Author's response to reviews

Title: Canadian oncogenic human papillomavirus cervical infection prevalence: Systematic review and meta-analysis

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Author's response to reviews: see over
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Dr. David Regan,
Associate Editor
BMC Infectious Disease

Dear Dr. Regan,

RE: MS 8058103995466278: “Canadian oncogenic human papillomavirus cervical infection prevalence: Systematic review and meta-analysis”

Thank you very much for your email dated July 18, 2011 and the included peer review comments. We are pleased that the BMC Infectious Disease is considering our manuscript for publication.

We have carefully reviewed the suggestions made by the peer reviewers and have revised the manuscript accordingly. Enclosed you will find a table with a point by point reply to the various recommendations, indicating where any changes have been made. The revised manuscript with tracked changes has been uploaded on your website, using the link provided in your e-mail.

Thank you for your considerations and best regards,

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Reviewer’s Comments and Responses: MS 8058103995466278: “Canadian oncogenic human papillomavirus cervical infection prevalence: Systematic review and meta-analysis”

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<th>Reviewer #</th>
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<td>1</td>
<td>1. In terms of HPV-type distribution, it is not clear whether any additional knowledge has been gained in comparison to larger more robust meta-analyses, which although not Canada-specific, show very similar findings. Indeed, the authors suggest that this is the first meta-analysis of cervical lesions other than normal cytology and cancer. However, such summaries for LSIL (Clifford et al, 2005 CEBP) and HSIL (Clifford et al, 2003 BJC) do already exist and are worthy of comparison to the present results. Also, the number of Canadian studies contributing to ASCUS, LSIL and HSIL remain very few. The percentage of these lesions that might be preventable by 16/18 vaccines is complicated by the issue of a high prevalence of multiple infections and lack of knowledge about which type has produced the lesion. This is much less an issue in cancer, which is the key basis for prevention decisions.</td>
<td>While we agree in principle with the reviewer, we still feel that our paper is merited. This is the most comprehensive systematic review and meta-analysis for a particular country. We have synthesized age-specific HPV data, as well as HPV prevalence across routine screening populations, among HPV-positive, and according to cytology or histology within a single systematic review, which is much more comprehensive than some of the previous reviews. Furthermore, previous reviews have lumped Canada together with the United States, yet this might not be valid because Canada is known to have a lower HPV prevalence. We note percentage of multiple infection (under study characteristics) and have put this in as a limitation to our systematic review. However, multiple infection was a limitation of all previous reviews on HPV prevalence as well. As the reviewer recommends, we added this paragraph to the discussion comparing our results to the Clifford reviews.</td>
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<td>2. I was unclear about the utility of Figure 4. Population-based data is better expressed as a population-based prevalence, unless a large gain in eligible data can be made by shifting to HPV-positive cases also among more opportunistic studies. This appears not to be the case, with the curious findings that there is one less eligible study for HPV52 in the wider inclusion criteria.</td>
<td>In order to get a clearer picture of HPV prevalence epidemiology in Canada, prevalence among HPV-positive is useful. There are 3 studies that were reported in both of the analyses for HPV-52. One of them was ineligible for the HPV-specific typing among those who are HPV positive meta-analysis because the authors only examined one HPV type (HPV 52; Aho 2003), thus there was no denominator data to calculate the prevalence. We have put a footnote in Figure 4 noting this discrepancy.</td>
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<td>3. The use of the term “false negatives” for a normal PAP smear in an HPV-positive women is mis-leading. In terms of disease-risk it could be that the HPV-test is “false-positive”.</td>
<td>We agree. We deleted this sentence in the abstract and conclusion and wrote this in the discussion section: “Our review identified a positive HPV test (e.g., 7.9% HPV-16 and 3.6% HPV-18) among females with a negative Pap test. Both tests have associated sensitivities and specificities, and while there is...</td>
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continuing research in identifying the best screening policies with these tests, vaccination remains an effective method to prevent infection with the major high risk HPV types.[85] In addition to errors due to diagnostic sensitivity and specificity, 12% of Canadians never go for a Pap test.[9]

4. I was not clear about how the use of "a representative sampling strategy", "attempted to address of non-respose bias" and other criteria of methodological quality were judged - they seem very open to interpretation. I was particularly surprised that 74% of studies somehow attempted to address non-respose bias, which in my opinion, is always almost impossible to know. Perhaps it is the definition of "attempting" which is the issue.

Please see Appendix 2 for an explanation of how the quality was appraised. We agree with the reviewer that methodological appraisal can be open to interpretation. However, two reviewers appraised all studies and compared answers, making this exercise more reliable.

5. The best definition for the 13 HR HPV types is now: Bouvard et al, Lancet Oncology, 2009, following the decision of the IARC Monograph working group.

We have added this reference.

6. It was not entirely clear if only studies with typing information were included. What about studies with HC2 only, and no genotyping. Perhaps there were no such studies but could/would they have contributed to the overall HR HPV prevalence estimates, even if no typing was done?

As stated in the eligibility criteria, we included any study with DNA confirmed HPV, whether this was identified using genotyping, HCI, or HC2. This means that studies with HC1 or HC2, without any additional genotyping, would contribute to the prevalence estimates. These studies would contribute to the overall prevalence meta-analysis but would not be included in any type specific prevalence meta-analyses. We have made this clearer in the eligibility criteria section.

2 Major Compulsory Revisions:
1. Methods/Results: The authors abstract a lot of data on study characteristics and data on study participants. Were there differences in prevalence based on the other study characteristics abstracted (e.g. study design, HPV detection method, sample size of the study, etc). Was there any evidence of publication bias? Were there differences in HPV prevalence between studies stratified by the characteristics assessed in the methodological quality tool?

We attempted to include as much literature (i.e., grey literature and unpublished material difficult to locate) as possible. We did not assess for publication bias statistically because our outcome is prevalence versus an effect size (e.g., odds ratio, relative risk). As the reviewer recommended, we did a series of additional analyses by study characteristics and methodological quality and did not find any differences in prevalence between studies. As such, we added a section in the results on “Sensitivity analysis”.

2. Methods/Results: Age-specific prevalences

The data shown in Figure 2 are from routine screening populations, as the HPV
were investigated among the routine screening populations. How did the prevalence estimates stratified by age group from the other populations compare to the routinely screened populations? Prevalence data were higher among the other populations. Routine screening data were presented, as they are more conservative estimates. We have added a sentence in the results section on this.

3. Discussion: Please compare the findings from this study with similar prevalence estimates from (pooled) studies in other regions as well. Is the HPV prevalence in Canada higher, lower, or similar than prevalence estimates from other regions reported in the literature? Thank you for this suggestion; we have added a paragraph in the discussion section, which compares our results to those from other regions.

**Minor Essential Revisions:**

1. Methods: Please reference Appendix 1 in the paper, as the search terms are not stated in the text. Why was the Ovid Medline search strategy the only one included in Appendix 1? What about the other searches? Appendix 1 is referred to in the text on page 6. Furthermore, we have provided details about the other searches under the “Information sources and search” heading.

2. Please describe how searches were carried out on web sites. Were the results from web sites vs. peer-reviewed publications different? Please also describe more clearly what you mean by “…the author’s personal files were searched, and HPV experts were contacted.” Many of the studies identified from the grey literature search were duplicates of results from the literature searches. As recommended by the reviewer, we have provided more information under the “Information sources and search” heading.

3. Results: The authors state that 30 reports and 21 companion reports met inclusion criteria. How many contributed data to the systematic review/meta-analysis? The 30 major publications contributed data to the meta-analysis. As reported in the methods section, companion reports were only used for supplementary data.

4. In study characteristics, please specify the denominator of the percentages listed. For example, 53% of how many studies (30, 30+21?) did not use a representative sampling strategy? The denominator is the major publication (30 in total). As suggested, we have added the denominator to the study characteristics section in the results.