Author's response to reviews

Title: Chlamydia and gonorrhoea in pregnant Botswana women: Time to discard the syndromic approach?

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

**MS: 6696762561174631**

Chlamydia and gonorrhoea in pregnant Botswana women: Time to discard the syndromic approach?

We are grateful for valuable comments and positive feedback from the two reviewers and for the opportunity to improve the manuscript. We have made changes in the original paper according to the referees’ comments; please see the point-by-point response below. During the revision, we used the opportunity to repeat all analyses and calculations. We’d like to notify you that we have changed Figure 1 slightly. We realized that one of the graphs in the figure had a minor error which did not affect the results. The correct graph is now in place, and the figure is presented in colours.

We believe that the alterations have enhanced the quality and value of the manuscript, and we are pleased to resubmit the paper.

Yours sincerely

Maria Romoren Johanne Sundby Manomany Velauthapillai

Mafizur Rahman Elise Klouman Per Hjortdahl
Response to reviewer Xiang-Sheng Chen’s report

**Major Compulsory Revisions**

None

**Minor Essential Revisions**

None

**Discretionary Revisions**

A clear description on statistical analysis strategies on risk factors (e.g. univariate and multivariate, significance level for identification of the risk factors) is needed.

We have extended the description of the multiple logistic regression analysis and the conduction of risk scores, and hope that this change is consistent with your request.

*Table 1 shows the results of univariate analysis but what are the results for the multivariate analysis?*

The results of the multiple logistic regression analysis are now included in a separate table (Table 3). The independent association of various factors with cervical infection is important, but not directly useful in the clinical setting. A detailed presentation or discussion of the multiple logistic regression analysis results is therefore not considered to be within the scope of this paper.

*The performance characteristics (sensitivity, specificity, etc) were evaluated by analyzing the association of the infections with symptoms (or clinical signs), and different risk assessment strategies. What are the results if the evaluation is based on the combinations of symptoms (or clinical signs) and risk assessment? E.g. what is the sensitivity and
specificity if the patients who have vaginal discharge AND who are aged less than 30 and unmarried?

In this paper, “risk assessment” is not only an assessment of sociodemographic risk factors such as age, education or marital status. The VDS algorithm and the clinical and microscopy risk scores, are diagnostic risk assessment strategies in which the evaluation of the patient’s total risk of infection is based on combinations of sociodemographic risk factors, subjective symptoms, clinical signs and microscopy results. The variables included in the three levels of risk scores are now shown in Table 1 in the paper.

No symptoms were associated with infection, and, as shown in Table 4, symptoms can not be used as a diagnostic tool to identify pregnant women with cervicitis. None of the risk scores have symptoms incorporated, as this would reduce the diagnostic quality of the score. The entry point of the syndromic algorithm is symptoms of vaginal discharge or lower abdominal pain, understandably a major disadvantage of the syndromic management of cervical infections.

We are asked for the sensitivity and specificity for the diagnostic criteria “for patients who have vaginal discharge AND who are aged less than 30 and unmarried”. The prevalence of cervical infection among antenatal care attendees with symptoms of vaginal discharge that are less than 30 years and unmarried is 12%. The sensitivity of these criteria combined is 0.18, the specificity 0.86, and the positive likelihood ratio 1.27. Due to their lacking discriminatory ability, we have not presented the evaluations of symptoms in combination with other diagnostic factors in the paper. Signs of vaginal discharge in women less than 30 years of age and unmarried corresponds to the clinical risk score (Table 4).

Regarding the suggestion to reallocate the resources to other STI measures, it may be better to have any evidence from cost-effectiveness analysis or a recommendation to have such analysis. Alternatively, recommendations on how to improve the current clinical practice of syndromic algorithms at antenatal care could be made using the findings from the study.
The results presented in this paper clearly show that syndromic management of cervical infections cannot be justified. As described and discussed, it is also clear that the use of risk factors can not improve the diagnostic quality of the current strategy sufficiently. We are currently working with a cost-effectiveness analysis on strategies to diagnose and treat infections with *C trachomatis* within antenatal care in Botswana. This is a relatively comprehensive task, the results of which will be presented in a separate paper. On the basis of the preliminary results from the economic analysis, we feel confident about our suggestion to reallocate the resources away from the syndromic management of cervical infections. The only way to substantially improve the management of cervical infections in antenatal care in developing countries is to introduce specific diagnostic point-of-care tests.

*In the columns “Infected” and “Uninfected” of Table 1, it will be better to use actual numbers rather than percentages (%).*

Because one of our reviewers would prefer numbers rather than percentages and one would prefer both, we have redone the table. Rather than inserting percentages under columns entitled “Infected” and “Uninfected”, as we did previously, we have entitled one column “Women with cervicitis”, with subtitles “No.” and “%”. We hope these changes meet both reviewers’ requests.

**Quality of written English**

*Needs some language corrections before being published*

In accordance with the recommendations of the first reviewer and the Editors, the paper has been professionally language edited before resubmission.

**Statistical review**

*Yes, but I do not feel adequately qualified to assess the statistics*
The statistician at Institute of General Practice and Community Medicine, University of Oslo (Magne Thoresen, see Acknowledgements), was involved in and supervised the univariate and multiple regression analyses and the computation of the risk scores. We are confident that the statistical methods have been used competently and that the results can be trusted. Within the limits of a paper it is difficult to describe all details of the methods used, but we would be pleased to any specific questions that you may have.

Response to reviewer Inger Johanne Bakken’s report

General

This paper describes a study from Botswana where pregnant women have been tested for C trachomatis, N gonorrhoeae, T vaginalis, bacterial vaginosis, and Candida species. Infected women received appropriate treatment. The objective of the study was to evaluate the “syndromic approach” which is currently used for management of cervicitis in developing countries. The prevalence of infection was high in this study.

Major Compulsory Revisions

In this study, women are tested for a variety of infections, but the main focus is on Chlamydia and Gonorrhoea (Background, Results and Discussion). The Abstract should be written accordingly.

We acknowledge the comment and have made changes in the abstract to emphasize that the focus of this paper is on cervical infections.

Original text:

Methods: In a cross-sectional study, 703 antenatal care attendees in Botswana were interviewed and examined, and specimens were collected for the identification of C
trachomatis, N gonorrhoeae, T vaginalis, bacterial vaginosis, and Candida species. Risk scores were computed based on identified risk factors and retrospectively applied.

Changed to:

**Methods:** In a cross-sectional study, 703 antenatal care attendees in Botswana were interviewed and examined, and specimens were collected for the identification of C trachomatis, N gonorrhoeae and other reproductive tract infections. Risk scores to identify attendees with cervical infections were computed based on identified risk factors, and their sensitivities, specificities, likelihood ratios and predictive values were calculated.

**Original text:**

**Conclusions:** Although extensively in use, the syndromic approach is unsuitable in antenatal care attendees in Botswana.

Changed to:

**Conclusions:** Although in extensive use, the syndromic approach is unsuitable for diagnosing cervical infections in antenatal care attendees in Botswana.

Abstract, results, first sentence. “The prevalence of cervical infection was 10%” is not sufficiently specific. Should state the prevalence of Chlamydia and Gonorrhea separately.

We have changed the sentence to “The prevalence of chlamydia was 8% and gonorrhoea was found in 3% of the attendees.”

State clearly in the Background that the women in the study were actually tested for infections in the present study.

**Original text:**

The aim of this study was to assess the validity of the ‘vaginal discharge syndrome and lower abdominal pain’ algorithm in the diagnosis of C trachomatis and N gonorrhoeae among antenatal care attendees in Botswana – both as a case management and as a screening tool.
The aim of this study was to determine the prevalence of *C. trachomatis* and *N. gonorrhoeae* among antenatal care attendees in Botswana, and to assess the validity of the ‘vaginal discharge syndrome and lower abdominal pain’ algorithm in the diagnosis of cervicitis in pregnancy.

How was the “convenient sample of the attendees” selected (p 5)? What was the proportion of women included to the study?

Each day at the clinic, the pregnant women were consecutively invited to be included in the study when they came for antenatal care. The number of patients included daily was either defined by the total number of women visiting the clinic that day, or, if there were many attendees, by the number of specimens that the laboratory could handle (usually specimens from 12 attendees). Only a few of the clinics had more than 12 attendees visiting per day. These clinics have many consulting rooms and several midwives performing antenatal care simultaneously. The study doctor would work in a separate consulting room, conducting the ordinary pregnancy control and collecting data for the study. In a study in a clinical setting like this, systematic randomization of the patients is virtually impossible to accomplish. It was incidental which women were seen by a clinic midwife and subsequently sent home, and which were seen by the study doctor. We have no reason to believe, however, that any systematic bias was involved in the selection of this attendee sample or that our sample is less representative than it would have been had our attendees been randomly chosen.

There are substantial differences between the richer and poorer areas of Gaborone, and we aimed at getting a sample representative of the antenatal care attendee population in the city. The proportion of attendees recruited from each clinic represents the proportion of attendees seen at that clinic yearly. There were 6300 women attending antenatal care in Gaborone yearly in 2000 and in 2001 – approximately 525 per month. With a study sample of 703, we have included roughly 27% of the antenatal care attendees in Gaborone in the data collection period in our study.
The text is changed as shown below. We could describe the sampling method in
greater detail if you think that it would improve the quality of the paper. If so, please
advise us what you believe to be lacking.

Original text:
In the majority of clinics, all attendees were included in the data collection; in the
busiest, a convenient sample of the attendees was included.

Changed to:
In the majority of clinics, all attendees were included in the study. In the busiest clinics,
only a sample of the attendees was included; the selection of attendees in these clinics
was incidental. Approximately one out of every four antenatal care attendees in
Gaborone was included in the study during the period of data collection.

Minor Essential Revisions

P 3 Background, first paragraph: “...major causes of morbidity” – What kind of
morbidity?

To our understanding, we have described the main disabilities associated with C
trachomatis and N gonorrhoeae. In case the word “morbidity” is unclear, however, we
have changed the text.

Original text:
These two sexually transmitted infections (STIs) are major causes of morbidity,
particularly in women [1]. A cervical infection with Neisseria gonorrhoeae or Chlamydia
trachomatis can cause serious complications such as ascending infections, infertility,
cervical cancer, spontaneous abortion, premature delivery and low birth weight [2].
Epidemiological and biological studies have shown that ulcerative and non-ulcerative
STIs can enhance HIV transmission [3,4].

Changed to:
These two sexually transmitted infections (STIs) have a major impact on health, particularly in women and neonates [1]. A cervical infection…etc.

P 4 “However, the new recommendations…” Citation needed.

The new recommendations are cited a few sentences later. We assume that the citation needed is for the non-validated study of female STI patients? This citation is now included.

P 4 “RTI” not defined. Is this abbreviation necessary?

There are minor changes in the text, and ‘reproductive tract infections’ is now used three times in the paper. It is defined, with the abbreviation, the first time it occurs in the text, and the abbreviation is used subsequently.

P 4 “As the nurses will not ignore…” – seems unnecessary. Could be removed, start sentence at “Asymptomatic women…”

The sentence is changed accordingly.

P 5 “all antenatal care attendees who attended” – should be rewritten

Original text:
A proportionate sample of attendees was recruited from each location, based on the percentage of all antenatal care attendees who attended that facility the previous year.

Changed to:
A proportionate sample of attendees was recruited from each location. This proportion corresponded to the percentage of all antenatal care attendees in Gaborone who visited that facility during the previous year.

P 7 “multiple logistic regression”, multivariate is used later on
Our statistician recommends that we use the terms “Univariate analysis” and “Multiple logistic regression analysis”. This is now done consequently.

_results p 7, how many women had more than one infection?

We describe the prevalence of five different reproductive tract infections in this paper. Chlamydia, gonorrhoea and trichomoniasis are sexually transmitted infections, while bacterial vaginosis and vulvovaginal candidiasis are not. Chlamydia, gonorrhoeae, trichomoniasis and bacterial vaginosis are thought to cause complications in women, and many of these complications are pregnancy-related. Candidiasis does not cause such complications. Combining these infections may not be particularly informative to the reader, but we have added a sentence about co-infections to illustrate the total burden of reproductive tract infections in this population: “A total of 561 (80 %) of the antenatal care attendees had one or more of these five reproductive tract infections.”

We have attached a table describing co-infections at the end of this document. If you think other information about co-infections is of specific interest, we are pleased to include it in the manuscript.

_results p 7, complaints by positivity should be stated

The frequency of symptoms and signs are described first, and their association with infection in the next paragraph and in Table 2. We believe this structure of the text is suitable.

_P 8 “These women are most likely to present symptoms...”, redundant

This part of the sentence is omitted.

Rearrange citations p 9, lines 4 and 5 from below (Two sentences, starting with “In our study...”)

Citations are rearranged.

Table 1. I would prefer to see the N for the Infected and Uninfected groups, not only the percentages. The column with the heading N could accordingly be removed.

See response to the other reviewer regarding this table.

**Discretionary Revisions**

The Background section could improve by restructuring. For instance, the “Syndromic approach” might be explained earlier in the section. Also, on p 3, the sentence “This case management... neither sensitive nor specific“ is a strong statement. Isn’t this part of the research question in the present study? Perhaps this statement could be toned down a bit or transferred to the Discussion?

We have restructured the Background section as suggested and made minor changes in the text. We hope that these alterations have improved the introduction. Instead of describing these changes in detail, we refer you to the differences between the original and the resubmitted paper.

The description of syndromic management of cervical infections as being neither sensitive nor specific is a strong statement, but it is established knowledge (see the references). This is why it was important to validate the VDS algorithm in our study population and evaluate if risk scores could be used as a supplement or alternative to this strategy. We believe the sentence serves its purpose.

The authors discuss the benefit rapid on-site tests would have in their study setting for diagnosis of sexually transmitted infections. Are rapid tests also important to ensure proper treatment of infected women? Or is the proportion of women returning for their test results and treatment adequate in this antenatal care setting?
Sensitive nucleic acid amplification tests (NAATs) are used to diagnose cervical infections in many western countries. In populations in the United States or Europe with low return rates, it can be recommended that the optimal NAATs be replaced with rapid, less sensitive tests to ensure the treatment of test-positive individuals who would not necessarily return for their results.

The syndromic approach is developed and in use by countries without laboratory support. In sub-Saharan Africa, resources in the public health system are scarce, laboratory services are basic, and NAATs are far out of reach. In this setting, the proportion of women returning for their test results is irrelevant, as sending specimens to the laboratory for advanced diagnostic tests is not an alternative. Simple, rapid tests provide the only possibility for diagnosing and treating asymptomatic cervical infections and reducing the massive overtreatment resulting from the high numbers of false positives in the syndromic management.

<table>
<thead>
<tr>
<th>Co-infections</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>No infection</td>
<td>142</td>
<td>20.2</td>
</tr>
<tr>
<td>Cervical infection</td>
<td>8</td>
<td>1.1</td>
</tr>
<tr>
<td>Trichomoniasis and/or bacterial vaginosis</td>
<td>119</td>
<td>16.9</td>
</tr>
<tr>
<td>Cervical infection + trichomoniasis and/or bacterial vaginosis</td>
<td>18</td>
<td>2.6</td>
</tr>
<tr>
<td>Candida</td>
<td>180</td>
<td>25.6</td>
</tr>
<tr>
<td>Cervical infection + candida</td>
<td>14</td>
<td>2.0</td>
</tr>
<tr>
<td>Trichomoniasis and/or bacterial vaginosis + candida</td>
<td>195</td>
<td>27.7</td>
</tr>
<tr>
<td>Cervical infection + trichomoniasis and/or bacterial vaginosis + candida</td>
<td>27</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>703</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>