Author’s response to reviews

Title: Type distribution of human papillomavirus among adult women diagnosed with invasive cervical cancer (stage 1b or higher) in New Zealand

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Author’s response to reviews: see over
Dear Editor,

Please find enclosed a manuscript entitled “Type distribution of human papillomavirus among adult women diagnosed with invasive cervical cancer (stage 1b or higher) in New Zealand” which we are resubmitting for further consideration by BMC Infectious Diseases.

Please also find the responses to your comments below. The authors appreciate the constructive feedback provided and have made the necessary modifications. Changes from the original submitted manuscript are highlighted in track changes.

We hope the revised manuscript is now acceptable for publication in BMC Infectious Diseases.

On behalf of all authors,

Yours sincerely,

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Both reviewers raised concerns about false HPV-negative cases due to the lack of an internal DNA control. It is admirable that the authors took steps to compensate for PCR inhibition, however this did not resolve all HPV-negative results and it remains unclear as to whether these are false negatives or true negatives. Therefore all analyses of HPV positivity rates are unsubstantiated.

The authors state that their aim was to assess genotype distribution, however a large portion of the results and discussion sections have been allocated to reporting and discussion of HPV positivity rates in ICC. It should be noted that references 11 and 23 also failed to address the issue of DNA adequacy with internal controls. Given the nature of the specimens (archival formalin-fixed paraffin-embedded tissue), DNA quality is a legitimate concern. The manuscript should therefore be amended to make this clear:

**Response:** The authors fully acknowledge that the lack of adequate DNA control is a major limitation to the study, and that ‘prevalence’ is the incorrect word to describe these results. While these data may not be fully substantiated, they currently offer the most complete nationwide picture available for New Zealand. Therefore, the authors feel they should be included with the full disclosure that they cannot accurately represent the prevalence in the population. We propose that these results are retained, but described as ‘HPV detection rate’ instead of ‘HPV prevalence’.

All instances of ‘prevalence’ in the context of overall HPV positivity have therefore been replaced with ‘detection rates’. In addition, the limitations section of the discussion has been updated to clearly reflect this (lines 345–349). If this proposal is not acceptable to the Editor or Reviewers, we will be willing to further discuss removing these data.

Title: Remove "Prevalence and", as this suggests that the study was also looking at HPV positivity rates; Abstract Line 35: Replace "prevalence" with "distribution"; Abstract Line 49: Remove "prevalence and"; Abstract Line 51: Remove "prevalence and"; Abstract Line 56: Remove "A high prevalence of HPV in women with ICC was found."; Abstract Line 58: Remove "Prevalence and"
Response: Requested modifications have been made to the title and abstract.


Response: The authors would like to clarify that in the Statistical analysis section, the estimation of sample size was based on the type-specific prevalence and not overall prevalence. Therefore, the section was not modified.

Results: State the detection rates for each cancer type in a small paragraph.

Response: As explained above, the HPV detection results have been retained.

Remove all reference to analysis of HPV prevalence (overall, by age, by ethnicity).

Response: All in-text references to ‘prevalence’ have been replaced with ‘detection rate’. We acknowledge that our estimation of HPV positivity could be an underestimation of the true HPV positivity due to the lack of an appropriate control, and this has been included in the limitations section (lines 345–349).

Table 1 Heading: Replace "prevalence and types" with "detection and type distribution";
Table 2: Remove HPV positive section (first three lines of data)

Response: Requested modifications to the tables have been made.

Discussion: It should be clearly stated either up front or in the paragraph on limitations of the study, that internal DNA adequacy controls were not used and therefore HPV negative samples may include false negatives; however the aim of the study was to report genotype distribution rather than HPV positivity rates in ICC.

Response: The authors thank the Editor for the constructive feedback and have added the following statements “Furthermore, since we did not include DNA controls to further test the HPV negative samples, some of the HPV negative samples might be false negatives. The detection rate in this study might therefore underestimate the true prevalence.” (lines 345–349)
Discussion Line 214: Remove "prevalence and";

Response: Requested modification has been made.

Discussion Lines 216 - 234: Remove section comparing positivity rates; not relevant to the aims of this study and misleading;

Response: The authors acknowledge that the estimation of HPV positivity could be an underestimation and this has been included in the limitation section (lines 345–349). Since the results pertaining to HPV detection rates were retained (‘HPV prevalence’ was replaced by ‘HPV detection rate’) the corresponding comparisons of HPV detection rates were retained in the Discussion.

Discussion Line 266: Replace "prevalence" with "type distribution"; Discussion Lines 271-273: Remove "HPV prevalence were observed between Maori and non-Maori women with ICC in our study. Similarly, there were no significant differences between groups in terms of"; Discussion Line 273: Add "... between Maori and non-Maori women with ICC." to end of sentence.

Conclusion Line 330: Remove "prevalence and"

Response: Requested modifications have been made.