Author’s response to reviews

Title: High seroprevalence of syphilis infection among pregnant women in Yiregalem Hospital Southern Ethiopia.

Authors:
Anteneh Amsalu (ant.amsalu@gmail.com)
Getachew Ferede (get29f@gmail.com)
Demissie Asseg (demissieasegu@yahoo.com)

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Author’s response to reviews:

Dear: Journal of BMC Infectious Diseases editorial office

RE: Responses to the Reviewers’

Title: Seroprevalence of syphilis infection among pregnant women in Yirgalem Hospital Southern Ethiopia: An awaking message to reinforce syphilis prevention strategies?

We are very grateful to the reviewers and editors who have critically revised the manuscript and provided us with points to improve its quality. Therefore, we have incorporated each and every comment of the reviewers in the revised manuscript with track change. Moreover, point-by-point responses are given below to the raised queries with red color.

We hope that each and every point is now addressed to the satisfaction of the reviewers and editors. We look forward to hearing from you soon.
Kind Regards,

Point by point response

Editors

1. Please do address the fact raised by the reviewers that the screening algorithm used (RPR and TPHA) cannot distinguish past from current syphilis infection and please address issues with the English language and grammar.

Response: Yes, treatment history can help to classify “new” and “old” but, due to recall bias of specific drugs taken by participants and a weak recording system of clinical history in our settings, we considered both RPR +TPHA reactive cases as “probable active syphilis(PAS)” or untreated syphilis. “Hama DC, Lina C, Newmanb L, Wijesooriyaa N S, Kamba M. Improving global estimates of syphilis in pregnancy by diagnostic test type: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2015; 130(0 1): S10–S14. doi:10.1016/j.ijgo.2015.04.012.” And also a small percentage of patient’s low positive titers persist despite receiving adequate therapy.

Moreover, we have also addressed the issue of English language and grammar.

Point by point response

Reviewer: 1

1. Background information of syphilis testing in the Yirgalem hospital

Line 63: "At the time of their first visit of the ANC clinic pregnant women's have been screened for syphilis and HIV/AIDS", suggested the syphilis testing is already there, if so, why additional "research testing for syphilis" needed?

Response: we agree with the reviewer assertion and we corrected as “…women’s are offered screening for HIV and syphilis”. Even if syphilis testing is there, the patient is treated only based on a single on-site rapid plasma reagin (RPR) test which is not confirmed with treponemal test.
2. Results: as RPR+TPPA positive was defined as a "syphilis case" in this study, I will suggest just present the 25 cases with both RPR and TPPA positive. In addition, in table 3, the HIV prevalence is confusing. Any records of participants' syphilis treatment history? As both RPR+TPPA positive may also be a previously treated case, this may help to classify "new" and "old" syphilis case.

Response: the comments are well taken; we thought this table can clarify the co-infection rate of syphilis/HIV, among RPR positive, and RPR+TPHA defined as a "syphilis case". As we made some brief in the exclusion part now, pregnant women who on treatment was not included in the study because of difficulty in getting the previous titer to predict the treatment response. Yes, treatment history can help to classify “new” and “old” but, due to recall bias of specific drugs taken by participants and a weak recording system of clinical history in our settings, we considered RPR +TPHA reactive cases as “probable active syphilis(PAS)” or untreated syphilis.


3. Data analysis. Table 4, adjusted odd ration needed for analyzing the associated factors.

Response: the comments are well taken; we have done AOR

4. Corrections: Line 126: add percentage after "sixteen women" (%)

Line 137: (Table 3) changes to (Table 4)

Response: the comments are well taken; we have added the percentage and changed the table number.

Reviewer: 2

1. Abstract line 2 remove "an" and replace with "the"
Response: we appreciate the curiosity of the reviewer on the language edition; we have replaced it according to the suggestion of the reviewer.

2. Introduction line 38. Remove "Apart from being a serious disease" and start with Syphilis "is"
   Response: the comment is well taken and we have removed it.

3. Line 41 remove "on the other hand"
   Response: the comment is well taken and we have removed it.

4. Line 45 remove "as compared to women screened and treated in the 3rd trimester"
   Response: the comment is well taken and we have removed it.

5. Line 43 change to "control of vertical transmission of syphilis and associated birth complications"
   Response: the comment is well taken and we have changed.

6. Introduction, please describe and provide citation for the current country recommendations or policy for syphilis screening in pregnancy/ANC
   Response: the comment is well taken; we have incorporated in the background section.

7. Introduction or discussion, Please provide and cite the current country recommendations for syphilis treatment in pregnancy
   Response: the comment is well taken; we have incorporated in the background section.

8. Introduction, please describe the current ANC syphilis screening recommendations and practices at the study hospital. Please include estimated syphilis screening coverage.
   Response: the comment is well taken; we have incorporated syphilis screening recommendations and practices in the study hospital in the background section. But difficult to estimate the screening coverage so we put in the limitation part of the manuscript.

9. Line 64, should this be "women are offered screening for HIV and syphilis"?
Response: the comment is well taken and we have incorporated the reviewer suggestion.

10. Line 59 remove "far"
Response: the comment is well taken and we have removed it

11. Line 79 "chart"
Response: the comment is well taken and we have corrected

12. Line 102 "A letter of support was…"
Response: the comment is well taken and we have corrected

13. Line 105 "Please describe the treatment for pregnant women with syphilis. Was this consistent with WHO treatment guidelines?"
Response: the comment is well taken and we have incorporated in the introduction and it was consistent with the WHO treatment guidelines.

14. Line 112"thirds" and "residents"
Response: the comment is well taken and we have corrected

15. Line 117 494 women "who" attended
Response: the comment is well taken and we have added.."who”

16. Line 119 The majority of "these women attending ANC late"
Response: the comment is well taken and we have corrected

17. Line 122 sub heading "Seroprevalence (spelling) of syphilis and HIV"
Response: we appreciate the curiosity of the reviewer; we corrected the spelling

18. Line 127 68.6% "knew of their HIV status"
Response: the comment is well taken and we have corrected

19. Line 131 Syphilis prevalence "increased"
Response: the comment is well taken and we have corrected

20. Line 130 associated factors, please designate those associated factors with significant ORs (95%CI) and p values

Response: Yes, totally we agree with the reviewers’ suggestion, we put ORs (95%CI) and p values for significant variables. But for those no significant association we stated with proportion.

21. Line 144 add Gondar, Ethiopia"

Response: the comment is well taken and we have corrected

22. Line 147, would remove Bangladesh and Brazil citations as limited relevance

Response: the comment is well taken; we have removed from the reference list

23. 160 Tanzania spelled wrong

Response: the comment is well taken and we have corrected

24. Line 160 would remove China citation as limited relevance

Response: the comment is well taken; we have removed from the reference list

25. Line 161 define "round"

Response: the comment is well taken; we used to mean have in circled sexual network

26. Line 163 "that" were urban residents

Response: the comment is well taken and we have incorporated

27. Lines 165-171 would delete this paragraph

Response: In accordance with the referees’ wishes; we have now deleted the paragraph

28. Line 178 "This" calls for

Response: we agree with the reviewers’ suggestion and corrected
29. Line 179 "integration" no "s"

Response: the comment is well taken; we have removed “s”

30. Line 180 …"implementation of rapid dual HIV/syphilis screening test in ANC clinics in 
Ethiopia to improve syphilis and HIV screening coverage, early detection, and maternal 
treatment to prevent infant infection"

Response: the comment is well taken and we have incorporated

31. Line 183"control of adverse pregnancy outcomes due to congenital syphilis" delete "syphilis in pregnancy….

Response: the comment is well taken; we have deleted “syphilis in pregnancy and increased risk for”

32. Line 192 "once" not one

Response: the comment is well taken; we have corrected

33. Line 194 "strengthen the existing ANC to include rapid point-of-care syphilis testing with on-site treatment to reduce mother to child transmission of syphilis

Response: the comment is well taken and we have incorporated

34. Recommend adding addition citations and discussion of global efforts to eliminate mother to child transmission of HIV and syphilis through improved ANC, and improved HIV and syphilis testing and treatment coverage. Rapid dual tests and program integration are important tool for countries to consider as they work to achieve elimination goals:


Response: we appreciate the reviewer for delivering us updated and relevant information. We used these references in our manuscript.

35. Line 198, add "sample size limited our ability to show significance for many demographic variables". We did not evaluate birth outcomes of mothers treated for syphilis". We did not evaluate or report on syphilis screening and treatment coverage within pregnant women seen at this facility overall.

Response: the comment is well taken, we accept the reviewer's suggestion

36. Line 203 "the seroprevalence of syphilis "among pregnant women in this hospital in Southern Ethiopia was considerably higher"

Response: the comment is well taken; we have corrected

37. Line 206 "delayed ANC in Ethiopia"

Response: the comment is well taken and we have abbreviated and add ..in Ethiopia.

38. Table 4 define COR

Response: the comment is well taken and we have defined COR as crude odds ratio in the foot note
39. Was a multivariate analysis performed?

Response: Thank you for critical comments and questions forwarded to increase the credibility of the manuscript. Yes, we did, but only HIV was the significantly associated we thought that no need of further adjustment. Now we did by taking variables which showed p-value <0.2 in the bivariate in to multivariate analysis.

Reviewer 3

1. Title could be improved - it isn't clear what is meant by "awakening message to reinforce syphilis prevention strategies"

Response: With all due respect to the reviewer; we thought that high prevalence of syphilis in our result will make aware the government or policy makers to strengthen syphilis prevention strategies like improving timing and frequency of ANC visit, screening and treatment.

Abstract

2. Specify what constitutes the "study area" - Ethiopia? Southern Ethiopia? Yiregalem Hospital?

Response: we agree with the reviewer assertion, now we have made some clarification to indicate the specific study area and its location in the country. The study area is Yirgalem hospital found in Southern part of Ethiopia.

3. There is very little information on the sample population; e.g., why Yiregalem Hospital, what are the exclusion/inclusion criteria (e.g. age of pregnant women, gestational age, recruitment during prenatal visit/labor & delivery, etc.)

Response: thank you for your concern; we assume that Yiregalem Hospital is found in Yirgalem town i.e the site representing all of the major ethnic group and both urban and peri-urban areas as well as it is the second largest hospital next to Hawassa referral hospital that large number of pregnant women will visit the hospital and. Our exclusion criteria were “pregnant women less than 18 years of age because we assume that they were few in number. Moreover, women who
on treatment (since difficult to get previous RPR titer) and delivery during recruitment were excluded.

4. In addition to HIV results, were serologic syphilis test results also abstracted from hospital records? What was the role of the labs and how were missing data/documentation issues resolved?

Response: thank you for your concern, but only HIV result were abstracted from the hospital follow-up chart since the country (including the hospital) have well-resourced HIV screening and follow-up. But all women may not be screened and treated for syphilis b/c of stock-out of reagents and treatment, no strict monitoring like HIV. Moreover, screening of syphilis is based on RPR only which may not indicate probable active syphilis (PAS). For these we did screening of syphilis 1st by RPR then by TPHA for positive cases.

5. What was the mean/median age of gestation at the time of first syphilis testing?

Response: the comment is well taken and it was good to express in mean/median; but we originally collected the gestational age as categorical not in week, so difficult to calculate the mean/median gestational age that is why we reported categorical percentage based on trimester in table 2.

6. The conclusion states the seroprevalence of syphilis is "high", but on what basis? There was no specific estimate of national prevalence or among a comparable group to support this conclusion.

Response: we agree with your idea, but to say this, we based on WHO, 2017 guidelines: www.who.int/reproductivehealth/publications/rtis/syphilis-ANC-screenandtreat-guidelines/en/ and we have national ANC-based sentinel surveillances (2012 and 2014) for HIV and syphilis which is lower than our result.

Introduction

7. Page 3, lines 43-45: It is important to note that repeat screenings, particularly in high-risk or -prevalence settings, are necessary for detecting new infections.
Response: the comment is well taken; we have clarified the time of recommended screening in the introduction part.

8. Lines 37-39: Grammar issues

Response: the comment is well taken; we have corrected

9. It isn't clear how previous studies conducted in Gondar is a limiting factor. Clarify how this study is addressing a gap in the literature.

Response: the comment is well taken; we thought to mean some of the information available was restricted in the Northern part of Ethiopia. It is known that epidemiology of STIs will vary with regard to socio-demographic and cultural practices. Now, we have modified it.

10. Lines 49-51: How soon should women be screened for syphilis and HIV to prevent congenital infections and/or adequate treatment?

Response: according to the WHO recommendation that we stated in the introduction part pregnant women should be screened and treated immediately at their first ANC visit (the first trimester) and followed for treatment response but in settings (prevalence >5%) screening should be repeated early in the third trimester and at delivery.

11. The objectives include assessing factors associated with syphilis. However, the litany of characteristics (e.g. age, residence, education, occupation, gravidity, prenatal care visits etc.) assessed as potential correlates should be better supported by a conceptual framework in the introduction.

Response: the comment is well taken; we have addressed

Methods

12. Lines 60-63: Grammar issue

Response: the comment is well taken; we have made some changes and correction
13. It is stated that Yirgalem hospital is the largest hospital in southern Ethiopia but only has 15 rooms…where are most women delivering (e.g. at home)? Are the women delivering at the hospital really representative of women from Southern Ethiopia? Probably not…

Response: the comment is well taken; we did transcriptional error by considering 15 rooms which were used for delivery only but a total of 69 bed rooms are available in the hospital for admission and follow-up. Since we used probability sampling method the sample we used is assumed to be representative for the catchment area of the hospital but may not be representative of the southern Ethiopia.

14. Lines 70-79: The sampling scheme is unclear. Do you mean that one pregnant woman was randomly selected each day, and every fifth patient thereafter?

Response: thank you for your concern; we randomly select 2 women each day in every fifth of the women.

15. Fix "follow-up char…"

Response: the comment is well taken; we have corrected as “follow-up chart”

16. Lines 81-85: Need an explanation regarding the potential correlates. Were serologic test results abstracted from medical records also, or obtained directly from labs? Find it strange that HIV test results would be available in the records but not for syphilis.

Response: thank for your concern, we didn’t abstracted syphilis result, only HIV result were abstracted from their follow-up chart.

17. Lines 91-92: Positive serologic tests alone do not confirm an active syphilis infection. Other information (previous nontreponemal test titers, treatment status) are needed to determine whether positive tests represent an old previously treated infection or new infection. This is exemplified by the result showing that syphilis infections increased with age; most of those "infections" among older women may be old previously treated infections. Authors should address the issue of misclassification and clarify if history of syphilis vs. active infection is the intended outcome.
Response: thank you for your concern, our intended outcome is probable active syphilis (PAS) infection. As we made some brief in the exclusion part now, pregnant women who are on treatment was not included in the study because of difficulty in getting the previous titer to predict the treatment response. Yes, treatment history can help to classify “new” and “old” but, due to recall bias of specific drugs taken by participants and a weak recording system of clinical history in our settings, we considered both RPR +TPHA reactive cases as “probable active syphilis(PAS)” or untreated syphilis. “Hama DC, Lina C, Newmanb L, Wijesooriyaa N S, Kamba M. Improving global estimates of syphilis in pregnancy by diagnostic test type: A systematic review and meta-analysis. Int J Gynaecol Obstet. 2015 130(0 1): S10–S14.” And also a small percentage of patient’s low positive titers persist despite receiving adequate therapy.

18. Line 96: What is meant by outcome variable(s)? Was HIV infection also assessed as an outcome? Thought it was just syphilis infection…

Response: the comment is well taken; we thought syphilis infection as outcome variable.

19. Line 97-98: Justify why just bivariate analysis was conducted, rather than testing best fit model for correlates that best explains the variance in the outcome? Crude estimates are biased and do not account for other factors that may be skewing the true relationship between the factor of interest and outcome.

Response: we agree with the reviewers’ comment, we thought that since only one variable (HIV) was significant in bivariate analysis no need of further analysis. Now based on your comment we have done multivariate analysis by taking P<0.2 in bivariate analysis.

20. How long did it take patients to complete the questionnaires? How many nurses were involved in consenting and collecting data from patients vs. abstracted from the medical records?

Response: thank you for your concern; two midwife nurses were involved as data collector and maximum of 10 minutes were taken to complete the questionnaire.
Results

21. Table 2 results are not interpreted in the text the way it is presented in the table. Also confusing if this is the total number of ANC visits (4 or more?). The sub-titles need to be fixed.

Response: the comment is well taken; we have modified the sub-title and modified the interpretation of table 2.

Discussion

22. Lines 152-153: One type of serologic test for syphilis (nontreponemal or treponemal test) is not sufficient for diagnosis. In addition, serologic tests for syphilis cannot differentiate between new infection or old previously treated infection.

Response: we appreciate your concern; we made some modification and concerning between new infection or old previously treated infection we have addressed in Q17.

23. The role of frequency of screening or access to health care services should be addressed. Clearly, women with better access to or proximity to care would be more likely to be screened and diagnosed with infections (e.g. health professionals, urban resident). Also those who are more closely followed up (e.g. HIV infected individuals).

Response: comment is well taken; we have addressed in the second paragraph of the discussion part.

24. Line 161: Clarify what is meant by "round sexual networks" in urban environments

Lines 165-171: address grammar issues; would recommend strengthening this section with prior literature to support the assertion that women with multiple pregnancies would be less inclined to attend prenatal care.

Response: the comment is well taken; we used this term to mean in circled or multiple sexual network but now to avoid confusion we removed the term "round sexual networks". We also deleted the paragraph 165-171, we thought not a significant result.
Generally, thank you for your critical and unreserved comments given due the time, as much as possible, we hope all the comments given and questions raised are addressed well.