Reviewer's report

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

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Reviewer: Walter Emil Philipp E Beyer

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see also attachment: 2700060098655244_article_remarks.doc

This review covers a relevant issue, in particular in the light of the ongoing discussion whether to include a fourth strain in the current trivalent influenza vaccine, and should certainly be published in BMJ Medicine. However, the presented classification of vaccine types and formulations (LAIV, TIV and ‘other’) weakens the analysis and must be revised (two strata only: live and inactivated vaccines, see below) including re-calculations according to the new strata.

The Results section should be completely rewritten in a way more accessible to the reader. It is not necessary to present every single confidence interval in the text. Use tables and figures for the details and focus on the main results in the text.

Minor remarks and comments are directly written into the manuscript, after conversion of the pfd-file to a Word-file. See document 2700060098655244_article_remarks.doc.

Major comments:

1. Classification of vaccine types and formulations

The present classification (LAIV, TIV other) is not valid. Two relevant vaccine types are to be covered:

(1) The systemically administered (im, sc) inactivated influenza vaccine (IIV), including different formulations: whole-virus, split (subvirion) and subunit, adjuvanted or not.

(2) The intranasally administered live influenza vaccine (LIV).

The valence of the vaccines (how many strains included) is not relevant for this review. Suppose, the vaccine contains strain XY. Then the only relevant questions for this review are whether the epidemic strain is reported, whether it belongs to the same (sub)type as XY, and if yes, whether it matches XY or not. It is not relevant whether the vaccine, besides XY, contains other influenza strains or not. Thus, mono- bi-, tri- and tetravalent vaccines should all be classified as either IIV or LIV. It makes no sense (not to say: it is misleading) to treat a trivalent vaccine differently from a bivalent vaccine. Valence is accidental and
reflects only the epidemiological situation. Up to 1978, vaccines were usually bivalent, as only A-H3N2 and B circulated. Only after the re-occurrence of A-H1N1, the vaccine became trivalent.

In three RCTs, recombinant hemagglutinin vaccine was used. This is simply an inactivated vaccine (comparable to the subunit formulation) and should be included in that stratum.

Thus, vaccines should be categorized as follows:

Ref. First author Current manuscript Revised strata
24 Leibovitz other MIV IIV
25 Beutner other MIV IIV
26 Rytel other bivalent LAIV LIV
27 Monto other bivalent LAIV LIV
28 Tannock TIV IIV
29 Keitel Y1 other WV IIV
29 Keitel Y2 other WV IIV
29 Keitel Y3 other WV IIV
29 Keitel Y4 other WV IIV
29 Keitel Y5 other WV + split IIV
30 Gruber TIV IIV
31 Edwards A LAIV LIV
31 Edwards B other BIV IIV
32 Clover A TIV IIV
32 Clover B other bivalent LAIV LIV
33 Govaert other QIV IIV
34 Powers A TIV IIV
34 Powers B other rHA IIV
35 Belshe LAIV LIV
36 Rudenko A LAIV LIV
36 Rudenko B TIV IIV
37 Belshe LAIV LIV
38 Bridges TIV IIV
39 Hoberman TIV IIV
40 Tam LAIV LIV
41 Vesikari LAIV LIV
42 Forrest LAIV LIV
12 Bracco Net LAIV LIV
43 Lum LAIV LIV
44 Langrey TIV IIV
13 Ohmit A LAIV LIV
13 Ohmit B TIV IIIV
14 Treanor other rHA IIIV
45 Beran TIV IIIV
46 Jackson TIV IIIV
15 Ohmit A LAIV LIV
15 Ohmit B TIV IIIV
47 Beran TIV IIIV
15 Monto A LAIV LIV
15 Monto B TIV IIIV
48 Frey A LAIV LIV
48 Frey B TIV IIIV
49 Treanor other rHA IIIV
50 Barrett TIV IIIV
51 Cowling TIV IIIV
52 Talaat other MIV IIIV

All trials can now be included in a hierarchic structure:
Vaccine type # Age class # (Primary/secondary outcome) # Match. This should also be the sequence for the Results section.

Table 1 in the present form contains much irrelevant information. Nobody is really interested in the fact that the placebo formulation in Belshe 2000 contained sucrose, phosphate and glutamate, for example. The column ‘Placebo composition’ can be removed, as well as the following ‘Route of administration’ as this information is already inherent to the vaccine type.

Importantly, the influenza B vaccine strains should all be characterised as either Yamagata or Victoria lineage.

Table 2
Edwards 1994: “All groups” under Age category should read: “Children/adults” as no elderly persons were included.

2. Presentation of antigenic match

This essential information, in fact the core of the whole work, is now hidden in Appendix 2, but should prominently appear in the main text, freed from irrelevant details and possibly linked to Table 1. Taxonomic names of virus strains should
be uniform throughout the table and according to WHO style (i.e., not ‘A/Port Chalmers’ or ‘A/Port Chalmers (H3N2)’, as in Beutner 1979, but ‘A/Port Chalmers/1/73 (H3N2)’).

Beutner 1979: ‘A/Victoria (H1N2)’? That should be an A-H3N2 strain.

Clover 1991 is classified as ‘match’, but is actually a major mismatch.

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

Yes: Received reimbursements from pharmaceutical companies:

Yes: Received honoraria for consultancies with pharmaceutical companies and grants for research projects:


2011 Project: Seroprotection and other correlates of protection against flu (grant Abbott Netherlands) € 9,600 (2011 ceased).

No stocks, shares, patents, or other financial competing interest, in general or related to this paper.