Author’s response to reviews

Title: Better care for babies: The added value of a modified reverse syphilis testing algorithm for the treatment of congenital syphilis in a Maternity Hospital in Central African Republic

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Author’s response to reviews:

Letter to Editor

BPED-D-18-01081

Dear Editor,

Please find enclosed the revised manuscript entitled: Better care for babies: The added value of a modified reverse syphilis testing algorithm for the treatment of congenital syphilis in a Maternity Hospital in Central African Republic, for publication in BMC Pediatrics

We have carefully addressed each one of the reviewers’ comments and have made the revisions accordingly.
Our detailed replies to the Reviewers comments are shown below. We are confident that you will find the revised manuscript suitable for publication.

Yours sincerely,

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Better care for babies: The added value of a modified reverse syphilis testing algorithm for the treatment of congenital syphilis in a Maternity Hospital in Central African Republic

Authors’ Reply to Editor

Thank you for your detailed review of the manuscript and your suggestions for changes. See below the responses and updates for each of the points raised during your review.

Authors’ Reply to Reviewer 1

Comment #1

I found the title 'The added value of a …’ a bit misleading as I rather assumed that this initiative was part of an overall control strategy that included early and late pregnancy screening to prevent MTCT. However, on reading further I found that this wasn't the case. Perhaps you could state clearly at the start of the background the conditions under which the novel strategy would be most effective.

Reply from authors: The content of the background has been modified to clarify this point. We have attempted to place it as early in the background as possible and preserve the coherency and flow of this section.

The manuscript has been revised as follows (starting at page 4 line 50 of the original manuscript):
In high-prevalence and low-resource settings (which often coincide) where there is a higher chance of maternal past infection, which carries a low-risk of congenital syphilis [5], the syphilis testing strategy needs to be tailored. In settings where syphilis testing is not guaranteed during antenatal care (ANC), syphilis testing at the time of delivery is warranted.

Comment #2

Abstract; there are a few minor mistakes in written English such as 'delivering women' and 'congested maternities' which need to be corrected. The rest of the document should also be checked by a native English speaker.

Reply from authors: The content has been reviewed again by native English speakers and minor mistakes have been corrected as recommended.

Comment #3

3 Page 4 line 32. What is the role of paired sera in diagnosis, or would this not be possible within the context of this population?

Reply from authors: Serial testing with paired sera is neither recommended nor done in Central African Republic, it is also challenging in areas with lower ANC coverage after the initial visit. This point has been added into the manuscript.

The manuscript has been revised as follows (starting at page 5 line 5 of the original manuscript): Along with 11 other countries, CAR has been targeted by the World Health Organization (WHO) for intensified support for the elimination of MTCT of syphilis [9]. Other syphilis testing strategies such as paired sera testing during pregnancy are not part of the testing algorithm for syphilis in CAR, single Venereal Disease research laboratory (VDRL) or Treponema pallidum hemagglutination assay (TPHA) are recommended, because ANC attendance, after the initial visit, in CAR is unreliable (11, 12).

Comment #4

4 Was PCR testing available?

Reply from authors: No PCR testing was available in this setting even at the highest level of care at the district hospitals. The following sentence has been added to mention this point.
The manuscript has been revised as follows (starting at page 5, first paragraph of the original manuscript): Polymerase chain reaction (PCR) testing is also not available in CAR, even at the highest level of care at the district hospitals (11).

Comment #5

5 Line 45. 'Neonatal risk depends on … maternal history' - do you have any information on the risk of syphilis infection in the mother, such as sex work and could this be included in the tables? Was there any information available on the mothers medical history, such as pregnancy outcomes, miscarriages, live births, etc.

Reply from authors: Data on sociodemographic risk factors other than maternal age were not in the routinely collected data. Data on parity and number of live births were included in individual maternal files which were in turn entered into a separate maternal database that is not linked to the neonatal data. The only maternal data available from the neonatal files were on maternal age and HIV status (which are included in the analyses). The manuscript has been modified to clarify this point.

The manuscript has been revised as follows (starting at page 9 line 35 of the original manuscript): Maternal and neonatal data were abstracted from project monthly situation reports and annual and trimestral reports, laboratory records, neonatal register and neonatal patient files. Only data on the mother’s age were available from these sources. No other sociodemographic data (e.g. Profession, parity, number of living children and psychosocial risk factors) were available.

Comment #6

6 Methods Page 6, line 25. outcomes for the neonate. Significant clinical outcomes relating to congenital syphilis may not been seen for a number of years - was this time delay taken into account in the analysis and are there plans to follow the patients up over time? (2-6 years)

Reply from authors: This point is mentioned as a limitation of the study in the discussion. The study site is a maternal and neonatal project without outpatient clinical capacity to follow up children past the post-natal care period so this data is not available. The part where this is mentioned in the discussion has been modified to further clarify this point.

The manuscript has been revised as follows (starting at page 17 line 60 of the original manuscript): Another limitation is that the study did not look at neonatal outcomes past the initial hospitalization period so late symptoms of congenital syphilis would have been missed.
This subject warrants further investigation in future studies. However, since all babies were treated with at least one dose of penicillin, the risk of late onset congenital syphilis is low [23].”

Comment #7

7 Page 7 line 43. How was the information on patient history obtained - was it from the patient or from medical records?

Reply from authors: The information on patient history was collected from women at the time of admission for delivery. The women do not typically have a patient file that they carry with them with this information, nor is this information available in a database or archive. The manuscript has been modified to clarify this point.

The manuscript has been revised as follows (starting at page 7 line 41 of the original manuscript): Pregnant women delivering in Castors Maternity Hospital were tested for syphilis at the time of or after delivery. Reliable information about prior syphilis infection could not usually be obtained. Any history of syphilis infection and/or treatment was solely based on self-reporting at the time of the delivery as women did not typically have an accessible patient file with this information.

Comment #8

8 Page 7 line 57. A chancre could be confused with a herpetic lesion - please could you say how this differential diagnosis was eliminated.

Reply from authors: At the study site a chancre like lesion found on physical exam was attributed to syphilis when the treponemal test was positive. Theoretically this could have led to more children receiving 10 days of penicillin for high risk of neonatal syphilis if the lesion was actually a herpetic lesion. Yet, in the study period no babies treated with 10 days of penicillin born to mothers with discordant RPR results (signs of syphilis in the mother but low RPR titer i.e. 1:2) were reported.

Comment #9

9 Page 16. Was the inappropriate treatment partly due to allergies reported by the patient?

Reply from authors: Based on the review of their patient files, there were no allergies reported for the neonates who received penicillin during the study period. The manuscript has been modified to clarify this point.
The manuscript has been revised as follows (starting at page 11 line 20 of the original manuscript): Among the 17 babies born to RPR reactive mothers who received inappropriate treatment, 7 (41%) were discharged earlier than ten days while the other 10 had treatments interrupted by death, transfer or leaving against medical advice. No treatment was discontinued due to an allergic reaction.

Comment #10

10 Page 17 line 35-41. In a middle income country early and late pregnancy screening would be affordable which would completely change the effectiveness of congenital syphilis prevention and control.

Reply from authors: This is indeed the case; the manuscript has been modified to clarify this point.

The manuscript has been revised as follows (starting at page 17 line 34 of the original manuscript): With the rise of ESBL and other resistant forms of neonatal sepsis in low and middle-income countries [24] an algorithm like this will contribute to reducing the risk of nosocomial infections with resistant pathogens in the hospitalized neonatal population. This effect would be much greater in the low income countries that have low ANC coverage and limited antenatal screening and treatment for syphilis (12).

Comment #11

11 Page 17 line. Could you provide more detail concerning the urban setting specifically why this carried an increase risk of syphilis infection, please?

Reply from authors: On page 15 on lines 48-60 of the original manuscript we explain that the opposite is the case in CAR. Specifically, in this urban setting there is a lower risk of syphilis infection, this is probably because of higher access to health care in Bangui and other urban centers that are less affected by the ongoing conflict.

Comment #12

I have attached a copy of the latest WHO estimates concerning congenital syphilis and maternal infection.
Authors’ Reply to Reviewer 2

Comment #1

(Methods)

"Routine programmatic data were analysed" not "Routine programmatic data was analysed"

Reply from authors: The grammar was edited wherever “data” appeared to correct this error in throughout the manuscript.

Comment #2

I would also like to suggest to insert a box with clinical features of congenital syphilis ("a neonatal physical examination consistent with congenital syphilis ……(see table…or box)..")

Reply from authors: The following box (as figure 1) was inserted into the manuscript. It will appear as shown below.

The manuscript has been revised as follows (starting at page 8 line 10 of the original manuscript):

Figure 1: Clinical features of early congenital syphilis, has been included.