Author's response to reviews

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

Authors:

Paul Gillard (paul.gillard@gsk.com)
Daniel Wai Sing Chu (chuwsd@ha.org.hk)
Shinn-Jang Hwang (sjhwang@vghtpe.gov.tw)
Pan-Chyr Yang (pcyang@ntu.edu.tw)
Prasert Thongcharoen (prasert.tho@mahidol.ac.th)
Fong Seng Lim (fong_seng_lim@nuhs.edu.sg)
Mamadou Dramé (Mamadou.X.Drame@gsk.com)
Karl Walravens (karl.x.walravens@gsk.com)
François Roman (francois.p.roman@gsk.com)

Version: 2
Date: 5 February 2014

Author's response to reviews: see over
Long-term booster schedules with AS03A-adjuvanted heterologous H5N1 vaccines induces rapid and broad immune responses in Asian adults

Feedback on comments

General from the editor

We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc1). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication.

Authors’ response:

Although this study was conducted in Asia, the drafting of this paper was supported by a PhD-qualified native-English medical writer & editor (as acknowledged) who has 15+ years’ experience in manuscript development and whom specializes in influenza vaccination. Therefore the style of the written English is the highest possible standard and is unlikely to be improved by the endorsed editing company. If copyediting is needed, we’d be grateful if more details of the specific areas to be addressed could be provided.

Reviewer #1

1) Methods. Vaccines and vaccination. Third paragraph.
The authors should disclose what kind of safety concern found in the vaccination at 24 months?

Authors’ response:

The safety concern was not identified in the study reported in the manuscript, but rather was raised during a pooled safety analysis across the vaccine development programme. This potential safety signal was deemed to be not relevant to the study and the hold was subsequently lifted. This has now been clarified:

“Vaccination at Month 24 was put on hold due to a potential safety concern that was raised during a pooled analysis across the development programme, but which was not specifically related to this trial. The concern was subsequently lifted, and following a protocol amendment, subjects who were originally scheduled to receive booster vaccination at Month 24 instead received the booster dose at Month 36.”
2) Results. First paragraph.
The authors write an age range between 21 and 62 years, but in methods they refer to a study with subjects aged 18 to 60 years.

Authors’ response:
The demographic details provided are those of the per-protocol immunogenicity cohort within the booster extension study as recorded at each booster time-point as stated in Table 1. However, the methods provide the inclusion criteria at the time of enrolment. The reason for the age range in Table 1 in the Month 36 group seemingly being outside of the specified range, is because whereas subjects may have been 18 to 60 years at enrolment, the Month 36 booster was given 3 years later, by which point, some subjects were outside of the upper age limit. As there were large intervals between enrolment and booster vaccination, we believe it is more informative to provide the demographic details at the point of booster vaccination, rather than at enrolment.

3) Results. Reactogenicity. Solicited general adverse events.
As in the discussion, the authors should include a sentence that specifies the absence of a higher frequency of AEs compared to the initial vaccination.

Authors’ response:
The following has been added to the discussion:

“The frequency of AEs observed after booster vaccination was consistent with that observed during the primary vaccination study [13].”

4) Results. Safety. Serious adverse events. First paragraph.
Why acute tonsillitis is included in serious adverse events?

Authors’ response:
It appears that a 21 year old male study subject experienced acute tonsillitis 167 days after the H5N1-vaccine booster dose received at Month 6; the event required hospitalisation and resolved after 12 days. Serious adverse events were reported when study subjects were hospitalized during the study period.

5) Results. Safety. Serious adverse events. Fourth paragraph.
How the authors considered a pulmonary embolism related to vaccination?

Authors’ response:
One subject, who did not receive a booster vaccination and thus was not included in the total vaccinated cohort, experienced an SAE (pulmonary embolism) three years after the second dose of the primary vaccination course. Blood tests revealed a low Protein S level. Although the event occurred three years after the study vaccine was given in the initial study, the investigator considered the event to be causally related to the study vaccine as there was no solid evidence to exclude its relationship with the SAE. The following has been added to the text:

“One subject who received primary vaccination but not booster vaccination experienced a pulmonary embolism three years after the second dose of primary vaccine. Blood tests revealed a low Protein S level and the investigator considered the SAE to be related to the study vaccine; despite the large interval between vaccination and the event, there was no solid evidence to exclude a causal relationship. The patient recovered upon treatment.”

Reviewer #2

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

Authors’ response:

Based on the median age and standard deviation in each cohort one may reasonably infer that the cohorts are statistically not different hence p-values will not bring deeper insight, and were therefore not computed. The following has been added to the text:

“The median age and standard deviations for each parameter across cohorts suggest that the groups were balanced for demographic characteristics.”

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?

Authors’ response:
The 95% confidence intervals for the immunogenicity parameters after one dose of adjuvanted vaccine in the group who had received adjuvanted vaccine versus after two doses of adjuvanted vaccine in the group who has received non-adjuvanted vaccine do not overlap and are widely separated – this will necessarily result in significant p-values; therefore, we do not feel that the additional post-hoc calculation of p-values will bring value. However, the interpretation of the CIs has been added to the ‘HI antibody responses to heterologous booster vaccination at Month 6’ results:

“The 95% CIs for the post-booster immunogenicity parameters do not overlap and are widely separated between the AS03\textsubscript{A}-H5N1 and the non-adjuvanted H5N1 primary vaccine groups. This suggests that AS03\textsubscript{A}-H5N1 primary vaccine followed by one dose of booster vaccine provides significantly higher HI antibody responses than non-adjuvanted H5N1 primary vaccine followed by two doses of booster vaccine.”

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 doses 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?

Authors’ response:

These data are not available, and the following has been added to the methods:

“Single-doses of heterologous booster vaccine were administered to subjects in the AS03\textsubscript{A}-adjuvanted H5N1 primary vaccine group at either Month 6, 12, or 36 post-priming; immunogenicity against the primary vaccine strain (A/Vietnam) and the booster strain (A/Indonesia) were assessed after each booster vaccination, and the persistence of immune responses were assessed in all subjects up to Month 48 post-priming. Given their lower responses to the primary vaccination shown in the initial study, all subjects in the non-adjuvanted H5N1 primary vaccine group received two doses of booster vaccine given 21 days apart at Month 6 post-priming, and immunogenicity was assessed 21 days after each booster dose.”

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)?

Authors’ response:

The above-mentioned assessments were not performed for the group of subjects with non-adjuvanted priming; these assessments were primarily generated to complement the immune response information of the candidate vaccine, hence the neutralising antibody response in the control group was not determined. This has been clarified in the methods:

“In the AS03\textsubscript{A}-adjuvanted H5N1 primary vaccine group, HI, neutralizing, and cell-mediated immunity antibody responses against A/Vietnam and A/Indonesia were assessed 21 days after booster vaccine given at Month 6, 12 or 36 post-priming, and immunogenicity persistence was evaluated at Month 12, 18, 24, 30, 36, 42, and 48 post-priming depending upon the timing of booster vaccination; in the non-adjuvanted-H5N1 primary vaccine group, HI antibody responses were assessed 21 days after each booster dose given at given at Month 6, and cell-mediated immunity antibody responses were assessed 21 days after each booster dose and at 12 months post-priming.”

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

Authors’ response: The abstract now states:

“The aim of the extension study was to evaluate different timings for heterologous AS03\textsubscript{A}-adjuvanted booster vaccination (A/Indonesia/5/2005; clade 2.1) given at Month 6, 12, or 36 post-primary vaccination.”

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?

Authors’ response:
One subject, who did not receive a booster vaccination and thus was not included in the total vaccinated cohort, experienced an SAE (pulmonary embolism) three years after the second dose of the primary vaccination course. Blood tests revealed a low Protein S level. Although the event occurred three years after the study vaccine was given in the initial study, the investigator considered the event to be causally related to the study vaccine as there was no solid evidence to exclude its relationship with the SAE. The following has been added to the text:

“One subject who received primary vaccination but not booster vaccination experienced a pulmonary embolism three years after the second dose of primary vaccine. Blood tests revealed a low Protein S level and the investigator considered the SAE to be related to the study vaccine; despite the large interval between vaccination and the event, there was no solid evidence to exclude a causal relationship.”