PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Varicella Zoster Virus Associated Morbidity and Mortality in Africa: A Systematic Review Protocol
AUTHORS	Hussey, Hannah; Abdullahi, Leila; Collins, Jamie; Muloiwa, Rudzani; Hussey, Gregory; Kagina, Benjamin

VERSION 1 - REVIEW

REVIEWER	David Patrick University of British Columbia, Canada
REVIEW RETURNED	19-Oct-2015

GENERAL COMMENTS	I'm extremely puzzled as to why I am being asked to review a draft protocol where the work has not been done and there are no results to present. I would have thought this would have been weeded out at the editorial level. The manuscript consists of a fair description of a protocol, written in the future tense and clearly not actualized. Some of it is appropriate narrative but it lapses into point form, as though cut and pasted from a protocol. With respect to the protocol, it appropriately focuses on VZV incidence and prevalence, but does not mention morbidity from PHN - which is likely to be very important in the African context. The review of epidemiology in temperate countries seems to describe the pre-vaccine scenario. Additional minor points for BMJ open are that the authors treat the term "data" as singular rather than pleural, the continental comma is used in place of the decimal (this could be picked up by the editorial team) and there is some general sloppiness. For example, the Background section, 3rd para 2nd sentence – the term varicella is used when zoster is correct. Unless BMJ open has taken to publish notional protocols, I'm not sure why this is being considered.

REVIEWER	Elisabetta Franco Dept. of Biomedicine and Prevention University Tor Vergata Rome, Italy I have collaboration with Vaccine Producers: GSK, Pfizer and SanofiPasteurMSD, without receiving personal fees.
REVIEW RETURNED	16-Nov-2015

GENERAL COMMENTS	This is a well written study protocol and I have seen many study protocols published in the last period, even if I do not perfectly understand the meaning of this kind of papers. I agree that we have no good data about Africa but trying a research

	in Pub Med with the criteria described by the Authors the resulting papers are very few. It is possible that something more could result from local database and I Think this should be cited as a limitation of the work. Recently more data about VZV epidemiology in high income countries have been published but I do no completely agree that we have a large amount of epidemiological data on VZV (as stated in the discussion).

REVIEWER	Roger E. Thomas Department of Family Medicine, Faculty of Medicine University of Calgary, Calgary Alberta
REVIEW RETURNED	21-Nov-2015

GENERAL COMMENTS	Your text leads to the conclusion that you think you may not retrieve much data at low risk of bias. Your key contribution is to assess how much data at low risk of bias and comprehensively described is available as a guide to future vaccination campaigns. The yellow fever vaccination campaigns in West Africa demonstrated how much missing clinical and laboratory data were missing over all countries. Literature search. Will you use Google translator for articles in languages you do not read? 1. You need to include the full CDC varicella Case Classification and for each article independently copy verbatim the text that supports your judgment: Probable An acute illness with Diffuse (generalized) maculo-papulovesicular rash, AND Lack of laboratory confirmation, AND Lack of epidemiologic linkage to another probable or confirmed case. Confirmed An acute illness with diffuse (generalized) maculo-papulovesicular rash, AND Epidemiologic linkage to another probable or confirmed case, OR Laboratory confirmation by any of the following: Isolation of varicella virus from a clinical specimen, OR Varicella antigen detected by direct fluorescent antibody test, OR Varicella-specific nucleic acid detected by polymerase chain reaction (PCR), OR Significant rise in serum anti-varicella immunoglobulin G (IgG) antibody level by any standard serologic assay. Comments Two probable cases that are epidemiologically linked would be considered confirmed, even in the absence of laboratory confirmation. 2. Risk of Bias. Please explain why you chose Hoy's method. You need to independently copy text from the articles to justify your decisions. And report author agreement with kappas. Otherwise appointing a point here and not there will be arbitrary. I recommend you practice on a set of 10 or 20 articles. This potentially longer file

	could go on the website. Please document what you mean in the your sentence for 85 year olds 1/2 had "an episode of varicella"

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comment 1: I'm extremely puzzled as to why I am being asked to review a draft protocol where the work has not been done and there are no results to present. I would have thought this would have been weeded out at the editorial level. The manuscript consists of a fair description of a protocol, written in the future tense and clearly not actualized. Some of it is appropriate narrative but it lapses into point form, as though cut and pasted from a protocol.

Response to comment 1, reviewer 1: This manuscript is a protocol for a systematic review that has not yet been completed. The benefits of publishing the protocol and not just the final review have been addressed above in the response to the editorial comment 1.

Comment 2: With respect to the protocol, it appropriately focuses on VZV incidence and prevalence, but does not mention morbidity from PHN - which is likely to be very important in the African context.

Response to comment 2, reviewer 1: In the “Data collection process” section we have now added the following to address this comment: “the prevalence of complications of VZV not requiring hospitalization”. Collecting this data is aimed to pick up the rates of PHN.

In addition, we have added the following statement in the discussion section on page 14 of the revised manuscript: “Furthermore if the rates of VZV complications and/or hospitalization were found to be high, it would provide a strong evidence for wider accessibility of drugs like Acyclovir or those needed to treat post-herpetic neuralgia on the continent”.

Comment 3: The review of epidemiology in temperate countries seems to describe the pre-vaccine scenario.

Response to comment 3, reviewer 1: We have revised the sentence to read as follows: “Prior to widespread usage of vaccines against varicella in temperate high income countries, 13-16 cases of varicella per 1000 population occured annually, with mostly children aged 1-9 years affected” (page 4).

We believe this is an appropriate as the varicella and herpes zoster vaccinations are not routinely used on the African continent.

Comment 4: Additional minor points for BMJ open are that the authors treat the term "data" as singular rather than pleural, the continental comma is used in place of the decimal (this could be picked up by the editorial team) and there is some general sloppiness. For example, the Background section, 3rd para 2nd sentence – the term varicella is used when zoster is correct.

Response to comment 4, reviewer 1: We have revised these minor points as suggested by the reviewer. In the revised manuscript, the term “data” is taken as plural: e.g “There are little data” (page 5) and “there are no synthesized VZV-associated epidemiological data in Africa” page 6. Additional

changes have been made in the following sections: Abstract, Strengths and Limitations, Background, Data collection process, Risk of bias assessment and Discussion. The continental comma in the background section has been replaced with the decimal as suggested. The error in the background section has been corrected, with “herpes zoster” now replacing the term “varicella”.

Reviewer: 2

Comment 1: I agree that we have no good data about Africa but trying a research in Pub Med with the criteria described by the Authors the resulting papers are very few. It is possible that something more could result from local database and I think this should be cited as a limitation of the work.

Response to comment 1, reviewer 2: We agree with the reviewer. In the section subtitled Risk of bias of included studies, the following sentences have been added: “As there is no standardised data collection for VZV across the continent, data from national health departments will also not be used. The practical difficulties of collecting this data are a further reason for not collecting it and this is a limitation of our study.” In addition, this same point is listed in the section titled strengths and limitations.

Comment 2: Recently more data about VZV epidemiology in high income countries have been published but I do no completely agree that we have a large amount of epidemiological data on VZV (as stated in the discussion).

Response to comment 2, reviewer 2: We agree to the comment. The first sentence of the revised manuscript in the discussion section (page 14) has been changed, and now reads: “While there is a relatively large amount of epidemiological data on VZV in high income countries, there are only limited data from African countries.”

Reviewer: 3

Comment 1: Literature search. Will you use Google translator for articles in languages you do not read?

Response to comment 1, Reviewer 3: Yes, we will use Google translator to check if the abstracts or full texts appears to meet our study selection and inclusion criteria. If yes, we will then seek help from our collaborators who are in the research field and are native speakers of the non-English published article. Should this option not work, we will pay for the services of a professional translator. We have added the following statement to address this comment in page 9 of the revised manuscript: “Google translator software will first be used to enable preliminary screening of non-English records by titles or abstracts that appear likely to be included. If the article still appears likely for inclusion, then we will seek translation support from our network of collaborators who is a native speaker of the language used in the article. If unsuccessful with this option, then we will seek professional translation services”.

Comment 2: You need to include the full CDC varicella Case Classification and for each article

independently copy verbatim the text that supports your judgement:

We initially wanted to use the CDC case definition of varicella as one of the inclusion criteria for this study. On discussion among authors, there was a concern we could be excluding potentially important studies, including almost all published before CDC developed the guidelines in 1990. Because we are not anticipating to retrieve many relevant records in Africa for this study, we will conduct a sub-group analysis (we have added this on page 12) based on the case definition of individual studies, such as those that have used the CDC case definition. Nevertheless, we will document the case definition used in each included study (see Data collection process).

Comment 3: Risk of Bias. Please explain why you chose Hoy's method. You need to independently copy text from the articles to justify your decisions. And report author agreement with kappas. Otherwise appointing a point here and not there will be arbitrary. I recommend you practice on a set of 10 or 20 articles. This potentially longer file could go on the website.

Response to comment 3, reviewer 3: We will use a modified Hoy's method due to its simplicity in scoring that results to a high degree of agreement. Hoy's method has been tested successfully in a prevalence systematic review, a type of systematic review that is similar to our study. To the best of our knowledge, there are very limited tools to assess and score the risk of bias in prevalence studies.Risk of bias assessment for all the studies will be done independently by the first and second authors.

We are thankful to the suggestion of generating a kappa analysis for the two reviewers. We have therefore added the following statement: “Two authors (HSH and LHA) will independently score the risk of bias using the tool and a Kappa agreement will be calculated” (page 11).

Comment 4: Please document what you mean in the your sentence for 85 year olds 1/2 had "an episode of varicella"

Response to comment 4, reviewer 3: Thank you for this correction. This was an error, where the term “varicella” was used instead of “herpes zoster”. This has now been corrected (see response to comment 4 by Reviewer 1). The sentence has also been edited for clarification and now reads: “half of all 85 year old individuals have experienced an episode of herpes zoster”.

VERSION 2 – REVIEW

REVIEWER	Roger E Thomas Department of Family Medicine, Faculty of Medicine, University of Calgary, Alberta, Canada
REVIEW RETURNED	07-Jan-2016

GENERAL COMMENTS	An important topic, good literature review, and well presented. The choice of a risk of bias tool is important. May I suggest you independently score e.g., 10 articles with the Newcastle-Ottawa and the Hoy and determine which does the most accurate job in assessing risk of bias. You don't actually mention that you will independently extract data into the data extraction form. This is an important guarantee of

	accuracy. I understand that you are following the CDC definition (good). What will you do with cases where there is a clinical description but no laboratory confirmation? Discard them?

VERSION 2 – AUTHOR RESPONSE

Comment 1:
The choice of a risk of bias tool is important. May I suggest you independently score e.g., 10 articles with the Newcastle-Ottawa and the Hoy and determine which does the most accurate job in assessing risk of bias.

Response to comment 1:
We agree that the choice of a risk bias tool is important. The Newcastle-Ottawa Quality Assessment Tool is used to evaluate non-randomised studies and has specific scales for cross-sectional and cohort studies. The tool developed by Hoy et al is partly based on the Newcastle-Ottawa Quality Assessment Tool, but adapted specifically for prevalence studies, which will most likely form the bulk of studies included in this review. We, therefore, believe it is appropriate to use only Hoy's risk of bias tool.

Comment 2:
You don't actually mention that you will independently extract data into the data extraction form. This is an important guarantee of accuracy.

Response to comment 2:
This is now stated explicitly in the latest draft. The first sentence of the “Data collection process” section now reads:
“Data will be independently extracted from the included studies by two reviewers, and recorded on a pre-designed form.”

Comment 3:
I understand that you are following the CDC definition (good). What will you do with cases where there is a clinical description but no laboratory confirmation? Discard them?

Response to comment 3:
The CDC case definition states that “laboratory confirmation of cases of varicella is not routinely recommended; laboratory confirmation is recommended for fatal cases and in other special circumstances” (1).

We will, therefore, not exclude studies that do not have laboratory confirmation. We will however note what exact case definition was used in each study. This information will be used as described in the “Subgroup analysis” section of our manuscript on page 12:

“The findings from each country will be reported separately as part of a subgroup analysis. In addition, further subgroup analyses will be conducted, where sufficient data exist, based on whether the study was conducted in the community or in a healthcare centre, the income status of the countries as classified by the World Bank, national background HIV/AIDS prevalence rates, case definition criteria and geographical setting or population density (urban vs rural settings).”

Reference:
1. Varicella | 2010 Case Definition [Internet]. [cited 2016 Jan 10]. Available from: http://wwwn.cdc.gov/nndss/conditions/varicella/case-definition/2010/

VERSION 3 - REVIEW

REVIEWER	Roger E Thomas University of Calgary, Calgary, Canada
REVIEW RETURNED	24-Jan-2016

GENERAL COMMENTS	This will be a helpful publication. You have still not justified your choice of a risk of bias tool, and choice of tool is crucial in sifting the evidence in the most appropriate manner..

VERSION 3 – AUTHOR RESPONSE

Comment 1:
Please state any competing interests or state 'None declared': None

Response to comment 1:
We already have the competing interest section in the manuscript (page 16). This section reads as follows:
"Competing interests: All authors have no competing interests."

Comment 2:
You have still not justified your choice of a risk of bias tool, and choice of tool is crucial in sifting the evidence in the most appropriate manner.

Response to comment 2:
The tool developed by Hoy et al is designed to measure bias in prevalence studies. It was formulated after an extensive literature review to identify potentially relevant items followed by an expert consensus exercise (1). The tool is relatively easy to use and has high levels of proven inter-rater agreement (1). While there are other tools available to assess study quality, those that are relevant to prevalence studies, are generally considered unsatisfactory and would require further refinement before we could use them. Several other systematic reviews looking at prevalence have made use of the tool by Hoy. A quick search on Pubmed shows at least 13 systematic reviews on disease prevalence that have used this tool.

We agree with the reviewer. The choice of a risk of bias tool is crucial and need to be justified. To address this comment, we have included a new paragraph to justify the choice of the tool on page 11 of the revised manuscript, as shown below:

"From the several quality assessment tools available, we chose to adapt the tool developed by Hoy et al for the following reasons: 1) it is specifically designed for prevalence studies; 2) it is an improved tool developed after a rigorous published process, including a review of the limitations of the existing tools; 3) detailed criteria to use the tool are provided, making it easier to use; 4) it has a high inter-

rater agreement; and, 5) it is robust in application, and for example can be used alongside the latest tool developed by the Joanna Briggs Institute (JBI) and the Cochrane Collaboration" (1,2).

References

1. Hoy D, Brooks P, Woolf A, Blyth F, March L, Bain C, et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012 Sep;65(9):934–9.
2. Munn Z, Moola S, Riitano D, Lisy K. The development of a critical appraisal tool for use in systematic reviews addressing questions of prevalence. Int J Health Policy Manag. 2014 Aug 13;3(3):123–8.