

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	The cost-effectiveness of human papillomavirus vaccine in China: a systematic review of modeling studies
<b>AUTHORS</b>	Shi, Wenchuan; Cheng, Xiaoli; Wang, Haitao; Zang, Xiao; Chen, Tingting

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Saba Abidi Delhi Pharmaceutical Sciences and Research University
<b>REVIEW RETURNED</b>	14-May-2021

<b>GENERAL COMMENTS</b>	<p>It is a very interesting article which focuses on a very specific public health intervention, however the presentation of the results should be improved. Likewise, the analysis and interpretation of the results of the discussion should be done in greater depth to help in decision-making.</p> <p>Introduction para 4 Please provide references for the information provided in this section.</p> <p>Introduction para 5 Please write about the outcomes of the study. write about the beneficiaries of the results of the your study</p> <p>Methods In this section, the presentation of information should be improved and the inclusion and exclusion criteria should be more clearly presented. Considering the objective of the study , it is important to evaluate the risk of bias of the included studies.</p> <p>Discussion Please write more elaborately about the effects of different aspects of vaccine on the ICER of HPV vaccine. For example: the effect of vaccine efficacy on ICER, What is the effect of the increase or decrease in the efficacy of the vaccine on ICER? Answer this question for all the aspects of vaccine like, duration, age, coverage etc. The discussion should explain and analyse the different sensitivity analysis carried out and their impact on the ICER.</p> <p>Main text: Language editing</p>
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<b>REVIEWER</b>	Jinghua Li Sun Yat-Sen University, School of public health
<b>REVIEW RETURNED</b>	11-Oct-2021

<b>GENERAL COMMENTS</b>	<p>This study gave a comprehensive review on modeling studies of the cost-effectiveness of HPV in China, which is significant for policy makers. The review is well conducted according to review guidelines and is well written. I only have some minor comments for the authors to address.</p> <ol style="list-style-type: none"> <li>1. please unify the words for the currency. Such as US\$, USD.</li> <li>2. some language editing is needed. For example, line 26-27, page 11, “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. ”, usually we do not start a sentence with Arabic number.</li> <li>3. In discussion, add some comparisons with countries in both low-and-middle incomes countries and high-income countries.</li> <li>4. please specify in the method whether this review is registered before the commencement of the study.</li> <li>5. Table 2, the unit cost reported should be specified if the unit refers to one dose or full doses, seems it is full doses</li> <li>6. Table 3, the unit for threshold should be per capita GDP rather than GDP.</li> <li>7. What is the timeframe and timestep used by the included studies, does that make a difference to the cost-effectiveness of HPV. Such as is there any difference in short-term and long-term effect?</li> </ol>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Saba Abidi, Delhi Pharmaceutical Sciences and Research University

Comments to the Author:

It is a very interesting article which focuses on a very specific public health intervention, however the presentation of the results should be improved. Likewise, the analysis and interpretation of the results of the discussion should be done in greater depth to help in decision-making.

Introduction para 4

Please provide references for the information provided in this section.

**RESPONSE: We have now added relevant references for the information provided in this paragraph.**

Introduction para 5

Please write about the outcomes of the study. write about the beneficiaries of the results of the your study

**RESPONSE: As we described in our objective statement in Paragraph, this study aims to compare cost-effectiveness results of various HPV vaccination programs from different studies and identify differences in modeling methods, designs and assumptions that may explain differences in cost-effectiveness outcomes.**

**We also note that the potential beneficiaries of the results of this study were explicated in Paragraph 4:**

*“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.”*

#### Methods

In this section, the presentation of information should be improved and the inclusion and exclusion criteria should be more clearly presented.

**RESPONSE: We have now added revisions to the text in the Methods section to better explicate our process of literature search, article selection, and data extraction and analysis, including adding a detailed description for the types of information we extracted for review and an explanation for why a meta-analysis was not performed (more details can be found in our response to the editor’s last comment). We would also appreciate the reviewer for pinpointing if there is information still unclearly presented following this revision and we are more than happy to make further changes to improve the clarity.**

Considering the objective of the study , it is important to evaluate the risk of bias of the included studies.

**RESPONSE: Please see our response to the editor’s Comment 2 and Comment 4.**

#### Discussion

Please write more elaborately about the effects of different aspects of vaccine on the ICER of HPV vaccine. For example: the effect of vaccine efficacy on ICER, What is the effect of the increase or decrease in the efficacy of the vaccine on ICER? Answer this question for all the aspects of vaccine like, duration, age, coverage etc.

**RESPONSE: Thank you for this suggestion. We have now added more discussion for how different assumptions of the characterizes of vaccine may affect the cost-effectiveness outcomes in Discussion Paragraph 2:**

*“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).”*

The discussion should explain and analyse the different sensitivity analysis carried out and their impact on the ICER.

**RESPONSE: We thank the reviewer for this comment. We note that information for the sensitivity analysis carried out in the reviewed studies was summarized in Table 3 and discussed in Results Paragraph 5. In Discussion, we provided further discussion for how the assumptions about cost and efficacy of vaccine may affect the cost-effectiveness estimate of HPV vaccination (primary findings from the uncertainty analysis review) in Paragraph 2 and the importance (and implications) for performing sensitivity analysis in Paragraph 4:**

*“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<sup>40</sup> 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.”*

Main text: Language editing

Reviewer: 2

Dr. Jinghua Li, Sun Yat-Sen University

Comments to the Author:

This study gave a comprehensive review on modeling studies of the cost-effectiveness of HPV in China, which is significant for policy makers. The review is well conducted according to review guidelines and is well written. I only have some minor comments for the authors to address.

1. please unify the words for the currency. Such as US\$, USD.

**RESPONSE: Thank you for capturing the inconsistent term used. We have now unified all the words for US dollar as USD throughout the manuscript.**

2. some language editing is needed. For example, line 26-27, page 11, “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. ”, usually we do not start a sentence with Arabic number.

**RESPONSE: We have now revised this sentence as follows in Results Paragraph 2:**

*“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)...”*

3. In discussion, add some comparisons with countries in both low-and-middle incomes countries and high-income countries.

**RESPONSE: Thank you for this advice. We have now added further discussion for the comparison of cost-effectiveness estimates of HPV vaccine between high-income and low-and-middle income counties in Discussion Paragraph 3:**

*“On the contrary, HPV vaccination, regardless of the type of vaccine and modeling design, was more consistently found in high-income countries,<sup>44 45</sup> due in large to higher willingness to pay thresholds and vaccine uptake.”*

4. please specify in the method whether this review is registered before the commencement of the study.

**RESPONSE: Thank you for this suggestion. We have now added a new section for *Protocol Registration* information in Methods Paragraph 6:**

*“This review was not previously registered.”*

5. Table 2, the unit cost reported should be specified if the unit refers to one dose or full doses, seems it is full doses

**RESPONSE:** Due to space limitation in the table, more detailed description for the unit cost was included in the table legend and denoted with asterisk (\*) in the table header: “\* total cost per girl/woman vaccinated, including medical cost for multiple doses and other relevant costs (e.g., vaccine administration).”

6. Table 3, the unit for threshold should be per capita GDP rather than GDP.

**RESPONSE:** Due to space limitation in the table, full spell out and more detailed description for the threshold measure was included in the table legend and is now denoted with circumflex (^) in the table header: “^ GDP: gross domestic product per capita”.

7. What is the timeframe and timestep used by the included studies, does that make a difference to the cost-effectiveness of HPV. Such as is there any difference in short-term and long-term effect?

**RESPONSE:** The timeframe used in the included studies was summarized in Table 1 and discussed in Results Paragraph 2 where 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. As for the other two models, the simulation timeframe was 50 years for one and unreported for the other.

**We have now added information for timestep (cycle length) in Table 1 and its potential implications for cost-effectiveness of HPV vaccine in Results Paragraph 2:**

*“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,<sup>39</sup> yearly cycles may have limited impact on biasing cost-effectiveness results given the long incubation period but can help reduce computation time.”*

**Regarding the short-term and long-term effect of HPV vaccine, underlying assumption used for the duration of vaccine protection was summarized in Table 2 and explicated in Results Paragraph 3.**

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Jinghua Li Sun Yat-Sen University, School of public health
<b>REVIEW RETURNED</b>	06-Nov-2021
<b>GENERAL COMMENTS</b>	the authors have addressed all my concerns. I have no further comments.