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# BMJ Open

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

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Manuscripts

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3 1 Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus

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5 2 Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling

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8 3 Analysis

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3 17 Abstract  
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6 18 Objectives  
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9 19 To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV)  
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11 20 vaccine for the prevention of cervical cancer in China.  
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17 22 Design  
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20 23 Health economic modelling using the Papillomavirus Rapid Interface for  
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22 24 Modelling and Economics (PRIME) model populated with China-specific data.  
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25 25

26 26 Setting  
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28 27 Individual cervical cancer prevention in China using the 9-valent HPV vaccine  
29  
30 28 from the perspective of private sector purchasers in relation to not receiving vaccination  
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32 29 and receiving other HPV vaccines for 16 years old females in China who had not been  
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34 30 previously infected with HPV.  
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41 32 Primary outcome measure  
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44 33 Incremental costs per disability-adjusted life year (DALY) prevented.  
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51 35 Results  
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3 36 In the base case, the incremental costs per DALY prevented were US\$23,012  
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5 37 when compared with no vaccination. The price thresholds for the 9-valent HPV vaccine  
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7 38 to be cost-effective and highly cost-effective in this comparison were \$680 and \$220,  
8  
9 39 respectively. However, the 9-valent vaccine was cost-ineffective for the prevention of  
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11 40 cervical cancers when compared with the bivalent and quadrivalent vaccines.  
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13 41 Specifically, the incremental costs per DALY prevented in relation to the bivalent and the  
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15 42 quadrivalent vaccines were \$35,000 and \$50,455, respectively. The cost-effectiveness  
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17 43 results were robust in most one-way sensitivity analyses.  
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## 25 45 Conclusions

26  
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28 46 Given the different cost-effectiveness inferences when different comparisons were  
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30 47 examined, policymakers and clinicians should carefully consider regional economic  
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32 48 realities when expanding the use of the 9-valent HPV vaccines in China.  
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39 50 Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia  
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3 52 Strengths and limitations of this study  
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5 53 1. The analyses covered various comparisons and scenarios of interest.  
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8 54 2. We presented not only the cost-effectiveness profiles but also the value-based  
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10 55 prices.  
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12 56 3. Only analysed individuals without prior infection.  
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14  
15 57 4. Used a static model instead of a dynamic model and did not consider herd  
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17 58 immunity.  
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19 59 5. Did not take into account the prevention of genital warts.  
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## 61 INTRODUCTION

62 Less than one year after the launch of the bivalent and quadrivalent human  
63 papillomavirus (HPV) vaccines in China, the 9-valent HPV vaccine was also approved by  
64 the China Food and Drug Administration in April 2018. Unlike the review processes of  
65 bivalent and quadrivalent HPV vaccines that took about ten years in China, the review  
66 process of 9-valent HPV vaccine took a record short period of nine days.[1] However, the  
67 9-valent HPV vaccine was only approved for use among 16-26 years old females whereas  
68 the bivalent and quadrivalent HPV vaccines were approved for use among 9-26 years old  
69 males and females.[2]

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

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3 84 without previous infection to use the 9-valent HPV vaccine. We compared the 9-valent  
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5 85 vaccine with no vaccination, the bivalent vaccines, and the quadrivalent vaccines,  
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8 86 respectively. The alternative comparisons were conducted to allow a comprehensive  
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10 87 understanding of the health economic profile of the 9-valent vaccine, which is important  
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12 88 because even the cost-effectiveness of the bivalent and the quadrivalent vaccines is not  
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15 89 without dispute in China.[5]  
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## 19 91 **METHODS**

20  
21 92 We adapted the Papillomavirus Rapid Interface for Modelling and Economics  
22  
23 93 (PRIME) model in the current analysis. The PRIME model is a health economic model  
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26 94 developed by the World Health Organization (WHO) that allows country-specific  
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28 95 evaluation of HPV vaccination among females without prior infection of HPV.[6, 7]  
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31 96 Country-specific cervical cancer incidence, mortality, HPV type distribution, and  
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33 97 economic data were built in the model. The model developers assessed the quality of  
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35 98 country-specific data as either “satisfactory” or “unsatisfactory”, and the Chinese data  
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38 99 were deemed “satisfactory”. [6] The model calculates the incremental costs per disability-  
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40 100 adjusted life year (DALY) prevented for vaccinated individuals over lifetime as well as  
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42 101 population outcomes such as cervical cancers prevented and deaths prevented. In  
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45 102 addition, the model was validated against previously published HPV vaccine cost-  
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47 103 effectiveness studies in the literature. More details of the model have been described  
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49 104 elsewhere and in Appendix 1.[6]  
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51 105 The current analysis only examined incremental costs per DALY prevented for  
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54 106 vaccinated individuals. Because the intervention of interest in the current analysis is 9-  
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3 107 valent HPV vaccination, we modified the model to use the proportion of cervical cancer  
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5 108 that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by  
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8 109 International Agency for Research on Cancer (IARC) HPV Information Centre instead of  
9  
10 110 only the proportion that was attributable to types 16/18 in the original model.[7, 8]  
11  
12 111 According to IARC estimates, 92% of cervical cancers in China were attributable to types  
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14 112 16/18/31/33/45/52/58.[8]  
15  
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17 113 The model also permitted customization of target age group, efficacy of vaccine  
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19 114 (percent of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer  
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21 115 treatment cost, discount rate, and disutility values of three cancer-related health states  
22  
23 116 (cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the  
24  
25 117 customized input fields can override the default data. In the current analysis, default data  
26  
27 118 of efficacy of vaccine, discount rate, and disutility values were used. It should be noted  
28  
29 119 that several other inputs could be customized in the model including coverage rate, birth  
30  
31 120 cohort size, and cohort size at the vaccination age. However, these inputs only affect  
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33 121 population outcomes that are not of interest in the current analysis and does not affect the  
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35 122 results of the cost-effectiveness results for vaccinated individuals.  
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40 123 In the base-case analysis, the target age group was 16 years old females because  
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42 124 this was the youngest group among the current age of licensure of the 9-valent vaccine in  
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44 125 China (additional explanation in Appendix 2). It is noteworthy that this was older than  
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46 126 the WHO-recommended primary target age window of 9-14 years.[9] The price of 9-  
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48 127 valent HPV vaccine in government procurement catalogue as of December 2018 was  
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50 128 used.[10, 11] We also assessed the prices at which the incremental costs per DALY  
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52 129 prevented were at the cost-effective threshold of three times the 2017 China gross  
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130 domestic product (GDP) per capita and at the highly cost-effective threshold of once the  
 131 2017 China GDP per capita to inform decision makers the value-based prices. Therefore,  
 132 the cost-effective threshold and the highly cost-effective thresholds are  
 133 US\$25,920/DALY prevented and US\$8,640/DALY prevented, respectively.[12] Default  
 134 data of vaccine administration costs per person in China in the PRIME model were used  
 135 but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices  
 136 in China.[13] In addition, cancer treatment costs in 2015 were updated to 2017 US  
 137 dollars.[13, 14] Input data are listed in the first panel of Table 1.

138

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

Parameter	Input data	
	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 <sup>a</sup>	NA	\$550	\$450
Price threshold of 9-valent vaccine to be highly cost-effective vs. other vaccines <sup>b</sup>	NA	\$435	\$335
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines <sup>c</sup>	NA	\$505	\$370

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3 141 Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER,  
4 142 incremental cost-effectiveness ratio measured as incremental costs per DALY prevented;  
5 143 NA, not applicable.

7 144 <sup>a</sup> For example, the 9-valent vaccine should be priced at \$550 for the full doses to be cost-  
8 145 effective when compared with the quadrivalent vaccine.

9 146 <sup>b</sup> For example, the 9-valent vaccine should be priced at \$435 for the full doses to be  
10 147 highly cost-effective when compared with the quadrivalent vaccine.

12 148 <sup>c</sup> At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when  
13 149 each of them was compared with not receiving vaccination if the price of the 9-valent  
14 150 vaccine is \$505 for the full doses. This is equivalent to saying the cost-effectiveness of  
15 151 the 9-valent vaccine vs. the 4-valent vaccine is the same as the cost-effectiveness of the  
16 152 quadrivalent vaccine vs. not receiving vaccination. The interpretation of the comparison  
17 153 vs. the bivalent vaccine is the same.  
19 154

21 155 In one-way sensitivity analyses, age at vaccination (each age between 13-26  
22 156 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups,  
23 157 cervical cancer mortality, all-cause mortality, cancer treatment costs, and disutility of  
24 158 terminal cancer were varied to examine the robustness of incremental costs per DALY  
25 159 prevented results. Parameters of interest other than age at vaccination and efficacy were  
26 160 increased and decreased by 25%.  
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## 37 162 Patient and Public Involvement

40 163 Patients were not involved.  
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## 48 166 RESULTS

50 167 The base-case results are displayed in the second panel of Table 1 (more detailed  
51 168 information on the base-case results is in Appendix 3). The incremental costs per DALY  
52 169 prevented were US\$23,012 when compared with no vaccination. This was slightly less

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3 170 than the cost-effective threshold but substantially above the highly cost-effective  
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5 171 threshold. In addition, the prices for the 9-valent HPV vaccine to be cost-effective and  
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8 172 highly cost-effective were \$680 and \$220, respectively.  
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10 173 The results of comparing the 9-valent vaccine with the bivalent and quadrivalent  
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12 174 vaccines are shown in the second panel of Table 1. The 9-valent vaccine was not cost-  
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15 175 effective when compared with either the bivalent or the quadrivalent vaccine. To be cost-  
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17 176 effective in relation to bivalent and quadrivalent vaccines, the 9-valent vaccine should be  
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19 177 priced at \$550 and \$450 for the full doses, respectively. To be highly cost-effective, the  
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21 178 price thresholds were \$435 and \$335. Furthermore, the 9-valent vaccine should be priced  
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24 179 at \$505 to reach the same ICER as the quadrivalent vaccine when both vaccines were  
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26 180 compared with not receiving vaccination, or at \$370 when the comparator was the  
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29 181 bivalent vaccine.

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31 182 The results of the one-way sensitivity analyses are presented in Appendix 4.  
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33 183 When the mortality rate of cervical cancer was reduced by 25%, the incremental costs per  
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35 184 DALY prevented in the comparison of the 9-valent vaccine and no vaccination were  
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38 185 \$30,246, which was above the cost-effective threshold. The results remained cost-  
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40 186 effective in all other scenarios. The results in the comparison with the bivalent and the  
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42 187 quadrivalent vaccines were also relatively sensitive to the mortality rate of cervical  
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45 188 cancer. However, none of the changes impacted the inference using either the cost-  
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47 189 effective threshold or the highly cost-effective threshold.  
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51 191 **DISCUSSION**  
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3 192 In the current analysis, the 9-valent HPV vaccine was cost-effective but not  
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5 193 highly cost-effective for the prevention of cervical cancers among 16-26 years old  
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8 194 Chinese females without prior HPV infection when compared with no vaccination. The  
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10 195 results were robust to changes in important parameters except cervical cancer mortality.

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12 196 The results suggest that the 9-valent HPV vaccine does provide value at the  
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14 197 current price when compared with not receiving vaccine at the three times the GDP per  
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16 198 capita threshold. However, there isn't a universal definition of cost-effective threshold  
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18 199 nor a consensus on such. Therefore, alternative thresholds should be considered. A  
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20 200 commonly used alternative cut-off is the highly cost-effective threshold. Based on this  
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22 201 threshold, the 9-valent HPV vaccine is not highly cost-effective in China. Clinicians and  
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24 202 policymakers are advised to consider local economic realities and patient financial status  
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26 203 when deciding whether to use the 9-valent vaccine.

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30 204 The results of comparing alternative vaccines are also important in certain  
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32 205 contexts. The 9-valent vaccine was cost-ineffective when compared with the bivalent  
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34 206 and the quadrivalent vaccines. These results are important to the extent that the marginal  
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36 207 benefit of investing in the bivalent or quadrivalent vaccines is more than that of the 9-  
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38 208 valent vaccine. Although the comparison with the bivalent vaccine may not be fair since  
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40 209 the bivalent vaccine does not protect against warts, the comparison with the quadrivalent  
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42 210 vaccine is not subject to the same limitation. As far as cervical cancer is concerned, our  
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44 211 results showed that the marginal health gain of an extra dollar in the healthcare budget to  
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46 212 be spent on the 9-valent vaccine would be the same as that on the quadrivalent and  
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48 213 bivalent vaccine if the 9-valent vaccine were to be priced at \$505 and \$370, respectively.  
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51 214 These findings should raise concerns over the already disputable cost-effectiveness  
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3 215 profiles of HPV vaccines in China.[5] A number of bivalent and quadrivalent Chinese-  
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5 216 manufactured HPV vaccines are already in the late stage of clinical trials and will likely  
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8 217 be marketed at lower prices than the imported counterparts. The entrance of these  
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10 218 products will further neutralize the edge of the 9-valent vaccine over the other vaccines  
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12 219 with regard to cost-effectiveness.

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15 220 While it is both intuitive and tempting to compare the 9-valent vaccine only with  
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17 221 the bivalent or the quadrivalent vaccines and to entirely dismiss the comparison with no  
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19 222 vaccination, it is not necessarily appropriate in China. Indeed, only comparing the 9-  
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21 223 valent vaccine with the other HPV vaccines suffices to inform decision-making if HPV  
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23 224 vaccination is already the standard of practice and the decision should pertain to  
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26 225 incremental cost-effectiveness in relation to the standard of practice. While this might be  
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28 226 true in high-income countries, it is not the case in China. Most Chinese females,  
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30 227 regardless of age, have not been inoculated with any HPV vaccine. Specifically, the total  
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32 228 number of HPV vaccine doses released by the National Institutes for Food and Drug  
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34 229 Control in all batches as of September 2018 was merely 6 million.[15] In addition, the  
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36 230 cost-effectiveness of the bivalent and quadrivalent vaccines at their current prices is not  
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38 231 necessarily conclusive.[5] As such, only comparing the 9-valent vaccine with the  
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40 232 alternative vaccines may potentially be misleading if the alternative vaccines are  
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42 233 themselves beyond the efficiency frontier.

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47 234 More, it is important to note the results of age-related sensitivity analyses do not  
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49 235 necessarily suggest vaccination is more cost-effective at older ages. The smaller ICERs at  
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51 236 older ages are caused by fewer years of discounting the benefits (Appendix 5).

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3 237 The current analysis is subject to several limitations. First, the PRIME tool was  
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5 238 not designed to model catch-up immunization for those individuals who have already had  
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7 239 prior infections.[7] Second, the analysis only considered the health benefits of preventing  
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9 240 cervical cancer but not the benefits of preventing genital warts. In addition to these  
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11 241 limitations, the model was also subject to other limitations that do not necessarily  
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13 242 undermine the validity of the current results. For example, the model doesn't evaluate  
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15 243 vaccination combined with cervical screening programs or assess herd immunity due to  
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17 244 vaccination.[7] Also, the model is only appropriate to evaluate vaccination among 9-13  
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19 245 years old females if the population outcomes are of interest because some individuals in a  
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21 246 cohort of older ages may have been previously infected. However, these limitations do  
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23 247 not affect the economic evaluation of vaccinating an individual who is known to have no  
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25 248 previous infection and decides to whether accept immunization. More, Chinese-  
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27 249 manufactured vaccines in future may affect the pricing of marketed products and the  
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29 250 CEA should be updated.  
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## 252 CONCLUSIONS

40 253 In conclusion, the 9-valent HPV vaccine is cost-effective but not highly cost-  
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42 254 effective to prevent cervical cancer among females without prior HPV infection at the  
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44 255 current price in China when compared with no vaccination. It is cost-ineffective when  
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46 256 compared with the bivalent and quadrivalent vaccines. Given these mixed results,  
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48 257 policymakers and clinicians should carefully consider regional economic realities when  
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50 258 expanding the use of the 9-valent HPV vaccines in China. In particular, it is important  
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52 259 that the clinicians consider both the clinical and economic profiles of the HPV vaccines  
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3 260 when discussing vaccination with clients. More, public health professionals should be  
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5 261 cautious about using the 9-valent vaccine as the primary choice at its current price if HPV  
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7 262 vaccines are to be provided as public goods. The 9-valent vaccine is more likely to  
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9 263 provide sufficient value if the price can be reduced substantially.  
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16  
17 266 **Contributors** Design and data collection: YJ, WN and JW. Analysis and interpretation:  
18  
19 267 YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript:  
20  
21 268 WN and JW.  
22  
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25  
26 270 **Competing interests** YJ, WN and JW report no conflicts of interests related to the  
27  
28 271 subject of the submitted work.  
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42 276 **Data sharing statement** The PRIME model is publicly available at  
43  
44 277 <http://primetool.org/about-hpv/>. The customized input data are listed in the table of the  
45  
46 278 submitted manuscript. No additional data are available.  
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285 **REFERENCES**

- 286 1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed. 2018.  
287 [https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed)  
288 [conditional-nod-lightning-speed](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed) (Accessed May 16 2018).
- 289 2. HPV vaccine becomes available in China for women between 16 to 26 years old. 2018.  
290 <https://www.firstwordpharma.com/node/1560878?tsid=6> (Accessed May 10 2018).
- 291 3. Levin CE, Sharma M, Olson Z, et al. An extended cost-effectiveness analysis of publicly  
292 financed HPV vaccination to prevent cervical cancer in China. *Vaccine* 2015;33(24):2830-41.
- 293 4. Canfell K, Shi JF, Lew JB, et al. Prevention of cervical cancer in rural China: evaluation of HPV  
294 vaccination and primary HPV screening strategies. *Vaccine* 2011;29(13):2487-94.
- 295 5. Yin Y. HPV vaccination in China needs to be more cost-effective. *Lancet*  
296 2017;390(10104):1735-1736.
- 297 6. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus  
298 vaccination in 179 countries: a PRIME modelling study. *Lancet Glob Health* 2014;2(7):e406-14.
- 299 7. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and Economics  
300 Tool User Manual. 2014. [http://primetool.org/wp-](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf)  
301 [content/uploads/documents/PRIME\\_Tool\\_Manual\\_v2.pdf](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf) (Accessed May 08 2018).
- 302 8. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact Sheet  
303 2017. 2017. [http://www.hpvcentre.net/statistics/reports/CHN\\_FS.pdf](http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf) (Accessed May 10 2018).
- 304 9. World Health Organization. Electronic address: sageexecsec@who.int.. Human papillomavirus  
305 vaccines: WHO position paper, May 2017-Recommendations. *Vaccine* 2017;35(43):5753-5755.
- 306 10. Information of Drug Winning Bid. 2018. <https://data.yaozh.com/yaopinzhongbiao> (Accessed  
307 December 17 2018).
- 308 11. XE Currency Table: USD - US Dollar. 2017. <https://www.xe.com/currencytables/> (Accessed  
309 May 10 2018).
- 310 12. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita. 2018.  
311 <http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD>  
312 (Accessed May 10 2018).
- 313 13. National Bureau of Statistics of China. Consumer Price Indices, Healthcare. 2017.  
314 <http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01> (Accessed May 17 2018).
- 315 14. Mo X, Gai Tobe R, Wang L, et al. Cost-effectiveness analysis of different types of human  
316 papillomavirus vaccination combined with a cervical cancer screening program in mainland  
317 China. *BMC Infect Dis* 2017;17(1):502.
- 318 15. National Institutes for Food and Drug Control. Batch-release inquiry of biological products.  
319 2018. <http://www.nifdc.org.cn/CL0694/> (Accessed September 20 2018).

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## 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]

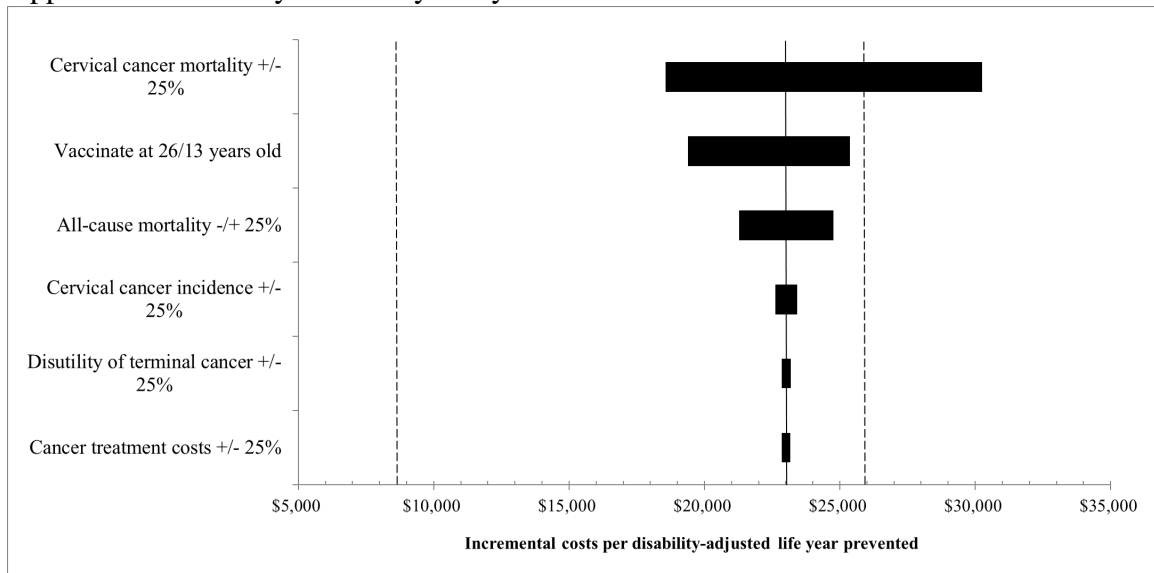
## Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

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 al., 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.

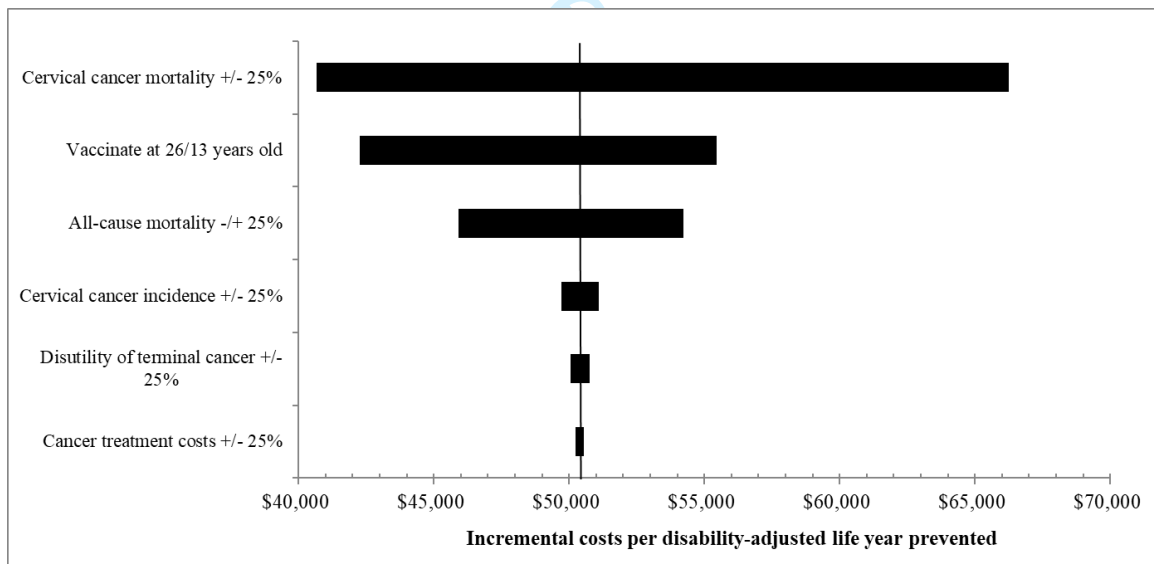
## Appendix 3. Additional information on the base-case results.

	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

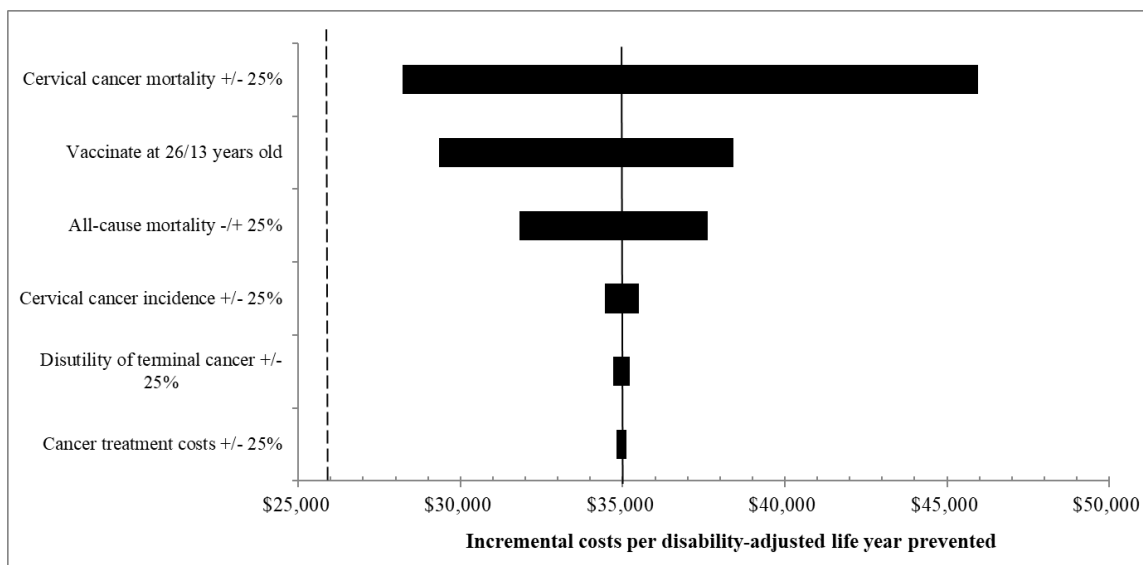
Appendix 4. One-way sensitivity analyses of the 9-valent HPV vaccine



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.

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- 3 3. Zhao FH, Tiggelaar SM, Hu SY, et al. A multi-center survey of age of sexual debut and sexual
- 4 behavior in Chinese women: suggestions for optimal age of human papillomavirus vaccination in
- 5 China. *Cancer Epidemiol* 2012;36(4):384-90.
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- 7 4. Guo W, Wu Z, Qiu Y, Chen G, Zheng X. The timing of sexual debut among Chinese youth. *Int*
- 8 *Perspect Sex Reprod Health* 2012;38(4):196-204.
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## 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
<b>Title and abstract</b>			
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
<b>Introduction</b>			
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
<b>Methods</b>			
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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 6
2				
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4	Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
5				
6	Estimating resources and costs	13a	<i>Single study-based economic evaluation:</i> 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
7				
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9		13b	<i>Model-based economic evaluation:</i> 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
10				
11	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
12				
13	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
14				
15	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 12-13
16	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
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19	<b>Results</b>			
20	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
21				
22	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
23				
24	Characterising uncertainty	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
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1		of methodological assumptions (such as discount rate, study perspective).	
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4		20b <i>Model-based economic evaluation</i> : 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
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7	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
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13	<b>Discussion</b>		
14	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
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19	<b>Other</b>		
20	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
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24	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
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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

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<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Sexual health, Infectious diseases, Public health
Keywords:	cost-effectiveness, HPV, vaccination, China, cervical neoplasia

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Manuscripts

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3 1 Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus

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5 2 Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling

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12 5 Yawen Jiang,<sup>a</sup> Ph.D., Weiyi Ni,<sup>b, c</sup> Ph.D., Jing Wu,<sup>b</sup> Ph.D.

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9 19 To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV)  
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11 20 vaccine for the prevention of cervical cancer in China.  
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17 22 Design  
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22 24 Modelling and Economics (PRIME) model populated with China-specific data.  
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31 27 Individual cervical cancer prevention in China using the 9-valent HPV vaccine  
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33 28 from the perspective of private sector purchasers in relation to receiving other HPV  
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35 29 vaccines and not receiving vaccination for 16 years old females in China who had not  
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37 30 been previously infected with HPV.  
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23 43 US\$35,000 and US\$50,455 compared with the quadrivalent and the bivalent vaccines,  
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25 44 both of which were above the cost-effective threshold of US\$25,920/DALY prevented.  
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27 45 To be cost-effective in these comparisons, the 9-valent vaccine should be priced at \$550  
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29 46 and \$450 for the full doses, respectively. To be highly cost-effective, the price thresholds  
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31 47 were \$435 and \$335. The incremental costs per DALY prevented in relation to no  
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33 48 vaccination was US\$23,012, making the 9-valent vaccine marginally cost-effective. The  
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35 49 results were robust in most one-way sensitivity analyses including changing vaccination  
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37 50 age to 13 and 26 years.  
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45 52 Conclusions  
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48 53 At the current price, the 9-valent HPV vaccine is not cost-effective compared with  
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50 54 the quadrivalent and the bivalent vaccines for young females in China who had not been  
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52 55 previously infected with HPV. Policymakers and clinicians should keep potential vaccine  
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3 56 recipients informed about the economic profile of the 9-valent vaccine and carefully  
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5 57 consider expanding its use in China at the current price.  
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11 59 Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia  
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For peer review only



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3 61 Strengths and limitations of this study  
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5 62 1. The study used a previously validated model.  
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8 63 2. The analyses used Chinese-specific input data.  
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10 64 3. Only analysed individuals without prior infection.  
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12 65 4. Used a static model instead of a dynamic model and did not consider herd  
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17 67 5. Did not take into account the prevention of genital warts.  
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## 69 INTRODUCTION

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

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

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3 92 cost-effectiveness of the 9-valent vaccines compared with alternative vaccines in other  
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5 93 countries,(3, 6-9) evidence in other healthcare systems is not portable to China for  
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8 94 numerous reasons such as different prices, cancer treatment costs and epidemiological  
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10 95 profiles. As such, the objective of the current study was to analyse the cost-effectiveness  
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12 96 of the 9-valent HPV vaccine for the prevention of cervical cancer among Chinese females  
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15 97 from the perspective of private sector purchasers because HPV vaccines are neither  
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17 98 publicly funded nor reimbursed by any payers to our knowledge. More specifically, this  
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19 99 study pertains to the clinical decision setting of whether it is cost-effective for a Chinese  
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22 100 female without previous infection to use the 9-valent HPV vaccine. We compared the 9-  
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24 101 valent vaccine with the quadrivalent vaccines, the bivalent vaccines, and no vaccination,  
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26 102 respectively. Among these, the comparison with the quadrivalent vaccine forms a specific  
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28 103 incremental efficacy evaluation of cervical cancer prevention. Thus, it serves as the  
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30 104 primary basis for discussion and conclusion. The comparison with the bivalent vaccine  
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32 105 may be complicated by the additional efficacy of preventing non-oncogenic HPV types  
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34 106 provided by the 9-valent vaccine, whereas the comparison with no vaccination is  
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36 107 arguably not incremental. However, the alternative comparisons were necessary to render  
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38 108 a comprehensive understanding of the health economic profile of the 9-valent vaccine,  
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40 109 which is important because even the bivalent and the quadrivalent vaccines are subject to  
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45 110 cost-effectiveness concerns for women living in rural areas of China.(10)

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## 112 **METHODS**

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

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3 115 developed by the World Health Organization (WHO) that allows country-specific  
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5 116 evaluation of HPV vaccination among females without prior infection of HPV.(11, 12)  
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7 117 Country-specific cervical cancer incidence, mortality, HPV type distribution, and  
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9 118 economic data were built in the model. The model developers assessed the quality of  
10  
11 119 country-specific data as either “satisfactory” or “unsatisfactory” based on availability of  
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13 120 data for each country and quality of methods used in data collection, and the Chinese data  
14  
15 121 were deemed “satisfactory”.(11) The model calculates the incremental costs per  
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17 122 disability-adjusted life year (DALY) prevented for vaccinated individuals over lifetime as  
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19 123 well as population outcomes such as cervical cancer prevented and deaths prevented. In  
20  
21 124 addition, the model was validated against previously published HPV vaccine cost-  
22  
23 125 effectiveness studies in the literature. More details of the model have been described  
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25 126 elsewhere and in Appendix 1.(11)  
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31 127 The current analysis only examined incremental costs per DALY prevented for  
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33 128 vaccinated individuals. Because the intervention of interest in the current analysis is 9-  
34  
35 129 valent HPV vaccination, we modified the model to use the proportion of cervical cancer  
36  
37 130 that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by  
38  
39 131 International Agency for Research on Cancer (IARC) HPV Information Centre instead of  
40  
41 132 only the proportion that was attributable to types 16/18 in the original model.(12, 13)  
42  
43 133 According to IARC estimates, 92% of cervical cancer in China were attributable to types  
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45 134 16/18/31/33/45/52/58.(13)  
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49 135 The model also permitted customization of target age group, efficacy of vaccine  
50  
51 136 (percentage of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer  
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53 137 treatment cost, discount rate, and disutility values of three cancer-related health states  
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3 138 (cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the  
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5 139 customized input fields can override the default data. In the current analysis, default data  
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7 140 of efficacy of vaccine, discount rate, and disutility values were used. It should be noted  
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9  
10 141 that several other inputs could be customized in the model including coverage rate (or  
11  
12 142 uptake rate), birth cohort size, and cohort size at the vaccination age. Except for coverage  
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14  
15 143 rate, these inputs only affect population outcomes that are not of interest in the current  
16  
17 144 analysis and does not affect the results of the cost-effectiveness results for vaccinated  
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19 145 individuals. We assumed a coverage rate of 100% in our analysis such that the mean  
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21  
22 146 population result is equivalent to that of an average vaccinated individual.

23  
24 147 In the base-case analysis, the target age group was 16 years old females because  
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26 148 this was the youngest group among the current age of licensure of the 9-valent vaccine in  
27  
28 149 China (additional explanation in Appendix 2). It is noteworthy that this was older than  
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30  
31 150 the WHO-recommended primary target age window of 9-14 years.(14) Regardless of  
32  
33 151 vaccination age, the time horizon was set so such that the cohort were followed up to 100  
34  
35 152 years old. The price of 9-valent HPV vaccine in government procurement catalogue as of  
36  
37  
38 153 December 2018 was used.(15, 16) We also assessed the prices at which the incremental  
39  
40 154 costs per DALY prevented were at the cost-effective threshold of three times the 2017  
41  
42 155 China gross domestic product (GDP) per capita and at the highly cost-effective threshold  
43  
44 156 of once the 2017 China GDP per capita to inform decision makers the value-based prices.  
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46  
47 157 Therefore, the cost-effective threshold and the highly cost-effective thresholds are  
48  
49 158 US\$25,920/DALY prevented and US\$8,640/DALY prevented, respectively.(17) Default  
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51  
52 159 data of vaccine administration costs per person in China in the PRIME model were used  
53  
54 160 but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices

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

163

164 Table 1. Input data and model results of the base-case analysis of the 9-valent HPV  
 165 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

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3 166 Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER,  
4 167 incremental cost-effectiveness ratio measured as incremental costs per DALY prevented;  
5 168 NA, not applicable.

6 169  
7  
8 170 In one-way sensitivity analyses, age at vaccination (each age between 13-26  
9  
10 171 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups,  
11  
12 172 cervical cancer mortality, all-cause mortality, cancer treatment costs, disutility of  
13  
14 173 terminal cancer, and discount rate (1% and 5%) were varied to examine the robustness of  
15  
16 174 incremental costs per DALY prevented results. Parameters of interest other than age at  
17  
18 175 vaccination, efficacy, and discount rate were increased and decreased by 25%.  
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23  
24 177 Patient and Public Involvement

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27 178 Patients were not involved.  
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## 31 32 180 **RESULTS**

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35 181 The base-case results of comparing the 9-valent vaccine with the quadrivalent and  
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37 182 bivalent vaccines are shown in Table 2 (more detailed information on the base-case  
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39 183 results is in Appendix 3). The incremental costs per DALY prevented compared with the  
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41 184 quadrivalent and the bivalent vaccines were US\$35,000 and US\$50,455, respectively.  
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43  
44 185 Therefore, the 9-valent vaccine was not cost-effective when compared with either the  
45  
46 186 quadrivalent or the bivalent vaccine. To be cost-effective, the 9-valent vaccine should be  
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48 187 priced at \$550 and \$450 for the full doses, respectively. To be highly cost-effective, the  
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50 188 price thresholds were \$435 and \$335. Furthermore, the 9-valent vaccine should be priced  
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52 189 at \$505 to reach the same ICER as the quadrivalent vaccine when both vaccines were  
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190 compared with no vaccination. The corresponding price was \$370 when the comparator  
 191 was the bivalent vaccine.

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

197  
 198 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 <sup>a</sup>	NA	\$550	\$450
Price threshold of 9-valent vaccine to be highly cost-effective vs. other vaccines <sup>b</sup>	NA	\$435	\$335
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines <sup>c</sup>	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



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vs. not being  
vaccinated

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

201 <sup>a</sup> For example, the 9-valent vaccine should be priced at \$550 for the full doses to be cost-  
202 effective when compared with the quadrivalent vaccine.

203 <sup>b</sup> For example, the 9-valent vaccine should be priced at \$435 for the full doses to be  
204 highly cost-effective when compared with the quadrivalent vaccine.

205 <sup>c</sup> At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when  
206 each of them was compared with not receiving vaccination if the price of the 9-valent  
207 vaccine is \$505 for the full doses. This is equivalent to saying the cost-effectiveness of  
208 the 9-valent vaccine vs. the quadrivalent vaccine is the same as the cost-effectiveness of  
209 the quadrivalent vaccine vs. not receiving vaccination. The interpretation of the  
210 comparison vs. the bivalent vaccine is the same.  
211

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

225

## 226 **DISCUSSION**

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3 227 In the present analysis, the 9-valent HPV vaccine was not cost-effective for the  
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5 228 prevention of cervical cancer among 16-26 years old Chinese females without prior HPV  
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7 229 infection when compared with either the quadrivalent or the bivalent vaccine, which  
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10 230 remained so in all the sensitivity analyses except for using a discount rate of 1%. The  
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12 231 results suggest that the price of the 9-valent HPV vaccine needs to be adjusted downward  
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14 232 to provide more value for Chinese female recipients. Since the highly cost-effective  
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16 233 threshold is more stringent, the 9-valent HPV vaccine is also not highly cost-effective in  
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18 234 China.

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21 235 The results are important to the extent that the marginal health gain of investing in  
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23 236 the quadrivalent or bivalent vaccine is more than that of the 9-valent vaccine. Although  
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25 237 the comparison with the bivalent vaccine may not be fair given that the bivalent vaccine  
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27 238 does not protect against warts, the comparison with the quadrivalent vaccine is not  
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29 239 subject to the same limitation. As far as cervical cancer is concerned, our results showed  
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31 240 that the marginal health gain of an extra dollar in the healthcare budget to be spent on the  
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33 241 9-valent vaccine would be the same as that on the quadrivalent and bivalent vaccine if the  
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35 242 9-valent vaccine were to be priced at \$505 and \$370, respectively. In the meantime, a  
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37 243 number of Chinese-manufactured bivalent and quadrivalent HPV vaccines are already in  
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39 244 the late stage of clinical trials and will likely be marketed at lower prices than the  
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41 245 imported counterparts. The entrance of these products will further neutralize the edge of  
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43 246 the 9-valent vaccine over the other vaccines in respect to cost-effectiveness. At the  
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45 247 current price level, clinicians and policymakers are advised to educate potential vaccine  
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47 248 recipients and keep them informed when suggesting vaccination.  
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3 249 The 9-valent HPV vaccine was cost-effective but not highly cost-effective for the  
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5 250 prevention of cervical cancer among 16-26 years old Chinese females without prior HPV  
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8 251 infection when compared with no vaccination. The results were robust to changes in  
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10 252 important parameters except for discount rates and cervical cancer mortality.

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12 253 While it is both intuitive and theoretically founded to compare the 9-valent  
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14 254 vaccine only with the quadrivalent and the bivalent vaccines, it should be noted that  
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17 255 further comparing the 9-valent vaccine with no vaccination may provide additional  
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19 256 insights when the standard of practice is absent. Indeed, only comparing the 9-valent  
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21 257 vaccine with the other HPV vaccines suffices to inform decision-making if HPV  
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24 258 vaccination is already the standard of practice and the decision should pertain to  
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26 259 incremental cost-effectiveness in relation to the standard of practice. While this might be  
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28 260 true in high-income countries, it is not necessarily the case in China. Most Chinese  
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30 261 females, regardless of age, have not been inoculated with any HPV vaccine. Specifically,  
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33 262 the total number of HPV vaccine doses released by the National Institutes for Food and  
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35 263 Drug Control in all batches as of September 2018 was merely 6 million,(20) indicating  
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37 264 the maximum number of females in China that would have received at least one dose of  
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39 265 HPV vaccine. Hence, the scenario that a portion of the individuals would only consider  
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41 266 either receiving the 9-valent vaccine or not being vaccinated should not be ruled out. For  
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43 267 these individuals, the comparison of the 9-valent vaccine with no vaccination relevant  
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45 268 for decision making. As such, we pertain to the comparison with the quadrivalent vaccine  
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47 269 as the primary analysis but also provide exploratory results of comparing with no  
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49 270 vaccination.

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3 271 It is important to note the results of age-related sensitivity analyses do not  
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5 272 necessarily suggest vaccination is more cost-effective at older ages. Smaller ICERs at  
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8 273 older ages are mainly caused by fewer years of discounting the benefits (Appendix 5).  
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10 274 The cost-effectiveness profile of the 9-valent vaccine based on the present  
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12 275 analysis contrasts that in several developed countries. A study found that the 9-valent  
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14 276 vaccine was cost-effective compared with the quadrivalent vaccine among 12-26 years  
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17 277 old females in the United States if the additional acquisition costs per dose was no more  
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19 278 than US\$13 (3). Their finding was confirmed by another US study (6). An Australian  
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21 279 study also showed that the 9-valent vaccine was a cost-effective alternative to the  
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23 280 quadrivalent vaccine for 12-year old females if the additional costs per dose was under  
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26 281 AUS\$36 (7). In Canada, Italy and Spain, the corresponding numbers were CAN\$24, €16  
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29 282 and €16 (8, 9, 21). These numbers were generally consistent with the real-world price  
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33 283 differences in the public sectors of the aforementioned countries (3, 8, 9). However, the  
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35 284 gaps between the prices of the 9-valent and quadrivalent vaccines in these markets were  
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38 285 substantially smaller than that in China, which is likely the main reason of the  
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40 286 inconsistent cost-effectiveness profiles. This highlights the importance of adjusting the  
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42 287 price of the 9-valent vaccine in China from the value perspective.  
43

44 288 The current analysis is subject to several limitations. First, our analysis did not  
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46  
47 289 model catch-up immunization for those individuals who have already had prior  
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49 290 infections.(12) It is reasonable to expect that the incremental benefit of the 9-valent  
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51 291 vaccine is smaller among these individuals. Second, the analysis only considered the  
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53 292 health benefits of preventing cervical cancer but not the benefits of preventing genital  
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3 293 warts. Taking into account the prevention of genital warts will favour the 9-valent  
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5 294 vaccine over the bivalent vaccine and no vaccination. In addition to these limitations, the  
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7 295 model was also subject to other limitations that do not necessarily undermine the validity  
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9  
10 296 of the current results. For example, the model doesn't evaluate vaccination combined  
11  
12 297 with cervical screening programs or assess herd immunity due to vaccination.(12) Also,  
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14 298 the model is only appropriate to evaluate vaccination among 9-13 years old females if the  
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16 299 population outcomes are of interest because some individuals in a cohort of older ages  
17  
18 300 may have been previously infected. In theory, these limitations do not affect the  
19  
20 301 economic evaluation of vaccinating an individual who is known to have no previous  
21  
22 302 infection and decides to accept immunization. Future economic evaluations should  
23  
24 303 examine screening and vaccination strategies in which a portion of the target population  
25  
26 304 were vaccinated. More, Chinese-manufactured vaccines in future may affect the pricing  
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28 305 of marketed products and the CEA should be updated accordingly. Even more, the  
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30 306 efficacy of the vaccine was assumed to stay fully protective throughout the time horizon.  
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32 307 This may not be necessarily the case in practice. However, the impact of this limitation is  
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34 308 unclear since it affects both the 9-valent vaccine and the other vaccines.  
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## 42 310 **CONCLUSIONS**

43  
44 311 In conclusion, the 9-valent HPV vaccine is not cost-effective when compared with  
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46 312 the quadrivalent vaccine for young females in China who had not been previously  
47  
48 313 infected with HPV at its current price. It is also not cost-effective when compared with  
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50 314 the bivalent vaccine, although it is marginally cost-effective yet not highly cost-effective  
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52 315 when compared with no vaccination. Given these results, policymakers and clinicians  
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3 316 should be conservative to expand the use of the 9-valent HPV vaccines in China unless  
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5 317 the price is reduced. In addition, it is important that the clinicians discuss the economic  
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7 318 profile of the 9-valent HPV vaccine to keep health-seeking individuals informed. More,  
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9 319 public health professionals should be cautious about using the 9-valent vaccine as the  
10  
11 320 primary choice at its current price if HPV vaccines are to be provided as public goods at  
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13 321 nationally.  
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21 324  
22  
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24  
25 326 YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript:  
26  
27 327 WN and JW.  
28  
29 328

30  
31 329 **Competing interests** YJ, WN and JW report no conflicts of interests related to the  
32  
33 330 subject of the submitted work.  
34  
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37  
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39  
40 333 public, commercial, or not-for-profit sectors.  
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45 335 **Data sharing statement** The PRIME model is publicly available at  
46  
47 336 <http://primetool.org/about-hpv/>. The customized input data are listed in the table of the  
48  
49 337 submitted manuscript. Further details about the country-specific cervical cancer incidence  
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3 338 and mortality data can be found at <http://gco.iarc.fr/databases.php>. No additional data are  
4  
5 339 available.

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346 **REFERENCES**

- 347 1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed 2018  
348 [Available from: [https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed)  
349 [hands-out-landmark-conditional-nod-lightning-speed](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed).
- 350 2. HPV vaccine becomes available in China for women between 16 to 26 years old 2018  
351 [Available from: <https://www.firstwordpharma.com/node/1560878?tsid=6>.
- 352 3. Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-  
353 effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified  
354 transmission model. *Hum Vaccin Immunother*. 2016;12(6):1363-72.
- 355 4. Levin CE, Sharma M, Olson Z, Verguet S, Shi J-F, Wang S-M, et al. An extended cost-  
356 effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China.  
357 *Vaccine*. 2015;33(24):2830-41.
- 358 5. Canfell K, Shi J-F, Lew J-B, Walker R, Zhao F-H, Simonella L, et al. Prevention of cervical  
359 cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies.  
360 *Vaccine*. 2011;29(13):2487-94.
- 361 6. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and  
362 state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States.  
363 *Proceedings of the National Academy of Sciences of the United States of America*.  
364 2016;113(18):5107.
- 365 7. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness  
366 of the next generation nonavalent human papillomavirus vaccine in the context of primary  
367 human papillomavirus screening in Australia: a comparative modelling analysis. 2016.
- 368 8. De La Fuente J, Hernandez Aguado JJ, Martín MS, Boix PR, Gómez SC, López NJHV, et al.  
369 Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent hpv  
370 vaccine in Spain.
- 371 9. Mennini FS, Bonanni P, Bianic F, Waure CD, Baio G, Plazzotta G, et al. Cost-effectiveness  
372 analysis of the nine-valent HPV vaccine in Italy. 2017;15(1):11.
- 373 10. Yin Y. HPV vaccination in China needs to be more cost-effective. *The Lancet*.  
374 2017;390(10104):1735-6.
- 375 11. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human  
376 papillomavirus vaccination in 179 countries: a PRIME modelling study. *The Lancet Global health*.  
377 2014;2(7):e406-e14.
- 378 12. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and  
379 Economics Tool User Manual 2014 [Available from: [http://primetool.org/wp-](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf)  
380 [content/uploads/documents/PRIME\\_Tool\\_Manual\\_v2.pdf](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf).
- 381 13. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact  
382 Sheet 2017 2017 [Available from: [http://www.hpvcentre.net/statistics/reports/CHN\\_FS.pdf](http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf).
- 383 14. World Health Organization. Human papillomavirus vaccines: WHO position paper, May  
384 2017–Recommendations. *Vaccine*. 2017;35(43):5753-5.
- 385 15. Phillippo DM, Ades AE, Dias S, Palmer S, Abrams KR, Welton NJ. Methods for population-  
386 adjusted indirect comparisons in health technology appraisal. *Medical Decision Making*.  
387 2018;38(2):200-11.
- 388 16. XE Currency Table: USD - US Dollar 2017 [Available from:  
389 <https://www.xe.com/currencytables/>.
- 390 17. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita  
391 2018 [Available from:  
392 <http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD>.



- 1  
2  
3 393 18. National Bureau of Statistics of China. Consumer Price Indices, Healthcare 2017  
4 394 [Available from: <http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01>.  
5 395 19. Mo X, Tobe RG, Wang L, Liu X, Wu B, Luo H, et al. Cost-effectiveness analysis of different  
6 396 types of human papillomavirus vaccination combined with a cervical cancer screening program  
7 397 in mainland China. BMC infectious diseases. 2017;17(1):502.  
8 398 20. National Institutes for Food and Drug Control. Batch-release inquiry of biological  
9 399 products 2018 [Available from: <http://www.nifdc.org.cn/CL0694/>.  
10 400 21. Mélanie D, Jean-François L, Marie-Claude B, Franco EL, Marc BJIJoC. Potential cost-  
11 401 effectiveness of the nonavalent human papillomavirus (HPV) vaccine. 2014;134(9):2264.

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## 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)

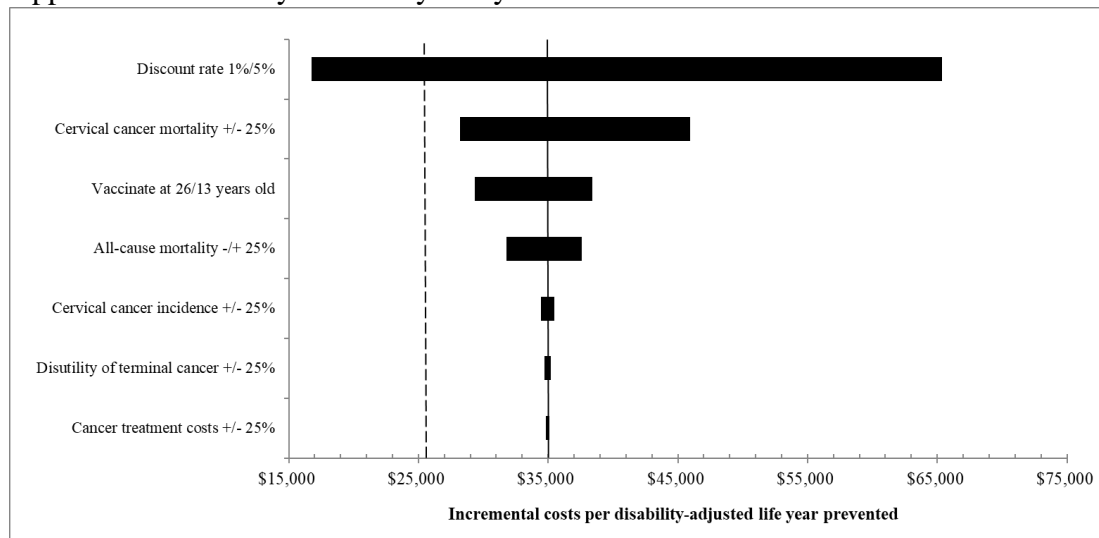
## Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

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 al., 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.

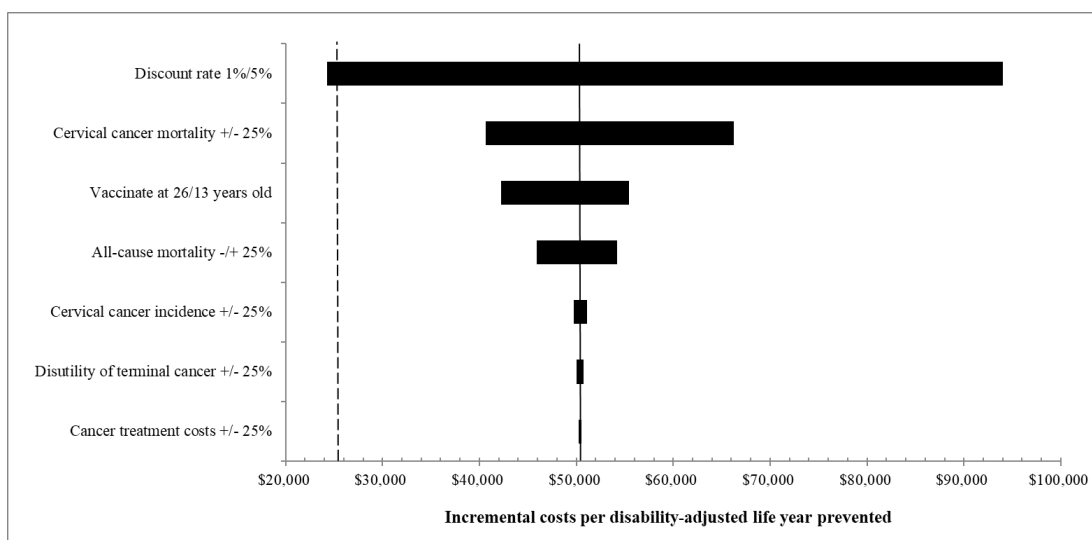
## Appendix 3. Additional information on the base-case results.

	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

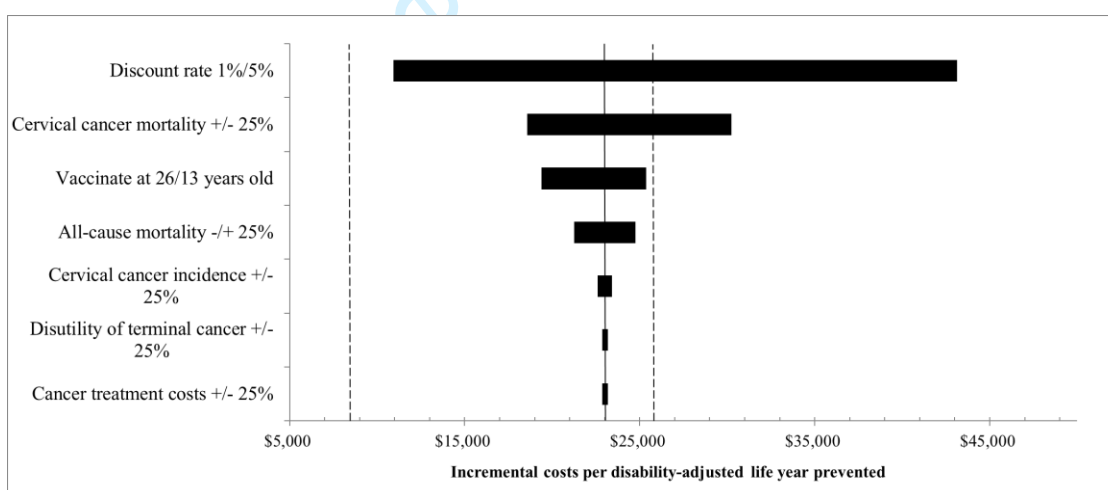
## Appendix 4. One-way sensitivity analyses of the 9-valent HPV vaccine



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
<b>Title and abstract</b>			
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
<b>Introduction</b>			
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
<b>Methods</b>			
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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	page 6
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4	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
5	valuation of preference			
6	based outcomes			
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8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> 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
9	and costs			
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15		13b	<i>Model-based economic evaluation:</i> 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
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22	Currency, price date,	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
23	and conversion			
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28	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
29				
30				
31	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 12-13
32				
33	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
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42	<b>Results</b>			
43	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
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48	Incremental costs and	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
49	outcomes			
50				
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53	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
54	uncertainty			
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1		of methodological assumptions (such as discount rate, study perspective).	
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4		20b <i>Model-based economic evaluation:</i> 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
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6			
7	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
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13	<b>Discussion</b>		
14	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
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20	<b>Other</b>		
21	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
22			
23			
24	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
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31 For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT  
 32 statement checklist

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 35 The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item  
 36 CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the  
 37 ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices  
 38 webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>  
 39

40  
 41 The citation for the CHEERS Task Force Report is:  
 42 Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards  
 43 (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication  
 44 guidelines good reporting practices task force. *Value Health* 2013;16:231-50.  
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# 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:	<i>BMJ Open</i>
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<b>Primary Subject Heading</b>:	Health economics
Secondary Subject Heading:	Public health, Sexual health, Infectious diseases
Keywords:	cost-effectiveness, HPV, vaccination, China, cervical neoplasia

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3 1 Cost-effectiveness and Value-based Prices of the 9-valent Human Papillomavirus

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5 2 Vaccine for the Prevention of Cervical Cancer in China: An Economic Modelling

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8 3 Analysis

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12 5 Yawen Jiang,<sup>a</sup> Ph.D., Weiyi Ni,<sup>b, c</sup> Ph.D., Jing Wu,<sup>b</sup> Ph.D.

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3 17 Abstract  
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6 18 Objectives  
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9 19 To evaluate the cost-effectiveness of the 9-valent human papillomavirus (HPV)  
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11 20 vaccine for the prevention of cervical cancer in China.  
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17 22 Design

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20 23 Health economic modelling using the Papillomavirus Rapid Interface for  
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22 24 Modelling and Economics (PRIME) model populated with China-specific data.  
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28 26 Setting

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31 27 Individual cervical cancer prevention in China using the 9-valent HPV vaccine  
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33 28 from the perspective of private sector purchasers in relation to receiving other HPV  
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35 29 vaccines and not receiving vaccination for 16 years old females in China who had not  
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37 30 been previously infected with HPV.  
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47 33 Not applicable.  
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53 35 Interventions  
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3 36 Vaccination using the 9-valent, the quadrivalent and the bivalent vaccines.  
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9 38 Primary outcome measure  
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12 39 Incremental costs per disability-adjusted life year (DALY) prevented.  
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18 41 Results  
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21 42 In the base case, the incremental costs per DALY prevented were respectively  
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23 43 US\$35,000 and US\$50,455 compared with the quadrivalent and the bivalent vaccines,  
24  
25 44 both of which were above the cost-effective threshold of US\$25,920/DALY prevented.  
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27 45 To be cost-effective in these comparisons, the 9-valent vaccine should be priced at \$550  
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29 46 and \$450 for the full doses, respectively. To be highly cost-effective, the price thresholds  
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31 47 were \$435 and \$335. The incremental costs per DALY prevented in relation to no  
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33 48 vaccination was US\$23,012, making the 9-valent vaccine marginally cost-effective. The  
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35 49 results were robust in most one-way sensitivity analyses including changing vaccination  
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37 50 age to 13 and 26 years.  
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45 52 Conclusions  
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48 53 At the current price, the 9-valent HPV vaccine is not cost-effective compared with  
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50 54 the quadrivalent and the bivalent vaccines for young females in China who had not been  
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52 55 previously infected with HPV. Policymakers and clinicians should keep potential vaccine  
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3 56 recipients informed about the economic profile of the 9-valent vaccine and carefully  
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5 57 consider expanding its use in China at the current price.  
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11 59 Key words: cost-effectiveness; HPV; vaccination; China; cervical neoplasia  
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3 61 Strengths and limitations of this study  
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5 62 1. The study used a previously validated model.  
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7 63 2. The analyses used Chinese-specific input data.  
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9 64 3. Only analysed individuals without prior infection.  
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11 65 4. Used a static model instead of a dynamic model and did not consider herd  
12 immunity.  
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16 67 5. Did not take into account the prevention of genital warts.  
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## 69 INTRODUCTION

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

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

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3 92 cost-effectiveness of the 9-valent vaccines compared with alternative vaccines in other  
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5 93 countries,(3, 6-9) evidence in other healthcare systems is not portable to China for  
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7 94 numerous reasons such as different prices, cancer treatment costs and epidemiological  
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10 95 profiles. As such, the objective of the current study was to analyse the cost-effectiveness  
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12 96 of the 9-valent HPV vaccine for the prevention of cervical cancer among Chinese females  
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14 97 from the perspective of private sector purchasers because HPV vaccines are neither  
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16 98 publicly funded nor reimbursed by any payers to our knowledge. More specifically, this  
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18 99 study pertains to the clinical decision setting of whether it is cost-effective for a Chinese  
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20 100 female without previous infection to use the 9-valent HPV vaccine. We compared the 9-  
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22 101 valent vaccine with the quadrivalent vaccines, the bivalent vaccines, and no vaccination,  
23  
24 102 respectively. Among these, the comparison with the quadrivalent vaccine forms a specific  
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26 103 incremental efficacy evaluation of cervical cancer prevention. Thus, it serves as the  
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28 104 primary basis for discussion and conclusion. The comparison with the bivalent vaccine  
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30 105 may be complicated by the additional efficacy of preventing non-oncogenic HPV types  
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32 106 provided by the 9-valent vaccine, whereas the comparison with no vaccination is  
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34 107 arguably not incremental. However, the alternative comparisons were necessary to render  
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36 108 a comprehensive understanding of the health economic profile of the 9-valent vaccine,  
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38 109 which is important because even the bivalent and the quadrivalent vaccines are subject to  
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40 110 cost-effectiveness concerns for women living in rural areas of China.(10)  
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## 112 **METHODS**

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



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3 115 developed by the World Health Organization (WHO) that allows country-specific  
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5 116 evaluation of HPV vaccination among females without prior infection of HPV.(11, 12)  
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8 117 Country-specific cervical cancer incidence, mortality, HPV type distribution, and  
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10 118 economic data were built in the model. The model developers assessed the quality of  
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12 119 country-specific data as either “satisfactory” or “unsatisfactory” based on availability of  
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14 120 data for each country and quality of methods used in data collection, and the Chinese data  
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16 121 were deemed “satisfactory”.(11) The model calculates the incremental costs per  
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18 122 disability-adjusted life year (DALY) prevented for vaccinated individuals over lifetime as  
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20 123 well as population outcomes such as cervical cancer prevented and deaths prevented. In  
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22 124 addition, the model was validated against previously published HPV vaccine cost-  
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24 125 effectiveness studies in the literature. More details of the model have been described  
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26 126 elsewhere and in Appendix 1.(11)  
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31 127 The current analysis only examined incremental costs per DALY prevented for  
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33 128 vaccinated individuals. Because the intervention of interest in the current analysis is 9-  
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35 129 valent HPV vaccination, we modified the model to use the proportion of cervical cancer  
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37 130 that was attributable to HPV types 16/18/31/33/45/52/58 in China reported by  
38  
39 131 International Agency for Research on Cancer (IARC) HPV Information Centre instead of  
40  
41 132 only the proportion that was attributable to types 16/18 in the original model.(12, 13)  
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43 133 According to IARC estimates, 92% of cervical cancer in China were attributable to types  
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45 134 16/18/31/33/45/52/58.(13)  
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49 135 The model also permitted customization of target age group, efficacy of vaccine  
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51 136 (percentage of cervical cancer reduction), vaccine price, vaccine delivery costs, cancer  
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53 137 treatment cost, discount rate, and disutility values of three cancer-related health states  
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3 138 (cancer diagnosis, non-terminal cancer sequelae, and terminal cancer). Data in the  
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5 139 customized input fields can override the default data. In the current analysis, default data  
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7 140 of efficacy of vaccine, discount rate, and disutility values were used. It should be noted  
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10 141 that several other inputs could be customized in the model including coverage rate (or  
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12 142 uptake rate), birth cohort size, and cohort size at the vaccination age. Except for coverage  
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15 143 rate, these inputs only affect population outcomes that are not of interest in the current  
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17 144 analysis and does not affect the results of the cost-effectiveness results for vaccinated  
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19 145 individuals. We assumed a coverage rate of 100% in our analysis such that the mean  
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22 146 population result is equivalent to that of an average vaccinated individual.

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24 147 In the base-case analysis, the target age group was 16 years old females because  
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26 148 this was the youngest group among the current age of licensure of the 9-valent vaccine in  
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28 149 China (additional explanation in Appendix 2). It is noteworthy that this was older than  
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31 150 the WHO-recommended primary target age window of 9-14 years.(14) Regardless of  
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33 151 vaccination age, the time horizon was set so such that the cohort were followed up to 100  
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35 152 years old. The price of 9-valent HPV vaccine in government procurement catalogue as of  
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38 153 December 2018 was used.(15, 16) We also assessed the prices at which the incremental  
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40 154 costs per DALY prevented were at the cost-effective threshold of three times the 2017  
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42 155 China gross domestic product (GDP) per capita and at the highly cost-effective threshold  
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44 156 of once the 2017 China GDP per capita to inform decision makers the value-based prices.  
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47 157 Therefore, the cost-effective threshold and the highly cost-effective thresholds are  
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49 158 US\$25,920/DALY prevented and US\$8,640/DALY prevented, respectively.(17) Default  
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51 159 data of vaccine administration costs per person in China in the PRIME model were used  
52  
53  
54 160 but adjusted to 2017 equivalent using the healthcare component Consumer Price Indices

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

163

164 Table 1. Input data and model results of the base-case analysis of the 9-valent HPV  
 165 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

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3 166 Abbreviations: HPV, human papillomavirus; DALY, disability-adjusted life year; ICER,  
4 167 incremental cost-effectiveness ratio measured as incremental costs per DALY prevented;  
5 168 NA, not applicable.

6 169  
7  
8 170 In one-way sensitivity analyses, age at vaccination (each age between 13-26  
9  
10 171 years), efficacy of vaccine (reduced to 90%), cervical cancer incidence of all age groups,  
11  
12 172 cervical cancer mortality, all-cause mortality, cancer treatment costs, disutility of  
13  
14 173 terminal cancer, and discount rate (1% and 5%) were varied to examine the robustness of  
15  
16 174 incremental costs per DALY prevented results. Parameters of interest other than age at  
17  
18 175 vaccination, efficacy, and discount rate were increased and decreased by 25%. In the  
19  
20 176 pivotal clinical trial based on which the quadrivalent HPV vaccine was approved by the  
21  
22 177 Chinese regulatory body, the efficacy against cervical intraepithelial neoplasia (CIN)  
23  
24 178 grades 1+ and 2+ related to HPV 6/11/16/18 was 100% at the end of the 12th month  
25  
26 179 (20). Also, the efficacy against cervical persistent infection was above 90% (20).  
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28  
29 180 Therefore, the efficacy was set to 90% in the sensitivity analyses to test the impact of  
30  
31 181 possible lower efficacy after vaccination.  
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### 38 183 Patient and Public Involvement

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41 184 Patients were not involved.  
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## 46 186 RESULTS

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48 187 The base-case results of comparing the 9-valent vaccine with the quadrivalent and  
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50 188 bivalent vaccines are shown in Table 2 (more detailed information on the base-case  
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52 189 results is in Appendix 3). The incremental costs per DALY prevented compared with the  
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54 190 quadrivalent and the bivalent vaccines were US\$35,000 and US\$50,455, respectively.  
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3 191 Therefore, the 9-valent vaccine was not cost-effective when compared with either the  
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5 192 quadrivalent or the bivalent vaccine. To be cost-effective, the 9-valent vaccine should be  
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7 193 priced at \$550 and \$450 for the full doses, respectively. To be highly cost-effective, the  
8  
9 194 price thresholds were \$435 and \$335. Furthermore, the 9-valent vaccine should be priced  
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11 195 at \$505 to reach the same ICER as the quadrivalent vaccine when both vaccines were  
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13 196 compared with no vaccination. The corresponding price was \$370 when the comparator  
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15 197 was the bivalent vaccine.  
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19 198 The results of comparing with no vaccination are displayed in Table 2. The  
20  
21 199 incremental costs per DALY prevented were US\$23,012. This was slightly less than the  
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23 200 cost-effective threshold but substantially above the highly cost-effective threshold. In  
24  
25 201 addition, the prices for the 9-valent HPV vaccine to be cost-effective and highly cost-  
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27 202 effective were \$680 and \$220, respectively.  
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31 203  
32  
33 204 Table 2. Base-case results  
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	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 <sup>a</sup>	NA	\$550	\$450
Price threshold of 9-valent vaccine to be	NA	\$435	\$335

highly cost-effective vs. other vaccines <sup>b</sup>			
Price threshold of 9-valent vaccine to be as cost-effective as other vaccines <sup>c</sup>	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

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

207 <sup>a</sup> For example, the 9-valent vaccine should be priced at \$550 for the full doses to be cost-  
 208 effective when compared with the quadrivalent vaccine.

209 <sup>b</sup> For example, the 9-valent vaccine should be priced at \$435 for the full doses to be  
 210 highly cost-effective when compared with the quadrivalent vaccine.

211 <sup>c</sup> At this price, the 9-valent vaccine is as cost-effective as the quadrivalent vaccine when  
 212 each of them was compared with not receiving vaccination if the price of the 9-valent  
 213 vaccine is \$505 for the full doses. This is equivalent to saying the cost-effectiveness of  
 214 the 9-valent vaccine vs. the quadrivalent vaccine is the same as the cost-effectiveness of  
 215 the quadrivalent vaccine vs. not receiving vaccination. The interpretation of the  
 216 comparison vs. the bivalent vaccine is the same.

217

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

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3 227 the 9-valent vaccine and no vaccination were \$43,145, which was above the cost-  
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5 228 effective threshold. Similarly, the corresponding result was \$30,246 when the mortality  
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8 229 rate of cervical cancer was reduced by 25%, which was also above the cost-effective  
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10 230 threshold. The results remained cost-effective in all other scenarios.

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## 13 232 **DISCUSSION**

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17 233 In the present analysis, the 9-valent HPV vaccine was not cost-effective for the  
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19 234 prevention of cervical cancer among 16-26 years old Chinese females without prior HPV  
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21 235 infection when compared with either the quadrivalent or the bivalent vaccine, which  
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23 236 remained so in all the sensitivity analyses except for using a discount rate of 1%. The  
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25 237 results suggest that the price of the 9-valent HPV vaccine needs to be adjusted downward  
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27 238 to provide more value for Chinese female recipients. Since the highly cost-effective  
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29 239 threshold is more stringent, the 9-valent HPV vaccine is also not highly cost-effective in  
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31 240 China.

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35 241 The results are important to the extent that the marginal health gain of investing in  
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37 242 the quadrivalent or bivalent vaccine is more than that of the 9-valent vaccine. Although  
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39 243 the comparison with the bivalent vaccine may not be fair given that the bivalent vaccine  
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41 244 does not protect against warts, the comparison with the quadrivalent vaccine is not  
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43 245 subject to the same limitation. As far as cervical cancer is concerned, our results showed  
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45 246 that the marginal health gain of an extra dollar in the healthcare budget to be spent on the  
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47 247 9-valent vaccine would be the same as that on the quadrivalent and bivalent vaccine if the  
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49 248 9-valent vaccine were to be priced at \$505 and \$370, respectively. In the meantime, a  
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51 249 number of Chinese-manufactured bivalent and quadrivalent HPV vaccines are already in  
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3 250 the late stage of clinical trials and will likely be marketed at lower prices than the  
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5 251 imported counterparts. The entrance of these products will further neutralize the edge of  
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8 252 the 9-valent vaccine over the other vaccines in respect to cost-effectiveness. At the  
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10 253 current price level, clinicians and policymakers are advised to educate potential vaccine  
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12 254 recipients and keep them informed when suggesting vaccination.  
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15 255 The 9-valent HPV vaccine was cost-effective but not highly cost-effective for the  
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17 256 prevention of cervical cancer among 16-26 years old Chinese females without prior HPV  
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19 257 infection when compared with no vaccination. The results were robust to changes in  
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22 258 important parameters except for discount rates and cervical cancer mortality.  
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24 259 While it is both intuitive and theoretically founded to compare the 9-valent  
25  
26 260 vaccine only with the quadrivalent and the bivalent vaccines, it should be noted that  
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28 261 further comparing the 9-valent vaccine with no vaccination may provide additional  
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30 262 insights when the standard of practice is absent. Indeed, only comparing the 9-valent  
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32 263 vaccine with the other HPV vaccines suffices to inform decision-making if HPV  
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34 264 vaccination is already the standard of practice and the decision should pertain to  
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37 265 incremental cost-effectiveness in relation to the standard of practice. While this might be  
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39 266 true in high-income countries, it is not necessarily the case in China. Most Chinese  
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42 267 females, regardless of age, have not been inoculated with any HPV vaccine. Specifically,  
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44 268 the total number of HPV vaccine doses released by the National Institutes for Food and  
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46 269 Drug Control in all batches as of September 2018 was merely 6 million,(21) indicating  
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49 270 the maximum number of females in China that would have received at least one dose of  
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51 271 HPV vaccine. Hence, the scenario that a portion of the individuals would only consider  
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54 272 either receiving the 9-valent vaccine or not being vaccinated should not be ruled out. For  
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3 273 these individuals, the comparison of the 9-valent vaccine with no vaccination relevant for  
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5 274 decision making. As such, we pertain to the comparison with the quadrivalent vaccine as  
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8 275 the primary analysis but also provide exploratory results of comparing with no  
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10 276 vaccination.

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12 277 It is important to note the results of age-related sensitivity analyses do not  
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14 278 necessarily suggest vaccination is more cost-effective at older ages. Smaller ICERs at  
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17 279 older ages are mainly caused by fewer years of discounting the benefits (Appendix 5).

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19 280 The cost-effectiveness profile of the 9-valent vaccine based on the present  
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21 281 analysis contrasts that in several developed countries. A study found that the 9-valent  
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23 282 vaccine was cost-effective compared with the quadrivalent vaccine among 12-26 years  
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25 283 old females in the United States if the additional acquisition costs per dose was no more  
26  
27 284 than US\$13 (3). Their finding was confirmed by another US study (6). An Australian  
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29 285 study also showed that the 9-valent vaccine was a cost-effective alternative to the  
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31 286 quadrivalent vaccine for 12-year old females if the additional costs per dose was under  
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33 287 AUS\$36 (7). In Canada, Italy and Spain, the corresponding numbers were CAN\$24, €16  
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36 288 and €16 (8, 9, 22). These numbers were generally consistent with the real-world price  
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39 289 differences in the public sectors of the aforementioned countries (3, 8, 9). However, the  
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41 290 gaps between the prices of the 9-valent and quadrivalent vaccines in these markets were  
42  
43 291 substantially smaller than that in China, which is likely the main reason of the  
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45 292 inconsistent cost-effectiveness profiles. This highlights the importance of adjusting the  
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47 293 price of the 9-valent vaccine in China from the value perspective.  
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3 294 The current analysis is subject to several limitations. First, our analysis did not  
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5 295 model catch-up immunization for those individuals who have already had prior  
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8 296 infections.(12) It is reasonable to expect that the incremental benefit of the 9-valent  
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10 297 vaccine is smaller among these individuals. Second, the analysis only considered the  
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12 298 health benefits of preventing cervical cancer but not the benefits of preventing genital  
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14 299 warts. Taking into account the prevention of genital warts will favour the 9-valent  
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16 300 vaccine over the bivalent vaccine and no vaccination. In addition to these limitations, the  
17  
18 301 model was also subject to other limitations that do not necessarily undermine the validity  
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20 302 of the current results. For example, the model doesn't evaluate vaccination combined  
21  
22 303 with cervical screening programs or assess herd immunity due to vaccination.(12) To the  
23  
24 304 extent that the concentration of the present study is shedding light on the cost-  
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26 305 effectiveness profiles of vaccines, including screening may obscure the focus as well as  
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28 306 create confusion in the selection of decision perspective. Also, the model is only  
29  
30 307 appropriate to evaluate vaccination among 9-13 years old females if the population  
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32 308 outcomes are of interest because some individuals in a cohort of older ages may have  
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34 309 been previously infected. In theory, these limitations do not affect the economic  
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36 310 evaluation of vaccinating an individual who is known to have no previous infection and  
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38 311 decides to accept immunization. Future economic evaluations should examine screening  
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40 312 and vaccination strategies in which a portion of the target population were infected.  
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42 313 More, Chinese-manufactured vaccines in future may affect the pricing of marketed  
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44 314 products and the CEA should be updated accordingly. Even more, the efficacy of the  
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46 315 vaccine was assumed to stay fully protective throughout the time horizon. This may not  
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3 316 be necessarily the case in practice. However, the impact of this limitation is unclear since  
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5 317 it affects both the 9-valent vaccine and the other vaccines.  
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10 319 **CONCLUSIONS**

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12 320 In conclusion, the 9-valent HPV vaccine is not cost-effective when compared with  
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14 321 the quadrivalent vaccine for young females in China who had not been previously  
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16 322 infected with HPV at its current price. It is also not cost-effective when compared with  
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18 323 the bivalent vaccine, although it is marginally cost-effective yet not highly cost-effective  
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20 324 when compared with no vaccination. Given these results, policymakers and clinicians  
21  
22 325 should be conservative to expand the use of the 9-valent HPV vaccines in China unless  
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24 326 the price is reduced. In addition, it is important that the clinicians discuss the economic  
25  
26 327 profile of the 9-valent HPV vaccine to keep health-seeking individuals informed. More,  
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28 328 public health professionals should be cautious about using the 9-valent vaccine as the  
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30 329 primary choice at its current price if HPV vaccines are to be provided as public goods at  
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32 330 nationally.  
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44 334 **Contributors** Design and data collection: YJ, WN and JW. Analysis and interpretation:  
45  
46 335 YJ, WN and JW. Drafting the manuscript: YJ. Reviewing and revising the manuscript:  
47  
48 336 WN and JW.  
49

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2  
3 338 **Competing interests** YJ, WN and JW report no conflicts of interests related to the  
4  
5 339 subject of the submitted work.  
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12  
13 342 public, commercial, or not-for-profit sectors.  
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19 344 **Data sharing statement** The PRIME model is publicly available at  
20  
21 345 <http://primetool.org/about-hpv/>. The customized input data are listed in the table of the  
22  
23 346 submitted manuscript. Further details about the country-specific cervical cancer incidence  
24  
25 347 and mortality data can be found at <http://gco.iarc.fr/databases.php>. No additional data are  
26  
27 348 available.  
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355 **REFERENCES**

- 356 1. Liu A. 9 days for Gardasil 9: China hands out landmark nod with lightning speed 2018  
357 [Available from: [https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed)  
358 [hands-out-landmark-conditional-nod-lightning-speed](https://www.fiercepharma.com/pharma-asia/9-days-for-gardasil-9-china-hands-out-landmark-conditional-nod-lightning-speed).
- 359 2. HPV vaccine becomes available in China for women between 16 to 26 years old 2018  
360 [Available from: <https://www.firstwordpharma.com/node/1560878?tsid=6>.
- 361 3. Chesson HW, Markowitz LE, Hariri S, Ekwueme DU, Saraiya M. The impact and cost-  
362 effectiveness of nonavalent HPV vaccination in the United States: Estimates from a simplified  
363 transmission model. *Hum Vaccin Immunother*. 2016;12(6):1363-72.
- 364 4. Levin CE, Sharma M, Olson Z, Verguet S, Shi J-F, Wang S-M, et al. An extended cost-  
365 effectiveness analysis of publicly financed HPV vaccination to prevent cervical cancer in China.  
366 *Vaccine*. 2015;33(24):2830-41.
- 367 5. Canfell K, Shi J-F, Lew J-B, Walker R, Zhao F-H, Simonella L, et al. Prevention of cervical  
368 cancer in rural China: evaluation of HPV vaccination and primary HPV screening strategies.  
369 *Vaccine*. 2011;29(13):2487-94.
- 370 6. Durham DP, Ndeffo-Mbah ML, Skrip LA, Jones FK, Bauch CT, Galvani AP. National- and  
371 state-level impact and cost-effectiveness of nonavalent HPV vaccination in the United States.  
372 *Proceedings of the National Academy of Sciences of the United States of America*.  
373 2016;113(18):5107.
- 374 7. Simms KT, Laprise JF, Smith MA, Lew JB, Caruana M, Brisson M, et al. Cost-effectiveness  
375 of the next generation nonavalent human papillomavirus vaccine in the context of primary  
376 human papillomavirus screening in Australia: a comparative modelling analysis. 2016.
- 377 8. De La Fuente J, Hernandez Aguado JJ, Martín MS, Boix PR, Gómez SC, López NJHV, et al.  
378 Estimating the epidemiological impact and cost-effectiveness profile of a nonavalent hpv  
379 vaccine in Spain.
- 380 9. Mennini FS, Bonanni P, Bianic F, Waure CD, Baio G, Plazzotta G, et al. Cost-effectiveness  
381 analysis of the nine-valent HPV vaccine in Italy. 2017;15(1):11.
- 382 10. Yin Y. HPV vaccination in China needs to be more cost-effective. *The Lancet*.  
383 2017;390(10104):1735-6.
- 384 11. Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human  
385 papillomavirus vaccination in 179 countries: a PRIME modelling study. *The Lancet Global health*.  
386 2014;2(7):e406-e14.
- 387 12. Hickman M, Jit M, Hutubessy R. Papillomavirus Rapid Interface for Modelling and  
388 Economics Tool User Manual 2014 [Available from: [http://primetool.org/wp-](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf)  
389 [content/uploads/documents/PRIME\\_Tool\\_Manual\\_v2.pdf](http://primetool.org/wp-content/uploads/documents/PRIME_Tool_Manual_v2.pdf).
- 390 13. World Health Organization. China: Human Papillomavirus and Related Cancers, Fact  
391 Sheet 2017 2017 [Available from: [http://www.hpvcentre.net/statistics/reports/CHN\\_FS.pdf](http://www.hpvcentre.net/statistics/reports/CHN_FS.pdf).
- 392 14. World Health Organization. Human papillomavirus vaccines: WHO position paper, May  
393 2017–Recommendations. *Vaccine*. 2017;35(43):5753-5.
- 394 15. Information of Drug Winning Bid 2018 [Available from:  
395 <https://data.yaozh.com/yaopinzhongbiao>.
- 396 16. XE Currency Table: USD - US Dollar 2017 [Available from:  
397 <https://www.xe.com/currencytables/>.
- 398 17. International Monetary Fund. GDP per capita, current prices - U.S. dollars per capita  
399 2018 [Available from:  
400 <http://www.imf.org/external/datamapper/NGDPDPC@WEO/OEMDC/ADVEC/WEOWORLD>.

- 1  
2  
3 401 18. National Bureau of Statistics of China. Consumer Price Indices, Healthcare 2017  
4 402 [Available from: <http://data.stats.gov.cn/english/adv.htm?m=advquery&cn=A01>.  
5 403 19. Mo X, Tobe RG, Wang L, Liu X, Wu B, Luo H, et al. Cost-effectiveness analysis of different  
6 404 types of human papillomavirus vaccination combined with a cervical cancer screening program  
7 405 in mainland China. *BMC infectious diseases*. 2017;17(1):502.  
8 406 20. Wei L, Xie X, Liu J, Zhao Y, Chen W, Zhao C, et al. Efficacy of quadrivalent human  
9 407 papillomavirus vaccine against persistent infection and genital disease in Chinese women: A  
10 408 randomized, placebo-controlled trial with 78-month follow-up. *Vaccine*. 2019;37(27):3617-24.  
11 409 21. National Institutes for Food and Drug Control. Batch-release inquiry of biological  
12 410 products 2018 [Available from: <http://www.nifdc.org.cn/CL0694/>.  
13 411 22. Mélanie D, Jean-François L, Marie-Claude B, Franco EL, Marc BJIJoC. Potential cost-  
14 412 effectiveness of the nonavalent human papillomavirus (HPV) vaccine. 2014;134(9):2264.

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## 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)

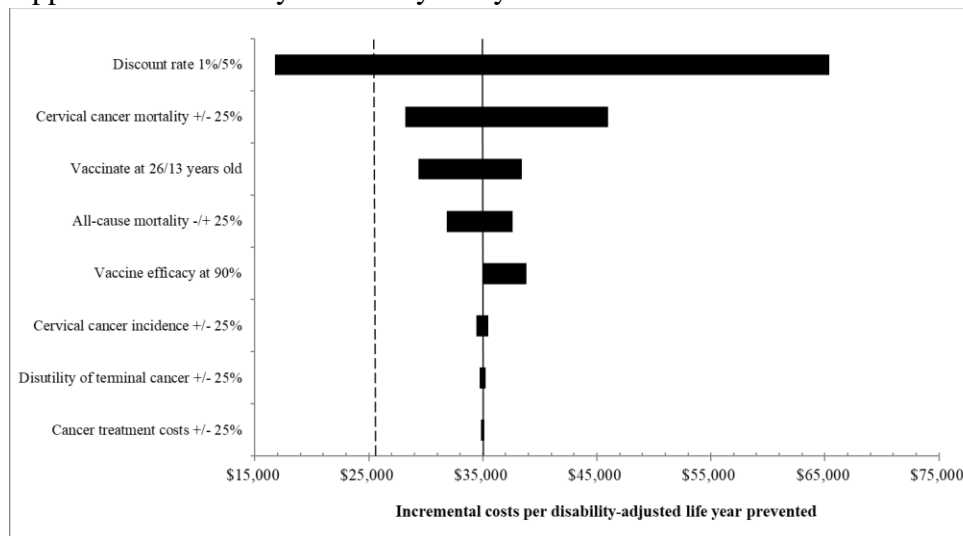
## Appendix 2. Very small chances of prior HPV infection among the 16 years old Chinese females

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 al., 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.

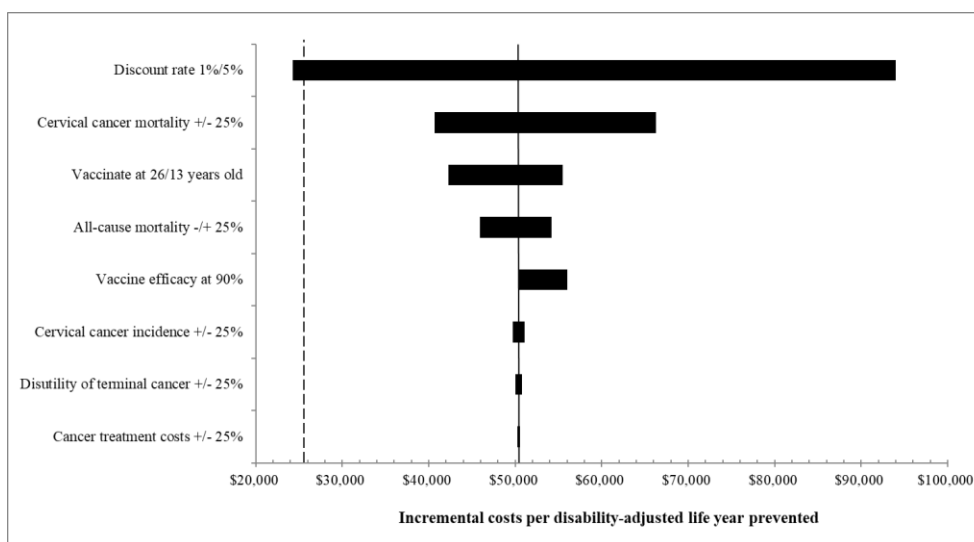
	Not receiving vaccination	9-valent vaccine	quadrivalent vaccine	bivalent vaccine
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18/31/33/45/52/58)	\$17	\$0	NA	NA
Discounted expected lifetime treatment costs of cervical cancer per individual (HPV types 16/18)	\$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

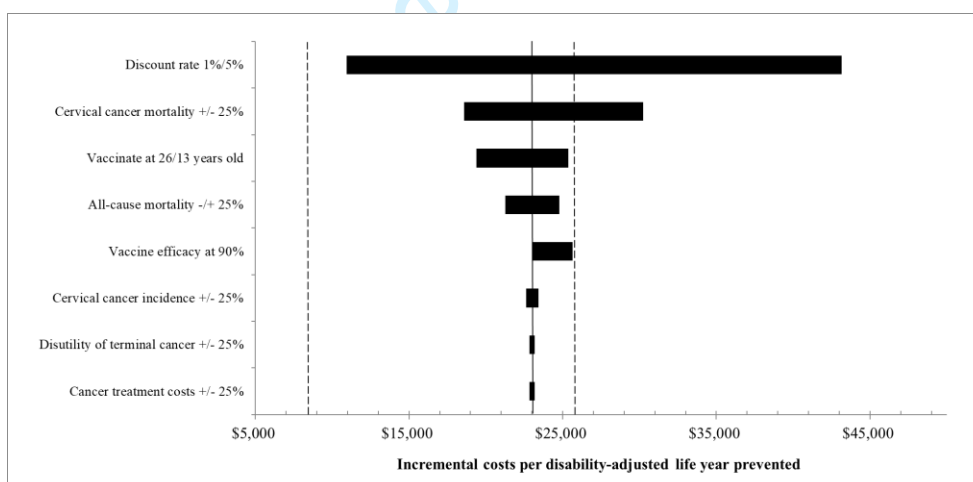


a. Sensitivity analysis results of comparing the 9-valent vaccine with the quadrivalent vaccine. The dash line on the left represents the cost-effective threshold.





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
<b>Title and abstract</b>			
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
<b>Introduction</b>			
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
<b>Methods</b>			
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	<i>Single study-based estimates:</i> Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	NA



1		11b	<i>Synthesis-based estimates:</i> Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	Table 1
2				
3				
4	Measurement and	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
5	valuation of preference			
6	based outcomes			
7				
8	Estimating resources	13a	<i>Single study-based economic evaluation:</i> 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
9	and costs			
10				
11				
12				
13				
14				
15		13b	<i>Model-based economic evaluation:</i> 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
16				
17				
18				
19				
20				
21				
22	Currency, price date,	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
23	and conversion			
24				
25				
26				
27				
28	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
29				
30				
31	Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	page 16-17
32				
33				
34	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
35				
36				
37				
38				
39				
40				
41				
42	<b>Results</b>			
43	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
44				
45				
46				
47				
48	Incremental costs and	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
49	outcomes			
50				
51				
52				
53	Characterising	20a	<i>Single study-based economic evaluation:</i> Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	NA
54	uncertainty			
55				
56				
57				
58				
59				
60				

1		of methodological assumptions (such as discount rate, study	
2		perspective).	
3			
4	20b	<i>Model-based economic evaluation</i> : Describe the effects on the	
5		results of uncertainty for all input parameters, and uncertainty	
6		related to the structure of the model and assumptions.	Appendix 4
7	Characterising	21	
8	heterogeneity		
9		If applicable, report differences in costs, outcomes, or cost-	
10		effectiveness that can be explained by variations between	
11		subgroups of patients with different baseline characteristics or	
12		other observed variability in effects that are not reducible by	NA
13		more information.	
14	<b>Discussion</b>		
15	Study findings,	22	
16	limitations,		
17	generalisability, and		
18	current knowledge		pages 11-12
19		Summarise key study findings and describe how they support	
20	<b>Other</b>		
21	Source of funding	23	
22			
23		Describe how the study was funded and the role of the funder	
24		in the identification, design, conduct, and reporting of the	page 19
25		analysis. Describe other non-monetary sources of support.	
26	Conflicts of interest	24	
27			
28		Describe any potential for conflict of interest of study	
29		contributors in accordance with journal policy. In the absence	
30		of a journal policy, we recommend authors comply with	
31		International Committee of Medical Journal Editors	page 18
32		recommendations.	

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.

