Author's response to reviews

Title: Safety of licensed vaccines in HIV-infected persons: a systematic review protocol

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Author's response to reviews: see over
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The Systematic Reviews Journal

Dear Editor:

Ref: MS1505622150129582-Response to reviewer comments

Thank you for re-reviewing our manuscript. The manuscript has continually benefited from the peer review process and we are very thankful.

We now trust the revised manuscript will receive a positive consideration to be published in your journal.

In this protocol, we propose to conduct a comprehensive and an up to date systematic review on the safety of vaccines administered to HIV-infected persons. We have narrowed our focus to safety following the comments we received from the previous reviewers.

Below, we have provided a point-by-point response to the reviewer comments.

Best regards,

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Title: Safety of licensed vaccines in HIV-infected persons: a systematic review
Protocol Version:3
Date:15 July 2014

Reviewer: Deepak Dr. Chawla
Reviewer's report:

Major compulsory revision:
1. Abstract: Background section can be shortened. For example lines like "The principle of effective immunization against potentially life-threatening infections is by induction of pathogen-immunity." can be deleted.

Response to comment 1: We agree to the suggestion by the reviewer. We have deleted this sentence in the abstract section of the revised manuscript. The deleted text can be viewed in the file we have submitted named: MS1505622150129582-marked-manu.docx

Main text:
2. In the revised version authors plan to evaluate safety profile of vaccines in HIV infected subjects. How RCTs and cRCTs will be used? Do authors plan to include RCTs comparing vaccination versus no vaccination arms of RCTs among HIV infected subjects? If there are no such trials how authors plan to compare the event rates among HIV infected subjects if rates in HIV uninfected are not studied. This issue is also relevant as plan of analysis is focused on comparisons in two arms.

Response to comment 2: RCTs and cRCTs will be used to assess the safety profile (rates of adverse events) between vaccinated and non-vaccinated groups or clusters. Our primary analyses will compare the safety profile of vaccines administered to HIV infected persons: vaccinated versus the control arm (unvaccinated). This type of study design will give us the strongest evidence on adverse events following immunization or no immunization in a homogeneous population of HIV infected persons. From our preliminary search, we are able to identify such studies.

However, we agree with the reviewer that studies on immunization of HIV-infected and uninfected may contribute to more information on the safety of adverse events following vaccination. We have therefore included a secondary analyses section that will compare the safety profile of vaccines administered to HIV infected and HIV-uninfected persons. Under the population subheading, we have added the following information on the inclusion of the studies for the secondary analyses:

“We will only include studies in which participants are HIV infected or both HIV-infected and uninfected. Included studies must have used defined and standard assays or tests to determine the HIV infection. Studies that evaluated the safety of the vaccines prior licensure will also be included provided the vaccines were later licensed”.

Studies that have assessed the safety of vaccines in HIV-uninfected persons only will not be included as there is many systematic reviews that have already addressed the safety of vaccines in HIV-uninfected persons, latest being a comprehensive study by Margaret A. Maglione, July 2014 in the Pediatrics journal of the American Academy of Pediatrics

(http://pediatrics.aappublications.org/content/early/2014/06/26/peds.2014-1079.full.pdf+html)

3. In my view more data may be available from ecological studies. For example what are vaccination adverse events in high HIV prevalence versus low HIV prevalence populations.

Response to comment 3: We will include ecological studies (which falls under observational studies). We have added this information in the “types of studies” section.

“Observational studies: case-series, interrupted time series (ITS), controlled before-and-after (CBA) studies, cohort studies, case-control studies, cross-sectional studies and ecological studies”.

We do not intend to compare adverse events following immunization in high versus low HIV prevalence settings because of the differences that exists in the monitoring of adverse events in these types of settings. Low HIV prevalence settings routinely have active adverse events monitoring settings, likely reporting more information regarding safety of vaccines than high HIV prevalence settings. These kind of comparisons will be affected strongly by the reporting bias, hence the decision not to do this analysis.

4. Do authors plan to assess safety profile of re-vaccination strategies or only primary vaccination schedules?

Response to comment 4: We plan to assess the safety profile of re-vaccination. We have clarified this plan by adding a secondary objective stating as follows:

“Secondary objective:
  1) To compare the safety profile of the WHO recommended vaccines re-administered to HIV-infected persons”

5. Some sections of background can be removed e.g. Page 4 para 4 last 2 lines (starting with Furthermore..); Page 6 para 2.

Response to comment 5: We agree to the suggestion from the reviewer. We have deleted this sentence in the background section of the revised
manuscript. In addition, we have deleted more sections as shown in the “MS1505622150129582-marked-manu.docx” file.

6. Primary objective is repeated as last line of background and then as a bullet point.

Response to comment 6: We have deleted this last sentence in the background section of the revised manuscript.

7. Table 1 seems to be irrelevant once effectiveness objective has been dropped.

Response to comment 7: We agree to this comment. We have deleted the table in the revised manuscript. The new Table 1 (initially table 2) now indicates the vaccines that we will focus on the review.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Response to comment 7

We have revised and corrected any grammatical errors.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Response to comment 7

Where applicable, we have added or deleted text to complement the change in objectives. Please see the file named “MS1505622150129582-marked-manu.docx” in the data analysis section for the changes that we have made.

Declaration of competing interests:

I declare that I have no competing interests