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) | Post-Licensure Herpes Zoster Vaccines Effectiveness: Systematic Review Protocol |
|---------------------|----------------------------------------------------------------------------------|
| AUTHORS             | Mbinta, James; Nguyen, Binh; Awuni, Prosper Mandela; Eme, Paul; Simpson, Colin |

VERSION 1 – REVIEW

| REVIEWER            | Barbara P Yawn, MD MSc University of Minnesota, USA |
|---------------------|-----------------------------------------------------|
|                     | I have served as a consultant for GSK on several studies of the epidemiology of herpes zoster. I have a GSK investigator initiated grant on herpes zoster immunization rates and interest in people with COPD and health care professionals caring for people with COPD. |
| REVIEW RETURNED     | 20-Sep-2020 |

GENERAL COMMENTS

This is an important undertaking. However, you have not defined the countries in which each of the vaccines is approved and available. This is a critical point since the ZVL has just been announced to be no longer distributed in the US. Your manuscript appears to be very US centric for the initial data---there are about 1 million case of HZ in the US alone--however, you do not say that in the introduction. In the list of comparators--what is the difference between no vaccination and no vaccine. You do not list incomplete vaccination and this is important since the recombinant vaccine is a two dose vaccination and incomplete vaccination--failure to get second dose may be more common in observational studies that in the trials. There is no comment on time since vaccination and that is very important and a distinguishing feature between the two available vaccines. In the introduction, a comment is made about the reactogenicity or side effects but this is not commented upon in the data extraction or outcomes. The PHN outcome says it will be assessed at 30, 60 and 90 days but in Appendix II you correctly identify PHN as pain after 90 days so that the data for 30 and 60 should not be considered PHN data. There is not comment on trying to supplement incomplete data by contacting authors. Using GRADE will should low levels of evidence by definition since you are looking at observational work and GRADE put this at a low level even though in the case of effectiveness--RCTs are not appropriate study design by definition.

| REVIEWER            | Sinéad Langan LSHTM, UK |
|---------------------|--------------------------|
| REVIEW RETURNED     | 25-Sep-2020              |
This protocol is interesting and important. I had a number of considerations to highlight.

1. The authors mention the need to focus on observational studies but don't fully justify the need to do this. The impression I get is that the reason for focusing on observational studies is that real world effectiveness may be different to the efficacy observed in trials, but it would be good to very clearly say this and justify in terms of both assessment of VE and external validity.
2. It would also be good to clearly state that assessment of the effectiveness of the two vaccines would be analysed separately as existing evidence suggests VE is likely to very different for the two zoster vaccines.
3. It would be useful to have some justification for using the appraisal tool for experimental studies. Why this approach as opposed to tools for observational studies?
4. Some further justification for the use of random effects MA would help.
5. Some of the terminology might benefit from modification. The terms effectiveness and efficacy are used interchangeably. The term retrospective is used instead of historical (STROBE recommendation)

| GENERAL COMMENTS |
|--------------------------------------------------|
| This protocol is interesting and important. I had a number of considerations to highlight. |
| 1. The authors mention the need to focus on observational studies but don't fully justify the need to do this. The impression I get is that the reason for focusing on observational studies is that real world effectiveness may be different to the efficacy observed in trials, but it would be good to very clearly say this and justify in terms of both assessment of VE and external validity. |
| 2. It would also be good to clearly state that assessment of the effectiveness of the two vaccines would be analysed separately as existing evidence suggests VE is likely to very different for the two zoster vaccines. |
| 3. It would be useful to have some justification for using the appraisal tool for experimental studies. Why this approach as opposed to tools for observational studies? |
| 4. Some further justification for the use of random effects MA would help. |
| 5. Some of the terminology might benefit from modification. The terms effectiveness and efficacy are used interchangeably. The term retrospective is used instead of historical (STROBE recommendation) |

| VERSION 1 – AUTHOR RESPONSE |
|--------------------------------------------------|
| Reviewer: 1 |
| Comments to the Author |
| [1] This is an important undertaking. However, you have not defined the countries in which each of the vaccines is approved and available. This is a critical point since the ZVL has just be announced to be no longer distributed in the US. |
| Answer |
| This sentence has been added: "These vaccines have been licensed and marketed in many high-income countries like the United States, New Zealand, Australia, Germany, Canada, France, and Japan" (page 4) |
| Details of zoster vaccination are presented in a new table titled “Zoster Vaccination” (Supplementary File, Appendix I) |
| [2] Your manuscript appears to be very US centric for the initial data---there are about 1 million case of HZ in the US alone--however, you do not say that in the introduction. |
| Answer |
| This sentence has been added: “It is estimated that each year there are one million cases in the USA, 130,000 new cases in Canada, and more than 1.7 million cases in Europe. In New Zealand, more than 9,000 zoster hospitalisations have been recorded in the past 10 years" (page 3). |
| [3] In the list of comparators--what is the difference between no vaccination and no vaccine. You do not list incomplete vaccination and this is important since the recombinant vaccine is a two dose vaccination and incomplete vaccination--failure to get second dose may be more common in observational studies that in the trials. |
| Answer |
We have clarified that incomplete vaccination will be considered in this review: "Incomplete vaccination (failure to get the second dose of recombinant vaccine) will be considered unvaccinated" (page 7).

[4] There is no comment on time since vaccination and that is very important and a distinguishing feature between the two available vaccines.

Answer
We have added the following in the introduction: “The effectiveness of ZVL against an episode of HZ decreases gradually after vaccination, from 69% to 50% during the first year to about 17% by the seventh year after vaccination.” (page 4).

Also, we have added the following in the data analysis: “We will assess pooled vaccine effectiveness by the vaccine type, time since vaccination, disease (zoster, PHN, herpes zoster ophthalmicus etc), and by study design.” (page 10).

[5] In the introduction, a comment is made about the reactogenicity or side effects but this is not commented upon in the data extraction or outcomes.

Answer
Adverse event following vaccination is not an outcome of interest in this planned systematic review. The comment made about side effects has now been removed. (page 4).

[6] The PHN outcome says it will be assessed at 30, 60 and 90 days but in Appendix II you correctly identify PHN as pain after 90 days so that the data for 30 and 60 should not be considered PHN data.

Answer
The PHN outcome has been modified to read as "Incidence of Postherpetic neuralgia (entire duration of follow-up): 90 days; Number of cases and person-years; Incidence rate per arm.” (page 7).

[7] There is not comment on trying to supplement incomplete data by contacting authors.

Answer
There is a comment on contacting authors in two sections (Assessment of methodological quality; Data extraction)
“Authors of papers will be contacted to request missing or additional data for clarification, where required.” (page 9).

[8] Using GRADE will should low levels of evidence by definition since you are looking at observational work and GRADE put this at a low level even though in the case of effectiveness--RCTs are not appropriate study design by definition.

Answer
We consulted one of the developers of JBI SUMARI, Assoc Prof Zachary Munn (Director Transfer Science, Director JBI Adelaide GRADE Centre, Joanna Briggs Institute), he advised that GRADE can be used for observational studies.

Reviewer 2
Comments to the Author
This protocol is interesting and important. I had a number of considerations to highlight.

[1] The authors mention the need to focus on observational studies but don't fully justify the need to do this. The impression I get is that the reason for focusing on observational studies is that real world effectiveness may be different to the efficacy observed in trials, but it would be good to very clearly say this and justify in terms of both assessment of VE and external validity.

Answer
"There is a need for a systematic review that will summarise real-world evidence of the effectiveness of herpes zoster vaccines from post-licensure studies with different designs, conducted in different populations. Vaccine performance has been shown to vary in routine public health practice (under
real-world conditions). Vaccine effectiveness (may be different from efficacy observed in trials) is influenced by host factors (age, comorbidity, previous exposure, co-administered vaccines and drugs and time since vaccination), vaccine characteristics (mode of administration, vaccine type and composition), and epidemiological factors (circulating strains, the force of infection and herd immunity). Vaccine effectiveness (protection attributable to a vaccine administered under field conditions to a given population) measured by observational post-licensure studies is important to inform public health programs and policies. The evidence will be obtained by searching, critically appraising, and synthesising the evidence from observational studies of published, and unpublished literature.” (page 5).

[2]. It would also be good to clearly state that assessment of the effectiveness of the two vaccines would be analysed separately as existing evidence suggests VE is likely to very different for the two zoster vaccines.

Answer
"We will assess pooled vaccine effectiveness by the vaccine type, time since vaccination, disease (zoster, PHN, herpes zoster ophthalmicus etc), and by study design." (page 10).

[3]. It would be useful to have some justification for using the appraisal tool for experimental studies. Why this approach as opposed to tools for observational studies?

Answer
Following consultation with Assoc Prof Zachary Munn (Director Transfer Science, Director JBI Adelaide GRADE Centre, Joanna Briggs Institute), the appraisal tools have been changed. "Eligible studies will be critically appraised by two independent reviewers at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for Cohort and case-control studies (Appendix IV). This will help us assess how each study has addressed bias in its design, conduct and analysis.” (page 9).

[4]. Some further justification for the use of random effects MA would help.

Answer
"Statistical analyses will be performed using a random-effects model. We will be reviewing studies that compare the proportion of people developing zoster in vaccinated and unvaccinated groups. We expect the effect sizes (OR, RR etc) to be similar but not the same. The effect size may vary depending on age and mix of participants, health status, and programme implementation. Hence the random-effects model (rather than the fixed-effect model) is more appropriate.”(pages 9 & 10).

[5]. Some of the terminology might benefit from modification. The terms effectiveness and efficacy are used interchangeably. The term retrospective is used instead of historical (STROBE recommendation)

Answer
We have used effectiveness throughout the manuscript (where it is applicable). Also, the term retrospective has been changed to historical: “This review will consider analytical observational studies including prospective and historical cohort studies, and case-control studies”. (page 7).

6. IN
Answer
We were unable to respond to this point but would be happy to provide a response with further clarification.

**VERSION 2 – REVIEW**

| REVIEWER | Barbara Yawn |
|----------|--------------|
|          | University of Minnesota, USA |
Have GSK grant related to HZ and COPD and have served as a consultant for both GSK and Merck related to vaccines and cost effectiveness.

**REVIEW RETURNED**
28-Nov-2020

**GENERAL COMMENTS**
You have adequately addressed the concerns and the information will add to the general literature.

**REVIEWER**
Sinead Langan
London School of Hygiene and Tropical Medicine

**REVIEW RETURNED**
23-Dec-2020

**GENERAL COMMENTS**
You have adequately addressed the concerns and the information will add to the general literature.

 reviewers: 2

[1] In addition to the discussions of bias, it would be good to consider and mention confounding. This would be helpful in the bulleted limitations summary at the start, in the assessment of methodological quality and in describing the data extraction process.

Answer

The last sentence of the bulleted limitations has been modified “Observational studies may produce evidence of possible bias and confounding.” (page 3)

Also, the Assessment of Methodological Quality section has been modified “Most observational studies are carried out using population-based databases that reflect daily medical practice. Potential confounding is common in studies of associations between vaccination and zoster using large databases. Predetermined data collection, absence of researcher control, completeness of recorded information, and misclassification can potentially affect the interpretation of any observed associations.” (page 9)

[2] There is no stated exclusion of immunosuppressed populations- it would be good to consider extracting information on immunosuppression and stratifying if appropriate, acknowledging that live vaccines such as Zostavax will be contraindicated in very immunosuppressed individuals.
Answer

The data extraction section has been modified by adding this sentence “Information on immunosuppression will also be extracted and stratified if appropriate.” (page 9).

The data analysis section has also been modified “We will assess pooled vaccine effectiveness by vaccine, time since vaccination, disease (zoster, PHN, herpes zoster ophthalmicus etc), immune status, and by study design. (page 10)

VERSION 3 – REVIEW

| REVIEWER           | Sinead Langan                        |
|--------------------|--------------------------------------|
|                    | The London School of Hygiene and Tropical Medicine, UK |

| REVIEW RETURNED    | 20-Jan-2021 |

| GENERAL COMMENTS   | The authors have responded to reviewers comments and the protocol is clear and addresses an important research question. I have no further comments. |
