Author's response to reviews

Title: Influenza vaccines licensed in the United States in healthy children: A systematic review and network meta-analysis (Protocol)

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Author's response to reviews: see over
Rochester, November 27, 2012

David Moher, Ph.D.
Paul G Shekelle, M.D, PhD
Lesley A Stewart, PhD
Editors-in-Chief
Systematic reviews
RE: Influenza vaccines licensed in the United States in healthy children: A systematic review and network meta-analysis (Protocol)

Dear Editors.

Thank you for such great comments and suggestions. They were really helpful and have significantly improved our protocol and final project. We went through all your suggestions. Please check below our answers to each of them.

All co-authors have seen and agree with the contents of the protocol and there is no financial interest to report. We certify that the submission is not under review at any other publication.

Thank you and your team for considering our work.

Sincerely yours,

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Answer to Referee 1: Brian Hutton

1. In paragraph 1 of the background, appears a comma should be used rather than a semi-colon after ‘worldwide each year’. In the second paragraph, appears the word ‘emphasizes’ should be the word ‘emphasis’.
2. On the fourth line of the first paragraph under study objectives, is TIV a typo that should be IIV?
3. The study objectives note that one of the objectives is to identify optimal vaccines for each age group, yet in the analysis description this subgroup is mentioned very low down in the details. Suggest moving this further up if this is a key objective.

A: These changes/corrections have all been done.

4. Have the authors checked that their inclusion criteria are in line with the existing reviews they plan to make use of? If not, how will this be addressed with regard to study selection?
5. The authors note they will use the lit searches of the existing reviews found and will re-run them to identify studies outside their current timeframe. Will the authors appraise the strength of the searches of the existing reviews to ensure they are not weak and possibly prone to missing studies?
A: We are planning to do so; we clarified it in the methods section.

6. The authors mention making use of the newcastle ottawa scale for observational studies and having no scoring system. This is a limited, unvalidated scale and I wonder if the authors would be better suited to the Downs and Black scale. The protocol should also note what will be done with this assessment exercise in their work.
A: No scoring system will be derived for risk of bias assessment because calculating a summary score inevitably involves assigning ‘weights’ to different items in the scale, and it is difficult to justify the weights assigned and scales are less likely to be transparent to the users of this review. A systematic review developed by Deeks et al. concluded after evaluating 182 tools for the assessment of non-randomized controlled trials that the two most useful tools are the Downs and Black instrument and the Newcastle-Ottawa Scale. We chose Newcastle-Ottawa Scale since we have more experience using it and we are more familiarized with its management and limitations.

7. The authors describe looking at I2 values, but do not actually note how they will be used to decide not to pool data. Is >50% being implied? This should be
explicit if so. Also, what will be done if pooling is not appropriate?
A: We have clarify this information in the Statistical analysis section

8. The authors note using Lumley’s approach for network meta-analysis. The bayesian approach for network MA does not generate RR s without assuming rarity of the event and I am wondering if this is the case for Lumley’s approach also. Do the authors need to specify any assumptions here?
A: Unlike the Bayesian approaches, we don’t need to assume rare events in the Lumley’s method. The assumptions made by the Lumley’s method include low incoherence (heterogeneity in network) to test exchangeability of comparisons and those common to traditional pair-wise meta-analysis.

9. The bayesian approach allows intuitive estimation of treatment rankings and probabilities of superiority that can be helpful for interpretations. Have the authors considered using this approach for these reasons?
A: We agree with reviewer that the Bayesian approach can generate a ranking probability for each intervention. However, considering that we only have two active interventions, we are not providing such probabilities and will only present results summarized as risk ratios.

10. An important assumption for network MA is homogeneity/similarity. The authors should note how they will assess these for the included data.
A: We agree. Some of the concerns we have that may lead to violation of the homogeneity/similarity assumptions would be studies conducted in different years (different viral strains) or in years when matching between the vaccine and circulating strain is poor. Therefore, we are going to quantitatively evaluate coherence by comparing the estimates from direct and indirect comparisons. Difference between these estimates that is beyond chance will make the pooling invalid. We thank reviewer for bringing this up, we clarified this in the limitation section as a possibility.

11. For Reporting, the authors should consider following ISPOR/NICE guidance on how to best report findings from a network meta-analysis and mentioning this in the protocol.
A: We thank reviewer. Now we have included these guidelines in the Reporting section and the corresponding reference. We plan to adhere to them.

12. The authors comment in the discussion that existing reviews ‘appear quite comprehensive’. How was this determined? By AMSTAR? This should be done/clarified.
A: We have clarified in the Methods/design and discussion section that the assessment of previous systematic reviews used AMSTAR criteria.

13. In addition to the table for the GRADE profile, the authors could include a table outlining the data they’ll capture in evidence tables to describe the studies and verify homogeneity/similarity.
A: We agree. We will present evidence tables describing the individual trials. We revised the text in the reporting section to highlight this.
1. In addition to finding the SRs of the area, the Authors plan to supplement any new RCTs that have been missed, by going to experts in the field.
   a. Firstly, why? Are the Authors not setting themselves up for a huge amount of extra work?
   A: The purpose of doing this is to verify that we are not missing any study. Since this systematic review will be develop with the support of the CDC, contacting the author will not imply as much effort. We consider that the extra effort it implies will positively impact in the quality of the final review.
   b. Will this mean that any new RCTs will require the re-run of any meta-analyses already undertaken?
   A: We plan to re-extract the data from the studies found by the previous systematic review; we will also extract the information from the new studies. Then, all this data will be pulled together.
   c. Should they also go to manufacturers to try and obtain *unpublished* RCTs? Withheld data has become a concern in modern times.
   A: This is an excellent point. We are lucky that the content experts from the CDC are aware of the studies developed by the pharmaceutical companies; some of them were even part of their development. We will attempt to decrease the effect of publication bias by searching for unpublished literature.

2. The Peters method of publication bias methods – but there is good argument for using this.
   A: In Egger’s and Peter’s method have comparable power and to detect publication bias under conditions of low between-study heterogeneity. We decided to use Peters method since it shows of appropriate type I error rates (Type I error rates for Egger’s regression test are higher) regardless of the size of the underlying OR, the number of primary studies in the meta-analysis, and the level of between-study heterogeneity.

3. The Authors quote Jefferson’s Cochrane review. After re-reading this, one wonders what this umbrella review will add that is not already addressed in this long and extensive review.
   A: Jefferson’s systematic review is mainly focused in the benefits of each vaccine compared to placebo, developing indirect comparisons between vaccines (LAIV vs. IIV) will allow us to evaluate if there is any additional benefit of one vaccine over the other. Considering that the number of direct comparisons is limited this could provide additional evidence and give enough support for the development of preferential recommendation.

4. Is it too restrictive to have only vaccines registered in the US?
   A: The goal of this review is to support the CDC in making recommendations specific to the US. Also, considering that there is a big difference between the strains that are used as scaffolds for the development of vaccines in different parts of the world, we decided to consider only the strains approved in the USA.
It is unclear at this point whether/how using a different scaffold strain affects immunity.