Author’s response to reviews

Title: Burden of varicella in Latin America and the Caribbean: findings from a systematic literature review

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Author’s response to reviews:

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Dear Editors

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Manuscript title: Burden of varicella in Latin America and the Caribbean: findings from a systematic literature review.

Thank you for the reviewer comments on our manuscript. As you requested, we are pleased to submit a point by point response to the reviewer comments and a clean version of the revised manuscript.
Thank you very much

Yours sincerely

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Reviewer reports:

Hannah Hussey (Reviewer 1):

This is a well-written review article. My main concern is that the methodology is not completely clear and systematic at all times. 24 articles were found in an appropriately systematic manner. Then an additional 6 Spanish articles were added, that were not picked up in the initial literature search. I appreciate that South America is producing research in English, Spanish and Portuguese and that this will make collating the data from the continent difficult. But how do we know that there were not more Spanish language articles that were eligible to be included, but were not, as they were not recommended by scientific leaders in LAC, like the 6 articles were?

Author reply: Thank you for your comments. We confirm that the searches for this systematic literature review were performed on the English-language literature (as described in the protocol in the supplement) and that scientific leaders in LAC who were coauthors on this paper were requested to identify additional publications in Spanish and Portuguese (please see manuscript page 7, line 2). These authors identified six Spanish/Portuguese six papers during preparation of the manuscript, as you mention. They now confirm – on reviewing this manuscript for resubmission – that no additional relevant papers in Spanish or Portuguese are considered relevant for inclusion.

In addition a number of studies and other sources of data were identified in the grey literature. How many exactly? If you are reporting their findings as part of the review results, they (along with the 6 Spanish articles), need to be indicated in the PRISMA diagram. It would also helpful
when reporting the results to make it explicit, if the data you are discussing is from the systematic review, the 6 extra articles, or the grey literature, as they are all discussed together and it is at times difficult to find out what information came from where.

Author reply: There are 71 references included in our review in total, including 24 papers identified during searches for the systematic literature review, six papers in Spanish/Portuguese identified by scientific leaders in LAC, and the remaining 41 sources of gray literature. In our view, it is appropriate that the PRISMA diagram is limited to papers identified during searches for the systematic literature review. We have adopted the approach in each section of discussing first the published papers and secondly the gray literature. For each section, we have mentioned where the discussion of the gray literature begins. We believe that this approach is preferable for greater readability than identifying every source as either a published paper or gray literature.

A systematic review looking at the epidemiology of varicella in South America was published by Bardach in 2012. It is now 6 years old and requires updating. How does this review tie in with the previous one? What does it add? Does it support the findings or Bardach or not?

While this study is not deeply flawed, it still has limitations, and these need to be discussed at some point please.

Author reply: We refer to the Bardach publication in our manuscript. As you mention, the Bardach paper was published in 2012. While both the Bardach and our paper conclude that there is limited information in LAC on the epidemiology and resource use for varicella, our paper includes approximately 60 publications dated subsequent to Bardach et al and is therefore more topical – particularly in regard to the data on vaccination. Specifically, we have cited new studies reporting on seroprevalence in the region in the prevaccination era, the doses and schedules of vaccination in LAC, the incidence of varicella before and after the introduction of vaccine in the region, complications before and after introduction of varicella vaccine, the economic burden of varicella infection and the cost-effectiveness of vaccination relating to health resource utilization and hospitalization. We have added new text at the start of the Discussion on page 24, line 26: “This review highlights the substantial clinical and economic burden of varicella in the LAC region in the absence of UVV, supplementing previous data published in 2012 from Bardach et al [11] with significant new data on seroprevalence and economic burden, implementation of varicella vaccination programs across the region, and evaluation of the implementation of UVV.”

SPECIFIC COMMENTS

Abstract, page 2 line 18: This is a key point, but there is no mention of it in either the results or discussion. Was any evidence found to suggest that the age of varicella onset has increased?
Author reply: We found no data to support an age-shift in varicella infection following vaccination in the studies investigated in LAC. We note that the recent paper by Baxter et al (Pediatrics. 2014 Jul;134(1):24-30) identified no evidence for an age-shift in a 15-year US study. The Abstract text is now amended to: “to prevent any potential for age-shifts in varicella infection”.

Methods, page 6, line 14: The fact that you have stated you will include individuals of any race, suggests that you think there is a race-based difference in varicella epidemiology that you have chosen to disregard. What is that difference?

My own preferred wording here would be “(1) Included individuals of all ages who had primary…” But I will leave this to the authors’ discretion.

Author reply: Please note that the study eligibility criteria were developed to be applicable to the systematic literature reviews that are being developed and published for four global regions, of which LAC is one. We therefore recommend to retain the current text.

Methods, page 7, line 7: What additional sources?

Author reply: The additional sources are listed in the second part of this sentence: “Ministry of Health websites for LAC countries, World Health Organization and Pan American Health Organization (PAHO) websites, SLIPE data review/position papers, and congress presentations”. Specific references to each of these sources is provided in the later manuscript sections.

Results, page 9, line 4: If a total of 30 studies were included, 6 (20%) were not identified in a systematic reproducible manner. I understand that the review was conducted in English, and that these extra 6 studies were in Spanish.

I am not familiar enough with the continent of South America to know what proportion of its research output is in English compared to Spanish, or what proportion of its Spanish research gets translated into English and listed on English language databases. And while I accept that English is most commonly used in health research globally, is there a justification for not performing a systematic Spanish language literature search when looking for data from South America?

Author reply: To perform an additional systematic review now to identify Spanish/Portuguese published papers would entail a delay in publication and – as mentioned above – is not considered likely to identify relevant papers in addition to those identified by the scientific leaders who are authors of this paper.

Results, page 12, line 1: Was any explanation given for this increase? Was it improved reporting or a true increase in incidence?
Author reply: The authors of this abstract (León-Castañeda et al) do not offer an explanation for the increase in varicella cases over time in Columbia.

Results, page 14, line 10: If 40% had uncomplicated varicella – why were they admitted to hospital then? The data from Argentina with 99% of inpatients having complications from varicella, and hence warranting their admission, sounds more reasonable. The next study from Peru also seems to imply that only complicated varicella was admitted to hospital.

Author reply: While the authors describe the reasons for hospitalization of the 60% of patients who had complications, they do not detail the reasons for hospitalization of the remaining 40% who were without complications.

Results, page 16, line 5: Pneumonia and encephalitis are two separate clinical entities that each could cause death in varicella.

Author reply: We adapted the exact wording in the original text, which was “encephalitis associated to pneumonia”.

Discussion, page 24, line 24: A systematic review of varicella epidemiology in LAC was published by Bardach in 2012. What does this review add, apart from being more up to date? Do the findings in this review support that of Bardach or were there any significant differences?

Author reply: Please see our reply above.

Discussion, page 26: line 5: Limitations of Study?

Author reply: Thank you - we have added a limitations section as requested, on page 26 line 7: “There are a number of limitations in our review relating to the interpretation of the burden of varicella in LAC: the paucity of published data in LAC, a high likelihood that the data available is an underestimate of the burden and costs of varicella, and the fact that many countries in LAC are not represented in the manuscript at all, as no data have been collected or analyzed.”

Conclusions, page 26, line 18: While it is beyond the scope of this article to assess the epidemiology of herpes zoster, some mention must be made of this disease, as the two are so intricately linked.

As there been any review looking at the epidemiology of herpes zoster in LAC, particularly in the vaccine era, where the concern is that varicella vaccination could increase the incidence of herpes zoster? Are LAC countries routinely vaccinating against zoster?

Author reply: There are no recent epidemiological studies published on herpes zoster that we identified. Rampakakis (2017 Int J Infect Dis. 2017 May;58:22-26) recently reported on the economic burden of HZ in LAC, but includes no local epidemiological data. We note that, in addition, that it is very difficult to study HZ in the elderly.
Meru Sheel (Reviewer 2):

This systematic review assesses the burden of varicella zoster virus/ varicella in Latin-America and Caribbean countries. Noting limited published data - the authors have attempted to summarise the data to the best of their possible knowledge. The SLR provides critical information that advocates for the LAC countries to implement universal vaccination for varicella. Overall, the article is well written; but some issues need to be addressed before it can be published.

The discussion needs a little more explanation on under-ascertainment and explanation around countries for which data is not available.

Author reply: Please see the suggested text on limitations now added on page 26, line 7, which mentions the paucity of published data in LAC, a high likelihood that the data available is an underestimate of the burden and costs of varicella, and the fact that many countries in LAC are not represented in the manuscript as no data have been collected or analyzed.

SPECIFIC COMMENTS

Background, page 4, line 5: what about that against severe varicella?

Author reply: The paper by Marin et al does not provide data on the two-dose estimate of vaccine effectiveness relating to severe varicella.

Background, page 4, line 16: out of how many countries? are there plans for other countries to introduce?

Author reply: Our study investigated a total of 35 countries in LAC (now mentioned on page 4, line 16), of which 14 have implemented universal varicella vaccination. The known vaccination programs are listed with available updates in Table 2. At this time, no other known introductions are planned but numerous countries in the region are considering introduction. We have added an addition to the text on page 4, line 22: “Currently, 80% of each birth cohort in South America, but only 20% of each birth cohort in Central America and the Caribbean, have access to universal varicella vaccination.“

Background, page 5, line 8: what about other LAC?

Author reply: Other LAC countries besides those listed in Table 2 have not implemented UVV to our knowledge.

Methods, page 7, line 8: need references
Author reply: Please note that references to LAC Ministry of Health websites, World Health Organization and Pan American Health Organization (PAHO) websites, SLIPE data review/position papers, and congress presentations are provided later in the manuscript within the specific relevant sections. We have added “(as cited below)” on page 7, line 10.

Methods, page 8, line 8: what is the source for these figures? need appropriate referencing

Author reply: The sources for the currency conversion data are the CCEMG - EPPI-Centre Cost Converter (https://eppi.ioe.ac.uk/costconversion/default.aspx) and the CPI Inflation Calculator (https://www.bls.gov/data/inflation_calculator.htm). These citations are now added into the manuscript (page 8, line 10).

Results, page 16, line 12: this is surprising - as even if there is no vaccination data available - if there is herd immunity; a reduction in number of deaths is anticipated ---- additional plausibility -- coverage?

Author reply: The vaccine in use was primarily the MAV strain vaccine and the efficacy of this vaccine against severe disease is not known.

Results, page 19, line 25: how has this been estimated? what does societal cost include/ estimate?

Author reply: The original paper states that: “The analysis was conducted from both the healthcare system perspective, including all direct medical costs (outpatient health-care facilities visits, laboratory tests, prescription medications and hospitalizations), and the societal perspective, incorporating non-medical and productivity costs, regardless of who incurs them.” The text is modified on page 19, line 25 accordingly.

Discussion, page 25, line 3: and data on all LAC are not available/ included? some of the lower economic countries are missing from this...

Author reply: We have added “where such data are available” as requested (page 25, line 6).

Discussion, page 25, line 15: although no evidence of reduced mortality?

Author reply: Unfortunately, as mentioned on page 15, line 16, limited data are available from published studies on the mortality associated with varicella both pre- and post-vaccination.

Figures, Figure 1: edit legend --- map includes non-LAC countries?

Author reply: The figure legend is now edited as requested with the addition of “and North America”.

Figures, Figure 10: this figure almost feels redundant
Author reply: We recommend to retain this figure. Figure 10 refers to Argentina, while Figure 9 refers to Brazil, Figure 11 refers to Costa Rica, and Figure 12 refers to Uruguay. The figures look similar, but derive from different countries.

Figures, Figure 11: is this data available in rates? number of cases not very helpful

Author reply: This is the figure as originally published and additional data on rates are not provided in the original manuscript.