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-analysis.” We appreciate your comments. 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 additional questions.

Warm regards,
Grace

Comments

1. In response to reviewer 2, comment 1, you have included additional text. Please check this text carefully and correct as for example "infections are one of the three major causes of neonatal infections" does not make sense. Please provide a reference for horizontal acquisition of GBS in neonates. Also check the sentence starting with "In resource-rich setting, interventions such as... "etc., as it does not make sense.

Response: Thank you, we apologize for this error. We corrected the text to read, “Infections are one of the three major causes of neonatal mortality...” (page 1)

The text, “Neonatal infections may be acquired horizontally (from the environment) or vertically (from mother)” is not specific to GBS but a general statement. We referenced Anita Zaidi’s article, Pathogens Associated With Sepsis in Newborns and Young Infants in Developing Countries, which suggests “Early onset sepsis is commonly considered maternally-acquired, the overwhelming majority of Gram-negative organisms, such as Klebsiella, Pseudomonas, and Acinetobacter and the frequency of S. aureus isolated in the first week of life among the studies reviewed, suggests that these infections may in fact be acquired from the hospital or community environment due to poor hygienic practices during delivery and postnatal care, rather than reflecting vertical transmission to the infant from exposure to vaginal tract flora.” (page 1)

We also revised the sentence starting with “In resource-rich settings...” to read “In resource-rich settings, interventions such as intrapartum antibiotic prophylaxis for high risk women has been effective in reducing the incidence of early-onset neonatal sepsis. In contrast, these interventions are rare or absent in resource-poor settings, which have the highest rates of neonatal mortality.” (page 1)

2. Your response to reviewer 2, comment 3 is still not clear. From Figure 1, depicting the risk of bias summary, I would conclude that studies with an unclear risk of either selection bias or misclassification bias, would be rated as unclear risk of bias. See for example Kishore 1987 and Goldenberg 2008, both with unclear risk of selection bias, low risk of misclassification bias, which were rated as unclear risk of bias. However, from the text and the response to the reviewer I understand that you would rate these as an overall low risk of bias. The rating as in Figure 1 would be consistent with the reviewer’s comment (and makes sense) and this suggests that the text needs adjustment.
Response: Thank you for clarifying this point. The reviewer and Figure 1 are correct in that studies with unclear risk of selection bias or misclassification bias would be rated as unclear risk of bias. We deleted the comment “or if one domain was low risk and the other domain was unclear risk” so the sentence now reads, “Studies were given an overall rating of low risk of bias if both selection and misclassification biases were at low risk.” (page 4).

3. In your response to the Editor’s comment 4, you indicate that an overall estimate is not calculated if the I-square is too high. However, you do report overall estimates for pooled subtotals for all categories for which the I-square is too high. These estimates cannot be interpreted and should therefore not be included. It is informative to include the I-square value but the estimates should preferably be removed from Figures 2-5 (and the text) when I-square is too high.

Response: Thank you, sorry for the confusion. We reported overall estimates for each combination of maternal exposure and neonatal outcome, but did not calculate and overall pooled estimate of the odds ratios across all combinations of maternal exposure and neonatal outcomes. On page 4, we clarified this by writing, “If there were two or more studies included in the meta-analysis, we assessed measures of heterogeneity with I² statistics. For each combination of maternal exposure and neonatal outcome, we calculated a pooled estimate of the odds ratios. Because of the substantial heterogeneity across all combinations of maternal exposures and neonatal outcomes, we did not calculate an overall pooled estimate of the odds ratios.” For example, in Figure 2, we calculated estimates for each combination, i.e. maternal lab confirmed and neonatal lab confirmed infection. We did not calculate an overall pooled estimate for all maternal infections and neonatal infections.

4. Check the manuscript including Tables and Figures, for appropriate nomenclature of bacteria, e.g. on page 13 Listeria species and Bacteriodes species instead of listeria and bacterioides.

Response: Thank you, we corrected the nomenclature of bacteria to read:

“Staphylococcus aureus, non-group B Streptococcus species, Group B streptococcus, Klebsiella pneumoniae, Escherichia coli, Ureaplasma species, Mycoplasma hominis” (page 5)
“Listeria species and Bacteriodes species infections.” (page 7)
“Staphylococcus aureus, 39.5% (95% CI 16.1-63.0) of the newborns had surface S. aureus colonization. In three studies where mothers were colonized with Escherichia coli, 34.3% (95% CI 4.2-64.5) of the newborns had E. coli colonization. In three studies where mothers were colonized with Ureaplasma species, 45.5% (95% CI 26.4-64.5) of the newborns were colonized with Ureaplasma species.” (page 9)
We italicized the genus and species names in Figures 3 and 4.