Reviewer's report

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

Version: 2 Date: 14 February 2013

Reviewer: Nancy Cox

Reviewer's report:

Comments to the authors

Major Compulsory Revision: The authors reviewed clinical trials that measured influenza vaccine efficacy (VE) and stratify results by whether circulating viruses “matched” the vaccine viruses or were "mismatched" / "unmatched". While this is a very thorough review and the meta-analysis methods appear solid, it is essential to improve the manuscript by defining what criteria were used to define "matched" vs. "unmatched" or "mismatched" vaccine viruses. The authors leave the readers unclear what the definition for matched and unmatched was, e.g. the cut off for HI that determined whether a virus was antigenically similar to a vaccine virus or not; cut off values were likely different depending on the study and/or year of the study. While, the authors discuss this issue in their limitations it is essential to understand the definition for “mismatched” for each study. Otherwise, no other researchers can replicate the work in an independent fashion. Furthermore, clinical trial factors are likely related to VE, including age and prior exposure to influenza viruses in the past. This may be reflected in the large difference noted in VE from matched and mismatched years among children but the small differences reported for adults (e.g. TIV 64% and 61%, respectively). In addition, age may be an effect modifier so lumping young children, who have a low likelihood of prior exposure, together with older individuals makes little sense when you are comparing VE for matched and mismatched vaccines. Finally, the study, treats all RTCs equally and some of the trials were conducted with non-standardized doses and routes of vaccination. Using stricter criteria for choosing which RTCs to include would improve the quality of the results (see below).

Minor essential revisions:

1. Intro – reference #2 should be replaced with more recent estimates (MMWR)
2. Figures – Figure legends appear to be missing. Methods: The authors should specify whether they included efficacy estimates for young children who had received one or two doses of vaccine.
4. Methods -included studies: All vaccines appear to be considered equally. Yet, there is variability in the antigen dose of the vaccines that could influence VE. Older studies using CCA units/ml may have imprecise doses. Can the authors discuss? Also, the route of delivery might be important, for example intranasal spray versus intranasal drops and IM versus SC.
5. Results: page 13 – Can the authors discuss their findings for LAIV in adults where “mismatched” vaccines appeared to have higher VE estimates than “matched” vaccines for adults.

6. Discussion- page 17, lines 327-334 - Without any data or report to substantiate a “degree of drift” argument, this is a less than satisfactory argument. Can you elaborate and provide references that substantiate this argument for the years these studies took place. Also, this paragraph oversimplifies what VE measures and how a virus is characterized to determine antigenic similarities. In reality, genetic and extensive serologic data supplement HI data when determining antigenic similarities with vaccine viruses.

7. Discussion page 19 (line 364). Potential misclassification of the major outcome of the study is a major limitation. There is also inter-laboratory variability of HI testing. Therefore, it would be very helpful to know what cut off values were used for each study and what the observed HI value was for the viruses in these studies.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.