Reviewer’s report

Title: A randomized, controlled non-inferiority trial comparing H1N1 2009 pandemic vaccine antigen, with and without AS03 adjuvant system, co-administered or sequentially administered with an inactivated trivalent seasonal influenza vaccine

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Reviewer: Jiehui Kevin Yin

Reviewer’s report:

The manuscript by Langley and colleagues presents an RCT on immune response comparing AS03-adjuvanted and non-adjuvanted Influenza A(H1N1)pdm09 vaccine with co- or sequentially given with TIVs. This is well-focused scope that certainly beneficiates from a RCT with comprehensive study design. The following points, however, should be addressed before it would be accepted for publication in BMC Infectious Diseases.

Major Compulsory Revisions
1. An important point of note is that CONSORT statement (http://www.consort-statement.org/consort-statement/) has been the international standard for the reporting of an RCT. Although the present manuscript adheres to this standard to some extent, fully following the CONSORT statement would help better deliver the message particularly for a RCT comprehensive like this.
2. There is a lack of Limitation section in Discussion.

Minor Essential Revisions
1. Try to use the new terminology for pandemic 2009 A (H1N1) virus (now is “Influenza A(H1N1)pdm09”, www.nejm.org/doi/full/10.1056/NEJMct1111078) in the whole manuscript.

Background
2. Page 5, the 1st paragraph: the 2nd and 3rd sentences should be removed from Background and their contents should be reflected in Results instead.
3. Inset an Objective section in Background. The authors stated their objectives starting from the 2nd paragraph on Page 17 until the 1st paragraph on Page 18 in Methods, which is not an appropriate place. Remove them to the end of Background.

Results and Discussion
4. Page 5, Line 11: the 1st sentence, “The study was conducted...” should be moved to Methods (Page 13, Line 6-7, right after “......and three in Canada”)
5. Page 5, Line 11, the sentence of “Of the 871 .....”: better to say “Of the 871 subjects approached and screened, 611 of them were enrolled and vaccinated...” I doubt if appropriate to say “enrolled” if a person was a
screening failure.

6. The Demographics section on Page 5: please give more information on the 4 study sites, i.e. what cities were they? How many participants from each site?

7. It would be better to move the “CHMP and CBER criteria” section (starting form Line 6 to 17 on Page 8) to Page 5 and just under the heading of “Immunogenicity”.

8. I wonder if slightly more comment is deserved on the controversy of this topic (whether TIV would confer cross-reacting antibodies to Influenza A[H1N1]pdm09 virus or cross-protection to Influenza A[H1N1]pdm09 disease). A serology study by Hancock (Hancock et al., 2009) reported that TIV did not seem to confer cross-reacting antibodies against Influenza A(H1N1)pdm09. Some other studies, i.e. Xia (Xie et al., 2011) and Lee (Lee et al., 2010) (Lee was already cited by the authors on Page 11), provided opposite results. It may worth commenting on the substantial heterogeneities of these results, for example, different population samples, study designs etc.. Adding to the 3rd paragraph on Page 11, the argument in this manuscript would become even stronger. At the vaccine effectiveness/efficacy level, the controversy also exists, probably to the bigger extent (i.e. the Mexican study (Garcia-Garcia et al., 2009), the Canadian data (Skowronski et al., 2010) et al.). How does this RCT add to the scope of this topic although it is an immunogenicity study? This inconsistency or consistency between immunogenicity and efficacy/effectiveness would seem to be worthy of comment.


References


Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

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

Declaration of competing interests:

I declare that I have no competing interests.