Optimal allocation strategies for HPV vaccination introduction and expansion in China accommodated to different supply and dose schedule scenarios: A modelling study

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Summary

Background A key barrier to cervical cancer elimination in China is low human papillomavirus (HPV) vaccine uptake, which is limited by supply constraints, high prices, and restriction to two/three-dose schedule. We explored optimal vaccination strategies for maximizing health and economic benefits accommodated to different supply and dose schedules.

Methods We evaluated different HPV vaccine strategies under 4 scenarios with different assumptions about vaccine availability and dose schedules. Each strategy involved different vaccine types, target ages, and modes of delivery. We used a previously validated transmission model to assess the health impact (cervical cancer cases averted), efficiency (number of doses needed to be given to prevent one case of cervical cancer [NND]), and value for money (incremental cost-effectiveness ratio [ICER] and return on investment [ROI]) of different strategies in Chinese females over a 100-year time horizon. All costs are expressed in 2021 dollars. We adopted a societal perspective and discounted quality-adjusted life-years (QALYs), costs and benefits by 3% annually for cost-effectiveness analysis and ROI calculation.

Findings In a supply-constrained and on-label use scenario, compared with no vaccination, two-dose routine vaccination of 14-year-olds would be the optimal, cost-saving strategy for a future national program (NNDs: 150–220, net cost saving: $15 164 million–$22 034 million, ROIs: 7–14, depending on vaccine type). If the one-dose schedule recommended by WHO is permitted in China, then reallocating the second dose from the routine cohorts to add a catch-up vaccination at 20-year-olds would be the most efficient strategy (NNDs: 73–107), and would be cost-saving compared with routine one-dose vaccination only (net cost saving: $4127 million–$6035 million, ROIs: 19–37). When supply constraints are lifted, scaling up vaccination in older females to 26 years could further expand the health benefits and still be cost-saving compared to maintaining the optimal vaccination strategy in the supply-constrained context.

Interpretation Our study provides timely evidence for the current and future HPV vaccination strategy planning in China, and may also be of value to other countries with supply and dose restrictions.

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Keywords: Human papillomavirus vaccination; Constrained supply; One-dose schedule; Efficiency; Value for money

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Research in context

Evidence before this study

Constrained human papillomavirus (HPV) vaccine supply and high vaccine prices hinder global HPV vaccination introduction, especially in low- and middle-income countries (LMICs), leading to worsened health inequities. In 2022, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) recommended a one-dose vaccine schedule, which would help to alleviate these constraints and to expedite HPV vaccination rollout globally. However, as one of the top contributors to the absolute number of global cervical cancer cases, China has not yet introduced HPV vaccination into its national program. We searched PubMed without language restrictions for studies about optimal use of HPV vaccines under conditions of constrained supplies published from Jan 1, 2000, to March 1, 2022, using the search terms ("human papillomavirus" or "HPV") and ("vaccine" or "vaccination") and ("modelling") and ("resource" or "supply"). Only one study that estimated the optimal HPV vaccination strategies in four LMICs (India, Vietnam, Uganda, and Nigeria) in the context of constrained resources was identified. Few studies have explicitly incorporated different conditions of vaccine supply availability and dose schedule scenarios when comparing the impact of different vaccine allocation strategies, and there is a lack of evidence to inform optimal vaccine strategies in China.

Added value of this study

In this study, we explored optimal vaccine allocation strategies in China under different supply availability (constrained up to 2025; unconstrained after 2025) and dose schedules (on-label use of two or three dose schedules; off-label use of one-dose schedule). We considered a range of outcomes including population-level clinical impact (cervical cancer cases averted), efficiency (number of doses needed to be given to prevent one case of cervical cancer [NND]), and value for money (return on investment [ROI] and incremental cost-effectiveness ratio [ICER]). The results indicate that leaving HPV vaccination uptake purely to market forces results in suboptimal health and economic outcomes. Better outcomes are achieved if the currently constrained vaccine supplies are prioritized to the older end of the 9–14 year old range (14 years) through a two-dose routine vaccination if the current strict dose schedule regulations need to be adhered to. If a one-dose schedule is permitted in China, then reallocating the second dose from the routine cohorts to add a catch-up vaccination at women aged 20 years with the same constrained vaccine supply level would accelerate the scale-up of vaccination and maximize the health and economic benefits. Multiple age cohort (MAC) vaccination up to women aged 26 years with or without a switch to a younger age (than 14 years) of routine immunization should be considered when supply constraints are eased.

Implications of all the available evidence

Achieving the World Health Organization's aim of cervical cancer elimination in the current constrained vaccine supply situation requires urgent action on HPV vaccine rollout as well as efficient allocation of limited vaccine supplies to achieve maximum health and economic benefits. Our study provides timely and strategic evidence for current and future HPV vaccination planning in China, and may also be of value to other countries with supply and dose restrictions. We also found health and economic benefits of adopting WHO SAGE's latest recommendation on a one-dose schedule for females aged 9–20 years. Hence our study provides China-based modelling evidence to the limited evidence based around the value of one-dose vaccination in alleviating the global supply constraints.

Introduction

Cervical cancer is a major global public health problem, especially in low- and middle-income countries (LMICs).[1] Human papillomavirus (HPV) vaccination is an effective cervical cancer prevention measure, and is recommended by World Health Organization (WHO). However, the pace of global vaccine introduction is still suboptimal, with 70% of girls worldwide living in countries that had not yet introduced the HPV vaccine by the end of 2019.[2] Vaccine supply and financial constraints are major factors hindering HPV vaccine introductions, especially in LMICs, leading to worsened health inequities.[3] In 2018, WHO announced a global call to eliminate cervical cancer and build a fairer, healthier world.[4,5] To achieve this, strategies need to be devised that can use limited doses efficiently to accelerate vaccine uptake until sufficient supply to meet demand is finally achieved. Recently, global evidence indicating that one-dose vaccination in young females provides comparable protection to full-course schedule has been accumulating.[6–10] In 2022, SAGE reviewed evidence on single-dose HPV vaccination, and recommended reduced dose schedules (one or two-dose in females 9–20 years, and two-dose with a 6-month interval for females≥21 years) for HPV as a potential measure to expedite the progress towards the goal of having 90% of girls vaccinated by the age of 15 by 2030.[11]

China is one of the top contributors to the global burden of cervical cancer, accounting for 18.6% of all cervical cancer cases worldwide in 2018 (106 000 of 570 000 total global cases).[1] Meanwhile, there is an increasing risk of HPV infection for Chinese females, especially for those of younger ages, given changes in sexual activity patterns. According to a latest systematic

review, females aged <25 years has a prevalence of 24.3% for high-risk HPV infection.[12] However, China has not introduced HPV vaccination into its national program. Five types of HPV vaccines are currently available through private purchasing in the Chinese market: Cecolin® (domestic HPV-2), Cervarix® (imported HPV-2), Gardasil® (HPV-4), Gardasil®9 (HPV-9), and a new domestically produced bivalent vaccine (Walrinvax™, Recombinant Human Papillomavirus Bivalent [Types 16, 18] Vaccine [Pichia pastoris]) that was licensed in 2022. However, according to the National Institutes for Food and Drug Control data, in 2020, there were three million bivalent vaccine (both imported and domestically produced) doses, seven million quadrivalent vaccine doses, and five million nonavalent vaccine doses available on the market in China. None of the above vaccine types is adequate to enable widespread vaccine access given this country's large population. In the absence of a national HPV vaccination program, the limited HPV vaccine supplies are purchased privately and mostly given to females aged 15 to 45 using a three-dose schedule, leaving the WHO-recommended primary target group of 9–14 year old females largely unvaccinated. In Shanghai, HPV vaccine coverage in girls ≤15 years was less than 1% between 2017 and 2019.[13] A population-based vaccination program based on a carefully designed strategy would better optimise the limited vaccine supply. Moreover, although WHO now recommends a one-dose vaccine schedule for 9–20 year old females, this has yet to be licensed by Chinese authorities due to lack of Chinese efficacy data to support it. As we await local trial data, mathematical models can be used to project the impact of one-dose schedules in a better optimised vaccine strategy to inform policy-making.

In this study, we aim to evaluate feasible vaccine strategies that account for constrained vaccine supply, in terms of health impact, efficiency, and value for money, to identify the optimal strategy for China. We then evaluate another set of strategies that include multiple age cohort (MAC) vaccination, that may become optimal further in the future when supply constraints are lifted, taking into account the expected increases in HPV vaccine production capacity. Both on-label use of a two/three-dose schedule and off-label use of a one-dose schedule were considered under different supply contexts. The results of this study are essential for vaccine policy in China, and may also provide qualitative guidance to inform policies in other LMICs facing similar HPV epidemiology and constraints on HPV vaccine supply.

Methods

We used a validated two-stage hybrid model (transmission-natural history) to project health and economic outcomes of different vaccine strategies. We considered all Chinese women living or projected to be born during the 100-year time horizon (2022–2122). The population was stratified by area of residence (urban and rural), sexual activity (high, low, none), and age group (0–84 per year, and 85+). Further details of the model structure are shown in the appendix (p 5) and previous publications.[14,15] The model assumptions and results were reported using the HPV-FRAME checklist and CHEERS 2022 checklist (appendix Table S2–S6).[16]

Vaccine supply and modelled scenarios

Our study included two supply scenarios. First, we assumed that in the current supply-constrained scenario, the available doses can only meet the base demand for vaccinating 90% of a single age cohort with two doses. Strategies accommodated to this supply level were assumed to be maintained over the 100-year time horizon. Then, we modelled a scenario where supply constraints are lifted in 2025 based on WHO supply projections.[17] In each supply scenario, strategies were evaluated under two sub-scenarios on dose schedule: 1) only on-label use of vaccines (i.e., two-dose for girls aged 9–14 years, and three-dose for females≥15 years) is possible; and 2) off-label use of a one-dose schedule (i.e., one-dose in females 9–20 years, and two-dose for females≥21 years) is permitted immediately. Mutually exclusive options accommodated to the above four scenarios were evaluated to identify the optimal ones.

In the supply-constrained scenario and assuming on-label dose schedules only (scenario 1), six two-dose routine vaccination strategies targeting different single age groups (between 9 and 14 years), together with an additional strategy representing current (private market) use of HPV vaccines in China[13] were included. The comparator was set as no vaccination (from either government-funded or privately-paid sources). For the six routine vaccination strategies, each age group was vaccinated at 90% coverage. For the private market scenario driven by the current market force, we assumed three-dose vaccination with annual uptake of 1.9% in females aged 15 to 45 regardless of the variations in ability to pay across socioeconomic groups as no official data were available. This annual uptake was estimated by assuming that the number of doses needed to vaccinate 90% of a single age group with two doses was spread over the entire age band between 15 and 45 years in a three-dose schedule (appendix Fig. S2). In the supply-constrained and off-label use scenario (scenario 2), new allocation alternatives adopting one-dose schedule are permitted. We explored whether reallocating the second dose from the routine cohorts to add a multi-year catch-up vaccination at 9 or 20 years could better optimise the limited vaccine supply. For those one-dose vaccination alternatives, we adopted the optimal target group for routine vaccination identified in scenario 1. To evaluate the trade-

offs involved in a one-dose schedule between freeing up vaccine doses to reach more girls and potentially lower vaccine efficacy of one dose compared to two, we incrementally evaluated the reallocation strategies in one-dose as well as the strategy that gives the second dose to routine target age group, compared with one-dose routine vaccination only (appendix Fig. S3). Coverage for catch-up vaccination was assumed to be 90%.

In scenarios where supply constraints are lifted in 2025 (scenario 3 for on-label use only scenario, and scenario 4 for off-label use scenario), we incrementally evaluated strategies that add a one-year MAC vaccination in 2025 compared to maintaining the optimal allocation strategies identified in the supply-constrained scenario. On-label and off-label use scenarios were considered separately. Those MAC vaccination strategies may involve one-year forward MAC vaccination of females through to age 26, one-year reverse MAC vaccination of younger girls down to age 9 followed by a switch in the routine vaccination target age of 9 years, or both (appendix Figs. S4 and S5). Coverage for MAC vaccination was also assumed to be 90%.

We assumed that current cytology-based screening was maintained in China. The age-specific screening coverage in rural and urban areas was derived from a nationally representative survey,[18,19] which is detailed in appendix (p 13; Fig. S6). Women with positive cytological results are assumed to be recalled for colposcopy examination and biopsy if clinically indicated. Women with negative cytological results are assumed to be followed up after three years.[20]

Detailed information on all the alternative vaccination strategies is provided in Table 1.

Model assumptions and inputs

We considered four types of HPV vaccines available in China (domestic HPV-2 [Cecolin®], imported HPV-2 [Cervarix®], HPV-4 [Gardasil®], and HPV-9 [Gardasil®9]) independently in this study. We assumed that the on-label vaccination schedule provides 100% lifelong protection against vaccine-targeted HPV types. Cross-protection efficacy against HPV types 31, 33, and 45 for imported HPV-2, and cross-protection efficacy against HPV type 31 for HPV-4 were assumed based on the results of a meta-analysis.[21] We made a conservative assumption that domestic HPV-2 and HPV-9 provide no cross-protection due to the absence of strong evidence.[22] The off-label use schedule was pessimistically assumed to provide 85% protection with a lifelong duration against vaccine-targeted HPV types, based on the lower bound target efficacy for one-dose HPV vaccination in a post hoc analyses of a randomized control trial with follow-up out to 10 years.[10] We assumed that the cross-protection efficacy for imported HPV-2 and HPV-4 was also proportionally reduced as the efficacy against vaccine-target types in off-label use schedules. We also considered scenarios in which the off-label use schedule would lose cross-protection in our scenario sensitivity analysis.

For the strategy representing current market use of HPV vaccines, we adopted the current vaccine market prices. For the national program that is paid from the central government budget, we assumed a lower tender price based on the Pan American Health Organization Revolving Fund (PAHO-RF) vaccine price for 2022,[23] given the bargaining power from the large potential size of the Chinese market, and since the income level of China is similar to that of many PAHO countries.[24] We assumed the cost of administration for vaccination to be $4.12 per dose based on a national study,[25] in which both operational and logistics costs were considered. The treatment cost for cervical intraepithelial neoplasia (CIN) and cervical cancer cases were derived from a nationwide multicentre cross-sectional, hospital-based survey. The detailed information on the price assumption and cost valuation was available in the appendix (p 6) and previous work.[14,15]

Base-case estimates and ranges for all parameters are listed in appendix Table S1.

Outcomes and analysis

We estimated the long-term health impact, efficiency, and value for money of different strategies over a 100-year time horizon. The optimal strategies accommodated to different scenarios were identified by considering a combination of these indicators. First, we estimated the cumulative cervical cancer cases averted by each strategy as our main health impact outcome. We also calculated the time to achieve 50% reduction in age-standardized cervical cancer incidence compared with no vaccination for different strategies. Second, we calculated the number of doses needed to be given to prevent one case of cervical cancer (NND) as an indicator of efficiency, by dividing the total number of doses given in a population by the cumulative number of cases of cervical cancer prevented. Both health impact and efficiency outcomes were undiscounted. Third, we calculated the return on investment (ROI) and the incremental cost-effectiveness ratio (ICER) as indicators of economic efficiency. ROI is the ratio of net benefits (benefits minus costs) to costs, which quantifies the net benefits gained from every dollar invested on vaccination. We adopted the cost-of-illness approach to estimate the economic burden prevented by averting cases and deaths through vaccination. We used gross domestic product (GDP) per capita in 2021 to approximate an individual's annual economic contribution to society and assumed constant over the time horizon. ICERs were calculated as the incremental healthcare cost per additional quality-adjusted life-years (QALYs) gained between one strategy and the next less costly strategy. In

Scenarios	Strategies	Allocation mode of vaccine supply				Comparator
		Private purchasing driven by market force	National program funded by government			
			Routine vaccination targeting a single-age cohort	Multi-year catch-up vaccination targeting a single-age cohort	One-year multiple-age cohort vaccination in 2025	
Scenario 1: Supply-constrained and only the on-label schedule is possible	1a: Private market use	√ (1.9% annual uptake for females aged 15 to 45)				No vaccination
	2a: Two-dose routine of 9 years		√(9-years-old, 2 dose)			No vaccination
	3a: Two-dose routine of 10 years		√(10-years-old, 2 dose)			No vaccination
	4a: Two-dose routine of 11 years		√(11-years-old, 2 dose)			No vaccination
	5a: Two-dose routine of 12 years		√(12-years-old, 2 dose)			No vaccination
	6a: Two-dose routine of 13 years		√(13-years-old, 2 dose)			No vaccination
	7a: Two-dose routine of 14 years		√(14-years-old, 2 dose)			No vaccination
Scenario 2: Supply-constrained and off-label use of one-dose schedule is possible immediately	1b: One-dose routine of 14 years*		√(14-years-old, 1 dose)			No vaccination
	2b: One-dose routine of 14 years* + multi-year reverse CU at 9 years		√(14-years-old, 1 dose)	√(9-years-old, 1 dose)		No vaccination; 1b
	3b: One-dose routine of 14 years* + multi-year CU at 20 years		√(14-years-old, 1 dose)	√(20-years-old, 1 dose)		No vaccination; 1b
	7a: Optimal allocation strategy in scenario 1		√(14-years-old, 2 dose)			No vaccination; 1b
Scenario 3: Supply constraints are lifted in 2025 and only the on-label schedule is possible	1c: Optimal allocation strategy in scenario 1 + forward MAC to 26 years		√(14-years-old, 2 dose)		√(MAC to 26 years)	7a (Optimal allocation strategy in scenario 1)
	2c: Optimal allocation strategy in scenario 1 + reverse MAC to 9 years		√(14-years-old, 2 dose)		√(MAC to 9 years)	7a
	3c: Optimal allocation strategy in scenario 1 + froward (to 26 years) and reverse (to 9 years) MAC		√(14-years-old, 2 dose)		√(MAC through 9–26 years)	7a
Scenario 4: Supply constraints are lifted in 2025 and off-label use of one-dose schedule is possible immediately	1d: Optimal allocation strategy in scenario 2+ forward MAC to 26 years		√(14-years-old, 1 dose)	√(20-years-old, 1 dose)	√(MAC to 26 years)	3b (Optimal allocation strategy in scenario 2)
	2d: Optimal allocation strategy in scenario 2 + reverse MAC to 9 years		√(14-years-old, 1 dose)	√(20-years-old, 1 dose)	√(MAC to 9 years)	3b
	3d: Optimal allocation strategy in scenario 2 + froward (to 26 years) and reverse (to 9 years) MAC		√(14-years-old, 1 dose)	√(20-years-old, 1 dose)	√(MAC through 9–26 years)	3b

MAC = multiple-age cohort vaccination. CU = catch-up vaccination.*14 years is the optimal target age for routine vaccination identified in scenario 1.

Table 1: **Alternative vaccination strategies evaluated in the study.**

the ROI calculation and cost-effectiveness analysis, we used a societal perspective to estimate broader costs and benefits of different strategies. The total costs include direct medical costs, direct non-medical costs, and indirect costs occur in vaccination, screening, and disease treatment. We adopted a discount rate of 3% for QALYs, costs and benefits.[26] For interventions that are cost-saving (more effective and less costly compared with comparator), the net cost savings (total costs saved minus costs of vaccination implementation) were reported instead of ICERs. All unit costs were adjusted to 2021 using the government-reported consumer price index for health care and then converted into US dollars using exchange rates in 2021 (i.e., 1.00 US dollar = 6.5 Chinese yuan). We used GDP per capita for 2021 ($12 457.85) as the cost-effectiveness threshold.[27] Details about calculating these indicators are in the appendix (pp 14–15).

Scenario analysis without cross-protection for off-label use schedule as well as probabilistic sensitivity analyses were conducted to capture uncertainty. Probabilistic sensitivity analysis was performed using 500 Monte Carlo simulations to sample parameter values from their distributions. Results are presented in median and 80% uncertainty intervals [UIs] (i.e., 10th–90th percentiles). All analyses were performed in R.

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

Impact of vaccination strategies with constrained supply and on-label vaccine use scenario

Among the six two-dose routine vaccination strategies targeting girls aged 9–14 years, vaccinating 14-year-old girls would avert 94 393 to 686 144 additional cervical cancer cases compared with the other strategies targeting younger ages in the 100-year time horizon, and the health benefits would occur earlier (Fig. 1; appendix Table S7). This strategy would produce the lowest NNDs among the six routine vaccination strategies, ranging from 150 to 220 compared with no vaccination, depending on vaccine type (Fig. 2; appendix Table S7). Vaccinating girls aged 14 was cost-saving, and dominated (less costly and more effective than) all the other five two-dose routine vaccination strategies (net cost savings between $15 164 million to $22 034 million, ROIs between 7 and 14, depending on vaccine type) (Fig. 4; appendix Table S6; Fig. S7).

Leaving HPV vaccination purely to market forces would prevent 0.6 million to 0.7 million fewer cervical cancer cases compared to two-dose routine vaccination targeting 14-year-olds, and would require 31 – 62 additional vaccine doses to prevent one case of cervical cancer (Fig. 2; appendix Table S7), depending on vaccine type. This strategy was also predicted to be not cost-effective, with its ICER far exceeded the cost-effectiveness threshold. Moreover, the ROIs of the private market use were lower than 1 (appendix Table S7; Fig. S7).

Impact of vaccination strategies with constrained supply and off-label use scenario

In off-label use scenario, we still chose routine vaccination of 14-year-old girls as the base strategy given that this was the optimal strategy in the supply-constrained context. Adopting one-dose routine vaccination of 14-year-olds could prevent 81%–98% of the cases averted

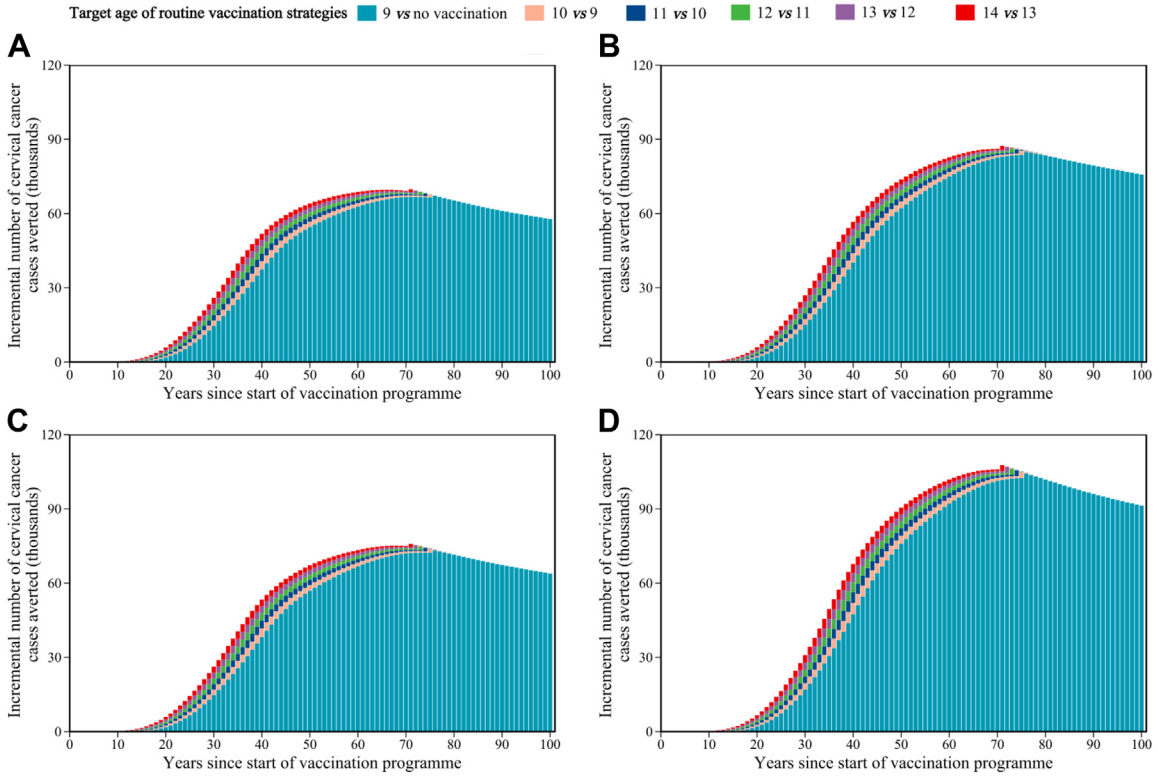

Fig. 1: **Incremental number of cervical cancer cases averted by 90% routine vaccination targeting girls aged 9 to 14 years.** (A) Domestic HPV-2 (B) Imported HPV-2 (C) HPV-4 (D) HPV-9. Light blue bars indicate the number of cervical cancer cases averted over the 100-year time horizon by routine vaccination targeting girls aged 9 compared with no vaccination. And bars in orange, dark blue, green, purple, and red indicate the incremental cases averted by vaccinating girls of an older age compared with the strategy targeting its next younger age. All the values are presented as the median of Monte Carlo simulations. Domestic HPV-2 = domestic bivalent vaccine [Cecolin®]. Imported HPV-2 = imported bivalent vaccine [Cervarix®]. HPV-4 = quadrivalent vaccine [Gardasil®]. HPV-9 = nonavalent vaccine [Gardasil®9].

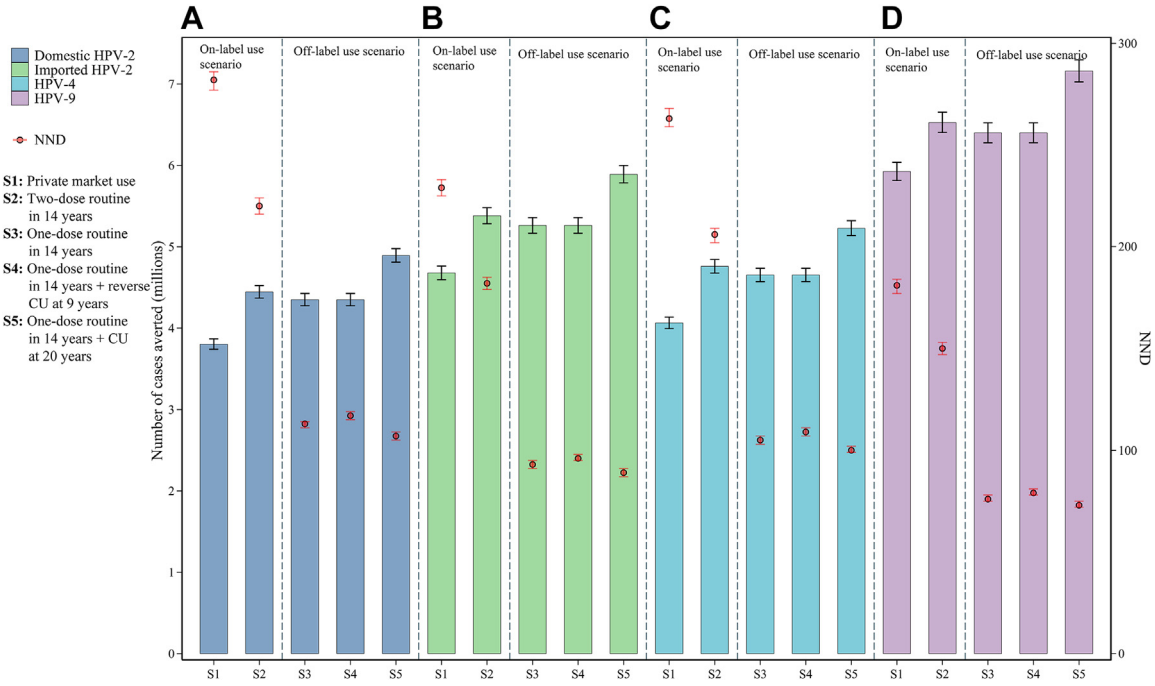

***Fig. 2:* Health impact and efficiency outcomes of different vaccine allocation strategies with constrained supply.** (A) Domestic HPV-2 (B) Imported HPV-2 (C) HPV-4 (D) HPV-9. S1 (private market use) and S2 (two-dose routine vaccination targeting girls aged 14 years) are representative feasible strategies under the scenario that only the on-label schedule (i.e., a two-dose schedule for girls aged 9–14 years, and a three-dose schedule for females≥ 15 years) is possible. S3 (one-dose routine vaccination targeting girls aged 14), S4 (one-dose routine vaccination of girls aged 14 years plus reverse multi-year catch-up at girls aged 9 years), and S5 (one-dose routine vaccination targeting girls aged 14 years plus multi-year catch-up at females aged 20 years) are additional vaccine allocation options when the off-label use schedule (i.e., one-dose schedule for females aged 9–20 years, and two-dose schedule for females≥ 21 years) is possible immediately. The on-label schedule was assumed to provide 100% lifelong protection against vaccine-targeted HPV types. The off-label schedule was assumed to provide 85% lifelong protection against vaccine-targeted HPV types. Both the number of cases averted and the NNDs were undiscounted. A one-dose schedule was assumed to reduce the efficacy against both vaccine-target and cross-protective types by the same proportion. Bars indicate the accumulated number of cervical cancer cases averted over a 100-year time horizon by five strategies compared with no vaccination. Strategies with different vaccine types are indicated by different colors (dark blue for domestic HPV-2; green for imported HPV-2; light blue for HPV-4; purple for HPV-9). The red points indicate NNDs. All values are presented as the median of Monte Carlo simulations, and error bars indicate the 80% uncertainty intervals. NND = number of doses needed to prevent one case of cervical cancer. CU = catch-up vaccination. Domestic HPV-2 = domestic bivalent vaccine [Cecolin®]. Imported HPV-2 = imported bivalent vaccine [Cervarix®]. HPV-4 = quadrivalent vaccine [Gardasil®]. HPV-9 = nonavalent vaccine [Gardasil®9].

by the two-dose schedule with only half the number of vaccine doses needed, even in the most pessimistic scenario that the one-dose schedule would lose cross-protection. That would result in a more efficient use of the vaccine (Fig. 2; appendix Table S8).

Using vaccine doses saved by the one-dose schedule to switch the target age group of vaccination from 14-year-olds to 9-year-olds after doing a multi-year reverse catch-up at 9 years would produce minimal additional health benefits. In contrast, reallocating the second dose from the routine cohorts to add a multi-year catch-up vaccination at 20-year-old females would prevent the most cervical cancer cases in the base case scenario where cross-protection efficacy was reduced proportionally (ranging from 4.9 million to 7.2 million compared with no vaccination). Compared with two-dose routine vaccination, this strategy would achieve a 50% reduction in age-standardized incidence 6–7 years earlier, depending on vaccine type. Also, this strategy would result in the most efficient use of constrained vaccine supply, with NNDs compared with no vaccination ranging from 73 to 107, depending on vaccine type (Fig. 3; appendix Table S8). In the worst-case scenario where one-dose vaccination gives no cross-protection, reallocating the second dose to add a catch-up could still result in a 50% reduction in incidence 4 or 6 years earlier compared with two-dose routine vaccination (depending on vaccine type), but would protect fewer cervical cancer cases in the long-term (Fig. 3). Compared with one-dose routine vaccination targeting 14-year-olds only, conducting one-dose catch-up vaccination to 20 years was estimated to be the most efficient use of the money, with the intervention being cost-saving (net cost savings between $4 127 million to $6 035 million, ROIs ranging from 19 to 37, depending on vaccine type and the assumption of cross-protection; see Fig. 4; appendix Table S9).

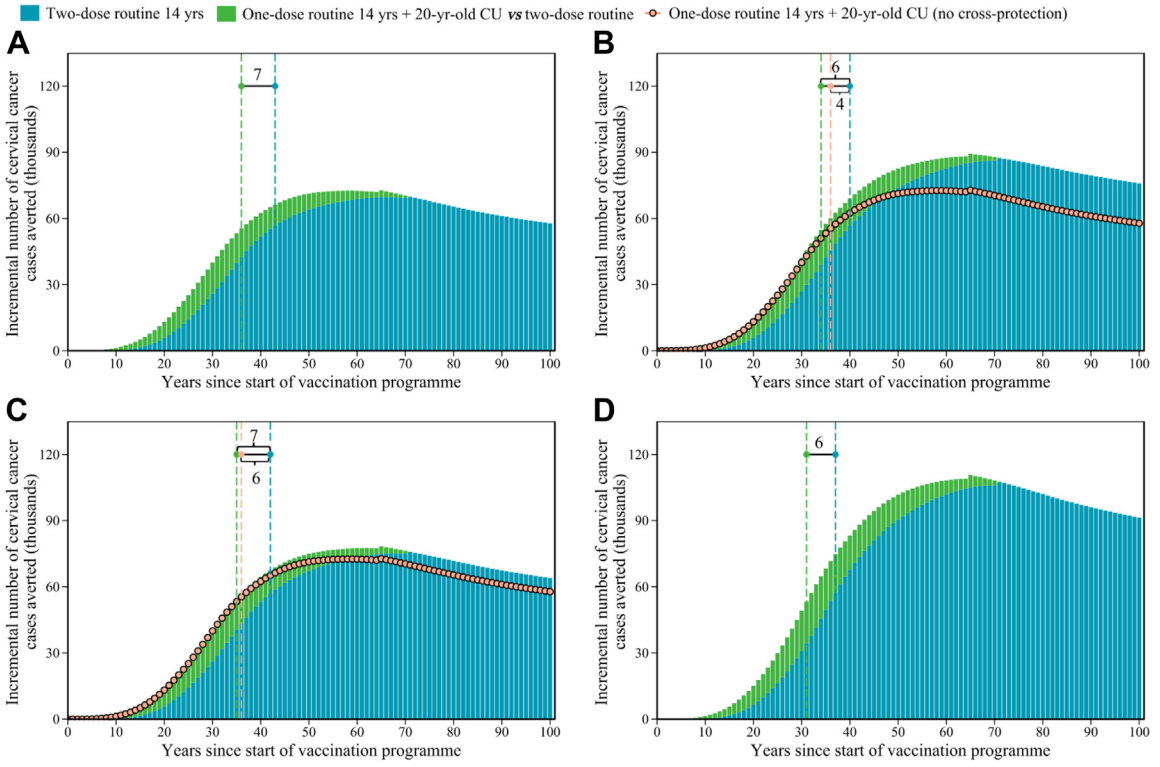

Fig. 3: **Incremental number of cervical cancer cases averted and time taken to achieve a 50% reduction in age-standardized cervical cancer incidence by optimal strategies in on-label use and off-label use scenarios.** (A) Domestic HPV-2 (B) Imported HPV-2 (C) HPV-4 (D) HPV-9. Light blue bars indicate the number of cervical cancer cases averted over a 100-year time horizon by two-dose routine vaccination targeting girls aged 14 years compared with no vaccination. Green bars indicate incremental numbers of cervical cancer cases averted by the one-dose reallocation strategy with the same supply level (i.e., one-dose routine vaccination of 14-year-olds plus multi-year catch-up at 20-year-olds) with base case assumption of cross-protection, compared with two-dose routine vaccination of 14 years. Orange points indicate the number of cervical cancer cases averted by the one-dose reallocation strategy based on the assumption that one-dose schedule would lose cross-protection. Vertical long-dash lines in blue, orange, and green indicate the time to achieve 50% reduction in age-standardized cervical cancer incidence for different strategies (blue for two-dose routine vaccination of 14 years, green for one-dose reallocation strategies with base case assumption of cross-protection, and orange for one-dose reallocation strategies based on the assumption that one-dose schedule would lose cross-protection). The numbers indicate the time difference in years. All the values are presented as the median of Monte Carlo simulations. Domestic HPV-2 = domestic bivalent vaccine [Cecolin®]. Imported HPV-2 = imported bivalent vaccine [Cervarix®]. HPV-4 = quadrivalent vaccine [Gardasil®]. HPV-9= nonavalent vaccine [Gardasil®9].

Impact of MAC strategies when supply constraints are lifted and on-label use scenario

Under the on-label use scenario, adding a reverse MAC vaccination in 2025 followed by a switch in the routine target age to 9 years would avert few additional cases averted (<10) compared with maintaining routine vaccination targeting girls aged 14. In contrast, adding MAC vaccination through to 26 years in 2025 to routine vaccination would result in about 0.8–1.1 million additional cases averted, and achieve a 50% reduction in age-standardized incidence 10–12 years earlier compared with routine vaccination only, depending on vaccine type (appendix Fig. S10; Table S10). Among the three MAC strategies evaluated, adding a one-year forward MAC vaccination to females aged 26 years in 2025 was predicted to be the optimal in health and economic efficiency, and being cost-saving (NNDs between 144 and 200, net cost savings between $5 285 million to $7 191 million, ROIs between 6 and 12, compared with maintaining the two-dose routine vaccination, depending on vaccine types) (Fig. 4; appendix Table S10).

Impact of MAC strategies when supply constraints are lifted and off-label use scenario

Similarly, under the off-label use scenario, adding a forward MAC vaccination to 26 years with or without reverse MAC vaccination in 2025 is estimated to protect an additional 0.3–0.4 million cervical cancer cases compared with maintaining the optimal one-dose vaccination strategy in the supply-constrained context, with NNDs ranging from 95 to 132, and the 50%

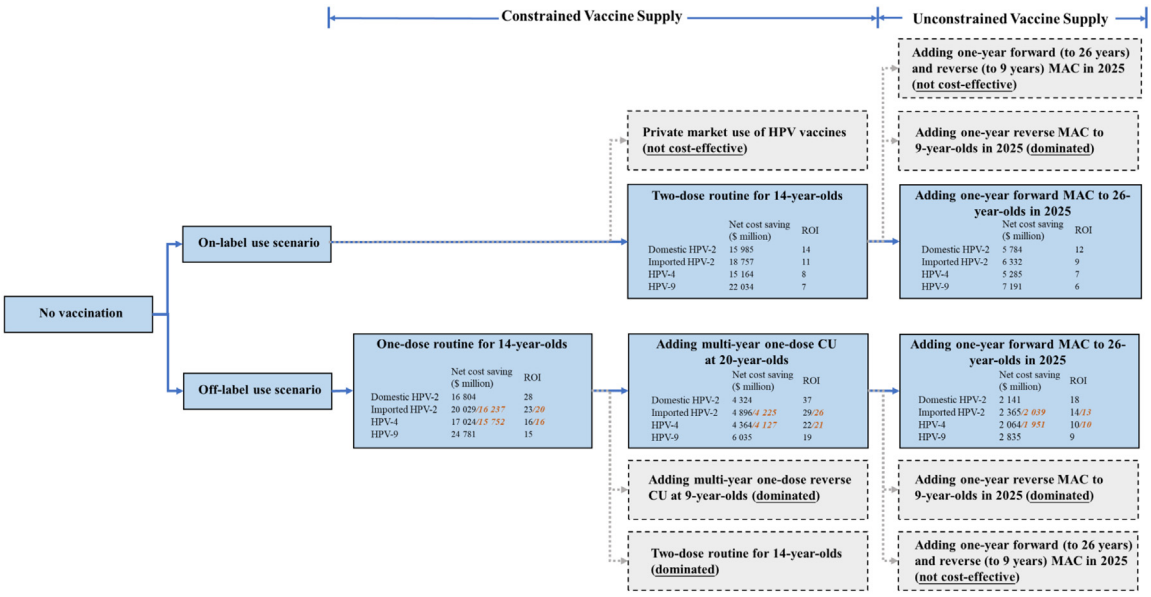

***Fig. 4:* Economic efficiency of different vaccination strategies in different supply and dose schedule scenarios**. The on-label use scenario represents a two-dose schedule for girls aged 9–14 years, and a three-dose schedule for females≥15 years, which was assumed to provide 100% lifelong protection against vaccine-targeted HPV types. The off-label use scenario represents a one-dose schedule for girls aged 9–20 years, and a two-dose schedule for females≥ 21 years, based on the latest recommendation from WHO's Strategic Advisory Group of Experts on Immunization. All the values are presented as the median of Monte Carlo simulations. The off-label use schedule was assumed to provide 85% lifelong protection against vaccine-targeted HPV types. For strategies under the off-label use scenario, numbers in black font were calculated based on the base case assumption of cross-protection for the off-label use schedule (with its efficacy proportionally reduced by the same amount as efficacy against vaccine-target types), and italic numbers in orange font were calculated based on the assumption that off-label use would lose all cross-protection. Strategies in the blue boxes with solid lines are those that are incrementally more cost-effective when giving additional vaccines to protect more individuals. Strategies in grey boxes with short-dotted lines indicate dominated (more costly and less effective) strategies or strategies that are not cost-effective (with ICERs far exceed the cost-effectiveness threshold). Each strategy was evaluated against a comparator using the same vaccine type as that used in the box with an arrow pointing to it. Both Net cost savings and ROIs were calculated by discounting costs and benefits at 3%. ROI = return on investment. ICER = incremental cost-effectiveness ratio. QALY = quality-adjusted life-year. CU = catch-up vaccination. MAC = multiple-age cohort vaccination; Domestic HPV-2 = domestic bivalent vaccine [Cecolin®]. Imported HPV-2 = imported bivalent vaccine [Cervarix®]. HPV-4 = quadrivalent vaccine [Gardasil®]. HPV-9 = nonavalent vaccine [Gardasil®9].

reduction in incidence happening 3–4 years earlier, depending on vaccine type and the assumption of cross-protection (appendix Figs. S12 and 13; Table S11). Adding MAC vaccination through to 26 years in 2025 was predicted to be cost-saving (net cost savings between $1 951 million to $2 835 million, ROIs between 9 and 18) compared with maintaining the optimal one-dose vaccination strategy, depending on vaccine type and the assumption of cross-protection for one-dose schedule (Fig. 4; appendix Table S11). However, adding both forward and reverse MAC was predicted to be not cost-effective.

Discussion

To address the uncertainty of future HPV vaccine availability and dose schedules, we included scenarios of different supply availability (constrained up to 2025; unconstrained after 2025) and dose schedules (on-label use of two or three dose schedules; off-label use of one-dose schedule). Mutually exclusive vaccination alternatives accommodated to each scenario were evaluated and the optimal ones were identified to inform the policy making. Our analysis suggests that even with supply constraints and dosing schedule restrictions to two or three doses, China could achieve larger and faster health and economic gains by initiating a national programme that would vaccinate 14-year-old girls routinely using a two-dose schedule. Our results also suggest that leaving HPV vaccination uptake purely to market forces results in suboptimal health and economic outcomes. If off-label use of a one-dose schedule was immediately possible in China, then adding an additional catch-up campaign in older females (e.g., to 20 years) using the doses saved would produce greater health and economic benefits that far outweigh the loss in health due to possibly lower efficacy of one dose schedules, and therefore result in optimal use of constrained vaccine supply. As vaccine supply increases, expanding the vaccination program will achieve greater benefits.

The optimal strategy would be a MAC to vaccinate females up to 26 years to protect more females and accelerate the pace of cervical cancer incidence reduction. A switch to a younger age of routine immunization following a reverse MAC vaccination could also be considered in the future to protect against potential HPV infection in girls who sexually debut before age 14.

The suboptimal performance of private markets in allocating limited vaccine supplies to achieve maximum health and economic benefits indicates an urgent need for national vaccination programs which can achieve both more efficient allocation and likely lower tender prices. Identifying the optimal target age for routine vaccination is the primary policy question during the initial phase of HPV introduction. Despite the lack of data on HPV prevalence among girls aged 9–14 years in China, the HPV prevalence in young adolescents should be very low. According to the latest nationwide survey of sexual debut and behaviour in China, the cumulative probability of sexual activity among young females aged 15 years was lower than 5%.[28] Based on the low sexual activity and therefore low HPV prevalence among girls aged 9–14 years in China, our results suggest that constrained vaccine supplies should be prioritized to the older end of the 9–14 year old range. This is supported by several previous modelling studies based on other settings,[29,30] even for those have a relatively high proportion of who are sexually active at 14 years. Drolet and colleagues suggested that LMICs such as Nigeria and India (with 15%–25% of girls aged 14 years that are sexually active) could start with routine vaccination of 14-year-old females to achieve faster gains, and once supplies become available switch to routine vaccination at age of 9 years after a reverse MAC vaccination.[29] Our results suggest that the additional benefits of vaccinating girls younger than 14 years through reverse catch-up are minimal in China. However, the more recent trend towards earlier sexual debut in China may increase the benefit of switching to younger target age in the future.[28]

Our study also highlights the value of conducting forward MAC vaccination once supply constraints are lifted, to immunize older females who would miss out on receiving the vaccine at 9–14 years. The benefits include preventing more cervical cancer cases, accelerating the pace of incidence reduction, and generating economic value (as evidenced by having positive ROIs and being a cost-saving intervention compared with routine vaccination only). According to a population-based pooled analysis, the age-specific prevalence of high-risk HPV in China has a bimodal distribution, which includes a secondary prevalence increase in older females.[31] Despite being implemented over a decade ago, uptake of government-funded cervical screening in China is still suboptimal.[18] In this situation, vaccinating older females through MAC campaigns could be a positive investment and an important supplemental strategy to accelerate cervical cancer elimination in China.

Emerging evidence from immunogenicity trials, efficacy trials, and post-licensure observational studies has indicated that one dose of vaccine could provide an equivalent level of protection against infection and clinical endpoints as two/three doses for more than 10 years. Even with a pessimistic assumption that the efficacy of one dose is lower than two/three doses, adopting a one-dose schedule would free up vaccine doses to allow more rapid scale-up of vaccination, and generate the greatest cost savings and health gains with constrained supply in China. Our results about the one-dose schedule are generally consistent with previous modelling studies,[29,30,32–34] which suggest promising health benefits (in terms of improving both impact and efficiency) and favourable cost-effectiveness of one-dose strategies. However, few studies have explicitly incorporated supply constraints when comparing the impact of adopting a one-dose schedule with other strategies. For LMICs facing more severe financial and supply constraints, a one-dose schedule would also provide opportunities for them to accelerate vaccine introduction by enhancing the logistic feasibility and affordability of introduction. Our results contribute China-based modelling evidence that supports the value of one-dose schedule in alleviating the global supply constraints. In the future, randomized trials in China may be incorporated into this framework and provide further empirical data to allow national licensure of one-dose schedules.

The Chinese government's commitment to accelerating the elimination of cervical cancer has provided an unprecedented opportunity for HPV vaccination introduction in China. Under the Healthy China Initiative, several pilot cities have started cervical cancer prevention and control programs in 2021. These efforts include government-funded HPV vaccination programmes targeted at young adolescents in middle school. Cities like Ordos, Chengdu, and Jinan have achieved vaccine coverage of ≥80% among girls in the target ages (12–14 years, depending on city) since the programs' first year. These achievements indicate the potential for rapid vaccination scale-up in China when government funding is available. This may also offer useful lessons and motivation for similar efforts at both local and national levels. Hence our study provides timely evidence for policymakers by investigating the benefit of vaccine strategies in the context of constrained supply and alternative dose schedules.

Our study has three main strengths. First, to our knowledge, this is the first modelling study evaluating HPV vaccine strategies in China that considers different vaccine supply contexts and dose schedule scenarios. Strategies with different vaccine types, target ages, mode of delivery (routine or MAC) were explored. Second, our results provide a synthesis of evidence on health impact,

efficiency and value for money, all of which are needed to inform country policymakers about funding priorities among different vaccination options. Few studies have evaluated the ROI of HPV vaccination. The ROI results in our study suggest that the implementation of a national HPV vaccination program is an investment that generates positive returns (higher than 6 times). This evidence may boost political will for sustained investment in HPV vaccination in China. Third, we included two innovative reallocation strategies for one-dose schedules adopting WHO SAGE's latest recommendation, to inform the possible vaccine use when supply is constrained and quantify the trade-offs of different dose schedules in China.

Our study also has some limitations. First, we did not consider possible improvements in cervical cancer screening capacity, uptake, and technology that may occur within the 100-year time horizon. Cervical cancer screening in our model is cytology-based, which is used as the primary screening test in China, although HPV DNA testing has been adopted as the primary test in many countries. Screening coverage is currently low and is assumed to remain unchanged in the model. That may lead to an overestimate of the burden that can be prevented by vaccination over the long term. Moreover, we do not consider cost savings that may arise by simplifying screening algorithms in vaccinated cohorts. Second, the value of vaccination in protecting the population against non-cervical cancers and genital warts was not considered in our study, leading to underestimations in the health and economic benefits associated with vaccination. Third, we did not consider the scenario of vaccination for boys. With a goal of cervical cancer elimination, the potential efficient and cost-effective use of constrained vaccine supply should be vaccinating those who could directly benefit from it. Moreover, Chinese mainland has not yet licensed the HPV vaccine for males. However, policymakers might consider vaccinating males when vaccine supply is lifted and when vaccination for males is licensed. This strategy would further expand the health benefits in preventing both cervical cancer and other HPV related disease. Fourth, in current market use scenario, we did not consider the different availability to vaccines due to the variations in ability to pay across socioeconomic groups. That may affect the estimation on the impact of private market use strategy. Last, we used GDP per capita to approximate an individual's annual economic contribution to society at the national average when calculating the ROIs, but did not consider the variations in different socioeconomic groups.

In summary, our study provides timely evidence to inform current and future HPV vaccine strategies in China. We show that the currently limited vaccine supplies should be prioritized for girls aged 14 through a two-dose routine vaccination if the current strict dose schedule regulations need to be adhered to. One-dose schedule is a promising option to accelerate the scale-up of vaccination and maximize its health and economic benefits, especially in a supply-constrained context. MAC vaccination should be considered when supply constraints are lifted, as this will give older females who were too old for the routine program to have a chance to be vaccinated. The general findings about HPV vaccination under different supply and dose schedule assumptions may be valuable to other countries, especially LMICs with resource constraints or strict dose schedule regulations that have not yet introduced HPV vaccines.

Contributors

FZ, and MJ contributed to funding acquisition of the study. TY, SH, and FZ co-designed the study. MJ also participated in the study design. TY, XZ, and MG accessed and verified all reported data. TY, SH, XZ, 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

YQ and FZ report grants from GlaxoSmithKline Biologicals, Merck & Co, and Xiamen Innovax Biotech to their institution, to undertake clinical trials on the human papillomavirus (HPV) vaccine. 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.eclinm.2022.101789.

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