Author's response to reviews

**Title:** The broader economic impact of vaccination: reviewing and appraising the strength of evidence

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**Author's response to reviews:** see over
Dear Dr. Alam,

Re: Revision of appraisal of the strength of evidence about the broader economic impact of vaccines

We thank the reviewers for their thoughtful and helpful comments, as well as the opportunity to revise our manuscript in response. Please find attached a revised manuscript as well as a point-by-point response to the comments.

We look forward to your response.

Thank you.

Yours sincerely

Mark Jit
Response to reviewers’ comments on “The broader economic impact of vaccination: reviewing and appraising the strength of evidence”

We thank the reviewers for their thoughtful and helpful comments.

Reviewer 1

The value of vaccines may lie not only with their immediate economic effects – preventing premature mortality and prolonging healthy life, while freeing caregivers from a child’s sick bed and health system resources for other uses. There may also be broader economic benefits, resulting not only from having a healthier population but also from the ways individuals, families, and societies change their decisions when they are confident that children will survive to healthy adulthood. The authors add to the literature concerning these potential broader economic effects of vaccines via a thorough systematic review of published studies, as well as a conceptual framework of causal pathways leading to vaccines’ potential broad economic benefits.

My concerns regarding the paper primarily have to do with presentation. I note that the authors describe two important study aims in the Background: 1) to construct a conceptual framework that captures causal pathways linking vaccines to economic benefits; 2) to conduct a review of the validity and strength of evidence for each pathway. I recommend that aim 1 receive a more thorough treatment in the text of the paper. Specific recommendations are as follows:

Major

1) The expert consultation, held over multiple years and meetings, was extensive and the approach taken is well-described at the start of Methods. The resulting conceptual framework, linking interventions to intermediate and final economic outcomes, is the product of a lot of work on the part of investigators and expert consultants. In fact, Table 1 and Figure 1 are results, and I would encourage you to describe them in the Results section. By describing Table 1 and Figure 1 in Results, you would have the opportunity to interpret them and provide readers with a higher level look at the detail contained within them. Table 1 and Figure 1 may be the most valuable part of the paper and are described as one of the aims of
the paper in Background, yet only get a brief mention in one Methods sentence. Their consideration throughout the paper would strengthen the study and its presentation.

We have now moved Table 1 and Figure 1 to the results section, and added further detail about the historical background to the framework as well as comparing it to other frameworks (see response 2).

2) The general biomedical reader of this journal would benefit from having Table 1 and Figure 1 put into the context of other, previously published conceptual frameworks, e.g. from Bloom, Canning, Bärnighausen and colleagues. How is the newly proposed framework similar and dissimilar from these others? What are the implications for investigators seeking to develop studies investigating potential causal pathways and addressing the knowledge gaps you have identified? While the Background and current Discussion cite this other work briefly, the Discussion would be strengthened by giving the reader more insight into the comparison.

We have added the following to the Discussion: “We have developed a conceptual framework of the pathways between vaccines and their proposed benefits, and assessed the strength of evidence behind each pathway. Our framework builds on previous lists of benefits [Baernighausen 2008, 2014], [Ozawa 2014], [Deogaonkar 2014) but in addition delineates potential causal relationships, outcome measures that could be used to capture each kind of benefit and assesses the existing strength of evidence behind each proposed benefit.”

We have also created Additional File 3 with further detail about the relationship between the different frameworks. In particular, the appendix contains (i) a brief description of the historical relationships between the different frameworks, (ii) a figure to accompany the description and (iii) a table showing the kinds of benefits captured by each framework.

3) The general reader might reasonably ask: Would you even expect to see associations between pathogen-specific vaccines and the broad economic benefits being described, without taking into account health systems as wholes or at least bigger components of health systems? Paragraph 4 in Discussion briefly addresses this concern, stating “[s]ince vaccines improve health, it may be reasonable to assume that the downstream relationship between health and its economic benefits also apply to vaccine.” Readers accustomed to thinking in
terms of specific pathogens causing specific diseases may not be convinced by this short argument, and I suggest the authors build the case out more in this paragraph.

This is a good point. We have added the following paragraph to the Discussion to highlight these points: “One limitation is that we focused on the vaccine-specific literature only, and did not explore the wider literature on the relationship between health in general (or other interventions that improve health) and broader economic benefits. Since vaccines improve health, it may be reasonable to assume that the downstream relationship between health and its economic benefits also apply to vaccines. Here, we have taken a conservative approach by ignoring any evidence relating to pathways in which immunization programmes were not the ultimate cause.

Conversely, vaccines are only one component of health systems that contribute to economic benefits. For instance, recent modelling work found that vaccines only avert around 27% of childhood diarrhoea and pneumonia deaths, so remaining mortality reductions come from other interventions such as nutrition, case management and hygiene (Bhatta et al., 2013). The benefits of vaccines themselves depend on favourable epidemiological, environmental, socioeconomic and health systems factors that may require investment in other interventions in health and other sectors. Hence it is important that the attention on the broader economic benefits of vaccination does not come at the expense other public health measures. Ideally, evaluations of vaccination should be considered alongside these measures rather than individually.”


4) In the Background and Discussion, it is being assumed that readers will be acquainted with an economic literature most are unaware of [e.g. Bloom DE and Canning D. “The Health and Wealth of Nations.” Science 2012 and many others). The case being made would be strengthened by referencing and briefly describing some of this work, as well as empiric studies supporting this more general framework.
We have now expanded our discussion of the background literature: “However, many cost-effectiveness studies only consider direct health benefits and medical cost savings. Some consider wider benefits such as indirect (herd) protection and short-term care-related productivity gains. However, economists have argued that improvements in health lead to economic growth through longer-term mechanisms such as decreasing fertility, strengthening macroeconomic stability and improving educational outcomes [Bloom 2004; Belli 2005]. More recently, this economic theory has been applied to investments in immunisation. Bärnighausen and co-workers suggested that the benefits of immunisation programmes could be divided into “narrow” and “broad” benefits [Bärnighausen 2008][Bärnighausen 2014].”

5) Methods, Analytical framework: General readers may misinterpret the authors when they say “causal relationship.” For most biomedical readers, causation means plausible molecular, physiological, or clinical relationships between cause and biological or medical effect. But a broader set of potential causal relationships, involving decision-making and choices by individuals, families and societies is also included within the definition of causation here, I think. This could potentially be a source of confusion for the reader, easily averted by defining causal relationship in the Methods.

We agree with the reviewer that causality in epidemiology is not a straightforward concept; this is even more true for economics and health services research. Even a randomised clinical trial, the gold standard for investigating causality in epidemiology, can be subject to bias and lack of external validity. If pushed, we would define validity using Rothman’s sufficient-component cause model; however we acknowledge that the definition is difficult to operationalize and impossible to prove.

We have added the following sentence: “We define causality as meaning: (i) vaccination under a given set of conditions inevitably produces the relevant benefits, and (ii) without vaccination the given set of conditions do not inevitably produce the relevant benefits.”

6) Methods, Data collection: “Upgrading” observational studies’ quality ratings based on whether they found a large or very large result seems problematic and should be
justified.

We have revised and clarified the description of our quality rating criteria. We agree with the reviewer that upgrading a study’s quality rating based on the effect sizes is problematic and wish to clarify that this was not our intent. We evaluated our studies based on GRADE criteria (http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665072.html), which include additional points for large positive effect sizes. However, the key distinction is that this “upgrading” refers to the quality or strength of evidence for the specific pathway or mechanism being evaluated in the study, not the methodological quality of the study itself i.e. a methodologically rigorous study that finds large positive effects for a particular intervention is considered to contribute more to the strength of evidence for that intervention, than a similarly methodologically rigorous study that finds no positive effects. This is a key conceptual difference, and we acknowledge that the original text does not make this sufficiently clear.

We have revised the description of our assessment to read: “A standardized electronic form for data collection and evaluation of the strength of evidence for each pathway was developed based on a simplified form of the Cochrane Systematic Review methodology”.

We have revised the relevant our description of the appraisal of observational studies to read:

“Observational studies that were methodologically sound with no obvious bias were regarded as providing ”high quality” evidence for the existence of pathway being evaluated if they were able to demonstrate very large effects, “moderate quality” evidence if the effect sizes were large, and “low quality” evidence if there were small or no effects. Observational studies that were not methodologically sound were by default considered be “low quality evidence”, regardless of effect size.”

7) Results, B. Productivity-related benefits: A brief definition of non-utility capabilities versus utility-related health consequences is needed for the general reader.

We have added the following footnote: “Most cost-effectiveness evaluations focus on maximising individual preference-based measures of health. Capabilities refer to the ability
of individuals to function in particular ways, and offer an alternative way to assess the value of health-altering interventions [Coast 2008].”

8) Figure 1: The quality of presentation needs to be improved. This figure could potentially serve as a valuable reference to investigators planning studies to address the knowledge gaps identified by the authors. However, I suggest that abbreviated definitions or outcome descriptions would be more informative to the reader, rather than the very general labels currently used. In addition, some thoughtful reordering of boxes would yield a flow diagram that allows the reader to process the information fully.

We have now expanded the descriptions in the boxes to include the full title category name as used in Table 1. We have also rearranged the boxes to improve the readability and visual appeal of the flow diagram.

Minor

9) typographical error in United Kingdom, page 13; suggest defining acronyms in sub-legend for Figure 1.

Thank you; these changes have been made.

Reviewer 2

This is an interesting and important piece of work by Jit et al on estimating the economic benefits of immunizations. The methodology and background review work seems solid and there are few quibbles with the conceptual framework being proposed.

A few points as below may help the average reader of BMC understand much better the context and relevance of this work. I summarize below

1. It isn’t clear what the value of undertaking an economic benefit analysis of immunizations in isolation adds. Could the authors defend this? In almost everything that we do, immunizations are part of a repertoire of health and related interventions and therefore the model needs to take the incremental value of immunizations into account. In a detailed
modeling exercise for impact of various interventions on childhood pneumonia and diarrhea, vaccinations including measles, pneumococcal and rotavirus vaccines were found to avert 20% of all child deaths at best, comparable to effects of nutrition, case management, WASH etc. Can the authors work this relative contribution out so we don’t overinflate the economic benefits of immunizations in relation to everything else? The authors acknowledge this as a limitation but don’t offer a satisfactory explanation as to why their approach is a real advance.

The reviewer makes an excellent point. We fully agree that there is a danger in searching particularly for economic benefits of immunization when the same “broader” criteria are not applied to evaluations of other child interventions which may be as or even more cost-effective. We also agree that there is value in evaluating packages or combinations of interventions using the same criteria rather than single interventions in isolation. Nevertheless, we feel that single intervention evaluations of vaccination cannot be avoided given the need for decision makers (national governments and donors). For instance, the recent review by Ozawa et al. (2014) found 108 articles on economic evaluations of vaccines in low and middle income settings in 2000-2010, most of which were single intervention studies. Given that such studies will continue and there is increasing attention being paid to the broader economic effects of vaccination, we feel that it is important to evaluate the evidence behind these proposed effects.

We have expanded the Discussion to highlight these points: “One limitation is that we focused on the vaccine-specific literature only, and did not explore the wider literature on the relationship between health in general (or other interventions that improve health) and broader economic benefits. Since vaccines improve health, it may be reasonable to assume that the downstream relationship between health and its economic benefits also apply to vaccines. Here, we have taken a conservative approach by ignoring any evidence relating to pathways in which immunization programmes were not the ultimate cause.

Conversely, vaccines are only one component of health systems that contribute to economic benefits. For instance, recent modelling work found that vaccines only avert around 27% of childhood diarrhoea and pneumonia deaths, so remaining mortality reductions come from other interventions such as nutrition, case management and hygiene (Bhutta et al., 2013). The benefits of vaccines themselves depend on favourable epidemiological, environmental, socioeconomic and health systems factors that may require investment in other interventions.
in health and other sectors. Hence it is important that the attention on the broader economic benefits of vaccination does not come at the expense other public health measures. Ideally, evaluations of vaccination should be considered alongside these measures rather than individually.”


2. How does maternal immunization fit into the conceptual framework and outcomes and does the framework take into account intergenerational effects?

*We have not explicitly taken account of maternal immunization, or intergenerational effects in the sense of vaccination of mothers conferring protection to children. However, we have considered inter-generational care-related productivity gains in the form of avoiding work loss due to taking care of sick children.*

*We have now stated this limitation explicitly: “Another limitation is that our framework does not consider the special benefits of maternal vaccination, such as improved maternal and child health outcomes following vaccines such as influenza.”*

3. I concur with the conclusions on the need for better information around behaviors post immunizations at societal level. I was hoping that the conceptual framework would also take into account issues related to adverse effects and vaccine hesitancy at a societal level and costs related to addressing these at population level.

*These are good points, although it is beyond the scope of the framework to address. However, we have added the following to the Discussion: “Our framework has focused on the broader economic benefits of vaccination. However, the broader economic costs of vaccination are also of increasing interest to decision making. These include costs related to addressing adverse effects following immunisation and vaccine hesitancy at a societal level.”*