Reviewer’s report

Title: Long-term booster schedules with AS03A-adjuvanted heterologous H5N1 vaccines induces rapid and broad immune responses in Asian adults

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Reviewer: Massimiliano Fabbiani

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In this manuscript Gillard et al. investigate immune responses after AS03A-adjuvanted heterologous booster vaccination (A/Indonesia/5/2005; clade 2.1) given at different times in Asian adult patients previously vaccinated with AS03A-adjuvanted or non-adjuvanted H5N1 split-virus vaccine (A/Vietnam/1194/2004; clade 1). Authors provide long term data on both humoral (HI and neutralizing antibodies) and cell-mediated immunity.

The paper is well written, findings are accurately reported and seems very interesting.

Some minor issues should be clarified before publication.

MINOR ESSENTIAL REVISIONS

1. Table 1. Please show a between groups comparison (showing p values) of the demographical characteristics to verify if the four groups are homogeneous.

2. Page 10. Section “HI antibody responses to heterologous booster vaccination at Month 6”:
   a. please compare (showing p values) post booster GMT and SCRs between the group of patients receiving adjuvanted and non-adjuvanted primary vaccine.
   b. It would be interesting to comment in the text on SPR, comparing post booster SPR between the group of patients who had received adjuvanted and non-adjuvanted primary vaccine. From the data showed in table 2, it seems that patients who had received adjuvanted primary vaccine obtained a higher SPR after a single dose of booster than subjects who had received non-adjuvanted primary vaccine and two doses of adjuvanted heterologous booster. Is this difference significant?

3. Page 10. Section “Persistence of HI antibody responses to heterologous booster up to Month 48”. Are data on persistence of HI antibody responses up to 48 months available in the group of patients who had received primary unadjuvanted vaccination and two dose of booster at 6 months? If not available it should be specified in the methods or results. If they are available, could they be compared with persistence of HI antibody responses (particularly SPR) in patients who had received primary adjuvanted vaccination and one dose of booster at 6 months?

4. Page 11. Section “Neutralizing antibody responses to heterologous booster vaccination at Month 6, 12, and 36”.


a. Please compare (showing p values) post booster GMT and SCR between the group of patients who had received adjuvanted and non-adjuvanted primary vaccine and 6 months 1 or 2 dose booster.

b. Are data on post booster titers >1:28 available in subjects who had received unadjuvanted primary vaccination? Could they be compared with subjects who had received adjuvanted primary vaccination and booster at 6 months?

5. Page 11. Section “Persistence of neutralizing antibody responses up to Month 48”. Are data on persistence of neutralizing antibody responses up to 48 months available in the group of patients who had received primary unadjuvanted vaccination and two dose of booster at 6 months? If they are available, could they be compared with persistence of neutralizing antibody responses (particularly titers >1:28) in patients who had received primary adjuvanted vaccination and one dose of booster at 6 months?

6. Page 12. Section “Cell-mediated immunity”. Could you compare cell mediated immunity between patients who had received primary adjuvanted or unadjuvanted vaccination (both with booster at 6 months)?

DISCRETIONARY REVISIONS
1. Page 2. Abstract, Methods: please specify that the heterologous booster vaccine was AS03A-adjuvanted.

2. Page 15: was the pulmonary embolism considered related to vaccination even if it occurred 3 years after vaccination? Or is it a typing error?

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