Author’s response to reviews

Title: The impact of repeated vaccination on influenza vaccine effectiveness: a systematic review and meta-analysis

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Dear Mr. Recchioni

Thank you for giving us the opportunity to respond to the reviewers’ comments regarding our manuscript. The feedback we received was very helpful and we are confident that the manuscript has improved from this process. We have covered all of the issues raised by the review team, as outlined below.

Thank you for your consideration of our revised manuscript,

Bryna Warshawsky
Revision Notes:

Reviewer #1:

In this manuscript, the authors present a meta-analysis of observational influenza vaccine effectiveness (VE) studies, specifically focusing on the effects of prior season's vaccination on current season VE. This is an important topic that is receiving a great deal of attention currently, so this review is very timely. I have a few suggestions for improving this manuscript.

Comment 1.1) Introduction, lines 71-77: The choice to consider prior vaccination from three different perspectives (two patient-focused, one policy focused) is an excellent way to approach this. It would help if the authors were more explicit about what policy question is being answered by the "policy-relevant scenario”.

Response 1.1) We have added clarification about the policy question that is addressed (Introduction paragraph 3, last sentence). The revised sentence now reads:

“This latter scenario is not relevant to patients because they cannot alter their vaccination history, however the findings may influence policy decisions regarding whether or not to offer annual vaccination to the entire population if there was evidence suggesting that repeated vaccination could negatively impact future VE.”

Comment 1.2) Methods, line 87: What is the reason for restricting to observational studies, and not including clinical trials?

Response 1.2) We restricted our inclusion criteria to observational studies because we believe that observational studies offer a broader patient population than clinical trials, and provide relevant data on vaccine effectiveness. As well, there are very few clinical trials of vaccination conducted across more than one year.

Comment 1.3) Methods, lines 109-114: It would help to be explicit about the meaning of delta VE - that delta VE values greater than 0% favor current season vaccination in all comparisons.

Response 1.3) We have added a more explicit explanation of delta VE to make the interpretation of our results clearer for our readers (Methods, paragraph 2, sentence 4).

“In both of the above scenarios, ΔVE greater than zero implies a higher VE estimate when vaccinated in both seasons than in either the current or the prior season only.”
Comment 1.4) Results: Why is there a forest plot (Figure 2) for A(H1N1) but not for A(H3N2) or B in the main manuscript?

Response 1.4) We previously included only one forest plot in the main manuscript to limit the number of figures, however we have now included all of our forest plots in the manuscript. We are open to including all or a selection of the forest plots in the manuscript and others as supplementary materials as the reviewers and journal see fit. The Results section has been modified to refer to figures rather than supplementary figures in paragraphs five, six and seven.

Comment 1.5) Results: In the forest plots, the sizes of the data points are not scaled by sample size, which is the typical approach in meta-analyses. Please either scale the data points or give sample sizes in the figures, so that readers can see which studies are the most influential.

Response 1.5) We have added a column to the figures to the right of the panel that shows the difference in VE that reports the weight (as a percent) of the study in the meta-analysis. We think that showing the weight of the difference in VE is the most useful for interpretation because it is based on the sample sizes and confidence intervals of both VE estimates that were used in the calculation of the difference.

Comment 1.6) On a related note, how much of the apparent vaccine interference for 2014/15 is driven by the single Canadian study (ref 6)?

Response 1.6) For the 2014-15 analysis, we re-ran the analysis after removing the Canadian study (Skowronski et al., 2016) and found that the conclusions do not change (i.e., the result remains significant). We found the pooled result changed from -54% (95% CI: -88%, -20%) to -42% (95% CI: -74%, -10%) when the analysis is based only on the two remaining studies (Petrie et al., 2016 and Valenciano et al., 2016).

Reviewer #2:

Comment 2.1) This is an excellent paper, much needed, in a highly topical and controversial area of influenza vaccinology. The systematic review and meta-analysis has been well executed and described, save for a complete absence of any risk of bias assessment. Without this, the reader cannot judge if the findings and conclusions are based on the pooling of data from high, medium, or low quality studies. This work needs to be undertaken and then added to the Methods (tools used), the Results (findings of risk of bias assessment) and the implications of the findings given the data quality (in the Discussion). I suggest some other minor changes to the Introduction and Discussion (attached). Apart from this, it is a great paper. The questions and subsequent analyses
are carefully formulated and presented to be relevant to both patients and policy makers. The important limitations are discussed. This paper is likely to be highly cited.

Response 2.1) We have conducted a risk of bias assessment using the Newcastle-Ottawa Scale (NOS), as suggested by the reviewer. We applied the NOS for case-control studies to both standard case-control studies as well as those conducted using the test-negative design (which was the majority of the included studies), and used the cohort study tool for the remaining studies.

We describe the tool used and how we applied it in the Methods section (paragraph 3). We include the results in the Results section (paragraph 4). We also reference a figure with a visual representation of our assessment as a supplementary figure. We mention the favourable results of our risk of bias assessment in the Discussion, but we also note that the theoretical underpinnings of the test-negative design are still in the process of explication, which is important to consider because the majority of the included studies used that design (Discussion paragraph 1).

Comment 2.2) In-text comments in attached manuscript

Response 2.2) We have incorporated more discussion in the Introduction and Discussion sections regarding older adults who have potentially received many consecutive influenza vaccines but rely on good protection in their later years when they are at greater risk of complications from influenza infection (Introduction paragraph 2; Discussion paragraph 5).