Author's response to reviews

Title: Public health value of vaccines beyond efficacy: methods, measures and outcomes

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Point by point response to editor and reviewers:

In addition to addressing the changes suggested by the reviewers, please address the following editorial requests.

a. Based on what you indicated in the cover letter, some of the comments made by the reviewers, and our editorial assessment, we feel that your manuscript would be better suited as an Opinion rather than a Technical Advance article. However, we would kindly ask that you revise the format according to our guidelines specific for Opinion pieces.

This requires the abstract to be structured (reflecting the format of the rest of the manuscript), and the body to be divided into background, main text (may be broken into sub-sections), and conclusions.

Response: We thank the editor for the opportunity to publish this manuscript as an Opinion piece. We have revised the format accordingly. The abstract is now structured, and the body of the manuscript is divided into background, main text plus sub-sections, and conclusions.
Reviewer reports:

Reviewer #1: Overall I thought it was a very well written manuscript that has an interesting take on how to efficacy/effectiveness pre- and post-licensure studies.

A few minor comments, the paper could be shortened a bit, but overall its a valuable read.

Response: Thank you for the positive comments. We have attempted to shorten the manuscript, and also kept the additional text short that was requested in the context of safety issues.

Page 4, line 8 - I think Figure 1 needs inclusion of vaccine safety in the value chain.

Response: We decided not to include safety into the figure as this manuscript does not address safety issues (although we refer in the text to recent excellent reviews on this topic).

Page 7, line 8 - I think its also worth including language on why it is important to repeat effectiveness and safety analysis in particular with infant vaccines, where every year you have a new birth cohort and various changes in the epidemiology of the disease, outbreaks. In addition, vaccination patterns are greatly different than what is completed in pre-licensure trials, there are so many difference vaccination patterns, from delays to refusers, and thousands of different vaccination combinations of simultaneous vaccinations that need to be accounted for or adjusted for when performing safety and effectiveness studies. Most Post licensure safety studies reassure the safety of our current vaccination schedules and in many cases, while observational studies vs randomized clinical trials add enormous value to the profile of a vaccine because the study was completed on hundreds of thousands of individuals vs just 35,000 in each arm.

Response: We expanded the list on above reasons for lower than estimated effectiveness post-licensure. We also added the statement that rare adverse events will only be discovered in post-licensure surveillance consistent with the reviewer’s comments.

Page 7, line 42 - many are observational also because its much cheaper vs a typical randomized trial. Even in the US, there is not enough resources to conduct huge randomized trails post-licensure trials on all newly licensed vaccines. The money just isn't there for these types of studies.

Response: We agree and in fact also state the post-licensure studies are usually of observational nature. Randomized trials post-licensure are often not indicated, are expensive, and should only done under certain circumstances as listed in the manuscript.

Page 9, line 17, the same concept is true for Vaccine safety, we often taken the inverse of the Risk difference or Attributable risk and look at the number needed to harm - Ie for every 10,000 vaccinated babies, we would expect to see 1 additional seizure case for MMRV vs MMR (just an example of language, not the true number)

Response: This paper is not about safety—and to clarify this, we have expanded this statement in the introduction. If we were to add safety issues at pre-and post-licensure level, it would double


the length of our manuscript. The objective of this paper is to broaden the understanding around efficacy at pre-licensure and effectiveness at post-licensure level.

Page 11, 35 - with regards to case definition, it is always important to have different case definition, there is a case definition for a physician diagnosis and identifying a potential case in real time, then there is a data case definition, which often can be quite different and require a different level of detail and specificity.

Response: We agree with the reviewer. However, this manuscript is not about case definitions. In the context of this paper on public health impact, we only highlight that we do not have good case definitions for severe disease, that is all. It would be beyond the scope and purpose of paper to explain the intricacies of case definitions.

Reviewer #2: The paper suggest innovative ways to assess vaccination impact both in pre- and post- marketing phase. Including indirect effects of vaccination is quite ambitious but worth to be highlighted.

Response: Thank you – indeed the key message of this paper is to move from the questions such as efficacy in preventing disease in an individual to the more ambitious but much more important question on the public health impact of vaccines, which includes the indirect effects. Such questions are particularly pertinent for vaccines with moderate efficacy around 40-70% but with a high indirect effect such as pneumococcal and HIB vaccines.

- Pre-licensure: the Author support the cRCT design to be used for registration purposes; whilst it is clear the advantages of such study design for specific settings/vaccines, it should be commented the level of risk of bias, since this is particularly relevant for registration purposes.

Response: We acknowledge regulatory concerns dictate an iRCT as the preferred design for phase IIB or III VE trials, but that a) circumstances such as seen during the Ebola epidemic may require novel designs that could be considered valid for licensure by regulatory agencies and b) phase IV trials that focus on public health outcomes should use cRCTs and report total vaccine impact on outcome incidence rates.

- Post-licensure: the Authors should comment on the costs of post-licensure evaluation and on who should cover such costs: public health? industry? Under this respect, some comment on complexity/costs of the proposed studies/study design should be provided. In my personal view, the lower the cost is the higher is the probability such studies are implemented.

Response: Funding of post-licensure evaluation studies generally fall into a grey area. In some circumstances, as a condition of licensure, countries may require a post-authorization commitment from the manufacturer. More generally, though, these studies are not required and thus may be funded by industry, public health agencies, or external organizations such as The Bill & Melinda Gates Foundation or Gavi. The precise source of funding will depend on the alignment of interests and resources. For example, industry may fund studies where they think their product is underutilized because its value has been underestimated, and in these cases may
try to perform studies that can be generalized to a broader group of settings. Public health agencies may fund studies to determine if vaccine is undervalued or overvalued in their population. External agencies usually support studies in resource poor areas.

However, a more efficient mechanism in most circumstances would be to incorporate regulatory and public health goals into a single study. For example, phase III pivotal trials always should include in the analytic plan reporting of incidence rate reductions and numbers needed to vaccinate, something that adds nothing to cost. Additionally, the analytic plans should include assessment of vaccine impact on clinical as well as etiologically confirmed outcomes (e.g., all cause hospitalizations, pneumonias, acute gastroenteritis, and others as appropriate to the vaccine target). This would add little if anything to study costs as these clinical outcomes usually are used for study entry so already are included in study databases. Lastly, manufacturers should consider inclusion of longer term outcomes such as the impact of vaccine on long-term effects of sequelae, or the impact of respiratory vaccines (e.g., RSV, influenza, and pneumococcal and Hib conjugates) on asthma. While this would add costs to the study, in principle these could be shared through a public/private partnership.

We have expanded the manuscript to reflect the above.

Response:

- Overall, the paper is mostly focusing on positive outcomes of vaccines.

Vaccine opponents are more and more vocal on unexpected AEFI. The role of post-licensure studies to investigate such AEFIs should be better highlighted

Response:

We have expanded on the role of post-licensure studies to investigate AEFIs but have kept the text short. We have clarified in the introduction that this paper is not on safety but on efficacy.