Informing HPV vaccine pricing for government-funded vaccination in mainland China: a modelling study

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Summary

Background The high price of HPV vaccines remains a significant barrier to vaccine accessibility in China, hindering the country's efforts toward cervical cancer elimination and exacerbating health inequity. We aimed to inform HPV vaccine price negotiations by identifying threshold prices that ensure that a government-funded HPV vaccination programme is cost-effective or cost-saving.

Methods We used a previously validated transmission model to estimate the health and economic impact of HPV vaccination over a 100-year time horizon from a healthcare payer perspective. Threshold analysis was conducted considering different settings (national, rural, and urban), cervical cancer screening scenarios (cytology-based or HPV DNA-based, with different paces of scale-up), vaccine types (four types available in China), vaccine schedules (two-dose or one-dose), mode of vaccination (routine vaccination with or without later switching to high-valency vaccines), willingness-to-pay thresholds, and decision-making criteria (cost-effective or cost-saving). Furthermore, we examined the budget impact of introducing nationwide vaccination at the identified threshold prices.

Findings Using the current market price, national routine HPV vaccination with any currently available vaccine is unlikely cost-effective. Under a two-dose schedule, the prices of the four available HPV vaccine types cannot exceed $26–$36 per dose (44.1%–80.2% reduction from current market prices) depending on vaccine type to ensure the cost-effectiveness of the national programme. Adopting vaccination at threshold prices would require an annual increase of 72.18%–96.95% of the total annual National Immunization Programme (NIP) budget in China. A cost-saving routine vaccination programme requires vaccine prices of $5–$10 per dose (depending on vaccine type), producing a 21.38%–34.23% increase in the annual NIP budget. Adding the second dose is unlikely to be cost-effective compared to a one-dose schedule, with the threshold price approaching or even falling below zero. Rural pilot vaccination programmes require lower threshold prices compared with a national programme.

Interpretation Our study could inform vaccine price negotiation and thus facilitate nationwide scale-up of current HPV vaccination pilot programmes in China. The evidence may potentially be valuable to other countries facing HPV introduction barriers due to high costs. This approach may also be adapted for other contexts that involve the introduction of a pricy vaccine.

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Keywords: HPV vaccination programme; Pricing; Threshold price; Cost-effective; Budget impact

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Research in context

Evidence before this study

The high price of HPV vaccines remains a significant barrier to vaccine accessibility in China, hindering the country's efforts toward cervical cancer elimination and exacerbating health inequity. It is imperative for China to negotiate a reasonable price for a government-funded HPV vaccination programme. Although many countries have included HPV vaccines in their National Immunization Programme (NIP), China struggles to obtain reliable references due to the confidentiality agreements surrounding tender prices, which could vary widely across countries. We searched PubMed without language restrictions for studies about HPV vaccine pricing published from January 1, 2000, to April 17, 2024, using the terms ("human papillomavirus" or "HPV") and ("vaccine" or "vaccination") and ("price" or "cost" or "pricing" or "price negotiation" or "negotiation" or "threshold price") and ("China" or "Chinese"). Most quantitative evidence from cost-effectiveness analyses has been based on assumed prices, providing limited insight into vaccine pricing. Among the six studies addressing the threshold vaccine price for ensuring the cost-effectiveness of HPV vaccination in China, two were conducted in Hong Kong and one in rural Shanxi Province. Two of the remaining studies adopted static models without considering herd effects, while the third study focused on three-dose HPV vaccination and Visual Inspection with Acetic Acid (VIA)/Lugol's Iodine (VILI)-based screening strategies, which no longer align with the current practices in China. Hence there is insufficient evidence for establishing pricing references in China based on currently relevant cervical cancer control strategies. This is a major evidence gap since China is a significant contributor to the global burden of cervical cancer, particularly as it undergoes the transition from pilot initiatives to a national immunization programme for HPV vaccination.

Added value of this study

Our results emphasize the need to negotiate lower tender prices for HPV vaccines in China to ensure the cost-effectiveness of scaling up vaccination efforts. To achieve cost-effectiveness for a two-dose national routine vaccination programme, a significant reduction in the price per dose to $26–$36 is necessary (depending on vaccine type). This represents a 44.1% to 80.2% reduction from their current market prices. However, for the national routine vaccination to be considered a cost-saving intervention, the price per dose should not exceed $5–$10. Rural pilot programmes in settings with limited financial resources would require a threshold price of approximately half of the national level. To better inform the pilot initiatives to nationwide HPV immunization in China, our analysis incorporates various factors, including different settings (national, rural, urban), cervical cancer screening scenarios (cytology-based or HPV DNA-based, with different pace of scale-up towards governmental targets), vaccine types (four types available in China), vaccine schedule (two-dose or one-dose), mode of vaccination (routine vaccination with or without later switching to high-valency vaccines), willingness-to-pay (WTP) thresholds, as well as decision-making criteria (cost-effective or cost-saving). We also evaluated the budget impact of introducing nationwide vaccination at the identified threshold prices, aiming to offer comprehensive evidence on vaccine pricing perspectives. We found that the national vaccination budget would need to increase by 72.18%–96.95% to introduce HPV vaccination at cost-effective threshold prices, and 21.38%–34.23% at cost-saving threshold prices.

Implications of all the available evidence

Despite the general understanding that tender-based vaccine prices are typically lower due to competitive bidding, the transparency of the process can vary significantly. Health authorities may sometimes choose not to disclose prices to secure better deals, but this may complicate the true pricing landscape. Moreover, the lack of detailed evidence on tender-based HPV vaccine pricing in China can hinder the government's ability to effectively negotiate and make informed procurement decisions. Our study offers the maximum estimate of HPV vaccine costs based on its potential value and assesses the budget impact of nationwide vaccination at identified threshold prices. These findings could inform pricing discussions in China regarding the potential inclusion of HPV vaccination into the NIP. Additionally, ensuring health equity poses a significant challenge during the pilot stage of HPV vaccination initiation in China. With pilot programmes funded by local governments, our findings provide timely evidence for policymakers in pilot regions on vaccine pricing tailored to local characteristics and decision-making priorities. Initiating the HPV vaccination programme at reasonable prices could not only ensure the positive benefit of vaccination, but also enhance vaccine accessibility and affordability, promote health equity, and eventually accelerate cervical cancer elimination in China. This approach may also facilitate the introduction of HPV vaccination in other countries, especially those with limited financial resources. Moreover, given the limited evidence in tender-based vaccine pricing, a similar exercise would be valuable for other vaccines, particularly for recently introduced vaccines with high prices.

Introduction

Human papillomavirus (HPV) vaccination is an effective cervical cancer prevention measure. In 2020, the WHO proposed a target for 90% of girls to be fully vaccinated with HPV vaccine by age 15 years by 2030 in order to accelerate cervical cancer elimination.[1] China, with 22.7% of global cervical cancer cases in 2022,[2] is also actively preparing for a nationwide vaccination programme. In 2022, China's National Health Commission announced the gradual rollout of free HPV vaccines nationwide to eligible girls, starting in pilot regions.[3] Based on the Healthy China Initiative, China has so far piloted HPV vaccinations in several provinces and cities funded by local governments. In 2023, the central government put forward the Action Plan for Accelerating Elimination of Cervical Cancer (2023–2030), which includes the objective of boosting vaccination rates among eligible girls nationwide.[4]

When incorporating a new vaccine into the National Immunization Programme (NIP), affordability, budget impact, and cost-effectiveness are important factors to be considered besides vaccine efficacy and safety. To date, China has approved five HPV vaccine products, with market prices ranging from $47.61 to $193.73 USD per dose. These include two domestically produced bivalent HPV vaccines (Cecolin®, Walrinvax® [domestically produced HPV-2]), an imported bivalent HPV vaccine (Cervarix® [imported HPV-2]), an imported quadrivalent HPV vaccine (Gardasil® [HPV-4]), and an imported nonavalent HPV vaccine (Gardasil-9® [HPV-9]). Without the benefit of low prices negotiated by Gavi, scaling up HPV vaccination could lead to significant financial burdens and may not be cost-effective, which may hinder the widespread adoption of HPV vaccines while exacerbating health inequality. This issue could be mitigated if the purchaser could negotiate purchasing prices through public-sector tendering for a national HPV vaccination programme funded by the central government.

Despite the general understanding that tender-based vaccine prices are typically lower due to competitive bidding, the complexities and variabilities in the transparency of the tender procurement negotiation process, along with the lack of detailed evidence on tender-based HPV vaccine pricing in China, can hinder the government's ability to effectively negotiate and make informed procurement decisions. Evaluating the maximum price to pay for a vaccine dose based on the potential value of vaccination and decision-making criteria, combined with assessing the budget impact of vaccine pricing would be valuable for price negotiations around the inclusion of HPV vaccination into the NIP. However, evidence to inform such estimates is notably limited in China. On the one hand, most cost-effectiveness analyses for Chinese HPV vaccination were conducted based on assumed prices,[5–9] providing limited insight into vaccine pricing. On the other hand, the limited number of studies that estimated threshold vaccine prices are also hindered by various limitations, making it challenging to use them to inform pricing of HPV vaccines in China. These limitations include being confined to specific regions rather than the entire nation,[10–12] using of static models that fail to comprehensively evaluate vaccine value,[11,13,14] and evaluating vaccination and screening scenarios that do not align with the current policy context.[12,13,15] Moreover, as China prepares to expand HPV vaccination efforts through pilot programmes funded by local governments, pilot regions also require tailored evidence reflecting local contexts to guide their decisions concerning context-specific vaccine pricing.

As global evidence accumulates, countries with established HPV vaccination programmes are reassessing and refining their immunization strategies. Several nations have transitioned from lower-valency HPV vaccines to higher-valency ones to maximize population-level health benefits.[16,17] Moreover, in 2022, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommended that countries can consider a one-dose schedule for HPV vaccination as a potential measure to expedite progress towards the goal of vaccinating 90% of girls by age 15 by 2030.[18] Incorporating the aforementioned potential strategies into evaluations and providing evidence to inform vaccine price negotiations for China would support effective optimization of future HPV vaccination strategies within the Chinese NIP.

In this study, our objective is to identify the threshold price for government-funded vaccination programme to be cost-effective or cost-saving in different settings in China, based on the public health and economic value of vaccination. We also aim to assess the budget impact of conducting nationwide vaccination at the identified threshold prices. The results of this study would provide invaluable insights for the HPV vaccine tendering in China to support the nationwide scale-up of current pilot programmes.

Methods

Model design

A previously validated two-stage hybrid model of HPV infection and diseases was used to evaluate the public health and economic impact of various HPV vaccination strategies in China. The model comprises a deterministic age-structured dynamic transmission model and a static compartmental natural history model. Rural and urban areas of China, which feature different characteristics of HPV and cervical cancer burden, were considered separately. Details of the model structure and the parameters used are presented in the Appendix and previous works.[19,20] Considering uncertainty around future demographic trends, we conservatively assumed that the urbanization rate and sexual activity level in China remain unchanged in our primary analysis. However, in our sensitivity analysis, we also assessed the effects of varying these factors (see Appendix p 6 and previous publications[19,20] for more details).

Vaccination scenarios and assumptions

In this study, we considered four types of HPV vaccines (domestically produced HPV-2 [analysis was based on the characteristics of Cervarix®], imported HPV-2, HPV-4, and HPV-9) independently. To investigate the cost-effectiveness of a national vaccination programme using current market prices and explore the threshold price for each vaccine type to be cost-effective or cost-saving, we included alternative scenarios involving vaccination of girls aged 14 years routinely at 90% coverage from 2023, as well as a scenario where a national programme is never introduced. Both two-dose and one-dose schedules were considered. We also included a scenario for Supplementary analysis involving vaccine type switch from lower-valency to higher-valency vaccines. We selected the most likely scenario where China adopts domestically produced HPV-2 for the national programme with a later switch to a nonavalent vaccine. In this Supplementary analysis, we explore the maximum additional price that could be paid for the nonavalent vaccine compared to bivalent vaccines for the type switch to be cost-effective or cost-saving. The switch from bivalent to nonavalent vaccines was assumed to occur in 2030 or 2040, based on the expected launch time of domestic nonavalent vaccines.[21,22]

Two-dose HPV vaccination was assumed to provide 100% lifelong protection against vaccine-targeted HPV types. For one-dose vaccination, we used a conservative estimate of 85% protection with a lifelong duration, based on the lower bound target efficacy for one-dose HPV vaccination in a *post hoc* analysis of a randomized control trial with follow-up out to 10 years.[23] We included a wide range for the efficacy of one-dose vaccination (70%–100%) in our probabilistic sensitivity analysis. This range is set to encompass the confidence interval of single-dose vaccine efficacy based on the currently available RCT evidence.[23,24] Cross-protection efficacy against HPV types 31, 33, and 45 for imported HPV-2, as well as against HPV type 31 for HPV-4 in the two-dose vaccination, was assumed based on existing literature (see appendix Supplementary Table S1).[25] We made a conservative assumption that domestically produced HPV-2 and HPV-9 provide no cross-protection due to the absence of strong evidence. We did not consider cross-protection for a one-dose schedule. This conservative assumption is based on the limited and inconsistent evidence currently available regarding cross-protection with a single dose. Moreover, the value of vaccination in preventing HPV-related non-cervical cancers and genital warts was not considered due to the limited evidence in China.

Screening scenarios and assumptions

In China, although cytology is still used as the primary screening test, the country's National Health Commission has issued new guidelines for the cervical cancer screening programme in 2022, recommending high-risk HPV testing as one of the primary screening techniques to improve the screening sensitivity.[26] The "Action Plan for Accelerating the Elimination of Cervical Cancer (2022–2030)", released by the Chinese government in early 2023, explicitly sets a goal of achieving a 70% cervical cancer screening rate among eligible women by 2030. Besides that, the increased government funding,[27] and successful initiatives like the "Healthy City" programme also indicate a likely future expansion of cervical cancer screening coverage, with significant improvements already observed, such as a 75.5% screening coverage in Ordos City over five years.[28] As such, we considered six scale-up screening scenarios to capture the possible technological advances or increase in coverage in the future. The screening scenarios were assumed to involve either HPV DNA-based screening at five-year intervals or Liquid-based cytology-based (LBC-based) screening at three-year intervals for the target population of women aged 35–64 years. For each screening method, we considered three screening coverage trends with linearly increasing uptake from the status quo in 2023 to 70% in 2030, 2050, or 2070, following a 1% increase every year until 90% is reached. The status quo screening strategy before 2023 in our model is cytology-based at three-year intervals, with age-specific screening coverage in rural and urban areas derived from a nationally representative survey.[29,30] We set the HPV DNA-based screening aiming for 70% coverage by 2030 as the base case screening scenario as per the action plan for accelerating the elimination of cervical cancer.[4] Annual screening coverage for non-target females aged 21–34 and over 65 years was assumed to remain the same as the status quo in all scenarios to account for the coverage of opportunistic screening (see Appendix 1.4 for more details).

Outcomes and analysis

For this study, we estimated the health and economic impacts of each scenario for all females in mainland China over a 100-year time horizon from a healthcare payer perspective. First, we explored the cost-effectiveness of vaccinating 14-year-old girls routinely in China using current market prices and a range of willingness-to-pay (WTP) thresholds. We set 51% gross domestic product (GDP) per capita as the baseline WTP threshold (i.e., $6464).[31] Second, we conducted a threshold analysis to find the maximum price per dose at which the routine vaccination remains cost-effective or cost-saving in China, compared to the no vaccination used scenario (detailed information can be found in Appendix p11). To address the uncertainty around WTP thresholds for policy-making, we also considered a wider range based on the lower and upper bounds of the cost-effectiveness threshold (30%–200% of GDP per capita for 2023) after integrating a range of relevant evidence (see Appendix 1.5 for detailed information).[32–35] The threshold price per dose for two-dose and one-dose schedules were evaluated separately. We also calculated the threshold incremental cost per dose for the second dose compared to maintaining a one-dose schedule, and for HPV-9 compared to domestically produced HPV-2, under various decision-making criteria (cost-effectiveness or cost-saving). We reported these threshold prices mainly at the national level since the central government would eventually pay a unified price for the NIP vaccines with a nationwide rollout. However, we also provided separate estimates for rural and urban settings to offer tailored insights for policymakers in regions considering pilot HPV vaccination programmes. Third, we assessed the budget impact of introducing HPV vaccination programmes at the threshold prices. We calculated the average undiscounted annual vaccination budget over the first five years and over 100 years, alongside the proportion of HPV vaccination budgets within the existing NIP budget. Additionally, the results of discounted costs were also calculated to provide a comprehensive view and allow decision-makers to see the impact from both perspectives. We conservatively estimate that the annual allocation from the central government for NIP is approximately four billion RMB (about $567 million), based on the information disclosed by the National Health Commission.[36] The HPV vaccination budget as a proportion of the total budget for cervical cancer control was also estimated.

All unit costs were converted to 2023 using the government-reported consumer price index (CPI) for health care and then converted into US dollars using exchange rates for 2023 (i.e., 1.00 US dollar = 7.05 RMB). Both quality-adjusted life-year (QALY) and costs were discounted at 3% per year for incremental cost-effectiveness ratio (ICER) calculation, as recommended by national guidelines.[37] We conducted a sensitivity analysis using a 5% discount rate and a zero discount rate to examine the effects of discount rates on threshold prices. Probabilistic sensitivity analysis was performed using 500 Monte Carlo simulations to sample parameter values from their distributions. Results are presented as medians with 80% uncertainty intervals [UIs] (i.e., 10th–90th percentiles). All analyses were performed in R. The results were reported following the HPV-FRAME checklist and CHEERS checklist (appendix Supplementary Tables S2–S5).

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.

Results

Cost-effectiveness of routine vaccination using current market prices

Fig. 1 and appendix Supplementary Figs. S7 and S8 show the cost-effectiveness acceptability curves for routine vaccination with current market prices compared with no vaccination across various settings and scenarios. When adopting 51% GDP per capita as the WTP threshold, none of the four types of vaccines at their current market prices considered for a national HPV vaccination programme was likely to be cost-effective (probability < 1.4%) despite variations in screening scenarios. Implementing a one-dose schedule would substantially improve the cost-effectiveness of the national programme using domestically produced HPV-2. Under the base case screening scenario (HPV 2030, HPV DNA-based screening reaching 70% coverage by 2030), a national programme using domestically produced HPV-2 would have a 98.6% probability of being cost-effective. However, for the other three vaccines, the probability of cost-effectiveness for a national programme was lower than 16.2% across screening scenarios. Furthermore, across all vaccine types and WTP thresholds, routine vaccination has the lowest probability of being cost-effective under the scenario with the highest test sensitivity and most rapidly scaling up (HPV 2030).

Threshold prices of HPV vaccines under different scenarios

For a two-dose national routine vaccination to be cost-effective with a 51% probability under the HPV 2030 screening scenario, the price per dose should not exceed specific thresholds: $26 for domestically produced HPV-2, $29 for imported HPV-2, $27 for HPV-4, and $36 for HPV-9 (Table 1). That represents a considerable reduction in price per dose compared to current market prices, ranging from 44.1% to 80.2% (depending on vaccine type). However, when the decision-making criterion is to make the national routine vaccination a cost-saving intervention, further price reductions on vaccines are necessary. Under the HPV 2030 screening scenario, the cost-saving threshold price per dose was $5 for domestically produced HPV-2, $6 for imported HPV-2, $6 for HPV-4, and $10 for HPV-9. Threshold prices would rise slightly under screening scenarios with slower scaling up and lower test sensitivity compared to the HPV 2030 scenario. In the poorest screening scenario (LBC 2070), the cost-effective threshold price would be $11–$15 higher than that under the HPV2030 scenario, while the cost-saving threshold price would be $1–$2 higher (depending on vaccine type). Furthermore, for rural areas with limited health and economic resources considering the initiation of a pilot vaccination programme, the threshold prices should be further reduced compared with the national level. Specifically, the price per dose under HPV 2030 screening scenario should be $17–25 for cost-effectiveness and $3–7 for cost-saving in rural areas (depending on vaccine type). Additional results using different WTP thresholds are available in appendix Supplementary Table S6.

With a one-dose schedule, the price per dose should not exceed $54–$74 (depending on vaccine type) to ensure the cost-effectiveness of the national vaccination programme under HPV 2030 scenario compared with no vaccination (Fig. 2). For a one-dose programme to be cost-saving, the threshold price per dose should be reduced to $14–$24, depending on vaccine type. Similar

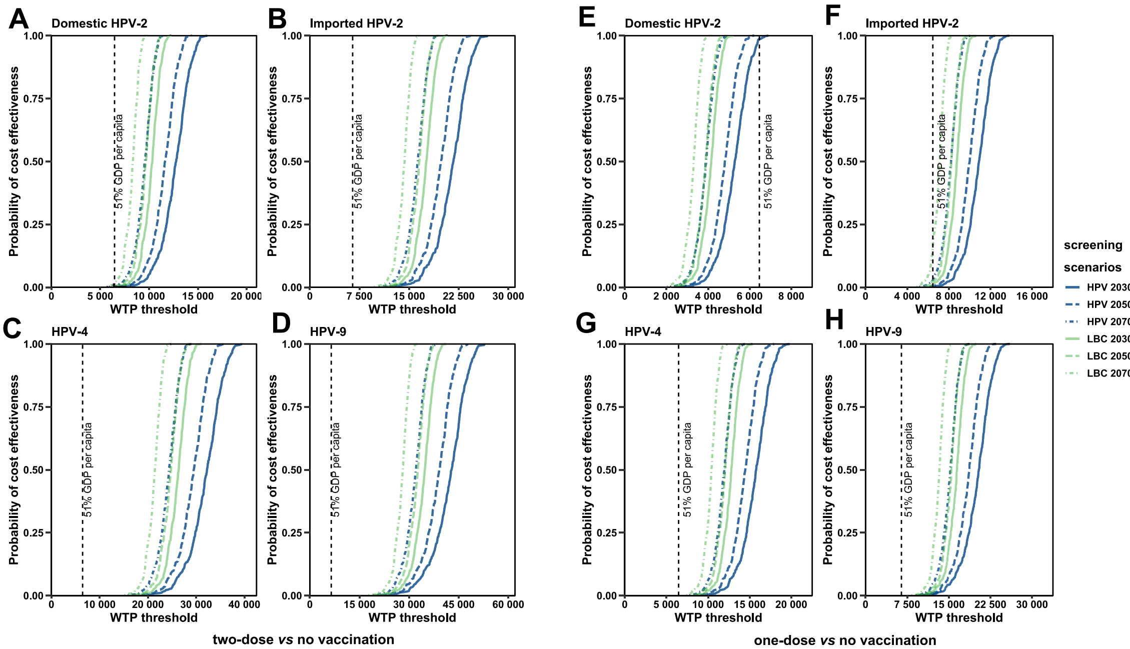

Fig. 1: **Cost-effectiveness acceptability curves for nationwide routine HPV vaccination at current market prices (compared with no vaccination).** The figure illustrates the probability of cost-effectiveness compared to no vaccination for nationwide routine HPV vaccination at current market prices, across various willingness-to-pay (WTP) thresholds. Panels A–D in the left display results for the two-dose schedule, while panels E–H in the right present results for the one-dose schedule. Results under HPV DNA-based screening scenarios are depicted in blue, while Liquid-based cytology-based (LBC-based) screening scenarios are shown in green. Under two screening strategies, different screening scale-up rates were set according to the year achieving 70% coverage, depicted by varying line styles in the figure. Consequently, the figure illustrates a total of six screening scenarios, each denoted by distinct abbreviations. For example, HPV 2030 represents HPV DNA-based screening reaching 70% coverage by the year 2030. These probabilities were calculated based on 500 Monte Carlo simulations. Domestic HPV-2 = domestically produced bivalent HPV vaccine (Cecolin®); Imported HPV-2 = imported bivalent HPV vaccine (Cervarix®); HPV-4 = quadrivalent HPV vaccine (Gardasil®); HPV-9 = nonavalent HPV vaccine (Gardasil-9®); WTP = willingness-to-pay; HPV 2030 = HPV DNA-based screening reaching 70% coverage by the year 2030; HPV 2050 = HPV DNA-based screening reaching 70% coverage by the year 2050; HPV 2070 = HPV DNA-based screening reaching 70% coverage by the year 2070; LBC 2030 = LBC-based screening reaching 70% coverage by the year 2030; LBC 2050 = LBC-based screening reaching 70% coverage by the year 2050; LBC 2070 = LBC-based screening reaching 70% coverage by the year 2070.

to findings for a two-dose schedule, threshold vaccine prices increase in screening scenarios with slower scaling up and lower test sensitivity compared to HPV 2030. Moreover, threshold prices for rural areas are lower than those at the national level. Adding the second dose to achieve 100% protection was not cost-effective compared with a one-dose schedule offering 85% lifelong protection, with negative cost-effective threshold prices for domestically produced HPV-2 and HPV-9 due to the high vaccination delivery costs. However, for imported HPV-2 and HPV-4, adding the second dose could be cost-effective under certain screening scenarios, driven by potential cross-protection benefits. The threshold prices for the second dose should be lower than $11 across both vaccine types and all screening scenarios. Moreover, adding the second dose was never cost-saving compared with a one-dose schedule for any of the vaccines, with all the cost-saving threshold prices lower than 0.

Switching from domestically produced HPV-2 to HPV-9 in the NIP by 2030 required a maximum additional vaccine price of $10–13 (depending on screening scenarios) per dose for HPV-9 compared with the bivalent one to ensure the cost-effectiveness of the switch. When aiming for the vaccine type switch to be a cost-saving intervention, the threshold additional price per dose would be $5–6 (appendix Supplementary Table S7). The effect of the year of switch was minimal; if the switch occurs in 2040, the threshold additional price per dose would be slightly higher (<$1) than that in the setting where the switch occurs in 2030, under the same screening scenarios.

Budget impact of funding a national HPV vaccination programme at threshold prices

Adopting the cost-effective threshold prices would require a considerable procurement budget. Under the HPV 2030 scenario, the two-dose routine HPV vaccination programme would require an average annual vaccination budget of $409.54 million to $550.09 million (depending on vaccine type) over the first five years. This represents 72.18%–96.95% of the total annual budget for the current NIP in China and

Vaccine type	Screening scenario	Cost-saving threshold price per dose ($)			Cost-effective threshold price per dose ($)		
		National	Rural	Urban	National	Rural	Urban
Domestic HPV-2	HPV 2030	5.07 (4.10–6.25)	2.72 (1.81–3.71)	7.40 (6.32–8.70)	26.11 (23.21–30.56)	17.42 (15.36–20.55)	35.30 (31.30–41.58)
	HPV 2050	5.27 (4.29–6.45)	2.84 (1.93–3.84)	7.65 (6.59–8.95)	28.22 (25.27–32.73)	18.65 (16.57–21.81)	38.57 (34.47–44.85)
	HPV 2070	5.69 (4.70–6.87)	3.12 (2.20–4.18)	8.20 (7.12–9.52)	33.33 (30.33–37.88)	21.77 (19.61–25.08)	46.24 (41.98–52.49)
	LBC 2030	5.93 (4.90–7.08)	3.37 (2.36–4.42)	8.46 (7.35–9.95)	31.36 (28.94–35.06)	20.63 (18.78–23.33)	43.51 (40.18–48.97)
	LBC 2050	6.09 (5.05–7.23)	3.47 (2.47–4.54)	8.67 (7.56–10.18)	33.12 (30.63–36.91)	21.68 (19.77–24.41)	46.29 (42.89–51.89)
	LBC 2070	6.45 (5.39–7.60)	3.71 (2.68–4.79)	9.15 (8.01–10.68)	37.56 (34.86–41.72)	24.39 (22.42–27.29)	52.86 (49.43–58.83)
Imported HPV-2	HPV 2030	6.48 (5.47–7.72)	3.72 (2.76–4.82)	9.18 (8.03–10.66)	29.00 (25.88–33.87)	19.47 (17.23–23.14)	39.03 (34.71–46.76)
	HPV 2050	6.69 (5.67–7.93)	3.86 (2.90–4.96)	9.47 (8.30–10.92)	31.26 (28.07–36.18)	20.78 (18.53–24.36)	42.62 (38.09–50.09)
	HPV 2070	7.13 (6.10–8.39)	4.17 (3.19–5.32)	10.09 (8.90–11.53)	36.81 (33.59–42.00)	24.22 (21.87–27.91)	51.04 (46.26–58.31)
	LBC 2030	7.38 (6.29–8.64)	4.38 (3.36–5.53)	10.32 (9.09–12.01)	34.69 (31.98–38.80)	22.92 (20.90–25.91)	47.97 (44.25–54.05)
	LBC 2050	7.56 (6.47–8.84)	4.51 (3.47–5.65)	10.55 (9.32–12.26)	36.58 (33.84–40.75)	24.04 (21.96–27.05)	50.90 (47.05–57.16)
	LBC 2070	7.96 (6.87–9.27)	4.76 (3.69–5.94)	11.10 (9.87–12.79)	41.46 (38.54–45.99)	27.07 (24.86–30.25)	58.19 (54.31–64.81)
HPV-4	HPV 2030	5.55 (4.56–6.73)	3.08 (2.13–4.08)	8.00 (6.85–9.39)	27.03 (24.13–31.77)	18.07 (15.97–21.45)	36.46 (32.44–43.50)
	HPV 2050	5.73 (4.76–6.92)	3.21 (2.26–4.21)	8.27 (7.13–9.63)	29.20 (26.24–33.95)	19.33 (17.20–22.69)	39.78 (35.65–46.69)
	HPV 2070	6.19 (5.18–7.40)	3.50 (2.53–4.56)	8.80 (7.69–10.20)	34.46 (31.35–39.23)	22.56 (20.36–25.90)	47.84 (43.31–54.65)
	LBC 2030	6.42 (5.34–7.58)	3.72 (2.71–4.76)	9.09 (7.91–10.62)	32.43 (29.93–36.30)	21.34 (19.48–24.16)	44.98 (41.57–50.61)
	LBC 2050	6.58 (5.50–7.74)	3.82 (2.81–4.88)	9.31 (8.16–10.85)	34.20 (31.72–38.18)	22.40 (20.50–25.28)	47.75 (44.28–53.55)
	LBC 2070	6.95 (5.87–8.13)	4.05 (3.02–5.17)	9.80 (8.64–11.34)	38.78 (36.12–43.05)	25.21 (23.24–28.21)	54.58 (50.95–60.82)
HPV-9	HPV 2030	10.40 (9.21–12.02)	6.52 (5.43–7.87)	14.26 (12.79–16.14)	36.49 (32.82–43.40)	24.74 (22.01–29.53)	48.85 (43.58–58.58)
	HPV 2050	10.63 (9.44–12.28)	6.67 (5.57–8.05)	14.58 (13.12–16.48)	39.16 (35.41–45.87)	26.29 (23.51–31.00)	53.02 (47.64–62.79)
	HPV 2070	11.14 (9.90–12.82)	6.98 (5.87–8.40)	15.26 (13.83–17.24)	45.81 (41.84–52.69)	30.41 (27.50–35.14)	63.09 (57.46–73.49)
	LBC 2030	11.36 (10.13–13.07)	7.22 (6.02–8.65)	15.46 (14.05–17.69)	43.24 (39.92–48.79)	28.74 (26.28–32.62)	59.55 (54.74–67.45)
	LBC 2050	11.57 (10.33–13.27)	7.34 (6.14–8.80)	15.75 (14.32–18.01)	45.48 (42.10–50.98)	30.07 (27.65–33.94)	62.99 (58.18–71.04)
	LBC 2070	12.00 (10.73–13.70)	7.60 (6.41–9.10)	16.31 (14.85–18.65)	51.42 (47.75–57.06)	33.68 (31.08–37.74)	71.82 (66.99–80.34)

Threshold vaccine prices per dose are estimated based on different settings (national, urban, and rural), screening scenarios (LBC-based or HPV DNA-based, with different pace of scale-up), and vaccine types (domestically produced HPV-2, imported HPV-2, HPV-4, and HPV-9). Results are presented as medians with 80% uncertainty intervals [UIs] (i.e., 10th–90th percentiles) based on Monte Carlo simulations. It should be noted that this analysis did not account for the vaccines' protection against genital warts and other non-cervical HPV-related cancers. If these are taken into consideration then it is likely that the threshold price for quadrivalent vaccines would be higher than for imported bivalent vaccines. Domestic HPV-2 = domestically produced bivalent HPV vaccine (Cecolin®); Imported HPV-2 = imported bivalent HPV vaccine (Cervarix®); HPV-4 = quadrivalent HPV vaccine (Gardasil®); HPV-9 = nonavalent HPV vaccine (Gardasil-9®); HPV 2030 = HPV DNA-based screening reaching 70% coverage by the year 2030; HPV 2050 = HPV DNA-based screening reaching 70% coverage by the year 2050; HPV 2070 = HPV DNA-based screening reaching 70% coverage by the year 2070; LBC 2030 = LBC-based screening reaching 70% coverage by the year 2030; LBC 2050 = LBC-based screening reaching 70% coverage by the year 2050; LBC 2070 = LBC-based screening reaching 70% coverage by the year 2070.

Table 1: **Threshold vaccine price per dose for routine vaccination by setting, screening scenario, and vaccine type (two-dose schedule).**

accounts for 19.23%–24.27% of the total average annual budget for cervical cancer control (Figs. 3 and 4, appendix Supplementary Table S8). If the cost-saving threshold prices for bulk purchase are adopted, the average annual vaccination budget would be $121.28 million to $194.19 million (depending on the vaccine type) over the first five years, accounting for 21.38%–34.23% of the current NIP budget in China and 6.60%–10.17% of the total budget for cervical cancer control. Under the screening scenarios with slower scaling up and lower test sensitivity compared with the HPV 2030 scenario, the HPV vaccination budget would be higher. Although vaccination does not lead to cost savings in screening and treatment in the first five years, it results in an annual cost savings of $179.98 million to $326.72 million in cervical cancer screening and treatment over the 100 years (depending on vaccine type and screening scenario, Fig. 3, appendix Supplementary Table S9).

Sensitivity analysis

The results of the sensitivity analysis indicate that the threshold price varies significantly with different discount rates. Under the same conditions, a higher discount rate will lead to a lower threshold price (appendix Supplementary Table S19). When accounting for potential increases in sociodemographic factors, threshold prices were approximately twice as high as those estimated in the primary analysis. Nevertheless, the general findings remain consistent between our primary analysis and sensitivity analysis (Appendix pp 33–40).

Discussion

Vaccine pricing significantly influences both the cost-effectiveness and the budget impact of vaccination, making it a crucial consideration for policymakers when incorporating a new vaccine into NIP. Our results

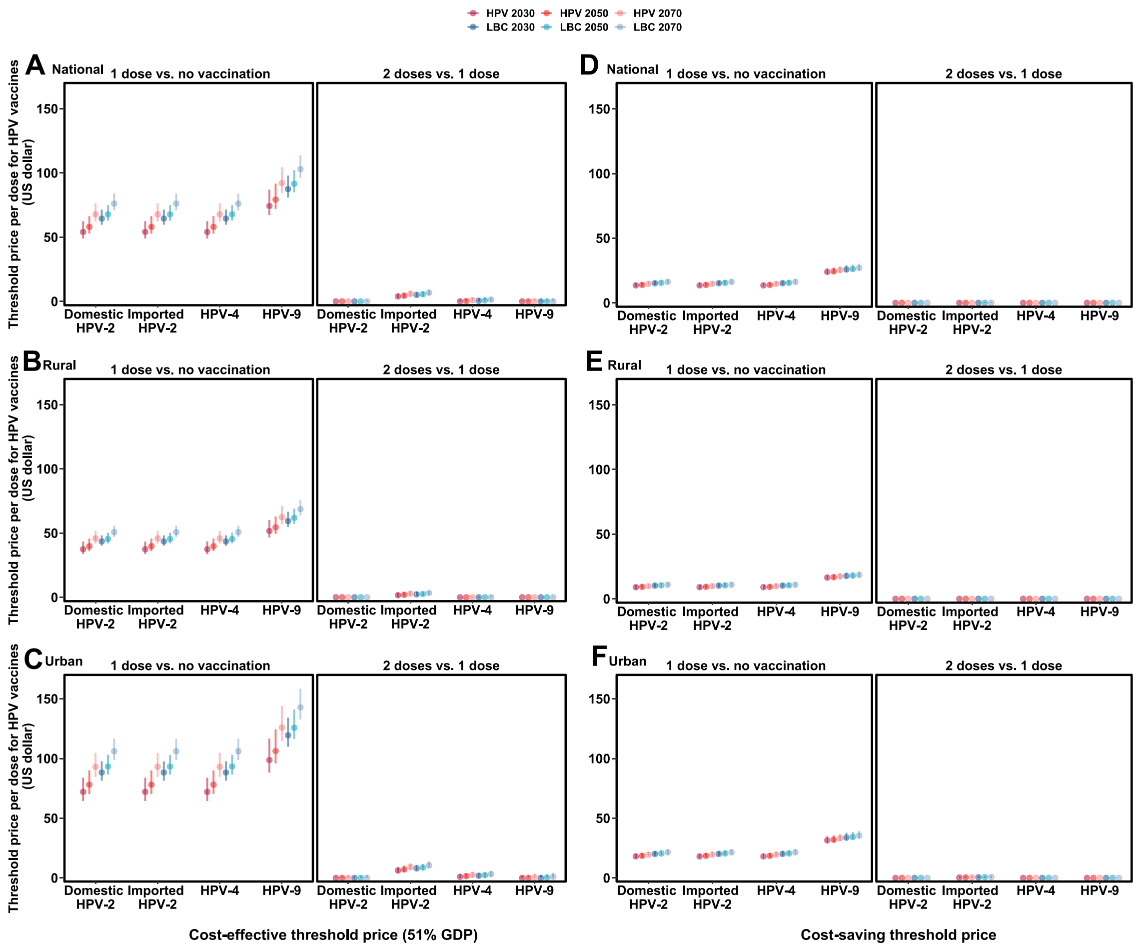

Fig. 2: **Threshold vaccine price per dose for routine vaccination by setting, screening scenario, and vaccine type (one-dose schedule).** Threshold vaccine prices are estimated across various settings (national, urban, and rural), screening scenarios (LBC-based or HPV DNA-based, with varying rates of scale-up), and vaccine types (domestically produced HPV-2, imported HPV-2, HPV-4, and HPV-9). The threshold prices for one-dose HPV vaccination (*vs* no vaccination) as well as the threshold prices for the second dose (*vs* maintaining the one-dose schedule) are included. Panels A–C display results for the cost-effective threshold prices, while panels D–F display results for the cost-saving threshold prices. The points in various colours represent the median values of Monte Carlo simulations corresponding to different screening scenarios, while error bars indicate the 80% uncertainty intervals (i.e., 10th–90th percentiles). Negative values are displayed as 0 in the figure. Domestic HPV-2 = domestically produced bivalent HPV vaccine (Cecolin®); Imported HPV-2 = imported bivalent HPV vaccine (Cervarix®); HPV-4 = quadrivalent HPV vaccine (Gardasil®); HPV-9 = nonavalent HPV vaccine (Gardasil-9®); HPV 2030 = HPV DNA-based screening reaching 70% coverage by the year 2030; HPV 2050 = HPV DNA-based screening reaching 70% coverage by the year 2050; HPV 2070 = HPV DNA-based screening reaching 70% coverage by the year 2070; LBC 2030 = LBC-based screening reaching 70% coverage by the year 2030; LBC 2050 = LBC-based screening reaching 70% coverage by the year 2050; LBC 2070 = LBC-based screening reaching 70% coverage by the year 2070.

highlight the necessity of negotiating lower prices for HPV vaccines to ensure the cost-effectiveness and affordability of government-funded vaccination programmes. With a two-dose schedule, the prices of four HPV vaccine types should not exceed $26–$36 per dose (represent a 44.1%–80.2% reduction from current market prices) depending on vaccine types to ensure the cost-effectiveness of a national routine HPV vaccination programme. Adopting these prices would require an average annual budget increase of 72.18% to 96.95% of the total annual NIP budget in China over the first five years. A cost-saving routine vaccination requires vaccine prices of $5–$10 per dose (depending on vaccine type), producing a 21.38% to 34.23% increase in the annual NIP vaccine budgets. Rural pilot vaccination programmes should aim for lower threshold prices, mostly due to their more limited healthcare and financial resources. Moreover, if a one-dose schedule is licensed for the national programme in China, the per-dose threshold prices would increase compared with a two-dose schedule. In this case, adding the second dose is unlikely to be cost-effective or cost-saving compared

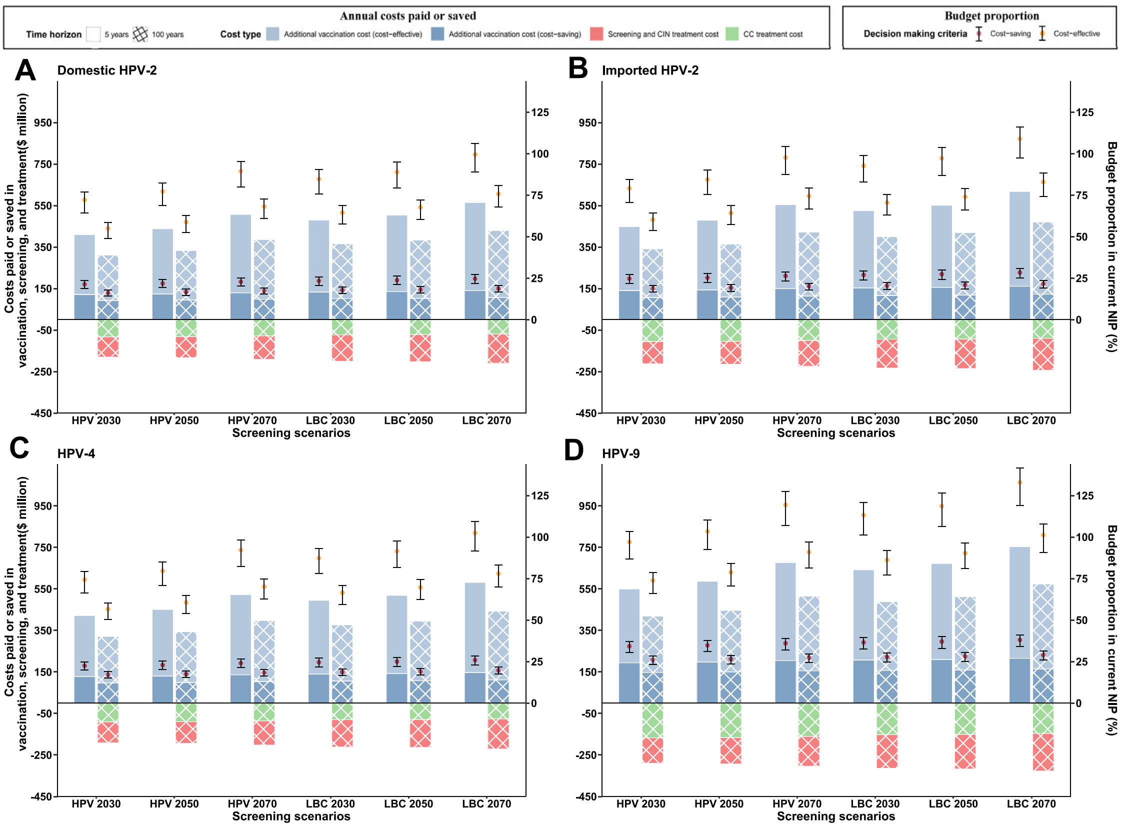

Fig. 3: **Budget impact of introducing nationwide HPV vaccination at identified threshold prices, offset by reduced cervical cancer screening and treatment costs in China.** Average annual costs paid or saved over the first five years and over 100 years are represented by solid colour blocks and colour blocks with grids, respectively. Bars in green and red with negative values indicate average cost savings attributed to reductions in cervical cancer treatment, and in screening and CIN treatment costs, respectively. Bars in dark blue represent the annual HPV vaccination budget at cost-saving threshold prices. The incremental vaccination costs at cost-effective threshold prices, compared with the vaccination budget at cost-saving prices, are presented as bars in light blue. Dots of different colours denote the proportion of the budget allocated for HPV vaccination within the current National Immunization Programme (NIP) budget at varying threshold prices (red for cost-saving threshold price, yellow for cost-effective threshold price). All values are undiscounted and depicted as the median of Monte Carlo simulations, and error bars indicate the 80% uncertainty intervals. CIN = Cervical Intraepithelial Neoplasia; CC = cervical cancer; Domestic HPV-2 = domestically produced bivalent HPV vaccine (Cecolin®); Imported HPV-2 = imported bivalent HPV vaccine (Cervarix®); HPV-4 = quadrivalent HPV vaccine (Gardasil®); HPV-9 = nonavalent HPV vaccine (Gardasil-9®); HPV 2030 = HPV DNA-based screening reaching 70% coverage by the year 2030; HPV 2050 = HPV DNA-based screening reaching 70% coverage by the year 2050; HPV 2070 = HPV DNA-based screening reaching 70% coverage by the year 2070; LBC 2030 = LBC-based screening reaching 70% coverage by the year 2030; LBC 2050 = LBC-based screening reaching 70% coverage by the year 2050; LBC 2070 = LBC-based screening reaching 70% coverage by the year 2070.

with maintaining the one-dose schedule in most scenarios.

Vaccines included in the NIP are often procured through public-sector tenders and negotiations, resulting in lower prices compared to the market prices. However, the mechanism by which prices are set has been unclear, and the tender prices in other countries might be subject to confidentiality agreements.[38] For China, the inadequate evidence on tender-based HPV vaccine pricing, can hinder the government's ability to effectively negotiate and make informed procurement decisions. In this case, our study provides an approach to inform vaccine pricing negotiations that goes beyond reliance solely on market forces. Specifically, it is based on estimating the health and economic impacts of vaccination and identifying the threshold value to ensure that vaccination remains cost-effective or cost-saving. It should be noted that the cost-saving threshold price serves as a lower bound for vaccine pricing, as the aim of healthcare spending is to improve population health and wellbeing, human capital development and economic growth rather than simply to save the health system money. However, given that vaccine introduction has a large immediate budget impact and

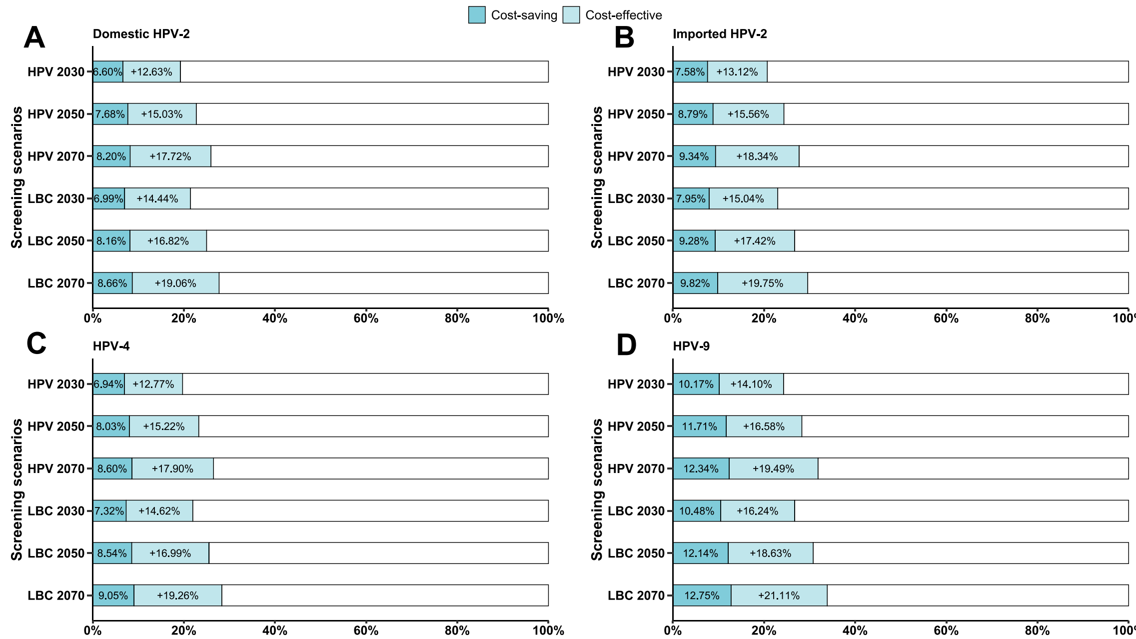

Fig. 4: **Average annual budget impact of HPV vaccination over first 5 years: proportion of total cervical cancer prevention budget at different threshold prices.** The dark blue bars represent the average annual budget proportion allocated to HPV vaccination at cost-saving threshold prices within the annual cervical cancer prevention budget. The light blue bars represent the incremental proportion of the vaccination budget at cost-effective threshold prices compared to cost-saving threshold prices. The cervical cancer prevention budget encompasses the budget for HPV vaccination, cervical cancer screening, and treatment for cervical intraepithelial neoplasias (CINs) and cervical cancer cases. All values are undiscounted and presented as the median of Monte Carlo simulations. Domestic HPV-2 = domestically produced bivalent HPV vaccine (Cecolin®); Imported HPV-2 = imported bivalent HPV vaccine (Cervarix®); HPV-4 = quadrivalent HPV vaccine (Gardasil®); HPV-9 = nonavalent HPV vaccine (Gardasil-9®); HPV 2030 = HPV DNA-based screening reaching 70% coverage by the year 2030; HPV 2050 = HPV DNA-based screening reaching 70% coverage by the year 2050; HPV 2070 = HPV DNA-based screening reaching 70% coverage by the year 2070; LBC 2030 = LBC-based screening reaching 70% coverage by the year 2030; LBC 2050 = LBC-based screening reaching 70% coverage by the year 2050; LBC 2070 = LBC-based screening reaching 70% coverage by the year 2070.

most of its financial cost savings will not occur until many years in the future, even a cost-effective vaccination programme may not be financially sustainable in the short-term without further price reductions. In this case, offering both the cost-effective and cost-saving thresholds provides policymakers with flexibility in price negotiation, allowing them to tailor their approach based on specific decision-making criteria.

Notably, the threshold price of the quadrivalent vaccine is lower than that of the imported bivalent vaccine in our study, which seems counterintuitive. This outcome arose because our analysis did not account for the vaccines' protection against genital warts and other HPV-related non-cervical cancers. Additionally, the higher cross-protection efficacy of the imported bivalent vaccine compared to quadrivalent vaccine, as established through a systematic review summarizing several clinical trials,[25] also contributed to this result. These threshold prices should serve as a guiding principle to ensure the cost-effectiveness or cost savings of HPV vaccination for cervical cancer prevention alone. This focus on cervical cancer prevention is aligned with the fact that current HPV vaccination-related policies or statements by government in China are framed within the context of 'cervical cancer prevention and control' or 'cervical cancer elimination', without mentioning genital warts or other diseases.[4,39–41] If the additional health benefits and economic savings from preventing other HPV-related diseases were taken into consideration, it is highly likely that quadrivalent vaccines would have a higher threshold price than imported bivalent vaccines.

In China, the procurement costs of NIP vaccines and required syringes are financed by the central government. However, for the pilot HPV vaccination programs, it is the local governments of the pilot regions that fund the programs and are responsible for their own pricing negotiations. The recently announced tender prices for HPV vaccines used in Chinese pilot cities suggested the potential for further price reductions. In 2023, Guangdong province announced tender prices of 116 RMB ($16.45, at an exchange rate of 1 USD = 7.05 RMB) per dose for Cecolin® and 146 RMB ($20.71) per dose for Walrinvax®.[42] In 2024, the tender price of Cecolin® in Jiangsu province was 86 RMB ($12.20) per dose.[43] However, both Guangdong and Jiangsu provinces are among the wealthiest regions in China. In China, the per capita fiscal subsidy for basic public health services was only $12.62 to cover the 19 basic public health service projects.[44] In low-resource settings, this subsidy is often the sole source of financial support available for supporting health services. Consequently, most pilot routine HPV vaccination programmes in low-resource areas can only be initiated with sponsorship from manufacturers or charitable organizations, typically of short-term duration. Our findings highlight the importance of setting vaccine prices for local government-funded pilot vaccination programs based on the unique context of each pilot region, particularly their willingness to pay, to ensure cost-effectiveness. This supports the implementation of tiered pricing among different pilot regions,[45] providing purchasers with flexibility to select price levels that suit their financial circumstances while maintaining cost-effectiveness. We also suggest that the central government offer policy incentives and financial support in low-resource settings to promote health equity during the transition from pilot to national HPV vaccination scale-up in China.

Even with the adoption of the cost-effective threshold price, there would be a substantial increase in the vaccination budget, leading to an average annual cost rise exceeding 60% of the total annual budget allocated for the current NIP (which covers 14 vaccines) in China. The substantial potential budget requirements may partially explain the delays in nationwide HPV vaccine introduction. Although China is not among the countries supported by Gavi, its significant market size and the current monopsonistic position of the government as the sole public sector purchaser for locally produced vaccines grant the central government considerable bargaining power. Moreover, the prices of most Category 1 vaccines (i.e., those funded by the central government, such as BCG and DTaP vaccines) available to the Chinese government were lower than those to the US and European countries and were comparable to UNICEF prices.[46] Therefore, the government could hopefully negotiate HPV vaccine prices that strike a balance between governmental affordability and manufacturers' return on investment.

A recent modelling study[47] evaluating the global impact and cost-effectiveness of one-dose HPV vaccination suggests that if a single dose provides protection for a long time (≥30 years), administering the second dose may only result in minor health gains at potentially high costs. Assuming an 85% lifetime efficacy of the one-dose schedule, our study indicates that adding the second dose indeed has minimal possibilities of being cost-effective under conservative assumptions that the level of urbanization and sexual activity level in China remain unchanged. In such scenarios, the threshold prices of the second dose approached or even fell below zero due to the high vaccination delivery costs. We also include a scenario where a national HPV vaccination programme is initiated using a domestically produced bivalent vaccine and then switches to a nonavalent vaccine when it becomes available, which represents the most likely switch scenario in the country. The nonavalent HPV vaccine is not yet considered an appropriate option for an immediate national programme in China because it only has a single global supplier with limited manufacturing capacity. Conversely, the domestically produced bivalent vaccine, with its lower prices and increasing production capacity, is more likely to be preferred by the Chinese government. The transition to domestically produced nonavalent vaccines is likely to occur in the foreseeable future, given their superior protection against HPV infection and promising production capacity, supported by at least five candidates currently undergoing phase III clinical trials (www.chinadrugtrials.org.cn; CTR20222154, CTR20210947, CTR20201389, CTR20201716, CTR20201791). By informing the threshold prices in the aforementioned potential strategies, our study may pave the way for the future optimization of HPV vaccination in China.

Our study has three main strengths. First, to our knowledge, this is the first modelling study informing HPV vaccine pricing in China that provides evidence on both cost-effective/cost-saving threshold prices and affordability. By incorporating a transmission dynamic model to assess vaccine value and setting up screening scenarios based on China's latest screening guidelines and Action Plan for Accelerating Elimination of Cervical Cancer, our study is the most comprehensive, timely and tailored piece of economic evidence to inform vaccine pricing and strategy. Second, our threshold analysis was conducted considering different settings, screening scenarios, economic affordability, and vaccination modes. Given that several regions are planning local government-funded HPV pilot vaccination programmes, our results also provide valuable evidence for policymakers in pilot regions on vaccine pricing based on their local characteristics and decision-making priorities. Although we used a simplified urban-rural division due to the lack of province-specific data, the urban-rural division gives an indication of prices that different provinces might pay, since some provinces are more urban than others. Moreover, it underscores the need for flexible and adaptive pricing strategies to ensure equitable vaccine access across diverse regions, particularly within the forementioned context of the current pilot efforts being implemented in China. Third, incorporation of one-dose schedule and vaccine type switching strategies represent a strategic integration of international best practices, which could lay the groundwork for optimizing HPV vaccination in China in the future. It may also help closing the gap between China's HPV vaccine immunization coverage and global standards.

Our study also has several limitations. First, the value of vaccination in protecting the population against HPV-related non-cervical cancers and genital warts was not considered in our study, leading to underestimations in the health and economic benefits associated with vaccination, especially for HPV-4 and HPV-9. Additionally, herd protection against HPV-related diseases in males was not included. The exclusion of these protective effects is due to the insufficient local evidence on these diseases. As such, our results should be interpreted with caution, as the threshold prices reflect only the value of the vaccines in controlling cervical cancer. Second, we did not include scenarios that included catch-up or multi-age cohort vaccination for older girls or vaccination for boys. These interventions have generally been found to be less cost-effective than routine vaccination of 9–14-year-old girls,[48] so incorporating them may require lower threshold prices. Third, we did not consider the possible simplification of screening algorithms or reduction in screening frequency in vaccinated cohorts in the future; if we had, the threshold price would be higher. Fourth, we did not evaluate whether these threshold prices could allow vaccine manufacturers to retain positive producer surpluses, as there is insufficient information regarding vaccine development and marketing costs in China. Nevertheless, it is probable that these threshold prices are acceptable for vaccine manufacturers, given that the cost-effective prices greatly exceed current UNICEF negotiated prices for HPV vaccines. With the cost-saving threshold price serving as a lower bound for price negotiation, there exists potential to negotiate a reasonable price that guarantees manufacturers' return on investment. Fifth, our study did not include analysis varying durations of protection provided by a one-dose vaccination, which may limit the exploration of a one-dose schedule. Last, the estimation of the proportion of vaccination costs within the four billion RMB budget is only approximate. The exact total budget for the current NIP in China remains undisclosed, and certain expenses related to cold chain storage and personnel may be covered by local governments. Nonetheless, the four billion RMB serves as a reasonable reference at the national level. Moreover, our vaccination cost calculations did not separately consider financial costs due to insufficient evidence.

In summary, our study offers timely evidence to inform the HPV vaccine price negotiation process in China for government-funded vaccination programmes. To ensure the cost-effectiveness of a national routine vaccination programme using a two-dose schedule, the vaccine price should not exceed $26–$36 per dose (depending on vaccine type). If the goal is for the intervention to be cost saving, reducing vaccine prices to $5–$10 per dose is necessary. During the pilot phase of HPV vaccination initiation, it is important for pilot governments to negotiate a reasonable price based on the unique local contexts, particularly considering their ability to pay, to ensure the cost-effectiveness of vaccination. Rural areas require policy incentives and financial support in this phase to increase population vaccination coverage and to mitigate health inequities. This approach may inform the introduction of HPV vaccination in other countries, especially those with low financial resources. Moreover, given the limited evidence around tender-based vaccine pricing, a similar exercise may be valuable for other vaccines, particularly recently introduced vaccines with high prices.

Contributors
FZ and MJ contributed to funding acquisition of the study. TY, XZ, FZ and MJ co-designed the study. TY, XZ, and CP accessed and verified all reported data. TY, XZ, CP, and MG contributed to the analysis and visualization of the study. TY drafted the manuscript. MJ, YL, YQ, and YZ contributed to the validation of the analysis and study findings, and critically revised the manuscript for intellectual content. All authors approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement
This study does not involve any patient data or participant data. Readers can access the data used in this study from the links to public domain resources provided in the Methods. The code used to generate the reported estimates is sensitive, interested parties should contact the corresponding author for more information.

Declaration of interests
FZ reports receiving grants from GlaxoSmithKline Biologicals, Merck & Co., and Xiamen Innovax Biotech to her institution for conducting clinical trials on the HPV vaccines. YQ reports receiving grants from Merck & Co., and Xiamen Innovax Biotech to his institution for similar clinical trials. YL reports receiving grants from BMGF, WHO, and InnoHK to her institution. MJ reports receiving research grants from NIHR, RCUK, BMGF, WHO, Gavi, Wellcome Trust, European Commission, InnoHK, TFGH, and CDC to his institution. The other co-authors declare no competing interests.

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Appendix A. Supplementary data
Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101209.

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