Reviewer's report

Title: Effect of influenza vaccination against mismatched strains: A systematic review and meta-analysis

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Reviewer: Heath Kelly

Reviewer's report:

This study is a systematic review and meta-analysis of influenza vaccine efficacy providing separate estimates for matched and mismatched strains. Overall this is a very thorough study, which fills a gap in the influenza meta-analytical literature. The writing is clear and precise. I note that the authors have followed the prescribed algorithms for performing and reporting this study. However I have a few comments.

1. Neither the abstract not the title of the manuscript indicates to the prospective reader that the meta-analysis is of both matched and mismatched strains. The conclusion in the abstract that efficacy is higher for matched strains cannot be drawn from the data provided in the abstract. May I suggest a revision of the title along the lines of “A comparison of influenza vaccine efficacy against matched and mismatched strains”? Please add findings on matched strains to the abstract.

2. Because the review is of RCTs, the authors generally refer to ‘efficacy’. Occasionally ‘effectiveness’ appears. Is the latter term intended?

3. Estimates of the number of influenza-related deaths and hospitalisations in the US are subject to some debate. The rationale for this study would stand without the first sentence of the Introduction.

4. Please define a ‘quasi-RCT’.

5. Some further clarification of the definition of mismatch would be helpful. As the authors note, this has not been satisfactorily attempted in previous meta-analyses.

   a. In the methods it might be easier to describe B mismatches more simply as lineage mismatches or drifts within lineages.

   b. I don’t think it is appropriate to call an H3 vaccine strain mismatched to an H1 circulating strain – if this is what is intended on p9. On re-reading perhaps this in intended only for bivalent vaccines with one H subtype. This would not apply to TIV. Can the authors please clarify?

   c. Our experience is that a combination of matched and mismatched strains may circulate together and often at different times during the season. The vaccine strain is thus matched to a proportion of circulating strains, ranging from zero to one. Match/mismatch is not an all or nothing phenomenon. How have the authors
dealt with this?

d. Match may be good for one or more of the vaccine strains and poor for one or more. When reporting overall VE against mismatched strains, how have you decided the ‘overall vaccine’ (all 3 strains) was mismatched?

I acknowledge the detailed work on trying to assess matching that the authors have undertaken. A little more clarity around the classification of mismatch would allow the reader to understand the limitations associated with the author’s approach.

6. Although you claim that VE against matched strains is higher than VE against mismatched strains, differences in VE have not been formally tested. In some instances, the general claim does not hold. For instance, for TIV, influenza A and adults, VE against matched strains was 64% (52,73) whereas VE against mismatched strains was 61% (9,84) (p15). These estimates are not likely to differ on formal testing. Moreover, even when the point estimate for matched strains was higher than the point estimate for mismatched strains, confidence intervals sometimes overlapped.

7. The use of serology is not optimal as an endpoint for assessing VE against TIV, giving potentially anomalous results, as described here. In this context it might be worth noting the work of Monto’s group on the choice of endpoints: JID 2011; 203:1309-15.

8. Another apparently anomalous finding was of a higher point estimate for protection against unmatched strains for LAIV in adults. The authors attribute this to possible confounding (p17). Is this strictly a confounder, as confounding is formally understood?

9. I think the authors need to provide further discussion on possible explanations for their findings. Can part of the findings be explained by some residual misclassification of matching, as explored in comment 5, above? Some of the findings are no doubt related to the poor recent discriminatory ability of H1 assays for H3 subtypes. This deserves further exploration. Finally, significant cross protection that is not detected by HI assays may exist, and this could be explored.

10. In a pooled 5 year observational study, we found similar results to those reported here, specifically VE for TIV in adults 20-64 years of 62% and no obvious association of VE with an assessment of match (IRV published online 17 October 2012 doi: 10.111/irv.12018 ). The results from this field broadly study support the conclusions of the meta-analysis of trials.

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:

no competing interests