Author's response to reviews

Title: Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta-analysis

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

Thank you for reviewing our manuscript, 8836495911329535 entitled, “Prevalence of early-onset neonatal infection among newborns of mothers with bacterial infection or colonization: a systematic review and meta.” We appreciate the helpful comments from the reviewers. We addressed the concerns of the reviewers. Please find our detailed responses below. We thank you for your continued interest in our manuscript.

Please feel free to contact me if you have any further questions.

Warm regards,

Grace

The following points were raised by Reviewer #1:

1. My understanding is that by 'lab diagnosis' of infection the authors refer only to culture based methods and have excluded studies using molecular diagnostic methods (e.g. PCR). This should be made more clear in the methodology.

Response:
Thank you for pointing out the need to clarify the definition of ‘lab diagnosis’. We included studies using molecular diagnostic methods although they were few in number. Specific descriptions of maternal infections are described for each study in Figure 2 Maternal infection and neonatal infection and Appendix Table 3 Maternal exposure and neonatal outcome prevalence. In the methodology section, we revised the definition of Laboratory confirmed bacterial infection (hereafter referred to as “lab”) to include “culture or PCR confirmed bacteremia, amnionitis, urinary tract infections, chorioamnionitis”. (Page 4).

2. PCR-based diagnosis of maternal and neonatal infection is becoming more widely used, in particular PCR for Group B Streptococcus. Even though this review does not include studies that have used PCR for laboratory diagnosis of infection the authors should include something in the discussion about PCR-based diagnostics. The point being that a proportion infections that are defined only by clinical signs would be laboratory confirmed if molecular methods such as PCR were used.

Response:
We added the following sentence to our discussion, “Not many studies utilized molecular diagnostic methods in our review. As PCR-based diagnoses of maternal and neonatal infections are becoming more widely used, our ability to detect true neonatal infections will improve.” (Page 17).

The following points were raised by Reviewer #2:
1. This systematic review and meta-analysis provides an extensive search and analysis of studies related to the burden of vertical transmission of bacterial pathogens. The methods and results are clear and well structured. What I miss however is explanation about the context. The background section is very short. It is not really clear why the review was done as reported. So the reader is left with many questions like:

- The rationale is reduction of neonatal deaths, but what is known about mortality among neonates with the reported outcomes?

- Why is the outcome an overall prevalence, with sensitivity analysis around studies with and without or unknown use of antibiotics, rather than a comparison between groups that had vs. did not have antibiotics, or at least an attempt to report prevalence in those subgroups? It seems that the authors are interested in the natural history, i.e. vertical transmission in absence of antibiotic treatment. Generally, if a maternal infection is suspected antibiotics treatment may be common in settings where studies are conducted? This point should come out more clearly, and the current guidelines for antibiotic use discussed, so we understand the context.

- What are interventions related to high prevalence of the studied outcomes?

Response:
Thank you for clarifying the need to explain the context of why this review was done. In the introduction, we added “Neonatal infections account for a significant proportion of neonatal deaths in the first week of life.[1] In sub-Saharan Africa, south Asia, and Latin America where neonatal infections are most prevalent, the case fatality risk associated with possible severe bacterial infections in the first month of life is 9.8%.[2] Infections are one of the three major causes of neonatal infection and account for approximately a quarter of newborn deaths in the first month of life.[3] Neonatal infections are acquired horizontally (from the environment) or vertically (from mother). Not much is known about the routes of transmission globally where different environments and risk factors may affect paths of transmission. In resource-rich settings, interventions such as antibiotic prophylaxis during labor based on risk-based screening, neonatal antibiotic treatment has been effective in reducing early-onset neonatal sepsis. In contrast, in resource-poor settings, which have the highest rates of neonatal mortality, such interventions are rare or absent. To develop research priorities and strategies for prevention, we need to better understand the prevalence of neonatal infections that are maternally acquired.” (page 1)

In the methods section, we wrote “In our sensitivity analyses, we repeated meta-analyses excluding studies with (i) some or unknown intrapartum antibiotics use to understand the natural history of vertical transmission in settings of most LIC where intrapartum antibiotics are not available…” (page 10)

In the results, we wrote, “A sensitivity analysis around studies without or unknown use of antibiotics was limited by the data available and only possible in the subgroup maternal colonization and neonatal infection. (Page 11)

2. The above applies to the background section, but also to the discussion and conclusions. If more studies are needed, could the authors discuss in a bit more detail what type of studies (design, outcomes) would be most useful and feasible. Also in relation about the earlier points about the use of antibiotic treatment.

Response: Thank you, we added to the discussion, “Our findings highlight the need for better screening and diagnostics to identify pregnant women with infections and/or colonization to better understand the population based prevalence of maternal infections and/or colonization with common EOS pathogens in LMIC, which if treated would have the potential to reduce the burden of early-onset
Additional studies, such as a randomized controlled trial on the effect of intrapartum antibiotic prophylaxis on early-onset neonatal sepsis in low resource settings, are also needed.” (Page 19)

3. Methods/page 8: what is the rationale for rating studies with one domain low risk and another domain unclear risk as low risk of bias? In my understanding low risk implies that one can be reasonably confident that bias did not distort the results, which is not the case if the risk is unclear.

Response: Thank you, we wrote “Studies were given an overall rating of low risk of bias if both selection and misclassification biases were at low risk (or if one domain was low risk and the other domain was unclear risk).” The study was still considered low risk of bias if at least selection and misclassification bias was at low risk of bias, as long as neither domain was high risk of bias.

4. Results/Table 1 (page 11): A study could report more than one maternal conditions but was used only once in each meta-analysis. How was decided for which condition such studies were included in a meta-analysis?

Response: Thank you, each study was only represented once in each meta-analysis to avoid having the same population counted twice. A study could include maternal lab confirmed infection, clinical signs of infection, and colonization data. For example, if a study included blood culture data, we included that data in the maternal lab confirmed infection meta-analysis. If the same study contained GBS swab data, we included that data in the colonization meta-analysis. Appendix Table 3 includes the break-down of how studies were included in the meta-analysis.

5. Results/page 12. Provide a rationale why urinary tract infection exposure was reason for exclusion.

Response: We did not include UTIs in the meta-analysis because the route of transmission from maternal UTI to newborn is likely to be different than the route of transmission from amniotic fluid or blood culture infections. Furthermore, the prevalence rate was low. We wrote on page 13, “We excluded five studies from the meta-analysis: three studies that measured maternal urinary tract infection exposure, which reported zero to two percent vertical transmission rates”.

6. In addition to point 1, the association with PROM/PPROM could be more clearly explained in the discussion, as bacterial infection may be a cause, and ROM would be a reason for women to report to a health facility and be included in a study.

Response: Thank you, in the discussion section, we added the statement “These risk factors may lead to bacterial infections, and may be indications for women to present to a health facility.” (page 17)

7. In the discussion, please provide an indication of possible bias from excluding the studies that were not reported in English and of possible publication bias.

Response: Thank you for bringing our attention to this missed point. In the discussion section, we added, “Authors are more likely to report positive findings in international English journals, whereas negative findings are published in non-English journals. We excluded non-English articles due to our limited resources. To assess for publication bias, we used funnel plots of standard error and prevalence to graph the correlation between the variance and distribution of effect sizes. Results were not statistically significant (p=0.10).”
8. The appendix tables 2, 3 and figure 1 are not sufficiently readable. The text in figure 1 is unreadable whatever screen enlargement is applied. The tables extend on additional pages without repeating 1st columns or headers. Try to narrow columns such that at least all columns fit on 1 page.

Response: Thank you, we reformatted Appendix Tables 2, 3, and Figure 1 to make them sufficiently readable.

**Minor Essential Revisions**

9. Figure 1 misses 1 arrow at the last step.

Response: Thank you, we added an arrow to the last step.

10. Table 1: a footnote explaining why row totals exceed 100%, and how this relates to the metaanalysis would make the table more stand-alone.
Response: We added a footnote to Table 1, “*Studies could be included in more than one meta-analysis (Maternal infections and neonatal infections, Maternal colonization and neonatal infections, Maternal colonization and neonatal colonization, and Maternal risk factors and neonatal infections)”

11. Abstract: should stand on it’s own, for a general readership. The way an earlier study by the authors is mentioned is not useful in the abstract.
Response: Thank you, we removed the sentence that describes the earlier study in the abstract.

The following points were raised by the Editor:
1). In addition to these, it would be appropriate to address the bias in the analysis of studies which look at colonization, as such studies by definition require laboratory facilities to detect colonization, as opposed to studies which can rely on clinical symptoms only.

Response: Thank you, on page 17, we wrote “Studies with colonization measures were also dependent on laboratory facilities and these findings may not be generalizable to populations without such facilities.”

2) The authors state that they included studies that either captured incidence or prevalence. The outcome is prevalence. It is unclear how the studies on incidence contributed to this. Was it recalculated? If so, how? Or are the incidence data assumed to be "period prevalence" estimates?

Response: Thank you. The incidence data were assumed to be “period prevalence” estimates. Our search strategy yielded studies that included incidence in their titles and we included those with the assumption that it represented period prevalence. We revised the methods section to read, “We included studies of any design that measured the prevalence or incidence (assumed to be period prevalence) of bacterial vertical transmission” (Page 7).

3) Later in the authors state that they "consider early-onset incidence over the first seven day of life". The meaning of this statement is unclear and just increases the confusion over the outcome. Especially since the tables show that for almost 40% the timing of the study is unclear.

Response: Thank you, we clarified this statement as follows, “We defined our outcome, early-onset neonatal infection, to the first seven days of life. Studies that used the term “early-onset neonatal sepsis” but did not specify timing (i.e. seven days or three days) were also included.” (Page 8).

4) I was rather impressed by the cautiousness of the authors regarding the pooling of data in the presence of heterogeneity. They even mention the I-square which they assumed to be too high for pooling. However, in all graphs, date are ruthlessly grouped despite the large majority having I-squares way above the threshold set by the authors. His needs an explanation.

Response: We presented the data in categories determined apriori as a way to organize the data. Presenting the I-square allows readers to understand the degree of heterogeneity. If the I-square were too high for pooling, we did not calculate the overall estimate. If the Editor wishes otherwise, we can provide the overall pooled estimate.

5) I miss the discussion on publication bias, and the plots that go with this analysis.

Response: Thank you, please see the response to Review #2, item #7 above.