Reviewer’s report

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

Version: 1 Date: 21 Apr 2018

Reviewer: Pedro Moro

Reviewer's report:

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

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

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.

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 current study. How did the women in cohorts 1 and 2 compared to the non-pregnant women of reproductive from that clinical trial?
Page 6, line 20: should say inquired not enquired

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.

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.

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.

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.

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.

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.

Reference 19 is incomplete.
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.
Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.
Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.
Yes

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