BMJ Open

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031186
Article Type:	Original research
Date Submitted by the Author:	20-Apr-2019
Complete List of Authors:	Jiang, Y; Sun Yat-Sen University, School of Public Health (Shenzhen) Ni, Weiyi; Tianjin University, School of Pharmaceutical Science and Technology; University of Southern California, Department of Pharmaceutical and Health Economics Wu, Jing; Tianjin University, School of Pharmaceutical Science and Technology
Keywords:	cost-effectiveness, HPV, vaccination, China, cervical neoplasia

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis

Yawen Jiang,[a] Ph.D., Weiyi Ni,[b, c] Ph.D., Jing Wu,[b] Ph.D.

Corresponding Author: Jing Wu

School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, China

Corresponding Email: jingwu@tju.edu.cn; Phone: 0086-15822450465.

[a] School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, Guangdong, China

[b] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, China

[c] Department of Pharmaceutical and Health Economics, University of Southern California, Los Angeles, California, USA

Abstract

Objectives

To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV) vaccine for the prevention of cervical cancer in China.

Design

Health economic modelling using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model populated with China-specific data.

Setting

Individual cervical cancer prevention in China using the 9-valent HPV vaccine from the perspective of private sector purchasers in relation to not receiving vaccination and receiving other HPV vaccines for 16 years old females in China who had not been previously infected with HPV.

Primary outcome measure

Incremental costs per disability-adjusted life year (DALY) prevented.

Results

In the base case, the incremental costs per DALY prevented were US$23,012 when compared with no vaccination. The price thresholds for the 9-valent HPV vaccine to be cost-effective and highly cost-effective in this comparison were $680 and $220, respectively. However, the 9-valent vaccine was cost-ineffective for the prevention of cervical cancers when compared with the bivalent and quadrivalent vaccines. Specifically, the incremental costs per DALY prevented in relation to the bivalent and the quadrivalent vaccines were $35,000 and $50,455, respectively. The cost-effectiveness results were robust in most one-way sensitivity analyses.

Conclusions

Given the different cost-effectiveness inferences when different comparisons were examined, policymakers and clinicians should carefully consider regional economic realities when expanding the use of the 9-valent HPV vaccines in China.

Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia

Strengths and limitations of this study

1. The analyses covered various comparisons and scenarios of interest.

2. We presented not only the cost-effectiveness profiles but also the value-based prices.

3. Only analysed individuals without prior infection.

4. Used a static model instead of a dynamic model and did not consider herd immunity.

5. Did not take into account the prevention of genital warts.

INTRODUCTION

Less than one year after the launch of the bivalent and quadrivalent human papillomavirus (HPV) vaccines in China, the 9-valent HPV vaccine was also approved by the China Food and Drug Administration in April 2018. Unlike the review processes of bivalent and quadrivalent HPV vaccines that took about ten years in China, the review process of 9-valent HPV vaccine took a record short period of nine days.[1] However, the 9-valent HPV vaccine was only approved for use among 16-26 years old females whereas the bivalent and quadrivalent HPV vaccines were approved for use among 9-26 years old males and females.[2]

The cost-effectiveness of bivalent and quadrivalent HPV vaccines for the prevention of cervical cancer has been previously analysed in the setting of China. The results of such analyses endorsed the cost-effectiveness of the bivalent and quadrivalent vaccines compared with no vaccination for the prevention of cervical cancer.[3, 4] However, the previous analyses in the literature were conducted before the introduction of the first HPV vaccine in China. Hence, they used price of vaccines that was far from the present reality. In the meantime, the cost-effectiveness of the 9-valent HPV vaccine in China is still unknown. In light of this, it is important to obtain evidence on the value of the 9-valent vaccine to determine whether it should be used more broadly. As such, the objective of the current study was to analyse the cost-effectiveness of the 9-valent HPV vaccine for the prevention of cervical cancer among Chinese females from the perspective of private sector purchasers because HPV vaccines are neither publicly funded nor reimbursed by any payers to our knowledge. More specifically, this study pertains to the clinical decision setting of whether it is cost-effective for a Chinese female

without previous infection to use the 9-valent HPV vaccine. We compared the 9-valent vaccine with no vaccination, the bivalent vaccines, and the quadrivalent vaccines, respectively. The alternative comparisons were conducted to allow a comprehensive understanding of the health economic profile of the 9-valent vaccine, which is important because even the cost-effectiveness of the bivalent and the quadrivalent vaccines is not without dispute in China.[5]

METHODS

We adapted the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model in the current analysis. The PRIME model is a health economic model developed by the World Health Organization (WHO) that allows country-specific evaluation of HPV vaccination among females without prior infection of HPV.[6, 7] Country-specific cervical cancer incidence, mortality, HPV type distribution, and economic data were built in the model. The model developers assessed the quality of country-specific data as either "satisfactory" or "unsatisfactory", and the Chinese data were deemed "satisfactory".[6] The model calculates the incremental costs per disability-adjusted life year (DALY) prevented for vaccinated individuals over lifetime as well as population outcomes such as cervical cancers prevented and deaths prevented. In addition, the model was validated against previously published HPV vaccine cost-effectiveness studies in the literature. More details of the model have been described elsewhere and in Appendix 1.[6]

The current analysis only examined incremental costs per DALY prevented for vaccinated individuals. Because the intervention of interest in the current analysis is 9-

valent HPV vaccination, we modified the model to use the proportion of cervical cancer that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by International Agency for Research on Cancer (IARC) HPV Information Centre instead of only the proportion that was attributable to types 16/18 in the original model.[7, 8] According to IARC estimates, 92% of cervical cancers in China were attributable to types 16/18/31/33/45/52/58.[8]

The model also permitted customization of target age group, efficacy of vaccine (percent of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer treatment cost, discount rate, and disutility values of three cancer-related health states (cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the customized input fields can override the default data. In the current analysis, default data of efficacy of vaccine, discount rate, and disutility values were used. It should be noted that several other inputs could be customized in the model including coverage rate, birth cohort size, and cohort size at the vaccination age. However, these inputs only affect population outcomes that are not of interest in the current analysis and does not affect the results of the cost-effectiveness results for vaccinated individuals.

In the base-case analysis, the target age group was 16 years old females because this was the youngest group among the current age of licensure of the 9-valent vaccine in China (additional explanation in Appendix 2). It is noteworthy that this was older than the WHO-recommended primary target age window of 9-14 years.[9] The price of 9-valent HPV vaccine in government procurement catalogue as of December 2018 was used.[10, 11] We also assessed the prices at which the incremental costs per DALY prevented were at the cost-effective threshold of three times the 2017 China gross

domestic product (GDP) per capita and at the highly cost-effective threshold of once the 2017 China GDP per capita to inform decision makers the value-based prices. Therefore, the cost-effective threshold and the highly cost-effective thresholds are US$25,920/DALY prevented and US$8,640/DALY prevented, respectively.[12] Default data of vaccine administration costs per person in China in the PRIME model were used but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices in China.[13] In addition, cancer treatment costs in 2015 were updated to 2017 US dollars.[13, 14] Input data are listed in the first panel of Table 1.

Table 1. Input data and model results of the base-case analysis of the 9-valent HPV vaccine and the exploratory analyses of the bivalent and quadrivalent HPV vaccines

Input data		
Parameter	Value	Reference/source
Vaccination age	16 years	NA
Percent of cervical cancers in China attributable to types 16/18/31/33/45/52/58	92.0%	[8]
Percent of cervical cancers in China attributable to types 16/18	69.1%	[8]
9-valent vaccine price for full doses (2017 US$)	$610	[10, 11]
Quadrivalent vaccine price for full doses (2017 US$)	$375	[10, 11]
Bivalent vaccine price for full doses (2017 US$)	$273	[10, 11]
Vaccine administration costs (2017 US$)	$18	Model default with inflation adjustment[13, 11]

Cancer treatment costs (2017 US$)	$7,183	[14, 13]
Efficacy of vaccine	100%	Model default
Discount rate	3%	Base-case assumption
Disutility weight of cancer diagnosis	0.08	Model default
Disutility weight of non-terminal cancer sequelae	0.11	Model default
Disutility weight of terminal cancer	0.78	Model default

Base-case and exploratory results			
	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted net costs	$611	$380	$278
Discounted DALYs prevented	0.0265	0.0199	0.0199
ICER vs. not being vaccinated	$23,012	$19,061	$13,944
ICER of 9-valent vaccine vs. other vaccines	NA	$35,000	$50,455
Price threshold to be cost-effective vs. not being vaccinated	$680	NA	NA
Price threshold to be highly cost-effective vs. not being vaccinated	$220	NA	NA
Price threshold of 9-valent vaccine to be cost-effective vs. other vaccines [a]	NA	$550	$450
Price threshold of 9-valent vaccine to be highly cost-effective vs. other vaccines [b]	NA	$435	$335
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines [c]	NA	$505	$370

Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio measured as incremental costs per DALY prevented; NA, not applicable.

[a] For example, the 9-valent vaccine should be priced at $550 for the full doses to be cost-effective when compared with the quadrivalent vaccine.

[b] For example, the 9-valent vaccine should be priced at $435 for the full doses to be highly cost-effective when compared with the quadrivalent vaccine.

[c] At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when each of them was compared with not receiving vaccination if the price of the 9-valent vaccine is $505 for the full doses. This is equivalent to saying the cost-effectiveness of the 9-valent vaccine vs. the 4-valent vaccine is the same as the cost-effectiveness of the quadrivalent vaccine vs. not receiving vaccination. The interpretation of the comparison vs. the bivalent vaccine is the same.

In one-way sensitivity analyses, age at vaccination (each age between 13-26 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups, cervical cancer mortality, all-cause mortality, cancer treatment costs, and disutility of terminal cancer were varied to examine the robustness of incremental costs per DALY prevented results. Parameters of interest other than age at vaccination and efficacy were increased and decreased by 25%.

Patient and Public Involvement

Patients were not involved.

RESULTS

The base-case results are displayed in the second panel of Table 1 (more detailed information on the base-case results is in Appendix 3). The incremental costs per DALY prevented were US$23,012 when compared with no vaccination. This was slightly less

than the cost-effective threshold but substantially above the highly cost-effective threshold. In addition, the prices for the 9-valent HPV vaccine to be cost-effective and highly cost-effective were $680 and $220, respectively.

The results of comparing the 9-valent vaccine with the bivalent and quadrivalent vaccines are shown in the second panel of Table 1. The 9-valent vaccine was not cost-effective when compared with either the bivalent or the quadrivalent vaccine. To be cost-effective in relation to bivalent and quadrivalent vaccines, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively. To be highly cost-effective, the price thresholds were $435 and $335. Furthermore, the 9-valent vaccine should be priced at $505 to reach the same ICER as the quadrivalent vaccine when both vaccines were compared with not receiving vaccination, or at $370 when the comparator was the bivalent vaccine.

The results of the one-way sensitivity analyses are presented in Appendix 4. When the mortality rate of cervical cancer was reduced by 25%, the incremental costs per DALY prevented in the comparison of the 9-valent vaccine and no vaccination were $30,246, which was above the cost-effective threshold. The results remained cost-effective in all other scenarios. The results in the comparison with the bivalent and the quadrivalent vaccines were also relatively sensitive to the mortality rate of cervical cancer. However, none of the changes impacted the inference using either the cost-effective threshold or the highly cost-effective threshold.

DISCUSSION

In the current analysis, the 9-valent HPV vaccine was cost-effective but not highly cost-effective for the prevention of cervical cancers among 16-26 years old Chinese females without prior HPV infection when compared with no vaccination. The results were robust to changes in important parameters except cervical cancer mortality.

The results suggest that the 9-valent HPV vaccine does provide value at the current price when compared with not receiving vaccine at the three times the GDP per capita threshold. However, there isn't a universal definition of cost-effective threshold nor a consensus on such. Therefore, alternative thresholds should be considered. A commonly used alternative cut-off is the highly cost-effective threshold. Based on this threshold, the 9-valent HPV vaccine is not highly cost-effective in China. Clinicians and policymakers are advised to consider local economic realities and patient financial status when deciding whether to use the 9-valent vaccine.

The results of comparing alternative vaccines are also important in certain contexts. The 9-valent vaccine was cost-ineffective when compared with the bivalent and the quadrivalent vaccines. These results are important to the extent that the marginal benefit of investing in the bivalent or quadrivalent vaccines is more than that of the 9-valent vaccine. Although the comparison with the bivalent vaccine may not be fair since the bivalent vaccine does not protect against warts, the comparison with the quadrivalent vaccine is not subject to the same limitation. As far as cervical cancer is concerned, our results showed that the marginal health gain of an extra dollar in the healthcare budget to be spent on the 9-valent vaccine would be the same as that on the quadrivalent and bivalent vaccine if the 9-valent vaccine were to be priced at $505 and $370, respectively. These findings should raise concerns over the already disputable cost-effectiveness

profiles of HPV vaccines in China.[5] A number of bivalent and quadrivalent Chinese-manufactured HPV vaccines are already in the late stage of clinical trials and will likely be marketed at lower prices than the imported counterparts. The entrance of these products will further neutralize the edge of the 9-valent vaccine over the other vaccines with regard to cost-effectiveness.

While it is both intuitive and tempting to compare the 9-valent vaccine only with the bivalent or the quadrivalent vaccines and to entirely dismiss the comparison with no vaccination, it is not necessarily appropriate in China. Indeed, only comparing the 9-valent vaccine with the other HPV vaccines suffices to inform decision-making if HPV vaccination is already the standard of practice and the decision should pertain to incremental cost-effectiveness in relation to the standard of practice. While this might be true in high-income countries, it is not the case in China. Most Chinese females, regardless of age, have not been inoculated with any HPV vaccine. Specifically, the total number of HPV vaccine doses released by the National Institutes for Food and Drug Control in all batches as of September 2018 was merely 6 million.[15] In addition, the cost-effectiveness of the bivalent and quadrivalent vaccines at their current prices is not necessarily conclusive.[5] As such, only comparing the 9-valent vaccine with the alternative vaccines may potentially be misleading if the alternative vaccines are themselves beyond the efficiency frontier.

More, it is important to note the results of age-related sensitivity analyses do not necessarily suggest vaccination is more cost-effective at older ages. The smaller ICERs at older ages are caused by fewer years of discounting the benefits (Appendix 5).

The current analysis is subject to several limitations. First, the PRIME tool was not designed to model catch-up immunization for those individuals who have already had prior infections.[7] Second, the analysis only considered the health benefits of preventing cervical cancer but not the benefits of preventing genital warts. In addition to these limitations, the model was also subject to other limitations that do not necessarily undermine the validity of the current results. For example, the model doesn't evaluate vaccination combined with cervical screening programs or assess herd immunity due to vaccination.[7] Also, the model is only appropriate to evaluate vaccination among 9-13 years old females if the population outcomes are of interest because some individuals in a cohort of older ages may have been previously infected. However, these limitations do not affect the economic evaluation of vaccinating an individual who is known to have no previous infection and decides to whether accept immunization. More, Chinese-manufactured vaccines in future may affect the pricing of marketed products and the CEA should be updated.

CONCLUSIONS

In conclusion, the 9-valent HPV vaccine is cost-effective but not highly cost-effective to prevent cervical cancer among females without prior HPV infection at the current price in China when compared with no vaccination. It is cost-ineffective when compared with the bivalent and quadrivalent vaccines. Given these mixed results, policymakers and clinicians should carefully consider regional economic realities when expanding the use of the 9-valent HPV vaccines in China. In particular, it is important that the clinicians consider both the clinical and economic profiles of the HPV vaccines

when discussing vaccination with clients. More, public health professionals should be cautious about using the 9-valent vaccine as the primary choice at its current price if HPV vaccines are to be provided as public goods. The 9-valent vaccine is more likely to provide sufficient value if the price can be reduced substantially.

Word count of main text: 2,140

Contributors Design and data collection: YJ, WN and JW. Analysis and interpretation: YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript: WN and JW.

Competing interests YJ, WN and JW report no conflicts of interests related to the subject of the submitted work.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement The PRIME model is publicly available at http://primetool.org/about-hpv/. The customized input data are listed in the table of the submitted manuscript. No additional data are available.

REFERENCES

1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed. 2018. https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed (Accessed May 16 2018).
2. HPV vaccine becomes available in China for women between 16 to 26 years old. 2018. https://www.firstwordpharma.com/node/1560878?tsid=6 (Accessed May 10 2018).
3. Levin CE, Sharma M, Olson Z, et al. An extended cost-effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China. *Vaccine* 2015;33(24):2830-41.
4. Canfell K, Shi JF, Lew JB, et al. Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. *Vaccine* 2011;29(13):2487-94.
5. Yin Y. HPV vaccination in China needs to be more cost-effective. *Lancet* 2017;390(10104):1735-1736.
6. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Health* 2014;2(7):e406-14.
7. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and Economics Tool User Manual. 2014. http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf (Accessed May 08 2018).
8. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact Sheet 2017. 2017. http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf (Accessed May 10 2018.
9. World Health Organization. Electronic address: sageexecsec@who.int.. Human papillomavirus vaccines: WHO position paper, May 2017-Recommendations. *Vaccine* 2017;35(43):5753-5755.
10. Information of Drug Winning Bid. 2018. https://data.yaozh.com/yaopinzhongbiao (Accessed December 17 2018).
11. XE Currency Table: USD - US Dollar. 2017. https://www.xe.com/currencytables/ (Accessed May 10 2018).
12. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita. 2018. http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD (Accessed May 10 2018).
13. National Bureau of Statistics of China. Consumer Price Indices, Healthcare. 2017. http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01 (Accessed May 17 2018).
14. Mo X, Gai Tobe R, Wang L, et al. Cost-effectiveness analysis of different types of human papillomavirus vaccination combined with a cervical cancer screening program in mainland China. *BMC Infect Dis* 2017;17(1):502.
15. National Institutes for Food and Drug Control. Batch-release inquiry of biological products. 2018. http://www.nifdc.org.cn/CL0694/ (Accessed September 20 2018).

Appendix 1. Additional information on the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model

The PRIME model is a model developed by the World Health Organization (WHO) to estimate country-specific cost-effectiveness of HPV vaccination among females. It models the effect of the vaccine by incorporating the reduction in age-dependent incidence of cervical cancer as a result of vaccination. The model assumes that the individuals finish all doses of the vaccine and the vaccine provides lifelong protection. Also, it does not consider herd immunity.

The model is pre-populated with country-specific input data. However, it also allows customization of the input data. We changed the inputs of target age group, price of vaccine, delivery costs (adjusted based on the default input), and cancer treatment costs. We also changed the Chinese-specific data of the proportion of cervical cancer attributable to HPV types 16/18 to that of HPV types 16/18/31/33/45/52/58 for the analysis of the 9-valent vaccine.

To cross-validate the model, the developers of the model extracted input data from previous HPV modeling studies and calculated the results using the PRIME model. The results were then compared with the previous studies, the difference from published results was tested using Cohen's Kappa. The developers showed that there was good agreement.

The model was adopted to evaluate the cost-effectiveness of HPV vaccination in Vietnam as a country-specific application in addition to multi-country application.[1] More details of the model have been described elsewhere.[2]

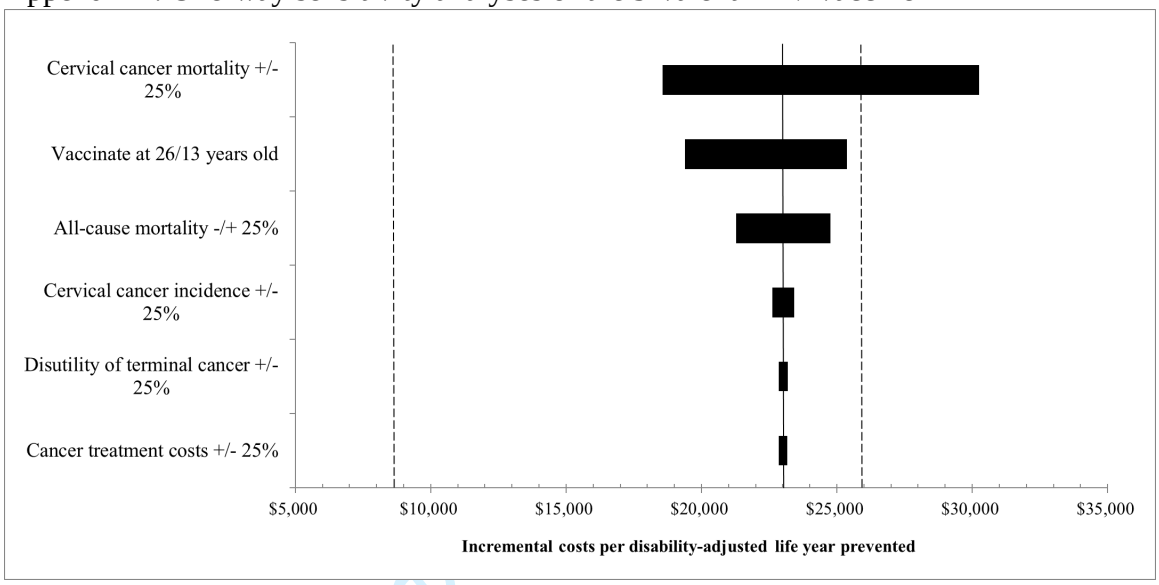
Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

In the base-case analysis, the target age group was 16 years old females because this was the youngest age group among the approved population for the use of the 9-valent vaccine in China. In China, the vast majority of the female individuals in this age are not infected with HPV. According to a study by Zhao et el., 6.9% of females in the age group 15-19 years old were sexually active in 2012.[3] This number should be lower for those who aged 16 years since this age is closer to the younger bound of the age group. Another study in the same year by Zheng et al. confirmed that sexual debut before age 18 was rare in China.[4] Granted, the estimates were not necessarily accurate since there might be social desirability bias and the situation could have evolved, but it is impossible to speculate on how substantial the bias and the change were. However, it is reasonable to think the proportion of sexually active individuals in the 16 years old females is still very low in China. Therefore, most 16 years old still did not have sexual debut and did not expose to HPV although a very small proportion of them would have had sexual debut. Additionally, taking into consideration that most of those who had sexual debut would not have been infected, the proportion of uninfected individuals in the age group of 16 years old would be even higher than the proportion without sexual debut.

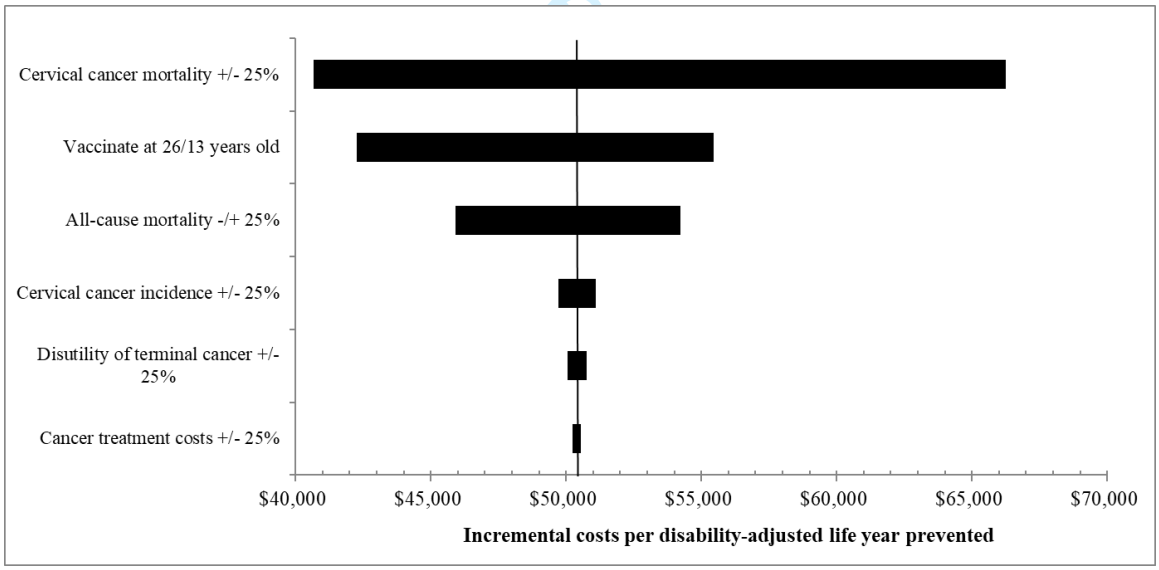
Appendix 3. Additional information on the base-case results.

	Not receiving vaccination	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18/31/33/45/52/58)	$17	$0	NA	NA
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18)	$13	NA	$0	$0
Total costs with vaccination	NA	$628	$393	$291
Discounted expected life years lost due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0250	0	NA	NA
Discounted expected life years lost due to cervical cancer (HPV types 16/18)	0.0188	NA	0	0
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0015	0	NA	NA
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0011	NA	0	0
Discounted net costs	NA	$611	$380	$278
Discounted DALYs prevented	NA	0.0265	0.0199	0.0199
ICER vs. not being vaccinated	NA	$23,012	$19,061	$13,944

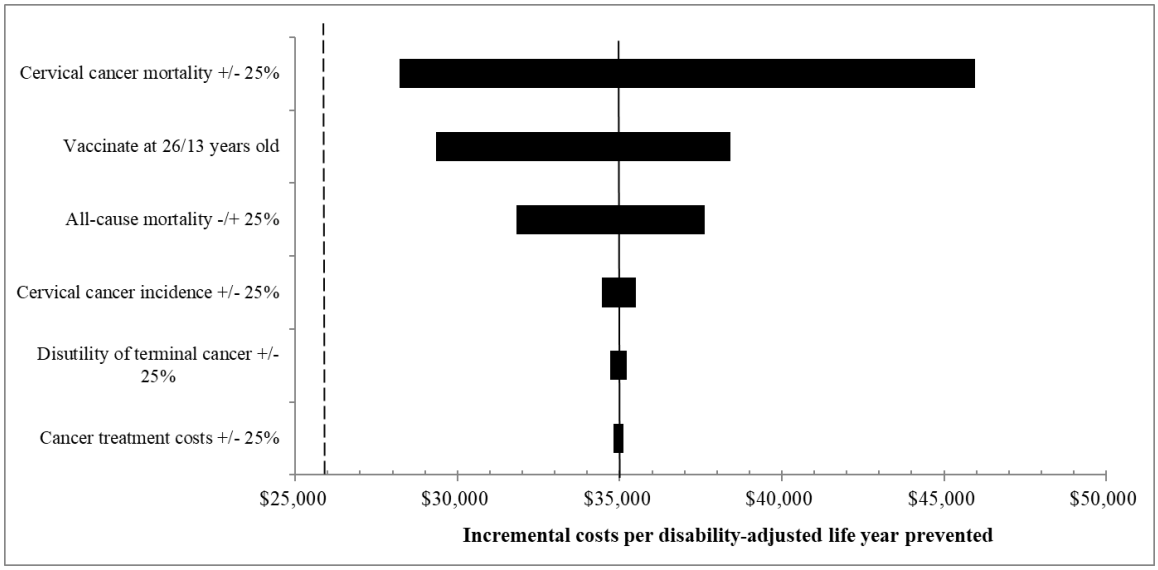
Appendix 4. One-way sensitivity analyses of the 9-valent HPV vaccine



a. Sensitivity analysis results of comparing the 9-valent vaccine with no vaccination. The left and right dash lines represent the highly cost-effective and cost-effective thresholds, respectively.



b. Sensitivity analysis results of comparing the 9-valent vaccine with the bivalent vaccine.



c. Sensitivity analysis results of comparing the 9-valent vaccine with the quadrivalent vaccine. The dash line on the left represents the highly cost-effective threshold.

Appendix 5. An example of discounted results vs. undiscounted results. The sensitivity analysis result that vaccinating at older ages was more cost-effective is counter-intuitive. It was because the loss of DALYs prevented caused by discounting exceeds the gain of DALYs prevented by vaccinating earlier. To further illustrate this, we present below an example using the default PRIME model without customizing any parameters except age. Hence, the results in the example only demonstrate how discounting affects model outputs and are not comparable to the results in the current study.

	Vaccinate at 16 years old		Vaccinate at 26 years old	
	Undiscounted	Discounted	Undiscounted	Discounted
Net costs	$42	$43	$42	$44
DALYs prevented	0.0482	0.0158	0.0445	0.0188
Incremental costs per DALY prevented	$867	$2,751	$945	$2,316

Abbreviations: DALY, disability-adjusted life year; PRIME, the Papillomavirus Rapid Interface for Modelling and Economics (PRIME).

References

1. Van Minh H, My NTT, Jit M. Cervical cancer treatment costs and cost-effectiveness analysis of human papillomavirus vaccination in Vietnam: a PRIME modeling study. *BMC Health Serv Res* 2017;17(1):353.
2. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Health* 2014;2(7):e406-14.

3. Zhao FH, Tiggelaar SM, Hu SY, et al. A multi-center survey of age of sexual debut and sexual behavior in Chinese women: suggestions for optimal age of human papillomavirus vaccination in China. *Cancer Epidemiol* 2012;36(4):384-90.
4. Guo W, Wu Z, Qiu Y, Chen G, Zheng X. The timing of sexual debut among Chinese youth. *Int Perspect Sex Reprod Health* 2012;38(4):196-204.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	pages 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	pages 5 and 12
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 7
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 5
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 12-13
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	page 7
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	page 8-9
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Appendix 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 10
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	page 14
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	page 14

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

BMJ Open

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031186.R1
Article Type:	Original research
Date Submitted by the Author:	29-Aug-2019
Complete List of Authors:	Jiang, Y; Sun Yat-Sen University, School of Public Health (Shenzhen) Ni, Weiyi; Tianjin University, School of Pharmaceutical Science and Technology; University of Southern California, Department of Pharmaceutical and Health Economics Wu, Jing; Tianjin University, School of Pharmaceutical Science and Technology
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Sexual health, Infectious diseases, Public health
Keywords:	cost-effectiveness, HPV, vaccination, China, cervical neoplasia

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis

Yawen Jiang,[a] Ph.D., Weiyi Ni,[b, c] Ph.D., Jing Wu,[b] Ph.D.

Corresponding Author: Jing Wu

School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, China

Corresponding Email: jingwu@tju.edu.cn; Phone: 0086-15822450465.

[a] School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, Guangdong, China

[b] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, China

[c] Department of Pharmaceutical and Health Economics, University of Southern California, Los Angeles, California, USA

Abstract

Objectives

To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV) vaccine for the prevention of cervical cancer in China.

Design

Health economic modelling using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model populated with China-specific data.

Setting

Individual cervical cancer prevention in China using the 9-valent HPV vaccine from the perspective of private sector purchasers in relation to receiving other HPV vaccines and not receiving vaccination for 16 years old females in China who had not been previously infected with HPV.

Participants

Not applicable.

Interventions

Vaccination using the 9-valent, the quadrivalent and the bivalent vaccines.

Primary outcome measure

Incremental costs per disability-adjusted life year (DALY) prevented.

Results

In the base case, the incremental costs per DALY prevented were respectively US$35,000 and US$50,455 compared with the quadrivalent and the bivalent vaccines, both of which were above the cost-effective threshold of US$25,920/DALY prevented. To be cost-effective in these comparisons, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively. To be highly cost-effective, the price thresholds were $435 and $335. The incremental costs per DALY prevented in relation to no vaccination was US$23,012, making the 9-valent vaccine marginally cost-effective. The results were robust in most one-way sensitivity analyses including changing vaccination age to 13 and 26 years.

Conclusions

At the current price, the 9-valent HPV vaccine is not cost-effective compared with the quadrivalent and the bivalent vaccines for young females in China who had not been previously infected with HPV. Policymakers and clinicians should keep potential vaccine

recipients informed about the economic profile of the 9-valent vaccine and carefully consider expanding its use in China at the current price.

Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia

Strengths and limitations of this study

1. The study used a previously validated model.
2. The analyses used Chinese-specific input data.
3. Only analysed individuals without prior infection.
4. Used a static model instead of a dynamic model and did not consider herd immunity.
5. Did not take into account the prevention of genital warts.

INTRODUCTION

Less than one year after the launch of the bivalent and quadrivalent human papillomavirus (HPV) vaccines in China, the 9-valent HPV vaccine was also approved by the China Food and Drug Administration in April 2018. Unlike the review processes of bivalent and quadrivalent HPV vaccines that took about ten years in China, the review process of 9-valent HPV vaccine took a record short period of nine days.(1) However, the 9-valent HPV vaccine was only approved for use among 16-26 years old females whereas the bivalent and quadrivalent HPV vaccines were approved for use among 9-26 years old males and females.(2)

Among the oncogenic HPV types, the bivalent and the quadrivalent vaccines are efficacious against types 16/18, whereas the 9-valent vaccine provides additional protection against types 31/33/45/52/58.(3) Both the quadrivalent and the 9-valent vaccines are also protective against HPV types 6/11, which can cause genital warts.(3) The cost-effectiveness of bivalent and quadrivalent HPV vaccines for the prevention of cervical cancer has been previously analysed in the setting of China. The results of such analyses were favourable to the cost-effectiveness of the bivalent and quadrivalent vaccines compared with no vaccination for the prevention of cervical cancer.(4, 5) However, the previous analyses in the literature were conducted before the introduction of the first HPV vaccine in China. Hence, the prices of HPV vaccines in the previous analyses was around $50, which did not reflect the present reality. In the meantime, the cost-effectiveness of the 9-valent HPV vaccine in China is still unknown. In light of this, it is important to obtain evidence on the value of the 9-valent vaccine to determine whether it should be used more broadly. Although previous studies have quantified the

cost-effectiveness of the 9-valent vaccines compared with alternative vaccines in other countries,(3, 6-9) evidence in other healthcare systems is not portable to China for numerous reasons such as different prices, cancer treatment costs and epidemiological profiles. As such, the objective of the current study was to analyse the cost-effectiveness of the 9-valent HPV vaccine for the prevention of cervical cancer among Chinese females from the perspective of private sector purchasers because HPV vaccines are neither publicly funded nor reimbursed by any payers to our knowledge. More specifically, this study pertains to the clinical decision setting of whether it is cost-effective for a Chinese female without previous infection to use the 9-valent HPV vaccine. We compared the 9-valent vaccine with the quadrivalent vaccines, the bivalent vaccines, and no vaccination, respectively. Among these, the comparison with the quadrivalent vaccine forms a specific incremental efficacy evaluation of cervical cancer prevention. Thus, it serves as the primary basis for discussion and conclusion. The comparison with the bivalent vaccine may be complicated by the additional efficacy of preventing non-oncogenic HPV types provided by the 9-valent vaccine, whereas the comparison with no vaccination is arguably not incremental. However, the alternative comparisons were necessary to render a comprehensive understanding of the health economic profile of the 9-valent vaccine, which is important because even the bivalent and the quadrivalent vaccines are subject to cost-effectiveness concerns for women living in rural areas of China.(10)

METHODS

We adapted the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model in the current analysis. The PRIME model is a health economic model

developed by the World Health Organization (WHO) that allows country-specific evaluation of HPV vaccination among females without prior infection of HPV.(11, 12) Country-specific cervical cancer incidence, mortality, HPV type distribution, and economic data were built in the model. The model developers assessed the quality of country-specific data as either "satisfactory" or "unsatisfactory" based on availability of data for each country and quality of methods used in data collection, and the Chinese data were deemed "satisfactory".(11) The model calculates the incremental costs per disability-adjusted life year (DALY) prevented for vaccinated individuals over lifetime as well as population outcomes such as cervical cancer prevented and deaths prevented. In addition, the model was validated against previously published HPV vaccine cost-effectiveness studies in the literature. More details of the model have been described elsewhere and in Appendix 1.(11)

The current analysis only examined incremental costs per DALY prevented for vaccinated individuals. Because the intervention of interest in the current analysis is 9-valent HPV vaccination, we modified the model to use the proportion of cervical cancer that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by International Agency for Research on Cancer (IARC) HPV Information Centre instead of only the proportion that was attributable to types 16/18 in the original model.(12, 13) According to IARC estimates, 92% of cervical cancer in China were attributable to types 16/18/31/33/45/52/58.(13)

The model also permitted customization of target age group, efficacy of vaccine (percentage of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer treatment cost, discount rate, and disutility values of three cancer-related health states

(cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the customized input fields can override the default data. In the current analysis, default data of efficacy of vaccine, discount rate, and disutility values were used. It should be noted that several other inputs could be customized in the model including coverage rate (or uptake rate), birth cohort size, and cohort size at the vaccination age. Except for coverage rate, these inputs only affect population outcomes that are not of interest in the current analysis and does not affect the results of the cost-effectiveness results for vaccinated individuals. We assumed a coverage rate of 100% in our analysis such that the mean population result is equivalent to that of an average vaccinated individual.

In the base-case analysis, the target age group was 16 years old females because this was the youngest group among the current age of licensure of the 9-valent vaccine in China (additional explanation in Appendix 2). It is noteworthy that this was older than the WHO-recommended primary target age window of 9-14 years.(14) Regardless of vaccination age, the time horizon was set so such that the cohort were followed up to 100 years old. The price of 9-valent HPV vaccine in government procurement catalogue as of December 2018 was used.(15, 16) We also assessed the prices at which the incremental costs per DALY prevented were at the cost-effective threshold of three times the 2017 China gross domestic product (GDP) per capita and at the highly cost-effective threshold of once the 2017 China GDP per capita to inform decision makers the value-based prices. Therefore, the cost-effective threshold and the highly cost-effective thresholds are US$25,920/DALY prevented and US$8,640/DALY prevented, respectively.(17) Default data of vaccine administration costs per person in China in the PRIME model were used but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices

in China.(18) In addition, cancer treatment costs in 2015 were updated to 2017 US dollars.(18, 19) Input data are listed in the first panel of Table 1.

Table 1. Input data and model results of the base-case analysis of the 9-valent HPV vaccine and the exploratory analyses of the bivalent and quadrivalent HPV vaccines

Input data		
Parameter	Value	Reference/source
Vaccination age	16 years	NA
Percentage of cervical cancer in China attributable to types 16/18/31/33/45/52/58	92.0%	(13)
Percentage of cervical cancer in China attributable to types 16/18	69.1%	(13)
9-valent vaccine price for full doses (2017 US$)	$610	(15, 16)
Quadrivalent vaccine price for full doses (2017 US$)	$375	(15, 16)
Bivalent vaccine price for full doses (2017 US$)	$273	(15, 16)
Vaccine administration costs (2017 US$)	$18	Model default with inflation adjustment(16, 18)
Cancer treatment costs (2017 US$)	$7,183	(18, 19)
Efficacy of vaccine	100%	Model default
Discount rate	3%	Base-case assumption
Disutility weight of cancer diagnosis	0.08	Model default
Disutility weight of non-terminal cancer sequelae	0.11	Model default
Disutility weight of terminal cancer	0.78	Model default

Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio measured as incremental costs per DALY prevented; NA, not applicable.

In one-way sensitivity analyses, age at vaccination (each age between 13-26 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups, cervical cancer mortality, all-cause mortality, cancer treatment costs, disutility of terminal cancer, and discount rate (1% and 5%) were varied to examine the robustness of incremental costs per DALY prevented results. Parameters of interest other than age at vaccination, efficacy, and discount rate were increased and decreased by 25%.

Patient and Public Involvement

Patients were not involved.

RESULTS

The base-case results of comparing the 9-valent vaccine with the quadrivalent and bivalent vaccines are shown in Table 2 (more detailed information on the base-case results is in Appendix 3). The incremental costs per DALY prevented compared with the quadrivalent and the bivalent vaccines were US$35,000 and US$50,455, respectively. Therefore, the 9-valent vaccine was not cost-effective when compared with either the quadrivalent or the bivalent vaccine. To be cost-effective, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively. To be highly cost-effective, the price thresholds were $435 and $335. Furthermore, the 9-valent vaccine should be priced at $505 to reach the same ICER as the quadrivalent vaccine when both vaccines were

compared with no vaccination. The corresponding price was $370 when the comparator was the bivalent vaccine.

The results of comparing with no vaccination are displayed in Table 2. The incremental costs per DALY prevented were US$23,012. This was slightly less than the cost-effective threshold but substantially above the highly cost-effective threshold. In addition, the prices for the 9-valent HPV vaccine to be cost-effective and highly cost-effective were $680 and $220, respectively.

Table 2. Base-case results

	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted net costs	$611	$380	$278
Discounted DALYs prevented	0.0265	0.0199	0.0199
ICER of 9-valent vaccine vs. other vaccines	NA	$35,000	$50,455
ICER vs. not being vaccinated	$23,012	$19,061	$13,944
Price threshold of 9-valent vaccine to be cost-effective vs. other vaccines [a]	NA	$550	$450
Price threshold of 9-valent vaccine to be highly cost-effective vs. other vaccines [b]	NA	$435	$335
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines [c]	NA	$505	$370
Price threshold to be cost-effective vs. not being vaccinated	$680	NA	NA
Price threshold to be highly cost-effective	$220	NA	NA

	vs. not being vaccinated

Abbreviations: DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio measured as incremental costs per DALY prevented; NA, not applicable.

[a] For example, the 9-valent vaccine should be priced at $550 for the full doses to be cost-effective when compared with the quadrivalent vaccine.

[b] For example, the 9-valent vaccine should be priced at $435 for the full doses to be highly cost-effective when compared with the quadrivalent vaccine.

[c] At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when each of them was compared with not receiving vaccination if the price of the 9-valent vaccine is $505 for the full doses. This is equivalent to saying the cost-effectiveness of the 9-valent vaccine vs. the quadrivalent vaccine is the same as the cost-effectiveness of the quadrivalent vaccine vs. not receiving vaccination. The interpretation of the comparison vs. the bivalent vaccine is the same.

The results of one-way sensitivity analyses are presented in Appendix 4. The results of comparing with the quadrivalent and the bivalent vaccines were relatively sensitive to using alternative discount rates. When the discount rate was 1%, the 9-valent vaccine was cost-effective compared with both the quadrivalent and the bivalent vaccines, but not highly cost-effective. However, none of the other changes impacted the inference using either the cost-effective threshold or the highly cost-effective threshold. In the comparison with no vaccination, both using alternative discount rates and changing the mortality rate of cervical cancer had substantial impacts on the results. When the discount rate was 5%, the incremental costs per DALY prevented in the comparison of the 9-valent vaccine and no vaccination were $43,145, which was above the cost-effective threshold. Similarly, the corresponding result was $30,246 when the mortality rate of cervical cancer was reduced by 25%, which was also above the cost-effective threshold. The results remained cost-effective in all other scenarios.

DISCUSSION

In the present analysis, the 9-valent HPV vaccine was not cost-effective for the prevention of cervical cancer among 16-26 years old Chinese females without prior HPV infection when compared with either the quadrivalent or the bivalent vaccine, which remained so in all the sensitivity analyses except for using a discount rate of 1%. The results suggest that the price of the 9-valent HPV vaccine needs to be adjusted downward to provide more value for Chinese female recipients. Since the highly cost-effective threshold is more stringent, the 9-valent HPV vaccine is also not highly cost-effective in China.

The results are important to the extent that the marginal health gain of investing in the quadrivalent or bivalent vaccine is more than that of the 9-valent vaccine. Although the comparison with the bivalent vaccine may not be fair given that the bivalent vaccine does not protect against warts, the comparison with the quadrivalent vaccine is not subject to the same limitation. As far as cervical cancer is concerned, our results showed that the marginal health gain of an extra dollar in the healthcare budget to be spent on the 9-valent vaccine would be the same as that on the quadrivalent and bivalent vaccine if the 9-valent vaccine were to be priced at $505 and $370, respectively. In the meantime, a number of Chinese-manufactured bivalent and quadrivalent HPV vaccines are already in the late stage of clinical trials and will likely be marketed at lower prices than the imported counterparts. The entrance of these products will further neutralize the edge of the 9-valent vaccine over the other vaccines in respect to cost-effectiveness. At the current price level, clinicians and policymakers are advised to educate potential vaccine recipients and keep them informed when suggesting vaccination.

The 9-valent HPV vaccine was cost-effective but not highly cost-effective for the prevention of cervical cancer among 16-26 years old Chinese females without prior HPV infection when compared with no vaccination. The results were robust to changes in important parameters except for discount rates and cervical cancer mortality.

While it is both intuitive and theoretically founded to compare the 9-valent vaccine only with the quadrivalent and the bivalent vaccines, it should be noted that further comparing the 9-valent vaccine with no vaccination may provide additional insights when the standard of practice is absent. Indeed, only comparing the 9-valent vaccine with the other HPV vaccines suffices to inform decision-making if HPV vaccination is already the standard of practice and the decision should pertain to incremental cost-effectiveness in relation to the standard of practice. While this might be true in high-income countries, it is not necessarily the case in China. Most Chinese females, regardless of age, have not been inoculated with any HPV vaccine. Specifically, the total number of HPV vaccine doses released by the National Institutes for Food and Drug Control in all batches as of September 2018 was merely 6 million,(20) indicating the maximum number of females in China that would have received at least one dose of HPV vaccine. Hence, the scenario that a portion of the individuals would only consider either receiving the 9-valent vaccine or not being vaccinated should not be ruled out. For these individuals, the comparison of the 9-valent vaccine with no vaccination relevant for decision making. As such, we pertain to the comparison with the quadrivalent vaccine as the primary analysis but also provide exploratory results of comparing with no vaccination.

It is important to note the results of age-related sensitivity analyses do not necessarily suggest vaccination is more cost-effective at older ages. Smaller ICERs at older ages are mainly caused by fewer years of discounting the benefits (Appendix 5).

The cost-effectiveness profile of the 9-valent vaccine based on the present analysis contrasts that in several developed countries. A study found that the 9-valent vaccine was cost-effective compared with the quadrivalent vaccine among 12-26 years old females in the United States if the additional acquisition costs per dose was no more than US$13 (3). Their finding was confirmed by another US study (6). An Australian study also showed that the 9-valent vaccine was a cost-effective alternative to the quadrivalent vaccine for 12-year old females if the additional costs per dose was under AUS$36 (7). In Canada, Italy and Spain, the corresponding numbers were CAN$24, €16 and €16 (8, 9, 21). These numbers were generally consistent with the real-world price differences in the public sectors of the aforementioned countries (3, 8, 9). However, the gaps between the prices of the 9-valent and quadrivalent vaccines in these markets were substantially smaller than that in China, which is likely the main reason of the inconsistent cost-effectiveness profiles. This highlights the importance of adjusting the price of the 9-valent vaccine in China from the value perspective.

The current analysis is subject to several limitations. First, our analysis did not model catch-up immunization for those individuals who have already had prior infections.(12) It is reasonable to expect that the incremental benefit of the 9-valent vaccine is smaller among these individuals. Second, the analysis only considered the health benefits of preventing cervical cancer but not the benefits of preventing genital

warts. Taking into account the prevention of genital warts will favour the 9-valent vaccine over the bivalent vaccine and no vaccination. In addition to these limitations, the model was also subject to other limitations that do not necessarily undermine the validity of the current results. For example, the model doesn't evaluate vaccination combined with cervical screening programs or assess herd immunity due to vaccination.(12) Also, the model is only appropriate to evaluate vaccination among 9-13 years old females if the population outcomes are of interest because some individuals in a cohort of older ages may have been previously infected. In theory, these limitations do not affect the economic evaluation of vaccinating an individual who is known to have no previous infection and decides to accept immunization. Future economic evaluations should examine screening and vaccination strategies in which a portion of the target population were vaccinated. More, Chinese-manufactured vaccines in future may affect the pricing of marketed products and the CEA should be updated accordingly. Even more, the efficacy of the vaccine was assumed to stay fully protective throughout the time horizon. This may not be necessarily the case in practice. However, the impact of this limitation is unclear since it affects both the 9-valent vaccine and the other vaccines.

CONCLUSIONS

In conclusion, the 9-valent HPV vaccine is not cost-effective when compared with the quadrivalent vaccine for young females in China who had not been previously infected with HPV at its current price. It is also not cost-effective when compared with the bivalent vaccine, although it is marginally cost-effective yet not highly cost-effective when compared with no vaccination. Given these results, policymakers and clinicians

should be conservative to expand the use of the 9-valent HPV vaccines in China unless the price is reduced. In addition, it is important that the clinicians discuss the economic profile of the 9-valent HPV vaccine to keep health-seeking individuals informed. More, public health professionals should be cautious about using the 9-valent vaccine as the primary choice at its current price if HPV vaccines are to be provided as public goods at nationally.

Word count of main text: 2,766

Contributors Design and data collection: YJ, WN and JW. Analysis and interpretation: YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript: WN and JW.

Competing interests YJ, WN and JW report no conflicts of interests related to the subject of the submitted work.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement The PRIME model is publicly available at http://primetool.org/about-hpv/. The customized input data are listed in the table of the submitted manuscript. Further details about the country-specific cervical cancer incidence

and mortality data can be found at http://gco.iarc.fr/databases.php. No additional data are available.

REFERENCES

1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed 2018 [Available from: https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed.
2. HPV vaccine becomes available in China for women between 16 to 26 years old 2018 [Available from: https://www.firstwordpharma.com/node/1560878?tsid=6.
3. Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified transmission model. Hum Vaccin Immunother. 2016;12(6):1363-72.
4. Levin CE, Sharma M, Olson Z, Verguet S, Shi J-F, Wang S-M, et al. An extended cost-effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China. Vaccine. 2015;33(24):2830-41.
5. Canfell K, Shi J-F, Lew J-B, Walker R, Zhao F-H, Simonella L, et al. Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. Vaccine. 2011;29(13):2487-94.
6. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(18):5107.
7. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. 2016.
8. De La Fuente J, Hernandez Aguado JJ, Martín MS, Boix PR, Gómez SC, López NJHV, et al. Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent hpv vaccine in Spain.
9. Mennini FS, Bonanni P, Bianic F, Waure CD, Baio G, Plazzotta G, et al. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. 2017;15(1):11.
10. Yin Y. HPV vaccination in China needs to be more cost-effective. The Lancet. 2017;390(10104):1735-6.
11. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-e14.
12. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and Economics Tool User Manual 2014 [Available from: http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf.
13. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact Sheet 2017 2017 [Available from: http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf.
14. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. Vaccine. 2017;35(43):5753-5.
15. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-adjusted indirect comparisons in health technology appraisal. Medical Decision Making. 2018;38(2):200-11.
16. XE Currency Table: USD - US Dollar 2017 [Available from: https://www.xe.com/currencytables/.
17. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita 2018 [Available from: http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD.

18. National Bureau of Statistics of China. Consumer Price Indices, Healthcare 2017 [Available from: http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01.
19. Mo X, Tobe RG, Wang L, Liu X, Wu B, Luo H, et al. Cost-effectiveness analysis of different types of human papillomavirus vaccination combined with a cervical cancer screening program in mainland China. BMC infectious diseases. 2017;17(1):502.
20. National Institutes for Food and Drug Control. Batch-release inquiry of biological products 2018 [Available from: http://www.nifdc.org.cn/CL0694/.
21. Mélanie D, Jean-Fran?Ois L, Marie-Claude B, Franco EL, Marc BJIJoC. Potential cost-effectiveness of the nonavalent human papillomavirus (HPV) vaccine. 2014;134(9):2264.

Appendix 1. Additional information on the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model

The PRIME model is a model developed by the World Health Organization (WHO) to estimate country-specific cost-effectiveness of HPV vaccination among females. It models the effect of the vaccine by incorporating the reduction in age-dependent incidence of cervical cancer as a result of vaccination. The model assumes that the individuals finish all doses of the vaccine and the vaccine provides lifelong protection. Also, it does not consider herd immunity.

The model is pre-populated with country-specific input data. However, it also allows customization of the input data. We changed the inputs of target age group, price of vaccine, delivery costs (adjusted based on the default input), and cancer treatment costs. We also changed the Chinese-specific data of the proportion of cervical cancer attributable to HPV types 16/18 to that of HPV types 16/18/31/33/45/52/58 for the analysis of the 9-valent vaccine.

To cross-validate the model, the developers of the model extracted input data from previous HPV modeling studies and calculated the results using the PRIME model. The results were then compared with the previous studies, the difference from published results was tested using Cohen's Kappa (0.845; indicates near perfect agreement). The developers showed that there was good agreement.

The model was adopted to evaluate the cost-effectiveness of HPV vaccination in Vietnam as a country-specific application in addition to multi-country application.(1) More details of the model have been described elsewhere.(2)

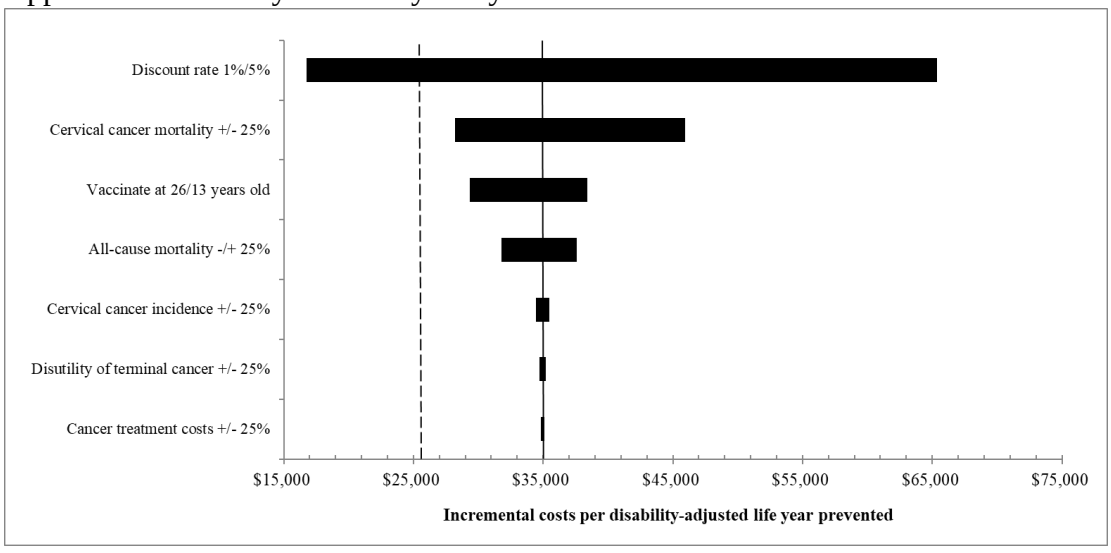
Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

In the base-case analysis, the target age group was 16 years old females because this was the youngest age group among the approved population for the use of the 9-valent vaccine in China. In China, the vast majority of the female individuals in this age are not infected with HPV. According to a study by Zhao et el., 6.9% of females in the age group 15-19 years old were sexually active in 2012.(3) This number should be lower for those who aged 16 years since this age is closer to the younger bound of the age group. Another study in the same year by Zheng et al. confirmed that sexual debut before age 18 was rare in China.(4) Granted, the estimates were not necessarily accurate since there might be social desirability bias and the situation could have evolved, but it is impossible to speculate on how substantial the bias and the change were. However, it is reasonable to think the proportion of sexually active individuals in the 16 years old females is still very low in China. Therefore, most 16 years old still did not have sexual debut and did not expose to HPV although a very small proportion of them would have had sexual debut. Additionally, taking into consideration that most of those who had sexual debut would not have been infected, the proportion of uninfected individuals in the age group of 16 years old would be even higher than the proportion without sexual debut.

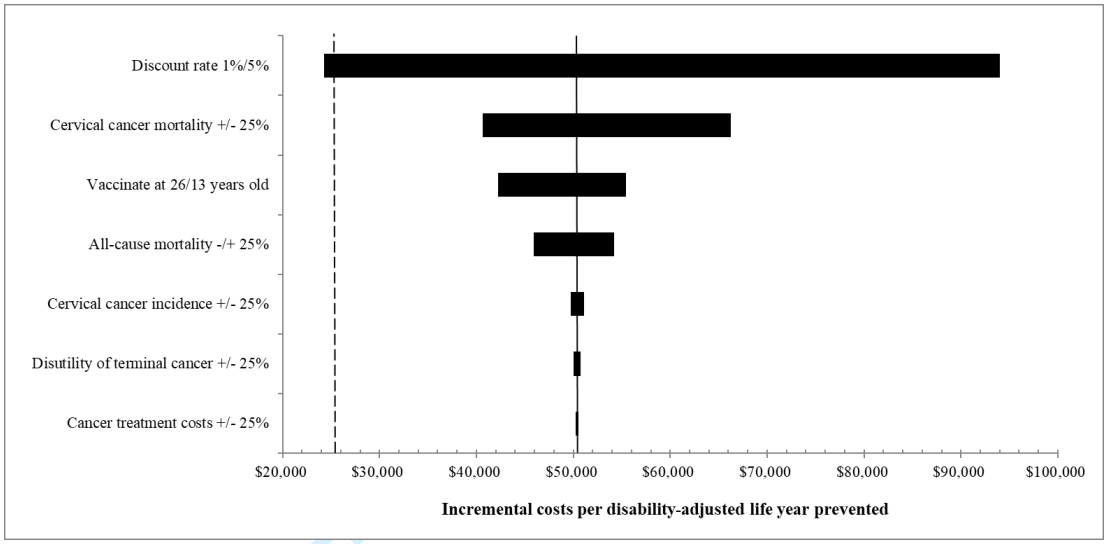
Appendix 3. Additional information on the base-case results.

	Not receiving vaccination	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18/31/33/45/52/58)	$17	$0	NA	NA
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18)	$13	NA	$0	$0
Total costs with vaccination	NA	$628	$393	$291
Discounted expected life years lost due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0250	0	NA	NA
Discounted expected life years lost due to cervical cancer (HPV types 16/18)	0.0188	NA	0	0
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0015	0	NA	NA
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0011	NA	0	0
Discounted net costs	NA	$611	$380	$278
Discounted DALYs prevented	NA	0.0265	0.0199	0.0199
ICER vs. not being vaccinated	NA	$23,012	$19,061	$13,944

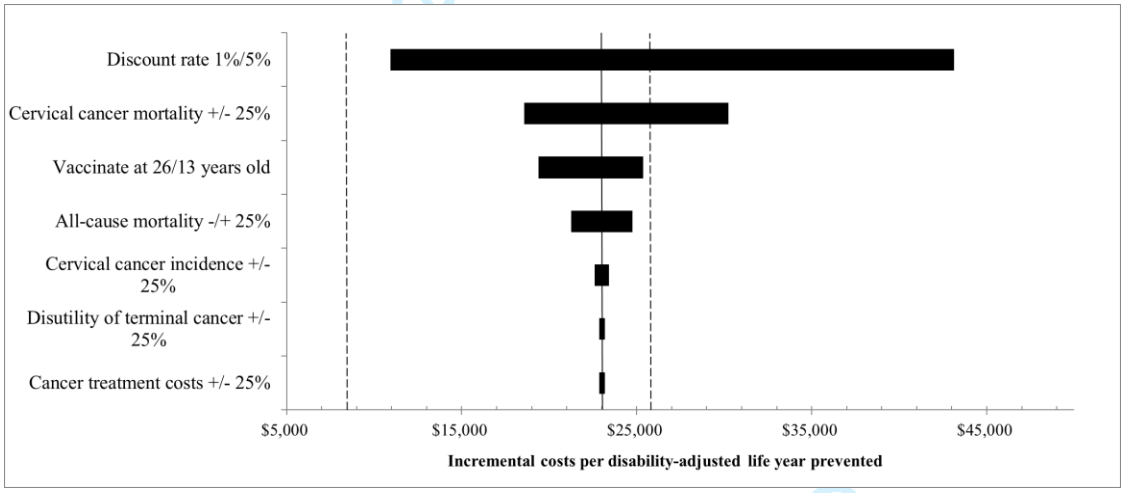
Appendix 4. One-way sensitivity analyses of the 9-valent HPV vaccine



a. Sensitivity analysis results of comparing the 9-valent vaccine with the quadrivalent vaccine. The dash line on the left represents the cost-effective threshold.



b. Sensitivity analysis results of comparing the 9-valent vaccine with the bivalent vaccine. The dash line on the left represents the cost-effective threshold.



c. Sensitivity analysis results of comparing the 9-valent vaccine with no vaccination. The left and right dash lines represent the highly cost-effective and cost-effective thresholds, respectively.

Appendix 5. An example of discounted results vs. undiscounted results. The sensitivity analysis result that vaccinating at older ages was more cost-effective is counter-intuitive. It was because the loss of DALYs prevented caused by discounting exceeds the gain of DALYs prevented by vaccinating earlier. To further illustrate this, we present below an example using the default PRIME model without customizing any parameters except age.

Hence, the results in the example only demonstrate how discounting affects model outputs and are not comparable to the results in the current study.

	Vaccinate at 16 years old		Vaccinate at 26 years old	
	Undiscounted	Discounted	Undiscounted	Discounted
Net costs	$42	$43	$42	$44
DALYs prevented	0.0482	0.0158	0.0445	0.0188
Incremental costs per DALY prevented	$867	$2,751	$945	$2,316

Abbreviations: DALY, disability-adjusted life year; PRIME, the Papillomavirus Rapid Interface for Modelling and Economics (PRIME).

References

1. Van Minh H, My NTT, Jit M. Cervical cancer treatment costs and cost-effectiveness analysis of human papillomavirus vaccination in Vietnam: a PRIME modeling study. BMC health services research. 2017;17(1):353.
2. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-e14.
3. Zhao F-H, Tiggelaar SM, Hu S-Y, Xu L-N, Hong Y, Niyazi M, et al. A multi-center survey of age of sexual debut and sexual behavior in Chinese women: suggestions for optimal age of human papillomavirus vaccination in China. Cancer epidemiology. 2012;36(4):384-90.
4. Guo W, Wu Z, Qiu Y, Chen G, Zheng X. The timing of sexual debut among Chinese youth. International perspectives on sexual and reproductive health. 2012:196-204.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 5
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 5
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	pages 5
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 5
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	pages 5 and 12
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 6
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	page 8
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 6
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 7
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 7
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 5
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 12-13
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	page 7
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	page 8-9
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Appendix 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 10
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	page 14
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	page 14

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.

BMJ Open

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031186.R2
Article Type:	Original research
Date Submitted by the Author:	12-Oct-2019
Complete List of Authors:	Jiang, Y; Sun Yat-Sen University, School of Public Health (Shenzhen) Ni, Weiyi; Tianjin University, School of Pharmaceutical Science and Technology; University of Southern California, Department of Pharmaceutical and Health Economics Wu, Jing; Tianjin University, School of Pharmaceutical Science and Technology
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Public health, Sexual health, Infectious diseases
Keywords:	cost-effectiveness, HPV, vaccination, China, cervical neoplasia

Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling Analysis

Yawen Jiang,[a] Ph.D., Weiyi Ni,[b, c] Ph.D., Jing Wu,[b] Ph.D.

Corresponding Author: Jing Wu

School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, 300072, China

Corresponding Email: jingwu@tju.edu.cn; Phone: 0086-15822450465.

[a] School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen, Guangdong, China

[b] School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, China

[c] Department of Pharmaceutical and Health Economics, University of Southern California, Los Angeles, California, USA

Abstract

Objectives

To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV) vaccine for the prevention of cervical cancer in China.

Design

Health economic modelling using the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model populated with China-specific data.

Setting

Individual cervical cancer prevention in China using the 9-valent HPV vaccine from the perspective of private sector purchasers in relation to receiving other HPV vaccines and not receiving vaccination for 16 years old females in China who had not been previously infected with HPV.

Participants

Not applicable.

Interventions

Vaccination using the 9-valent, the quadrivalent and the bivalent vaccines.

Primary outcome measure

Incremental costs per disability-adjusted life year (DALY) prevented.

Results

In the base case, the incremental costs per DALY prevented were respectively US$35,000 and US$50,455 compared with the quadrivalent and the bivalent vaccines, both of which were above the cost-effective threshold of US$25,920/DALY prevented. To be cost-effective in these comparisons, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively. To be highly cost-effective, the price thresholds were $435 and $335. The incremental costs per DALY prevented in relation to no vaccination was US$23,012, making the 9-valent vaccine marginally cost-effective. The results were robust in most one-way sensitivity analyses including changing vaccination age to 13 and 26 years.

Conclusions

At the current price, the 9-valent HPV vaccine is not cost-effective compared with the quadrivalent and the bivalent vaccines for young females in China who had not been previously infected with HPV. Policymakers and clinicians should keep potential vaccine

recipients informed about the economic profile of the 9-valent vaccine and carefully consider expanding its use in China at the current price.

Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia

Strengths and limitations of this study

1. The study used a previously validated model.
2. The analyses used Chinese-specific input data.
3. Only analysed individuals without prior infection.
4. Used a static model instead of a dynamic model and did not consider herd immunity.
5. Did not take into account the prevention of genital warts.

INTRODUCTION

Less than one year after the launch of the bivalent and quadrivalent human papillomavirus (HPV) vaccines in China, the 9-valent HPV vaccine was also approved by the China Food and Drug Administration in April 2018. Unlike the review processes of bivalent and quadrivalent HPV vaccines that took about ten years in China, the review process of 9-valent HPV vaccine took a record short period of nine days.(1) However, the 9-valent HPV vaccine was only approved for use among 16-26 years old females whereas the bivalent and quadrivalent HPV vaccines were approved for use among 9-26 years old males and females.(2)

Among the oncogenic HPV types, the bivalent and the quadrivalent vaccines are efficacious against types 16/18, whereas the 9-valent vaccine provides additional protection against types 31/33/45/52/58.(3) Both the quadrivalent and the 9-valent vaccines are also protective against HPV types 6/11, which can cause genital warts.(3) The cost-effectiveness of bivalent and quadrivalent HPV vaccines for the prevention of cervical cancer has been previously analysed in the setting of China. The results of such analyses were favourable to the cost-effectiveness of the bivalent and quadrivalent vaccines compared with no vaccination for the prevention of cervical cancer.(4, 5) However, the previous analyses in the literature were conducted before the introduction of the first HPV vaccine in China. Hence, the prices of HPV vaccines in the previous analyses was around $50, which did not reflect the present reality. In the meantime, the cost-effectiveness of the 9-valent HPV vaccine in China is still unknown. In light of this, it is important to obtain evidence on the value of the 9-valent vaccine to determine whether it should be used more broadly. Although previous studies have quantified the

cost-effectiveness of the 9-valent vaccines compared with alternative vaccines in other countries,(3, 6-9) evidence in other healthcare systems is not portable to China for numerous reasons such as different prices, cancer treatment costs and epidemiological profiles. As such, the objective of the current study was to analyse the cost-effectiveness of the 9-valent HPV vaccine for the prevention of cervical cancer among Chinese females from the perspective of private sector purchasers because HPV vaccines are neither publicly funded nor reimbursed by any payers to our knowledge. More specifically, this study pertains to the clinical decision setting of whether it is cost-effective for a Chinese female without previous infection to use the 9-valent HPV vaccine. We compared the 9-valent vaccine with the quadrivalent vaccines, the bivalent vaccines, and no vaccination, respectively. Among these, the comparison with the quadrivalent vaccine forms a specific incremental efficacy evaluation of cervical cancer prevention. Thus, it serves as the primary basis for discussion and conclusion. The comparison with the bivalent vaccine may be complicated by the additional efficacy of preventing non-oncogenic HPV types provided by the 9-valent vaccine, whereas the comparison with no vaccination is arguably not incremental. However, the alternative comparisons were necessary to render a comprehensive understanding of the health economic profile of the 9-valent vaccine, which is important because even the bivalent and the quadrivalent vaccines are subject to cost-effectiveness concerns for women living in rural areas of China.(10)

METHODS

We adapted the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model in the current analysis. The PRIME model is a health economic model

developed by the World Health Organization (WHO) that allows country-specific evaluation of HPV vaccination among females without prior infection of HPV.(11, 12) Country-specific cervical cancer incidence, mortality, HPV type distribution, and economic data were built in the model. The model developers assessed the quality of country-specific data as either "satisfactory" or "unsatisfactory" based on availability of data for each country and quality of methods used in data collection, and the Chinese data were deemed "satisfactory".(11) The model calculates the incremental costs per disability-adjusted life year (DALY) prevented for vaccinated individuals over lifetime as well as population outcomes such as cervical cancer prevented and deaths prevented. In addition, the model was validated against previously published HPV vaccine cost-effectiveness studies in the literature. More details of the model have been described elsewhere and in Appendix 1.(11)

The current analysis only examined incremental costs per DALY prevented for vaccinated individuals. Because the intervention of interest in the current analysis is 9-valent HPV vaccination, we modified the model to use the proportion of cervical cancer that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by International Agency for Research on Cancer (IARC) HPV Information Centre instead of only the proportion that was attributable to types 16/18 in the original model.(12, 13) According to IARC estimates, 92% of cervical cancer in China were attributable to types 16/18/31/33/45/52/58.(13)

The model also permitted customization of target age group, efficacy of vaccine (percentage of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer treatment cost, discount rate, and disutility values of three cancer-related health states

(cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the customized input fields can override the default data. In the current analysis, default data of efficacy of vaccine, discount rate, and disutility values were used. It should be noted that several other inputs could be customized in the model including coverage rate (or uptake rate), birth cohort size, and cohort size at the vaccination age. Except for coverage rate, these inputs only affect population outcomes that are not of interest in the current analysis and does not affect the results of the cost-effectiveness results for vaccinated individuals. We assumed a coverage rate of 100% in our analysis such that the mean population result is equivalent to that of an average vaccinated individual.

In the base-case analysis, the target age group was 16 years old females because this was the youngest group among the current age of licensure of the 9-valent vaccine in China (additional explanation in Appendix 2). It is noteworthy that this was older than the WHO-recommended primary target age window of 9-14 years.(14) Regardless of vaccination age, the time horizon was set so such that the cohort were followed up to 100 years old. The price of 9-valent HPV vaccine in government procurement catalogue as of December 2018 was used.(15, 16) We also assessed the prices at which the incremental costs per DALY prevented were at the cost-effective threshold of three times the 2017 China gross domestic product (GDP) per capita and at the highly cost-effective threshold of once the 2017 China GDP per capita to inform decision makers the value-based prices. Therefore, the cost-effective threshold and the highly cost-effective thresholds are US$25,920/DALY prevented and US$8,640/DALY prevented, respectively.(17) Default data of vaccine administration costs per person in China in the PRIME model were used but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices

in China.(18) In addition, cancer treatment costs in 2015 were updated to 2017 US dollars.(18, 19) Input data are listed in the first panel of Table 1.

Table 1. Input data and model results of the base-case analysis of the 9-valent HPV vaccine and the exploratory analyses of the bivalent and quadrivalent HPV vaccines

Input data		
Parameter	Value	Reference/source
Vaccination age	16 years	NA
Percentage of cervical cancer in China attributable to types 16/18/31/33/45/52/58	92.0%	(13)
Percentage of cervical cancer in China attributable to types 16/18	69.1%	(13)
9-valent vaccine price for full doses (2017 US$)	$610	(15, 16)
Quadrivalent vaccine price for full doses (2017 US$)	$375	(15, 16)
Bivalent vaccine price for full doses (2017 US$)	$273	(15, 16)
Vaccine administration costs (2017 US$)	$18	Model default with inflation adjustment(16, 18)
Cancer treatment costs (2017 US$)	$7,183	(18, 19)
Efficacy of vaccine	100%	Model default
Discount rate	3%	Base-case assumption
Disutility weight of cancer diagnosis	0.08	Model default
Disutility weight of non-terminal cancer sequelae	0.11	Model default
Disutility weight of terminal cancer	0.78	Model default

Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio measured as incremental costs per DALY prevented; NA, not applicable.

In one-way sensitivity analyses, age at vaccination (each age between 13-26 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups, cervical cancer mortality, all-cause mortality, cancer treatment costs, disutility of terminal cancer, and discount rate (1% and 5%) were varied to examine the robustness of incremental costs per DALY prevented results. Parameters of interest other than age at vaccination, efficacy, and discount rate were increased and decreased by 25%. In the pivotal clinical trial based on which the quadrivalent HPV vaccine was approved by the Chinese regulatory body, the efficacy against cervical intraepithelial neoplasia (CIN) grades 1+ and 2+ related to HPV 6/11/16/18 was 100% at the end of the 12th month (20). Also, the efficacy against cervical persistent infection was above 90% (20). Therefore, the efficacy was set to 90% in the sensitivity analyses to test the impact of possible lower efficacy after vaccination.

Patient and Public Involvement

Patients were not involved.

RESULTS

The base-case results of comparing the 9-valent vaccine with the quadrivalent and bivalent vaccines are shown in Table 2 (more detailed information on the base-case results is in Appendix 3). The incremental costs per DALY prevented compared with the quadrivalent and the bivalent vaccines were US$35,000 and US$50,455, respectively.

Therefore, the 9-valent vaccine was not cost-effective when compared with either the quadrivalent or the bivalent vaccine. To be cost-effective, the 9-valent vaccine should be priced at $550 and $450 for the full doses, respectively. To be highly cost-effective, the price thresholds were $435 and $335. Furthermore, the 9-valent vaccine should be priced at $505 to reach the same ICER as the quadrivalent vaccine when both vaccines were compared with no vaccination. The corresponding price was $370 when the comparator was the bivalent vaccine.

The results of comparing with no vaccination are displayed in Table 2. The incremental costs per DALY prevented were US$23,012. This was slightly less than the cost-effective threshold but substantially above the highly cost-effective threshold. In addition, the prices for the 9-valent HPV vaccine to be cost-effective and highly cost-effective were $680 and $220, respectively.

Table 2. Base-case results

	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted net costs	$611	$380	$278
Discounted DALYs prevented	0.0265	0.0199	0.0199
ICER of 9-valent vaccine vs. other vaccines	NA	$35,000	$50,455
ICER vs. not being vaccinated	$23,012	$19,061	$13,944
Price threshold of 9-valent vaccine to be cost-effective vs. other vaccines [a]	NA	$550	$450
Price threshold of 9-valent vaccine to be	NA	$435	$335

highly cost-effective vs. other vaccines [b]			
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines [c]	NA	$505	$370
Price threshold to be cost-effective vs. not being vaccinated	$680	NA	NA
Price threshold to be highly cost-effective vs. not being vaccinated	$220	NA	NA

Abbreviations: DALY, disability-adjusted life year; ICER, incremental cost-effectiveness ratio measured as incremental costs per DALY prevented; NA, not applicable.

[a] For example, the 9-valent vaccine should be priced at $550 for the full doses to be cost-effective when compared with the quadrivalent vaccine.

[b] For example, the 9-valent vaccine should be priced at $435 for the full doses to be highly cost-effective when compared with the quadrivalent vaccine.

[c] At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when each of them was compared with not receiving vaccination if the price of the 9-valent vaccine is $505 for the full doses. This is equivalent to saying the cost-effectiveness of the 9-valent vaccine vs. the quadrivalent vaccine is the same as the cost-effectiveness of the quadrivalent vaccine vs. not receiving vaccination. The interpretation of the comparison vs. the bivalent vaccine is the same.

The results of one-way sensitivity analyses are presented in Appendix 4. The results of comparing with the quadrivalent and the bivalent vaccines were relatively sensitive to using alternative discount rates. When the discount rate was 1%, the 9-valent vaccine was cost-effective compared with both the quadrivalent and the bivalent vaccines, but not highly cost-effective. However, none of the other changes impacted the inference using either the cost-effective threshold or the highly cost-effective threshold. In the comparison with no vaccination, both using alternative discount rates and changing the mortality rate of cervical cancer had substantial impacts on the results. When the discount rate was 5%, the incremental costs per DALY prevented in the comparison of

the 9-valent vaccine and no vaccination were $43,145, which was above the cost-effective threshold. Similarly, the corresponding result was $30,246 when the mortality rate of cervical cancer was reduced by 25%, which was also above the cost-effective threshold. The results remained cost-effective in all other scenarios.

DISCUSSION

In the present analysis, the 9-valent HPV vaccine was not cost-effective for the prevention of cervical cancer among 16-26 years old Chinese females without prior HPV infection when compared with either the quadrivalent or the bivalent vaccine, which remained so in all the sensitivity analyses except for using a discount rate of 1%. The results suggest that the price of the 9-valent HPV vaccine needs to be adjusted downward to provide more value for Chinese female recipients. Since the highly cost-effective threshold is more stringent, the 9-valent HPV vaccine is also not highly cost-effective in China.

The results are important to the extent that the marginal health gain of investing in the quadrivalent or bivalent vaccine is more than that of the 9-valent vaccine. Although the comparison with the bivalent vaccine may not be fair given that the bivalent vaccine does not protect against warts, the comparison with the quadrivalent vaccine is not subject to the same limitation. As far as cervical cancer is concerned, our results showed that the marginal health gain of an extra dollar in the healthcare budget to be spent on the 9-valent vaccine would be the same as that on the quadrivalent and bivalent vaccine if the 9-valent vaccine were to be priced at $505 and $370, respectively. In the meantime, a number of Chinese-manufactured bivalent and quadrivalent HPV vaccines are already in

the late stage of clinical trials and will likely be marketed at lower prices than the imported counterparts. The entrance of these products will further neutralize the edge of the 9-valent vaccine over the other vaccines in respect to cost-effectiveness. At the current price level, clinicians and policymakers are advised to educate potential vaccine recipients and keep them informed when suggesting vaccination.

The 9-valent HPV vaccine was cost-effective but not highly cost-effective for the prevention of cervical cancer among 16-26 years old Chinese females without prior HPV infection when compared with no vaccination. The results were robust to changes in important parameters except for discount rates and cervical cancer mortality.

While it is both intuitive and theoretically founded to compare the 9-valent vaccine only with the quadrivalent and the bivalent vaccines, it should be noted that further comparing the 9-valent vaccine with no vaccination may provide additional insights when the standard of practice is absent. Indeed, only comparing the 9-valent vaccine with the other HPV vaccines suffices to inform decision-making if HPV vaccination is already the standard of practice and the decision should pertain to incremental cost-effectiveness in relation to the standard of practice. While this might be true in high-income countries, it is not necessarily the case in China. Most Chinese females, regardless of age, have not been inoculated with any HPV vaccine. Specifically, the total number of HPV vaccine doses released by the National Institutes for Food and Drug Control in all batches as of September 2018 was merely 6 million,(21) indicating the maximum number of females in China that would have received at least one dose of HPV vaccine. Hence, the scenario that a portion of the individuals would only consider either receiving the 9-valent vaccine or not being vaccinated should not be ruled out. For

these individuals, the comparison of the 9-valent vaccine with no vaccination relevant for decision making. As such, we pertain to the comparison with the quadrivalent vaccine as the primary analysis but also provide exploratory results of comparing with no vaccination.

It is important to note the results of age-related sensitivity analyses do not necessarily suggest vaccination is more cost-effective at older ages. Smaller ICERs at older ages are mainly caused by fewer years of discounting the benefits (Appendix 5).

The cost-effectiveness profile of the 9-valent vaccine based on the present analysis contrasts that in several developed countries. A study found that the 9-valent vaccine was cost-effective compared with the quadrivalent vaccine among 12-26 years old females in the United States if the additional acquisition costs per dose was no more than US$13 (3). Their finding was confirmed by another US study (6). An Australian study also showed that the 9-valent vaccine was a cost-effective alternative to the quadrivalent vaccine for 12-year old females if the additional costs per dose was under AUS$36 (7). In Canada, Italy and Spain, the corresponding numbers were CAN$24, €16 and €16 (8, 9, 22). These numbers were generally consistent with the real-world price differences in the public sectors of the aforementioned countries (3, 8, 9). However, the gaps between the prices of the 9-valent and quadrivalent vaccines in these markets were substantially smaller than that in China, which is likely the main reason of the inconsistent cost-effectiveness profiles. This highlights the importance of adjusting the price of the 9-valent vaccine in China from the value perspective.

The current analysis is subject to several limitations. First, our analysis did not model catch-up immunization for those individuals who have already had prior infections.(12) It is reasonable to expect that the incremental benefit of the 9-valent vaccine is smaller among these individuals. Second, the analysis only considered the health benefits of preventing cervical cancer but not the benefits of preventing genital warts. Taking into account the prevention of genital warts will favour the 9-valent vaccine over the bivalent vaccine and no vaccination. In addition to these limitations, the model was also subject to other limitations that do not necessarily undermine the validity of the current results. For example, the model doesn't evaluate vaccination combined with cervical screening programs or assess herd immunity due to vaccination.(12) To the extent that the concentration of the present study is shedding light on the cost-effectiveness profiles of vaccines, including screening may obscure the focus as well as create confusion in the selection of decision perspective. Also, the model is only appropriate to evaluate vaccination among 9-13 years old females if the population outcomes are of interest because some individuals in a cohort of older ages may have been previously infected. In theory, these limitations do not affect the economic evaluation of vaccinating an individual who is known to have no previous infection and decides to accept immunization. Future economic evaluations should examine screening and vaccination strategies in which a portion of the target population were infected. More, Chinese-manufactured vaccines in future may affect the pricing of marketed products and the CEA should be updated accordingly. Even more, the efficacy of the vaccine was assumed to stay fully protective throughout the time horizon. This may not

be necessarily the case in practice. However, the impact of this limitation is unclear since it affects both the 9-valent vaccine and the other vaccines.

CONCLUSIONS

In conclusion, the 9-valent HPV vaccine is not cost-effective when compared with the quadrivalent vaccine for young females in China who had not been previously infected with HPV at its current price. It is also not cost-effective when compared with the bivalent vaccine, although it is marginally cost-effective yet not highly cost-effective when compared with no vaccination. Given these results, policymakers and clinicians should be conservative to expand the use of the 9-valent HPV vaccines in China unless the price is reduced. In addition, it is important that the clinicians discuss the economic profile of the 9-valent HPV vaccine to keep health-seeking individuals informed. More, public health professionals should be cautious about using the 9-valent vaccine as the primary choice at its current price if HPV vaccines are to be provided as public goods at nationally.

Word count of main text: 2,878

Contributors Design and data collection: YJ, WN and JW. Analysis and interpretation: YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript: WN and JW.

Competing interests YJ, WN and JW report no conflicts of interests related to the subject of the submitted work.

Funding This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement The PRIME model is publicly available at http://primetool.org/about-hpv/. The customized input data are listed in the table of the submitted manuscript. Further details about the country-specific cervical cancer incidence and mortality data can be found at http://gco.iarc.fr/databases.php. No additional data are available.

REFERENCES

1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed 2018 [Available from: https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed.
2. HPV vaccine becomes available in China for women between 16 to 26 years old 2018 [Available from: https://www.firstwordpharma.com/node/1560878?tsid=6.
3. Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified transmission model. Hum Vaccin Immunother. 2016;12(6):1363-72.
4. Levin CE, Sharma M, Olson Z, Verguet S, Shi J-F, Wang S-M, et al. An extended cost-effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China. Vaccine. 2015;33(24):2830-41.
5. Canfell K, Shi J-F, Lew J-B, Walker R, Zhao F-H, Simonella L, et al. Prevention of cervical cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies. Vaccine. 2011;29(13):2487-94.
6. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States. Proceedings of the National Academy of Sciences of the United States of America. 2016;113(18):5107.
7. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness of the next generation nonavalent human papillomavirus vaccine in the context of primary human papillomavirus screening in Australia: a comparative modelling analysis. 2016.
8. De La Fuente J, Hernandez Aguado JJ, Martín MS, Boix PR, Gómez SC, López NJHV, et al. Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent hpv vaccine in Spain.
9. Mennini FS, Bonanni P, Bianic F, Waure CD, Baio G, Plazzotta G, et al. Cost-effectiveness analysis of the nine-valent HPV vaccine in Italy. 2017;15(1):11.
10. Yin Y. HPV vaccination in China needs to be more cost-effective. The Lancet. 2017;390(10104):1735-6.
11. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-e14.
12. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and Economics Tool User Manual 2014 [Available from: http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf.
13. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact Sheet 2017 2017 [Available from: http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf.
14. World Health Organization. Human papillomavirus vaccines: WHO position paper, May 2017–Recommendations. Vaccine. 2017;35(43):5753-5.
15. Information of Drug Winning Bid 2018 [Available from: https://data.yaozh.com/yaopinzhongbiao.
16. XE Currency Table: USD - US Dollar 2017 [Available from: https://www.xe.com/currencytables/.
17. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita 2018 [Available from: http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD.

18. National Bureau of Statistics of China. Consumer Price Indices, Healthcare 2017 [Available from: http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01.
19. Mo X, Tobe RG, Wang L, Liu X, Wu B, Luo H, et al. Cost-effectiveness analysis of different types of human papillomavirus vaccination combined with a cervical cancer screening program in mainland China. BMC infectious diseases. 2017;17(1):502.
20. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human papillomavirus vaccine against persistent infection and genital disease in Chinese women: A randomized, placebo-controlled trial with 78-month follow-up. Vaccine. 2019;37(27):3617-24.
21. National Institutes for Food and Drug Control. Batch-release inquiry of biological products 2018 [Available from: http://www.nifdc.org.cn/CL0694/.
22. Mélanie D, Jean-Fran?Ois L, Marie-Claude B, Franco EL, Marc BJIJoC. Potential cost-effectiveness of the nonavalent human papillomavirus (HPV) vaccine. 2014;134(9):2264.

Appendix 1. Additional information on the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model

The PRIME model is a model developed by the World Health Organization (WHO) to estimate country-specific cost-effectiveness of HPV vaccination among females. It models the effect of the vaccine by incorporating the reduction in age-dependent incidence of cervical cancer as a result of vaccination. The model assumes that the individuals finish all doses of the vaccine and the vaccine provides lifelong protection. Also, it does not consider herd immunity.

The model is pre-populated with country-specific input data. However, it also allows customization of the input data. We changed the inputs of target age group, price of vaccine, delivery costs (adjusted based on the default input), and cancer treatment costs. We also changed the Chinese-specific data of the proportion of cervical cancer attributable to HPV types 16/18 to that of HPV types 16/18/31/33/45/52/58 for the analysis of the 9-valent vaccine.

To cross-validate the model, the developers of the model extracted input data from previous HPV modeling studies and calculated the results using the PRIME model. The results were then compared with the previous studies, the difference from published results was tested using Cohen's Kappa (0.845; indicates near perfect agreement). The developers showed that there was good agreement.

The model was adopted to evaluate the cost-effectiveness of HPV vaccination in Vietnam as a country-specific application in addition to multi-country application.(1) More details of the model have been described elsewhere.(2)

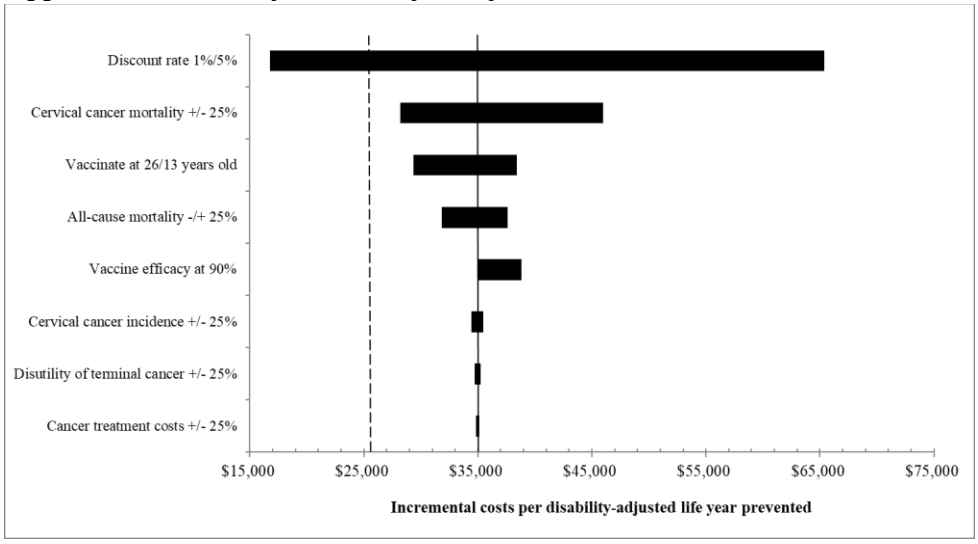
Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

In the base-case analysis, the target age group was 16 years old females because this was the youngest age group among the approved population for the use of the 9-valent vaccine in China. In China, the vast majority of the female individuals in this age are not infected with HPV. According to a study by Zhao et el., 6.9% of females in the age group 15-19 years old were sexually active in 2012.(3) This number should be lower for those who aged 16 years since this age is closer to the younger bound of the age group. Another study in the same year by Guo et al. confirmed that sexual debut before age 18 was rare in China.(4) Granted, the estimates were not necessarily accurate since there might be social desirability bias and the situation could have evolved, but it is impossible to speculate on how substantial the bias and the change were. However, it is reasonable to think the proportion of sexually active individuals in the 16 years old females is still very low in China. Therefore, most 16 years old still did not have sexual debut and did not expose to HPV although a very small proportion of them would have had sexual debut. Additionally, taking into consideration that most of those who had sexual debut would not have been infected, the proportion of uninfected individuals in the age group of 16 years old would be even higher than the proportion without sexual debut.

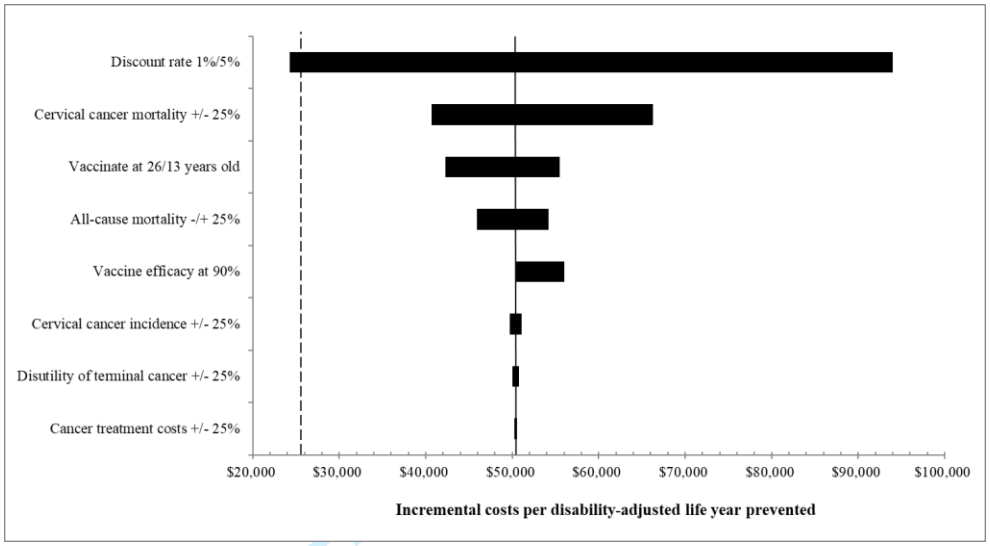
Appendix 3. Additional information on the base-case results.

	Not receiving vaccination	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18/31/33/45/52/58)	$17	$0	NA	NA
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18)	$13	NA	$0	$0
Total costs with vaccination	NA	$628	$393	$291
Discounted expected life years lost due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0250	0	NA	NA
Discounted expected life years lost due to cervical cancer (HPV types 16/18)	0.0188	NA	0	0
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0015	0	NA	NA
Discounted non-fatal DALYs due to cervical cancer (HPV types 16/18/31/33/45/52/58)	0.0011	NA	0	0
Discounted net costs	NA	$611	$380	$278
Discounted DALYs prevented	NA	0.0265	0.0199	0.0199
ICER vs. not being vaccinated	NA	$23,012	$19,061	$13,944

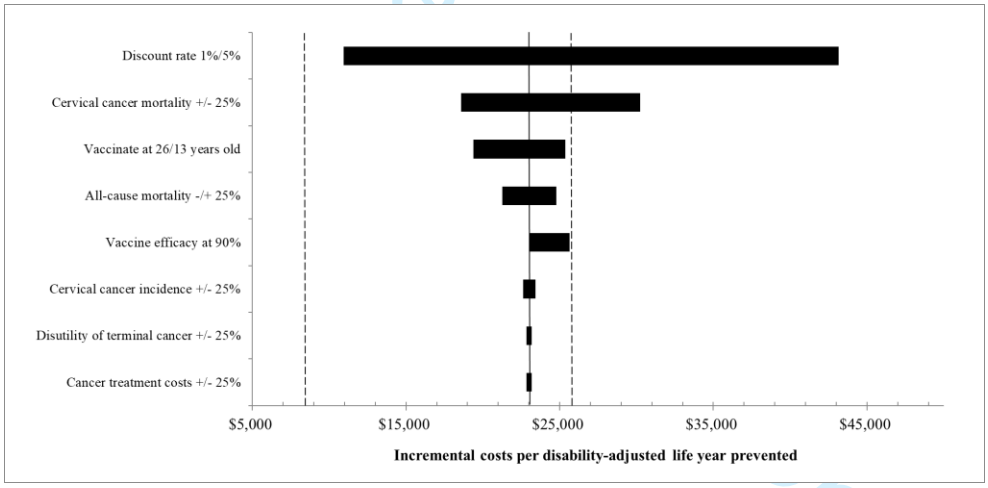
Appendix 4. One-way sensitivity analyses of the 9-valent HPV vaccine



a. Sensitivity analysis results of comparing the 9-valent vaccine with the quadrivalent vaccine. The dash line on the left represents the cost-effective threshold.



b. Sensitivity analysis results of comparing the 9-valent vaccine with the bivalent vaccine. The dash line on the left represents the cost-effective threshold.



c. Sensitivity analysis results of comparing the 9-valent vaccine with no vaccination. The left and right dash lines represent the highly cost-effective and cost-effective thresholds, respectively.

Appendix 5. An example of discounted results vs. undiscounted results. The sensitivity analysis result that vaccinating at older ages was more cost-effective is counter-intuitive. It was because the loss of DALYs prevented caused by discounting exceeds the gain of DALYs prevented by vaccinating earlier. To further illustrate this, we present below an example using the default PRIME model without customizing any parameters except age.

Hence, the results in the example only demonstrate how discounting affects model outputs and are not comparable to the results in the current study.

	Vaccinate at 16 years old		Vaccinate at 26 years old	
	Undiscounted	Discounted	Undiscounted	Discounted
Net costs	$42	$43	$42	$44
DALYs prevented	0.0482	0.0158	0.0445	0.0188
Incremental costs per DALY prevented	$867	$2,751	$945	$2,316

Abbreviations: DALY, disability-adjusted life year; PRIME, the Papillomavirus Rapid Interface for Modelling and Economics (PRIME).

References

1. Van Minh H, My NTT, Jit M. Cervical cancer treatment costs and cost-effectiveness analysis of human papillomavirus vaccination in Vietnam: a PRIME modeling study. BMC health services research. 2017;17(1):353.
2. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRIME modelling study. The Lancet Global health. 2014;2(7):e406-e14.
3. Zhao F-H, Tiggelaar SM, Hu S-Y, Xu L-N, Hong Y, Niyazi M, et al. A multi-center survey of age of sexual debut and sexual behavior in Chinese women: suggestions for optimal age of human papillomavirus vaccination in China. Cancer epidemiology. 2012;36(4):384-90.
4. Guo W, Wu Z, Qiu Y, Chen G, Zheng X. The timing of sexual debut among Chinese youth. International perspectives on sexual and reproductive health. 2012:196-204.

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force,* provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	page 2
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	page 7
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	page 9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	pages 7
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	page 7
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	pages 7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	page 8
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Table 1
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	page 8
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Table 1
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	page 10; Table 1
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	page 10
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	page 8
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 16-17
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	NA
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Table 1
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 1
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA

		of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Appendix 4
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	pages 11-12
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	page 19
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	page 18

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.