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:

Thank you for your e-mail. We are 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.

We greatly appreciated the valuable comments and critiques by the peer reviewers, which have been constructive to improve our work. Please kindly express my sincere gratefulness to both of them. In accordance with your instructions, we have endeavored to fully address the comments, which have guided us throughout the revision of this manuscript. As you will see as below, we provided a point-by-point response to the referees’ comments.

In this study, we assessed the cost-effectiveness of prophylactic human papillomavirus (HPV) vaccination for the prevention of cervical cancer in Taiwan with the Markov decision model. Assuming the lifelong protection by HPV vaccine, the massive vaccination among preadolescent girls in Taiwan would bring about reduction in incidence of cervical cancer from 1,773 down to 473 cases per 100,000 person-years. The incremental cost-effectiveness ratio was US$13,674 per quality-adjusted life year (QALY) gained, which seems close to the findings of previous Taiwanese studies. As the model has been delicately calibrated by existing both morbidity and mortality data for cervical
cancer in Taiwan, we believed this study could probably improve the validity of estimation of the cost-effectiveness of HPV vaccination in our country. Moreover, our study also highlighted the importance of improving the compliance rate of cervical cytological screening programs among the older women, even if the massive HPV vaccination program is adopted by the government of Taiwan in the future.

For the reviewers’ convenience, we have underlined the revised sentences in the updated manuscript. If there is any more revision needed, please kindly inform us at your earliest convenience.

We are looking forwards to your reply.

Kindest Regards,

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Reviewer: Anna Garcia-Altes

Although HPV vaccination has not demonstrated its effectiveness preventing cervical cancers, its relative importance in Taiwan could make this an important topic.

The paper will be reinforced if authors make a stronger case for the possible potential benefits of vaccination in Taiwan, where it seems that the infection rates are higher, and the compliance with cervical screening is low. Also, some more technical details should be made clear. Finally, please revise carefully all references, because it seems that they are not related to what you are mentioning on the text.

Response:

Thanks for the kind advice. We have cherished every comment and responded point-by-point in our revision. We have also completely revised the list of our references. For example, we have replaced the previous Ref. 7-12 by Ref. 13-26, and deleted two of previous Ref. 15-17 and left the previous Ref. 15 as the newly cited Ref. 30.

Major Compulsory Revisions:

Comment 1:
Title. You are not assessing the cost-effectiveness of the “vaccine”. You are assessing the effectiveness of a vaccination program. Please, rephrase the title.

Response:
Thanks for your kind comment. We have modified our title to “Cost-effectiveness of human papillomavirus vaccination for prevention of cervical cancer in Taiwan”.

Comment 2:
Background. Here is your opportunity to show readers that HPV infection and cervical cancer are important in Taiwan. It could be convenient to show infection rates, cervical screening compliance, cervical cancer mortality rates, and breast cancer mortality rates (as another important mortality cause among women).

Response:
Following your constructive recommendation, we have added the related information with numerical data in this section. Please kindly refer to:

(Page 5, ll. 4-10) Nonetheless, the compliance with cervical screening in Taiwan remains suboptimal that the annual screening rate was 28.6% for women aged over 30 years [1], and the incidence of cervical cancer is consistently higher than those in neighboring countries [2]. In 2006, there was an annual incidence rate of 16.2 per 100,000 people for invasive cervical cancer and a mortality rate of 7.8 per 100,000 people in comparison with breast cancer incidence and mortality of 61.1 and 12.8 per 100,000 people, respectively [3].

(Page 5, ll. 12-14) Genital infection with human papillomavirus (HPV) has been well established to be the determining cause of cervical cancer [4, 5]. Researchers reported the HPV prevalence in Taiwan was around 10-20% [6-9].

Comment 3:
On the second paragraph, after talking about the efficacy of the vaccine, you
should be honest mentioning that the vaccine has not proven its efficacy preventing cervical cancer, but surrogate endpoints.

**Response:**

Many thanks for your kind reminding. We have revised the sentences as follows:

(Page 5, ll. 19-23) Safety and satisfactory efficacy against type-specific HPV infection and related precancerous lesions have been demonstrated for both vaccines. Although their efficacy for preventing cervical cancer has not been comprehensively proven yet, it seems reasonable to expect such an outcome.

Comment 4:

Methods. Decision model. References 15-17 are an example of misplacement.

**Response:**

We have checked and adjusted the citation of references.

(Page 6, line 14) We developed a Markov model [30] to assess the cost-effectiveness of the prophylactic vaccine against high-risk HPV infections and related cervical cancers in Taiwan……

Comment 5:

Methods. Decision model. The sentence starting with “Our base case” is unnecessary here. You should move it to the “Sensitivity analysis” part.

**Response:**

We have moved the sentences to the section of “Sensitivity analyses”.

(Page 11, ll. 11-14) Our base case analysis assumed a universal vaccination strategy for 12-year-old girls. We also examined the impact of starting vaccination at different ages on the cost-effectiveness ratio for HPV vaccine in sensitivity analyses
Comment 6:

Methods. Quality of life. The sentence starting with “Accordingly” is unnecessary. Also, it seems that those quality of life values respond to your expert criteria. You should mention that.

Response:

We have dropped the unnecessary sentence while adding another one to illustrate that the quality of life values responded to our expert criteria.

(Page 9, ll. 17-21) For invasive cervical carcinoma, a woman’s utility was assumed to reduce down to 0.70 after diagnosis to reflect the severity of her disease and its effects on her quality of life. Follow-up of cervical cancer was assigned a moderate utility (0.95) once cancer went into remission. The chosen values responded to our expert criteria.

Comment 7:

Methods. Quality of life. The sentence starting with “Cervical cancer costs” should be under a new heading called “Costs”. A bit more detail could be added here enumerating, at least, the costs included in the analysis: direct, indirect, short-term, long-term, etc. Reference number 17 does not include any cost. Please check, and refer the reader to the correct sources. You should also mention the year of reference of the cost data.

Response:

We have added the title of this subsection, Costs. In accordance with your valuable comments, we have amended this paragraph as follows:

(Page 9, line 24 ~ Page 10, line 3) Only direct medical costs are considered in this
study. Cervical screening costs and treatment costs of SIL and invasive cancer were based on published literature by Tang et al. (2009) [41], expert opinions and official tariff lists of the National Health Insurance. All costs are reported in 2009 US dollars with the exchange rate of 33 New Taiwan dollars to US$1.

Comment 8:

Methods. Outcome measures. The “cost perspective” is commonly known as “perspective of analysis”. This should be mentioned at the very beginning of the methods section, together with the “time horizon” considered.

Response:

We have made revision according to your recommendations.

(Page 6, ll. 17-19) The perspective of analysis considered in this study was that of the healthcare payers. The target population for our analysis included all adolescent girls in Taiwan; the time horizon was lifetime.

Comment 9:

Methods. Sensitivity analysis. Here you should mention all the different analysis that you have really done and mentioned in the previous paragraphs: efficacy of the vaccine, different populations, different coverages, etc.

Response:

We have included further description about the sensitivity analyses that we have done.

(Page 11, ll. 4-7) 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.
Comment 10:
Results. Model validation. You should add numerical results to this paragraph.

Response:
Thanks for the valuable comment. We have added numerical results about the model validation to this paragraph as follows:

(Page 11, line 21 ~ Page 12, line 3) The model predicted the incidence rate for cervical cancer would be 21.1 per 100,000 females 12 or older, given the assumption that women would receive cervical screening with compliance rates of the current practice. Predicted cervical cancer incidence showed good correspondence with observed data from the National Cancer Registry of Taiwan between 2001 and 2005 that the overall incidence of cervical cancer cases was 22.7 per 100,000 females aged over 10 years (Figure 2).

(Page 12, ll. 6-8) The predicted cervical cancer mortality would be 7.2 per 100,000 females 12 or older, while the observed overall cervical cancer mortality was 7.8 per 100,000 people for women aged over 10 years.

Comment 11:
Results. Base case analysis. The sentence starting by “We used” is unnecessary.

Response:
We have deleted this sentence by your suggestion.

Comment 12:
Results. Sensitivity analysis. The last two paragraphs are misleading, and
should be eliminated.

**Response:**

We agree that the last paragraph for sensitivity analyses in the Results is confusing, so we have dropped this whole paragraph. However, we would like to keep the other paragraph illustrating the results of sensitivity analysis on discount rate.

Comment 13:

Discussion: The sentence starting with “Given the limitations” is unnecessary. The sentence starting with “Although there has been” is inaccurate, and should be eliminated. The sentence starting with “This figure is not astonishing” is unnecessary. The sentence starting with “The undiscounted” is misleading and should be eliminated. Comments to undiscounted results are misleading, and should be kept only when commenting sensitivity analysis results.

**Response:**

Following your constructive advice, we have deleted almost all the sentences you mentioned above. But since another reviewer also expresses his opinion on the threshold value for cost-effectiveness, please allow us to revise the following sentence referring to the criteria of cost-effectiveness ratio, as follows:

*(Page 14, ll. 8-16)* Although there has been no domestic consensus on the threshold of the cost-effectiveness ratio for the National Health Insurance system to decide whether to reimburse a new medical intervention, the results of our analysis suggest that prophylactic vaccination against oncogenic HPV administered in preadolescent girls in Taiwan would be usually cost-effective based on the World Health Organization proposed criteria of 1-3 times the gross domestic product (GDP) per capita being cost-effective or less than GDP per capita being very cost-effective [35]*
since the GDP per capita of Taiwan was approximately US$17,082 in 2008.

Comment 14:
Conclusions. Again, here your cost-effectiveness results could be related to the particular characteristics of the Taiwanese context (high rates of HPV infection, high mortality rates) to make a case for its usefulness in this particular context.

Response:
Thanks for your valuable comment. We have revised the first sentence in the Conclusion to reflect the context.

(Page 17, ll. 9-12) Our analysis suggested that vaccination of adolescent girls with an HPV vaccine seems to be cost-effective in Taiwan where the HPV infection rate and the incidence as well as the mortality of cervical cancer are relatively higher than those in other developed countries.

Comment 15:
Table 1. Unnecessary.
Figure 2. Unnecessary.

Response:
We have eliminated the previous Table 1 about undiscounted lifetime health outcomes. Nonetheless, we would like to keep the Figure 2 showing the calibration results of age-specific incidence and mortality of cervical cancer because the good correspondence between the predicted results and the observed data is one of the strengths in our study compared to similar published papers.
Comment 16:

Appendix table. This is a very important table and should be added in the main body of the paper. Please, check the references carefully.

Response:

In accordance with your recommendation, we have moved the previous Appendix Table to the main body of the manuscript as new Table 1. And we have verified the cited references carefully again.

(Page 7, ll. 19-21) Detailed information is provided in Table 1 which depicts the base case value, range for sensitivity analysis, and data source for input parameters.
Reviewer: Jaume Puig-Junoy

MAJOR COMPULSORY REVISIONS

I find surprising that a recent and previous paper performing a cost-utility analysis of HPV vaccine in Taiwan is not referenced in this paper (Dasbach et al, “The cost-effectiveness of a quadrivalent human papillomavirus vaccine in Taiwan”, Asian Pacific Journal of Cancer Prevention 2008, 9: 459-66). Dasbach et al presents the results of an economics evaluation estimated using a transmission dynamic model which is more appropriate and complicated than that used in the paper submitted to this journal. In fact, Dasbach et al report that vaccination of 12-years old girls strategy is weakly dominated by no vaccination! It is at least surprising that the results of this paper do not deserve any attention to the authors of the submitted paper. The authors should convince the editor and the referees about the contribution to the literature of the submitted paper taken into consideration similar published papers.

Response:

Thanks for your critique. We have cited the paper of Dasbach et al. in this revised manuscript according to your kind advice. We compared their study with ours, and there were following strengths and weaknesses:

1. While modeling the dynamic transmission could accommodate sexual behavior into the results of projection theoretically, the availability of relevant epidemiological data for parameterization is a major concern. For example, the sexual behavior in adolescents and young people in Taiwan may be very different from that in western countries. As the relevant data are still inadequate,
borrowing information from western countries generally requires making more assumptions and needs further validation.

Likewise, Dasbach et al. set most parameters, such as the natural history of HPV infection, based on international data previously reported. However, to our knowledge, the HPV infection rate and the incidence of cervical cancer in Taiwan were higher than those in western developed countries, which must be accounted for in the cost-effectiveness analysis for HPV vaccine. Our study based on the existing epidemiological data of HPV infection and cervical cancer incidence specific to Taiwan would probably improve the validity of estimation of the cost-effectiveness of HPV vaccination in our country.

2. Variations may exist in the cost-effectiveness analyses of different studies even for the same country. Compared with the incremental cost-effectiveness ratios (ICERs) of adding HPV vaccination that were reported in Taiwan previously, the result of our base case estimation appears similar to theirs. The ICER of our base case was NT$451,200 per QALY gained, which seems close to the NT$437,400 per QALY gained and NT$557,248 per QALY gained estimated by Dasbach et al., and Debicki et al. (Vaccine 2008, 26 Suppl 5:F16-28), respectively.

3. Our model has been delicately adjusted by existing clinical and epidemiological data of cervical cancer in Taiwan. The results of the model calibration showed good correspondence between the predicted values for the current practice strategy before vaccination and the observed data from the national cancer statistics (please kindly refer to Figure 2). This picture reflected a fact that the baseline estimation in our study probably matched well with the current conditions in Taiwan. Moreover, our study also highlighted the
importance of improving the current practice with cervical cytological screening programs, given the massive HPV vaccination program might be adopted by the government of Taiwan.

Accordingly, we have also revised several parts of the content in this amended manuscript. Please kindly refer to:

(Page 6, ll. 3-8) Indeed, the cost-effectiveness of HPV vaccination varies between regions by many factors including different epidemiologies of HPV infection and cervical screening efforts; Puig-Junoy and Lopez-Valcarcel reported that large variations existed in the cost-effectiveness results of different studies even for the same country [27]. Currently, there are still limited data evaluating the economic impact of cervical cancer vaccination in Taiwan [28, 29].

(Page 15, ll. 9-17) Methodological differences may also account for variations in the results of different cost-effectiveness evaluations [27, 44]. Although dynamic transmission model has been developed and applied [17, 18, 22, 23, 25, 28], it generally requires investigators to make more assumptions on putting into parameter values related to viral transmission. As the sexual behavior in adolescents and young people in Taiwan may be different from that in western countries and the relevant data were insufficient, we took an alternative approach to adapt a simpler Markov model as previous studies [13, 14, 24], but more delicately adjusted the model with existing clinical and epidemiological data of cervical cancer in Taiwan.

(Page 17, ll. 3-6) Nonetheless, the conservative assessment for the ICER of HPV vaccine in our study, together with the results of other relevant research [28, 29], would increase the credibility of the cost-effectiveness for a prophylactic HPV vaccination program in Taiwan.
MINOR ESSENTIAL REVISIONS

In my opinion, independently of the previous main objection to the paper, the interest of the paper is moderate, and some other problems should be solved by the authors before publication:

Comment 1:

The authors should provide a more comprehensive and appropriate list of references containing at least the various surveys on HPV vaccine cost-utility analysis that have been published in the past recent years. I recommend to carefully check references 7-12 because many of them, despite what the authors claim, do not correspond to economic evaluations of HPV.

Response:

Thanks for your suggestions. We have improved the citation with relevant literature in this revision. We have removed one previous reference and added 9 new references, as follows:


Comment 2:

The decision model used in the paper should be clearly compared with those other used in this literature for other countries in order to show similarities and differences, and their implications.

**Response:**

In accordance with your valuable comment, we have added a new paragraph and revised another paragraph in the Discussion section to address this issue.

(Page 15, ll. 9-22) Methodological differences may also account for variations in the results of different cost-effectiveness evaluations [27, 44]. Although dynamic transmission model has been developed and applied [17, 18, 22, 23, 25, 28], it generally requires investigators to make more assumptions on putting into parameter values related to viral transmission. As the sexual behavior in adolescents and young
people in Taiwan may be different from that in western countries and the relevant data were insufficient, we took an alternative approach to adapt a simpler Markov model as previous studies [13, 14, 24], but more delicately adjusted the model with existing clinical and epidemiological data of cervical cancer in Taiwan. Our approach did not consider the herd immunity and the protection by HPV vaccination for genital warts or other HPV related cancers. Thus, we would underestimate the overall effectiveness of the vaccination program, which would generally make the cost-effectiveness of the HPV vaccine even more favorable if herd immunity or protection for other diseases existed [21, 45].

(Page 14, line 21 ~ Page 15, line 3) Compared to the previous studies mostly performed in Western countries [16, 22-26], the HPV vaccination strategy in our study appeared to be attractive in terms of a lower ICER. However, this figure of cost-effectiveness in Taiwan could be largely owing to the high prevalence of HPV infection [6-9] and lower compliance rate with cervical cytological screening [1] that resulted in higher background incidence of cervical cancer, since we employed similar assumptions of time horizon, discount rate, vaccine efficacy and lifelong vaccine protection as most of those studies.

Comment 3:
Results of the sensitivity analysis should be presented and described in a more detailed way. A table including maximum and minimum values under each of the scenarios considered in the sensitivity analysis should be included and discussed in the paper.

Response:
Following your constructive advice, we have revised several parts in our revised
manuscript, including the Figure 3. We have provided the numbers of the ratio between the maximum value/the minimum value in sensitivity analysis over the base case ICER in an illustrative and straightforward way, as follows:

**Figure legends: (Page 25-26)**

**Figure 3. One-way sensitivity analyses on the incremental cost-effectiveness ratio (ICER).** The range of input parameter for the sensitivity analysis is indicated in the parentheses on the left of the vertical axis. The vertical line represents the ICER under base case assumptions. The numbers in brackets alongside the bar represent the ratio between the maximum value (right) and the minimum one (left) in sensitivity analysis respectively over the base case ICER.

![Incremental cost-effectiveness of vaccination (US$/QALY)](image)

(Page 7, ll. 19-21) Detailed information is provided in Table 1 which depicts the base case value, range for sensitivity analysis, and data source for input parameters.

(Page 14, ll. 18-21) In addition to the discount rate, the duration of the vaccine immunity accounted for the most influential source of variations in the ICER of
incorporating HPV vaccination within our investigation (Figure 3), which is consistent with other studies [27].

Compared to the previous studies mostly performed in Western countries [16, 22-26], the HPV vaccination strategy in our study appeared to be attractive in terms of a lower ICER. However, this figure of cost-effectiveness in Taiwan could be largely owing to the high prevalence of HPV infection [6-9] and lower compliance rate with cervical cytological screening [1] that resulted in higher background incidence of cervical cancer, since we employed similar assumptions of time horizon, discount rate, vaccine efficacy and lifelong vaccine protection as most of those studies.

Comment 4:
Using the results of a cost-utility analysis, a health intervention can only be considered cost-effective or cost-ineffective when an arbitrary exogeneous threshold is introduced. Then, it is not scientifically appropriate to state that HPV vaccine may be cost effective without clearly indicating the threshold (i.e., in the abstract and the conclusions of the paper).

Response:
Thanks for the comment. In addition to the statement about the threshold value of intervention cost-effectiveness in Discussion, we have also revised the sentences in the abstract and the conclusions of our manuscript to address this concern.

Abstract: Although gains in life expectancy may be modest at the individual level, the results indicate that prophylactic HPV vaccination of preadolescent girls in Taiwan would result in substantial population benefits with a favorable cost-effectiveness ratio.
Although there has been no domestic consensus on the threshold of the cost-effectiveness ratio for the National Health Insurance system to decide whether to reimburse a new medical intervention, the results of our analysis suggest that prophylactic vaccination against oncogenic HPV administered in preadolescent girls in Taiwan would be usually cost-effective based on the World Health Organization proposed criteria of 1-3 times the gross domestic product (GDP) per capita being cost-effective or less than GDP per capita being very cost-effective [43] since the GDP per capita of Taiwan was approximately US$17,082 in 2008.

Our analysis suggested that vaccination of adolescent girls with an HPV vaccine seems to be cost-effective in Taiwan where the HPV infection rate and the incidence as well as the mortality of cervical cancer are relatively higher than those in other developed countries.

Comment 5:
Variation in ICERs reported in the results section should be explained. The main sources of ICER variation should be identified and their implications should be discussed. The authors should compare their ICER obtained in this paper with those reported in the recent literature (see for example, the Dutch study published by de Kok et al 2009), and justify results variation observed.

Response:
Thanks for your comment and constructive advice. We have revised several paragraphs and discussed their implication in this new manuscript, as follows:

If every woman in Taiwan obtained a Pap test every 3 years from the age of 30, the ICER of vaccination would slightly increase to US$17,199/QALY 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.

(Page 14, line 18 ~ Page 15, line 7) In addition to the discount rate, the duration of the vaccine immunity accounted for the most influential source of variations in the ICER of incorporating HPV vaccination within our investigation (Figure 3), which is consistent with other studies [27]. Compared to the previous studies mostly performed in Western countries [16, 22-26], the HPV vaccination strategy in our study appeared to be attractive in terms of a lower ICER. However, this figure of cost-effectiveness in Taiwan could be largely owing to the high prevalence of HPV infection [6-9] and lower compliance rate with cervical cytological screening [1] that resulted in higher background incidence of cervical cancer, since we employed similar assumptions of time horizon, discount rate, vaccine efficacy and lifelong vaccine protection as most of those studies. For example, as the projected incidence of cervical cancer under the current screening practice in a study from the Netherlands [26] was lower than that in our study by 3.5 times and the vaccination costs were 1.5 times more expensive, the ICER reported by them was much higher than the figure in our study (approximately 5.8 times).

Comment 6:
Sensitivity of conclusions to current screening compliance rate should be stressed given that screening and HPV vaccination are not substitutes, and that the authors recommend increasing compliance rates.

Response:
We totally agree with your opinion and have revised this sentence to highlight this idea, as follows:
Even in the case of favorable cost-effectiveness ratio of prophylactic vaccination against oncogenic HPV, there is still room for improvement of the compliance with Pap screening tests in Taiwan, especially for older women, because vaccination should not yet be regarded as the substitute for cytological screening. It calls attention to the importance of continuing research that investigates primary and secondary preventive measures against cervical cancer.

Comment 7:
A sub-section on costs should also be included in the Methods section. Monetary units used in the paper, the year of reference, and used exchange rates should also be reported.

Response:
Many thanks for your kind notification. We have added the title of this subsection, “Costs”. Following your advice, we have revised this paragraph as follows:

Only direct medical costs are considered in this study. Cervical screening costs and treatment costs of SIL and invasive cancer were based on published literature by Tang et al. (2009) [41], expert opinions and official tariff lists of the National Health Insurance. All costs are reported in 2009 US dollars with the exchange rate of 33 New Taiwan dollars to US$1.