Author's response to reviews

Title: Extended antigen sparing potential of AS03-adjuvanted pandemic H1N1 vaccines in adults and children: Results from two randomised trials

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Author's response to reviews: see over
Dear Editor,

Thank you for giving us the opportunity to revise our manuscript. Please find enclosed our responses to your questions and to reviewer’s comments in an itemized fashion.

We hope that the revised version of the manuscript is now suitable for publication in BMC infectious diseases journal.

We remain at your disposal for any further questions or comments.

Best regards,

Dr O LAUNAY

Editors comment:

* Please name the specific ethics committees that approved the study within the methods section. If there are a large number of these please include the main committee for each country and include the others in an additional file.

Response: The information has been added to the Methods as requested.

Reviewer’s report: Istvan Jankovics
The question is posed by the authors well defined, and the methods are appropriate and well described. Global influenza antigen manufacturing capacity is limited, and the formulation of H1N1 vaccines with oil-in-water adjuvants using reduced amounts of virus antigen match or surpass immunogenicity compared to unadjuvanted formulations allowing for an increased number of doses from the available antigen bulk (antigen sparing). The antigen sparing is especially important producing the vaccines against avian influenza A viruses in the future.

Minor Essential Revisions

1. question
The original text is the following: “The study vaccines were monovalent, split-virion, inactivated influenza A (H1N1) 2009 vaccines prepared from virus propagated in the allantoic cavity of embryonated hens’ eggs.” (Methods. Vaccines). Is this vaccine virus was a wild type or reassortant strain?

Response: The vaccine virus is the reassortant X-179A strain derived from the A/California/7/2009 (H1N1)v virus. This information has been added to the methods. Throughout the text the vaccine strain is referred to as “A/California/7/2009 (H1N1)v-like”.

2. question
The original text is the following: “The humoral immune response to vaccination was assessed by measuring antibody inhibition of haemagglutination (HI) against the vaccine strain as previously described [13].” (Methods. Immunogenicity assessment). I propose to correct precisely the virus strain using in HI assay for example influenza A/California/07/09 (H1N1) wild type.

Response: The strain used in the HI assay was the A/California/7/2009 (H1N1)v-like strain. This information has been added to the methods as suggested.
**Reviewer's report: Helen M Oh**

1. The questions posed by the authors are well defined. In the background section, the authors had explained the importance of providing reassurance on the comparability of the 2 formulations D-Pan and Q-Pan H1N1 by demonstrating immunological equivalence between the 2 vaccines.

2. The methods for both the adult and children studies are appropriate and well described especially the end-points for the immunogenicity i.e. seroconversion rate and seroconversion factor.

3. The data are sound, clearly stating the criteria to meet the primary objectives. In fact the immunogenicity in adults and children exceeded CHMP and CBER regulatory acceptance criteria.

4. Yes, the manuscript does adhere to the relevant standards for reporting and data deposition.

5. The discussion and conclusions are well balanced and adequately supported by the data. The pediatric data demonstrated the reduction of HA dose resulted in a strong immune response in children as well as antibody persistence 6 months post vaccination. The implication of the antigen sparing potential of ASO3 adjuvant is to allow an increase in the number of doses from available antigen bulk.

**Response:** We thank the reviewer for the comments above.

In discussing the reactogenicity and safety profile of Q-Pan and D-Pan, the authors also mentioned the reports on the increased risk of narcolepsy in children and adolescents vaccinated with Pandemrix in Europe. Their data on adverse events in adults (Germany and France) and children (Philippines and Thailand) did not reveal any case on narcolepsy or Guillain-Barre syndrome.

Discretionary revision: Include stronger references for risk of narcolepsy in children and young people receiving ASO3 adjuvanted H1N1 vaccine –

**Response:** The references by Miller and Nohynek, available since the submission of this paper, have been added as suggested.

6. The limitations of work were clearly stated by the authors for the age group 10 to 18 years which was not studied in the two randomised trials. They did provide several relevant references for the immunogenicity data for this age group. However, the authors should have discussed the importance of evaluating the immunogenicity of ASO3 adjuvanted H1N1 vaccine in older adults (age > 65 years). Obviously more studies need to be done to evaluate the immunogenicity and safety of adjuvanted H1N1 vaccine in this age group.

**Response:** We thank the reviewer for this pertinent comment. There have been several studies conducted with H1N1-AS03 in elderly individuals and both Q-Pan and D-Pan vaccines have been employed. The Discussion has been amended to highlight this age group and reference to available data is given.
Discretionary revision: One additional reference for the use of ASO3 adjuvanted H1N1 vaccine in children is Langley JM et al. The Ped Infect Dis J2012;31:848-58.

**Response:** The reference by Langley has been added to the Discussion as suggested.

7. The authors acknowledged the need to investigate the possibility of further reduction of the antigen dose to children.

**Response:** We thank the reviewer for this comment.

8. The title and abstract does not accurately reflect what has been found in this study. The objectives stated in the manuscript in the last sentence of the background section are correct.

Major Compulsory revision: Title - Extended antigen sparing potential of ASO3-adjuvanted pandemic H1N1 vaccine in children and immunologicalequivalence of 2 formulations of ASO3-adjuvanted H1N1 vaccines: Results from 2 randomised trials.

**Response:** The title has been amended as recommended by the reviewer.

Abstract conclusion - …… different HA doses elicit an adequate immuneresponse through 180 days post vaccination in children (aged 3 – 9 years).

**Response:** The abstract conclusion has been modified as suggested.

9. The writing is acceptable.
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.