PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study
AUTHORS	Bauchau, vincent; Nazareth, Irwin; Tavares Da Silva, Fernanda; Rosillon, Dominique; Haguinet, François

VERSION 1 - REVIEW

REVIEWER	Black, Steven Cincinnati ChilDr.ens Hospital I serve on the DSMB for three GSK sponsored studies
REVIEW RETURNED	15-Oct-2012

GENERAL COMMENTS	1. Since AS03 vaccines from different manufacturing sites could have different safety profiles, the brand name should be included in the abstract. 2. It is stated on page 18 that only 18/22 AESI met the criteria to be included in the analysis. The reason for the rejection of the others should be stated. 3. Page 17 and 18: It is stated that for neuritis, the O/E ratio was higher than anticipated for the one case. Given that there is only one case, it is important to understand more about this case. It is stated that the symptoms started on the day the vaccine was received. Was this in the same extremity as the vaccine was received? Is it possible that the patient had symptoms and then came in for an evaluation and was then given a flu shot? More detail is required. 4. On page 21 it is stated at the top of the page that the O/E ratio is "overly sensitive". What is meant I believe is that for very rare events, one case can be statistically significant especially in an analysis that does not take into account the multiplicity of comparisons. Was an analysis which took into account the number of comparisons made undertaken and, if so, what were these results. 5. I believe the results should be stratified by age (at least child versus adult) 6. Page 22: the word traumatism should be replaced by trauma I believe

REVIEWER	Le Kang Research Fellow US Food and Drug Administration USA no competing interest.
REVIEW RETURNED	31-Oct-2012

THE STUDY	The manuscript studies the safety of AS03-adjuvanted split-virion H1N1 pandemic influenza vaccine. The authors conclude that the vaccine is generally well tolerated in regarding to the safety profile. The article is well written. I only have one concern as follows. The O/E analysis has been known not always appropriate for risk comparison between groups. In your article, you consider age stratification in O/E analysis. How about gender strata and different risk group? There is little detail in O/E analysis. Did you report the result across all ages? I did not see age-specific results. Please elaborate more, e.g. how you perform the analysis, software/package you use in getting the results.
GENERAL COMMENTS	Minor: Page 4, line 16, 21 Use “Eighty-seven” in the beginning, rather than numbers. Similar with 9143. Page 4, line 37 , Solicited AEs No comma. And use complete phrase “Solicited adverse events (AEs)” for the first time. Page 6, line 29 The most frequently reported Page 10, line 16 Use word in the beginning. Also, please use exact number. Page 15, line 4-8 The statement is confusing. Be clear with SIR and SMR. Page 16, line 40 Use word in the beginning. Page 18, line 24 From Table 5, I see 14 participants have at least one AESI. However, in the article, it is stated that 22 participants reported at least one potential AESI. There is some inconsistency here. I understand that only 14 met the criteria to be considered in O/E analysis. But some clarification is still needed. Page 19, line 25-30 For AESI, I think you are talking about SIR. Please clarify.

REVIEWER	Zoltan Vajo, MD, PhD. Honorary Professor of Medicine
REVIEW RETURNED	25-Nov-2012

GENERAL COMMENTS	In general, this is a very important topic and the authors seem to have invested an enormous amount of work. The authors appropriately address the weaknesses of the study, which is a plus. The abstract contains very little information of the study. For instance, not even the age groups of the participants are defined (i.e. adult, pediatric, elderly). The introduction is appropriate. Methods:

	Define "spleen dysfunction" Again, the age groups should be clearly identified, even if references are provided. What is meant by age "0-1 years" ? Obviously, there we no newborns vaccinated. What was the lowest age vaccinated? 6 months? This needs to be lcarified. Results: The relation of MAEs and SAEs to vaccination should be reported (i.e. possibly or probably related, not related, etc). Conclusions: In my opinion, a vaccine with this high rate of AEs (> 75 % for some events) cannot be described as "well tolerated" especially since some of the high rate events were systemic. The references are incomplete. Many more previous vaccine trials are relevant to this study and should be referenced. Minor points: There are several typographical errors in the manuscript that should be corrected (i.e. "wereable" in the discussion).

REVIEWER	Hideyuki Ikematsu, MD Professor, Chief Department of Clinical Trials Center for Advanced Medical Innovation Kyushu University Fukuoka, Japan
REVIEW RETURNED	03-Dec-2012

GENERAL COMMENTS	The manuscript provides very informative results concerning safety for AS03-adjuvanted pandemic influenza vaccine.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Steven Black
Cincinnati Childrens Hospital

1. Since AS03 vaccines from different manufacturing sites could have different safety profiles, the brand name should be included in the abstract.
Response:
The brand name (Pandemrix™) was added to the abstract. In addition, the manufacturing place of the antigen was specified in the main text, in the Methods section.

2. It is stated on page 18 that only 18/22 AESI met the criteria to be included in the analysis. The reason for the rejection of the others should be stated.
Response:
The following text was added to the Results section (‘MAEs, SAEs and AESIs’) section of the manuscript:
AESIs not included in analyses were: 2 cases of anaphylactic reaction experienced by 2 participants, which occurred at 69 and 145 days after vaccination, and were causally associated to other medications (atracurium besylate in one case and terbinafine in the other case); 1 case of polymyalgia rheumatica which was not associated with vasculitis; and 5 cases of circulatory collapse in 5 elderly participants. These 5 cases were excluded as anaphylaxis, as they were assessed by the investigators as being associated to the patients’ coexisting cardiovascular diseases.

3. Page 17 and 18: It is stated that for neuritis, the O/E ratio was higher than anticipated for the one

case. Given that there is only one case, it is important to understand more about this case. It is stated that the symptoms started on the day the vaccine was received. Was this in the same extremity as the vaccine was received? Is it possible that the patient had symptoms and then came in for an evaluation and was then given a flu shot? More detail is required.

Response:
A description of this case of neuritis was added to the Results section ('Observed-to-expected analysis'):
This event was not considered serious and it was reported in one non-immunocompromised at risk 86-year old male with no relevant past medical history. On the same day as vaccination, the participant experienced cervical stiffness and paresthesias on left hand and was diagnosed with neuritis (not specified otherwise). No clinical details or relevant diagnostic test results were provided by investigator.

4. On page 21 it is stated at the top of the page that the O/E ratio is "overly sensitive". What is meant I believe is that for very rare events, one case can be statistically significant especially in an analysis that does not take into account the multiplicity of comparisons. Was an analysis which took into account the number of comparisons made undertaken and, if so, what were these results.
Response:
There was no attempt to take into account the number of comparisons made (no correction for multiplicity). The O/E was characterised as oversensitive not only for this reason, but also and mostly because prevalent and/or not fully validated cases may have been included. This is already stated in the manuscript. Absence of adjustment for multiplicity statement was added to the Discussion section ('Statement of principal findings').

5. I believe the results should be stratified by age (at least child versus adult)
Response:
The O/Es analysis results were stratified by age. Additional results on AESIs and fatalities according to age group were added in the Results section as follows:
These 14 participants included: 1 participant <2 years old, 1 from the 10−17 years age group; 1 from the 18−44 years age group; 3 from the 45−60 years age group and 8 from the >60 years age group. The majority of fatality reports described participants older than 60 years (50/56, 89.3%) and were identified as possibly associated with the presence of pre-existing chronic medical conditions. No fatalities were reported in participants younger than 45 years of age.

6. Page 22: the word traumatism should be replaced by trauma I believe
Response:
The word traumatism was replaced by trauma.
Reviewer: Le Kang
Research Fellow, US Food and Drug Administration, USA

The manuscript studies the safety of AS03-adjuvanted split-virion H1N1 pandemic influenza vaccine. The authors conclude that the vaccine is generally well tolerated in regarding to the safety profile. The article is well written. I only have one concern as follows.

1. The O/E analysis has been known not always appropriate for risk comparison between groups. In your article, you consider age stratification in O/E analysis. How about gender strata and different risk group? There is little detail in O/E analysis. Did you report the result across all ages? I did not see age-specific results. Please elaborate more, e.g. how you perform the analysis, software/package you use in getting the results.
Response:
Some O/Es were stratified by sex (when relevant data were available and relevant to the AESI). Many

of the O/Es were stratified by age. The manuscript only report the O/E summed over all strata (when there is stratification). The software used for the statistical analyses was SAS (Statistical Analysis System) version 9.2. This additional information was added to the Methods section.

2. Minor:
Page 4, line 16, 21
Use “Eighty-seven” in the beginning, rather than numbers. Similar with 9143.
Response:
“87” was replaced by “eighty-seven”. 9134 was not spelled because it was considered too long and difficult to read, but the sentence structure has been changed so as not to begin with a number.

3. Page 4, line 37
, Solicited AEs
No comma. And use complete phrase “Solicited adverse events (AEs)” for the first time.
Page 6, line 29
The most frequently reported
Response:
The suggested corrections have been incorporated.

4. Page 10, line 16
Use word in the beginning. Also, please use exact number.
Response:
The structure of the sentence was changed so as not to begin with a number and to increase clarity.

5. Page 15, line 4-8
The statement is confusing. Be clear with SIR and SMR.
Response:
The statement in the Statistical analysis was rephrased to provide more clarity. Additionally, there were some places in the manuscript where SMR was used instead of SIR. These have been changed accordingly to ensure consistency throughout the manuscript.

6. Page 16, line 40
Use word in the beginning.
Response:
The structure of the sentence was changed in order not to begin with a number.

7. Page 18, line 24
From Table 5, I see 14 participants have at least one AESI. However, in the article, it is stated that 22 participants reported at least one potential AESI. There is some inconsistency here. I understand that only 14 met the criteria to be considered in O/E analysis. But some clarification is still needed.
Response:
During the 181-day post-vaccination period, 22 participants reported 26 potential AESI. After medical review, only 18 AESIs (including confirmed cases and cases for which there was insufficient information confirm the certainty of diagnosis) in 14 participants were considered for the Observed-to-expected (O/E) analyses. The AESIs not included in the analysis are now described in the Results section (‘MAEs, SAEs and AESIs’), as well as the reasons for their exclusion from the analysis of these AESIs:
AESIs not included in analyses were: 2 cases of anaphylactic reaction experienced by 2 participants, which occurred at 69 and 145 days after vaccination, and were causally associated to other medications (atracurium besylate in one case and terbinafine in the other case); 1 case of polymyalgia rheumatica which was not associated with vasculitis; and 5 cases of circulatory collapse in 5 elderly participants. These 5 cases were excluded as anaphylaxis, as they were assessed by the

investigators as being associated to the patients' coexisting cardiovascular diseases.

8. Page 19, line 25-30
For AESI, I think you are talking about SIR. Please clarify.
Response:
In the observed-to-expected analysis for AESIs, this should read SIR. This was corrected here and in Table 5.

Reviewer: Zoltan Vajo, MD, PhD. Honorary Professor of Medicine, University of Debrecen

In general, this is a very important topic and the authors seem to have invested an enormous amount of work. The authors appropriately address the weaknesses of the study, which is a plus.

1. The abstract contains very little information of the study. For instance, not even the age groups of the participants are defined (i.e. adult, pediatric, elderly).
Response:
Additional information regarding the population included in the study was added to the abstract. However, we are limited in the detail that we can add due to word count limit.

The introduction is appropriate.
2. Methods:
Define "spleen dysfunction"
Response:
Spleen dysfunction or asplenia was defined as absent or defective splenic function. All pre-existing conditions were self-reported by participants. This statement was added to the Methods section.

3. Again, the age groups should be clearly identified, even if references are provided. What is meant by age "0-1 years" ? Obviously, there we no newborns vaccinated. What was the lowest age vaccinated? 6 months? This needs to be clarified.
Response:
In this study, individuals vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom were enrolled. The minimum age of the study cohort was 7 months and maximum age 97 years. Information regarding the age groups was added in the Methods section. Additionally, the "0-1 years group" in Table 1 was changed to "<2 years group" and in the footnote, we have added that this group included participants 7−23 months of age.

4. Results:
The relation of MAEs and SAEs to vaccination should be reported (i.e. possibly or probably related, not related, etc).
Response:
All adverse events were reviewed/analysed in the manuscript, not only those considered as related with the study vaccination. The following statements were added in the Methods and Results sections:
The investigators assessed some of the reported AEs as possibly related to the vaccination and general descriptive information on these related AEs is provided here. However to increase sensitivity, all analyses included all reported AEs, irrespective whether or not they were considered vaccination-related, as per investigator's assessment.
One hundred and fifty four participants experienced at least one MAE assessed by investigators as possibly related to vaccination, with the most frequently reported event PTs being: lower respiratory tract infection (16/9143), upper respiratory tract infection (10/9143) and cough (10/9143).
Eleven participants experienced at least one SAE assessed by investigators as possibly related to

vaccination, with asthma/asthmatic crisis being the most frequently reported event PTs (3/9143).

5. Conclusions:
In my opinion, a vaccine with this high rate of AEs (> 75 % for some events) cannot be described as "well tolerated" especially since some of the high rate events were systemic.
Response:
This study has shown that the 2009 pandemic influenza vaccine adjuvanted with the AS03 Adjuvant System showed a clinically acceptable reactogenicity and safety profiles in all age and risk groups studied. The Conclusion section was rephrased to reflect this and “well tolerated” was deleted.

6. The references are incomplete. Many more previous vaccine trials are relevant to this study and should be referenced.
Response:
Additional references were added as follows:
Madhun AS, Akselsen PE, Sjursen H, et al. An adjuvanted pandemic influenza H1N1 vaccine provides early and long term protection in health care workers.Vaccine 2010;29:266-73.
Nicholson KG, Abrams KR, Batham S, et al. Immunogenicity and safety of a two-dose schedule of whole-virion and AS03A-adjuvanted 2009 influenza A (H1N1) vaccines: a randomised, multicentre, age-stratified, head-to-head trial. Lancet Infect Dis 2011;11:91-101.
Roman F, Vaman T, Kafeja F, Hanon E, Van Damme P. AS03(A)-Adjuvanted influenza A (H1N1) 2009 vaccine for adults up to 85 years of age. Clin Infect Dis 2010; 51:668-677

7. Minor points:
There are several typographical errors in the manuscript that should be corrected (i.e. "wereable" in the discussion).
Response:
The manuscript was spellchecked again throughout and typographical errors were corrected.

Reviewer: Hideyuki Ikematsu, MD
Professor, Chief, Department of Clinical Trials
Center for Advanced Medical Innovation, Kyushu University, Fukuoka, Japan

1. The manuscript provides very informative results concerning safety for AS03-adjuvanted pandemic influenza vaccine.
Response:
We thank you for your review of this manuscript and positive comments.

VERSION 2 – REVIEW

REVIEWER	Zoltan Vajo, MD, PhD. Honorary Professor of Medicine University of Debrecen Hungary
REVIEW RETURNED	02-Jan-2013

GENERAL COMMENTS	The authors adequately responded to all queries. I have no further comments or concerns.