Author's response to reviews

Title: Cost-effectiveness of human papillomavirus vaccination for prevention of cervical cancer in Taiwan

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Author's response to reviews: see over
Dear Editors:

We are re-submitting this amended manuscript entitled “Cost-effectiveness of human papillomavirus vaccination for prevention of cervical cancer in Taiwan” for your consideration to be published on your esteemed journal.

Once again, we greatly appreciate the valuable comments and critiques by the peer reviewers, which have been constructive to improve our work. We also express our sincere gratefulness to both of them in the Acknowledgement section of this updated manuscript. As you will see in the following pages, we have provided a point-by-point response to the referees’ comments.

For the reviewers’ convenience, we have underlined the revised words or sentences in the revised manuscript.

We are looking forwards to hearing from you soon.

Kindest Regards,

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Reviewer: Anna Garcia-Altes

Major Compulsory Revisions:

Comment 1:
Page 9. Costs. All costs included should be mentioned. It is not enough to say “cervical screening costs and treatment costs of SIL”. You should mention what costs are included under those headings. Also, vaccination costs should be detailed: vaccine costs, vaccine administration costs, management of the program, etc. The cost of the vaccine itself should be stated on the text.

Response:
Following your constructive recommendation, we have revised this paragraph in more details as follows:

(Page 9, line 24 ~ Page 10, line 9) Only direct medical costs are considered in this study, which include the costs associated with the health care items reimbursed by the National Health Insurance (NHI) and the out-of-pocket payments such as outpatient registration fees, some drug charges or medical equipment expenses not covered by the NHI. Pap testing costs were US$16 per test. The cost of treatment for SIL or cervical cancer was based on cost of initial colposcopy and biopsy, therapy, and subsequent follow-up. These costs were estimated by published literature of Tang et al. (2009) [41], expert opinions and official tariff lists of the NHI. The vaccination cost for three doses was assumed to be US$364, which include the cost of the HPV vaccine itself, personnel, and administration. All costs were reported in 2009 US dollars with the exchange rate of 33 New Taiwan dollars to US$1.
Comment 2:
Page 11. Sensitivity analyses. “Sensitivity analyses” should be rewritten as “Sensitivity analysis”. The sentence “Our base case...” should be eliminated, since it has been already mentioned. The last sentence “We also examined” should be written together with the first sentence of the paragraph. “Sensitivity analyses” should be rewritten as “Sensitivity analysis”.

Response:
In accordance with your comments, the subheading “Sensitivity analyses” has been revised as “Sensitivity analysis”, and the duplicate sentence “Our base case...” has been eliminated. Please kindly refer to:

(Page 11, ll. 9-19) Sensitivity analysis

Sensitivity analyses were performed to account for important model assumptions and uncertainties including the vaccine characteristics, adherence to cervical screening, costs or health utilities for various conditions, parameters related to the natural history of disease, discount rate, etc; we also examined the impact of starting vaccination at different ages on the cost-effectiveness ratio for HPV vaccine in sensitivity analysis. The ranges for costs were varied from minus 25% to plus 25% of the base case estimate. For clinical variables, our ranges for sensitivity analysis represented our judgment of the uncertainties and/or variations likely to be encountered in clinical practice, based on both the literature and the opinions of experts (Table 1).

Comment 3:
Response:
Following your advice, we have removed the words associated with undiscounted results.

Comment 4:
Page 13. “Sensitivity analyses” should be rewritten as “Sensitivity analysis”. The sentence “Assuming that vaccination could provide” should be eliminated, since you already mentioned this result in the base case analysis. The explanation of results should go to the discussion section. It would be the case of the sentence “because the marginal effectiveness...”. The sentence “Vaccination of preadolescent girls” should be deleted since it refers to undiscounted results. In the last sentence “Vaccination cost however” should be rewritten as “Vaccination cost-effectiveness however”.

Response:
Many thanks for the kind comments. We have rewritten the subheading “Sensitivity analyses” as “Sensitivity analysis”; we have corrected the word “cost” as “cost-effectiveness” in the sentence “Vaccination cost, however, would be…”. We have eliminated the sentences that you suggested to delete, and we also moved the sentence explaining the results to the discussion section.

(Page 12, line 25) Sensitivity analysis

(Page 13, ll. 15-17) Vaccination cost-effectiveness, however, would be US$37,480/QALY at a discounted rate of 5% since higher discount rates augment the relative weight of the initial vaccination costs.

(Page 15, line 25 ~ Page 16, line 2) (Discussion) The relatively high risk level of
invasive cervical cancer in Taiwan implies the urgency to improve the compliance rate of cervical screening to the early detection of SIL and cervical cancer, even though the ICER of prophylactic vaccination would rise accordingly because the marginal effectiveness of vaccination would be diminished as improvement in cytological screening would decrease the baseline incidence of invasive cervical cancer without adding HPV vaccination.
Reviewer: Jaume Puig-Junoy

Discretionary Revisions

I suggest to consider in a more explicit way, in the discussion section, the main differences of the results of this paper when compared to those of Dasbach et al, 2008. In fact, the authors should stress their hypothesis about how Dasbach et al could report that vaccination of 12-years old girls strategy in Taiwan is weakly dominated by no vaccination (note that, to my knowledge, this is the only paper in the literature with such a conclusion!).

Response:

Thanks for your comment. My colleagues and I think Dasbach et al have used a misleading term of “weakly dominated” to describe the cost-effectiveness ratio of vaccination of 12-year-old girls in their Table 3 (Dasbach et al., Asian Pacific J Cancer Prev 2008, 9(3): 459-466), because vaccination of 12-years old girls only is not associated with less effectiveness along with a higher cost to be regarded as “being dominated”. Instead, what they found appears similar to ours, namely, HPV vaccination seems cost-effective. The incremental cost-effectiveness ratio (ICER) of vaccination of 12-years old girls relative to no vaccination calculated from their Table 3 would be NT$437,400 per QALY ( = NT$204,704,960 / 468QALYs ), which is less efficient than that of the catch-up program, or, NT$410,477 per QALY. As both vaccination strategies are compared with no vaccination to obtain the above figures, none of them is dominated by no vaccination. In fact, the ICER they estimated is close to our result of NT$451,200 per QALY gained comparing adding HPV vaccination with no vaccination. Thus, we think that they used the
inappropriate term which may not deserve words to falsify. In other words, please kindly allow my team simply to include their positive findings and take a milder tone on this issue.

We also include their Table 3 here for your kind reference, as follows:

Table 3. Cost-effectiveness Analysis of Alternative Vaccination Strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Total Costs</th>
<th>Total QALYs</th>
<th>Incremental Costs</th>
<th>Incremental QALYs</th>
<th>Incremental Costs/ QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vaccination</td>
<td>192,653,749</td>
<td>2,700,559</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12-year-old girls</td>
<td>397,358,710</td>
<td>2,701,027</td>
<td>204,704,960</td>
<td>468</td>
<td>Weakly dominated</td>
</tr>
<tr>
<td>12-year-old girls + 12–24 female catch-up program</td>
<td>482,947,608</td>
<td>2,701,266</td>
<td>290,293,859</td>
<td>707</td>
<td>410,477</td>
</tr>
</tbody>
</table>

*All costs are measured in 2006 New Taiwan (NT) dollars. Assumed cost of vaccination series is NT$11,800 and duration of protection is lifelong. Costs and QALY are discounted at a 3.0% annual rate. Compared with the preceding non-dominated strategy. QALY = quality-adjusted life-year.