Title: More men than women make mucosal IgA antibodies to Human Papillomavirus type 16 (HPV-16) and HPV-18: a study of oral HPV and oral HPV antibodies in a normal healthy population.

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Version: 6 Date: 12 May 2006

Author's response to reviews: see over
The Editor,
BMC Infectious Diseases

Dear Sir,

Please find in accompaniment to this letter, a revised manuscript entitled: “More men than women make mucosal IgA antibodies to Human Papillomavirus type 16 (HPV-16) and HPV-18: a study of oral HPV and oral HPV antibodies in a normal healthy population”. We would like to resubmit the manuscript for possible publication in BMC Infections Diseases. We have attempted to address all the points raised by the one reviewer and the letter of responses to the reviewer comments has been attached below.

We sincerely hope that you will now consider the manuscript suitable for publication. The manuscript has not been submitted or accepted for publication elsewhere. All authors have seen and approved the content of the manuscript and have contributed significantly to the work described therein.

Sincerely,

Dr Dianne Marais

Here are the responses (in bold) to the reviewer comments to the manuscript as titled below.

Reviewer’s report
Title: More men than women make mucosal IgA antibodies to Human Papillomavirus type 16 (HPV-16) and HPV-18: a study of oral HPV and oral HPV antibodies in a normal healthy population.
Version: Date: 24 April 2006
Reviewer: John Sellors
Reviewer’s report:
General

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

Abstract, last sentence of Results section - not given what the 95% CI is for - if it is for OR, the OR should be given.
Response: Odds Ratios were added in the revised manuscript as indicated.

Abstract, last sentence of Conclusions section - the reference to ‘fewer men than women make antibodies’ is not supported by any of the Results.
Response: This sentence was changed in the revised manuscript to read “reportedly fewer men than women make antibodies”

pg 5, last sentence - the authors have missed the point that the utility of including men in a HPV vaccination program to protect women from cervical cancer is currently being debated and it is not appropriate to make such a categorical statement.

Response: The statement about vaccination of men was changed in the revised manuscript to include reference to the debate as to the relevance of including men in a vaccination program.

pg 6, last sentence of Study population subsection - ‘...12 had cleared their CIN (CIN0) (CIN patients).’ is difficult to interpret and there is no information given to explain how it is known that these women had cleared a previous CIN.

Response: In the revised manuscript it was made clear that all women had been referred to the colposcopy clinic when a pap smear had indicated high grade cervical disease (CIN2/3). The diagnosis of “cleared”/no CIN was made on subsequent histology and colposcopy or in a few cases colposcopy only.

Page 13, 1st sentence - The data are not given to support the assertion that an association between FEH and type 13 is supported.

Response: In the revised manuscript results it was stated that one woman with FEH was infected with oral HPV-13 and a reference made to Table 3 where this was tabled.

Conclusion, 1st sentence - The evidence for this statement is lacking.

Response: In the revised manuscript the first sentence of the conclusion was changed to read “We believe that sampling oral fluid for HPV antibodies shows promise as a simple, non-invasive method to test for the presence of antibody responses to HPV infection. However larger studies are required to validate the oral fluid antibody sampling as either a surrogate for serum testing or as a biomarker of anogenital HPV infection.”

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct).

pg 5, 2nd line - ‘Using this test...’ the authors are referring to a sampling method not a test/assay here.

Response: In the revised manuscript “test” was changed to “sampling method” as suggested.

pg 6, 2nd line - ‘...increased sexual activity.’ is incorrect and should refer to relatively higher rates of sexual activity.

Response: In the revised manuscript ‘increased sexual activity” was changed as suggested.
Pg 7, 2nd sentence - the reference to the exclusion of subjects in whom the buccal samples were collected by swab should be deleted as this is confusing unless further information is given.

Response: The reference to the swab collected buccal samples was removed as suggested from the revised manuscript.

Pg 7, last sentence of Sample collection subsection - the reference to the women from the colposcopy clinic as CIN patients is probably an incorrect characterization of this group. This group is referred to similarly in subsequent places in the paper.

Response: The women from the colposcopy clinic were referred there because of Pap diagnosed CIN however some were found on histology/colposcopy to be CIN free. All these women were referred to in the revised manuscript as CC women (colposcopy clinic women)

Page 7, 4th sentence HPV DNA determinations subsection - No information is given on the method used for sampling the cervices of these women. Acknowledgement of Roche should be put in the Acknowledgements section at end of paper.

Response: The method for the collection of cervical samples was included in the revised manuscript. Roche was acknowledged in the acknowledgement section and not in the method section in the revised manuscript.

Page 10, Statistical analysis subsection - a reference to the kappa coefficient statistic should be given.

Response: A reference for the kappa static was given in the revised manuscript.

Results section, page 10 - in the Oral HPV DNA and Oral antibodies in children, adolescents and adults subsections - there is an absence of p values when comparisons are being made between groups on prevalences of DNA and antibodies.

Response: An attempt was made to ensure that all references to antibody prevalences were accompanied by P values in the revised manuscript.

In last line of Oral HPV DNA subsection, the statement that 'There was no apparent gender difference in oral HPV prevalence.' is not supported by any data or statistical testing.

Response: In the revised manuscript a reference was made to the 9 males and 8 females of the 17 individuals with oral HPV infection and a P value included and the relevant table with the data was referred to.

Similarly for the next sentence referring to oral antibodies.

Response: The next sentence referred to above is: “In contrast to the oral HPV prevalence, the prevalence of oral HPV antibodies was lowest in the children, increased in adolescents and was highest in adults (Fig 1).” Figure 1 indicates by visual means that this sentence is true.

Page 11, 4th sentence - saying that 'There was no concordance..' is not the same as what is expressed by a kappa <0.4
Response: In the revised manuscript the sentence above was changed to read “there was low concordance” which better describes what is expressed by a kappa < 0.4.

Page 12, Antibodies in women with CIN subsection, 2nd sentence - the 44 women from the colposcopy clinic did not all have CIN and it is presumed that one cannot say that all of the 69 other women were not evaluated by colposcopy to enable one to say that they are 'normal' with respect to cervical neoplasia.
Response: The 69 women from the dental clinic were not evaluated with regard to their cervical neoplasia and the reference to them as “normal” was removed from the revised manuscript.

Page 12, same subsection, 4th sentence - this is an example of the kappa values that are given throughout the paper, always referring to < 0.4. More explanation needs to be given as to why this level of kappa has been chosen as a cutpoint and a p value or 95% CI should be given for each result.
Response: An explanation as to the use of the kappa statistic was included in the methods section and P values and 95% CIs include in the revised manuscript.

Page 13, 3rd and 5th sentences - Both are difficult to comprehend.
Response: The above sentences were reworded for more clarity in the revised manuscript.