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RESEARCH PAPER

Modeling the epidemiological impact and cost-effectiveness of a combined schoolgirl HPV vaccination and cervical cancer screening program among Chinese women

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ABSTRACT

Human papillomavirus (HPV) infection is common in women and also the main cause of cervical cancer. Based on a dynamic compartmental model, we aimed to evaluate the population impact and cost-effectiveness of strategies that combined cervical cancer screening and HPV schoolgirl vaccination for Chinese women. The effectiveness of interventions was assessed by comparing modeled scenarios to the status quo, where a 3-y cervical cancer screening program remained at a 20% coverage and without a universal HPV vaccination program. Our study demonstrated that increasing screening coverage from 20% to 50% would reduce the high-risk HPV (HR-HPV) prevalence to 5.4%, whereas a universal schoolgirl vaccination program using the quadrivalent vaccine (qHPV) with a coverage of 50% would reduce the prevalence to 2.9% by 2069. Scaling-up the cervical screening coverage to 50% will prevent 16,012 (95% CI: 8,791 to 25,913) Disability-Adjusted Life-Years (DALYs) per year, with an incremental cost-effectiveness ratio (ICER) of US$ 10,958 (95% CI: $169 to $26,973)/DALY prevented. At the current qHPV price, vaccinating 50% of school girls will prevent 13,854 (95% CI: 8,355 to 20,776) DALYs/year, but the corresponding incremental cost-effectiveness ratio (ICER, US$ 83,043, 95% CI: $52,234 to $138,025) exceeds cost-effectiveness threshold (i.e., 3 times GDP per-capita of China: $30,792). The qHPV vaccine requires at least a 50% price reduction to be cost-effective. Vaccinating schoolgirls will result in a large population health benefit in the long term, but such a universal HPV vaccination program can only be cost-effective with a substantial price reduction.

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Human papillomavirus; cervical cancer; screening; vaccination; intervention; cost-effectiveness; economic evaluation

Background

Human Papillomaviruses (HPV) include high-risk HPV (HR-HPV) and low-risk HPV (LR-HPV) subtypes.[1] HR-HPV infection can cause cervical cancer in infected women,[2] while LR-HPV types can cause genital warts. Approximately 12.0% of women are living with HPV of any genotype globally;[3] whereas this rate is around 15% in China.[4] In 2014, the age-adjusted mortality rate of cervical cancer was reported to be 3.21/100,000 in China, higher than the global average (2.98/100,000[5,6]). In the past decade, the development of HPV vaccines (bivalent [16/18, bHPV], quadrivalent [6/11/16/18, qHPV] and nonavalent [6/11/16/18/31/33/45/52/58, nHPV]) has significantly improved HPV control and prevention.[7–10] Large randomized controlled trials reported that the efficacy of qHPV against HPV-16 and −18 related cervical cancer and cancer precursors can reach 93.3–100%, and the efficacy against HPV-6/11/16/18 related genital warts is 95.4–99.9%.[11]

By 2017, 80 countries have included vaccination against HPV as a part of their national vaccination schedule.[12] Australia initiated its universal HPV vaccination program for schoolgirls aged between 12 and 13 in 2007 and this was later expanded to include schoolboys in 2013. In 2018, an Australian national surveillance program reported that in the state of Victoria, the vaccine-targeted HPV genotypes were detected in only 1.7% of women aged between 18 and 25.[13] Genital warts have also become very rare in young Australian women and heterosexual men in the post-vaccination era.[14] Australia provides strong evidence that high coverage of HPV vaccine (women: 80%, men: 76% in 2019) can significantly reduce the prevalence of HPV in a population.[15] Indeed, Australia may become the first country to eliminate HPV.[16] In China, the high cost of HPV vaccines limits their usage. Although both bHPV and qHPV have been approved by the China Food and Drug Administration in 2017, and nHPV in 2018, the prices of the vaccines (bHPV: US$ 260; qHPV: US$ 450; nHPV: US$ 576) are not affordable for an average Chinese family.[17] A recent national survey reported that less than 6% of the Chinese women were willing to purchase the HPV vaccine at a price of higher than US$ 300 for themselves or their daughters.[18]

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In the absence of a universal vaccination program, HPV DNA-based cervical cancer screening is currently the only option recommended by the government for the early prevention of cervical cancer. The latest Chinese cervical cancer prevention guideline indicates that cervical cancer screening is recommended to be performed every 3 y for women aged 25–65.[19] Starting in 2012, China expanded the state-sponsored cervical cancer screening program to 1,140 counties, covering 30 million rural women.[20] As a result, a study conducted during 2013–2014 reported that around 20% of Chinese women over the age of 21 had received at least one cervical cancer screening in over the last 3 y.[21] However, scaling-up of cervical cancer screening (with HPV detection and follow-up treatments) is not an efficient approach for HPV prevention. It needs to combine with effective HPV vaccination to significantly reduce the burden of HPV infection.[22,23] With the approval of the first domestic bivalent HPV vaccine Cecolin in December 2019, the Chinese government is facing an unprecedented opportunity to establish a universal schoolgirl vaccination program along with scaling-up the cervical cancer screening in adult women to achieve the goal of eliminating HPV[24-27].

Mathematical models have been widely used for HPV epidemic trend forecasting and economic evaluation.[28–33] Based on a compartmental model, we aimed to evaluate the population impact and cost-effectiveness of intervention strategies that combined cervical cancer screening with HPV schoolgirl vaccination and also identified the key factors that impact on the cost-effectiveness for women in a Chinese setting.

Methods

Data source

Epidemiological data were obtained from our previous systematic review on HPV infection for China.[4] To calibrate the primary model outputs, we synthesized the yearly prevalence of HPV infection and cervical intraepithelial neoplasia (CIN) for Chinese women over 2000–2017. An additional literature search was conducted to collect data on cervical cancer incidence and genital wart prevalence.[34–39] The epidemiology, behavior, intervention, and monetary parameters were collected for cervical cancer, precancerous lesions of CIN1-3, and genital warts (Table S1.1). If multiple values were reported for the same parameter, we pooled them using a weighted average (Table S1.2).

Model description

We first constructed a compartmental model, simulating the natural progression of HPV infection in Chinese women over the 2020–2069 period. By comparing the status quo trajectories to hypothetical scenarios of new interventions, we estimated the changes in prevalence, including HR (high risk) HPV, LR (low risk) HPV, CIN, cervical cancer, and genital wart (Figure 1). 'Similar model framework has been published for HPV and other sexually transmitted infections.[1-3]

1. Zhang, L., et al., Neisseria gonorrhoeae Transmission Among Men Who Have Sex With Men: An Anatomical Site-Specific Mathematical Model Evaluating the Potential Preventive Impact of Mouthwash. Sex Transm Dis, 2017. 44 (10): p. 586–592.

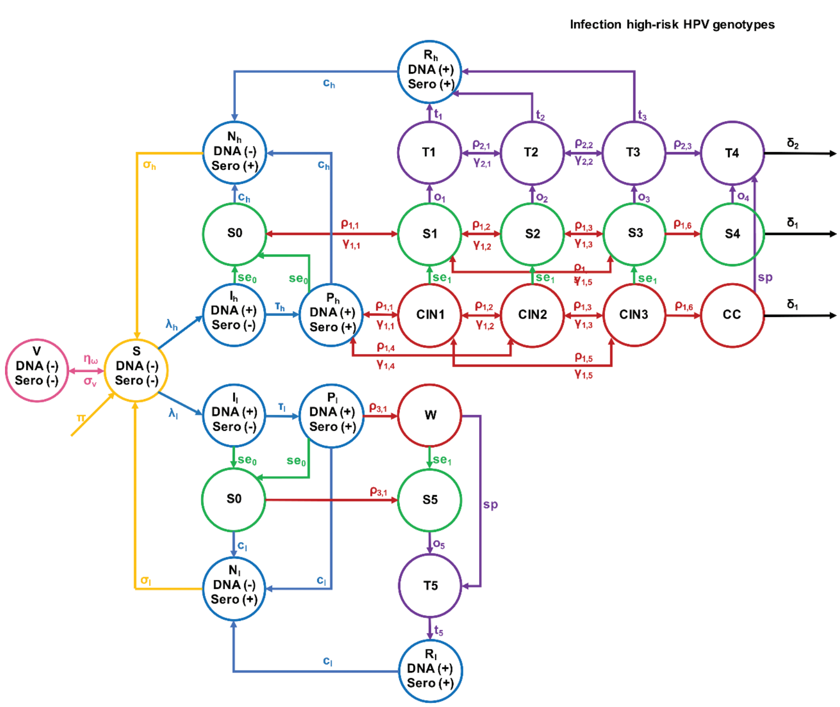

Figure 1. Model diagram.

2. Xianglong Xu, Eric P.F. Chow, Jason J. Ong, Christian JPA Hoebe, Deborah Williamson, Mingwang Shen, F.Y.S. Kong, Jane S Hocking, Christopher K. Fairley, Zhang L. Modelling the contribution that different sexual practices involving the oropharynx and saliva have on Neisseria gonorrhoeae infections at multiple anatomical sites in men who have sex with men. Sexually Transmitted Infections. DOI: 10.2139/ssrn.3578740. (accepted).

3. Xianglong Xu, Eric P.F Chow, Jason J Ong, Christian JPA Hoebe, Zhuoru Zou, Jane S Hocking, Christopher K Fairley, Zhang L. Chlamydia trachomatis transmission between the oropharynx, urethra and anorectum in men who have sex with men: A mathematical model. BMC Medicine; (accepted).

4. Zhang, L., et al., Targeted human papillomavirus vaccination for young men who have sex with men in Australia yields significant population benefits and is cost-effective. Vaccine, 2017. **35**(37): p. 4923–4929.

We primarily modeled the schoolgirl vaccination program with qHPV, which prevents the infection of HPV 6, 11, 16, and 18. We did not consider the cross-protective effects for other HPV genotypes. The impact of other STIs over HPV progression was not considered. We simulated eight natural disease progression stages for HR-HPV infections and five for LR-HPV infections. Women with HR and LR-HPV infections were conceptually stratified into four conditions following their diagnosis and treatment status, including undiagnosed/natural disease progression, screened and diagnosed, receiving treatment, and recovering from treatment (Figure 1). Notably, the suggested cervical cancer screening approaches differentiate in women at different ages. In this model, we assessed the following tests according to the Chinese HPV prevention guidelines: women aged 25–30 received cytology-based cervical cancer screening (liquid-based cytology, pap smear, or visual inspection with acetic acid (VIA)), whereas women aged >30 received combined cytological tests and HPV genotyping.[40,41] Our model stipulated that individuals with a positive HPV screening test or showing cytological abnormalities would then accept colposcopy or biopsy examinations for confirmation.[40,41] All women diagnosed with a condition of genital wart, CIN2+, or cervical cancer would accept subsequent treatments (loop electrosurgical excision procedure, cold knife conization, or hysterectomy). However, in practice, about half of the women (45.7%) diagnosed with CIN1[42] would choose to wait and observe, rather than accepting treatment for CIN1 at once. HPV positive women without clinical manifestation would also avoid any therapeutic interventions. We assumed, prior to treatment, cervical lesions progressed at the same rate in both diagnosed women and undiagnosed women; and the post-screening treatment usually occurred 2–3 months after diagnosis. Additionally, 90% of women who noticed their symptoms of cervical cancer and 60% of women with genital warts[42] sought treatment on their own. The detailed description of the model compartmental structure and the system of differential equations with parameter explanation were included in the appendix.

Population in simulation

The universal vaccination program in our model was implemented for schoolgirls aged 9–16, and the scale-up cervical cancer screening intervention was for women aged 25–65. A catch-up vaccination rate of 5%, corresponding to the voluntary vaccination rate, was implemented for girls aged 17–25. Given that women aged ≤25 are seldomly afflicted by cervical concerns in China[43–45] and prevalence calibration data were only available for >25 women, only women aged >25 were simulated in the intervention projection module (Figure 1: high-risk and low-risk two branches). The population size of women aged >25 was estimated from the census statistics released by the National Bureau of Statistics of China.[46] In 2015, approximately 632 million Chinese women were registered in census surveys, and 69.1% of whom aged >25. Prospectively, the population size will shrink over the next few decades, the size of women aged >25 is estimated to be around 350 million by 2069.[47] We anticipated that the population structure in China would change over the next 50 y. Population growth rate matched with current mortality rate were both set as constants, to couple with prospective population size estimation. Since the group of vaccinated schoolgirls were not included in the intervening projection compartment (Figure 1: compartment V), we calculated the vaccinated female population size who would enter their 25 and inputted this number to the intervening projection compartment on a yearly basis to realize the vaccination intervention (Figure 1: high-risk and low-risk branches).

Intervention strategy

The current coverage of the 3-y cervical cancer screening program was around 20% in women,[21] but no population-level study has yet reported any HPV vaccination coverage for China. Therefore, for intervention projection, we allowed qHPV vaccination coverage to vary between 0% and 90%, and the 3-y cervical cancer screening coverage to vary between 20% and 70% (each by 1% increment). In each intervening scenario, the median with a 95% confidence intervals (95% CIs) of the total number of CIN2/3 cases, cervical cancer cases, cervical cancer deaths, genital wart cases, and cervical cancer DALYs prevented was calculated. For each intervening scenario, the number of more cases reverted beyond which in the baseline scenario (20% screening) was also recorded.

Population impact and cost-effectiveness analysis (CEA)

Cost-effectiveness ratios were calculated for eleven intervening combinations (three screening-only, two vaccination-only, and six combined interventions) in a 50-y time window. We used the 'Disability Adjusted Life Years (DALYs) prevented' as the indicator to assess the intervention effectiveness.[48] Cervical cancer screening cost, vaccination cost, and treatment cost (genital wart/CIN1/CIN2/CIN3/cervical cancer) are three major components for medical expenditure calculation (Table S4). We used the currency exchange rate in 2020[49] and the yearly price discounting rate of 3% to estimate the cost in US Dollar (US$). The World Health Organization (WHO) recommended 1 and 3 times the GDP per capita (US$ 10,264 in 2020, appendix) as thresholds of 'very cost-effective' and 'cost-effective' for public health interventions, and the horizontal threshold equals to zero as cost-saving.[50] Incremental Cost-Effectiveness Ratio (ICER) was calculated as 'Incremental cost per DALY prevented' in this study. The accumulated cases of cervical cancers, genital warts, cervical cancer deaths, and DALYs, as well as the overall number of cervical cancers, genital warts, death cases, and DALYs prevented, with their 95% CIs, were reported in each intervention scenario. We also varied the qHPV price, by discounting the current price at a rate varying from 10% to 90% (by 10% increment).

Budget analysis for cervical cancer prevention

Based on the official report from the Chinese government, the current annual budget for cervical cancer prevention is estimated around ~US$ 47.8 million, which is the amount of funding to maintain a 20% cervical cancer screening coverage every 3 y.[51] In high-income countries, such as the USA, cervical cancer screening coverage is maintained at 60–70% among adult women.[52] With a fixed yearly fund of US$ 47.8 million, we searched potential strategy combinations (at step length of 1% for the coverage of each intervention) of cervical cancer screening scale-up and universal schoolgirl vaccination to identify the ‘optimal strategy’. The ‘optimal strategy’ was defined as the strategy that would result in the most DALYs prevented given the fixed amount of funding (US$ 47.8 m).

Uncertainty and sensitivity analysis

A probability sensitivity analysis was also performed on cost fluctuation and uncertainties around prevalence variations. A Latin Hypercubic sampling method was adopted to randomly extract values from price ranges, and epidemiological parameter ranges to construct parametric matrices for simulation. One-thousand random scenarios were generated to visualize the uncertainty, as shown in Figure 3. Another univariate sensitivity analysis with delayed HPV vaccination (initiated in 2025 and 2030, Figure S5-6) were conducted to investigate the impact of delayed initiation on HPV epidemics. In addition to a 50-y cost-effective analysis, we also performed an analysis in a 20-y time window (Table S5.1). We projected the alternative vaccination intervention at the same strenth by replacing qHPV to bHPV, to contrast the effectiveness between vaccines. bHPV derived results were included in the Appendix (Table S5.2). Our intervention projection did not include nHPV due to its high commercial price and limited availability in mainland China in 2020. The simulation of HPV natural disease progression and subsequent intervention projection were both conducted in MATLAB R2019a.

Results

Projected HPV infection in the status quo

Our model indicated that at status quo (3-y screening coverage of 20%), the prevalence of HR-HPV in Chinese women would reduce from 16.0% in 2020 to 12.0% in 2069; cervical cancer incidence would decrease from 2.7/100,000 to 2.3/100,000, and the mortality rate would decrease from 1.0/100,000 to 0.7/100,000. In contrast, the genital wart incidence would only decline slightly from 0.046% to 0.042% during this period (Figure 2).

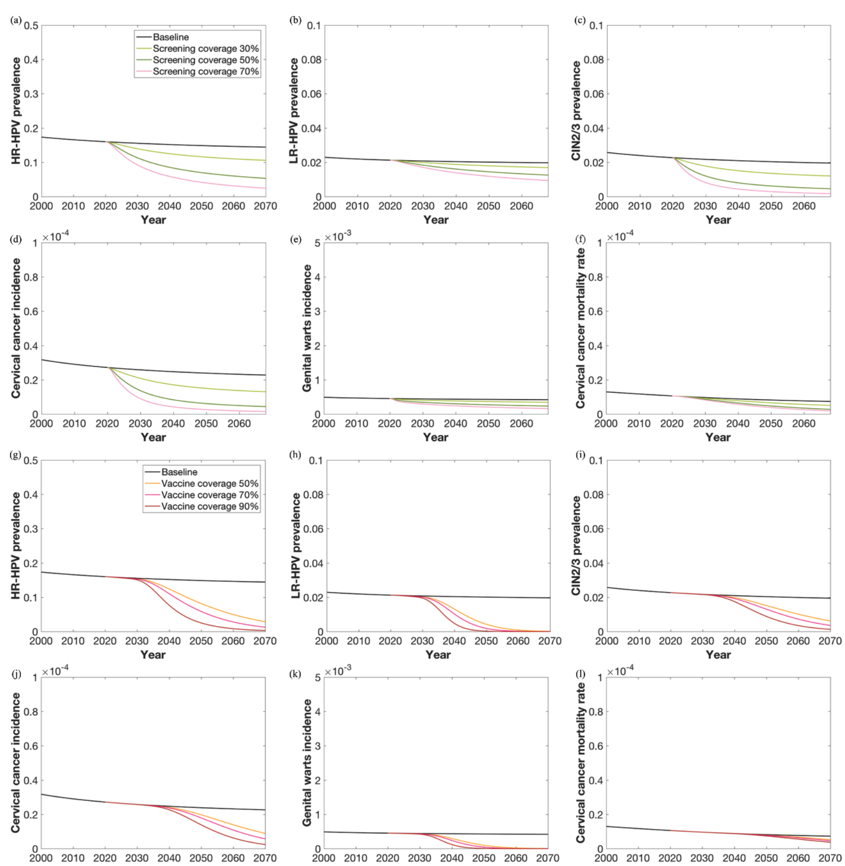

Figure 2. Temporal projection of the HPV epidemic among Chinese women aged >25, with (a–f) qHPV schoolgirls vaccination program only; (g–l) scale-up cervical cancer screening only, 2020–2069.

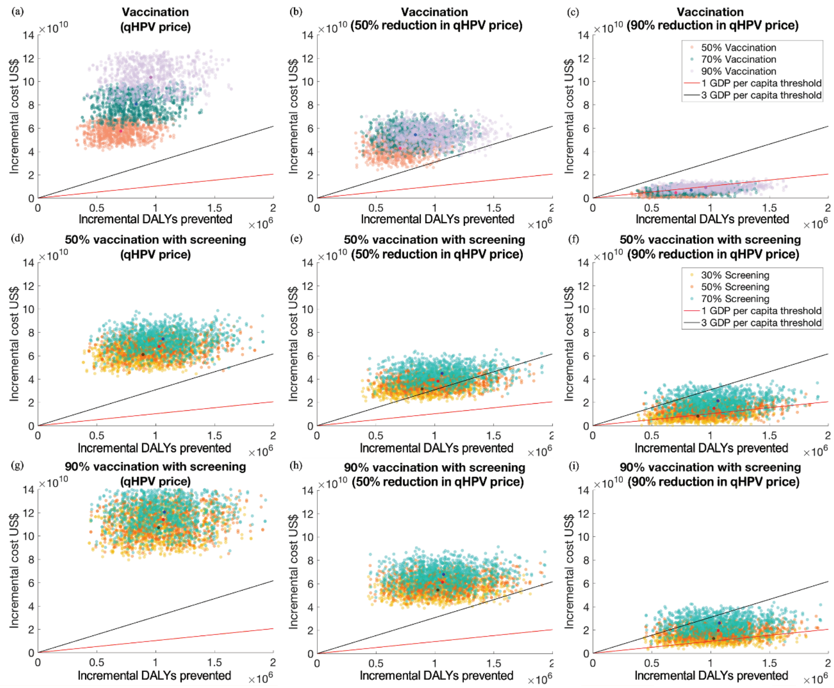

Figure 3. Two-dimensional cost-effectiveness plane demonstrating the distribution of 1,000 simulations for incremental cost and DALYs prevented under intervening strategies with different vaccine prices. (a–c): single intervention with qHPV at different price levels; (d)-(f) 50% vaccination with scale-up screening strategies; (g–i): 90% vaccination with scale-up screening strategies.

Projected HPV infection and CEA in the scaled-up cervical cancer screening scenario

Increasing cervical cancer screening coverage to 30% would reduce the prevalence of HR-HPV to 10.6% in 2069, preventing 427 (95% CI: 129 to 1,145) cervical cancer cases and 360 (95% CI: 113 to 943) deaths annually in 2020–2069. Increasing screening coverage to 50% or 70% would further reduce the prevalence to 5.4% and 2.5%, preventing 856 (95% CI: 265 to 2,273) and 1,028 (95% CI: 323 to 2,721) cervical cancer cases, 771 (95% CI: 240–2,003) and 983 (95% CI: 311 to 2,550) deaths annually. The screening scale-up revealed a minimal impact on genital wart in these scenarios (Figure 2(a–f), Table 1).

Scaling-up cervical cancer screening alone would be cost-effective and even cost-saving (ICER of US$ 5,429 [95% CI: −9,104 to 18,676] per DALY prevented, Table 1). A screening with 30% coverage would require maximumly an extra US$ 8 billion over the next five decades, but expect to reduce 8,500 (95% CI: 4,497 to 13,906) DALYs each year, corresponding to an ICER of US$5,470 (95% CI: −9,116 to 18,663) per DALY prevented. In contrast, increasing the screening coverage to 50% or 70% would result in ICERs of US$ 10,958 (95% CI: 169 to 26,973) and 15,673 (95% CI: 3,212 to 37,021) for each DALY prevented, respectively (Table 1). Probabilistic sensitivity analyses indicated that 99.6–100.0% of these scenarios (70–30% coverage) were cost-effective, and 50.3–88.3% were very cost-effective (Figure 3, Figure S7.1).

Projected HPV infection and CEA in where HPV vaccination implemented at the baseline level of cervical cancer screening

With the current cervical cancer screening coverage, vaccinating 50% schoolgirls would reduce the prevalence of HR-HPV from 16.0% to 2.9% by 2069, preventing 363 (95% CI: 115 to 861) cervical cancer cases and 148 (95% CI: 50 to 342) deaths annually from 2020 to 2069 due to the lag effect of vaccination. Vaccinating 70% or 90% schoolgirls would reduce HR-HPV prevalence to 1.4% and 0.3%, and would prevent 468 (95% CI: 147 to 1,125) and 631 (95% CI: 194 to 1,539) cervical cancer cases, 194 (95% CI: 65 to 445) and 281 (95% CI: 92 to 674) deaths annually, respectively. LR-HPV could be nearly eradicated (<0.1%) in four decades with qHPV vaccination at a 50% coverage level (Figure 2(g–l)).

Schoolgirl vaccination programs could hardly be cost-effective under the current high price of the qHPV vaccine. Vaccinating 50% of schoolgirls would require an extra US$ 57 (45 to 68) billions over the next five decades. This strategy would reduce 13,854 (95% CI: 8,355 to 20,776) DALYs in each year, corresponding to an ICER of US$ 83,043 (95% CI: 52,234 to 138,025) for each prevented DALY. Vaccinating 70% and 90% schoolgirls would reduce 16,427 (95% CI: 9,594 to 24,858) and 18,992 (95% CI: 10,692 to 29,032) DALYs annually, corresponding to an ICER of US$ 98,100 (95% CI: 61,800 to 168,200) and 110,500 (95% CI: 69,000 to 192,700) for each DALY (Table 1). Whereas, in the vaccination-only scenarios where the qHPV cost was 90% discounted, the ICERs decreased to US$ 6,541 (95% CI: 512 to 13,204), 8,190 (95% CI: 2,796 to 15,421) and 9,558 (95% CI: 4,241 to 17,179) for 50%, 70%, and 90% coverage levels, respectively (Figure 3(a–c), Table 1).

Combining the HPV vaccination program with scaled-up cervical cancer screening

We assessed multiple combined vaccination and screening strategies. In particular, vaccinating 50% schoolgirls and

Table 1. Cost-effective analysis of qHPV vaccination and screening strategies with a 50-year forecast, 2020 – 2069

Scenarios qHPV vac %	scn %	Extra investment qHPV price ($) 10^9	Extra investment bHPV price ($) 10^9	Number of CCs10^3	Number of GWs 10^3	Accumulative deaths10^3	Number of DALYs 10^3	Number of CCs averted per year	Number of GWs averted per year 10^3	Number of deaths averted per year	Number of DALYs averted per year 10^3	ICERCost/DALY averted, qHPV price ($) 10^3	ICERCost/DALY averted, 50% reduction in qHPV price ($) 10^3	ICERCost/DALY averted, 90% reduction in qHPV price ($) 10^3
0	20	-	-	70 (22 to 179)	421 (271 to 553)	138 (47 to 348)	1,062 (589 to 1,650)	-	-	-	-	-	-	-
0	30	2 (-3 to 8)	-	49 (15 to 125)	345 (223 to 448)	120 (40 to 296)	639 (359 to 986)	427 (129 to 1,145)	2 (1 to 2)	360 (113 to 943)	9 (4 to 14)	5.4 (-9.1 to 18.6)	-	-
0	50	9 (0 to 17)	-	27 (8 to 71)	233 (154 to 305)	99 (34 to 241)	250 (142 to 406)	856 (265 to 2,273)	4 (2 to 5)	771 (240 to 2,003)	16 (9 to 26)	10.9 (0.2 to 26.9)	-	-
0	70	15 (3 to 27)	-	18 (6 to 48)	162 (109 to 211)	88 (30 to 213)	101 (53 to 175)	1028 (323 to 2,721)	5 (3 to 7)	983 (311 to 2,550)	19 (10 to 30)	15.6 (3.2 to 37.4)	-	-
50	20	57 (45 to 68)	27 (20 to 34)	52 (16 to 136)	4 (2 to 8)	131 (44 to 329)	363 (173 to 657)	363 (115 to 861)	8 (5 to 11)	148 (50 to 342)	14 (8 to 20)	83.0 (52.2 to 138.0)	40.2 (25.6 to 67.3)	6.5 (0.5 to 13.2)
90	20	103 (83 to 122)	50 (40 to 61)	38 (11 to 104)	0 (0 to 0)	124 (41 to 311)	114 (43 to 259)	631 (194 to 1,539)	8 (5 to 11)	281 (92 to 674)	18 (10 to 29)	110.5 (69.0 to 192.7)	54.3 (33.7 to 94.3)	9.5 (4.2 to 17.1)
50	30	61 (47 to 73)	31 (23 to 39)	36 (11 to 97)	3 (1 to 6)	115 (39 to 285)	184 (87 to 336)	681 (210 to 1,721)	8 (5 to 11)	461 (143 to 1,157)	17 (10 to 27)	67.8 (41.5 to 116.3)	36.1 (22.3 to 61.7)	9.0 (2.7 to 18.6)
50	50	68 (52 to 82)	38 (27 to 48)	21 (7 to 58)	2 (1 to 4)	97 (33 to 235)	50 (22 to 109)	963, (302 to 2,528)	8 (5 to 11)	820 (258 to 2,128)	20 (11 to 31)	70.4 (43.2 to 120.1)	37.9 (22.5 to 65.9)	14.3 (5.5 to 30.2)
50	70	74 (55 to 90)	44 (30 to 57)	16 (5 to 42)	1 (1 to 2)	87 (30 to 211)	17 (7 to 42)	1,084 (339 to 2,843)	8 (5 to 11)	1010 (321 to 2,601)	20 (12 to 32)	71.7 (43.2 to 124.1)	43.0 (24.5 to 76.9)	19.9 (8.1 to 42.4)
90	30	107 (86 to 126)	54 (42 to 66)	28 (9 to 78)	0 (0 to 0)	110 (37 to 273)	52 (20 to 127)	845 (259 to 2,137)	8 (5 to 11)	552 (1,752 to 1,375)	20 (11 to 31)	107.4 (66.3 to 18.8)	54.2 (33.9 to 95.3)	12.4 (5.9 to 22.7)
90	50	114 (90 to 135)	61 (47 to 74)	18 (6 to 51)	0 (0 to 0)	94 (32 to 230)	16 (5 to 43)	1,031 (322 to 2,692)	8 (5 to 11)	865 (271 to 2,223)	20 (11 to 32)	109.7 (67.4 to 191.2)	58.9 (36.4 to 103.1)	18.2 (8.8 to 35.7)
90	70	115 (70 to 201)	67 (51 to 84)	14 (4 to 39)	0 (0 to 0)	85 (29 to 208)	9 (3 to 24)	1,110 (347 to 2,920)	8 (5 to 11)	1027 (329 to 2,650)	21 (12 to 32)	115.2 (70.7 to 201.9)	64.6 (39.2 to 113.5)	24.1 (11.5 to 48.8)

screening 50% women for cervical cancer would prevent 963 (95% CI: 302 to 2,528) cervical cancer cases, 820 (95% CI: 258 to 2,128) deaths, 8,390 (95% CI: 5,401 to 11,026) genital warts and avert 20,138 (95% CI: 11,468 to 31,090) DALYs in each year from 2020 to 2069. Genital wart incidence would decline significantly with the increase of vaccination coverage; cervical cancer cases and cervical cancer deaths are more sensitive to variations in cervical cancer screening coverage (Figure S4).

Budget analysis of the combined interventions for an optimal strategy

The optimal intervention strategy varied with vaccine price discounting. If the current annual budget for HPV interventions would increase to 3 times of the current level (that is, US$ 143.4 million/year), and the vaccine price remains unchanged, our model indicated that all investments should be directed to cervical cancer screening. This would allow 67% women to receive cervical cancer screening in a 3-y interval, and 950,000 DALYs would be prevented in five decades. In comparison, with a 90% vaccine price deduction, the strategy of 40% screening coverage and 65% vaccination coverage would result in the largest DALY reduction of 1,017,000 units over the next 50 y (Table 1, Figure S4).

Discussion

Our analysis indicates that the current cervical cancer screening program targeting adult women will moderately reduce HPV infections and cervical cancer cases over the next five decades. The addition of a universal schoolgirl vaccination program using qHPV is effective in reducing more than half of cervical cancer incidence by 2069. However, given the high price of the vaccine, HPV prevention of cervical cancer should focus on cervical cancer screening to maximize its attainable coverage for now. A schoolgirl vaccination program can approach the cost-effective threshold with a 50% vaccine price deduction and could be very cost-effective with a 90% vaccine price reduction. With an anticipated three times increase in government investment for HPV prevention, we found that the optimal strategy in the context of a 90% deduction in qHPV price, was to have a 65% vaccination coverage and 40% screening coverage. This scenario would result in the aversion of an extra 67,000 DALYs than the current optimal strategy (i.e., 67% screening coverage) with no reduction in vaccine price (950,000 DALYs). An HPV vaccination alone without cervical cancer screening for adult women will not be very effective for cancer prevention.

The consensus from the published literature is that adding HPV vaccination to existing cervical cancer screening program is the most effective strategy for reducing new cancer cases and cervical cancer mortality.[29–33,53] Our study adds to the cumulating evidence that combined interventions of schoolgirl vaccination and the scale-up of cervical cancer screening programs will result in a significant reduction in both new infections and cervical cancer mortality.[29,30,32] The optimal price of HPV vaccines for Chinese women remains a matter of debate. Some modeling studies[30,31] suggest that HPV vaccines at the current price have significant population impact, while others argue that the vaccine price needs to be at least 50–90% lower to be financially feasible.[32,33,53,54] Our study finding seems to be consistent with the latter.

A substantial reduction in HPV vaccine price is necessary to guarantee the feasibility of a universal vaccination program. However, such a reduction is unlikely if all vaccines are imported. The commercial quadrivalent HPV vaccines have been very popular among urban women since they entered the Chinese market, but they are under-supply in mainland China. Women often have to wait up to 12 months to schedule their first injection.[55] Confined by these circumstances, the implementation of a universal schoolgirl HPV vaccination program seems not to be possible. It is likely that the domestically developed bivalent vaccines Cecolin will dramatically change this situation. First, according to the manufacturing of Gardasil it costs around US$2.5 per dose,[56] which is only 0.6% of the current market price of qHPV in China (US$450), demonstrating room for a substantial reduction. The expiration of the patent for Gardasil qHPV production in 2023 also serves as another good stimulus for local manufacturer production.[57] The domestic vaccine Cecolin became available in community hospitals in multiple provinces for purchase and injection in May 2020.[58] The market price for Cecolin[59] (about US$ 46.5/dose) is much lower than the comparable imported Cervarix vaccine. State procurement of a large amount of the vaccine for a vaccination program will likely further reduce the price. Second, as the Chinese government stipulates, the production of mandatory vaccines for children should be under the regulation of the Chinese National Vaccination Scheme.[60] Domestic vaccines will face less resistance in implementation at the regulation and operation levels.

A high HPV vaccination coverage is necessary to achieve the goal of HPV elimination in China. Our study indicates that at a 90% vaccine price reduction, a 65% vaccination and 40% screening coverage may result in the best economic outcome. Consistent with previous studies,[26,61] our finding indicates that although increasing cervical cancer screening could be cost-effective without a universal HPV vaccination program, screening alone cannot eliminate cervical cancer. First, cervical cancer screening only detects HPV infection after the infection occurs and thus cannot prevent the initial acquisition of HPV. Once infected, women are facing the risk of persistent HPV infections without instant and effective management.[62] In contrast, HPV vaccination reduces HPV acquisition risk in schoolgirls before their sexual debut, lowering the risk of cervical cancer in their later lives.[63] Second, cervical cancer screening coverages vary substantially across populations with various socioeconomic backgrounds.[64] People from resource-limited settings are less likely to accept regular screening.[65] Hence, a state-funded universal vaccination program can provide relatively fair access to HPV prevention to disadvantaged groups and complement the access inequality in cervical cancer screening.

Our studies have several limitations. First, data for calibration were obtained from a secondary source, given that access to first-hand surveillance data for HPV is restricted in China. Our modeling estimation may not adequately reflect the HPV prevalence trend in recent years. Also, as data were extracted from peer-reviewed articles, most cervical cancer screening test results were only available in women age >25 and thus not very representative for the entire population. Second, we did not include the cross-protective effect of the vaccine over other untargeted genotypes when simulating the consequences of HPV persistence; therefore, we may underestimate the vaccine efficacy against HPV infection. HPV prevalence differs by region of residence.[66] Although the HPV prevalence was higher in rural women than in urban women,[4] that difference was not statistically significant in our previous analysis. Therefore, we did not stratify the population by their residence in this model. Third, cervical cancer incidence increases with age. China has a rapidly aging population, and the birth control policy is expected to change in the future, yet we assumed a fixed age structure over time in this model. Fourth, we assumed a homogenous cervical cancer screening sensitivity in the simulated population. However, the adoption of screening test varies by graphical regions, and the variation was not captured in this model. Fifth, we only assessed the preventive effects of a single type of HPV vaccine (bHPV or qHPV) in each scenario but did not consider the mixed usage, which is close to the real situation.

In conclusion, our study indicates that scaling-up cervical cancer screening in adult women is the most affordable strategy to maximize health benefits. Vaccinating schoolgirls will result in a large population benefit in the long term, but a universal HPV vaccination program can only be cost-effective with a substantial price reduction. Domestic vaccines may potentially be the game-changer.

Disclosure of potential conflicts of interest

Listed authors had no conflict of interest to report.

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