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Author/s:

Zou, Z;Fairley, CK;Ong, JJ;Hocking, J;Canfell, K;Ma, X;Chow, EPF;Xu, X;Zhang, L;Zhuang, G

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Date:

2020-10-01

Citation:

Zou, Z., Fairley, C. K., Ong, J. J., Hocking, J., Canfell, K., Ma, X., Chow, E. P. F., Xu, X., Zhang, L. & Zhuang, G. (2020). Domestic HPV vaccine price and economic returns for cervical cancer prevention in China: a cost-effectiveness analysis. *Lancet Global Health*, 8 (10), pp.e1335-e1344. [https://doi.org/10.1016/S2214-109X\(20\)30277-1](https://doi.org/10.1016/S2214-109X(20)30277-1).

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Domestic HPV vaccine price and economic returns for cervical cancer prevention in China: a cost-effectiveness analysis

Zhuoru Zou, Christopher K Fairley, Jason J Ong, Jane Hocking, Karen Canfell, Xiaomeng Ma, Eric P F Chow, Xianglong Xu, Lei Zhang*, Guihua Zhuang*



Summary

Background Coinciding with the release of the first Chinese domestic human papillomavirus (HPV) vaccine Cecolin in 2019, and the substantial advancements in cervical cancer screening technology, we aimed to evaluate the cost-effectiveness of the combined strategies of cervical cancer screening programmes and universal vaccination of girls (aged 9–14 years) with Cecolin in China.

Methods We did a cost-effectiveness analysis in China, in which we developed a Markov model of cervical cancer to evaluate the incremental cost-effectiveness ratios of 61 intervention strategies, including a combination of various screening methods at different frequencies with and without vaccination, and also vaccination alone, from a health-care system perspective. We did univariate and probabilistic sensitivity analyses to assess the robustness of the model's findings.

Findings Compared with no intervention, various combined screening and vaccination strategies would incur an additional cost of US\$6157 000–22146 000 and result in 691–970 quality-adjusted life-years (QALYs) gained in a designated cohort of 100 000 girls aged 9–14 years over a lifetime. With a willingness-to-pay threshold of three times the Chinese per-capita gross domestic product (GDP), *careHPV* screening (a rapid HPV test) once every 5 years with vaccination would be the most cost-effective strategy with an incremental cost-effectiveness ratio of \$21799 per QALY compared with the lower-cost non-dominated strategy on the cost-effectiveness frontier, and the probability of it being cost-effective (44%) outperformed other strategies. Strategies that combined screening and vaccination would be more cost-effective than screening alone strategies when the vaccination cost was less than \$50 for two doses, even with a lower willingness-to-pay of one times the per-capita GDP.

Interpretation *careHPV* screening once every 5 years with vaccination is the most cost-effective strategy for cervical cancer prevention in China. A reduction in the domestic HPV vaccine price is necessary to ascertain a good economic return for the future vaccination programme. The findings provide important evidence that informs health policies for cervical cancer prevention in China.

Funding National Natural Science Foundation of China.

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Introduction

Cervical cancer is the fourth most common cancer in women globally.¹ In 2018, an estimated 568 847 new cervical cancer diagnoses and 311 365 deaths were reported worldwide.¹ However, cervical cancer is largely preventable with the human papillomavirus (HPV) vaccine, and timely screening can prevent cancer development and substantially reduce cancer morbidity and mortality.² In 2018, WHO called for global action to eliminate cervical cancer and proposed that 90% of girls aged 9–14 years receive the HPV vaccine, 70% of women are screened twice in a lifetime for cervical cancer, and 90% of identified women are treated for precancer or cancer by 2030.³

In China, both the vaccination and screening coverage remain low despite the substantial morbidity and

mortality from cervical cancer cases caused by HPV.⁴ In 2018 alone, China reported 106 430 new cervical cancer cases and 47 739 deaths, corresponding to 18.7% of diagnoses and 15.3% of deaths from cervical cancer worldwide.⁵ As of August, 2020, there is no HPV vaccination programme in China. The 2009 National Cervical Cancer Screening Programme in Rural Areas was based on the Papanicolaou test (Pap) or visual inspection with acetic acid (VIA), but this programme only served a small proportion of eligible women (around 10% of 290 million eligible women received free screening from the programme during 2012–14).⁶ The programme has been implemented for more than 10 years, but the incidence and mortality of cervical cancer are still increasing in China. In 2019, the Chinese Government incorporated the programme into the

Lancet Glob Health 2020; 8: e1335–44

*Contributed equally to study supervision

For a Chinese translation of the abstract see Online for appendix 1

China–Australia Joint Research Centre for Infectious Diseases, School of Public Health, Xi'an Jiaotong University Health Science Centre, Xi'an, Shaanxi, China (Z Zou MM, Prof C K Fairley PhD, J J Ong PhD, J Hocking PhD, X Ma MM, X Xu MM, Prof L Zhang PhD, Prof G Zhuang PhD); Melbourne Sexual Health Centre, Alfred Health, Melbourne, VIC, Australia (Prof C K Fairley, J J Ong, E P F Chow PhD, X Xu, Prof L Zhang); Central Clinical School, Faculty of Medicine, Monash University, Melbourne, VIC, Australia (Prof C K Fairley, J J Ong, E P F Chow PhD, X Xu, Prof L Zhang); Department of Epidemiology and Biostatistics, College of Public Health, Zhengzhou University, Zhengzhou, Henan, China (Prof L Zhang); Sexual Health Unit, Melbourne School of Population and Global Health, Faculty of Medicine, Dentistry and Health Sciences, University of Melbourne, VIC, Australia (J Hocking, E P F Chow); Cancer Research Division, Cancer Council NSW, Sydney, NSW, Australia (Prof K Canfell PhD); Prince of Wales Clinical School, The University of New South Wales, Sydney, NSW, Australia (Prof K Canfell); and School of Public Health, University of Sydney, Sydney, NSW, Australia (Prof K Canfell)

Correspondence to: Prof Lei Zhang, China–Australia Joint Research Centre for Infectious Diseases, School of Public Health, Xi'an Jiaotong University Health Science Centre, Xi'an, Shaanxi 710061, China lei.zhang1@monash.edu

or

Prof Guihua Zhuang,
China–Australia Joint Research
Centre for Infectious Diseases,
School of Public Health,
Xi'an Jiaotong University Health
Science Centre, Xi'an, Shaanxi
710061, China
zhuanggh@mail.xjtu.edu.cn

Research in context

Evidence before this study

Human papillomavirus (HPV) vaccination and cervical cancer screening are highly effective and cost-effective in the prevention of cervical cancer in women. In China, there is no HPV vaccination programme because of high prices of imported vaccines, and the coverage of cervical cancer screening remains low. The first Chinese domestic bivalent HPV vaccine (Cecolin, two doses) released in 2019, has similar efficacy to the imported bivalent HPV (Cervarix, three doses) but costs half as much, raising hope for a state-sponsored nationwide HPV vaccination programme in China. We searched PubMed, Embase, and Web of Science between Jan 1, 2000, and Sept 30, 2018, with no language restrictions, with the terms “China” or “Chinese”, “HPV vaccine”, “screening”, and “cost-effectiveness”, to identify published economic evaluations on HPV vaccination and cervical cancer screening strategies. Only two studies have evaluated the cost-effectiveness of HPV vaccination, cervical cancer screening, and the combined strategy in mainland China. Both studies were done before the first commercial HPV vaccine became available in mainland China in 2016. Neither addressed the potential effect of a domestic vaccine, and the alternatives of cervical cancer screening in the previous studies were not comprehensive. The release of the first Chinese domestic HPV vaccine and the advancements in cervical cancer screening technology highlights the importance of timely re-evaluation of the intervention strategies.

Added value of this study

We did a cost-effectiveness analysis to evaluate 61 intervention strategies in mainland China. These include a combination of various screening methods at different screening frequencies in the presence and absence of a national HPV vaccination programme for girls aged 9–14 years and a hypothetical scenario with vaccination alone. In our study, we found that among all investigated strategies, *careHPV* screening once every 5 years with vaccination was the most cost-effective strategy. Further reduction of the vaccination cost to less than US\$50 for two doses would enable combined strategies to become more cost-effective than screening alone even at a low willingness-to-pay threshold of one-times the per-capita GDP. If the total vaccination cost was substantially reduced to less than \$10 for two doses, vaccination alone could be the most cost-effective strategy only if the willingness-to-pay is very low, suggesting a combined strategy is always more preferable.

Implications of all the available evidence

Our findings suggest that *careHPV* screening once every 5 years with vaccination is the most cost-effective strategy in China. A reduction in domestic HPV vaccine price is necessary to ascertain a good economic return for the future vaccination programme.

national basic public health services to ensure sustainable financing for cervical cancer prevention. Identifying a cost-effective and sustainable strategy for vaccination and cervical cancer screening is a top priority for the prevention and control of cervical cancer in China.

The first Chinese domestic HPV vaccine against HPV 16 and 18 (Cecolin, Inovax, Xiamen, China) was licensed by the Chinese Food and Drug Administration on Dec 31, 2019, providing an unprecedented opportunity for China. Although imported vaccines, such as the bivalent HPV (Cervarix, US\$262 for three doses), quadrivalent HPV (Gardasil, \$360 for three doses), and nonavalent HPV (Gardasil 9, \$586 for three doses) vaccines have been licensed in China since 2016, the vaccines are expensive and only available in limited supply. These vaccines are purchased mainly by women aged 18–45 years, while girls aged 9–14 years remain largely unvaccinated. The new vaccine Cecolin is priced at ¥329 (\$47.7) per dose (about half of the price of Cervarix) and has similar efficacy to Cervarix.^{7,8} Cecolin is approved for a two-dose schedule for girls aged 9–14 years, as its immunogenicity has been proven to be non-inferior to a three-dose schedule for young women.⁹ The reduction in cost of vaccination with Cecolin raises hope for a state-sponsored nationwide HPV vaccination programme for girls aged 9–14 years.

To date, several studies have evaluated the cost-effectiveness of preventive interventions for cervical cancer in

mainland China, but only two studies compared HPV vaccination, cervical cancer screening, and the combined strategy.^{10,11} Both studies were done before the first commercial HPV vaccine became available in mainland China in 2016, and therefore many important parameters were based on assumptions. The release of Cecolin highlights the importance of a timely re-evaluation of a universal vaccination programme for girls aged 9–14 years in China. Furthermore, technological advancements allow several options for cervical cancer screening. Conventional screening methods include VIA, Pap, or liquid-based cytology, and an HPV test represented by Hybrid Capture-2 (HC-2).² *careHPV* (Qiagen, Gaithersburg, MD, USA)—a rapid HPV test developed for use in low-income and middle-income countries—has been approved by the Chinese Food and Drug Administration.¹² Co-testing that involves cytology plus the HPV test was recommended by the American College of Obstetricians and Gynaecologists in 2016, although in 2018, the United States Preventive Services Task Force recommended either primary HPV screening or co-testing in the USA.¹³ Co-testing has been implemented in some resource-rich regions in China. Built on previous findings, our study intends to include all the available cervical cancer screening strategies to explore the most cost-effective strategy for the current setting in China.

Following the release of Cecolin and evolving technologies that increase cervical cancer screening options, we aimed to analyse the cost-effectiveness of a comprehensive list of combined strategies of state-sponsored vaccination for girls aged 9–14 years and cervical cancer screening programmes to identify the most cost-effective strategy. We also evaluated the effect of a potential future decrease in the vaccine price on cost-effectiveness.

Methods

Study design

We did a model-based economic evaluation to assess the cost-effectiveness of combined strategies of vaccination and cervical cancer screening in China, from a health-care system perspective. The model was constructed using TreeAge Pro 2019 and the analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards statement and the HPV-FRAME reporting standards for HPV models.^{14,15}

Modelling

A Markov model was constructed to simulate the disease progression of high-risk HPV infection to cervical cancer

or regression to the susceptible state in a designated initial cohort of 100 000 girls aged 9–14 years for a lifetime (life expectancy 80 years). The model consisted of 20 health states from susceptible to cervical cancer stages (appendix 2 p 1). We assumed that these susceptible girls aged 9–14 years were infected at age-specific rates for HPV 16 and 18, and other high-risk HPV types (appendix 2 p 5). Individuals infected with high-risk HPV (including cervical intraepithelial neoplasia [CIN]1) can progress to CIN2 and CIN3 or regress to the susceptible state. We assumed the progression and regression rates were associated with the duration of infection according to the infected types (appendix 2 pp 7–8). CIN2 or CIN3 can progress to cervical cancer or regress to the susceptible or infected state (appendix 2 pp 7–8). Approximately 20% of women aged 30 years and older and diagnosed with CIN3 had a hysterectomy and were no longer at risk for cervical cancer.¹⁶ The cervical cancer stage consisted of local, regional, and distant cancer states. The model assumed that in the absence of active screening, women with CIN2, CIN3, or cervical cancer would be diagnosed by self-initiated examinations according to state-specific probabilities (table).¹⁷ Diagnosed individuals would receive state-specific

See Online for appendix 2

	Base-case	Range	Distribution	Reference
Vaccine coverage	70%	50–95%	Triangular (0.5, 0.7, 0.95)	Assumed and Barbara et al (2016) ¹⁸
Vaccine efficacy against HPV-16 and 18 infection	94%	80–99%	Triangular (0.8, 0.94, 0.99)	Qiao et al (2019) ⁷ , Zhu et al (2014) ⁸ , Hu et al (2019) ⁹
Screening coverage	50%	20–80%	Triangular (0.2, 0.5, 0.8)	Assumed and Li et al (2012) ¹⁹
VIA performance*	Our meta-analysis (appendix 2, pp 9–10)
Sensitivity	58%	45–72%	Beta (29.47, 21.26)	..
Specificity	86%	81–92%	Beta (120.23, 19.25)	..
Pap performance*	Our meta-analysis (appendix 2, pp 9–10)
Sensitivity	40%	12–69%	Beta (4.26, 6.26)	..
Specificity	91%	85–98%	Beta (65.3, 6.38)	..
careHPV performance*	Our meta-analysis (appendix 2, pp 9–10)
Sensitivity	86%	81–91%	Beta (156.93, 26.18)	..
Specificity	86%	85–88%	Beta (1437.96, 226.35)	..
HC-2 performance*	Our meta-analysis (appendix 2, pp 9–10)
Sensitivity	92%	88–97%	Beta (132.63, 11.38)	..
Specificity	83%	79–87%	Beta (249.59, 51.85)	..
LBC performance*	Our meta-analysis (appendix 2, pp 9–10)
Sensitivity	82%	77–88%	Beta (150.52, 32.15)	..
Specificity	96%	94–97%	Beta (616.67, 27.04)	..
Annual self-initiated examination	Campos et al (2014) ¹⁷
CIN2 or CIN3	0.01	0.005–0.02	Triangular (0.005, 0.01, 0.02)	..
Local cancer	0.1899	0.15–0.2	Triangular (0.15, 0.1899, 0.2)	..
Regional cancer	0.5999	0.4–0.65	Triangular (0.4, 0.5999, 0.65)	..
Distant cancer	0.9	0.85–0.95	Triangular (0.85, 0.9, 0.95)	..

(Table continues on next page)

	Base-case	Range	Distribution	Reference
(Continued from previous page)				
Eligible for cryosurgery	Goldie et al (2007) ³⁰
HPV infection†	0.9	0.5–1	Triangular (0.5, 0.9, 1)	..
CIN2	0.7	0.5–1	Triangular (0.5, 0.7, 1)	..
CIN3	0.4	0.0–0.5	Triangular (0.0, 0.4, 0.5)	..
Local cancer	0.3	0.0–0.5	Triangular (0.0, 0.3, 0.5)	..
Regional or distant cancer	0.1	0.0–0.5	Triangular (0.0, 0.1, 0.5)	..
Efficacy of cryosurgery‡	Dolman et al (2014) ²¹
HPV infection	0.9	0.83–0.96	Beta (84.53, 9.92)	..
CIN2 or CIN3	0.83	0.74–0.92	Beta (57.47, 11.85)	..
Efficacy of LEEP	0.92	0.85–0.99	Beta (50.49, 4.45)	Wu et al (2016) ²²
Proportion of hysterectomies in CIN3§	0.2	0.1–0.5	Triangular (0.1, 0.2, 0.5)	Zou et al (2012) ¹⁶
Compliance of follow-up visits	0.85	0.5–0.9	Triangular (0.5, 0.85, 0.9)	Tse et al (2016) ²³
Costs, US\$¶				
Vaccination, two doses	99.8	74.9–99.8	Triangular (74.9, 99.8, 99.8)	Manufacturer and Development and Reform Commission of Henan Province ²⁴
VIA	2.5	1.9–3.1	Triangular (1.9, 2.5, 3.1)	Official public data from the NDRC
Pap	6.6	5.9–7.4	Triangular (5.9, 6.6, 7.4)	Official public data from the NDRC
careHPV	10	5.9–14.2	Triangular (5.9, 10, 14.2)	Official public data from the NDRC
HC-2	48.6	33.6–63.8	Triangular (33.6, 48.6, 63.8)	Official public data from the NDRC
LBC	26	15.1–34.9	Triangular (15.1, 26, 34.9)	Official public data from the NDRC
Colposcopy	5.9	1.7–10.1	Triangular (1.7, 5.9, 10.1)	Official public data from the NDRC
Biopsy	16.4	11–21.8	Triangular (11, 16.4, 21.8)	Official public data from the NDRC
Cryotherapy	4.5	1.7–7.4	Triangular (1.7, 4.5, 7.4)	Official public data from the NDRC
LEEP	123.5	92.4–181.6	Triangular (92.4, 123.5, 181.6)	Official public data from the NDRC
Hysterectomy	315.6	151.3–479.8	Triangular (151.3, 315.6, 479.8)	Official public data from the NDRC
Per-capita screening administration	2.8	1.4–4.2	Triangular (1.4, 2.8, 4.2)	Peng et al (2014) ²⁵
Cervical cancer treatment costs (US\$)	Wu et al (2018) ²⁶
Local cancer	4299	2047–6550	Gamma (14.01, 4.90)	..
Regional cancer	5420	1766–9073	Gamma (8.45, 2.35)	..
Distant cancer	7176	4670–9682	Gamma (31.50, 6.61)	..
Annual health-care costs (US\$)	Liu et al (2016) ²⁷
Local cancer	633	316–949	Triangular (316, 633, 949)	..
Regional cancer	798	399–1197	Triangular (399, 798, 1197)	..
Distant cancer	1056	528–1585	Triangular (528, 1056, 1585)	..
Utility score				
Cryotherapy or LEEP	0.98	0.9–1.0	Beta (183.64, 3.75)	..
Post-hysterectomy	0.85	0.82–0.88	Triangular (0.82, 0.85, 0.88)	..
Local cancer	0.83	0.79–0.87	Beta (280.36, 57.42)	..
Regional cancer	0.72	0.65–0.78	Beta (131.26, 51.05)	..
Distant cancer	0.6	0.43–0.77	Beta (18.54, 12.36)	..
Cured cancer	0.87	0.70–0.99	Triangular (0.70, 0.87, 0.99)	..
Discount rate	0.03	0.0–0.08	..	Walker et al (2010) ²⁹

There are no units for utility score, but they range from 0 (death) to 1 (perfect health). VIA=visual inspection with acetic acid. Pap=Papanicolaou test. HC-2=Hybrid Capture-2. LBC=liquid-based cytology. CIN=cervical intraepithelial neoplasia. LEEP=loop electrosurgical excision procedure. NDRC=National Development and Reform Commission. *Estimated based on the detection of CIN2+ on histology. †Women who have HPV infection and have a false-positive result in screening with the screen-and-treat approach might receive cryotherapy. ‡Cryosurgery is considered ineffective for cervical cancer. §Only women aged 30 years or older were considered. ¶Adjusted according to Chinese consumer price indexes in the category of health, 2019 as the base year. ||The disutility to quality of life was considered only in the year of treatment.

Table: Parameters used in the model

treatments, whereas undiagnosed individuals remained untreated. We assumed age-specific natural background death rates in women, and that women with cervical

cancer face cause-specific mortality from cervical cancer in addition to a natural background death rate. Women in any post-treatment cancer states were considered

cured if they survived in that state for 20 years or more. Model cycle length was 1 year, and a half-cycle correction was applied.

Intervention strategies

We defined no intervention as the status quo in China because the coverage of HPV vaccination among girls aged 9–14 years is close to nil and cervical cancer screening coverage is very low in general across the country.

61 intervention strategies were investigated in our study. These included a combination of six screening methods (VIA, Pap, *care*HPV, HC-2, Pap plus HC-2, and liquid-based cytology plus HC-2) at five screening frequencies (once per lifetime, twice per lifetime, once every 10 years, once every 5 years, and once every 3 years) in the presence and absence of a vaccination programme, and a hypothetical scenario with vaccination alone (appendix 2 p 3). We assumed that vaccination was implemented when the cohort entered the model and screening was implemented when the cohort progressed to the designated age by running the model.

The target population for cervical cancer screening was women aged 30–59 years. We assumed that once per lifetime screening was done at the age of 35 years because the highest prevalence of cervical precancerous lesions and undetected cervical cancers could be detected at this age (appendix 2 p 12) and that twice per lifetime screening was done at 35 and 45 years.³ The screening, diagnosis, and treatment procedures are shown in appendix 2 (p 2). We assumed that the anticipated screening coverage would reach 50% (range 20–80), based on a pilot study in high-risk areas for cervical cancer in China.¹⁹ The Chinese-specific sensitivities and specificities of the screening methods were estimated with use of a meta-analysis (appendix 2 pp 9–10). Diagnosis and treatment compliance, as well as treatment effectiveness, were included in the model (table).^{20–23}

We assumed the two-dose domestic bivalent HPV vaccination programme would be school-based, and the anticipated coverage among girls aged 9–14 years would reach 70% (range 50–95).¹⁸ The efficacy against HPV 16 and 18 persistent infection for young women aged 18–26 years receiving a three-dose vaccination was reported as 97·8% (range 87·1–99·9) for Cecolin and 94·2% (range 62·7–99·9) for Cervarix in two independent studies.^{7,8} The immunogenicity of Cecolin is non-inferior to a two-dose vaccination for girls aged 9–14 years compared with a three-dose vaccination for young women aged 18–26 years.⁹ Therefore, we estimated the efficacy of the two-dose schedule at 94% (range 80–99) on the basis of the previous findings. Cross-protective effects on other high-risk HPV types were not considered. We assumed HPV vaccines provide lifetime protection in vaccine-sensitive recipients (ie, those who receive the vaccine and develop an immune response).

Data analysis

We calibrated the type-specific and age-specific incidence of high-risk HPV infection with use of a likelihood-based approach (appendix 2 pp 3–7). The probabilities of annual transition were derived from published literature on the natural history of cervical cancer (appendix 2 pp 7–8). Cancer mortality was estimated on the basis of the survival rates of patients with cervical cancer (appendix 2 pp 7–8), while background age-specific mortality was obtained from the China Population & Employment Statistics Yearbook, 2019.³⁰ The reported population morbidity and mortality of cervical cancer in China, as well as 5-year and 10-year cumulative risk of CIN grade 2+ (CIN2+) for HPV infection in Chinese women were used to validate the reliability of the model (appendix 2 pp 10–12).

The costs of the screening programme included the costs of screening, diagnosis, treatment, and administration (table).²⁵ Cervical cancer treatment costs included the costs of initial hospitalisation and subsequent annual health-care costs (table).^{26,27} The costs of vaccination included the vaccine price (\$95·4 for two doses), the cost of staff services (including disposable syringes) in vaccination (\$4 for two doses),²⁴ and the cost of advocacy for vaccination (\$0·4 per person).²⁵ Hence, the overall cost for two-dose HPV vaccination was estimated to be \$99·8. In the scenario in which a state-sponsored schoolgirl HPV vaccination programme is to be launched, the price of vaccination would probably be further negotiated down. We therefore assumed a decline in this parameter in the sensitivity analyses. Costs were converted from Chinese renminbi to US dollars (\$1=¥6·8968, in 2019).

Utility scores for HPV-related states were obtained from the quality-of-life assessments in Chinese patients with cervical lesions (table).²⁸ We assumed a discount rate of 3% (range 0–8) for both quality-adjusted life-years (QALYs) and cost. The choice of distribution for all parameters was based on consideration of the properties of the parameters and data informing the parameters.

The expected QALYs and costs discounted to 2019 for each strategy were obtained from the model. We calculated the incremental costs and incremental QALYs for each intervention strategy compared with no intervention. We identified the cost-effectiveness frontier and calculated the incremental cost-effectiveness ratio (ICER), defined as the incremental cost per QALY gained for each strategy on the cost-effectiveness frontier compared with a lower-cost non-dominated strategy to identify the most cost-effective strategy. We adopted a definition of cost-effectiveness from WHO (highly cost-effective, cost-effective, or not cost-effective with an ICER <1, 1–3, or >3-times the per-capita gross domestic product [GDP]; Chinese per-capita GDP was \$10 276 in 2019).²⁹

Univariate sensitivity analysis was done for all parameters within their respective ranges to identify the most sensitive parameters. Probabilistic sensitivity analysis

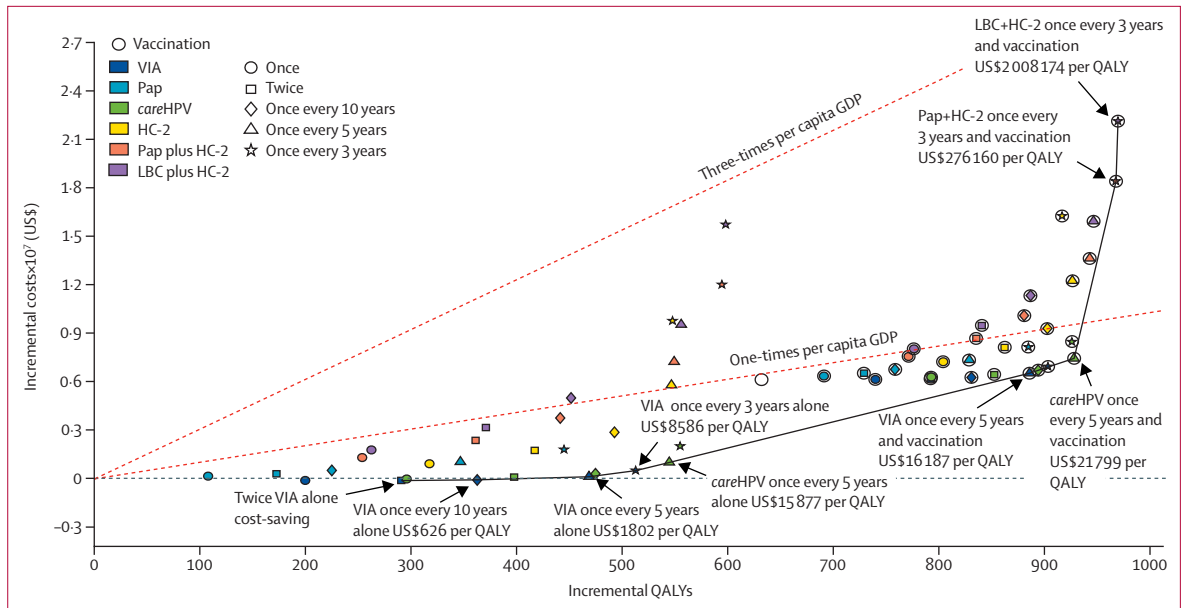


Figure 1: Cost-effectiveness frontier for all intervention strategies (100 000 cohort members)
 Incremental QALYs and incremental costs of intervention strategies compared with the no intervention scenario. Names of the strategies located on the cost-effectiveness frontier and their incremental cost-effectiveness ratios compared with the lower-cost non-dominated strategy are shown. The strategies on the upper left of the frontier are dominated by the strategies on the lower right of them. Incremental QALYs and incremental costs are expressed as the value on Dec 31, 2019. VIA=visual inspection with acetic acid. Pap=Papanicolaou test. HC-2=Hybrid Capture-2. LBC=liquid-based cytology. QALY=quality-adjusted-life-year. GDP=gross domestic product.

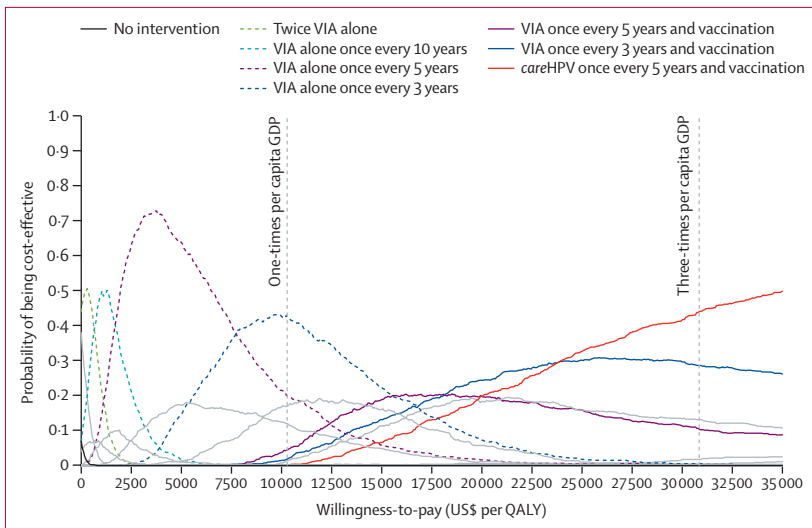


Figure 2: Cost-effectiveness acceptability curves for all strategies
 Intervention strategies that never have the highest probability of being cost-effective within the willingness-to-pay threshold of three-times the Chinese per-capita GDP are represented in grey. VIA=visual inspection with acetic acid. QALYs=quality-adjusted life-years. GDP=gross domestic product.

was done based on 10000 simulations to establish the probability of being cost-effective for each intervention strategy compared with all others.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. ZZ, LZ, and GZ had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified the incremental costs and incremental QALYs for the 61 intervention strategies, compared with no intervention in a designated cohort of 100 000 girls aged 9–14 years over a lifetime (appendix 2 pp 13–14). Overall, screening alone strategies with various methods and frequencies would incur an additional cost of \$–107 000 to 15 737 000. These strategies would result in 108–598 QALYs gained. By comparison, a vaccination alone strategy would incur an additional cost of \$6 142 000 and result in 632 QALYs gained. Further, combined screening and vaccination strategies would incur an additional cost of \$6 157 000–22 146 000 and result in 691–970 QALYs gained.

Figure 1 shows the most cost-effective strategy, according to willingness-to-pay (WTP) thresholds. On the cost-effectiveness frontier, twice per lifetime VIA screening alone was cost-saving compared with no intervention, which was then followed by the same VIA method but with more frequent screening—that is, once every 10 years (ICER=\$626 per QALY), once every 5 years (ICER=\$1802 per QALY), and once every 3 years (ICER=\$8586 per QALY). However, VIA screening alone strategies only dominated at a WTP lower than one-times the per-capita GDP. With a higher WTP up to three-times the Chinese per-capita GDP (\$30 828), the

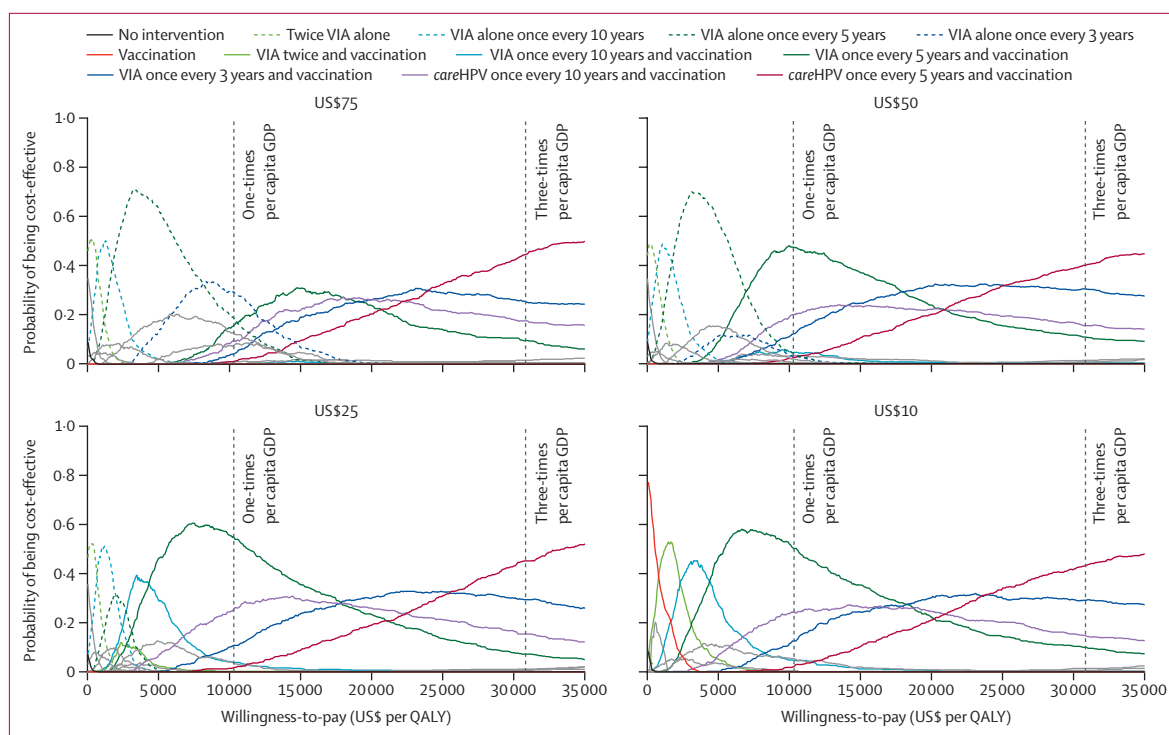


Figure 3: Cost-effectiveness acceptability curves for all strategies at various costs of vaccination

Intervention strategies that never have the highest probability of being cost-effective within the willingness-to-pay threshold of three-times the Chinese per-capita GDP are represented in grey. VIA=visual inspection with acetic acid. QALY=quality adjusted life-year. GDP=gross domestic product.

most cost-effective strategy became *careHPV* screening alone once every 5 years (ICER=\$15 877 per QALY), followed by VIA screening once every 5 years with vaccination (ICER=\$16 187 per QALY), and *careHPV* screening once every 5 years with vaccination (ICER=\$21 799 per QALY). Combined Pap plus HC-2 or liquid-based cytology plus HC-2 screening once every 3 years and vaccination represented the next two strategies on the cost-effectiveness frontier, but both were not cost-effective when compared with the lower-cost non-dominated strategy (ICER=\$276 160 per QALY, and \$2008 174 per QALY), which were far more than three-times the per-capita GDP.

Figure 2 shows the cost-effectiveness acceptability curves for all strategies at a range of WTP between 0 and three-times the per-capita GDP. At a WTP threshold of three-times the per-capita GDP, *careHPV* screening once every 5 years with vaccination showed a 44% probability of being cost-effective and outperformed other strategies. For a WTP between \$18 200 and \$23 900, VIA screening once every 3 years with vaccination had the highest probability of being cost-effective. When WTP was reduced to between \$15 500 and \$18 200, VIA screening once every 5 years with vaccination had the highest probability of being cost-effective. When the WTP was further reduced, VIA screening alone once every 3 years had the highest probability of being cost-effective if the WTP was between \$8000 and \$15 500; VIA screening

alone once every 5 years had the highest probability of being cost-effective if the WTP was between \$2000 and \$8000; VIA screening alone once every 10 years had the highest probability of being cost-effective if the WTP was between \$700 and \$2000; and twice per lifetime VIA screening alone had the highest probability of being cost-effective if the WTP was less than \$700.

We assessed the effect of different vaccination costs on the most cost-effective intervention strategy (figure 3). The cost-effectiveness of all combined screening and vaccination strategies improved when the vaccination cost was reduced. Notably, when the vaccination cost was less than \$50 for two doses, any combined screening and vaccination strategies showed a higher probability of being cost-effective than screening alone strategies even at a WTP of one-times the per-capita GDP. VIA screening once every 5 years with vaccination had the greatest probability of being cost-effective when the vaccination cost was less than \$50 for two doses at a WTP of one-times the per-capita GDP. If the vaccination cost was less than \$10 for two doses, combined screening and vaccination strategies would always outperform screening alone strategies at all WTP levels. Vaccination alone became most cost-effective only when WTP was very low (<\$800).

Univariate sensitivity analysis showed that varying any parameters did not substantially vary the ranking of cost-effectiveness of the 61 intervention strategies (appendix 2

pp 14–16). To conservatively estimate the vaccine efficacy of the two-dose schedule, we pessimistically evaluated the cost-effectiveness acceptability for all strategies when the vaccine efficacy was only 80% or even 70% (appendix 2 p 16). Reducing the vaccine efficacy to 80% or 70% did not affect the conclusion on the most cost-effective intervention strategy.

Discussion

Coinciding with the release of the first Chinese domestic HPV vaccine in 2019 and the substantial advancements in cervical cancer screening technology, we comprehensively analysed the cost-effectiveness of strategies combining various screening methods at different frequencies with vaccination. Our study found that among all investigated strategies, *careHPV* screening once every 5 years with vaccination was the most cost-effective strategy and should be the prioritised strategy for cervical cancer prevention in China. Further reduction of the vaccination cost to less than \$50 for two doses will enable combined vaccination and screening strategies to become more cost-effective than screening alone strategies even at a low WTP of one-times the per-capita GDP.

Our research showed that implementing a domestic HPV vaccination programme for girls aged 9–14 years combined with *careHPV* screening once every 5 years for women was more cost-effective than any screening alone strategies at the current WTP threshold of three-times the per-capita GDP. A high price has always been a substantial obstacle for rolling-out a national HPV vaccination programme in China. Notably, the price of Cecolin is only about half of that of the imported bivalent HPV vaccines, and requires only two doses. This factor could substantially reduce the cost associated with vaccination and increase the full-course coverage rate. The market release of Cecolin will fill the current market gap and provides a competitive option for the HPV vaccination programme. Despite the fact that we pessimistically assumed that the efficacy of the two-dose Cecolin could be inferior to that of a three-dose vaccine, with a reduced vaccine efficacy to only 70%, the conclusion regarding the cost-effectiveness of the combined strategies did not change.

The anticipated reduction in HPV vaccine price in the foreseeable future could further facilitate the implementation of a national HPV vaccination programme. In response to WHO's global target of cervical cancer elimination, political drive and momentum are building for the Chinese Government to introduce an HPV vaccine into its national immunisation programme for girls. If the Chinese Government adopts price negotiation and centralised procurement, it is likely to reduce the current vaccine price further. Besides, as more alternative domestic HPV vaccines are being developed and are likely to be approved in the foreseeable future, manufacturers could secure a market share by

reducing prices in fierce market competition. In this context, our model suggests that if the vaccination cost falls to less than \$50 for two doses, combined screening and vaccination strategies would be more cost-effective than screening alone even at a low WTP of one-times the per-capita GDP. If the vaccination cost is further reduced to \$10 for two doses, combined strategies would become more cost-effective than screening alone strategies at any WTP levels. Notably, vaccination alone is not the most cost-effective strategy unless the WTP is very low, suggesting a combined strategy is always more preferable.

Although *careHPV* screening has been shown to be the most preferable screening strategy in terms of cost-effectiveness, its implementation requires careful consideration of the regional diversity in economic development in China. At a WTP of three-times the Chinese per-capita GDP, *careHPV* screening will always outperform VIA screening as the most cost-effective strategy. Consistently, studies in low-income and middle-income country settings have shown that the *careHPV* test is only slightly inferior to HC-2 but outperforms the VIA and Pap test.^{12,31} Additionally, the cost of the *careHPV* test is less than a quarter of that of HC-2, and it can be done without running water, electricity, or modern laboratory infrastructure.³¹ Further, the diagnostic results of the *careHPV* test can be available within 3 h, which is important for point-of-care treatment and reduces the potential loss to follow-up. Therefore, the *careHPV* test is a well suited candidate for resource-limited settings. In 2012, the *careHPV* test had also been approved by the Chinese Food and Drug Administration and has since become increasingly accepted for cervical cancer screening across the country. However, given China is a large country with substantial regional differences in economic development, it can be difficult for all Chinese jurisdictions to implement the same screening strategy, as things stand currently. Consistent with our findings, in jurisdictions where their WTP is particularly low (eg, one-times the Chinese per-capita GDP), VIA should be retained until their economic development becomes practically feasible to roll-out screening with the *careHPV* test. Other factors, such as budget impact and equity should also be taken into consideration.

Our study has several limitations. First, we used a static model and did not consider the effects of herd immunity. This method is likely to underestimate the population effects and cost-effectiveness of the interventions involving vaccination. Second, because of the scarcity of relevant epidemiological data in China, our model did not take into account the cross-protection against genotypes other than HPV 16 and 18, nor other HPV-related diseases caused by HPV 16 and 18 infection, such as vulvar, vaginal, oropharyngeal, and anal cancers. This method again underestimates the population effects and cost-effectiveness of

intervention strategies involving vaccination. Third, we only considered a national schoolgirl vaccination programme but did not assess the vaccination effect on targeted populations such as older women, schoolboys, and men who have sex with men. Fourth, we acknowledge the coexistence of multiple cervical cancer screening approaches in China and the estimated local coverage of each cervical cancer screening programme is difficult to obtain.

In conclusion, our results indicate that *careHPV* screening once every 5 years with vaccination is the most cost-effective strategy in China at a WTP of three-times the per-capita GDP. We highlight a threshold of the vaccination cost of \$50 for two doses that benchmark the upper-end vaccination cost for a future vaccination programme to be most cost-effective even at a lower WTP. Our study contributes important evidence for policies for the prevention and control of cervical cancer in China and also contributes to the global efforts of cervical cancer elimination.

Contributors

ZZ designed the project, designed and constructed the model, ran the modelled analyses, interpreted, graphed, and tabulated the results, and was responsible for write up of the document. CKF, JJO, JH, KC, and EPFC contributed to technical and modelling advice throughout the project and critically revised the manuscript. XM and XX participated in the interpretation of results. LZ and GZ supervised all aspects of the study, contributed to the design of the project, the design of the model, interpretation of the results, and critically revised the manuscript. All authors reviewed the manuscript and approved the final version.

Declaration of interests

KC is co-principal investigator of an unrelated investigator-initiated trial of cervical cytology and primary HPV screening in Australia (Compass), which is being carried out and funded by the VCS Foundation, a government-funded health promotion charity. The VCS Foundation has received equipment and a funding contribution for the Compass trial from Roche Molecular Systems and Ventana USA. However, neither she nor her institution on her behalf (Cancer Council NSW) receives direct funding from industry. All other authors declare no competing interests.

Acknowledgments

LZ is supported by the National Natural Science Foundation of China (grant number 8191101420); Outstanding Young Scholars Funding (3111500001); Xi'an Jiaotong University Basic Research and Profession Grant (xtr022019003); and Xi'an Jiaotong University Young Talent Support Program (YXJ004).

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