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The cost-effectiveness of human papillomavirus vaccine in China: a systematic review of modeling studies

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Abstract

Objectives: China suffers from high burdens of human papillomavirus (HPV) and cervical cancer, whereas the uptake of HPV vaccine remains low. The first Chinese domestic HPV vaccine was released in 2019. However, collective evidence on cost-effectiveness of HPV vaccination in China has yet to be established. We executed a systematic review of published cost-effectiveness studies of HPV vaccine in China.

Methods: We searched PubMed, EMBASE, China National Knowledge Infrastructure and Wanfang Data for cost-effectiveness articles published in English and Chinese until January 2021. We extracted information from the selected studies focusing on cost-effectiveness results of various vaccination programs and key contextual and methodological factors influencing cost-effectiveness estimates.

Results: A total of 14 studies were included for review. Considerable heterogeneity was found in terms of the methodologies used and HPV vaccination strategies evaluated in different studies. The reviewed studies generally supported the cost-effectiveness of HPV vaccine in China, although some reached alternative conclusions, particularly when assessed incremental to cervical cancer screening. Cost of vaccination was consistently identified as a key determinant for the cost-effectiveness of HPV vaccination programs.

Conclusions: Implementing HPV vaccination programs should be complemented with expanded cervical cancer screening, while the release of lower-priced domestic vaccine offers more promising potential for initiating public HPV vaccination programs. Findings of this study contributes important evidence for policies for cervical cancer prevention in China and methodological implications for future modeling efforts.

Keywords: human papillomavirus; vaccine; cost-effectiveness; systematic review; cervical cancer

Strengths and limitations of this study

- The first systematic review on the cost-effectiveness of human papillomavirus (HPV) vaccination strategies in the setting of China.
- A total of 14 modeling studies with disparate methodologies focusing on various HPV vaccination programs and strategies were included for view.
- We performed a review of four databases in both English and Chinese on a comprehensive set of contextual and methodological factors to identify key determinants for cost-effectiveness results and optimal vaccination programs.
- No all aspects and assumptions of a model were evaluated in this review but only the ones we believed were most influential on cost-effectiveness results.

Introduction

As the leading cause of cervical cancer, human papillomavirus (HPV) is one of the most common sexually transmitted infections both in China and globally.[1] A recent meta-analysis of nearly 200 studies on the prevalence of HPV revealed that as high as 19.0% (95% confidence interval: 17.1%-20.9%) of women in China were infected with high-risk HPVs, while the subtypes with the highest infection rates were 16, 52, 58, 53 and 18.[2] Meanwhile, cervical cancer is the forth most common cancer for women worldwide, accounting for over 100,000 new cases and 47,000 deaths each year in China.[3] Among all the newly diagnosed cervical cancer cases in China, around 2/3 were found within the age group of 44-64 years.[3] HPV is predominately transmitted through sexual contacts and is also responsible for many other diseases such as anal cancer, oropharyngeal cancer, vaginal and vulvar cancer, penile cancer and genital wart.[4 5]

Cervical cancer is preventable and curable in the early stages. To mobilize efforts to eliminate cervical cancer, the World Health Organization (WHO) has set strategic targets for all countries by 2030, known as the 90-70-90 targets: 90% of girls fully vaccinated by age 15; 70% of women screened twice in a lifetime for cervical cancer (by age 35 and 45); 90% of women identified with cervical disease receive treatment.[6] HPV vaccine has been endorsed as the most effective approach for preventing HPV infection and associated diseases. The United States, Australia, Canada, and the United Kingdom were among the first countries to introduce HPV vaccine into national immunization programs.[7] Population-level impact of HPV vaccine has been evidenced by many prior studies,[8-10] and a

recently published study following over 2,000 women from Nordic countries who have received three doses of quadrivalent HPV vaccine for 14 years demonstrated a remarkable 100% effectiveness against HPV16/19-related high-grade cervical dysplasia.[11]

It was not until July 2016, a decade after the first HPV vaccine's licensing in the United States, when the first commercial HPV vaccine, Cervarix, was approved to use in mainland China.[12] The first Chinese domestic HPV vaccine (Cecolin), a bivalent vaccine against HPV 16 and 18, was licensed by the Chinese Food and Drug Administration in Dec 2019 and priced only half of Cervarix.[13] However, HPV vaccine coverage rate remains low. As of March 2021, there are no HPV vaccination programs in China. According to an online cross-sectional survey of 4,220 female students from 136 Chinese universities in 2019, only 11% of participants reported have received HPV vaccine.[14] An even lower HPV vaccination coverage level (3.6% among females, 1.9% among males) was found in another online survey of college students in 2019.[15] The low rate of HPV vaccination is attributable to many causes, including late introduction of HPV vaccines, high out-of-pocket costs, lack of awareness, and misunderstandings about HPV and HPV vaccines among the public.[15 16]

Cost-effectiveness analysis is widely used to evaluate the public health and economic value of health interventions and policies. A number of systematic reviews have assessed cost-effectiveness models evaluating HPV vaccination programs across different policy settings.[4 17-19] However, none of them have focused on Chinese context. Although most suggested that HPV vaccination

programs were likely to be cost-effective in many settings, some reached discordant conclusions. Many contextual and methodological factors may affect the estimated cost-effectiveness of HPV vaccination, such as baseline risk of HPV infection, uptake of cervical cancer screening and treatment, analytical perspective, model type, cost of vaccine, vaccine efficacy and duration of protection, and comparison strategies. Therefore, caution should be taken when interpreting or extending these study findings and when developing new economic models. Given the increasing awareness of HPV and availability of HPV vaccines (more options and lower price) among the public, a targeted review of latest cost-effectiveness models of HPV vaccination in the setting of China will be of substantial value for public health policy making. Furthermore, an understanding of the range of methods and assumptions used in analyzing the cost-effectiveness of HPV vaccination can help guide future modeling development efforts.

We executed a systematic review of published cost-effectiveness studies of HPV vaccination in China. We comprehensively compared differences in cost-effectiveness results of various HPV vaccination programs alone, in addition to, or in combination with other cervical cancer prevention interventions as a result of various modeling methods, designs and assumptions.

Methods

Search Strategy

We performed a systematic review of literature published in English and Chinese following the PRISMA guidelines[20] for reporting of systematic reviews (Supplementary Appendix Table S1). The systematic literature search was conducted on January 2, 2021 in databases MEDLINE (PubMed), and EMBASE for articles in English, as well as in databases China National Knowledge Infrastructure (CNKI) and Wanfang Data for articles in Chinese. No review protocol exists for this study. We developed search terms using a combination of the following keywords: 'HPV/cervical cancer', 'vaccine', 'cost-effectiveness' and 'China' (see Supplementary Appendix Table S2, S3 for detailed search strategies). Corresponding terms in Chinese were used in searching Chinese databases. Our searches covered all published literature up to our last search on January 2, 2021 with no limitations on publication date.

Selection Criteria

Cost-effectiveness studies fulfilling the following selection criteria were included in review: (1) studies focusing on HPV vaccination interventions explicitly, alone or in combination with other interventions; (2) studies analyzing the cost-effectiveness of HPV vaccination using a modeling approach, excluding those where costs were not assessed or using a non-modeling approach; (3) studies conducted in the setting of China (including the special administrative regions of Hong Kong and Macau), excluding those examining a broader context where China was a

subregion in the analysis; (4) studies published as full-length articles (excluding conference abstracts and commentaries).

Data Extraction and Analysis

Information pertaining to the cost-effectiveness results and different contextual and methodological factors that might influence cost-effectiveness results was extracted for each selected study. Data extraction was independently performed by two reviewers and any differences were resolved with a third reviewer. For articles published in Chinese, data extraction was conducted in the original language and translated into English for analysis.

We converted cost-effectiveness results and unit cost for vaccine from all studies in different currencies and years to 2021 USD according to the Consumer Price Index Inflation and USD/CNY exchange rate in January 2021 (1USD=6.5CNY). For studies where the currency year was not stated, we assumed it to be the year of a study's publication. We also provided an assessment of the reviewed economic evaluations using the CHEERS checklist[21] to determine the percentage of checklist items (a total of 24) that each study met as a score for quality.

Patient and Public Involvement statement

Neither patients nor the public were involved in this review.

Results

Figure 1 presents a flow diagram of the study search and selection process. A total of 136 articles (69 in English and 67 in Chinese) were identified after removing the duplicates (N=78). Following screening of titles and abstracts, 35 full text articles were evaluated, among which 14 met the selection criteria (ten in English and four in Chinese) and were included for review.[13 22-34] Of these 14 included studies, all were published after 2010 and 12 after 2016 (the year when the first HPV vaccine was licensed to use) (Table 1). Most studies evaluated HPV vaccination at the national level (8/14), as opposed to focusing on one providence (4/14) or city (2/14). All studies except one (in Hong Kong) were conducted in the setting of mainland China.

Study Design

The majority of studies (13/14) adopted a cohort-based model that stratifies the study population into groups according to each individual's characteristics and health state, whereas only one used an individual-based model (Table 1). In addition to the susceptible and death states, most models considered a similar set of disease states, including different stages of cervical intraepithelial neoplasia/squamous intraepithelial lesion and cervical cancer. Three studies included additional states for HPV infection (stratified by risk level) prior to developing cervical intraepithelial neoplasia, and only two also accounted for genital wart as possible consequence of HPV infection. Although HPV is an infectious disease that is transmitted through sexual contacts, dynamic models that capture changing risk of infection (as a function the number of infectious individuals

in the population at a given time point)[35] were only used in 4/14 studies. The study population simulated in each model were in line with the type of model used, where population of both males and females were considered all in dynamic models to construct transmission dynamics and potential herd immunity (other models considered females only). The majority of models assessed (12/14) considered a lifetime (or 100-year) time horizon to capture all possible long-term benefits and consequences of alternative interventions. In estimating relevant costs, over half studies (7/12) framed their analysis from the perspective of healthcare sector/payer, two from the perspective of government, and only three adopted a broader societal perspective, whereas two did not explicitly report their perspectives. 11/14 studies used utility-based measure for health outcomes, such as quality-adjusted life years (QALYs) and disability-adjusted life year (DALYs), while the remaining estimated health benefits in the unit of life year saved or death averted. A 3% discounting rate was universally applied in all studies (except one whose discounting rate was unreported). Model calibration and validation are both recommended by modeling guidelines and are critical steps to establish the credibility and reliability of economic models against empirical data.[36 37] However, only nine studies incorporated either calibration or validation (two performed both) in their analysis.

HPV Vaccine

The type of HPV vaccine modeled and pertaining features and assumptions varied across different studies (Table 2). All studies focused on the vaccination of females only. While in most studies (12/14) vaccination was considered to be implemented

among preadolescent girls under age 18 (before sexual debut); two studies focused on vaccination at the age of 18-25, one examined HPV vaccination at different ages between 12-55, and one also considered expanded catch-up programs among females aged 16-39 (the primary program still focused on preadolescent girls). Different types of vaccine were considered in different studies: eight studies focused on a bivalent vaccine, one on a quadrivalent vaccine, one on a nonavalent vaccine, two compared all these three types in one study, while two did not specify the valence of vaccine. Three-dose schedule was considered in nine studies; the remaining either assumed a two-dose schedule or did not report required doses. Although most models derived estimates for vaccine efficacy against cervical cancer and other HPV-related disease states from real-world data (clinical trials or observational studies), a few studies (5/14) assumed a 100% vaccine efficacy, which might result in possible overestimation for the impact and cost-effectiveness of HPV vaccine. Regarding vaccination coverage for the modeled interventions, half studies assumed a 70% coverage in their primary analysis (which may vary in sensitivity analysis), following by a coverage level of 100% (3/14), 80% (1/14), 50% (1/14) and 20% (1/14), while one aimed to explore different coverage levels (25%, 50%, 75%). Most studies (13/14) assumed lifelong vaccine protection (in which one also explored other durations of protection) while only one considered a waning of immunity over time. Cost of vaccination, including medical cost for multiple doses and relevant administration cost, varied between studies on different types of vaccine ranging from US$54.2 to US$663. Most (8/14)

chose a cost between US$300-500. The first domestic vaccine was analyzed in Zou et al.[13] study that was priced at US$99.8 per vaccination (in 2019 USD).

Cost-effectiveness of HPV Vaccination Strategies

Despite no established cost-effectiveness threshold in China, almost all studies used the heuristic cost-effectiveness threshold proposed by the WHO based on local gross domestic product (GDP) per capita, even though two studies did not use a utility-based measure for health outcomes (Table 3). The only exception was one that used an extended cost-effectiveness framework whose primary outcome was not incremental cost-effectiveness ratio (and thus did not specify the threshold). Various HPV vaccination strategies were assessed in the reviewed studies. Eight studies examined the impact and cost-effectiveness of HPV vaccination programs incremental to either existing screening programs or opportunistic vaccination programs or none at all, among which three stratified their analysis by different vaccination coverage levels, different ages of vaccination, and different income levels of target population. Although these eight studies sought to address slightly different study questions, they appeared to reach a consistent conclusion that HPV vaccination was cost-effective. One study examining the effect of vaccination age showed that vaccination was cost-effective at any age under 23 years in rural and any age under 25 years in urban areas. One study compared the value of nonavalent vaccine to quadrivalent and bivalent vaccine for the prevention of cervical cancer and found it not cost-effective unless the nonavalent vaccine could be priced lower than US$550 and US$450 for the full doses (as opposed to US$663 used in the study, in 2017 USD), respectively.

The other five studies, on the other hand, analyzed combination strategies for HPV vaccination with various HPV screening methods or frequencies, three of which also created cost-effective frontiers to identify an optimal strategy. However, findings of these studies were less consistent, and sometimes contradictory. Canfell et al. study examined the association between cost-effectiveness of HPV vaccination strategies (in combination with screening interventions) and cost per vaccinated girl (CGV), and found strategies involving vaccination would be cost-effective only at CVGs of US$50–54 or less (if CVG>US$54, screening-only strategies would be more cost-effective).[22] Ma et al. study found that the addition of universal vaccination to screening programs was not cost-effective unless with at least a 50% reduction on the vaccine price (from US$451 to US$226).[29] The optimal combination of vaccine type and screening method identified in Mo et al. study was nonavalent vaccination and visual inspection with acetic acid (VIA).[30] However, another finding of this study was that quadrivalent and nonavalent vaccine both denominated bivalent vaccine regarding the cost-effectiveness, conversely to Jiang et al.'s results.[24] Although Song et al. showed that the combination of vaccination at age 15 and screening twice in a lifetime (at age 35 and 45) was cost-effective compared to no intervention, but it was not cost-effective when compared to only screening twice in a lifetime (optimal strategy).[32] Zou et al. was the only study that included the domestic vaccine in their analysis (with lower price than the imported vaccines) and they identified the optimal strategy to be vaccination with careHPV screening once every five years.[13] They also determined that adding vaccination to screening programs would be

consistently more cost-effective than screening alone when vaccination cost could be lower than US$50.

Uncertainty Analysis and Study Quality

To assess model uncertainty, many studies explicitly incorporated sensitivity analysis (SA), including one-way SA (in ten studies), two-way SA (in one study), and probabilistic SA (in five studies) (Table 3, some studies incorporated multiple types of SA). Among those performed one-way SA, the parameters that cost-effectiveness results were most sensitive to included discounting rate, cost of vaccine, and vaccine efficacy. Quality assessment of the reviewed studies against the CHEERS checklist suggested that most of them upheld a high level of quality in reporting, with an average score of 85 and ranging from 46 to 100 (where 100 represented 100% of checklist items were complied with) (Supplementary Appendix Table S4).

Discussion

To our knowledge, this study provides the first systematic review on the cost-effectiveness of introducing HPV vaccination programs in the setting of China. In this review, we performed a comprehensive and in-depth assessment of 14 model-based cost-effectiveness studies regarding their findings, study design, and assumptions for HPV vaccine and vaccination programs. Despite considerable heterogeneity in the methodologies used in different models, our findings show that HPV vaccination is estimated to have substantial potential to be a cost-effective addition to existing/other cervical cancer prevention interventions in China. However, the cost-effectiveness of HPV vaccination is likely to depend on considerations such as cost of vaccination, age of vaccination, vaccine efficacy, as well as complementary and/or competing strategies (e.g., cervical cancer screening).

Among all the influential factors, cost of vaccine was consistently identified as a key determinant for the cost-effectiveness of HPV vaccination. Cost estimates varied considerably across studies for different vaccines and years; acquiring more reliable evidence on vaccine cost will help reduce uncertainty surrounding cost-effectiveness results. Six of the reviewed studies performed additional threshold analysis to determine the cost at which adding HPV vaccination to cervical cancer screening programs would become/remain (more) cost-effective. While three studies suggested disparate thresholds for the cost per fully vaccinated girl/woman ranging from US$226-US$689, findings of the other three were more consistent showing a lower threshold of US$50. The Zou et al. study assessed the first

domestic bivalent HPV vaccine at a unit cost of US$99.8, substantially cheaper than the imported vaccines.[13] Given more domestic vaccines under development and growing initiatives to include HPV vaccine into national immunization program, further reduction in HPV vaccine price was expected in the foreseeable future.

Findings of the reviewed studies were generally consistent with other systematic reviews focusing on cost-effectiveness of HPV vaccination in low- and middle-income countries.[19 38 39] Most of these studies concluded that vaccination was likely to be cost-effective, particularly in contexts without organized cervical cancer screening programs. Based on the summary of evidence, a few recommendations may be provided for implementing HPV vaccination programs to enhance its cost-effectiveness. HPV vaccine is most recommended for routine vaccination for girls at younger age (before 16) while will still remain valuable for women of older age (under 23 years in rural and under 25 years in urban areas) according to one reviewed study that explored different vaccination ages.[26] The US Centers for Disease Control and Prevention recommended vaccination for everyone (including men) at age 11 through age 26 years.[40] In the United Kingdom, men and women aged 12 to 13 years are routinely offered HPV vaccination and can access free vaccination up until their 25th birthday.[41] Regarding the type of vaccine for recommendation, two studies reached contradicting conclusions about the relative cost-effectiveness between nonavalent, quadrivalent and bivalent vaccines. This difference is likely attributable to disparate costs applied for different vaccines in the two models. In Jiang et al.'s model,[24] nonavalent vaccine was assumed to

be 60% and 116% more expensive than quadrivalent and bivalent vaccines, respectively, while it costed only 11% more than the other two vaccines in Mo et al.'s study.[30] Future investigations of different vaccines and their pricing, efficacy and population impacts may be required for more rigorous recommendation strategies. Meanwhile, the reviewed studies demonstrated strong synergies between HPV vaccination and cervical cancer screening that the greatest public health benefits, and sometimes also the optimal strategy, could be achieved only when these two interventions were implemented simultaneously. However, in identifying the optimal combination strategies, two studies indicated that screening alone might outperform strategies with the addition of HPV vaccination, while there was less consistency regarding the screening methods (pap, VIA or careHPV test) and testing frequencies. Given current low uptake of screening in China, establishing appropriate strategies to substantially expand cervical cancer screening should be prioritized prior to or simultaneously with implementing HPV vaccination programs.

From the methodological point of view, a few recommended model design and practice may be highlighted for future modeling efforts. First, a key finding of this review was that the majority of reviewed studies applied a static model in simulating HPV infection that was unable to capture potential herd immunity when HPV vaccination reached a high level of coverage. According to the modeling guideline, dynamic design is important to consider when an intervention affects a pathogen's ecology or when the intervention affects disease transmission.[35] Incorporating dynamic design will ensure capturing the indirect effects of HPV

vaccination that arise from averted infections, i.e., individuals not reached by the vaccination program can still benefit by experiencing a lower infection risk. However, applying such a dynamic model may require modeling the population of men (who are non-recipients of HPV vaccine) as well as additional model parameters. Second, cost-effectiveness models are built upon various input data and assumptions and are inevitably subject to uncertainty. Handling model uncertainty is important and can help assess the robustness of model results and enhance our confidence in a chosen course of action. Model calibration and SA are both recommended practices[36] to address uncertainty but were not performed in all models (calibration in 7/14 models, sensitivity analysis in 12/14 models). For the conduct of uncertainty analysis, we also recommend carefully choosing uncertainty ranges for parameters to meaningfully reflect their plausible values (rather than imposing an arbitrarily range) and explicitly reporting the rationale. Third, although cervical cancer is the primary disease following HPV infection, it is also important to account for other possible consequences and diseases, without which the impact and cost-effectiveness of HPV vaccination may be underestimated.

Our review may have some limitations. First, we did not attempt to exhaustively include all aspects and assumptions of a model in this review (such as utility estimates, force of infection, disease progression) but only the ones we believed were most influential on cost-effectiveness results. Second, the quality of evidence used to support a model is another central factor in ensuring credibility and reliability of model inferences but was not assessed in this review. Third, we were

unable to perform a meta-analysis due to the variability across studies in the strategies evaluated and outcomes reported. Nevertheless, all studies have compared the estimated cost-effectiveness with the WHO-CHOICE cost-effectiveness benchmark using local (national, provincial, or city-level) GDP per capita, providing a consistent criterion across studies.

The body of evidence from this systematic review of cost-effectiveness modeling studies on HPV vaccine suggests that implementing HPV vaccination programs for young girls is likely warranted in China and should be paired with expansion of cervical cancer screening to maximize their impact. Cost of vaccination was found to significantly affect the cost-effectiveness estimates and policy recommendations. As domestic vaccines become available and their prices continue to drop, HPV vaccination will become a more viable option in designing cervical cancer prevention programs. Future modeling studies following established best-practice standards are needed to reduce decision uncertainty and definitively establish the cost-effectiveness of HPV vaccination in combination with screening programs.

Contributors

WS and TC conceptualized the study. WS, XC conducted data collection. WS, HW and XZ performed data analyses. WS and TC wrote the first draft of the article. XC, HW and XZ helped to interpret results and critically revise the manuscript. All authors approved the final draft.

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Competing interests

The authors have no conflicts of interest to declare.

Data sharing statement

There is no additional unpublished data associated with this study. All data are available in the manuscript and supplementary appendix.

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Figure 1. Flow diagram of study selection
Legend: CEA: cost-effectiveness analysis

Table 1. Study design of selected modeling studies

Reference	Year of publication	Setting	Model type	Disease states modelled	Study population	Timeframe	Perspective	Discount rate	Health measure	Calibration /validation	Year of cost
Canfell	2011	Shanxi Province (rural)	Cohort, Dynamic	CIN (3), cervical cancer	Males + females (of all ages)	Lifetime	Societal	3%	Life year	Calibration	2010
Choi	2018	Hong Kong	Cohort dynamic (for transmission) + individual-based (for disease)	CIN (3) Cervical cancer: 4 stages+ asymptomatic/symptomatic	Males + females (10-85 years)	Lifetime	Societal	3%	Life year, QALY	Calibration	2018*
Jiang	2019	China	Cohort, Static	Cervical cancer	Females of 16 years	Lifetime	Healthcare payer	3%	DALY	No	2017
Levin	2015	China	Individual, Static	CIN (3), cervical cancer	Females (9 years and older)	Lifetime	Government	Unclear	Deaths averted	Calibration	2009
Liu	2016	China (rural, urban)	Cohort, Static	CIN (3), cervical cancer	Females of 12-55 years	Lifetime	Healthcare payer	3%	QALY	Calibration, Validation	2016*
Luo P	2020	Wuhan City	Cohort, Static	Cervical cancer	Females of 12 years	Lifetime	Unclear	3%	DALY	No	2020*
Luo Y	2020	Zhejiang Province	Cohort, Static	High-risk HPV infection Low-grade SIL High-grade SIL Cervical cancer	Females of 12 years	Lifetime	Government	3%	QALY	No	2020*
Ma	2020	China	Cohort, Dynamic	HPV infection (high/low-risk) CIN (3) Cervicl cancer Genital wart	Females (of all ages)	50 years	Unclear	3%	DALY	Calibration	2020
Mo	2017	China	Cohort, Static	HPV infection (high/low-risk) CIN (3) Cervicl cancer Genital wart	Females of 12 years	Lifetime	Societal	3%	QALY	Calibration	2015
Qie	2017	Zhejiang Province	Cohort, Static	CIN (3), cervical cancer	Females of 18-25 years	Unclear	Healthcare sector	3%	QALY	No	2017*
Song	2017	China	Cohort, Dynamic	CIN (3), cervical cancer	Males + females	100 years	Healthcare sector	3%	Life year	Validation	2017*
Sun	2017	Jiangsu Province	Cohort, Static	CIN (3), cervical cancer	Females of 18-25 years	Lifetime	Healthcare sector	3%	QALY	No	2017*
Zhang	2016	China (rural, urban)	Cohort, Static	CIN (3), cervical cancer	Females of 12 years	Lifetime	Healthcare payer	3%	QALY	Validation	2013
Zou	2020	China	Cohort, Static	CIN (3), cervical cancer	Females of 9-14 years	Lifetime	Healthcare sector	3%	QALY	Calibration, Validation	2019

Legend: * no year of cost reported, using publication year instead. CIN (3): cervical intraepithelial neoplasia (3 stages); SIL: squamous intraepithelial lesion; QALY: quality-adjusted life year; DALY: disability-adjusted life year.

Table 2. Model assumptions and parameters for HPV vaccine evaluated

Reference	Age of vaccination	Vaccine type	No. of doses	Vaccine efficacy	Vaccine coverage	Duration of protection	Unit cost reported*	Unit cost in 2021 US$
Canfell	15	Unspecified	3	100%	70%	Lifelong	Varied in the analysis	Varied in the analysis
Choi	12	Nonavalent	2	95.5% (90.0%-98.4%) for HPV-16 95.8% (84.1%-99.5%) for HPV-18 96.0% (94.4%-97.2%) for HPV-OV 0% for HPV/NV	25%, 50% and 75%	20 years, 30 years and lifelong (various scenarios)	US$284	US$303.1
Jiang	16	Bivalent Quadrivalent Nonavalent	Unclear	100%	100%	Lifelong	Nonavalent: US$628 Quadrivalent: US$393 Bivalent: US$291	Nonavalent: US$682.5 Quadrivalent: US$427.1 Bivalent: US$316.3
Levin	<12	Unspecified	3	100%	70%	Lifelong	US$46	US$61.1
Liu	12-55	Bivalent	3	93.2% against CC 64.9% against CIN2/3 50.3% against CIN1	70%	Lifelong	1954 CNY	US$333.2
Luo P	12	Bivalent	3	95% (63%-100%)	100%^	Lifelong	1999 CNY	US$308.4
Luo Y	12	Bivalent	2	76.78% (40%-100%)	70%	Lifelong	1040 CNY	US$160.4
Ma	9-16	Quadrivalent	Unclear	78.9% (74.5%-82.4%)	50%	5% rate of immunity waning	US$ 451	US$452.3
Mo	12	Bivalent Quadrivalent Nonavalent	3	Bivalent: 80.7% (57.5%-98.9%) Quadrivalent: 81.5% (58.8%-98.2%) Nonavalent: 90.8% (66.5%-100%)	20% (10%-100% in SA)	Lifelong	Bi/Quadrivalent: US$408 Nonavalent: US$ 452	Bi/Quadrivalent: US$459.6 Nonavalent: US$509.1
Qie	18-25	Bivalent	3	100%	80%	Lifelong	1842 CNY	US$308.0
Song	Primary: 15 Expanded: 16-39	Bivalent	3	100%	70%	Lifelong	1995 CNY	US$333.6
Sun	18-25	Bivalent	3	94.2% (62.7%-99.9%)	100%^	Lifelong	2000 CNY	US$334.4
Zhang	12	Bivalent	3	93.2% (78.9%-98.7%) against CC 64.9% (52.7%-74.9%) against CIN2/3 50.3% (40.2%-58.8%) against CIN1	70%	Lifelong	301 CNY	US$54.2
Zou	9-14	Bivalent	2	94% (80%-99%)	70% (50-95% in SA)	Lifelong	US$ 99.8	US$104.7

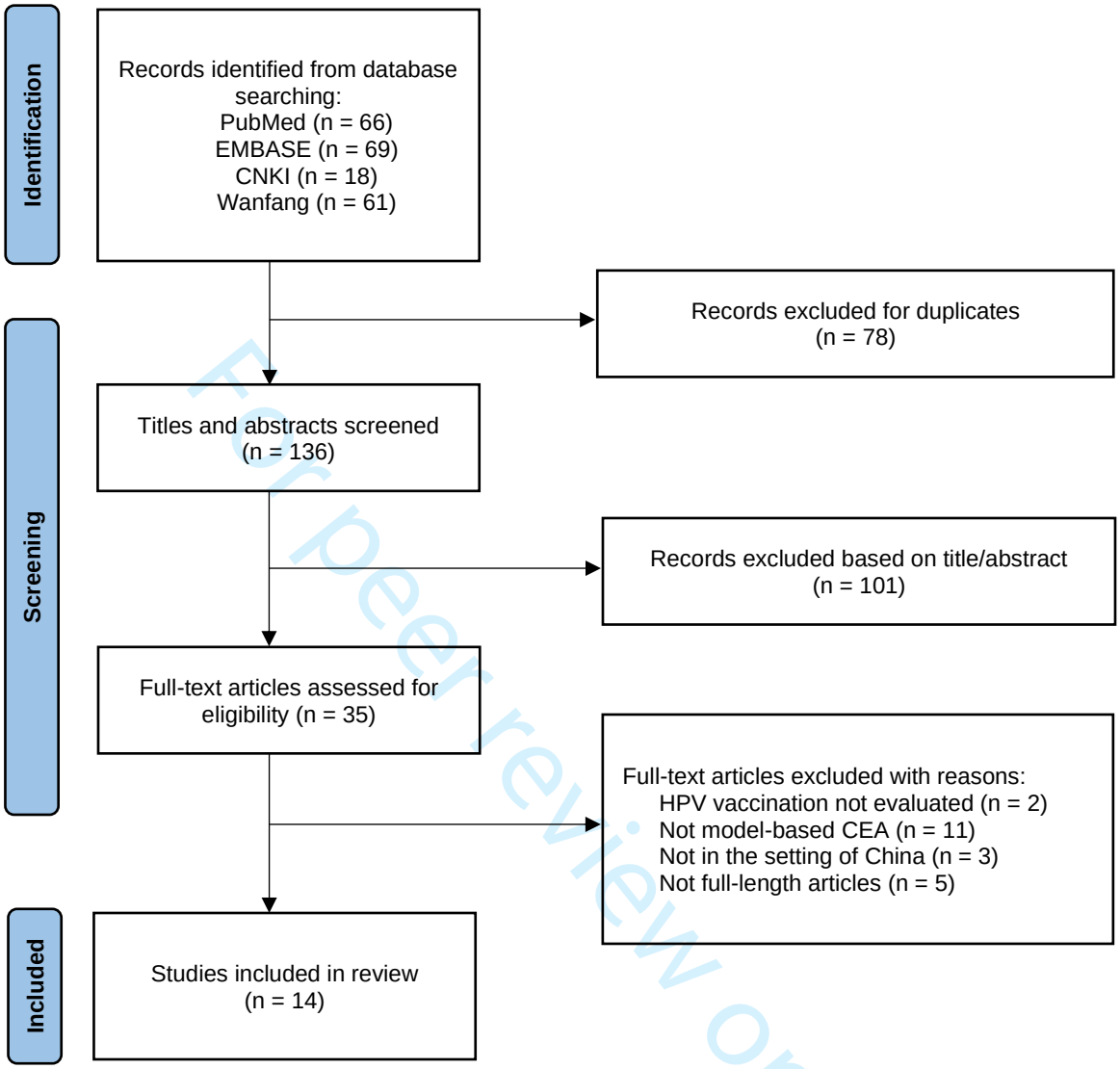
Legend: * total cost per girl/woman vaccinated, including medical cost for multiple doses and other relevant costs (e.g., vaccine administration). ^ among individuals with negative screening results. CC: cervical cancer; CIN: cervical intraepithelial neoplasia; OV: other five high-risk HPV targeted by the nonavalent vaccine; NV: non-vaccine high-risk HPV; CNY: Chinese yuan.

Table 3. Cost-effectiveness of HPV vaccination strategies

Reference	Intervention	Comparator	ICER reported	ICER in 2021 US$	Threshold	Conclusion	Sensitivity analysis	Most sensitive parameters
Canfell	Combination of: vaccination and different screening strategies (with different frequencies)	No vaccination, no screening	-	-	GDP: $3,077	Strategies involving vaccination would be cost-effective at CVGs of US$50–54 or less, but at CVGs >$54, screening-only strategies would be more cost-effective	One-way, probabilistic	Discounting rate Cost of HPV screening Duration of protection
Choi	Vaccination (routine) at different coverage levels	Opportunistic vaccination (12% coverage)	-	-	GDP: $40,099	Cost-effective across all three vaccination coverage levels. Wil remain cost-effective if the cost of fully vaccinating one girl is no greater than $689 ($646–734), respectively.	Probabilistic	-
Jiang	Nonavalent vaccine	Quadrivalent, bivalent vaccine	US$35,000/DALY vs. quadrivalent US$50,455/DALY vs. bivalent	$38,040/DALY vs. quadrivalent $54,837/DALY vs. bivalent	1-3 * GDP: US$8,640	Not cost-effective compared with the quadrivalent and the bivalent vaccines. To be cost-effective, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively	One-way	Discounting rate CC mortality Age of vaccination
Levin	Vaccination (targeting different income groups) + screening	Screening only	US$10,920 - US$13,277 per death averted	$14,504 - $17,635 per death averted	-	Cost-effective across all income groups. Would remain cost-effective if the cost is less than US$50 per vaccinated girl.	One-way	Not reported
Liu	Vaccination (at different ages) + Pap test	Pap test only	Varied by age	-	1-3 * GDP: 41,908 CNY	Vaccination is cost-effective at any age under 23 years in rural and any age under 25 years in urban areas. Catch-up vaccination to the age of 25 years in addition to routine vaccination in 12-year-old in both rural and urban can be cost-effective.	No	-
Luo P	Vaccination	No vaccination	83,496 CNY/DALY	$12,881/DALY	1-3 * GDP: 52,000 CNY	Very cost-effective	One-way	Discounting rate Cost of vaccine Cost of CC treatment
Luo Y	Vaccination	No vaccination	12,472 CNY/QALY	$1,924/QALY	1-3 * GDP: 92,100 CNY	Very cost-effective	One-way	Cost of vaccine Discounting rate QALY estimates
Ma	Combination of: universal vaccination (coverage : 0%-90%) and screening (coverage: 20%-70%)	Status quo (0% vaccination coverage and 20% screening coverage)	-	-	1-3 * GDP: US$ 10,264	The addition of universal vaccination to screening programs is not cost-effective. The vaccine requires at least a 50% price reduction to be cost-effective.	Probabilistic	-
Mo	Combination of: different types of vaccination and screening methods	No vaccination, no screening	-	-	1-3 * GDP: US$ 7,960	Optimal: nonavalent vaccination + VIA screening. Quadrivalent/nonavalent vaccine, in combination with current screening strategies, is highly cost-effective and dominates bivalent vaccine	One-way	Vaccine efficacy Cost of vaccine Discounting rate
Qie	Vaccination + Pap test	Pap test only	43,490 CNY/QALY	$7,272/QALY	1-3 * GDP: 52,000 CNY	Very cost-effective	No	-
Song	Combination of: different vaccination (at different ages) and VIA/VILI screening (with different frequencies) strategies	No vaccination, no screening	-	-	1-3 * GDP: 50,696 CNY	Vaccination (at age 15) + screening twice in a lifetime (at age 35 and 45) is cost-effective compared to no intervention. Optimal: screening twice in a lifetime*	One-way	Discounting rate Cost of vaccine Vaccine coverage

Sun	Vaccination + Pap test	Pap test only	43,489 CNY/QALY	$7,272/QALY	1-3 * GDP: 52,000 CNY	Very cost-effective	One-way	Discounting rate Vaccine efficacy Cost of vaccine
Zhang	Vaccination + screening	Screening only	Rural: 11,365 CNY/QALY Urban: 6,124 CNY/QALY	Rural: $2,047/QALY Urban: $1,103/QALY	1-3 * GDP: 41,908 CNY	Very cost-effective. Would remain very cost-effective if vaccine cost is below 630 CNY in rural and 750 CNY in urban; and remain cost-effective if below 1,700 CNY in rural and 1,900 CNY in urban	One-way, two-way, probabilistic	Cost of vaccine Discounting rate HPV infection rate
Zou	Combination of: vaccination and various screening methods with different frequencies	No vaccination, no screening	-	-	1-3 * GDP: US$ 10,276	Optimal: vaccination + careHPV screening every 5 years. Strategies that combined vaccination and screening would be more cost-effective than screening alone strategies when the vaccination cost was less than $50	One-way, probabilistic	-

Legend: * based on analysis of the reported cost-effectiveness frontier outcomes (rather than what the authors reported). ICER: incremental cost-effectiveness ratio; GDP: gross domestic product per capita; CVG: cost per vaccinated girl; VIA: visual inspection with acetic acid; CC: cervical cancer; CNY: Chinese yuan; QALY: quality-adjusted life year; DALY: disability-adjusted life year.



Supplementary Appendix

Table S1 PRISMA Checklist

Section / topic	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro, par 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro, par 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, par 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, par 1-2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, par 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, par 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, par 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, par 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, par 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, par 4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, par 4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, par 1

characteristics			
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 20).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	Results, par 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, par 1-2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, par 5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, par 3-4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgement

Intro: introduction; par: paragraph; NA: not applicable

Table S2 Search strategy and key terms in PubMed and EMBASE databases

	AND	AND	AND	AND
OR	Human papillomavirus	Vaccine	Cost-effectiveness	China
OR	HPV	Vaccination	Cost-benefit	
OR	Cervical cancer	Immune*	Cost-utility	
OR			Cost-effective	
OR			Model*	
OR			Economic evaluation	
OR			Pharmacoeconomic*	

The search was conducted by title/abstract.

Table S3 Search strategy and key terms in China National Knowledge Infrastructure and Wanfang databases

	AND	AND	AND	AND
OR	人乳头瘤病毒	疫苗	成本效用	中国
OR	HPV	免疫	成本收益	
OR	宫颈癌		成本效益	
OR			成本效果	
OR			模型分析	
OR			经济学评价	
OR			药物经济学评价	

The search was conducted by title/abstract

Table S4 Quality assessment of model reporting against CHEERS checklist

Reference	Canfell	Choi	Jiang	Levin	Liu	Luo P	Luo Y	Ma	Mo	Qie	Song	Sun	Zhang	Zou
Title and abstract														
Title	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Abstract	1	1	1	1	1	0.5	1	1	1	0.5	1	0.5	1	1
Introduction														
Background & objectives	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1
Methods														
Target population & subgroup	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Setting and location	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study perspective	1	0	1	0	1	0	1	0	1	0	1	1	1	1
Comparators	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Time horizon	1	1	1	1	1	0	1	1	1	0	1	1	1	1
Discount rate	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Choice of health outcomes	1	1	1	1	1	0	1	1	1	0	1	0	1	1
Measures of effectiveness	1	1	0	0	1	0	1	1	1	0	0	1	1	1
Preference based outcomes	N/A	1	0	N/A	1	0	1	1	1	0	N/A	1	1	1
Estimating resources & costs	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1
Currency, price date, and conversion	1	0	0	1	0	0	0	1	1	0	0	0	1	1
Choice of model	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Assumptions	1	1	1	1	1	0	1	1	1	0	1	1	1	1
Analytical methods	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1
Results														
Study parameters	1	1	1	1	1	0.5	1	1	1	0.5	0.5	1	1	1
Incremental costs & outcomes	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Characterizing uncertainty	1	1	1	1	0	1	1	1	1	0	1	1	1	1
Characterizing heterogeneity	1	N/A	N/A	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
Discussion														
Study findings, limitations, generalizability & knowledge	0.5	1	1	1	1	0.5	1	1	1	0.5	0.5	1	1	1
Other														
Source of funding	1	1	1	1	1	0	1	1	1	0	1	0	1	1
Conflicts of interest	1	1	1	1	1	0	1	1	1	0	0	0	1	1
Total % of Yes	93%	87%	87%	83%	92%	52%	96%	96%	100%	46%	77%	80%	100%	100%

‘‘1”: meets the assessment criteria; ‘‘0.5”: partially meets the assessment criteria; “0”: does not meets the assessment criteria.

PRISMA Checklist

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Intro: introduction; par: paragraph; NA: not applicable

CHEERS checklist

Reference	Canfell	Choi	Jiang	Levin	Liu	Luo P	Luo Y	Ma	Mo	Qie	Song	Sun	Zhang	Zou
Title and abstract														
Title	0	0	1	1	1	1	1	1	1	1	1	1	1	1
Abstract	1	1	1	1	1	0.5	1	1	1	0.5	1	0.5	1	1
Introduction														
Background & objectives	1	1	1	1	1	0.5	1	1	1	1	1	1	1	1
Methods														
Target population & subgroup	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Setting and location	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study perspective	1	0	1	0	1	0	1	0	1	0	1	1	1	1
Comparators	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Time horizon	1	1	1	1	1	0	1	1	1	0	1	1	1	1
Discount rate	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Choice of health outcomes	1	1	1	1	1	0	1	1	1	0	1	0	1	1
Measures of effectiveness	1	1	0	0	1	0	1	1	1	0	0	1	1	1
Preference based outcomes	N/A	1	0	N/A	1	0	1	1	1	0	N/A	1	1	1
Estimating resources & costs	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1
Currency, price date, and conversion	1	0	0	1	0	0	0	1	1	0	0	0	1	1
Choice of model	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Assumptions	1	1	1	1	1	0	1	1	1	0	1	1	1	1
Analytical methods	1	1	1	1	1	1	1	1	1	0.5	1	1	1	1
Results														
Study parameters	1	1	1	1	1	0.5	1	1	1	0.5	0.5	1	1	1
Incremental costs & outcomes	1	1	1	0	1	1	1	1	1	1	1	1	1	1
Characterizing uncertainty	1	1	1	1	0	1	1	1	1	0	1	1	1	1
Characterizing heterogeneity	1	N/A	N/A	1	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	1
Discussion														
Study findings, limitations, generalizability & knowledge	0.5	1	1	1	1	0.5	1	1	1	0.5	0.5	1	1	1
Other														
Source of funding	1	1	1	1	1	0	1	1	1	0	1	0	1	1
Conflicts of interest	1	1	1	1	1	0	1	1	1	0	0	0	1	1
Total % of Yes	93%	87%	87%	83%	92%	52%	96%	96%	100%	46%	77%	80%	100%	100%

‘‘1”: meets the assessment criteria; ‘‘0.5”: partially meets the assessment criteria; “0”: does not meets the assessment criteria.

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The cost-effectiveness of human papillomavirus vaccine in China: a systematic review of modeling studies

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Abstract

Objectives: China suffers from high burdens of human papillomavirus (HPV) and cervical cancer, whereas the uptake of HPV vaccine remains low. The first Chinese domestic HPV vaccine was released in 2019. However, collective evidence on cost-effectiveness of HPV vaccination in China has yet to be established. We summarized evidence on the cost-effectiveness of HPV vaccine in China.

Design: Systematic review and narrative synthesis

Data sources: PubMed, EMBASE, China National Knowledge Infrastructure and Wanfang Data were searched through January 2, 2021

Eligibility criteria for selecting studies: Cost-effectiveness studies using a modeling approach focusing on HPV vaccination interventions in the setting of China were included for review

Data extraction and synthesis: We extracted information from the selected studies focusing on cost-effectiveness results of various vaccination programs, key contextual and methodological factors influencing cost-effectiveness estimates and an assessment of study quality.

Results: A total of 14 studies were included for review. Considerable heterogeneity was found in terms of the methodologies used, HPV vaccination strategies evaluated, and study quality. The reviewed studies generally supported the cost-effectiveness of HPV vaccine in China, although some reached alternative conclusions, particularly when assessed incremental to cervical cancer screening. Cost of vaccination was consistently identified as a key determinant for the cost-effectiveness of HPV vaccination programs.

Conclusions: Implementing HPV vaccination programs should be complemented with expanded cervical cancer screening, while the release of lower-priced domestic vaccine offers more promising potential for initiating public HPV vaccination programs. Findings of this study contributes important evidence for

policies for cervical cancer prevention in China and methodological implications for future modeling efforts.

Keywords: human papillomavirus; vaccine; cost-effectiveness; systematic review; cervical cancer

Strengths and limitations of this study

- The first systematic review on the cost-effectiveness of human papillomavirus (HPV) vaccination strategies in the setting of China.
- A total of 14 modeling studies with disparate methodologies focusing on various HPV vaccination programs and strategies were included for view.
- We performed a review of four databases in both English and Chinese on a comprehensive set of contextual and methodological factors to identify key determinants for cost-effectiveness results and optimal vaccination programs.
- Not all aspects and assumptions of a model were evaluated in this review but only the ones we believed were most influential on cost-effectiveness results.

Introduction

As the leading cause of cervical cancer, human papillomavirus (HPV) is one of the most common sexually transmitted infections both in China and globally.[1] A recent meta-analysis of nearly 200 studies on the prevalence of HPV revealed that as high as 19.0% (95% confidence interval: 17.1%-20.9%) of women in China were infected with high-risk HPVs, while the subtypes with the highest infection rates were 16, 52, 58, 53 and 18.[2] Meanwhile, cervical cancer is the forth most common cancer for women worldwide, accounting for over 100,000 new cases and 47,000 deaths each year in China.[3] Among all the newly diagnosed cervical cancer cases in China, around 2/3 were found within the age group of 44-64 years.[3] HPV is predominately transmitted through sexual contacts and is also responsible for many other diseases such as anal cancer, oropharyngeal cancer, vaginal and vulvar cancer, penile cancer and genital wart.[4 5]

Cervical cancer is preventable and curable in the early stages. To mobilize efforts to eliminate cervical cancer, the World Health Organization (WHO) has set strategic targets for all countries by 2030, known as the 90-70-90 targets: 90% of girls fully vaccinated by age 15; 70% of women screened twice in a lifetime for cervical cancer (by age 35 and 45); 90% of women identified with cervical disease receive treatment.[6] HPV vaccine has been endorsed as the most effective approach for preventing HPV infection and associated diseases. The United States, Australia, Canada, and the United Kingdom were among the first countries to introduce HPV vaccine into national immunization programs.[7] Population-level impact of HPV vaccine has been evidenced by many prior studies,[8-10] and a

recently published study following over 2,000 women from Nordic countries who have received three doses of quadrivalent HPV vaccine for 14 years demonstrated a remarkable 100% effectiveness against HPV16/19-related high-grade cervical dysplasia.[11]

It was not until July 2016, a decade after the first HPV vaccine's licensing in the United States, when the first commercial HPV vaccine, Cervarix, was approved to use in mainland China.[12] The first Chinese domestic HPV vaccine (Cecolin), a bivalent vaccine against HPV 16 and 18, was licensed by the Chinese Food and Drug Administration in Dec 2019 and priced only half of Cervarix.[13] However, HPV vaccine coverage rate remains low. As of March 2021, there are no HPV vaccination programs in China. According to an online cross-sectional survey of 4,220 female students from 136 Chinese universities in 2019, only 11% of participants reported have received HPV vaccine.[14] An even lower HPV vaccination coverage level (3.6% among females, 1.9% among males) was found in another online survey of college students in 2019.[15] The low rate of HPV vaccination is attributable to many causes, including late introduction of HPV vaccines, high out-of-pocket costs, lack of awareness, and misunderstandings about HPV and HPV vaccines among the public.[15 16]

Cost-effectiveness analysis is widely used to evaluate the public health and economic value of health interventions and policies. A number of systematic reviews have assessed cost-effectiveness models evaluating HPV vaccination programs across different policy settings.[4 17-19] However, none of them have focused on Chinese context. Although most suggested that HPV vaccination

programs were likely to be cost-effective in many settings, some reached discordant conclusions. Many contextual and methodological factors may affect the estimated cost-effectiveness of HPV vaccination, such as baseline risk of HPV infection, uptake of cervical cancer screening and treatment, analytical perspective, model design, cost of vaccine, vaccine efficacy and duration of protection, and comparison strategies.[19-21] Therefore, caution should be taken when interpreting or extending these study findings and when developing new economic models. Given the increasing awareness of HPV and availability of HPV vaccines (more options and lower price) among the public, a targeted review of latest cost-effectiveness models of HPV vaccination in the setting of China will be of substantial value for public health policy making. Furthermore, an understanding of the range of methods and assumptions used in analyzing the cost-effectiveness of HPV vaccination can help guide future modeling development efforts.

We executed a systematic review of published cost-effectiveness studies of HPV vaccination in China. We comprehensively compared differences in cost-effectiveness results of various HPV vaccination programs alone, in addition to, or in combination with other cervical cancer prevention interventions as a result of various modeling methods, designs and assumptions.

Methods

Search Strategy

We performed a systematic review of literature published in English and Chinese following the PRISMA guidelines[22] for reporting of systematic reviews (Supplementary Appendix Table S1). The systematic literature search was conducted in databases MEDLINE (PubMed), and EMBASE for articles in English, as well as in databases China National Knowledge Infrastructure (CNKI) and Wanfang Data for articles in Chinese. We developed search terms using a combination of the following keywords: 'HPV/cervical cancer', 'vaccine', 'cost-effectiveness' and 'China' (see Supplementary Appendix Table S2, S3 for detailed search strategies). Corresponding key terms in Chinese were used in searching Chinese databases. Our searches covered all published literature up to our last search on January 2, 2021 with no limitations on publication date.

Selection Criteria

Cost-effectiveness studies fulfilling the following selection criteria were included in review: (1) studies focusing on HPV vaccination interventions explicitly, alone or in combination with other interventions; (2) studies analyzing the cost-effectiveness of HPV vaccination using a modeling approach, excluding those where costs were not assessed or using a non-modeling approach; (3) studies conducted in the setting of China (including the special administrative regions of Hong Kong and Macau), excluding those examining a broader context where China was only a subregion in the analysis; (4) studies published as full-length original research

articles, excluding conference abstracts and commentaries, to ensure sufficient details were provided (in the manuscript or supplementary appendix) for the information required for this review.

Data Extraction and Analysis

Information pertaining to the cost-effectiveness results and different contextual and methodological factors aforementioned that might influence cost-effectiveness results was extracted for each selected study. These factors were generally grouped in four categories: (1) study design, including both model structural design and analytical design; (2) HPV vaccine, such as type, efficacy, price and other assumptions; (3) HPV vaccination strategies compared and evaluation approach; and (4) uncertainty analysis and study quality. Data extraction was independently performed by two reviewers (WS and XC) and any differences were resolved with a third reviewer (HW or XZ). For articles published in Chinese, data extraction was conducted in the original language and translated into English for analysis.

We converted cost-effectiveness results and unit cost for vaccine from all studies in different currencies and years to 2021 USD according to the Consumer Price Index Inflation and USD/CNY exchange rate in January 2021 (1USD=6.5CNY). For studies where the currency year was not stated, we assumed it to be the year of the study's publication. We also provided an assessment of the reviewed economic evaluations using the Consensus on Health Economic Criteria (CHEC)-list[23] to determine the percentage of checklist items (a total of 19) that each study met as a score for study quality. Given the heterogeneity in modeling designs and methods, study population (e.g., girls/women of different ages), interventions (e.g.,

type of vaccine), health outcomes, comparator strategies, as well as some practical challenges (e.g., no sample size for weight assignment), a meta-analysis is rarely feasible for cost-effectiveness outcomes and thus was not performed in this study.[24]

Patient and Public Involvement statement

Neither patients nor the public were involved in this review.

Protocol Registration

This review was not previously registered.

Results

Figure 1 presents a flow diagram of the study search and selection process. A total of 136 articles (69 in English and 67 in Chinese) were identified after removing the duplicates (N=78). Following screening of titles and abstracts, 35 full text articles were evaluated, among which 14 met the selection criteria (ten in English and four in Chinese) and were included for review.[13 25-37] Of these 14 included studies, all were published after 2010 and 12 after 2016 (the year when the first HPV vaccine was licensed to use) (Table 1). Most studies evaluated HPV vaccination at the national level (8/14), as opposed to focusing on one providence (4/14) or city (2/14). All studies except one (in Hong Kong) were conducted in the setting of mainland China.

Study Design

The majority of studies (13/14) adopted a cohort-based model that stratifies the study population into groups according to each individual's characteristics and health state, whereas only one used an individual-based model (Table 1). In addition to the susceptible and death states, most models considered a similar set of disease states, including different stages of cervical intraepithelial neoplasia/squamous intraepithelial lesion and cervical cancer. Three studies included additional states for HPV infection (stratified by risk level) prior to developing cervical intraepithelial neoplasia, and only two also accounted for genital wart as possible consequence of HPV infection. Although HPV is an infectious disease that is transmitted through sexual contacts, dynamic models that capture changing risk of infection (as a function the number of infectious individuals

in the population at a given time point)[38] were only used in 4/14 studies. The study population simulated in each model were in line with the type of model used, where population of both males and females were considered all in dynamic models to construct transmission dynamics and potential herd immunity (other models considered females only). The majority of models assessed (12/14) considered a lifetime (or 100-year) time horizon to capture all possible long-term benefits and consequences of alternative interventions. Only eight models explicitly described the cycle length used in the model simulation, among which six used a yearly cycle and two used a monthly cycle. Although a shorter cycle may better capture the continuous-time reality and incidence of HPV infection during the period,[39] yearly cycles may have limited impact on biasing cost-effectiveness results given the long incubation period but can help reduce computation time. In estimating relevant costs, over half studies (7/12) framed their analysis from the perspective of healthcare sector/payer, two from the perspective of government, and only three adopted a broader societal perspective, whereas two did not explicitly report their perspectives. Out of the 14 studies, 11 used utility-based measure for health outcomes, such as quality-adjusted life years (QALYs) and disability-adjusted life year (DALYs), while the remaining estimated health benefits in the unit of life year saved or death averted. A 3% discounting rate was universally applied in all studies (except one whose discounting rate was unreported). Model calibration and validation are both recommended by modeling guidelines and are critical steps to establish the credibility and reliability of economic models against empirical data.[40]

[41] However, only nine studies incorporated either calibration or validation (two performed both) in their analysis.

HPV Vaccine

The type of HPV vaccine modeled and pertaining features and assumptions varied across different studies (Table 2). All studies focused on the vaccination of females only. While in most studies (12/14) vaccination was considered to be implemented among preadolescent girls under age 18 (before sexual debut); two studies focused on vaccination at the age of 18-25, one examined HPV vaccination at different ages between 12-55, and one also considered expanded catch-up programs among females aged 16-39 (the primary program still focused on preadolescent girls). Different types of vaccine were considered in different studies: eight studies focused on a bivalent vaccine, one on a quadrivalent vaccine, one on a nonavalent vaccine, two compared all these three types in one study, while two did not specify the valence of vaccine. Three-dose schedule was considered in nine studies; the remaining either assumed a two-dose schedule or did not report required doses. Although most models derived estimates for vaccine efficacy against cervical cancer and other HPV-related disease states from real-world data (clinical trials or observational studies), a few studies (5/14) assumed a 100% vaccine efficacy, which might result in possible overestimation for the impact and cost-effectiveness of HPV vaccine. Regarding vaccination coverage for the modeled interventions, half studies assumed a 70% coverage in their primary analysis (which may vary in sensitivity analysis), following by a coverage level of 100% (3/14), 80% (1/14), 50% (1/14) and 20% (1/14), while one aimed to explore

different coverage levels (25%, 50%, 75%). Most studies (13/14) assumed lifelong vaccine protection (in which one also explored other durations of protection) while only one considered a waning of immunity over time. Cost of vaccination, including medical cost for multiple doses and relevant administration cost, varied between studies on different types of vaccine ranging from 54.2 to 663 USD. Most (8/14) chose a cost between 300-500 USD. The first domestic vaccine was analyzed in Zou et al.[13] study that was priced at 99.8 USD per vaccination (in 2019 USD).

Cost-effectiveness of HPV Vaccination Strategies

Despite no established cost-effectiveness threshold in China, almost all studies used the heuristic cost-effectiveness threshold proposed by the WHO based on local gross domestic product (GDP) per capita, even though two studies did not use a utility-based measure for health outcomes (Table 3). The only exception was one that used an extended cost-effectiveness framework whose primary outcome was not incremental cost-effectiveness ratio (and thus did not specify the threshold). Various HPV vaccination strategies were assessed in the reviewed studies. Eight studies examined the impact and cost-effectiveness of HPV vaccination programs incremental to either existing screening programs or opportunistic vaccination programs or none at all, among which three stratified their analysis by different vaccination coverage levels, different ages of vaccination, and different income levels of target population. Although these eight studies sought to address slightly different study questions, they appeared to reach a consistent conclusion that HPV vaccination was cost-effective. One study examining the effect of vaccination age showed that vaccination was cost-effective

at any age under 23 years in rural and any age under 25 years in urban areas. One study compared the value of nonavalent vaccine to quadrivalent and bivalent vaccine for the prevention of cervical cancer and found it not cost-effective unless the nonavalent vaccine could be priced lower than 550 and 450 USD for the full doses (as opposed to 663 USD used in the study, in 2017 USD), respectively. The other five studies, on the other hand, analyzed combination strategies for HPV vaccination with various HPV screening methods or frequencies, three of which also created cost-effective frontiers to identify an optimal strategy. However, findings of these studies were less consistent, and sometimes contradictory. Canfell et al. study examined the association between cost-effectiveness of HPV vaccination strategies (in combination with screening interventions) and cost per vaccinated girl (CGV), and found strategies involving vaccination would be cost-effective only at CVGs of 50–54 USD or less (if CVG>54 USD, screening-only strategies would be more cost-effective).[25] Ma et al. study found that the addition of universal vaccination to screening programs was not cost-effective unless with at least a 50% reduction on the vaccine price (from 451 to 226 USD).[32] The optimal combination of vaccine type and screening method identified in Mo et al. study was nonavalent vaccination and visual inspection with acetic acid (VIA).[33] However, another finding of this study was that quadrivalent and nonavalent vaccine both denominated bivalent vaccine regarding the cost-effectiveness, conversely to Jiang et al.'s results.[27] Although Song et al. showed that the combination of vaccination at age 15 and screening twice in a lifetime (at age 35 and 45) was cost-effective compared to no intervention, but it was not cost-effective when

compared to only screening twice in a lifetime (optimal strategy).[35] Zou et al. was the only study that included the domestic vaccine in their analysis (with lower price than the imported vaccines) and they identified the optimal strategy to be vaccination with careHPV screening once every five years.[13] They also determined that adding vaccination to screening programs would be consistently more cost-effective than screening alone when vaccination cost could be lower than 50 USD.

Uncertainty Analysis and Study Quality

To assess model uncertainty, many studies explicitly incorporated sensitivity analysis (SA), including one-way SA (in ten studies), two-way SA (in one study), and probabilistic SA (in five studies) (Table 3, some studies incorporated multiple types of SA). Among those performed one-way SA, the parameters that cost-effectiveness results were most sensitive to included discounting rate, cost of vaccine, and vaccine efficacy. Quality assessment of the reviewed studies against the CHEC-list suggested that most of them upheld a high level of quality in reporting, with an average score of 85 and ranging from 53 to 100 (where 100 represented 100% of checklist items were complied with) (Supplementary Appendix Table S4).

Discussion

To our knowledge, this study provides the first systematic review on the cost-effectiveness of introducing HPV vaccination programs in the setting of China. In this review, we performed a comprehensive and in-depth assessment of 14 model-based cost-effectiveness studies regarding their findings, study design, and assumptions for HPV vaccine and vaccination programs. Despite considerable heterogeneity in the methodologies used in different models, our findings show that HPV vaccination is estimated to have substantial potential to be a cost-effective addition to existing/other cervical cancer prevention interventions in China. However, the cost-effectiveness of HPV vaccination is likely to depend on considerations such as cost of vaccination, age of vaccination, vaccine efficacy, as well as complementary and/or competing strategies (e.g., cervical cancer screening).

Among all the influential factors, cost of vaccine was consistently identified as a key determinant for the cost-effectiveness of HPV vaccination. Cost estimates varied considerably across studies for different vaccines and years; acquiring more reliable evidence on vaccine cost will help reduce uncertainty surrounding cost-effectiveness results. Six of the reviewed studies performed additional threshold analysis to determine the cost at which adding HPV vaccination to cervical cancer screening programs would become/remain (more) cost-effective. While three studies suggested disparate thresholds for the cost per fully vaccinated girl/woman ranging from 226 to 689 USD, findings of the other three were more consistent showing a lower threshold of 50 USD. The Zou et al. study assessed the first

domestic bivalent HPV vaccine at a unit cost of 99.8 USD, substantially cheaper than the imported vaccines.[13] Given more domestic vaccines under development and growing initiatives to include HPV vaccine into national immunization program, further reduction in vaccine price and improved cost-effectiveness is attainable in the foreseeable future. Furthermore, some other characteristics and assumptions of HPV vaccine and vaccination programs were also found to be associated with increased cost-effectiveness of HPV vaccination, such as higher vaccine efficacy, longer duration of vaccine immunity, younger age being vaccinated, and higher vaccination coverage (although most models did not account for herd immunity).

Findings of the reviewed studies were generally consistent with other systematic reviews focusing on cost-effectiveness of HPV vaccination in low- and middle-income countries.[19 42 43] Most of these studies concluded that vaccination was likely to be cost-effective, particularly in contexts without organized cervical cancer screening programs. On the contrary, HPV vaccination, regardless of the type of vaccine and modeling design, was more consistently found in high-income countries,[44 45] due in large to higher willingness to pay thresholds and vaccine uptake. Based on the summary of evidence, a few recommendations may be provided for implementing HPV vaccination programs to enhance its cost-effectiveness. HPV vaccine is most recommended for routine vaccination for girls at younger age (before 16) while will still remain valuable for women of older age (under 23 years in rural and under 25 years in urban areas) according to one reviewed study that explored different vaccination ages.[29] The US Centers for Disease Control and Prevention recommended vaccination for everyone (including

men) at age 11 through age 26 years.[46] In the United Kingdom, men and women aged 12 to 13 years are routinely offered HPV vaccination and can access free vaccination up until their 25th birthday.[47] Regarding the type of vaccine for recommendation, two studies reached contradicting conclusions about the relative cost-effectiveness between nonavalent, quadrivalent and bivalent vaccines. This difference is likely attributable to disparate costs applied for different vaccines in the two models. In Jiang et al.'s model,[27] nonavalent vaccine was assumed to be 60% and 116% more expensive than quadrivalent and bivalent vaccines, respectively, while it costed only 11% more than the other two vaccines in Mo et al.'s study.[33] Future investigations of different vaccines and their pricing, efficacy and population impacts may be required for more rigorous recommendation strategies. Meanwhile, the reviewed studies demonstrated strong synergies between HPV vaccination and cervical cancer screening that the greatest public health benefits, and sometimes also the optimal strategy, could be achieved only when these two interventions were implemented simultaneously. However, in identifying the optimal combination strategies, two studies indicated that screening alone might outperform strategies with the addition of HPV vaccination, while there was less consistency regarding the screening methods (pap, VIA or careHPV test) and testing frequencies. Given current low uptake of screening in China, establishing appropriate strategies to substantially expand cervical cancer screening should be prioritized prior to or simultaneously with implementing HPV vaccination programs.

From the methodological point of view, a few recommended model design and practice may be highlighted for future modeling efforts. First, a key finding of this review was that the majority of reviewed studies applied a static model in simulating HPV infection that was unable to capture potential herd immunity when HPV vaccination reached a high level of coverage. According to the modeling guideline, dynamic design is important to consider when an intervention affects a pathogen's ecology or when the intervention affects disease transmission.[38] Incorporating dynamic design will ensure capturing the indirect effects of HPV vaccination that arise from averted infections, i.e., individuals not reached by the vaccination program can still benefit by experiencing a lower infection risk. However, applying such a dynamic model may require modeling the population of men (who are non-recipients of HPV vaccine) as well as additional model parameters. Second, cost-effectiveness models are built upon various input data and assumptions and are inevitably subject to uncertainty. Handling model uncertainty is important and can help assess the robustness of model results and enhance our confidence in a chosen course of action. Model calibration and SA are both recommended practices[40] to address uncertainty but were not performed in all models (calibration in 7/14 models, sensitivity analysis in 12/14 models). For the conduct of uncertainty analysis, we also recommend carefully choosing uncertainty ranges for parameters to meaningfully reflect their plausible values (rather than imposing an arbitrarily range) and explicitly reporting the rationale. Third, although cervical cancer is the primary disease following HPV infection, it is also important to account for other possible consequences and diseases, without

which the impact and cost-effectiveness of HPV vaccination may be underestimated.

Our review may have some limitations. First, we did not attempt to exhaustively include all aspects and assumptions of a model in this review (such as utility estimates, force of infection, disease progression) but only the ones we believed were most influential on cost-effectiveness results. Second, the quality of evidence used to support a model is another central factor in ensuring credibility and reliability of model inferences but was not assessed in this review. Third, we were unable to perform a meta-analysis due to the variability across studies in the strategies evaluated and outcomes reported. Nevertheless, all studies have compared the estimated cost-effectiveness with the WHO-CHOICE cost-effectiveness benchmark using local (national, provincial, or city-level) GDP per capita, providing a consistent criterion across studies.

The body of evidence from this systematic review of cost-effectiveness modeling studies on HPV vaccine suggests that implementing HPV vaccination programs for young girls is likely warranted in China and should be paired with expansion of cervical cancer screening to maximize their impact. Cost of vaccination was found to significantly affect the cost-effectiveness estimates and policy recommendations. As domestic vaccines become available and their prices continue to drop, HPV vaccination will become a more viable option in designing cervical cancer prevention programs. Future modeling studies following established best-practice standards are needed to reduce decision uncertainty and definitively establish the cost-effectiveness of HPV vaccination in combination with screening programs.

Contributors

WS and TC conceptualized the study. WS, XC conducted data collection. WS, HW and XZ performed data analyses. WS and TC wrote the first draft of the article. XC, HW and XZ helped to interpret results and critically revise the manuscript. All authors approved the final draft.

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Competing interests

The authors have no conflicts of interest to declare.

Data sharing statement

There is no additional unpublished data associated with this study. All data are available in the manuscript and supplementary appendix.

Ethical Approval Statement

Not applicable

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Figure 1. Flow diagram of study selection
Legend: CEA: cost-effectiveness analysis

Table 1. Study design of selected modeling studies

Reference	Year of publication	Setting	Model type	Disease states modelled	Study population	Timeframe (cycle length)	Perspective	Discount rate	Health measure	Calibration /validation	Year of cost
Canfell	2011	Shanxi Province (rural)	Cohort, Dynamic	CIN (3), cervical cancer	Males + females (of all ages)	Lifetime (1 year)	Societal	3%	Life year	Calibration	2010
Choi	2018	Hong Kong	Cohort dynamic (for transmission) + individual-based (for disease)	CIN (3) Cervical cancer: 4 stages+ asymptomatic/symptomatic	Males + females (10-85 years)	Lifetime (1 month)	Societal	3%	Life year, QALY	Calibration	2018*
Jiang	2019	China	Cohort, Static	Cervical cancer	Females of 16 years	Lifetime (unclear)	Healthcare payer	3%	DALY	No	2017
Levin	2015	China	Individual, Static	CIN (3), cervical cancer	Females (9 years and older)	Lifetime (1 month)	Government	Unclear	Deaths averted	Calibration	2009
Liu	2016	China (rural, urban)	Cohort, Static	CIN (3), cervical cancer	Females of 12-55 years	Lifetime (1 year)	Healthcare payer	3%	QALY	Calibration, Validation	2016*
Luo P	2020	Wuhan City	Cohort, Static	Cervical cancer	Females of 12 years	Lifetime (unclear)	Unclear	3%	DALY	No	2020*
Luo Y	2020	Zhejiang Province	Cohort, Static	High-risk HPV infection Low-grade SIL High-grade SIL Cervical cancer	Females of 12 years	Lifetime (1 year)	Government	3%	QALY	No	2020*
Ma	2020	China	Cohort, Dynamic	HPV infection (high/low-risk) CIN (3) Cervicl cancer Genital wart	Females (of all ages)	50 years (1 year)	Unclear	3%	DALY	Calibration	2020
Mo	2017	China	Cohort, Static	HPV infection (high/low-risk) CIN (3) Cervicl cancer Genital wart	Females of 12 years	Lifetime (1 year)	Societal	3%	QALY	Calibration	2015
Qie	2017	Zhejiang Province	Cohort, Static	CIN (3), cervical cancer	Females of 18-25 years	Unclear (unclear)	Healthcare sector	3%	QALY	No	2017*
Song	2017	China	Cohort, Dynamic	CIN (3), cervical cancer	Males + females	100 years (unclear)	Healthcare sector	3%	Life year	Validation	2017*
Sun	2017	Jiangsu Province	Cohort, Static	CIN (3), cervical cancer	Females of 18-25 years	Lifetime (unclear)	Healthcare sector	3%	QALY	No	2017*
Zhang	2016	China (rural, urban)	Cohort, Static	CIN (3), cervical cancer	Females of 12 years	Lifetime (unclear)	Healthcare payer	3%	QALY	Validation	2013
Zou	2020	China	Cohort, Static	CIN (3), cervical cancer	Females of 9-14 years	Lifetime (1 year)	Healthcare sector	3%	QALY	Calibration, Validation	2019

Legend: * no year of cost reported, using publication year instead. CIN (3): cervical intraepithelial neoplasia (3 stages); SIL: squamous intraepithelial lesion; QALY: quality-adjusted life year; DALY: disability-adjusted life year.

Table 2. Model assumptions and parameters for HPV vaccine evaluated

Reference	Age of vaccination	Vaccine type	No. of doses	Vaccine efficacy	Vaccine coverage	Duration of protection	Unit cost reported*	Unit cost in 2021 USD ($)
Canfell	15	Unspecified	3	100%	70%	Lifelong	Varied in the analysis	Varied in the analysis
Choi	12	Nonavalent	2	95.5% (90.0%-98.4%) for HPV-16 95.8% (84.1%-99.5%) for HPV-18 96.0% (94.4%-97.2%) for HPV-OV 0% for HPV/NV	25%, 50% and 75%	20 years, 30 years and lifelong (various scenarios)	284 USD	$303.1
Jiang	16	Bivalent Quadrivalent Nonavalent	Unclear	100%	100%	Lifelong	Nonavalent: 628 USD Quadrivalent: 393 USD Bivalent: 291 USD	Nonavalent: $682.5 Quadrivalent: $427.1 Bivalent: $316.3
Levin	<12	Unspecified	3	100%	70%	Lifelong	46 USD	$61.1
Liu	12-55	Bivalent	3	93.2% against CC 64.9% against CIN2/3 50.3% against CIN1	70%	Lifelong	1954 CNY	$333.2
Luo P	12	Bivalent	3	95% (63%-100%)	100%^	Lifelong	1999 CNY	$308.4
Luo Y	12	Bivalent	2	76.78% (40%-100%)	70%	Lifelong	1040 CNY	$160.4
Ma	9-16	Quadrivalent	Unclear	78.9% (74.5%-82.4%)	50%	5% rate of immunity waning	451 USD	$452.3
Mo	12	Bivalent Quadrivalent Nonavalent	3	Bivalent: 80.7% (57.5%-98.9%) Quadrivalent: 81.5% (58.8%-98.2%) Nonavalent: 90.8% (66.5%-100%)	20% (10%-100% in SA)	Lifelong	Bi/Quadrivalent: 408 USD Nonavalent: 452 USD	Bi/Quadrivalent: $459.6 Nonavalent: $509.1
Qie	18-25	Bivalent	3	100%	80%	Lifelong	1842 CNY	$308.0
Song	Primary: 15 Expanded: 16-39	Bivalent	3	100%	70%	Lifelong	1995 CNY	$333.6
Sun	18-25	Bivalent	3	94.2% (62.7%-99.9%)	100%^	Lifelong	2000 CNY	$334.4
Zhang	12	Bivalent	3	93.2% (78.9%-98.7%) against CC 64.9% (52.7%-74.9%) against CIN2/3 50.3% (40.2%-58.8%) against CIN1	70%	Lifelong	301 CNY	$54.2
Zou	9-14	Bivalent	2	94% (80%-99%)	70% (50-95% in SA)	Lifelong	99.8 USD	$104.7

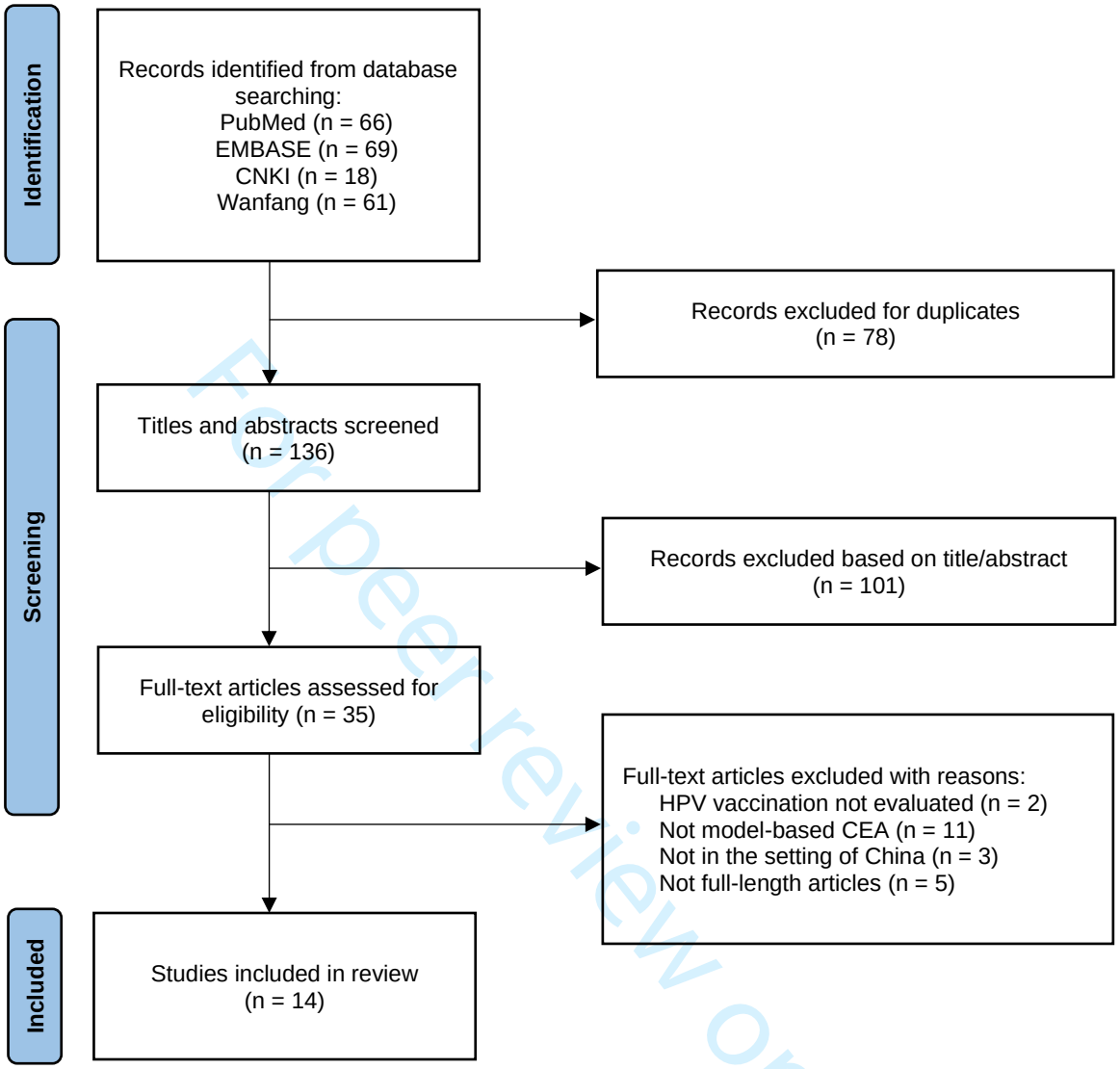
Legend: * total cost per girl/woman vaccinated, including medical cost for multiple doses and other relevant costs (e.g., vaccine administration). ^ among individuals with negative screening results. CC: cervical cancer; CIN: cervical intraepithelial neoplasia; OV: other five high-risk HPV targeted by the nonavalent vaccine; NV: non-vaccine high-risk HPV; CNY: Chinese yuan; SA: sensitivity analysis.

Table 3. Cost-effectiveness of HPV vaccination strategies

Reference	Intervention	Comparator	ICER reported	ICER in 2021 USD ($)	Threshold	Conclusion	Sensitivity analysis	Most sensitive parameters
Canfell	Combination of: vaccination and different screening strategies (with different frequencies)	No vaccination, no screening	-	-	GDP^: 3,077 USD	Strategies involving vaccination would be cost-effective at CVGs of 50–54 USD or less, but at CVGs > 54 USD, screening-only strategies would be more cost-effective	One-way, probabilistic	Discounting rate Cost of HPV screening Duration of protection
Choi	Vaccination (routine) at different coverage levels	Opportunistic vaccination (12% coverage)	-	-	GDP^: 40,099 USD	Cost-effective across all three vaccination coverage levels. Wil remain cost-effective if the cost of fully vaccinating one girl is no greater than 689 646–734) USD, respectively.	Probabilistic	-
Jiang	Nonavalent vaccine	Quadrivalent, bivalent vaccine	35,000 USD/DALY vs. quadrivalent 50,455 USD/DALY vs. bivalent	$38,040/DALY vs. quadrivalent $54,837/DALY vs. bivalent	1-3 * GDP^: 8,640 USD	Not cost-effective compared with the quadrivalent and the bivalent vaccines. To be cost-effective, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively	One-way	Discounting rate CC mortality Age of vaccination
Levin	Vaccination (targeting different income groups) + screening	Screening only	10,920 - 13,277 USD per death averted	$14,504 - $17,635 per death averted	-	Cost-effective across all income groups. Would remain cost-effective if the cost is less than 50 USD per vaccinated girl.	One-way	Not reported
Liu	Vaccination (at different ages) + Pap test	Pap test only	Varied by age	-	1-3 * GDP^: 41,908 CNY	Vaccination is cost-effective at any age under 23 years in rural and any age under 25 years in urban areas. Catch-up vaccination to the age of 25 years in addition to routine vaccination in 12-year-old in both rural and urban can be cost-effective.	No	-
Luo P	Vaccination	No vaccination	83,496 CNY/DALY	$12,881/DALY	1-3 * GDP^: 52,000 CNY	Very cost-effective	One-way	Discounting rate Cost of vaccine Cost of CC treatment
Luo Y	Vaccination	No vaccination	12,472 CNY/QALY	$1,924/QALY	1-3 * GDP^: 92,100 CNY	Very cost-effective	One-way	Cost of vaccine Discounting rate QALY estimates
Ma	Combination of: universal vaccination (coverage : 0%-90%) and screening (coverage: 20%-70%)	Status quo (0% vaccination coverage and 20% screening coverage)	-	-	1-3 * GDP^: 10,264 USD	The addition of universal vaccination to screening programs is not cost-effective. The vaccine requires at least a 50% price reduction to be cost-effective.	Probabilistic	-
Mo	Combination of: different types of vaccination and screening methods	No vaccination, no screening	-	-	1-3 * GDP^: 7,960 USD	Optimal: nonavalent vaccination + VIA screening. Quadrivalent/nonavalent vaccine, in combination with current screening strategies, is highly cost-effective and dominates bivalent vaccine	One-way	Vaccine efficacy Cost of vaccine Discounting rate
Qie	Vaccination + Pap test	Pap test only	43,490 CNY/QALY	$7,272/QALY	1-3 * GDP^: 52,000 CNY	Very cost-effective	No	-
Song	Combination of: different vaccination (at different ages) and VIA/VILI screening (with different frequencies) strategies	No vaccination, no screening	-	-	1-3 * GDP^: 50,696 CNY	Vaccination (at age 15) + screening twice in a lifetime (at age 35 and 45) is cost-effective compared to no intervention. Optimal: screening twice in a lifetime*	One-way	Discounting rate Cost of vaccine Vaccine coverage

Sun	Vaccination + Pap test	Pap test only	43,489 CNY/QALY	$7,272/QALY	1-3 * GDP^: 52,000 CNY	Very cost-effective	One-way	Discounting rate Vaccine efficacy Cost of vaccine
Zhang	Vaccination + screening	Screening only	Rural: 11,365 CNY/QALY Urban: 6,124 CNY/QALY	Rural: $2,047/QALY Urban: $1,103/QALY	1-3 * GDP^: 41,908 CNY	Very cost-effective. Would remain very cost-effective if vaccine cost is below 630 CNY in rural and 750 CNY in urban; and remain cost-effective if below 1,700 CNY in rural and 1,900 CNY in urban	One-way, two-way, probabilistic	Cost of vaccine Discounting rate HPV infection rate
Zou	Combination of: vaccination and various screening methods with different frequencies	No vaccination, no screening	-	-	1-3 * GDP^: 10,276 USD	Optimal: vaccination + careHPV screening every 5 years. Strategies that combined vaccination and screening would be more cost-effective than screening alone strategies when the vaccination cost was less than $50	One-way, probabilistic	-

Legend: * based on analysis of the reported cost-effectiveness frontier outcomes (rather than what the authors reported); ^ GDP: gross domestic product per capita. ICER: incremental cost-effectiveness ratio; CVG: cost per vaccinated girl; VIA: visual inspection with acetic acid; CC: cervical cancer; CNY: Chinese yuan; QALY: quality-adjusted life year; DALY: disability-adjusted life year.



Supplementary Appendix

Table S1 PRISMA Checklist

Section / topic	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro, par 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro, par 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, par 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, par 1-2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, par 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, par 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, par 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, par 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, par 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, par 4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, par 4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, par 1

characteristics			
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 20).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	Results, par 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, par 1-2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, par 5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, par 3-4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgement

Intro: introduction; par: paragraph; NA: not applicable

Table S2 Search strategy and key terms in PubMed and EMBASE databases

	AND	AND	AND	AND
OR	Human papillomavirus	Vaccine	Cost-effectiveness	China
OR	HPV	Vaccination	Cost-benefit	
OR	Cervical cancer	Immune*	Cost-utility	
OR			Cost-effective	
OR			Model*	
OR			Economic evaluation	
OR			Pharmacoeconomic*	

The search was conducted by title/abstract.

Table S3 Search strategy and key terms in China National Knowledge Infrastructure and Wanfang databases

	AND	AND	AND	AND
OR	人乳头瘤病毒	疫苗	成本效用	中国
OR	HPV	免疫	成本收益	
OR	宫颈癌		成本效益	
OR			成本效果	
OR			模型分析	
OR			经济学评价	
OR			药物经济学评价	

The search was conducted by title/abstract

Table S4 Quality assessment of model reporting using CHEC-list

Checklist item	Canfell	Choi	Jiang	Levin	Liu	Luo P	Luo Y	Ma	Mo	Qie	Song	Sun	Zhang	Zou
1. Is the study population clearly described?	1	1	1	1	1	1	1	1	1	1	0	1	1	1
2. Are competing alternatives clearly described?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
3. Is a well-defined research question posed in answerable form?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
4. Is the economic study design appropriate to the stated objective?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
5. Is the chosen time horizon appropriate in order to include relevant costs and consequences?	1	1	1	1	1	0	1	1	1	0	1	1	1	1
6. Is the actual perspective chosen appropriate?	1	0	1	0	1	0	1	0	1	0	1	1	1	1
7. Are all important and relevant costs for each alternative identified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
8. Are all costs measured appropriately in physical units?	1	1	1	1	1	1	1	1	1	0	1	1	1	1
9. Are costs valued appropriately?	1	0	1	1	0	0	0	1	1	0	0	0	1	1
10. Are all important and relevant outcomes for each alternative identified?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
11. Are all outcomes measured appropriately?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
12. Are outcomes valued appropriately?	N/A	1	0	N/A	1	0	1	1	1	0	N/A	1	1	1
13. Is an incremental analysis of costs and outcomes of alternatives performed?	1	1	1	NA	1	1	1	1	1	1	1	1	1	1
14. Are all future costs and outcomes discounted appropriately?	1	1	1	0	1	1	1	1	1	1	1	1	1	1
15. Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	1	1	1	1	0	1	1	1	1	0	1	1	1	1
16. Do the conclusions follow from the data reported?	1	1	1	1	1	1	1	1	1	1	1	1	1	1
17. Does the study discuss the generalizability of the results to other settings and patient/client groups?	1	1	0	1	1	0	1	0	1	0	0	0	1	1
18. Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	1	1	1	1	1	0	1	1	1	0	1	0	1	1
19. Are ethical and distributional issues discussed appropriately?	1	0	0	1	1	0	0	1	1	0	0	0	1	0
Total % of Yes	100%	84%	84%	88%	89%	63%	89%	89%	100%	53%	78%	79%	100%	95%

‘‘1”: meets the assessment criteria; “0”: does not meets the assessment criteria; N/A: not applicable.

PRISMA Checklist

Section / topic	#	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title
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Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Intro, par 4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Intro, par 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Methods, par 1
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Methods, par 1-2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Methods, par 1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Methods, par 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Methods, par 3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Methods, par 4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	NA
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Methods, par 3
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Methods, par 4
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Methods, par 4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Results, par 1

characteristics			
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 20).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies.	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression	Results, par 5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Discussion, par 1-2
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Discussion, par 5
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Discussion, par 3-4
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Acknowledgement

Intro: introduction; par: paragraph; NA: not applicable