is positioned to be the first to achieve cervical cancer elimination, through decades of mass HPV vaccination and cervical cancer screening. In our study, we estimate that China would take more than 50 years to achieve elimination if it were to adopt the optimal strategy from 2020 onwards because of the relatively higher baseline burden of cervical cancer and the inadequate control measures in China. We did not model the mortality of cervical cancer because the mortality results from a combination of the incidence and advances in treatment; the effects of treatment are difficult to accurately measure, and the corresponding expenditures are not covered by the budget for cervical cancer prevention in China.

A previous global modelling study[28] predicted that the age-standardised incidence of cervical cancer in China would reduce to less than four new cases per 100 000 women in 2060–65 by rapid scale-up of screening and vaccination coverage from 2020 onwards. Estimates in this global modelling study have several limitations, which we have addressed in our study. First, the baseline incidence of cervical cancer was estimated from 12 selected cancer registries in China whereas, in our study, this incidence was extracted from 339 qualified cancer registries from all 31 provinces in China.[31,32] Second, in the previous study,[28] the trend in cervical cancer incidence was estimated from two Chinese cancer registries, showing a 10·8% increase per year in 2012–20, and no change in 2021–99—an abrupt cessation of a sharp growth trend. Finally, the estimates in the previous study were based on several strong assumptions. For example, use of a nonavalent vaccine with 80–100% coverage from 2020 onwards seems impossible in the foreseeable future in China, when considering the expensive prices and inadequate supplies of the nonavalent vaccine.[3]

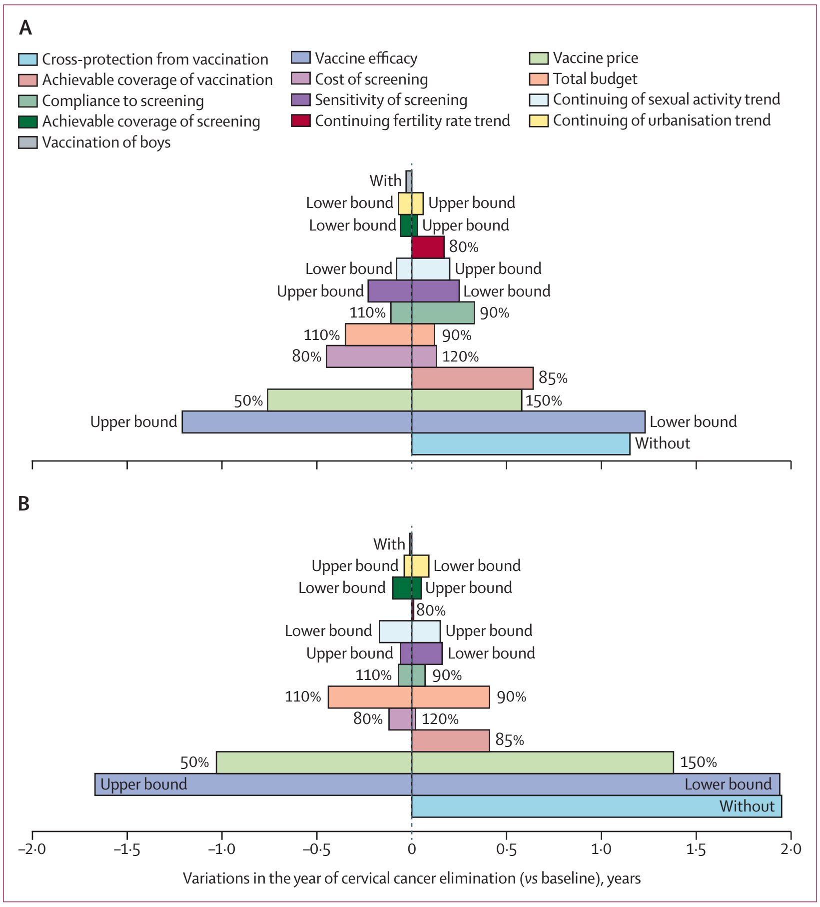

Figure 4: **Sensitivity analysis of the factors affecting the likely year of cervical cancer elimination, given the current (2012–18) budget in urban China (A) and rural China (B)**

Data labels are the proportion of baseline values or the lower and upper bound of 95% CIs of variables. With and without indicate the presence or absence of the assumption of cross-protection from vaccination or vaccination of boys. For achievable coverage of vaccination and screening, the labels represent the absolute values of population coverage.

Our findings imply that the elimination of cervical cancer could be achieved in LMICs by adopting optimal measures. Compared with high-income countries, where a lower incidence of cervical cancer and a higher population coverage with the HPV vaccine are reported, LMICs are likely to take several more decades to eliminate cervical cancer. Encouragingly, many LMICs have gained HPV vaccines through HPV vaccination pilot studies, and national programmes.[33] Since 2013, Gavi has approved support for several programmes,[34] with a goal of vaccinating at least 30 million girls by 2020. Lessons learnt from these LMICs can inform global and national decision makers how best to implement HPV vaccination, whether through phased introduction or simultaneous national roll-out.[35] As such, the HPV vaccine is likely to have a substantial effect on the future burden of cervical cancer, particularly where screening is non-existent or restricted in scale.

In summary, we estimate that the incidence of cervical cancer will substantially increase in China between

2015 and 2100, if the current coverage of vaccination and screening is maintained. However, if China adopts the optimal cervical cancer prevention strategy (ie, introducing vaccination for girls aged 12 years and expanding population coverage of once in a lifetime cervical cancer screening for women) from 2020 onwards, under the current budget, cervical cancer could be effectively eliminated as a public health concern in China by the early 2070s or, at the earliest, the late 2050s if the budget were increased and coverages of vaccination and screening were maximised.

Contributors

FZ obtained funding for the study. CX and FZ designed the study. CX and FZ collected the data. CX and SH cleaned and verified data. CX analysed the data. SH and FZ supervised the analysis and generation of the results. CX drafted and finalised the manuscript. CX, XX, XZ, YQ, NB, KC, RH, and FZ interpreted the results and critically revised the manuscript for intellectual content and approved the final version of the manuscript. All authors have read and approved the final manuscript.

Declaration of interests

YQ and FZ report grants from GlaxoSmithKline Biologicals, Merck & Co, and Xiamen Innovax Biotech to their institution, to undertake clinical trials on the human papillomavirus (HPV) vaccine. KC is the co-principal investigator of an investigator-initiated trial of cytology and primary HPV screening in Australia (COMPASS), which is conducted and funded by the VCS Foundation, a government-funded health promotion charity. The VCS Foundation previously received equipment and a funding contribution for the COMPASS trial from Roche Molecular Systems and Roche Tissue Diagnostics (AZ, USA). However, neither KC nor her institution (on her behalf) receives direct funding from industry for this trial or any other project. CX, SH, XX, XZ, NB, and RH declare no competing interests.

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References

1 WHO. WHO Director-General calls for all countries to take action to help end the suffering caused by cervical cancer. May 19, 2018. https://www.who.int/reproductivehealth/call-to-action-elimination-cervical-cancer/en/ (accessed Aug 13, 2019).

2 Hall MT, Simms KT, Lew JB, et al. The projected timeframe until cervical cancer elimination in Australia: a modelling study. *Lancet Public Health* 2019; **4:** e19–27.

3 Zhao F, Qiao Y. Cervical cancer prevention in China: a key to cancer control. *Lancet* 2019; **393:** 969–70.

4 Bao H, Zhang L, Wang L, et al. Significant variations in the cervical cancer screening rate in China by individual-level and geographical measures of socioeconomic status: a multilevel model analysis of a nationally representative survey dataset. *Cancer Med* 2018; **7:** 2089–100.

5 Kim JJ, Goldie SJ. Health and economic implications of HPV vaccination in the United States. *N Engl J Med* 2008; **359:** 821–32.

6 Choi HCW, Jit M, Leung GM, Tsui KL, Wu JT. Simultaneously characterizing the comparative economics of routine female adolescent nonavalent human papillomavirus (HPV) vaccination and assortativity of sexual mixing in Hong Kong Chinese: a modeling analysis. *BMC Med* 2018; **16:** 127.

7 Walker R, Nickson C, Lew JB, Smith M, Canfell K. A revision of sexual mixing matrices in models of sexually transmitted infection. *Stat Med* 2012; **31:** 3419–32.

8 Liu S, Liang HY. Study on the trend of age gap change of married couples and the reasons in China since 1990. *South China Population* 2014; **29:** 43–50.

9 Dong L, Hu SY, Zhang Q, et al. Risk prediction of cervical cancer and precancers by type-specific human papillomavirus: evidence from a population-based cohort study in China. *Cancer Prev Res (Phila)* 2017; **10:** 745–51.

10 Pan S. Sexuality of Chinese 2000–2015: main results from four national population sampling surveys. Hong Kong: 1908 Company Limited, 2017 (in Chinese).

11 Zhao FH, Lewkowitz AK, Hu SY, et al. Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: a pooled analysis of 17 population-based studies. *Int J Cancer* 2012; **131:** 2929–38.

12 Szarewski A, Poppe WA, Skinner SR, et al. Efficacy of the human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine in women aged 15–25 years with and without serological evidence of previous exposure to HPV-16/18. *Int J Cancer* 2012; **131:** 106–16.

13 Pan Q J, Hu SY, Zhang X, et al. Pooled analysis of the performance of liquid-based cytology in population-based cervical cancer screening studies in China. *Cancer Cytopathol* 2013; **121:** 473–82.

14 Qiao YL, Sellors JW, Eder PS, et al. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol* 2008; **9:** 929–36.

15 Bao HL, Wang LH, Wang LM, et al. Study on the coverage of cervical and breast cancer screening among women aged 35–69 years and related impact of socioeconomic factors in China, 2013. *Chin J Epidemiol* 2018; **39:** 208–12.

16 UN Development Programme China, Development Research Center of the State Council of China. China national human development report 2016: social innovation for inclusive human development. 2016. http://hdr.undp.org/sites/default/files/reports/2783/undp-ch-_nhdr_2016_en.pdf (accessed July 13, 2019).

17 Shi JF, Chen JF, Canfell K, et al. Estimation of the costs of cervical cancer screening, diagnosis and treatment in rural Shanxi Province, China: a micro-costing study. *BMC Health Serv Res* 2012; **12:** 123.

18 Liu YJ, Zhang Q, Hu SY, Zhao FH. Effect of vaccination age on cost-effectiveness of human papillomavirus vaccination against cervical cancer in China. *BMC Cancer* 2016; **16**: 164.

19 State Council of the People's Republic of China. Programme book of cervical and breast cancer screenings in rural China: government notification. 2009. http://www.gov.cn/zwgk/2009-06/30/content_1353784.htm (accessed Aug 13, 2019; in Chinese).

20 Government of Beijing. Optimizing and integrating cervical and breast cancer screenings in Beijing: government notification. 2018. http://www.beijing.gov.cn/zhengce/zhengcefagui/201905/t20190522_61459.html (accessed Aug 13, 2019; in Chinese).

21 Qiao YL, Wu T, Li RC, et al. Efficacy, safety, and immunogenicity of an *Escherichia coli*-produced bivalent human papillomavirus vaccine: an interim analysis of a randomized clinical trial. *J Natl Cancer Inst* 2019; published online May 14. DOI:10.1093/jnci/djz074.

22 Clendinen C, Zhang Y, Warburton RN, Light DW. Manufacturing costs of HPV vaccines for developing countries. *Vaccine* 2016; **34:** 5984–89.

23 Yu W, Lu M, Wang H, et al. Routine immunization services costs and financing in China, 2015. *Vaccine* 2018; **36:** 3041–47.

24 Cui F, Shen L, Li L, et al. Prevention of chronic hepatitis B after 3 decades of escalating vaccination policy, China. *Emerg Infect Dis* 2017; **23:** 765–72.

25 State Council of the Peoples' Republic of China. China national program for women's development (2011–2020). 2011. http://www.gov.cn/gongbao/content/2011/content_1927200.htm (accessed July 13, 2019; in Chinese).

26 Pitman R, Fisman D, Zaric GS, et al. Dynamic transmission modeling: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force—5. *Value Health* 2012; **15:** 828–34.

27 Baussano I, Bray F. Modelling cervical cancer elimination. *Lancet Public Health* 2019; **4:** e2–3.

28 Simms KT, Steinberg J, Caruana M, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020–99: a modelling study. *Lancet Oncol* 2019; **20:** 394–407.

29 Xia C, Ding C, Zheng R, et al. Trends in geographical disparities for cervical cancer mortality in China from 1973 to 2013: a subnational spatio-temporal study. *Chin J Cancer Res* 2017; **29:** 487–95.

30 Chen W, Zheng R, Zhang S, et al. Cancer incidence and mortality in China, 2013. *Cancer Lett* 2017; **401:** 63–71.

31 Chen W, Sun K, Zheng R, et al. Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 2018; **30:** 1–12.

32 Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136:** E359–86.

33 Gallagher KE, Howard N, Kabakama S, et al. Human papillomavirus (HPV) vaccine coverage achievements in low and middle-income countries 2007–2016. *Papillomavirus Res* 2017; **4**: 72–78.

34 LaMontagne DS, Bloem PJN, Brotherton JML, Gallagher KE, Badiane O, Ndiaye C. Progress in HPV vaccination in low- and lower-middle-income countries. *Int J Gynaecol Obstet* 2017; **138** (suppl 1)**:** 7–14.

35 Howard N, Mounier-Jack S, Gallagher KE, et al. The value of demonstration projects for new interventions: the case of human papillomavirus vaccine introduction in low- and middle-income countries. *Hum Vaccin Immunother* 2016; **12:** 2475–77.