Author's response to reviews

Title: Syphilis screening in the antenatal care: a cross-sectional study from Botswana

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Author's response to reviews: see over
Oslo, 30.5.06

Dear Editor,

MS: 1030473365985120

Syphilis screening in the antenatal care: a cross-sectional study from Botswana

We are grateful for valuable comments and positive feedback from the three reviewers and for the opportunity we got 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. We believe the alterations have enhanced the quality and the value of the manuscript, and we are pleased to resubmit the paper.

Yours sincerely

Maria Romoren       Mafizur Rahman
Response to reviewer David Mabey’s report

Major Compulsory Revisions

A sample of attenders was selected from each clinic proportionate to the total number of attenders. The authors should explain HOW the sample was selected. Was this a random sample, or were consecutive women enrolled? We are told that the only exclusion criterion was the use of antibiotics in the two weeks prior to the visit. How many were excluded for this reason?

We have included the requested information in the methods section.

Original text:
Included in this study were 703 antenatal care attendees who visited 13 primary health care clinics in Gaborone, the capital of Botswana, between October 2000 and February 2001. A proportionate sample of attendees was chosen from each clinic, based on the total load of antenatal care attendees at that clinic during the same period in the previous year. All participants gave written, informed consent. The only exclusion criterion was the use of antibiotics in the two weeks prior to their visit.

Changed to:
The median age of the 703 antenatal care attendees was 25 years (range 15-43). Other socio-demographic characteristics are described elsewhere [6]. Eight women reported symptoms and five women had signs of genital ulcers, but all of them were RPR negative. There were 157 women coming for the first antenatal visit, with a median gestational age of 20 weeks (range 8-37). Among the 546 women coming for a repeat visit, 71 (13%) had not been screened for syphilis in the routine antenatal programme. Among the 475 repeat attendees who had been tested, the median gestational age when the blood had been drawn was 19 weeks (range 4-38). Of these 475, 14 (3%) women had been found RPR positive during the screening. Two had not been treated; for the remaining 12 women, the mean time between blood being drawn and treatment being prescribed was five weeks. The screening test results for these 14 women, the treatment delay and the syphilis serology found in the study later in pregnancy is shown in Table 1.
Among the women with negative RPR or those lacking RPR results earlier in pregnancy, of whom 103 were in gestational week >36, none had been retested.

**Minor Essential Revisions**

*Methods:* when they say a non-specific syphilis test, do they mean non-treponemal?

Yes. Non-specific is corrected to non-treponemal

*Results, paragraph 2:* 32 out of 74 is not 5%.

The indistinct sentence is changed to: “A total of 74 (11%) of the 703 attendees were TPHA positive, indicating past or present syphilis. In all, 32 (5%) women had active syphilis (RPR+/TPHA+) and 11 (2%) had high-titre active syphilis (RPR $\geq$1:8/TPHA+).”

*Discussion, para 1:* The authors cite syphilis prevalence from a review of lab books as being 12% in 1992, and 4% in 2003. How was syphilis defined here? TPHA positive (ie syphilis ever), or TPHA and RPR positive, or RPR positive?

Syphilis was in the review defined as VDRL positive. VDRL is now defined earlier in the text, and the description of the review is changed to: “A recent review of laboratory logbooks in Francistown, the largest town of northern Botswana, found that the prevalence of VDRL positive antenatal care attendees declined from 12% in 1992 to 4% in 2003 [10].”

**Discretionary Revisions**

*It is said to be national policy in Botswana to retest all pregnant women at 34-36 weeks gestation. The authors state that three women who initially tested negative had high titre syphilis when tested for the study. It would be helpful if they could calculate the incidence*
of syphilis during pregnancy, which should be possible from their data, which could provide a justification for this retesting policy.

This is indeed an interesting comment. We have analyzed the available data and added the following paragraphs to the results section: “We do not have data on the exact incidence of syphilis during pregnancy, but among the 461 attendees who were RPR negative in the routine screening, 451 were retested in the study setting with both RPR and TPHA. Median 11 weeks later in their pregnancy, 16 (3.5%) of these 451 initially RPR negative women had active syphilis; one with high and 15 with low titres. Of the 16 women, 15 reported having had one partner the last 12 months, and 14 said that they had been in the relationship more than two years.” The results are also commented in the discussion section.

What proportion of women fails to return for their tests results? If many fail to return, testing at the point of care should be considered.

The clients are (supposed to be) asked to return for their test results after one week. Many women do not return for the results, but they receive their results at the next routine visit. As we have shown, the mean number of weeks from blood was drawn until the patients return and treatment is prescribed was five. We do not have data on pregnant women who only attend for antenatal care once and thus never receive their test results. Anyhow, testing at the point of care is discussed in general.

What proportion of women complete the course of treatment prescribed?

Botswana guidelines for the management of RPR/VDRL positive cases (regardless of titre) are three injections with benzathine penicillin 2.4 million units at weekly intervals. The first injection is given at the visit when syphilis results are provided. Of 475 women screened, 14 women were found RPR reactive: two had not been treated, three had been prescribed and received one injection and the remaining nine had been prescribed and treated with three injections. These 14 women had been compliant to the treatment
regimen prescribed, but this study was not designed to evaluate compliance. Mullick et al. show in a study from urban South Africa (a similar setting with identical treatment guidelines) that 65% of 188 RPR positive antenatal care attendees were treated with three injections, 6% received two doses, 13% received one and 16% were not treated. Watson-Jones et al. has shown that single dose penicillin is effective in preventing adverse pregnancy outcomes attributable to maternal syphilis. If this is the case, patient compliance to the full course of treatment is of secondary importance compared to the patients being tested, receiving their test result and prescribed at least one injection with penicillin—as early as possible in pregnancy - and not being reinfected by a partner.

Response to reviewer Ornella Lincetto’s report

General

To make the data more relevant to programs the authors should focus more on missed opportunities, which seem to be: a) women not screened at the first antenatal care visit; b) women not retested at the second antenatal care visit (both those who had not been tested at the first visit and those who according to the national policy were supposed to be tested again); c) women who tested positively and were not treated.

The three reviewers are consistent in their request to focus more on the missed opportunities; to discuss why they exist and to include recommendations on how these should be addressed. We have done our best to change the manuscript accordingly. We believe that rather than to list all the changes, it is better to refer to the discussion section.

Major Compulsory Revisions

None

Minor Essential Revisions
Key words: "prenatal"; however, this word was never used in the manuscript, "antenatal" was used instead.

When providing key works, we aimed at using MeSH terminology. Prenatal care is an established MeSH term, antenatal care is not. However, we have changed the key word according to the reviewer’s preference.

Abstract: add to methods the information on number of health facilities and location, as the data provided by the manuscript cannot be generalized to whole Botswana.

The information is added as requested.

Background: it may be more correct to mention that the target population of the study is mainly urban, as there are differences in population and services in urban and rural settings.

We have changed the text to “The aim of this study was to determine the prevalence of syphilis among antenatal care attendees in Gaborone, Botswana;...”

Methods: the sampling method is not fully clear, was it a consecutive sample or a convenience sample? If it was a proportionate sample, which proportion of pregnant women was included?

The requested information is included in the method section (see response to reviewer David Mabey).

Methods: in relation to venous blood samples, specify in the text if these were taken from all women (not only the repeat visits) and if these were done in addition to routine care. In practice, should it be assumed that RPR was done twice in some women (as part of routine care and for the study)?
For clarity, we have changed the text as follows:

Original text:
For study purposes, venous blood samples were collected from and tested with the RPR test and the specific *Treponema pallidum* haemagglutination assay (TPHA) at the National Health Laboratory.

Changed to:
For study purposes, additional venous blood samples were collected from both new and repeat attendees. The maternal sera were tested at the National Health Laboratory with the RPR test and the specific *Treponema pallidum* haemagglutination assay (TPHA).

Results: specify how many women with STI symptoms were coming for the first visit.

It is not clear to us what the reviewer requests. In the text we have written the following: “Eight women reported symptoms and five women had signs of genital ulcers, but all of them were RPR negative.” It was a small number of women who had symptoms of genital ulcer, and none of the ulcers were due to syphilis infection. We do not believe that it provides any additional information to specify that three of the women with symptoms of genital ulcers were new and five were repeat attendees. Or does the reviewer request how many new attendees who had other STI symptoms than genital ulcer? We did not include other STI symptoms in this paper as it is not strictly relevant to syphilis infection, but the data are published elsewhere (ref. 6 in the paper).

Results: specify if the 71 women (13%) not screened in the antenatal program, refer to the first visits or both first and repeat visits.

To our understanding, this is specified in the original text: “Among the 546 women coming for a repeat visit, 71 (13%) had not been screened for syphilis in the routine antenatal programme.”
Results: specify if the 14 (3%) women found positive at the screening were 3% of total or 3% of repeat visits only.

For clarity, we have changed the text as follows:

Original text:
Of the 475 women tested, the median gestational age when the blood had been drawn was 19 weeks (range 4-38). Among the 14 (3%) women found RPR reactive during the screening, two had not been treated. The mean number of weeks from blood was drawn until treatment was prescribed was five.

Changed to:
Among the 475 repeat attendees who had been tested, the median gestational age when the blood had been drawn was 19 weeks (range 4-38). Of these 475, 14 (3%) women had been found RPR positive during the screening. Two had not been treated; for the remaining 12 women, the mean time between blood being drawn and treatment being prescribed was five weeks.

In general, when "routine antenatal care" is mentioned it is not fully clear if the authors mean only the policy of testing at the first antenatal visit or the policy of testing at the first visit and retesting at subsequent visits.

We do refer to the screening programme in the routine antenatal care as described in the text: “Blood is collected from all attendees at the first antenatal visit and analyzed with a non-treponemal syphilis test at a centralized laboratory. According to the guidelines, high risk women should be retested at 34-36 weeks of gestation.”

Discussion: in terms of policy recommendations, consider to add the importance of intensifying efforts where needs are higher (rural areas).

All published data on the syphilis prevalence in rural areas are based on non-treponemal tests. Thus, differences in urban and rural areas may theoretically be caused by a higher level of false positive results in rural areas caused by other conditions than syphilis.
However, at the reviewer’s request, we added the following to the discussion: “Rural districts seem to be in special need of intensified prevention efforts, as prevalences up to 13% were found in less densely populated areas such as the Kalahari Desert.”

**Discretionary Revisions**

_The authors may consider to provide more information on the missed opportunities, for example why women were not retested at the repeat antenatal visits despite a national policy recommending retesting._

We do not know why the why attendees not are retested at the repeat antenatal visits; our study was not designed to answer why operational difficulties exist in the syphilis screening programme. It is an issue of great importance, but as described in the paper, such data are virtually non-existing. We have tried our best to address these issues in the discussion.

_Some information on perinatal outcomes would be interesting, if available._

We agree. Unfortunately, we did not follow the antenatal care attendees in the study and do therefore not know their pregnancy outcome. The health statistics in Botswana are not of adequate quality regarding this issue, and to refer the reported perinatal outcomes would be misleading.

**Quality of written English**

_Needs some language corrections before being published._

The paper has been revised by a professional language editor
Major Compulsory Revisions

None

Minor Essential Revisions

Background section line 5 and line 8: remove “the” from before antenatal care.

Done

Results section line 5: add the word “weeks” after 20.

Done

Discretionary Revisions

In the results it would be useful to include any data that the authors have on whether or not partners of infected women were treated particularly since reinfection rates are presented.

Unfortunately, we don’t have any study data on partner notification and treatment. The only information available regarding males and syphilis is the total number of females and males registered as RPR/VDRL positive. In 2002 (the most recent health statistics report), there were 1083 females and 886 males registered as RPR/VDRL positive.

Limitations of the data sources and the study methods should be discussed in the discussion.

We have added the following to the discussion:
“Our results indicate a need for improved coverage of the screening and improved adherence to treatment guidelines. However, it is a limitation of the study that we do not have information on why the guidelines are not followed. Data on the impact of maternal syphilis on pregnancy outcome are also lacking. A targeted approach to improving the syphilis screening programme requires that more knowledge be gathered about the specific problems, where they exist, and why.”

Discussion should include how generalizable are the results of the study, how representative are the study clinics of other clinics in the country.

In addition to adding more thorough information on the sampling methods, the following paragraph is added:

“The study population is representative for antenatal care attendees in Gaborone, and the level of health care is supposed to be the same throughout the country. However, conditions such as communication, transport, educational level and standard of living are less favourable in the rural areas. To the best of our understanding, it is reasonable to expect the same or higher prevalence of syphilis, as well as the same or greater operational difficulties in the rest of the country. We believe that the results of this study are also of relevance to other developing countries.”

The current recommendation for syphilis screening and treatment and retesting in Botswana should be included in the background section. Also a description on the recommendation for partner treatment should be included.

We moved the description of the syphilis screening guidelines from the methods to the background section and added information on the (lacking) recommendations for partner treatment.

Discussion of why despite the operational difficulties mentioned syphilis rates from surveillance data have declined.
The authors of the logbook review which showed a decline in VDRL positive antenatal care attendees suggest that a decline in risky sexual behaviour due to interventions to control the HIV epidemic may have resulted in a reduced prevalence of syphilis. The introduction of syndromic management of STIs in 1992, which implies that 150 000 to 200 000 STI clients have been treated with multiple antibiotics yearly, may also have contributed to reduce the prevalences of curable STIs. This is added to the discussion.

*It is not clear in the methodology how the data was collected on identification of the operational difficulties yet this was outlined as an objective at the outset of the paper.*

We have described that for the attendees coming for a repeat visit, we recorded the gestational age when blood was drawn for the non-treponemal syphilis test, the test results and the treatment prescribed, all which is documented in the patient-held antenatal records. These data were used to calculate the screening and treatment coverage, the gestational weeks when the attendees had been tested and the number of weeks from the blood was drawn to the treatment was provided. Among the women who were identified as RPR positive in the screening programme, we used the RPR/TPHA results from the study to see if RPR titres had declined. Among the initially RPR negative women we could identify RPR seroconversion.

*The discussion of this paper could be strengthened considerably by including some discussion on the relevance of these prevalence findings for the clinics concerned and their broader relevance. There is also some need for a discussion on why some of the operational difficulties exist. Last, some clear recommendations on how these should be addressed beyond increased commitment from stakeholders should be included. Are there any recommendations on what data could be collected routinely, strengthening routine data, consideration of other approaches to screening and treatment? The paper is clear that the prevalence of syphilis remains high and that operational difficulties exist, but how these should be addressed is not articulated as clearly.*
As replied to reviewer Ornella Lincetto, the three reviewers are consistent in their request to focus more on the missed opportunities; to discuss why they exist and to include recommendations on how these should be addressed. We are grateful for these comments and have done our best to change the manuscript accordingly. We believe the input from the reviewers have resulted in a paper of increased quality.