Author’s response to reviews

Title: Safety of a bivalent, killed, whole-cell oral cholera vaccine in pregnant women in Bangladesh: Evidence from a randomized placebo-controlled trial

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Responses to reviewer’s comments
Editor Comments:

1) Under the heading "Ethics approval and consent to participate", please include an explanation of how consent to participate was obtained for minors. You can re-use the statement you made in the Methods section.

Response: In this component of study there was no minor as we have enrolled only pregnant women.

2) Please change the heading "Availability of data, materials and consent to publish" to "Availability of data, materials" and include a statement in line with our editorial policies: https://www.biomedcentral.com/getpublished/editorial-policies#availability+of+data+and+materials

Response: Corrected (lines 336-340).

3) Please move the statement "The funder had no role in data collection, data analysis, data interpretation, or writing of this report." under the heading "Funding".

Response: Corrected (lines 345-346).

4) Figure titles (eg. Figure 1. Assembling the study population for analysis ) and legends (max 300 words) should be provided in the main manuscript, not in the graphic file.

Response: Corrected.

Reviewer reports:

David Sack (Reviewer 1): This study of pregnancy outcomes of women who inadvertently received oral cholera vaccine (OCV) when pregnant is a valuable confirmation of the safety of OCV during pregnancy. While previous studies have found similar results, this study is unique in
several respects. 1) The data is from a randomized placebo controlled trial and is thus, much less likely to be biased compared to previous studies. 2) Most of the exposures of OCV in pregnancy occurred during the first trimester. 3) The follow-up included data on low-birth weight. Thus, this study adds valuable information to support safety of the vaccine.

Unfortunately, some of the sentences need to be revised by a native English writer. Some of the sentences which need revision are listed below, but there are other sentences which will benefit by some edits.

Response: Thank you for your comment.

Some specific comments include:

Line 82. I recommend revising this statement, "However, the OCVs are still not recommended for the pregnant women due to limited data on its safety profile." As stated earlier (line 75), WHO does recommend that OCV be given to women who are pregnant, but the package insert is ambivalent. The wording might be, "the package insert for OCV still recommends caution for use during pregnancy due to lack of data."

Response: Corrected as per suggestion (now line 88).

Line 99 typo on the number of residents.

Response: Corrected (line 108).

Line 129. This sentence should be clarified. I interpret this to mean, If a pregnancy outcome had already occurred at the time of the screening visit, this was considered a retrospective follow up.

Response: The sentence is revised for clarification (lines 141-144).

Line 179. Remove the word "could."

Response: Corrected as per suggestion (line 191).

Line 206. I am not familiar with the term "accidental abortion." Please explain.
Response: Accidental abortion is an unintentional abortion (usually termed a miscarriage) caused by a fall, blow, or any other accidental injury.

Line 219. Change wording to "Previously reported studies in pregnant women receiving OCV have observed a non-significant increase in adverse pregnancy outcomes among women receiving OCV."

Response: The statement has been changed as per suggestion (lines 141-144).

Line 229 - change the awkward sentence.

Response: We have deleted the sentence (line 251).

Line 241. I am not sure why the authors feel these high rates are not surprising. It would seem that these high rates need to be explained. It seems likely that the surveillance for adverse pregnancy outcome was much more intense than the previous studies; but the authors should provide their own explanation. Although induced abortion is illegal, menstrual regulation is widely available, so it would seem there is less stigma in Bangladesh. This should be explained.

Response: We have take out the statement from the manuscript (lines 263-264).

Line 247. I assume the authors are talking about placental blood volume; this should be clarified.

Response: The sentence has been revised (line 269-270).

Line 249. Revise this awkward sentence.

Response: The sentence has been revised (lines 273-274).

Line 281. Change sentence to "...cholera vaccination campaigns frequently exclude pregnant..."

In fact most OCV campaigns now do not exclude pregnant women and this is consistent with WHO recommendations. This should be highlighted.

Response: Revised as per suggestion (lines 307-308).
Pedro Moro (Reviewer 2): This study evaluated the safety of a bivalent, killed, whole cell oral cholera vaccine, Duchoral (OCV), among pregnant women inadvertently exposed to the vaccine during pregnancy. The study participants were part of a randomized placebo-control trial conducted in Dhaka, Bangladesh. The authors specifically looked at the risk of spontaneous abortion and stillbirth (primary endpoints) and preterm delivery and low birth weight (secondary endpoints) among OCV recipients compared to placebo. This study provides important safety information on this cholera vaccine in pregnant women and the evidence is consistent with other studies done in pregnant women with this vaccine. I think this study merits publication, however, I have a number of comments and questions for the authors.

Background

Page 4, line 30: add the word 'used' after 'a killed whole-cell OCV is currently being

Response: Corrected as per suggestion (line 78).

Page 4, line 34, should be replicate instead of replication. Should say The world health organization…

Response: Corrected as per suggestion (line 81).

Page 5, line 25: Please, clarify the last where the authors say ' we took the opportunity of the practicalities…' . I suggest to simply state what the goal of the study was.

Response : Revised as per suggestion (line 103-104).

Methods

Page 5, line 34-49, under study population: the cohorts of this study were derived from the clinical trial conducted in Dhaka, Bangladesh and the findings published in NEJM, 2016, 374(18):1723-1732. In that clinical trial, pregnant women were excluded. So it sounds that those women who were initially in the study but later were found to be pregnant were excluded but were part of this analysis. This should be more clearly brought forward and explained in the
How did the women in cohorts 1 and 2 compare to the non-pregnant women of reproductive age from that clinical trial?

Response: Yes, in the main clinical trial, pregnant women were excluded. Upon completion of the vaccination we had run a pregnancy screening immediately among the women of childbearing age who had received study agents. Vaccine and placebo were administered through individual randomization technique. Participants were un-blinded for the analysis and distributed into two cohorts, 1 and 2. This now mentioned in the study population section (lines 112-113).

Page 6, line 20: should say inquired not enquired

Response: Corrected as per suggestion (line 125).

Page 6, line 22: the authors state that if the LMP was more than 4 weeks, the patient had irregular periods, or this were unknown or uncertain then they were ineligible to participate. How come then 14.3% or so of women in the OCV group (cohort 1) were in the second or third trimester (based on the information in table 1). Please clarify this.

Response: We have described the exclusion criteria for the vaccine recipients in the statement. But some participants forgot the told their wrong LMP. During this pregnancy outcome study we again recorded their LMP by trained study staffs and also compare with the pregnancy status.

Page 8, lines 3-8: why did the authors choose a definition of < 28 weeks for miscarriage and ≥28 weeks for stillbirth? The WHO definition is <22 weeks for spontaneous abortion and ≥ 22 weeks for stillbirth. Other studies that have assessed the safety of cholera vaccines in pregnancy have used < 20 weeks for spontaneous abortion and ≥ 20 weeks for stillbirth (Grout et al, PLoS Negl Trop Dis 2015 9(12): e0004274; Ali M, et al, The Lancet Infectious Diseases, 2017 May;17(5):538-544). We should try to harmonize adverse event definitions.

Response: We used this definition as Bangladesh perspective. Another study conducted in Bangladesh by (DaVanzo et al. 2012) uses the same definition.

Results

Page 9, lines 18-37: rather than combine miscarriage and stillbirth together and call it adverse pregnancy outcomes, the authors should state the rates of miscarriage and stillbirth separately as they do for preterm delivery and low birth weight.

Response: It has been corrected accordingly. Adverse pregnancy outcomes has been mentioned separately (lines 213-217).

Table 2: under the columns for crude RR and adjusted RR delete the p-value, which is confusing and not necessary since you are already providing the 95% confidence intervals. Either spell out RR as relative risk when first used or define it in a footnote or in the title of the table.

Response: We have elaborated RR where first used in the Table 2.

Discussion

Page 10, first paragraph: again, state the rate of miscarriages and stillbirths separately and not together. It is re-assuring that the rates of these among OCV recipients was lower than among placebo and this should be highlighted. I would delete or modify the next sentence stating the rates were higher than in previous studies. What matters is the comparison with the placebo group and background rates, if these background rates were adequately assessed. The studies they cite seem to have very different methodology. It just does not sound right to compare data from a randomized trial to that of observational studies.

Response: We have modified the statement (lines 233-234).

Page 11, line 15: the sentence ' In our study we observed a high miscarriage rate and low stillbirth rate in cohort 1'…. This sounds alarming. The miscarriage and stillbirth rates were definitely not high as they were comparable to placebo rates for cohort 1. The rates from other studies is fine to mention but they could have been due to differences in methodology and study design.

Response: The sentence has been revised (lines 255-256).
Reference 19 is incomplete.

Response: Corrected.

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