Author's response to reviews

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

Authors:

Benjamin M Kagina Dr. (bkagina@yahoo.com)
Charles S Wiysonge Prof. (charlesw@sun.ac.za)
Maia Lesosky Dr. (lesosky@gmail.com)
Shabir A Madhi Prof. (ShabirM@nicd.ac.za)
Gregory D Hussey Prof. (gregory.hussey@uct.ac.za)

Version: 3 Date: 3 July 2014

Author's response to reviews: see over
3 July 2014

The Systematic Reviews Journal

Dear Editor:

Ref: MS1505622150129582-Response to reviewers and editorial requests

Thank you for reviewing our manuscript. The manuscript has significantly benefited from the peer review process and we trust it is now ready for your consideration to be published.

Our revised manuscript is now titled “Safety of licensed vaccines in HIV-infected persons: a systematic review protocol” for publication in The Systematic Reviews Journal.

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

In separate files, we have provided a point by point response to the reviewers as well as the editorial requests.

Declaration by authors:

Professor Shabir Madhi agreed to donate R98,250 (USD 9,527) to Professor Gregory Hussey to help carry out the systematic review (please see attached letter)

Dr. Benjamin Kagina is funded by University of Cape Town to conduct the systematic review as part of the postdoctoral fellowship (Please see attached letter).

Professor Charles Wiysonge and Dr. Maia Lesosky do not have funding for this project.

All authors have approved the submission of the manuscript and declare that similar review has not been carried out previously.

We look forward to your reply.

Best regards,

Dr. Benjamin Kagina

Vaccines For Africa Initiative
Institute of Infectious Diseases and Molecular Medicine
University of Cape Town
N2.09A Werner and Beit Building
Anzio Road
Observatory 7925
South Africa
Email: bkagina@yahoo.com; bkagina@gmail.com; bm.kagina@uct.ac.za

Phone: +27 21 404 7736
Response to reviewer 1 comments (Regina El Dib):

Reviewer 1, comment 1:
When I first read the title "Safety, immunogenicity and effectiveness of licensed vaccines in HIV infected persons: a systematic review protocol" I thought the authors was planning to perform a systematic review in order to verify the effectiveness and safe of vaccines versus no intervention in the quality of life, adverse events, etc on HIV-infected patients. Besides that, in the abstract the authors mentioned "We are therefore conducting a systematic review to assess the vaccine safety, effectiveness and durability of protection in HIV-infected persons."...the authors never mentioned about non infected HIV person. However, throughout the background section I noticed that the authors will evaluate infected- and non infected- HIV persons. So, I am not sure whether the study design adequately test the authors's hypothesis because their objective is "Our aim is to compare the immune responses induced by vaccination between HIV-infected and uninfected persons." So, I wonder whether a systematic review of prognosis will be more adequate here taking into account that they have a case group (infected-HIV people) and a control group (non infected-HIV people) and the authors wish to verify the immune responses (outcome) from vaccination (an exposure factor). If this is the case, RCT is not the study design authors wish to identify and the authors should plan to do a prognosis SR.

Response to comment 1, reviewer 1
Thank you for this comment.

We have narrowed down our review to focus on the safety of vaccines in HIV-infected persons. We will not focus on the aspect of immune responses because a recent paper by Solen et al., 2014 has already addressed the question.

We agree with the reviewer’s comments that our study design is not adequate to address the research question if we are including the non-HIV infected persons. To address this comment, in our revised manuscript, we have stated that we will only focus on HIV-infected persons only. We will not focus on non-HIV infected participants.

Reviewer 1, comment 2:
At the last paragraph authors said "To understand the impact of HIV infection on the immunogenicity, persistence of vaccine-induced immunity as well as safety and effectiveness of vaccines, we will conduct a comprehensive systematic review focusing on children and older individuals." Here is the place where authors should make more explicit the aim of their study. Why don't say something like: we will conduct a prognosis systematic review to verify the patterns and safety profile of immune responses to the WHO recommended vaccines in HIV-infected persons and compared them in a non-infected population?

Response to comment 2, reviewer 1
Thank you for this comment.
We have revised this last sentence to explicitly state our aim of the study. Because we are not focusing on the immune response to vaccines anymore, we have changed this section to read as follows:

“As far as we know, there is no systematic review on the safety profiles of many routinely used vaccines in HIV infected persons. Therefore, we will conduct a systematic review to establish the safety profile of the WHO recommended vaccines in HIV-infected persons”.

Reviewer 1, comment 3:
Also, the authors proposed as a secondary objective to assess "the impact of ART, repeated vaccinations, nutritional supplementation and immunomodulatory agents on the vaccine-induced immunity in HIV infected persons" which now this is an interventional systematic review. I particularly disapprove the conduction of two different clinical questions (prognosis versus intervention) in one systematic review as for each clinical question we have different plans of actions in the study design, population criteria, statistical analysis and so on.

Response to comment 3, reviewer 1
Thank you for this comment.

We agree with the reviewer and we have addressed this. In our revised manuscript, we will only focus on the safety of the vaccines. We now do not have this secondary objective.

Reviewer 1, comment 4:
The authors mentioned "Additionally, there is insufficient evidence as to whether immunogenicity/effectiveness of vaccines specifically targeted at HIV infected adolescents/adults are immunogenic and efficacious in this group (compared to HIV uninfected)." How do authors know there is insufficient evidence on it if they haven't done a systematic review to scrutinize the literature yet and drawn a conclusion?

Response to comment 4, reviewer 1
Thank you for the comment.

Prior to submitting our protocol, we had not seen any published work on our proposed research question. However, Reviewer 2 has pointed to us recent systematic review by Solen et al., CID, 2014 that shows HIV-infection impairs long term vaccine induced immunity.

In our revised manuscript, we will only focus on the safety aspect of the vaccine administered to HIV infected persons and not on immune responses. As far as we know, there is no published systematic review on the safety of vaccines in HIV infected population.

Reviewer 1, comment 5:
In the item "Assessment of risk of bias in included studies", the authors said "The quality of studies will be assessed using the Cochrane Collaboration’s tool for assessing risk of bias for experimental studies and the Scottish Intercollegiate Guidelines Network (SIGN)
checklist for other study designs." Although they are corrected in the use of the Cochrane tool (Higgins 2011) to assess the risk of bias in RCTs included, why did they mention the SIGN checklist here? First, the SIGN has implemented the GRADE process, please see it: "As part of the changes related to GRADE, SIGN decided as of 2013 not to continue with the ABCD grading of recommendations that had been in use since 2001. Reasons for this decision are set out in a separate policy document." Second, one thing is to assess the risk of bias and, other is to rate the strength of evidence and drawn a conclusion based on some variables such as indirectness, heterogeneity, applicability and risk of bias which GRADE system provides it. So, accordingly to those variables (which include the risk of bias) one can drawn a conclusion and recommend the use of such an intervention from a very low evidence to a very high evidence. Furthermore, accordingly to GRADE system, authors will then downgrading the evidence based also in the design of the study (i.e., observational studies will not start from the very high evidence). So, authors have mixed between to grade evidence using a grading system and to assess the risk of bias using Cochrane tool.

Response to comment 5, reviewer 1

Thank you for the comment.

Our revised manuscript has specified we will use GRADE system to assess the quality of evidence. We will use the two systems (SIGN and GRADE) separately for different purposes and not mix them. We have added the following text to address this comment:

“We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of evidence (based on the clinical methods used to assess adverse events).”

Reviewer 1, comment 6:
Under "Sensitivity analysis" item, the authors also mixed the planned analysis between sensitivity (the effect of study designs) with a subgroup (immunological assays used and the geographical settings) analysis. I would suggest the authors to separate by clinical and methodological diversities.

Response to comment 6, reviewer 1

Thank you for the comment.

We agree with the reviewer. In the absence of immunological outcomes, diverse methods used to assess safety across studies are like to influence the summary of the findings. We will there conduct a sensitivity analysis with the variables that the reviewer has suggested.

Our revised statement now reads:
““We will conduct sensitivity analysis to establish if the meta-analysis results are influenced by clinical and methodological diversities”.

Reviewer 1, comment 7:
Why authors did not consider run the search on both EMBASE and LILACS?
Response to comment 7, reviewer 1

Thank you for the comment.

The Scopus database will index most if not all publications in EMBASE. Our university does not have a license for EMBASE but have a license for Scopus, hence our preference for the Scopus. The reason for us not selecting LILACS as one of our database is, most of the published full text work in this database is non-English and we are limited with funding for translation services. We will be able to access most of the LILACS indexed articles in our other selected databases.
Response to reviewer 2 comments (Deepak Dr. Chawla):

Reviewer 2, comment 1: Similar to what authors propose here, there has been a more recent attempt to look broadly at all the vaccines in HIV infected patients (http://www.ncbi.nlm.nih.gov/pubmed/24415637). Results of these studies need to be discussed while building rationale of the proposed study.

Response to comment 1, reviewer 2
Thank you for the comment and the reference, which we had missed out. Indeed, we have looked at this Solen et al., 2014 paper and the authors have addressed the immunological questions we had proposed to investigate. Therefore, we will limit our review to the safety of the vaccines, which Solen et al., did not address.

The title of our revised manuscript has now changed to “Safety of licensed vaccines in HIV-infected persons: a systematic review protocol”.

Reviewer 2, comment 2: Authors mention that they will include licensed vaccines only. Some of the studies may have been conducted when vaccines have not been licensed yet, but become licensed later on.

Response to comment 2, reviewer 2
Thank you for the comment.

We will also include studies that may have been conducted prior to the licensure, provided that the vaccines in these studies were later licensed. We have included a statement under population subheading to address the reviewer’s comment in the revised manuscript.

This section now reads as follows: “We will only include studies in which the participants are HIV infected, and which 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”.

Reviewer 2, comment 3: Do authors intend to compare studies which have included only HIV infected subjects with those studies which enrolled HIV uninfected subjects. This seems to be so when authors mention that "We will only include studies in which some or all the participants are HIV infected, and which clearly define the assays or tests that were used to determine the infection"

Response to comment 3, reviewer 2
Thank you for the comment.

This comment is similar to that of reviewer 1, comment 1 that we have already addressed as follows:

We agree with the reviewer’s comments that our study design is not adequate to address the research question if we are including the non-HIV infected persons. To
address this comment, in our revised manuscript, we have stated that we will only focus on HIV-infected persons only. We will not focus on non-HIV infected participants.

Reviewer 2, comment 4: Do authors plan to conduct subgroup analysis based on severity of HIV infection.

Response to comment 4, reviewer 2

Yes, we will conduct subgroup analysis based on the CD4 cell counts and viral load if we have sufficient number of studies reporting these variables. To address this comment, we have included the following statement under sensitivity analysis subheading:

“We will conduct sensitivity analysis to establish if the meta-analysis results are influenced by clinical and methodological diversities. Subgroup analysis based on the CD4 cell counts and the viral load may be conducted if we have sufficient number of studies reporting these variables”.

Reviewer 2, comment 5: How do authors plan to handle data from case control studies and case series. Plan of analysis based in RR may be too simplistic for the type of review planned. Similarly what approach will be used to handle confounding factors like PEM, age at HIV infection, co-morbidities like tuberculosis. This is especially important as I anticipate large proportion of the studies to be of non-RCT design. Doing subgroup analysis for all these confounders may be impractical.

Response to comment 5, reviewer 2

Thank you for the comment and suggestion.

We agree with the reviewer. We omitted to propose the use of mixed effects models that we anticipate to use. In our revised manuscript, we have addressed this comment under the data synthesis paragraph, which now reads:

“Where possible, mixed effects models will be used to adjust for confounding factors such as co-morbidities, HIV related protein and energy malnutrition (PEM)”.

Reviewer 2, comment 6: Role of each author in the study should be described more clearly.

Response to comment 6, reviewer 2

The role of each author is now added to the manuscript under the “Authors contribution section” which appears just before the references and read as following:

Authors’ contributions

“BMK developed the study protocol; will conduct the initial search, screening of the search outputs, data extraction, data interpretation and manuscript preparation. CSW guided the development of the study protocol and will be consulted on studies that need to be included. ML wrote the data management and statistical analyses sections. SAM guided protocol development, will be consulted on the interpretation of the results and preparation of the manuscript. GDH conceived the study, guided protocol development, will resolve disagreement on the selected studies for inclusion into the study, will be consulted with interpretation of results and preparation of the manuscript.”
All authors read and approved the final manuscript

Editorial requests:
1) Please include the email address of each author on the title page.

Response to editorial request 1:
The email address of all authors has now been added on the title page.

*Corresponding author: email address: bkagina@yahoo.com
Author’s email address: charlesw@sun.ac.za, lesosky@gmail.com, ShabirM@nicd.ac.za and gregory.hussey@uct.ac.za

2) Please move the competing interest section to just before the reference section.

Response to editorial request 2:
We have done this in the revised manuscript.

3) Please format your abstract correctly. The Abstract of the manuscript should not exceed 350 words and must be structured into separate sections: Background, the context and purpose of the study; Methods, how the study was performed and statistical tests used; Results, the main findings; Conclusions, brief summary and potential implications. Please minimize the use of abbreviations and do not cite references in the abstract. Systematic review registration, if your reports the results of a controlled health care intervention, please list your registry, along with the unique identifying number (e.g. Systematic review registration: PROSPERO CRD0123456789). Please note that there should be no space between the letters and numbers of your registration number.

Response to editorial request 3:
We have done this in the revised manuscript. The abstract has 312 words.

4) Please include your PROSPERO registration number at the end of your abstract. Alternatively, if you have not registered with PROSPERO then please mention this in your Methods section.

Response to editorial request 4:
We have included the registration number in the revised manuscript at the end of the abstract.

“Systematic review registration: PROSPERO CRD42014009794”

5) If applicable, please include an acknowledgement section at the end of the manuscript
before the reference list. Please acknowledge anyone who contributed towards the study by making substantial contributions to conception, design, acquisition of data, or analysis and interpretation of data, or who was involved in drafting the manuscript or revising it critically for important intellectual content, but who does not meet the criteria for authorship. Please also include the source(s) of funding for all authors. Authors should obtain permission to acknowledge from all those mentioned in the Acknowledgements. Please state clearly whether or not you have funding in the acknowledgement section. If there is no funding, please state this.

Response to editorial request 5:
We do not have anyone to acknowledge and therefore no acknowledgement section. However, we have added the source of funding as follows:

“Source of funding: BMK and GDH from the University of Cape Town. SAM from National Institute of Communicable Diseases (NICD)”.

6) Please include an Authors’ Contributions section at the end of the manuscript, before the reference list. Each author should be listed individually. We suggest the following kind of format (please use initials to refer to each author’s contribution): AB carried out the molecular genetic studies, participated in the sequence alignment and drafted the manuscript. JY carried out the immunoassays. MT participated in the sequence alignment. ES participated in the design of the study and performed the statistical analysis. FG conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

Response to editorial request 6:
We have done this in the revised manuscript and the added section reads as follows:

Authors’ contributions

“BMK developed the study protocol; will conduct the initial search, screening of the search outputs, data extraction, data interpretation and manuscript preparation. CSW guided the development of the study protocol and will be consulted on studies that need to be included. ML wrote the data management and statistical analyses sections. SAM guided protocol development, will be consulted on the interpretation of the results and preparation of the manuscript. GDH conceived the study, guided protocol development, will resolve disagreement on the selected studies for inclusion into the study, will be consulted with interpretation of results and preparation of the manuscript. All authors read and approved the final manuscript”

7) Please move the tables to after the reference section.

Response to editorial request 7:
We have complied to this request in the revised manuscript.
We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also highlight (with 'tracked changes/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

Please also ensure that your revised manuscript conforms to the journal style (http://www.systematicreviewsjournal.com/info/instructions/). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 12 July 2014. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.systematicreviewsjournal.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=1505622150129582. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

The Systematic Reviews Editorial Team

e-mail: editorial@systematicreviewsjournal.com
Web: http://www.systematicreviewsjournal.com/

To submit your revised manuscript

----------------------------------