Author's response to reviews

Title: Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries.

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Author's response to reviews: see over
Title: Systematic review of studies evaluating the broader economic impact of vaccination in low and middle income countries.

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We thank the two reviewers for their positive comments, and have revised the manuscript to address the issues raised by the first reviewer. In addition, we have shortened existing parts of the manuscript slightly in order to incorporate the additional material. All revisions are highlighted in yellow in the latest version of the manuscript.

Specific responses to comments are also listed below in point form:

Minor Issues Not For Publication:

“• Abstract: Results: Twenty-six requires a dash between twenty and six.

• Conclusion: Paragraph Five: non-monetary either requires a dash, or can be written as one word (nonmonetary)

• Acknowledgements: the ‘to’ is missing in ‘we would like TO thank the...’”

Corrections to the above have been made.

Major Compulsory Revisions:

1. The authors indicate in the first paragraph of the Results that half the studies incorporated both narrow and broad economic benefits of vaccination, while the other half solely incorporated broader benefits. Table 1, which categorizes the benefits of vaccination is indeed a helpful table, however this reviewer was unable to identify where and how the authors defined narrow versus broad benefits. A definition of the authors’ delineation between narrow and broader benefits is critical to this paper.
This is an interesting question, as the distinction between narrow and broad benefits is not well defined in the literature (eg. Barnighausen et al). We have added a working definition to paragraph 1 of the methods section:

“For the purpose of this review, “narrow benefits” are defined as health effects, healthcare costs and short-term productivity losses to patients and caregivers. These benefits are typically incorporated into economic evaluations. They are generally short-term (lasting not much longer than the duration of the illness and its sequelae) and are restricted to the vaccinated individual and closely related individuals (such as caregivers). “Broader” benefits are defined as potential benefits of vaccination aside from these; they typically involve longer term effects and/or wider externalities.”

This definition is consistent with that expressed by other authors in recent studies (Barnighausen et al), although it is more explicit than the definitions in the existing literature.

We have also revised the abstract to specify the “broader” benefit categories.

2. Paragraph Two in the Methods section did not specify the number of reviewers identifying studies for inclusion.

We have added the following to the authors’ contribution section to explain the authors who contributed to each step of the review process:

“The search filters were developed by RD and reviewed by MJ. Initial categorisation of search results based on title and abstract and the subsequent review of articles for inclusion was conducted by RD. The final list of included articles was reviewed by MJ and RH. RD reviewed the shortlisted articles with input from MJ, RH, IvdP and SE.”

3. The article did not indicate how many of the final 26 articles included were identified from the grey literature reports and working papers. It is important to clarify for the purposes of reproducibility if indeed all 26 were found through Medline, Econlit and NHSEED searches.

The following statement has been inserted in paragraph 1 of the results section – “Three of these 26 studies were grey literature reports or working papers and were not retrieved from a database [29, 31, 32].”
4. It would be helpful to readers to understand whether or not there was a pattern in the retrieved articles with respect to vaccine characteristics and broader benefit investigated. For example, do some vaccines lend themselves to certain broader benefits more so than others? Is there a relationship between the type of vaccine (dosage, age of administration, etc.) and study type/broader economic impacts?

We have now added Table 2 which shows the relationship between vaccine antigen and age group targeted with the categories of benefit discussed. We have also added the following paragraph to the results:

“Table 2 shows the number of articles mentioning different categories of benefit, and the associated vaccine antigens and targeted age groups discussed. While there were no clear patterns, on the whole outcome-related productivity gains and equity were discussed most often (31/32 and 5/5 mentions respectively) in articles dealing with vaccines targeted at children under five years old. Financial sustainability was discussed most often (9/12 mentions respectively) in articles dealing with vaccines targeted at both children and adults. Ecological externalities were discussed equally often in both types of articles. Also, the majority of the studies using a willingness-to-pay approach to estimate societal value of a vaccine were in articles dealing with older age groups (Table 1).”

5. It is noted from the summary table for of all included studies (additional file 3) that the majority of studies (22/26) included only a single economic impact. Given that this article is a review of studies evaluating the broader economic impact of vaccination in LMIC, the article would be enhanced by the authors addressing in greater depth the methodological challenges and benefits of incorporating multiple broader economic impacts in economic evaluations of vaccines in general, and in LMICs in particular. This comment goes beyond the data collection limitations in the sixth paragraph of the Conclusion noting a lack of capacity and/or surveillance systems to perform sophisticated analyses in LMICs.

As the reviewer mentions, it is noteworthy that the majority of studies include only a single broader economic impact. We have added the following paragraph to the Discussion to explain potential reasons for this finding as well as to make recommendations for further work:

“Most (22/26) of the reviewed studies included only a single category of broader economic impact. There may be several reasons for this. Most (16/26) of the
studies were observational, willingness to pay, return on investment or cost of illness studies rather than full economic evaluations (cost-effectiveness or cost-benefit analyses) that attempt to comprehensively estimate all important costs and outcomes of an intervention. The economic evaluations mostly presented a comprehensive range of traditional (narrow) measures of impact such as direct medical costs, cases avoided or lives saved. The limited number of broader categories of impact presented by each study underscores the current novelty of these measures, as well as the lack of comprehensive guidelines for economic evaluations about which of these broader measures should be reported and in what way."

6. **This reviewer appreciates the authors noting that several evaluation techniques need to be implemented in order to obtain a representative set of outcome measures. It is becoming increasingly recognized that complex problems require multiple interventions, thus necessitating multiple evaluation techniques (which is also briefly touched on in reference to Niessen et al. ’s article). However, there is a dearth of clear discussion and recommendations around future research. Future research, for example, may indeed require implementing several evaluation techniques – can the authors propose a clearer picture of which combination and why? Other future research options may include looking at whether there are other barriers for the lack of use WHO’s proposed macroeconomic approach, or conducting pilot testing and validations studies in LMICs of the guidance document. It may be useful to create a database of linked articles (where articles are classified by vaccine, country, region, target population, etc.) that is added to over time, from which a longitudinal perspective may potentially be drawn. The authors may also wish to consider in greater depth what a multisectoral approach to vaccination would look like, considering the short and longer-term potential economic gains to be had. It may be easier to incorporate recommendations on future research (e.g. appropriate a macroeconomic approach, including projections of long-term (e.g. >10yrs) productivity gains from vaccination in a table.**

We have revised the Discussion and added a summary list of recommendations as suggested.

7. **The limitations of this review are not addressed and need to be clearly stated.**

We have revised the Conclusion section to include the following paragraph stating the limitations of our study:
“This review has limitations, because it was designed for a broad overview of existing literature rather than for detailed quantitative synthesis. Only one person was responsible for study selection, and the studies were not weighted by quality scores. However, the permissive methods and inclusion criteria allowed a variety of study types and measurement techniques to be reviewed, including those employing unconventional tools and techniques. Also, our study was restricted to methods applied to LMICs only, since it was motivated by decision making in these settings, where conventional economic evaluation methods have not always addressed necessary issues. As a result, we may not have captured novel techniques being developed in high income settings.”

8. Finally, there is an opportunity in this paper’s Discussion/Conclusion to provide donors and stakeholders with an enhanced rationale for the positive externalities, short and long-term, to be gained for investing in vaccination in LMICs, as well as for funding further research. This reviewer believes a stronger and more convincing argument can be made by the authors, based on their review of the existing studies. It may be a matter of tightening the writing or slightly re-organizing the conclusion; additionally, it would be helpful for readers of this article were the authors to provide a summary table of assertive recommendations and arguments for donors and national/sub-national level decision-makers to represent the broader benefits and value of vaccines.

We have revised the Discussion and added a summary list of recommendations as suggested.

Discretionary Revision:

9. This reviewer notes that the authors identify the difficulty involved in quantify the broader benefits of vaccination due to complexity of the relationship between health and other developmental outcomes. The authors postulate that the scope of economic assessments should be broad enough to address the needs of a variety of decision makers. It would be interesting were the authors to present their views and expand the discussion on which, if any, economic assessment study type or broader economic outcomes approaches the ideal for being understandable by various sectors (e.g. lost earnings?), or lends itself the best to this purpose.
We have expanded the Discussion and included a summary recommendation list in order to address the need to understand what study types or approaches are suitable for different decision makers. However, we believe that it is premature for us to present our own views on the details of this subject because we did not find much information on this in the literature. Hence any views we present at this stage would be speculative and based on anecdote alone. However, we hope that as our recommendations are taken up it will be possible to make such observations in the future.