Author's response to reviews

Title: Efficacy and Safety of Prophylactic Vaccines against Cervical HPV Infection and Diseases among Women: A Systematic Review & Meta-Analysis

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Version: 2 Date: 15 December 2010

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Response to Reviewers’ Queries

Reviewer #1

- Comment #1:
The introduction is poor and need to be reinforced. Some important HTA reports on HPV vaccination are missing. As an example, the authors did not cite the following:

A. DACEHTA. Reduction in the risk of cervical cancer by vaccination against Human Papillomavirus (HPV). Health Technology Assessment 2007; 9(1).

The second one was particularly important since for the first time it reported a systematic review and meta-analysis of 5 RCTs concerning efficacy of quadrivalent vaccine.

The authors reported that the aim of the study was to perform a systematic review “to allow informed decision-making based on all existing evidence”. According to the reviewer, this point must be re-written, since this point is unrealistic. The authors should report the aim strictly related to scientific purposes.

Response:

Thank you for your suggestions. We've revised the introduction accordingly to include the suggested references and also added another reference (La Torre, Vaccine, 2010) summarizing current knowledge on both quadrivalent and bivalent HPV vaccines. We've also simplified the objectives of the study which reads:

“The present study aims to provide a comprehensive assessment of vaccine safety and efficacy against multiple virological and clinical endpoints using the techniques of systematic review and meta-analysis.”

- Comment #2:
It is not clear how the methodological quality was assessed. The authors must explain why they did not choose very used scale, such as Jadad or Chalmer scale.

Response:

The methodological quality of RCTs was evaluated using the risk of bias table and subgroup analyses as recommended in the Cochrane Handbook for Systematic Reviews of Interventions (5.0.2). The use of Jadad or Chalmers scale is no longer recommended for quality assessment. The risk of bias table assesses the adequacy in the reporting of allocation concealment, blinding, effect size, power calculation, and participant withdraw and drop-out in each publication. The relevant information was included in Table 1 (Characteristics of randomized controlled trials included in the review). We've also went beyond the risk of bias table and evaluated other potential sources of bias with respect to study population, intervention, comparator, clinical protocol, endpoints and efficacy populations, as presented in Table 1 and 2. Subgroup analyses were carried out to identify potential risk of bias from each source specified above.

- Comment #3:
The sensitivity analysis was only reported in a descriptive way, without giving a robust possible explanation of the heterogeneity between studies.

Response:

Thank you for your comments. Due to space constraints we’ve previously provided only descriptive sensitivity analysis. We’ve now revised the statement on sensitivity analysis to specify potential sources of heterogeneity examined in the present study and to include relevant statistics in the text. The revised statement reads as follows:

“Sensitivity analysis was performed to identify potential sources of heterogeneity that was observed in the ITT analyses of CIN1+ and CIN2+ associated HPV 16. The included trials did not differ by methodological qualities in terms of allocation concealment, blinding, effect size, power calculation, and participant withdraw and drop-out. Therefore, heterogeneity was unlikely attributed to the methodological quality. We further examined the heterogeneity among included trials according to study characteristics including study population, inclusion/exclusion criteria, intervention, comparator, endpoints chosen and efficacy populations defined, as well as participant baseline characteristics such as age, HPV prevalence and lifetime number of sex partners. The pooled efficacy estimates for FUTURE trials were significantly lower than those for all other RCTs (CIN2+: FUTURE II 0.59, 95% CI: 0.44-0.78 vs. Other RCTs 0.11, 95% CI: 0.05-0.23; CIN1+: FUTURE I 0.55, 95% CI: 0.40-0.75 vs. Other RCTs 0.15, 95% CI: 0.07-0.29). With the FUTURE trials excluded, the observed heterogeneity dissipated for either endpoint (CIN2+: I²=59%, p=0.09; CIN1+: I²=0%, p=0.70). The previously observed heterogeneity and lower efficacy reported by the FUTURE trials was likely due to inclusion of a larger proportion of trial participants already infected with vaccine HPV types at baseline in the ITT cohorts, some of whom may have progressed to cervical neoplasia during the follow-up period.”

Comment #4:

In the discussion the authors reported as limitation of the study the fact they “were not able to evaluate prophylactic efficacy against anogenital warts, vulvar, vaginal or anal diseases associated with vaccine HPV due to the limited number of trials [13, 14, 19] that reported such endpoints as well as the common use of composite endpoints that included infection and disease of various sites”. According to this judgment, the authors should have not performed this systematic review, since in their analyses they pooled the results from 2 to 4 RCTs. For all these outcomes (anogenital warts, vulvar, vaginal or anal diseases HPV related), at least two RCTs could be pooled.

Response:

Thank you for your comments. We have modified the text to improve clarity. The main issue with evaluating additional outcomes listed was that data were not extractable for efficacy assessment of individual outcomes such as anogenital warts, vulvar, vaginal or anal diseases. Composite endpoints were used in all RCTs that reported such outcomes and the compositions were not comparable across RCTs. Therefore it was not possible to isolate individual outcomes for evaluation. For instance, Garland et al (citation #13) evaluated efficacy against the combined incidence of condyloma, vulvar, or vaginal intraepithelial neoplasia (VIN, VaIN) associated with HPV 6, 11, 16 or 18. Munoz et al (citation #14) presented efficacy for the combined incidence of infection, lesion and cancer at various anogenital sites including 6-month persistent infection, CIN, VIN, ValN; adenocarcinoma in situ (AIS); cervical, vulvar, or vaginal cancer; and genital warts related to HPV 6, 11, 16, or 18. Villa et al (citation #19) reported efficacy for combined incidence of CIN, VIN, ValN, AIS, external genital warts or cervical, vulvar, or vaginal cancer associated with vaccine HPV types. To improve clarity, we have revised the paragraph as follows:

“We were not able to evaluate prophylactic efficacy against anogenital warts, vulvar or vaginal diseases associated with vaccine HPV due to the common use of composite endpoints in individual RCTs that
combined infections, lesions and cancers of various anogenital sites, and were often incomparable across RCTs [13, 14, 19]."

- **Comment #5:**
  Publication bias was not assessed, via funnel plot.

**Response:**

Thank you for your comments. We have now added the funnel plot for the primary endpoint, CIN2+ associated with HPV 16/18 which includes 3 RCTs. In addition, we have also added the statistical test results from our publication bias assessment. However, due to space constraints we are providing only the p values for Begg and Egger's test in the text and the funnel plot in the appendix. The statement on publication bias reads: "The Begg and Egger funnel plot (Appendix: Figure 2) for the primary endpoint, CIN2+ associated with HPV 16/18 in the ITT cohorts (p=0.602) indicated no significant publication bias."

The detailed test statistics for primary endpoints are summarized below for your reference:

**Assessment of Publication Bias for the Primary Endpoint: HPV 16/18 Associated CIN2+**

**Begg's Test**

adj. Kendall's Score (P-Q) = -1  
Std. Dev. of Score = 1.91  
Number of Studies = 3  

\[ z = -0.52 \]  
\[ Pr > |z| = 0.602 \]

\[ z = 0.00 \text{ (continuity corrected)} \]  
\[ Pr > |z| = 1.000 \text{ (continuity corrected)} \]

**Egger's test**

| Std_Eff | Coef. | Std. Err. | t  | P>|t| | [95% Conf. Interval] |
|---------|-------|-----------|----|------|---------------------|
| slope   | .6505295 | .1338216  | 4.86 | 0.129 | -1.049835 - 2.350894 |
| bias    | -.7807398 | .5951079 | -1.31 | 0.415 | -8.342302 6.780823 |

**Reviewer #2**

- **Comment #1:**
  1. Page 5, line 8 - italicize "a priori"
  2. Ref #4 - change "Cmaj" to "CMAJ"
  3. Ref #8 and 11 - change "Bmj" to "BMJ"
  4. Ref #15 - change "Bjog" to "BJOG"
  5. Ref #17 - change "Jama" to "JAMA"
Response:

Thank you for your suggestions. The styles previously presented were the products of automated styling function in EndNote software. We've made manual corrections accordingly.

Reviewer #3

It is a very well written paper, given the latest details concerning the efficacy and safety data based only on RCT, related to the two existing prophylactic HPV vaccines. It is worthy of publication, because exactly the actuality of these informations is mostly needed from the general public and the physicians for the promotion of the primery prevention of cervical cancer via the vaccine.

Response: Thank you.