Reviewers report

Title: A large, population-based study of age-related associations between vaginal pH and human papillomavirus infection

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Reviewer: Lenka Vodstrcil

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A large, population-based study of age-related associations between vaginal pH and human papillomavirus infection

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Thank you for the opportunity to review this paper which investigated the relationship between vaginal pH and HPV in a large population-based study. The researchers describe the detection of HPV in women and found it was positively correlated with vaginal pH in women under 35 years of age. They also found that increasing vaginal pH is associated with LSIL.

Strengths:
The paper has a number of strengths and is important in the evaluation of how vaginal pH may be epidemiologically linked to HPV infection and cancer development. The study cohort size is large and includes women from multiple age groups. Both pre- and post-menopausal women are included in the analysis. This study also provides evidence that elevated vaginal pH may be associated with other sexually transmitted infections such as C trachomatis.

Major Revisions:

Comment 1: General comment
The results describe the association between vaginal pH and either HPV, LSIL or C trachomatis for varying age groups stratified by age at visit. Each study visit was counted as a unit of analysis. Considering there are women who would have had multiple visits during the course of the study, are the authors able to comment on whether or not vaginal pH or any other measurement changed over time for these women? For example, did women who had a vaginal pH >5.0 at their initial visit have a similar reading at every visit? Did HPV detection also change over time? The authors may have incorporated this in their statistical analysis, however I am unsure that the longitudinal data is presented clearly enough and it may need further review by a statistician. I think these would be interesting results that could strengthen the manuscript.

The authors may wish to consider some of the following points:
Comment 2: Methods
An ethics declaration should be included in the methods of the document.

Comment 3: Results Pg 10 ln 212
The authors describe the relationship between vaginal pH #5.0 and LSIL as positive for all age groups but most significant in women aged <25, 25-34 or 65+. The authors should be cautious using the term ‘most significant’ as the relationship is not significant in other age groups (ie in ages 35-64) even though a trend may be present. There is a positive trend in all groups that is not always significant based on the 95% confidence intervals presented in the tables.

Comment 4: Results Pg 10 ln 220
The authors report a positive association between vaginal pH and C trachomatis DNA. Are the authors reporting a positive association between elevated vaginal pH and increasing amounts of C trachomatis DNA? Or elevated vaginal pH and the presence of C trachomatis DNA? This should be clarified. It is also unclear whether the authors are reporting that women <25 are more likely to have a C trachomatis infection detected or have multiple infections over the follow up period. The sentence is long and may be confusing to understand.

Comment 5: Discussion Pg 11 ln 245
The discussion regarding the link between high vaginal pH and BV is important; however the authors should be cautious in linking their findings of high vaginal pH with other research on the associations of BV with HPV and/or C trachomatis considering their study did not clinically measure BV status. A limitation of the study was that BV was not clinically diagnosed in these women.

Comment 6: Discussion Pg 12 Ln 270
In the discussion the authors have identified a limitation of their study is the lack of male sexual behaviour data which may help explain their findings. In fact all sexual behaviour including gender of partners, condom use and number of partners could be associated with vaginal pH and HPV infection independently. Please elaborate on this further in the discussion. The authors may also wish to speculate how sexual behaviours might influence vaginal pH and/or HPV infection.

Comment 7: Discussion Pg 13 Ln 279
The authors briefly mention the significance of their findings and how knowing vaginal pH may be beneficial when identifying HPV infection and the development of cancer. The significance of the study should be discussed in more detail. How might knowing a women’s vaginal pH be used clinically?

Minor essential revisions:

8: Abstract Pg 3 Ln 52
The conclusions in the abstract could be more specific. The authors could
expand on what they mean by ‘…certain age groups’ and also comment on the overall significance of their findings, or what further research is required.

9: Pg 6 Ln 118
The sentence reads ‘For the current analysis focused…’ please change ‘For’ to ‘As’

10: Methods Paragraph 1, pg 5
The number of women approached and the number of eligible participants would be clearer to understand if supported by a consort diagram.

11: Pg 9 Ln 181
The explanation as to why the dichotomous variable of pH was split to <5.0 and #5.0 may be confusing for some readers given the description of a pH of >4.5 as abnormal in the following sentence. Please re-phrase the explanation as this description is important to understand when reading the results.

12: Pg 9 Ln 192
The sentence reads ‘The majority of women younger than age 45…’ the word ‘age’ can be removed.

13: Pg 9 Ln 198
The sentence reads ‘The prevalence of HPV was highest at age 25-35 years…’ please change to ‘…in the 25-34 age group…’

14: Pg 10 Ln 200
In general, the paragraphs describing the results refer to the table at the beginning of the sentence. I would suggest starting with a description of the findings and then referring to the table as is done for table 3 in the third paragraph.

15: Pg 10 Ln 201
The sentence reads ‘… with about a 10-20% increased risk for a vaginal pH #5.0.’ What the increased risk is referring to should be inserted ie. ‘…increased risk of HPV detection with a vaginal pH #5.0.’

16: Pg 10 Ln 215
The authors report that there was no association between HSIL and elevated pH. However there are no data present in the tables reflecting this. Please either include the data table or state that data is not shown.

17: Discussion Pg 12 Ln 264
In the discussion the authors write that their findings in post-menopausal women may be because of a ‘link between the decline in circulating estrogens…’ Please elaborate on this further in your discussion to include how estrogens are known to be involved in regulation of vaginal pH.
Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:
I declare that I have no competing interests