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Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No		Recommendation
Title and abstract	1	✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2		Explain the scientific background and rationale for the investigation being reported
Objectives	3		State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	✓	Present key elements of study design early in the paper
Setting	5	✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6		(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		✓	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7		Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	N	Describe any efforts to address potential sources of bias
Study size	10	✓	Explain how the study size was arrived at
Quantitative variables	11	✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	✓	(*a*) Describe all statistical methods, including those used to control for confounding
		✓	(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed
		N	*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		X	(*e*) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*		(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		✓	(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*		*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
		✓	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		✓	(*b*) Report category boundaries when continuous variables were categorized
		N	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	✓	Summarise key results with reference to study objectives
Limitations	19	✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	✓	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Title Page

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

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ABSTRACT

Objectives: To assess the safety of an AS03-adjuvanted split virion H1N1 (2009) vaccine in persons vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom.

Design: Prospective, cohort, observational, post-authorisation safety study.

Setting: 87 general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England.

Participants: 9143 men and women who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the United Kingdom were enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with any other H1N1 pandemic vaccine before study enrolment and any child in care.

Primary and secondary outcome measures: Medically attended events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs), and adverse events of special interest (AESI) following vaccination were collected for all participants, Solicited AEs were assessed in a subset of participants (reactogenicity subset).

Results: MAEs were reported in 1219 and SAEs in 113 participants during the 31-day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%) and muscle aches in children age 5–17 years (61.9%) and adults (46.9%). Eighteen AESIs experienced by 14 subjects met the criteria to be considered for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case

within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected.

Conclusions: These results indicate that the AS03-adjuvanted H1N1 pandemic vaccine was generally well tolerated with a clinically acceptable reactogenicity and safety profile.

Trial registration: ClinicalTrials.gov, NCT00996853

SUMMARY

Article focus

- The outbreak of the H1N1 (2009) influenza pandemic led to vaccination of high risk groups with novel pandemic vaccines targeting the A/California/7/2009 (H1N1)v-like strain. Limited data about the clinical safety of these novel vaccines were available.
- In this paper we report the results of a post-authorisation safety study designed as a pharmacovigilance activity to evaluate safety endpoints related to the H1N1 pandemic vaccination.

Key messages

- The Most frequently reported medically-attended events and serious adverse events were consistent with events expected to be reported during the winter season.
- The observed number of adverse events of special interest —Bell's palsy, Guillain-Barré syndrome and demyelination— were below the expected number.
- The AS03-adjuvanted H1N1 (2009) vaccine was generally well-tolerated in the age and risk groups studied, with clinically acceptable reactogenicity and safety profiles.

Strengths and limitations of this study

- General practices, the primary point of contact for persons in the UK to access the National Health Service, were able to provide an extensive overview of the safety profile of the AS03-adjuvanted H1N1 pandemic influenza vaccine.

- Sample size was not estimated for each risk group (immunocompromised, at risk or healthy participants). Thus, it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes in the general UK population.

INTRODUCTION

Following the identification of several patients with swine-origin influenza that underwent human-to-human transmission,[1-3] a Pandemic Alert announcement was issued by the World Health Organisation. The lack of similarity of the pandemic virus strain to the current seasonal circulating influenza virus resulted in large scale vaccination programmes, particularly in high risk groups.[4;5]

In response, a pandemic vaccine was manufactured by GlaxoSmithKline Vaccines, *Pandemrix*™. This split-virion vaccine against the A/California/7/2009 H1N1 strain was adjuvanted with an α-tocopherol oil-in-water emulsion-based Adjuvant System containing squalene (AS03).[6,7] The development of this vaccine was based on the experience acquired with H5N1 "mock-up" vaccines.[7-9] These H5N1 vaccines were highly immunogenic and had clinically acceptable safety profiles in children aged ≥6 months and adults.[7-9]

In response to this lack of available safety data, the European Medicines Agency (EMA) provided recommendations on pharmacovigilance activities that should be undertaken during the pre-pandemic and pandemic periods. During the 2009 pandemic influenza outbreak, the EMA recommended that vaccine manufacturers actively liaise with public health and regulatory authorities to explore the possibility of an association between A/H1N1 vaccines and severe adverse events.[10] In the United Kingdom (UK), a national immunisation programme against pandemic influenza was initiated in October 2009 by the UK Department of Health.[11,12] Priority for vaccination was given to persons that were aged between six months and 65 years in the current seasonal influenza clinical risk groups: persons with chronic respiratory disease and asthma; chronic heart, renal, liver, or neurological disease; diabetes; or immunosuppression.[11,13]

The current UK study was suggested by the Medicines and Healthcare products Regulatory Agency (MHRA) and was implemented as a commitment to the authorities based on the recommendations of the EMA.

This study was a post-authorisation safety study (PASS) designed as a pharmacovigilance activity in addition to analysing signal detection from spontaneous adverse events (AEs) reporting. Data were provided promptly and periodically to the authorities after the study start. We have previously reported a preliminary analysis based on the cohort of women known to be pregnant at the time of vaccination in this study,[14] and so pregnancy outcomes are not included in this report. Here, we discuss the other safety endpoints related to the H1N1 pandemic vaccination evaluated in all participants of this study.

METHODS

Study design

This was a prospective, observational, multicentre, single cohort study of persons vaccinated with the H1N1 (2009) pandemic influenza vaccine (*Pandemrix*™, GSK Biologicals) in the UK. 9000 participants were to be enrolled in six age-stratified groups according to recommendations from the Committee for Medicinal Products for Human Use (CHMP) of the EMA[10] and solicited adverse events were to be assessed in a subset of 600 participants. The study was sponsored by GSK as part of the AS03 adjuvanted H1N1 (2009) vaccine Risk Management Plan.

This study was conducted through general practices largely distributed throughout England and which were part of the Medical Research Council (MRC) General Practice Research Framework (GPRF). The vaccine was administered at the general practice according to the local pandemic influenza programme. Individuals were invited to participate in the study within 24h after vaccination. General practices collected background information (such as demographics, relevant medical history), data on medication and vaccinations administered during the study, reactogenicity data via patient self-completed diary cards and safety data related to the study endpoints. Participants were contacted by the general practice or other delegated party at specific time points (24–96h after any dose, 28–42 days after the last dose, 180–210 days after the last dose) to ensure that all clinical data pertaining to AEs was reported. The duration of the study was 7–8 months per participant; the first participant was enrolled on the 31st October 2009 and the last participant was enrolled on the 15th December 2009.

This study was conducted in accordance with good clinical practice (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki. The study protocol and informed consent forms were reviewed and approved by a national Independent Ethics Committee. This study is registered at ClinicalTrials.gov (NCT00996853). A summary of the study protocol is available at www.gsk-clinicalstudyregister.com (Study ID 113585).

Study objectives

The primary objective of this study was to estimate the incidence of medically-attended adverse events (MAEs) in all enrolled vaccinated participants within 31 days after vaccination. The secondary objectives were to assess vaccine reactogenicity within seven days after vaccination, and to estimate the incidence of serious adverse events (SAEs) and adverse events of special interest (AESIs) in different age groups following an active surveillance of all enrolled vaccinated participants within 6 months after vaccination. An AESI was an event considered by the CHMP as worthy of closer follow-up as described in their recommendations for the Pharmacovigilance Plan following the administration of H1N1 pandemic vaccines. It included the following specific events for close monitoring: anaphylactic reaction, Bell's palsy, convulsion, demyelinating disorders, non-infectious encephalitis, Guillain-Barré syndrome (GBS), neuritis, vasculitis and vaccination failure.[10]

Study participants

Participants were included in the national H1N1 swine flu vaccination programme in the UK. Eligible participants included male and female persons vaccinated with at least one dose of H1N1 (2009) pandemic influenza vaccine shortly before being recruited (less that 24 h) by a general practice that was participating in the study, and participants who the investigator believed that they or their parents/legally acceptable representative could and would comply with the requirements of the study protocol. Persons already vaccinated with any other H1N1 pandemic vaccine before study enrolment and any child in care were excluded from participation. Written informed consent was provided by the participant or participant's parent or legally acceptable representative. A subset of the participants, who had at least one non-missing data for at least one solicited symptom, was asked to be a part of the reactogenicity cohort. Diary cards for assessment of reactogenicity were provided to participants in the reactogenicity cohort.

Participants were classified according to their risk of complications from influenza infection according to the definitions of the UK Department of Health:[13] immunocompromised, at risk, or healthy participants. Immunocompromised participants were those who reported immunosuppression at the administration of the first dose of vaccine. At risk participants were participants who were not classified as immunocompromised and reported any of the following conditions at the administration of the first dose: spleen dysfunction or asplenia; chronic respiratory disease, including asthma; chronic neurological diseases and neurodevelopmental disorders; chronic renal disease; chronic liver disease; metabolic disease; immune system disorders; chronic haematological disorders; or gastrointestinal disorders. All other participants were classified as healthy participants.

Criteria for evaluation

The primary endpoint was MAEs occurring within 31 days (D0–D30) after any dose. The secondary endpoints were solicited local (pain, redness, swelling) and general (children <5 years: fever, irritability, drowsiness, loss of appetite; participants ≥5 years: fever, headache, fatigue, gastrointestinal symptoms, joint pain, muscle ache, shivering, sweating) AEs self-reported during a 7 day follow-up period (D0–D6) after any dose, and SAEs and AESIs occurring within 181 days (D0–D180) after any dose. As recommended by the CHMP, the safety database was searched for all AESIs corresponding to the recommended preferred terms (PTs) or narrow Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs).[10] Potential cases were identified according to available case definitions such as those developed by the Brighton Collaboration (http://www.brightoncollaboration.org) or medical judgment. A medically qualified person evaluated all cases reported for diagnosis ascertainment to identify confirmed cases of interest among all the potential cases identified. The medical evaluation of diagnosis certainty had three possible outcomes for each potential case:

- Diagnosis confirmed (confirmed AESI),
- Reported without sufficient information to conclude on diagnosis certainty, or
- Diagnosis excluded (non-AESI).

Cases with a confirmed diagnosis and cases reported without sufficient information to conclude on diagnosis certainty were included in the Observed-to-Expected (O/E) analyses of AESIs, with the exception of two cases of anaphylactic shock that were related to concomitant medications.

Statistical analysis

The sample size was determined based on the recommendations of the EMA for post-authorisation evaluation of medicines for human use.[10] The target population consisted of at least 9000 participants vaccinated according to the national vaccination programme at participating general practices. According to the EMA power estimations, "a total sample size of 9000 participants would be able to rule out at 95% confidence events [MAEs, SAEs and AESIs] occurring with a frequency of 1 per 3000 if no event is observed (provided that the event occur in all age categories)".

Demographics characteristics were summarised by descriptive statistics. The incidence of solicited AEs in the reactogenicity subset, and the proportion of unsolicited AEs, SAEs, MAEs and AESIs in the total vaccinated cohort were calculated along with the associated 95% confidence intervals (CIs) using an exact method. MAEs, SAEs and AESI were categorised according to the MedDRA PT. Missing data was not replaced for the analysis of solicited symptoms. Analysis of MAEs, SAEs and AESIs included all vaccinated participants, and participants that did not report the event were considered as participants without the event. Incidences were computed for the overall population, per age group, risk groups and for pregnancy status.

Observed-to-expected analyses were performed for AESIs and fatalities. In order to take the age distribution of the study population into account, an age-stratified expected number of cases was calculated. The observed incidences for AESIs within 31 and 181 days following the first dose were compared to expected incidences available for convulsion,[15] optic neuritis,[16] Bell's palsy,[17] GBS,[18] and Multiple Sclerosis for demyelination.[19] The expected rate was age-stratified and the

standardised incidence ratio (SIR) was calculated as observed/expected. Expected mortality rates were retrieved from the Office for National Statistics, UK.[20] The standardised mortality ratio (SMR) was calculated as observed incidence rate (IR) divided by expected IR. The date of the event was defined as the date of death and not the date of onset of the associated AE. For any participants that were lost to follow-up, a request was sent to the National Health Service (NHS) Information Centre Medical Research Department in order to identify any fatality that was not recorded.

RESULTS

Demographics

From the MRC GPRF, 120 English general practices were asked to partake in the study. Of these, 87 general practices participated and these were largely distributed throughout England. A total of 9215 participants were enrolled and data for analysis was available on 9143 participants (Study cohort). Further, 72 participants were eliminated for not complying fully with the written informed consent process. The mean (± SD) age of the study cohort was 54.7 ± 20.2 years and 51.1% were female (Table 1). The majority (80.8%) of participants were in the non-immunocompromised and at risk group, 6.3% were immunocompromised and 12.8% were healthy participants. 94.4% (N=8633/9143) of the participants completed the 6 month follow-up. Reasons for non-completion of the study are detailed in Figure 1.

Reactogenicity

682 participants (52.8% females) were included in the reactogenicity analysis (Table 1). Overall, the most frequently reported solicited local AE was injection site pain (children ≤17 years: 79.5%, adults: 78.3%) followed by injection site redness (children: 49.6%, adults: 19.8%) for both age groups (Figure 2A). The median duration of local symptoms ranged between 2 and 5 days for any symptom. In children, incidence of local symptoms was higher in at risk participants than healthy children, especially for swelling (43.4% [32.1–55.3] vs. 19.5% [8.8–34.9]) (Table 2). In adults, local pain was more frequently reported by healthy participants (80.0%) and participants at risk (78.5%) than immunocompromised participants (73.0%). Local

redness (27.0%) and swelling (21.6%) were more frequently reported in immunocompromised participants than in healthy participants or participants at risk (Table 2). The median duration of local symptoms was somewhat longer in immunocompromised participants (4.0–4.5 days) compared to healthy participants (2.0–3.0 days) and participants at risk (3.0 days).

In children <5 years of age, irritability was the most common solicited general AE (61.8%; Figure 2B). Most solicited general AEs were reported more often for children aged <5 years that were considered healthy compared to those at risk (Table 2). Myalgia (muscle aches) was the most common solicited general AE in children aged 5–17 years (61.9%) and adults aged >17 years (46.9%). The overall proportion of participants with Grade 3 solicited symptoms did not exceed 7.7%. In children aged 5–17 years, most symptoms were commonly observed in at risk children, except for fever which was more frequently observed in healthy children (28.6% vs. 14.3%) and for joint pain for which there was no difference between the groups (28.6% in both groups). In adults, the reactogenicity profile was generally highest in the immunocompromised participants compared to the healthy participants and participants at risk (Table 2). In all age groups, the median duration of a grade 3 solicited general symptoms ranged between 1–2 days.

MAEs, SAEs and AESIs

At least one MAE was reported by investigators for 13.3% (1219/9143) of participants within the 31-day post-vaccination period (Table 3). The most frequently reported MAEs were associated with “infections and infestations”. Lower and upper respiratory tract infections were the most frequently reported event PTs. A higher proportion of MAEs (any symptom) were reported in the

immunocompromised participants (18.5%) compared to at risk (13.0%) and healthy (13.3%) participants.

At least one SAE was reported for 4.5% (411/9143) of participants in the study cohort during the 181-day post-vaccination period with pneumonia (16 cases), lower respiratory tract infections (13 cases) and asthma (13 cases) the most frequently reported event PTs (Table 4). Of these, 1.2% (113/9143) of participants reported at least one SAE during the 31-day post-vaccination period, with lower respiratory tract infection (0.07%, 6/9143) the most frequently reported event PT.

During the 181-day post-vaccination period, 22 participants reported at least one potential AESI. The most frequently reported AESI was convulsion: 11 episodes of convulsion occurring in 8 participants. After medical review, only 18 AESIs experienced by 14 participants met the criteria to be considered for the Observed-to-expected *(O/E)* analyses (Table 5).

There were 53 deaths (0.58%) reported during the entire study period, with an additional three cases retrieved from the NHS Information Centre Medical Research Department. In particular, 41 deaths occurred during the 181-day period after vaccination, one additional case was retrieved from the NHS Information Centre Medical Research Department, corresponding to an incidence mortality rate of 940 per 100,000 person*years (95% CI: 675–1275). None of the fatalities reported (40 cases) were considered by the investigator as related to vaccination, while the one additional fatality was assessed by a GlaxoSmithKline safety physician who considered that there was no reasonable possibility that the fatal event was related to vaccination, but rather related to the participant's medical conditions. 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.

Observed-to-expected (O/E) analyses

The observed number of fatalities was below the expected number of fatalities (SMR: 0.45; [95% CI: 0.32–0.61]). There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction. According to the O/E analysis, incidence of AESI was higher than expected for two AESIs. The first AESI is neuritis, for which a single case occurred within 30 days (SMR: 65.51 [1.66–365.01]). The second AESI is convulsions with two cases reported within the 30 days (3.84 [0.47–13.89]), but was only significant for the 181 day interval (2.65 [1.14–5.22]).

DISCUSSION

Statement of principal findings

This prospective observational study was set-up in time to enrol the first participant when the mass vaccination campaign began in the UK. Overall target recruitment was exceeded for both the study cohort and the reactogenicity cohort. Only a limited number of participants were lost to follow-up (<6%). The solicited adverse events reported were primarily common local and general symptoms: injection site-related AEs, irritability in young children and muscle aches in older children and adults. MAEs were reported for 1219 participants during the 31 day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events anticipated to be reported by the populations under study particularly during the winter season: i.e. respiratory tract infections. The observed number of fatalities was below the expected number of fatalities. There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction were received.

Confirmed cases of AESIs were rare (0.15%). The observed number of Bell's palsy, GBS and demyelination was below the expected number. The observed number of convulsions was higher than expected for the 181 day interval, but not for the 31-day interval; the lack of temporal association with vaccination is reassuring. The observed number of neuritis cases was higher than expected for the 30 day-interval, considering that only one case was retrieved. This event occurred in a non-immunocompromised at risk 86 years old male with no relevant past medical history. On day of vaccination the subject experienced neck stiffness and paraesthesias of his left hand. No clinical details or relevant diagnostic test results were provided and the final diagnosis

was neuritis. In general, the O/E analysis was overly sensitive, as both, prevalent cases and cases reported without sufficient information to conclude on diagnosis certainty were included.

Strengths and weaknesses of the study

General practices are the primary contact point for persons in the UK to access the National Health Service. The general practices were able to provide an almost complete overview of all medical events that occurred throughout the study,[14] so an almost complete ascertainment of the safety profile of the AS03 adjuvanted H1N1 (2009) pandemic influenza vaccine is the main strength of this study. A second strength of this study was the number of participants (i.e. over 9000) enrolled, which exceeded the sample size recommended by EMA for pharmacovigilance activities concerning pandemic vaccines.[10] Nevertheless, there are some limitations in this study. Firstly, no sample size estimations of the number of participants that should have been enrolled in each risk group (immunocompromised, at risk, and healthy participants) were performed. Thus it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes such as reactogenicity and MAEs in the general UK population. Additionally, the majority of participants involved in the study (81%) were classified as at risk according to the definitions of the UK Department of Health[13] and consequently enrolled in at risk group, resulting in a sample structure that differ from the general population. Second, a related limitation of this study is that the sample size may not be large enough for the assessment of the potential for the vaccine to be associated with rare adverse events such as autoimmune diseases. Another limitation is that there was no comparator group, so proportions of observed outcomes were compared with the available background rates from the general population derived from literature.

Strengths and weaknesses of the study in relation to other studies

The reactogenicity and safety profiles of healthy participants were generally comparable to those observed in other trials on the H1N1 pandemic[7,21] and H5N1 prepandemic[8] vaccines. However, in the <5 years group, all general symptoms tended to be higher when compared to an H1N1 pandemic vaccine clinical trial (for example, irritability 46.2% vs. 61.8% in this study).[22] Also in the <5 years group, drowsiness and irritability tended to be higher when compared to an H1N1 pandemic vaccine[23] and an H5N1 prepandemic vaccine clinical trial (for instance drowsiness 24.5% vs. 38.2% and irritability 36.7% vs. 61.8%).[24]

There were 18 AESIs reported with the most common being 11 episodes of convulsions in eight participants. Five of these participants had a medical history of convulsion or epilepsy and, according to the study's investigators the convulsive episode was triggered by other possible causes (e.g. traumatism, acute infection, alcohol consumption or lack of compliance with treatment). Febrile convulsion was only reported in one participant, a healthy 8 months old female. The remaining participants experienced a first convulsive episode occurring 38 days and 123 days respectively after vaccination, with no apparent cause. The incidence of convulsions, in particular febrile convulsions, has recently received much attention after an increased incidence of severe febrile convulsions in young children led to the suspension of the 2010 seasonal influenza vaccination program in Western Australia.[25] Further investigation into the cause of these convulsions showed that it was due to vaccination with one particular brand of trivalent seasonal influenza vaccine and not associated with prior vaccination with the seasonal influenza or 2009 H1N1 pandemic vaccine.[26] Indeed, a recent study did not demonstrate an association

between an increased risk of convulsions and vaccination with seasonal trivalent influenza vaccines (over a 10-year surveillance period) or the AS03-adjuvanted pandemic H1N1 vaccine in 2009–2010.[27]

Another AESI of particular interest is demyelination. Some forms of demyelination attack the central nervous system (the main example being multiple sclerosis), while others affect the peripheral nervous system (the main example being Guillain-Barré syndrome, which was analysed separately as AESI). There was one case of GBS reported in this study diagnosed as a possible mild GBS, occurring 106 days after vaccination in a 78 years old non-immunocompromised and at risk male who had a pre-existing medical condition of polyneuropathy (not otherwise specified). A previous mass vaccination campaign that ended in 1976 against swine influenza in the US was suspended due to the significantly increased rate of GBS in adults of all ages.[28] Although no increased risk of GBS following influenza vaccination was detected during the two subsequent seasonal influenza seasons,[29,30] the incidences of GBS and similar AEs following mass vaccination campaigns are still a concern. While a systemic review of meta-analysis of clinical trials assessing the effectiveness of the pandemic influenza A/H1N1 2009 vaccine did not detect any cases of GBS following vaccination,[31] a preliminary analysis by the Centers for Disease Control in the US suggested a significant association between the 2009 H1N1 vaccination and GBS.[32] Recent studies performed in several European countries reported no increased risk of GBS with pandemic influenza A/H1N1 2009 vaccine.[33,34] It has been a matter of debate whether vaccination may have the potential to exacerbate pre-existing relaxing-remitting conditions such as multiple sclerosis. This study was not adequately powered to rule out a clinically relevant association between the 2009 H1N1 vaccination and a pre-existing relaxing-remitting condition. In our study, there was one participant who had a pre-

existing secondary progressive multiple sclerosis that experienced a possible aggravation or flare-up occurring 62 days after vaccination. Multiple sclerosis relapse has been considered when assessing the evidence of a possible association with influenza vaccines. Clinical studies with cohorts of multiple sclerosis patients generally concluded that influenza vaccination did not appear to be associated with an increased risk of multiple sclerosis relapse.[35-38]

Conclusions

This study has shown that the 2009 pandemic influenza vaccine adjuvanted with the AS03 Adjuvant System was generally well tolerated in all age and risk groups studied with clinically acceptable reactogenicity and safety profiles. There was limited safety data available regarding the safety of this vaccine in both children and adults before the outbreak of the pandemic. Thus, the experience acquired with this vaccine will be of benefit for the development of future vaccines against pandemic influenza outbreaks.

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TABLES

Table 1: **Demographic characteristics of the study cohort and the reactogenicity cohort**

Characteristic at vaccination	Study Cohort (N=9143)	Reactogenicity Cohort (N=682)
Age (years)		
Mean ± SD	54.7 ± 20.22	47.5 ± 24.27
Median (min–max)	60.0 (0–97)	54.0 (0–88)
Age groups	**n(%)**	**n(%)**
0–1 years	34 (0.4)	14 (2.0)
2–4 years	134 (1.5)	47 (6.9)
5–9 years	182 (2.0)	31 (4.5)
10–17 years	319 (3.5)	35 (5.1)
18–44 years	1717 (18.8)	125 (18.3)
45–60 years	2391 (26.1)	168 (24.6)
>60 years	4365 (47.7)	262 (38.4)
Gender	**n(%)**	**n(%)**
Female	4672 (51.1)	360 (52.8)
Male	4471 (48.9)	322 (47.2)
Risk Group (†	**n(%)**	**n(%)**
Healthy	1170 (12.8)	117 (17.2)
Immunocompromised	579 (6.3)	39 (5.7)
Non-immunocompromised & at risk	7392 (80.9)	526 (77.1)

Max=maximum; min=minimum; N=number of participants in the cohort; SD=standard deviation; n(%)= number (percentage) of participant in the category

†Information regarding risk group was missing for two participants in the Study Cohort

Table 2: Proportion (%) of participants with solicited local and general adverse events (AEs) reported within the 7-day post-vaccination period (Reactogenicity cohort N=682).

	Children (≤17 years)			Adults (>17 years)		
	ImmunoComp	At Risk	Healthy	Immunocomp	At Risk	Healthy
	N=0	N=76	N=41	N=37	N=424	N=70
Pain		82.9 (72.5–90.6)	73.2 (57.1–85.8)	73.0 (55.9–86.2)	78.5 (74.3–82.4)	80.0 (68.7–88.6)
Grade 3		10.5 (4.7–19.7)	2.4 (0.1–12.9)	2.7 (0.1–14.2)	3.1 (1.6–5.2)	5.7 (1.6–14.0)
Redness		53.9 (42.1–65.5)	41.5 (26.3–57.9)	27.0 (13.8–44.1)	20.5 (16.8–24.7)	11.4 (5.1–21.3)
Grade 3		11.8 (5.6–21.3)	0 (0–8.6)	10.8 (3.0–25.4)	1.7 (0.7–3.4)	0 (0–5.1)
Swelling		43.4 (32.1–55.3)	19.5 (8.8–34.9)	21.6 (9.8–38.2)	16.7 (13.3–20.6)	17.1 (9.2–28.0)
Grade 3		9.2 (3.8–18.1)	0 (0–8.6)	5.4 (0.7–18.2)	0.5 (0.1–1.7)	4.3 (0.9–12.0)

	Children (<5 years)		Children (5–17 years)		Adults (>17 years)		
	At Risk	Healthy	At Risk	Healthy	Immunocomp	At Risk	Healthy
All General (N)	28	27	49	14	38	431	70
Drowsiness	28.6 (13.2–48.7)	48.1 (28.7–68.1)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Irritability	57.1 (37.2–75.5)	66.7 (46.0–83.5)					
Grade 3	7.1 (0.9–23.5)	7.4 (0.9–24.3)					
Loss of appetite	39.3 (21.5–59.4)	37.0 (19.4–57.6)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Fever	10.7 (2.3–28.2)	22.2 (8.6–42.3)	14.3 (5.9–27.2)	28.6 (8.4–58.1)	5.3 (0.6–17.7)	2.1 (1.0–3.9)	4.3 (0.9–12.0)
Grade 3	0 (0–12.3)	3.7 (0.1–19.0)	2.0 (1.0–10.9)	0 (0–23.2)	0 (0–9.3)	0.5 (0.1–1.7)	0 (0–5.1)
Fatigue			46.9 (32.5–61.7)	35.7 (12.8–64.9)	55.3 (38.3–71.4)	32.7 (28.3–37.4)	40.0 (28.5–52.4)

Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	7.9 (1.7–21.4)	1.9 (0.8–3.6)	7.1 (2.4–15.9)
Gastrointestinal	24.5 (13.3–38.9)	21.4 (4.7–50.8)	31.6 (17.5–48.7)	15.8 (12.5–19.6)	20.0 (11.4–31.3)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.4 (0.5–3.0)	5.7 (1.6–14.0)
Headache	44.9 (30.7–59.8)	28.6 (8.4–58.1)	39.5 (24.0–56.6)	34.3 (29.9–39.0)	41.4 (29.8–53.8)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	5.3 (0.6–17.7)	1.2 (0.4–2.7)	5.7 (1.6–14.0)
Joint pain	28.6 (16.6–43.3)	28.6 (8.4–58.7)	44.7 (28.6–61.7)	26.0 (21.9–30.4)	28.6 (18.4–40.6)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	0 (0–9.3)	1.9 (0.8–3.6)	5.7 (1.6–14.0)
Muscle aches	65.3 (50.4–78.3)	50.0 (23.0–77.0)	65.8 (48.6–80.4)	43.9 (39.1–48.7)	55.7 (43.3–67.6)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	7.9 (1.7–21.4)	2.1 (1.0–3.9)	5.7 (1.6–14.0)
Shivering	28.6 (16.6–43.3)	14.3 (1.8–42.8)	36.8 (21.8–54.0)	15.3 (12.0–19.1)	17.1 (9.2–28.0)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.6 (0.7–3.3)	2.9 (0.3–9.9)
Sweating	20.4 (10.2–34.3)	7.1 (0.2–33.9)	21.1 (9.6–37.3)	11.4 (8.5–14.8)	15.7 (8.1–26.4)
Grade 3	0 (0–7.3)	0 (0–23.2)	0 (0–9.3)	1.4 (0.5–3.0)	1.4 (0–7.7)

%(95% CI)=percentage of participants reporting the event with exact 95% confidence limit (lower limit–upper limit); N=number of participants in the cohort;

Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F).

Grade 3 redness was defined as being >50 mm, grade 3 swelling was > 50 mm and Grade 3 fever was >39°C.

Table 3: Most frequently reported (≥9 cases) medically attended adverse events (MAEs) within the 31-day post-vaccination period

Medically Attended Events (MAEs)[†]	ImmunoComp	At risk	Healthy	Total*
	N= 579	**N**= 7392	**N**= 1170	**N**= 9143
	n (%)	**n (%)**	**n (%)**	**n (%)**
At least one MAE	107 (18.5)	958 (13.0)	154 (13.2)	1219 (13.3)
Lower respiratory tract infection	12 (2.1)	94 (1.3)	4 (0.3)	110 (1.2)
Upper respiratory tract infection	5 (0.9)	56 (0.8)	14 (1.2)	75 (0.8)
Cough	5 (0.9)	49 (0.7)	6 (0.5)	60 (0.7)
Urinary tract infection	5 (0.9)	36 (0.5)	12 (1.0)	53 (0.6)
Asthma	1 (0.2)	39 (0.5)	1 (0.1)	41 (0.5)
Back pain	2 (0.4)	25 (0.3)	2 (0.2)	29 (0.3)
Abdominal pain	4 (0.7)	20 (0.3)	2 (0.2)	26 (0.3)
Diarrhoea	2 (0.4)	17 (0.2)	2 (0.2)	21 (0.2)
Arthralgia	0	16 (0.2)	4 (0.3)	20 (0.2)
Oropharyngeal pain	2 (0.4)	16 (0.2)	2 (0.2)	20 (0.2)
Chronic obstructive pulmonary disease	0	18 (0.2)	0	18 (0.2)
Conjunctivitis	1 (0.2)	13 (0.2)	3 (0.3)	17 (0.2)
Headache	2 (0.4)	10 (0.2)	5 (0.4)	17 (0.2)
Dyspnoea	5 (0.9)	9 (0.1)	3 (0.3)	17 (0.2)
Rash	0	16 (0.2)	1 (0.1)	17 (0.2)
Herpes zoster	1 (0.2)	13 (0.2)	2 (0.2)	16 (0.2)
Chest pain	1 (0.1)	13 (0.2)	1 (0.1)	15 (0.2)
Sinusitis	0	10 (0.1)	5 (0.4)	15 (0.2)
Pain in extremity	3 (0.5)	10 (0.1)	2 (0.2)	15 (0.2)
Otitis externa	0	13 (0.2)	1 (0.1)	14 (0.2)
Dizziness	0	11 (0.2)	3 (0.3)	14 (0.2)
Dyspepsia	0	11 (0.2)	2 (0.2)	13 (0.1)
Vomiting	2 (0.4)	8 (0.1)	2 (0.2)	12 (0.1)
Pyrexia	0	7 (0.1)	4 (0.3)	11 (0.1)
Bronchitis	2 (0.4)	6 (0.1)	2 (0.2)	10 (0.1)
Cellulitis	2 (0.4)	7 (0.1)	1 (0.1)	10 (0.1)
Pharyngitis	3 (0.5)	5 (0.1)	2 (0.2)	10 (0.1)
Musculoskeletal chest pain	1 (0.2)	9 (0.1)	0	10 (0.1)
Influenza-like illness	3 (0.5)	6 (0.1)	0	9 (0.1)
Fall	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)
Wheezing	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)

Immunocomp=participants identified as immunocompromised on study initiation; N=number of participants in the cohort; n (%)=number of participants reporting the event (percentage);
[†]MAEs were defined as events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a MAE led to hospitalization (or met any other SAE criteria), it was to be reported as a SAE.

*Information regarding risk group was missing for two participants

Table 4: Most frequently reported (≥5 cases) serious adverse events (SAEs) during the 181-day post-vaccination period (N=9143)

Serious Adverse Event (SAE)	Total† n (%)	Time from previous vaccination dose to SAE (range in days)
At least one SAE	411 (4.50)	
Pneumonia	16 (0.17)	30–178
Lower respiratory tract infection	13 (0.14)	6–171
Asthma	13 (0.14)	1–170
Chest pain	10 (0.11)	3–180
Urinary tract infection	9 (0.10)	14–147
Chronic obstructive pulmonary disease	8 (0.09)	5–172
Myocardial infarction	7 (0.08)	17–148
Acute coronary syndrome	6 (0.07)	55–172
Atrial fibrillation	6 (0.07)	1–157
Abdominal pain	6 (0.07)	<1–74
Vomiting	6 (0.07)	<1–176
Transient ischaemic attack	6 (0.07)	2–173
Cholecystitis	5 (0.05)	43–118
Bronchopneumonia	5 (0.05)	1–103
Sepsis	5 (0.05)	12–172
Radius fracture	5 (0.05)	66–156
Colon cancer	5 (0.05)	1–84
Pulmonary embolism	5 (0.05)	11–157

† n (%)=number of participants reporting the event (percentage)

Table 5. Adverse events of special interest (AESIs) reported within the 181-day post-vaccination period (N=9143)

Adverse Events of Special Interest (AESIs)†	n (%)	SMR [95% CI]
At least one AESI	14 (0.15)	
Convulsions	8 (0.09)	2.65 [1.14–5.22]
Non-febrile convulsions	7 (0.08)	
Febrile convulsion	1 (0.01)	
Bell's Palsy	3 (0.03)	2.70 [0.56–7.89]
Guillain-Barré syndrome	1 (0.01)	18.11 [0.46–100.89]
Neuritis	1 (0.01)	11.46 [0.29–63.85]
Demyelination	1 (0.01)	4.88 [0.12–27.17]

95% CI=95% confidence interval (lower limit–upper limit); n (%)=number of participants reporting event (percentage), more than one event could be reported for a participant

† The Adverse Events of Special Interest (AESI) for this study were: Anaphylactic reaction, Bell's palsy, convulsions, demyelination, Guillain-Barré syndrome, neuritis, non-infectious encephalitis, vaccination failure, vasculitis

FIGURES

Figure Legends

Figure 1

Flow diagram depicting the completion of study contact points with the reasons for discontinuation. Participants with contacts not performed for other reasons could have had following contacts. If only one dose of vaccine was given, Contact 2 was considered "Missing confirmed".

Figure 2

Solicited local (A) and general (B) adverse events reported during a 7-day follow-up period after any dose (Reactogenicity cohort N=682).

The general symptoms of drowsiness, irritability and loss of appetite were only assessed in children <5 years while fatigue, gastrointestinal, headache, joint pain, muscle aches, shivering and sweating were assessed in children aged 5–17 years and in adults. Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F). Data are shown as percentage of participants reporting the symptom with 95% confidence interval.

Figure 1

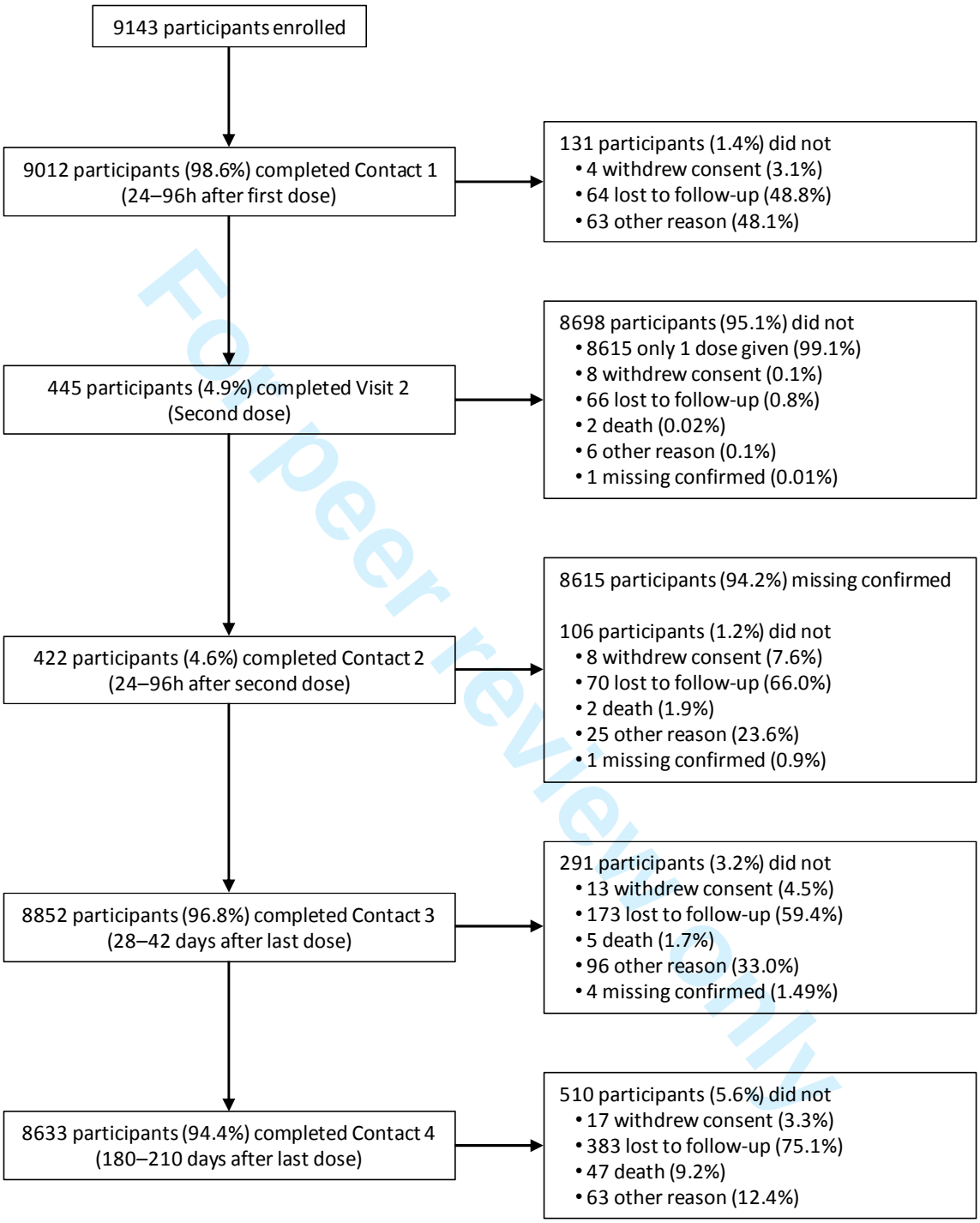
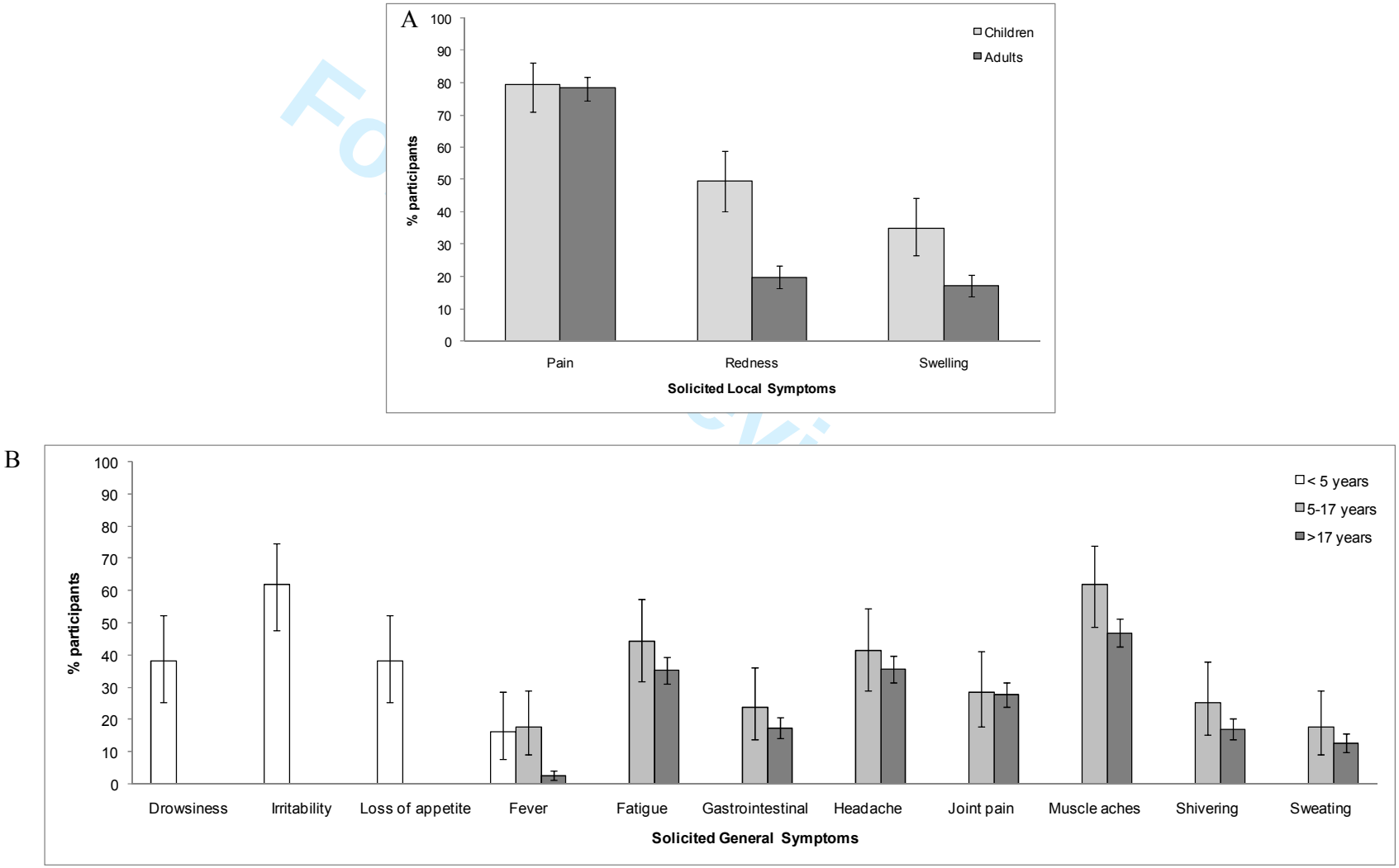


Figure 2


A
100
90
80
70
60
50
40
30
20
10
0
% participants
Children
Adults
Pain
Redness
Swelling
Solicited Local Symptoms
B
100
90
80
70
60
50
40
30
20
10
0
% participants
< 5 years
5-17 years
>17 years
Drowsiness
Irritability
Loss of appetite
Fever
Fatigue
Gastrointestinal
Headache
Joint pain
Muscle aches
Shivering
Sweating
Solicited General Symptoms

Title Page

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

Irwin Nazareth *professor of primary care & population health*[1], Fernanda Tavares *Therapeutic Area Safety Head*[2], Dominique Rosillon[2], François Haguinet *biostatistician*[2], Vincent Bauchau *senior epidemiologist*[2]

ABSTRACT

Objectives: To assess the safety of an AS03-adjuvanted split virion H1N1 (2009) vaccine in persons vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom.

Design: Prospective, cohort, observational, post-authorisation safety study.

Setting: 87 general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England.

Participants: 9143 men and women who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the United Kingdom were enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with any other H1N1 pandemic vaccine before study enrolment and any child in care.

Primary and secondary outcome measures: Medically attended events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs), and adverse events of special interest (AESI) following vaccination were collected for all participants, Solicited AEs were assessed in a subset of participants (reactogenicity subset).

Results: MAEs were reported in 1219 and SAEs in 113 participants during the 31-day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%) and muscle aches in children age 5–17 years (61.9%) and adults (46.9%). Eighteen AESIs experienced by 14 subjects met the criteria to be considered for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case

within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected.

Conclusions: These results indicate that the AS03-adjuvanted H1N1 pandemic vaccine was generally well tolerated with a clinically acceptable reactogenicity and safety profile.

Trial registration: ClinicalTrials.gov, NCT00996853

SUMMARY

Article focus

- The outbreak of the H1N1 (2009) influenza pandemic led to vaccination of high risk groups with novel pandemic vaccines targeting the A/California/7/2009 (H1N1)v-like strain. Limited data about the clinical safety of these novel vaccines were available.
- In this paper we report the results of a post-authorisation safety study designed as a pharmacovigilance activity to evaluate safety endpoints related to the H1N1 pandemic vaccination.

Key messages

- The Most frequently reported medically-attended events and serious adverse events were consistent with events expected to be reported during the winter season.
- The observed number of adverse events of special interest —Bell's palsy, Guillain-Barré syndrome and demyelination— were below the expected number.
- The AS03-adjuvanted H1N1 (2009) vaccine was generally well-tolerated in the age and risk groups studied, with clinically acceptable reactogenicity and safety profiles.

Strengths and limitations of this study

- General practices, the primary point of contact for persons in the UK to access the National Health Service, were able to provide an extensive overview of the safety profile of the AS03-adjuvanted H1N1 pandemic influenza vaccine.

- Sample size was not estimated for each risk group (immunocompromised, at risk or healthy participants). Thus, it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes in the general UK population.

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Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

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Title Page

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

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ABSTRACT

Objectives: To assess the safety of an AS03-adjuvanted split virion H1N1(2009) vaccine (*Pandemrix*™) in persons vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom.

Design: Prospective, cohort, observational, post-authorisation safety study.

Setting: Eighty-seven general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England.

Participants: A cohort of 9143 individuals aged 7 months to 97 years who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the United Kingdom was enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with other H1N1 pandemic vaccine and any child in care. **Primary and secondary outcome measures**: Medically attended events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs), and adverse events of special interest (AESI) following vaccination were collected for all participants. Solicited adverse events (AEs) were assessed in a subset of participants.

Results: MAEs were reported in 1219 and SAEs in 113 participants during the 31-days post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%), muscle aches in children age 5–17 years (61.9%) and adults (46.9%). Eighteen AESIs experienced by 14 subjects met the criteria to be considered for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case

within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected.

Conclusions: Results indicate that the AS03-adjuvanted H1N1 pandemic vaccine showed a clinically acceptable reactogenicity and safety profile in all age and risk groups studied.

Trial registration: ClinicalTrials.gov, NCT00996853

SUMMARY

Article focus

- The outbreak of the H1N1 (2009) influenza pandemic led to vaccination of high risk groups with novel pandemic vaccines targeting the A/California/7/2009 (H1N1)v-like strain. Limited data about the clinical safety of these novel vaccines were available.
- In this paper we report the results of a post-authorisation safety study designed as a pharmacovigilance activity to evaluate safety endpoints related to the H1N1 pandemic vaccination.

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- The most frequently reported medically-attended events and serious adverse events were consistent with events expected to be reported during the winter season.
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Strengths and limitations of this study

- General practices, the primary point of contact for persons in the UK to access the National Health Service, were able to provide an extensive overview of the safety profile of the AS03-adjuvanted H1N1 pandemic influenza vaccine.

- Sample size was not estimated for each risk group (immunocompromised, at risk or healthy participants). Thus, it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes in the general UK population.

INTRODUCTION

Following the identification of several patients with swine-origin influenza that underwent human-to-human transmission,[1-3] a Pandemic Alert announcement was issued by the World Health Organisation. The lack of similarity of the pandemic virus strain to the current seasonal circulating influenza virus resulted in large scale vaccination programmes, particularly in high risk groups.[4;5]

In response, two pandemic vaccines were manufactured by GlaxoSmithKline Vaccines, including *Pandemrix*™. This split-virion vaccine against the A/California/7/2009 H1N1 strain was adjuvanted with an α-tocopherol oil-in-water emulsion-based Adjuvant System containing qualene (AS03)[6,7] and was produced in GlaxoSmithKline Vaccines' Dresden (Germany) facility. The development of this vaccine was based on the experience acquired with H5N1 "mock-up" vaccines.[7-9] These H5N1 vaccines were highly immunogenic and had clinically acceptable safety profiles in children aged ≥6 months and adults.[7-9]

In response to this lack of available safety data, the European Medicines Agency (EMA) provided recommendations on pharmacovigilance activities that should be undertaken during the pre-pandemic and pandemic periods. During the 2009 pandemic influenza outbreak, the EMA recommended that vaccine manufacturers actively liaise with public health and regulatory authorities to explore the possibility of an association between A/H1N1 vaccines and severe adverse events.[10] In the United Kingdom (UK), a national immunisation programme against pandemic influenza was initiated in October 2009 by the UK Department of Health.[11,12] Priority for vaccination was given to persons that were aged between six months and 65 years in the current seasonal influenza clinical risk groups: persons with chronic respiratory disease and

asthma; chronic heart, renal, liver, or neurological disease; diabetes; or immunosuppression.[11,13] The current UK study was suggested by the Medicines and Healthcare products Regulatory Agency (MHRA) and was implemented as a commitment to the authorities based on the recommendations of the EMA.

This study was a post-authorisation safety study (PASS) designed as a pharmacovigilance activity in addition to analysing signal detection from spontaneous adverse events (AEs) reporting. Data were provided promptly and periodically to the authorities after the study start. We have previously reported a preliminary analysis based on the cohort of women known to be pregnant at the time of vaccination in this study,[14] and so pregnancy outcomes are not included in this report. Here, we discuss the other safety endpoints related to the H1N1 pandemic vaccination evaluated in all participants of this study.

METHODS

Study design

This was a prospective, observational, multicentre, single cohort study of persons vaccinated with the H1N1 (2009) pandemic influenza vaccine (*Pandemrix*™, GlaxoSmithKline Vaccines) in the UK. The study vaccine was produced in GlaxoSmithKline Vaccines Dresden, Germany. According to recommendations from the Committee for Medicinal Products for Human Use (CHMP) of the EMA[10] solicited adverse events were planned to be assessed in a subset of 600 participants. The study was sponsored by GSK as part of the AS03 adjuvanted H1N1 (2009) vaccine Risk Management Plan.

This study was conducted through general practices largely distributed throughout England and which were part of the Medical Research Council (MRC) General Practice Research Framework (GPRF). The vaccine was administered at the general practice according to the local pandemic influenza programme. Individuals were invited to participate in the study within 24h after vaccination. General practices collected background information (such as demographics, relevant medical history), data on medication and vaccinations administered during the study, reactogenicity data via patient self-completed diary cards and safety data related to the study endpoints. Participants were contacted by the general practice or other delegated party at specific time points (24–96h after any dose, 28–42 days after the last dose, 180–210 days after the last dose) to ensure that all clinical data pertaining to AEs was reported. The duration of the study was 7–8 months per participant; the first participant was enrolled on the 31st October 2009 and the last participant was enrolled on the 15th December 2009.

This study was conducted in accordance with good clinical practice (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki. The study protocol and informed consent forms were reviewed and approved by a national Independent Ethics Committee. This study is registered at ClinicalTrials.gov (NCT00996853). A summary of the study protocol is available at www.gsk-clinicalstudyregister.com (Study ID 113585).

Study objectives

The primary objective of this study was to estimate the incidence of medically-attended adverse events (MAEs) in all enrolled vaccinated participants within 31 days after vaccination. The secondary objectives were to assess vaccine reactogenicity within seven days after vaccination, and to estimate the incidence of serious adverse events (SAEs) and adverse events of special interest (AESIs) in different age groups following an active surveillance of all enrolled vaccinated participants within 6 months after vaccination. An AESI was an event considered by the CHMP as worthy of closer follow-up as described in their recommendations for the Pharmacovigilance Plan following the administration of H1N1 pandemic vaccines. It included the following specific events for close monitoring: anaphylactic reaction, Bell's palsy, convulsion, demyelinating disorders, non-infectious encephalitis, Guillain-Barré syndrome (GBS), neuritis, vasculitis and vaccination failure.[10]

Study participants

Participants were included in the national H1N1 swine flu vaccination programme in the UK. Eligible participants included male and female persons vaccinated with at least one dose of H1N1 (2009) pandemic influenza vaccine shortly before being recruited (less that 24 h) by a general practice that was participating in the study, and participants who the investigator believed that they or their parents/legally acceptable representative could and would comply with the requirements of the study protocol. Persons already vaccinated with any other H1N1 pandemic vaccine before study enrolment and any child in care were excluded from participation. Written informed consent was provided by the participant or participant's parent or legally acceptable representative. A subset of the participants, who had at least one non-missing data for at least one solicited symptom, was asked to be a part of the reactogenicity cohort. Diary cards for assessment of reactogenicity were provided to participants in the reactogenicity cohort.

Participants were classified according to their risk of complications from influenza infection according to the definitions of the UK Department of Health:[13] immunocompromised, at risk, or healthy participants. Immunocompromised participants were those who reported immunosuppression at the administration of the first dose of vaccine. At risk participants were participants who were not classified as immunocompromised and reported any of the following conditions at the administration of the first dose: spleen dysfunction or asplenia (defective or absent splenic function, respectively); chronic respiratory disease, including asthma; chronic neurological diseases and neurodevelopmental disorders; chronic renal disease; chronic liver disease; metabolic disease; immune system disorders; chronic haematological disorders; or gastrointestinal disorders. Pre-existing conditions were reported by the participants at the time of enrolment based on medical history. All other participants were classified as healthy participants.

Criteria for evaluation

The primary endpoint was MAEs occurring within 31 days (D0–D30) after any dose. The secondary endpoints were solicited local (pain, redness, swelling) and general (children <5 years: fever, irritability, drowsiness, loss of appetite; participants ≥5 years: fever, headache, fatigue, gastrointestinal symptoms, joint pain, muscle ache, shivering, sweating) AEs self-reported during a 7 day follow-up period (D0–D6) after any dose, and SAEs and AESIs occurring within 181 days (D0–D180) after any dose. As recommended by the CHMP, the safety database was searched for all AESIs corresponding to the recommended preferred terms (PTs) or narrow Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs).[10] Potential cases were identified according to available case definitions such as those developed by the Brighton Collaboration (http://www.brightoncollaboration.org) or medical judgment. A medically qualified person evaluated all cases reported for diagnosis ascertainment to identify confirmed cases of interest among all the potential cases identified. The medical evaluation of diagnosis certainty had three possible outcomes for each potential case:

- Diagnosis confirmed (confirmed AESI),
- Reported without sufficient information to conclude on diagnosis certainty, or
- Diagnosis excluded (non-AESI).

Cases with a confirmed diagnosis and cases reported without sufficient information to conclude on diagnosis certainty were included in the Observed-to-Expected (O/E) analyses of AESIs, with the exception of two cases of anaphylactic shock that were related to concomitant medications.

The investigators assessed some of the AEs as possibly related to the vaccination and general descriptive information on these related AEs is provided here. However to increase sensitivity all main analyses included all reported AEs, irrespective whether or not they were considered vaccination-related, as per investigator's assessment.

Statistical analysis

The sample size was determined based on the recommendations of the EMA for post-authorisation evaluation of medicines for human use.[10] The target population consisted of at least 9000 participants vaccinated according to the national vaccination programme at participating general practices. According to the EMA power estimations, "a total sample size of 9000 participants would be able to rule out at 95% confidence events [MAEs, SAEs and AESIs] occurring with a frequency of 1 per 3000 if no event is observed (provided that the event occur in all age categories)".

Demographics characteristics were summarised by descriptive statistics. The incidence of solicited AEs in the reactogenicity subset, and the proportion of unsolicited AEs, SAEs, MAEs and AESIs in the total vaccinated cohort were calculated along with the associated 95% confidence intervals (CIs) using an exact method. MAEs, SAEs and AESI were categorised according to the MedDRA PT. Missing data was not replaced for the analysis of solicited symptoms. Analysis of MAEs, SAEs and AESIs included all vaccinated participants, and participants that did not report the event were considered as participants without the event. Incidences were computed for the overall population, per age group, risk groups and for pregnancy status. The following age groups were considered for the analysis: < 2 years, 2-4

years, 5-9 years, 10-17 years, 18-44 years, 45-60 years, and >60 years. Observed-to-expected analyses were performed for AESIs and fatalities. In order to take the age distribution of the study population into account, an age-stratified expected number of cases was calculated. The observed incidences for AESIs within 31 and 181 days following the first dose were compared to expected incidences available for convulsion,[15] optic neuritis,[16] Bell's palsy,[17] GBS,[18] and Multiple Sclerosis for demyelination.[19] The expected rate was age-stratified and the standardised incidence ratio (SIR) was calculated as observed/expected .SIR was presented by age group and overall, with 95% CIs based on the CI of the numerator. As only one case of GBS was identified in a male single male participant, the observed number of cases was compared to the expected number of cases for males only. Expected mortality rates were retrieved from the Office for National Statistics, UK.[20] The standardised mortality ratio (SMR) was calculated for the follow-up periods of 31 and 181 days after each dose as observed incidence rate (IR) divided by expected IR. SMR was presented by age group and overall, with 95% CIs based on the CI of the numerator. The date of the event was defined as the date of death and not the date of onset of the associated AE. For any participants that were lost to follow-up, a request was sent to the National Health Service (NHS) Information Centre Medical Research Department in order to identify any fatality that was not recorded.

The software used for all statistical analyses was SAS (Statistical Analysis System) version 9.2.

RESULTS

Demographics

From the MRC GPRF, 120 English general practices were asked to partake in the study. Of these, 87 general practices participated and these were largely distributed throughout England. A total of 9215 participants were enrolled and data for analysis was available on 9143 participants (Study cohort). Further, 72 participants were eliminated for not complying fully with the written informed consent process. The mean (± SD) age of the study cohort was 54.7 ± 20.2 years (range 7 months to 97 years) and 51.1% were female (Table 1~~Table 1~~). The majority (80.8%) of participants were in the non-immunocompromised and at risk group, 6.3% were immunocompromised and 12.8% were healthy participants. 94.4% (N=8633/9143) of the participants completed the 6 month follow-up. Reasons for non-completion of the study are detailed in Figure 1~~Figure 1~~.

Reactogenicity

The reactogenicity analysis included 682 participants (52.8% females) (Table 1~~Table 1~~). Overall, the most frequently reported solicited local AE was injection site pain (children ≤17 years: 79.5%, adults: 78.3%) followed by injection site redness (children: 49.6%, adults: 19.8%) for both age groups (Figure 2~~Figure 2~~A). The median duration of local symptoms ranged between 2 and 5 days for any symptom. In children, incidence of local symptoms was higher in at risk participants than healthy children, especially for swelling (43.4% [32.1–55.3] vs. 19.5% [8.8–34.9]) (Table 2~~Table 2~~). In adults, local pain was more frequently reported by healthy

participants (80.0%) and participants at risk (78.5%) than immunocompromised participants (73.0%). Local redness (27.0%) and swelling (21.6%) were more frequently reported in immunocompromised participants than in healthy participants or participants at risk (Table 2~~Table 2~~). The median duration of local symptoms was somewhat longer in immunocompromised participants (4.0–4.5 days) compared to healthy participants (2.0–3.0 days) and participants at risk (3.0 days).

In children <5 years of age, irritability was the most common solicited general AE (61.8%; Figure 2~~Figure 2~~B). Most solicited general AEs were reported more often for children aged <5 years that were considered healthy compared to those at risk (Table 2~~Table 2~~). Myalgia (muscle aches) was the most common solicited general AE in children aged 5–17 years (61.9%) and adults aged >17 years (46.9%). The overall proportion of participants with Grade 3 solicited symptoms did not exceed 7.7%. In children aged 5–17 years, most symptoms were commonly observed in at risk children, except for fever which was more frequently observed in healthy children (28.6% vs. 14.3%) and for joint pain for which there was no difference between the groups (28.6% in both groups). In adults, the reactogenicity profile was generally highest in the immunocompromised participants compared to the healthy participants and participants at risk (Table 2~~Table 2~~). In all age groups, the median duration of a grade 3 solicited general symptoms ranged between 1–2 days.

MAEs, SAEs and AESIs

At least one MAE was reported by investigators for 13.3% (1219/9143) of participants within the 31-day post-vaccination period (Table 3~~Table 3~~). The most frequently reported MAEs were

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associated with “infections and infestations”. Lower and upper respiratory tract infections were the most frequently reported event PTs. A higher proportion of MAEs (any symptom) were reported in the immunocompromised participants (18.5%) compared to at risk (13.0%) and healthy (13.3%) participants. 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 infections (16/9143) and upper respiratory tract infection (10/9143) and cough (10/9143).

At least one SAE was reported for 4.5% (411/9143) of participants in the study cohort during the 181-day post-vaccination period with pneumonia (16 cases), lower respiratory tract infections (13 cases) and asthma (13 cases) the most frequently reported event PTs (Table 4~~Table 4~~). Of these, 1.2% (113/9143) of participants reported at least one SAE during the 31-day post-vaccination period, with lower respiratory tract infection (0.07%, 6/9143) the most frequently reported event PT. 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).

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 (Table 5~~Table 5~~). 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 most frequently reported AESI was convulsion: 11 episodes of convulsion occurring in 8 participants. For

participants with more than one episode of convulsion, only the first occurrence after vaccination was included in the analyses. 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,

There were 53 deaths (0.58%) reported during the entire study period, with an additional three cases retrieved from the NHS Information Centre Medical Research Department. In particular, 41 deaths occurred during the 181-day period after vaccination, one additional case was retrieved from the NHS Information Centre Medical Research Department, corresponding to an incidence mortality rate of 940 per 100,000 person*years (95% CI: 675–1275). None of the fatalities reported (40 cases) were considered by the investigator as related to vaccination, while the one additional fatality was assessed by a GlaxoSmithKline safety physician who considered that there was no reasonable possibility that the fatal event was related to vaccination, but rather related to the participant's medical conditions. 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.

Observed-to-expected (O/E) analyses

The observed number of fatalities was below the expected number of fatalities (SMR: 0.45; [95% CI: 0.32–0.61]). There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction. According to the O/E analysis, incidence of AESI was higher than expected for two AESIs. The first AESI was neuritis, for which a single case occurred within 30 days (SIR: 65.51 [1.66–365.01]). This event was not considered serious. 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 paresthesia in the left hand and was diagnosed with neuritis (not specified otherwise). No clinical details or relevant diagnostic test results were provided by investigator. The second AESI was convulsions with two cases reported within the 30 days (3.84 [0.47–13.89]), but was only significant for the 181 day interval (2.65 [1.14–5.22]).

DISCUSSION

Statement of principal findings

This prospective observational study was set-up in time to enrol the first participant when the mass vaccination campaign began in the UK. Overall target recruitment was exceeded for both the study cohort and the reactogenicity cohort. Only a limited number of participants were lost to follow-up (<6%). The solicited adverse events reported were primarily common local and general symptoms: injection site-related AEs, irritability in young children and muscle aches in older children and adults. MAEs were reported for 1219 participants during the 31 day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events anticipated to be reported by the populations under study particularly during the winter season: i.e. respiratory tract infections. The observed number of fatalities was below the expected number of fatalities. There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction were received.

Confirmed cases of AESIs were rare (0.15%). The observed number of Bell's palsy, GBS and demyelination was below the expected number. The observed number of convulsions was higher than expected for the 181 day interval, but not for the 31-day interval; the lack of temporal association with vaccination is reassuring. The observed number of neuritis cases was higher than expected for the 30 day-interval, considering that only one case was retrieved. This event occurred in a non-immunocompromised at risk 86 years old male with no relevant past medical history. On day of vaccination the subject experienced neck stiffness and paraesthesias of his left hand. No clinical details or relevant diagnostic test results were provided and the final diagnosis

was neuritis. In general, the O/E analysis was overly sensitive, as both, prevalent cases and cases reported without sufficient information to conclude on diagnosis certainty were included. Furthermore, no correction for the multiplicity of comparisons was done.

Strengths and weaknesses of the study

General practices are the primary contact point for persons in the UK to access the National Health Service. The general practices were able to provide an almost complete overview of all medical events that occurred throughout the study,[14] so an almost complete ascertainment of the safety profile of the AS03 adjuvanted H1N1 (2009) pandemic influenza vaccine is the main strength of this study. A second strength of this study was the number of participants (i.e. over 9000) enrolled, which exceeded the sample size recommended by EMA for pharmacovigilance activities concerning pandemic vaccines.[10] Nevertheless, there are some limitations in this study. Firstly, no sample size estimations of the number of participants that should have been enrolled in each risk group (immunocompromised, at risk, and healthy participants) were performed. Thus it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes such as reactogenicity and MAEs in the general UK population. Additionally, the majority of participants involved in the study (81%) were classified as at risk according to the definitions of the UK Department of Health[13] and consequently enrolled in at risk group, resulting in a sample structure that differ from the general population. Second, a related limitation of this study is that the sample size may not be large enough for the assessment of the potential for the vaccine to be associated with rare adverse events such as autoimmune diseases. Another limitation is that there was no comparator group,

so proportions of observed outcomes were compared with the available background rates from the general population derived from literature.

Strengths and weaknesses of the study in relation to other studies

The reactogenicity and safety profiles of healthy participants were generally comparable to those observed in other trials on the H1N1 pandemic[7,21,22-24,26] and H5N1 prepandemic[8] vaccines. However, in the <5 years group, all general symptoms tended to be higher when compared to an H1N1 pandemic vaccine clinical trial (for example, irritability 46.2% vs. 61.8% in this study).[25] Also in the <5 years group, drowsiness and irritability tended to be higher when compared to an H1N1 pandemic vaccine[26] and an H5N1 prepandemic vaccine clinical trial (for instance drowsiness 24.5% vs. 38.2% and irritability 36.7% vs. 61.8%).[27]

There were 18 AESIs reported with the most common being 11 episodes of convulsions in eight participants. Five of these participants had a medical history of convulsion or epilepsy and, according to the study's investigators the convulsive episode was triggered by other possible causes (e.g. trauma, acute infection, alcohol consumption or lack of compliance with treatment). Febrile convulsion was only reported in one participant, a healthy 8 months old female. The remaining participants experienced a first convulsive episode occurring 38 days and 123 days respectively after vaccination, with no apparent cause. The incidence of convulsions, in particular febrile convulsions, has recently received much attention after an increased incidence of severe febrile convulsions in young children led to the suspension of the 2010 seasonal influenza vaccination program in Western Australia.[28] Further investigation into the cause of these convulsions showed that it was due to vaccination with one particular brand of trivalent

seasonal influenza vaccine and not associated with prior vaccination with the seasonal influenza or 2009 H1N1 pandemic vaccine.[29] Indeed, a recent study did not demonstrate an association between an increased risk of convulsions and vaccination with seasonal trivalent influenza vaccines (over a 10-year surveillance period) or the AS03-adjuvanted pandemic H1N1 vaccine in 2009–2010.[30]

Another AESI of particular interest is demyelination. Some forms of demyelination attack the central nervous system (the main example being multiple sclerosis), while others affect the peripheral nervous system (the main example being Guillain-Barré syndrome, which was analysed separately as AESI). There was one case of GBS reported in this study diagnosed as a possible mild GBS, occurring 106 days after vaccination in a 78 years old non-immunocompromised and at risk male who had a pre-existing medical condition of polyneuropathy (not otherwise specified). A previous mass vaccination campaign that ended in 1976 against swine influenza in the US was suspended due to the significantly increased rate of GBS in adults of all ages.[31] Although no increased risk of GBS following influenza vaccination was detected during the two subsequent seasonal influenza seasons,[32,33] the incidences of GBS and similar AEs following mass vaccination campaigns are still a concern. While a systemic review of meta-analysis of clinical trials assessing the effectiveness of the pandemic influenza A/H1N1 2009 vaccine did not detect any cases of GBS following vaccination,[34] a preliminary analysis by the Centers for Disease Control in the US suggested a significant association between the 2009 H1N1 vaccination and GBS.[35] Recent studies performed in several European countries reported no increased risk of GBS with pandemic influenza A/H1N1 2009 vaccine.[36,37] It has been a matter of debate whether vaccination may have the potential to exacerbate pre-existing relaxing-remitting conditions such as multiple sclerosis. This study was not adequately powered

to rule out a clinically relevant association between the 2009 H1N1 vaccination and a pre-existing relaxing-remitting condition. In our study, there was one participant who had a pre-existing secondary progressive multiple sclerosis that experienced a possible aggravation or flare-up occurring 62 days after vaccination. Multiple sclerosis relapse has been considered when assessing the evidence of a possible association with influenza vaccines. Clinical studies with cohorts of multiple sclerosis patients generally concluded that influenza vaccination did not appear to be associated with an increased risk of multiple sclerosis relapse.[38-41]

Conclusions

This study has shown that the 2009 pandemic influenza vaccine adjuvanted with the AS03 Adjuvant System showed clinically acceptable reactogenicity and safety profiles in all age and risk groups studied. There were limited safety data available regarding the safety of this vaccine in both children and adults before the outbreak of the pandemic. Thus, the experience acquired with this vaccine will be of benefit for the development of future vaccines against pandemic influenza outbreaks.

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TABLES

Table 1: **Demographic characteristics of the study cohort and the reactogenicity cohort**

Characteristic at vaccination	Study Cohort (N=9143)	Reactogenicity Cohort (N=682)
Age (years)		
Mean ± SD	54.7 ± 20.22	47.5 ± 24.27
Median (min–max)	60.0 (0–97)	54.0 (0–88)
Age groups	**n(%)**	**n(%)**
<2 years*	34 (0.4)	14 (2.1)
2–4 years	134 (1.5)	47 (6.9)
5–9 years	182 (2.0)	31 (4.5)
10–17 years	319 (3.5)	35 (5.1)
18–44 years	1717 (18.8)	125 (18.3)
45–60 years	2391 (26.2)	168 (24.6)
>60 years	4365 (47.7)	262 (38.4)
Gender	**n(%)**	**n(%)**
Female	4672 (51.1)	360 (52.8)
Male	4471 (48.9)	322 (47.2)
Risk Group †	**n(%)**	**n(%)**
Healthy	1170 (12.8)	117 (17.2)
Immunocompromised	579 (6.3)	39 (5.7)
Non-immunocompromised & at risk	7392 (80.9)	526 (77.1)

Max=maximum; min=minimum; N=number of participants in the cohort; SD=standard deviation; n(%)= number (percentage) of participant in the category
*The <2 years age group included participants 7─23 months of age
†Information regarding risk group was missing for two participants in the Study Cohort

Table 2: Proportion (%) of participants with solicited local and general adverse events (AEs) reported within the 7-day post-vaccination period (Reactogenicity cohort N=682).

	Children (≤17 years)			Adults (>17 years)		
	ImmunoComp	At Risk	Healthy	Immunocomp	At Risk	Healthy
	N=0	N=76	N=41	N=37	N=424	N=70
Pain		82.9 (72.5–90.6)	73.2 (57.1–85.8)	73.0 (55.9–86.2)	78.5 (74.3–82.4)	80.0 (68.7–88.6)
Grade 3		10.5 (4.7–19.7)	2.4 (0.1–12.9)	2.7 (0.1–14.2)	3.1 (1.6–5.2)	5.7 (1.6–14.0)
Redness		53.9 (42.1–65.5)	41.5 (26.3–57.9)	27.0 (13.8–44.1)	20.5 (16.8–24.7)	11.4 (5.1–21.3)
Grade 3		11.8 (5.6–21.3)	0 (0–8.6)	10.8 (3.0–25.4)	1.7 (0.7–3.4)	0 (0–5.1)
Swelling		43.4 (32.1–55.3)	19.5 (8.8–34.9)	21.6 (9.8–38.2)	16.7 (13.3–20.6)	17.1 (9.2–28.0)
Grade 3		9.2 (3.8–18.1)	0 (0–8.6)	5.4 (0.7–18.2)	0.5 (0.1–1.7)	4.3 (0.9–12.0)

	Children (<5 years)		Children (5–17 years)		Adults (>17 years)		
	At Risk	Healthy	At Risk	Healthy	Immunocomp	At Risk	Healthy
All General (N)	28	27	49	14	38	431	70
Drowsiness	28.6 (13.2–48.7)	48.1 (28.7–68.1)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Irritability	57.1 (37.2–75.5)	66.7 (46.0–83.5)					
Grade 3	7.1 (0.9–23.5)	7.4 (0.9–24.3)					
Loss of appetite	39.3 (21.5–59.4)	37.0 (19.4–57.6)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Fever	10.7 (2.3–28.2)	22.2 (8.6–42.3)	14.3 (5.9–27.2)	28.6 (8.4–58.1)	5.3 (0.6–17.7)	2.1 (1.0–3.9)	4.3 (0.9–12.0)
Grade 3	0 (0–12.3)	3.7 (0.1–19.0)	2.0 (1.0–10.9)	0 (0–23.2)	0 (0–9.3)	0.5 (0.1–1.7)	0 (0–5.1)
Fatigue			46.9 (32.5–61.7)	35.7 (12.8–64.9)	55.3 (38.3–71.4)	32.7 (28.3–37.4)	40.0 (28.5–52.4)

Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	7.9 (1.7–21.4)	1.9 (0.8–3.6)	7.1 (2.4–15.9)
Gastrointestinal	24.5 (13.3–38.9)	21.4 (4.7–50.8)	31.6 (17.5–48.7)	15.8 (12.5–19.6)	20.0 (11.4–31.3)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.4 (0.5–3.0)	5.7 (1.6–14.0)
Headache	44.9 (30.7–59.8)	28.6 (8.4–58.1)	39.5 (24.0–56.6)	34.3 (29.9–39.0)	41.4 (29.8–53.8)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	5.3 (0.6–17.7)	1.2 (0.4–2.7)	5.7 (1.6–14.0)
Joint pain	28.6 (16.6–43.3)	28.6 (8.4–58.1)	44.7 (28.6–61.7)	26.0 (21.9–30.4)	28.6 (18.4–40.6)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	0 (0–9.3)	1.9 (0.8–3.6)	5.7 (1.6–14.0)
Muscle aches	65.3 (50.4–78.3)	50.0 (23.0–77.0)	65.8 (48.6–80.4)	43.9 (39.1–48.7)	55.7 (43.3–67.6)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	7.9 (1.7–21.4)	2.1 (1.0–3.9)	5.7 (1.6–14.0)
Shivering	28.6 (16.6–43.3)	14.3 (1.8–42.8)	36.8 (21.8–54.0)	15.3 (12.0–19.1)	17.1 (9.2–28.0)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.6 (0.7–3.3)	2.9 (0.3–9.9)
Sweating	20.4 (10.2–34.3)	7.1 (0.2–33.9)	21.1 (9.6–37.3)	11.4 (8.5–14.8)	15.7 (8.1–26.4)
Grade 3	0 (0–7.3)	0 (0–23.2)	0 (0–9.3)	1.4 (0.5–3.0)	1.4 (0–7.7)

%(95% CI)=percentage of participants reporting the event with exact 95% confidence limit (lower limit–upper limit); N=number of participants in the cohort;

Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F).

Grade 3 redness was defined as being >50 mm, grade 3 swelling was > 50 mm and Grade 3 fever was >39°C.

Table 3: Most frequently reported (≥9 cases) medically attended adverse events (MAEs) within the 31-day post-vaccination period

Medically Attended Events (MAEs)[†]	ImmunoComp	At risk	Healthy	Total*
	N= 579	**N**= 7392	**N**= 1170	**N**= 9143
	n (%)	**n (%)**	**n (%)**	**n (%)**
At least one MAE	107 (18.5)	958 (13.0)	154 (13.2)	1219 (13.3)
Lower respiratory tract infection	12 (2.1)	94 (1.3)	4 (0.3)	110 (1.2)
Upper respiratory tract infection	5 (0.9)	56 (0.8)	14 (1.2)	75 (0.8)
Cough	5 (0.9)	49 (0.7)	6 (0.5)	60 (0.7)
Urinary tract infection	5 (0.9)	36 (0.5)	12 (1.0)	53 (0.6)
Asthma	1 (0.2)	39 (0.5)	1 (0.1)	41 (0.5)
Back pain	2 (0.4)	25 (0.3)	2 (0.2)	29 (0.3)
Abdominal pain	4 (0.7)	20 (0.3)	2 (0.2)	26 (0.3)
Diarrhoea	2 (0.4)	17 (0.2)	2 (0.2)	21 (0.2)
Arthralgia	0	16 (0.2)	4 (0.3)	20 (0.2)
Oropharyngeal pain	2 (0.4)	16 (0.2)	2 (0.2)	20 (0.2)
Chronic obstructive pulmonary disease	0	18 (0.2)	0	18 (0.2)
Conjunctivitis	1 (0.2)	13 (0.2)	3 (0.3)	17 (0.2)
Headache	2 (0.4)	10 (0.1)	5 (0.4)	17 (0.2)
Dyspnoea	5 (0.9)	9 (0.1)	3 (0.3)	17 (0.2)
Rash	0	16 (0.2)	1 (0.1)	17 (0.2)
Herpes zoster	1 (0.2)	13 (0.2)	2 (0.2)	16 (0.2)
Chest pain	1 (0.2)	13 (0.2)	1 (0.1)	15 (0.2)
Sinusitis	0	10 (0.1)	5 (0.4)	15 (0.2)
Pain in extremity	3 (0.5)	10 (0.1)	2 (0.2)	15 (0.2)
Otitis externa	0	13 (0.2)	1 (0.1)	14 (0.2)
Dizziness	0	11 (0.2)	3 (0.3)	14 (0.2)
Dyspepsia	0	11 (0.2)	2 (0.2)	13 (0.1)
Vomiting	2 (0.4)	8 (0.1)	2 (0.2)	12 (0.1)
Pyrexia	0	7 (0.1)	4 (0.3)	11 (0.1)
Bronchitis	2 (0.4)	6 (0.1)	2 (0.2)	10 (0.1)
Cellulitis	2 (0.4)	7 (0.1)	1 (0.1)	10 (0.1)
Pharyngitis	3 (0.5)	5 (0.1)	2 (0.2)	10 (0.1)
Musculoskeletal chest pain	1 (0.2)	9 (0.1)	0	10 (0.1)
Influenza-like illness	3 (0.5)	6 (0.1)	0	9 (0.1)
Fall	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)
Wheezing	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)

Immunocomp=participants identified as immunocompromised on study initiation; N=number of participants in the cohort; n (%)=number of participants reporting the event (percentage);
[†]MAEs were defined as events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a MAE led to hospitalization (or met any other SAE criteria), it was to be reported as a SAE.

*Information regarding risk group was missing for two participants

Table 4: Most frequently reported (≥5 cases) serious adverse events (SAEs) during the 181-day post-vaccination period (N=9143)

Serious Adverse Event (SAE)	Total[†] n (%)	Time from previous vaccination dose to SAE (range in days)
At least one SAE	411 (4.50)	
Pneumonia	16 (0.17)	30–178
Lower respiratory tract infection	13 (0.14)	6–171
Asthma	13 (0.14)	1–170
Chest pain	10 (0.11)	3–180
Urinary tract infection	9 (0.10)	14–147
Chronic obstructive pulmonary disease	8 (0.09)	5–172
Myocardial infarction	7 (0.08)	17–148
Acute coronary syndrome	6 (0.07)	55–172
Atrial fibrillation	6 (0.07)	1–157
Abdominal pain	6 (0.07)	<1–74
Vomiting	6 (0.07)	<1–176
Transient ischaemic attack	6 (0.07)	2–173
Cholecystitis	5 (0.05)	43–118
Bronchopneumonia	5 (0.05)	1–103
Sepsis	5 (0.05)	12–172
Radius fracture	5 (0.05)	66–156
Colon cancer	5 (0.05)	1–84
Pulmonary embolism	5 (0.05)	11–157

[†] n (%)=number of participants reporting the event (percentage)

Table 5. Adverse events of special interest (AESIs) reported within the 181-day post-vaccination period (N=9143)

Adverse Events of Special Interest (AESIs)[†]	n (%)	SIR [95% CI]
At least one AESI	14 (0.15)	
Convulsions	8 (0.09)	2.65 [1.14–5.22]
Non-febrile convulsions	7 (0.08)	
Febrile convulsion	1 (0.01)	
Bell's Palsy	3 (0.03)	2.70 [0.56–7.89]
Guillain-Barré syndrome	1 (0.01)	18.11 [0.46–100.89]
Neuritis	1 (0.01)	11.46 [0.29–63.85]
Demyelination	1 (0.01)	4.88 [0.12–27.17]

95% CI=95% confidence interval (lower limit–upper limit); n (%)=number of participants reporting event (percentage), more than one event could be reported for a participant; SIR = standardised incidence ratio

[†] The Adverse Events of Special Interest (AESI) for this study were: Anaphylactic reaction, Bell's palsy, convulsions, demyelination, Guillain-Barré syndrome, neuritis, non-infectious encephalitis, vaccination failure, vasculitis

FIGURES

Figure Legends

Figure 1

Flow diagram depicting the completion of study contact points with the reasons for discontinuation. Participants with contacts not performed for other reasons could have had following contacts. If only one dose of vaccine was given, Contact 2 was considered "Missing confirmed".

Figure 2

Solicited local (A) and general (B) adverse events reported during a 7-day follow-up period after any dose (Reactogenicity cohort N=682).

The general symptoms of drowsiness, irritability and loss of appetite were only assessed in children <5 years while fatigue, gastrointestinal, headache, joint pain, muscle aches, shivering and sweating were assessed in children aged 5–17 years and in adults. Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F). Data are shown as percentage of participants reporting the symptom with 95% confidence interval.

Figure 1

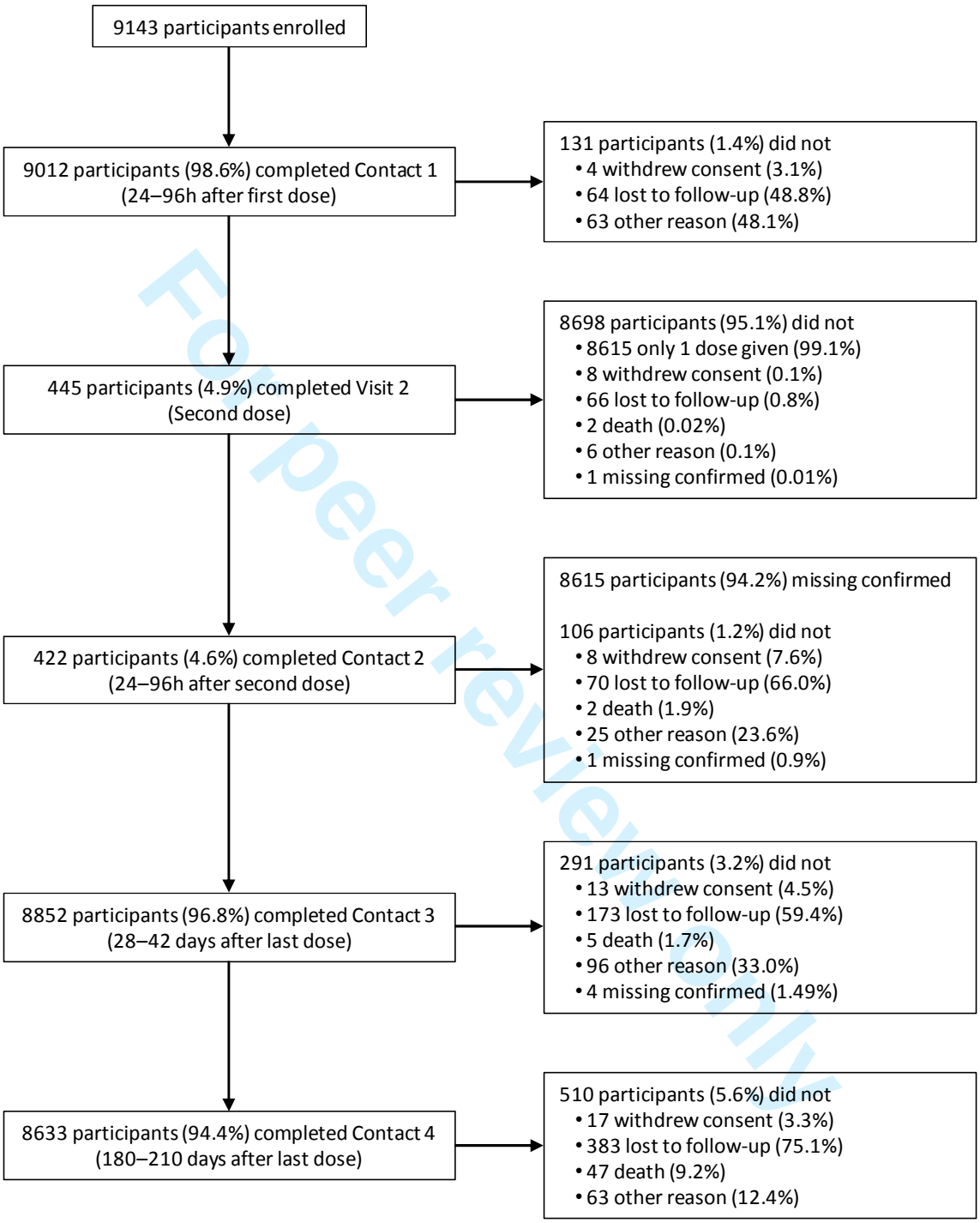
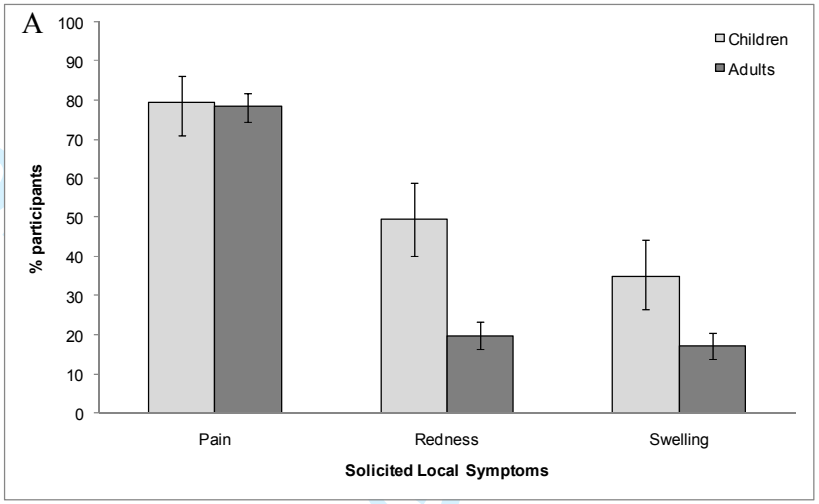


Figure 2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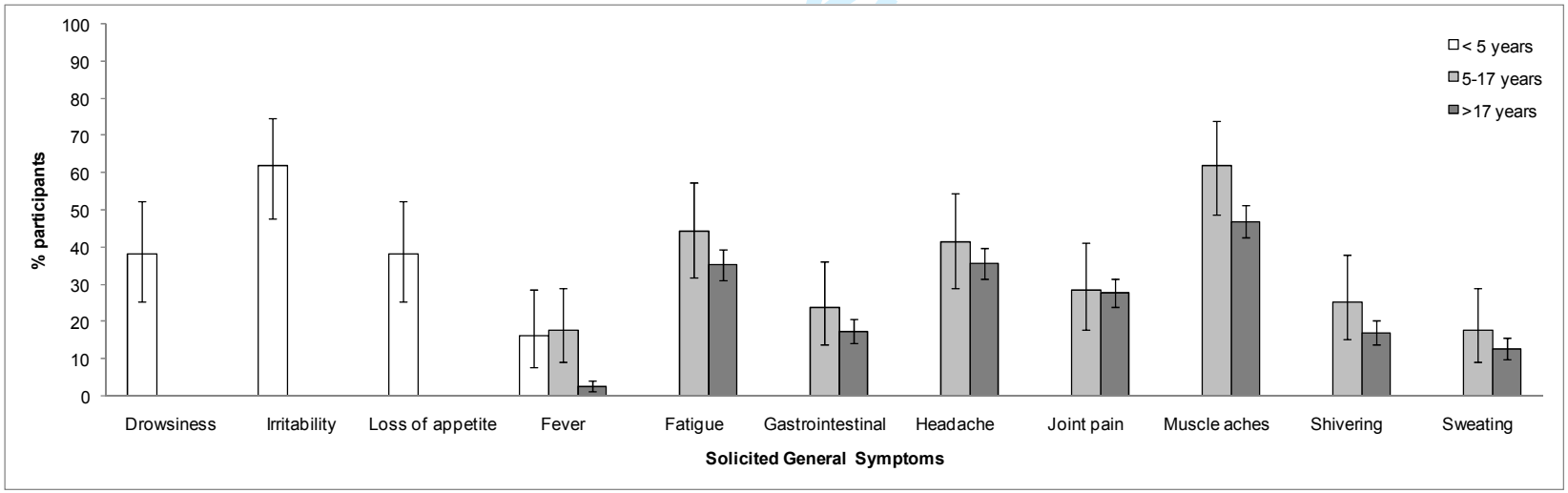
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Loss of appetite
Fever
Fatigue
Gastrointestinal
Headache
Joint pain
Muscle aches
Shivering
Sweating
Solicited General Symptoms

Title Page

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

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ABSTRACT

Objectives: To assess the safety of an AS03-adjuvanted split virion H1N1 (2009) vaccine (*Pandemrix*™) in persons vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom.

Design: Prospective, cohort, observational, post-authorisation safety study.

Setting: ~~87~~ Eighty-seven general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England.

Participants: A cohort of ~~We enrolled~~ 9143 ~~men and women~~individuals aged ~~between~~ 7 months ~~and~~to 97 years ~~>6 months old~~ who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the United Kingdom ~~were~~ was enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with ~~any~~ other H1N1 pandemic vaccine ~~before study enrolment~~ and any child in care.

Primary and secondary outcome measures: Medically attended events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs), and adverse events of special interest (AESI) following vaccination were collected for all participants. ~~,~~ Solicited adverse events (AEs) were assessed in a subset of participants ~~(reactogenicity subset)~~.

Results: MAEs were reported in 1219 and SAEs in 113 participants during the 31-days post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%), ~~and~~ muscle aches in children age 5–17 years (61.9%) and adults (46.9%). Eighteen AESIs experienced by 14 subjects met the criteria to be considered

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for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected.

Conclusions: ~~These r~~Results indicate that the AS03-adjuvanted H1N1 pandemic vaccine ~~was~~ showed ~~generally well tolerated with~~ a clinically acceptable reactogenicity and safety profile in all age and risk groups studied.

Trial registration: ClinicalTrials.gov, NCT00996853

SUMMARY

Article focus

- The outbreak of the H1N1 (2009) influenza pandemic led to vaccination of high risk groups with novel pandemic vaccines targeting the A/California/7/2009 (H1N1)v-like strain. Limited data about the clinical safety of these novel vaccines were available.
- In this paper we report the results of a post-authorisation safety study designed as a pharmacovigilance activity to evaluate safety endpoints related to the H1N1 pandemic vaccination.

Key messages

- The m~~M~~ost frequently reported medically-attended events and serious adverse events were consistent with events expected to be reported during the winter season.
- The observed number of adverse events of special interest —Bell's palsy, Guillain-Barré syndrome and demyelination— were below the expected number.
- The AS03-adjuvanted H1N1 (2009) vaccine was generally well-tolerated in the age and risk groups studied, with clinically acceptable reactogenicity and safety profiles.

Strengths and limitations of this study

- General practices, the primary point of contact for persons in the UK to access the National Health Service, were able to provide an extensive overview of the safety profile of the AS03-adjuvanted H1N1 pandemic influenza vaccine.

- Sample size was not estimated for each risk group (immunocompromised, at risk or healthy participants). Thus, it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes in the general UK population.

INTRODUCTION

Following the identification of several patients with swine-origin influenza that underwent human-to-human transmission,[1-3] a Pandemic Alert announcement was issued by the World Health Organisation. The lack of similarity of the pandemic virus strain to the current seasonal circulating influenza virus resulted in large scale vaccination programmes, particularly in high risk groups.[4;5]

In response, two~~a~~ pandemic vaccines were~~as~~ manufactured by GlaxoSmithKline Vaccines, including *Pandemrix*™. This split-virion vaccine against the A/California/7/2009 H1N1 strain was adjuvanted with an α-tocopherol oil-in-water emulsion-based Adjuvant System containing ~~s~~squalene (AS03)~~.~~.[6,7] and ~~vaccine~~ was produced in GlaxoSmithKline Vaccines' ~~GSK Biologicals'~~ Dresden (Germany) facility. The development of this vaccine was based on the experience acquired with H5N1 "mock-up" vaccines.[7-9] These H5N1 vaccines were highly immunogenic and had clinically acceptable safety profiles in children aged ≥6 months and adults.[7-9]

In response to this lack of available safety data, the European Medicines Agency (EMA) provided recommendations on pharmacovigilance activities that should be undertaken during the pre-pandemic and pandemic periods. During the 2009 pandemic influenza outbreak, the EMA recommended that vaccine manufacturers actively liaise with public health and regulatory authorities to explore the possibility of an association between A/H1N1 vaccines and severe adverse events.[10] In the United Kingdom (UK), a national immunisation programme against pandemic influenza was initiated in October 2009 by the UK Department of Health.[11,12] Priority for vaccination was given to persons that were aged between six months and 65 years in the current seasonal influenza clinical risk groups: persons with chronic respiratory disease and

asthma; chronic heart, renal, liver, or neurological disease; diabetes; or immunosuppression.[11,13] The current UK study was suggested by the Medicines and Healthcare products Regulatory Agency (MHRA) and was implemented as a commitment to the authorities based on the recommendations of the EMA.

This study was a post-authorisation safety study (PASS) designed as a pharmacovigilance activity in addition to analysing signal detection from spontaneous adverse events (AEs) reporting. Data were provided promptly and periodically to the authorities after the study start. We have previously reported a preliminary analysis based on the cohort of women known to be pregnant at the time of vaccination in this study,[14] and so pregnancy outcomes are not included in this report. Here, we discuss the other safety endpoints related to the H1N1 pandemic vaccination evaluated in all participants of this study.

METHODS

Study design

This was a prospective, observational, multicentre, single cohort study of persons vaccinated with the H1N1 (2009) pandemic influenza vaccine (*Pandemrix*™, GlaxoSmithKline ~~Biologicals~~Vaccines) in the UK. The study vaccine was produced in GlaxoSmithKline Vaccines Dresden, Germany. ~~9000 participants were to be enrolled in six age stratified groups.~~ A~~a~~ccording to recommendations from the Committee for Medicinal Products for Human Use (CHMP) of the EMA[10] ~~9000 participants were planned to be enrolled in six age stratified groups and~~ solicited adverse events were planned to be assessed in a subset of 600 participants. The study was sponsored by GSK as part of the AS03 adjuvanted H1N1 (2009) vaccine Risk Management Plan.

This study was conducted through general practices largely distributed throughout England and which were part of the Medical Research Council (MRC) General Practice Research Framework (GPRF). The vaccine was administered at the general practice according to the local pandemic influenza programme. Individuals were invited to participate in the study within 24h after vaccination. General practices collected background information (such as demographics, relevant medical history), data on medication and vaccinations administered during the study, reactogenicity data via patient self-completed diary cards and safety data related to the study endpoints. Participants were contacted by the general practice or other delegated party at specific time points (24–96h after any dose, 28–42 days after the last dose, 180–210 days after the last dose) to ensure that all clinical data pertaining to AEs was reported. The duration of the study was 7–8 months per participant; the first participant was enrolled on the 31st October 2009 and the last participant was enrolled on the 15th December 2009.

This study was conducted in accordance with good clinical practice (GCP) and all applicable regulatory requirements, including the Declaration of Helsinki. The study protocol and informed consent forms were reviewed and approved by a national Independent Ethics Committee. This study is registered at ClinicalTrials.gov (NCT00996853). A summary of the study protocol is available at www.gsk-clinicalstudyregister.com (Study ID 113585).

Study objectives

The primary objective of this study was to estimate the incidence of medically-attended adverse events (MAEs) in all enrolled vaccinated participants within 31 days after vaccination. The secondary objectives were to assess vaccine reactogenicity within seven days after vaccination, and to estimate the incidence of serious adverse events (SAEs) and adverse events of special interest (AESIs) in different age groups following an active surveillance of all enrolled vaccinated participants within 6 months after vaccination. An AESI was an event considered by the CHMP as worthy of closer follow-up as described in their recommendations for the Pharmacovigilance Plan following the administration of H1N1 pandemic vaccines. It included the following specific events for close monitoring: anaphylactic reaction, Bell's palsy, convulsion, demyelinating disorders, non-infectious encephalitis, Guillain-Barré syndrome (GBS), neuritis, vasculitis and vaccination failure.[10]

Study participants

Participants were included in the national H1N1 swine flu vaccination programme in the UK. Eligible participants included male and female persons ~~over 6 months of age~~ vaccinated with at least one dose of H1N1 (2009) pandemic influenza vaccine shortly before being recruited (less that 24 h) by a general practice that was participating in the study, and participants who the investigator believed that they or their parents/legally acceptable representative could and would comply with the requirements of the study protocol. Persons already vaccinated with any other H1N1 pandemic vaccine before study enrolment and any child in care were excluded from participation. Written informed consent was provided by the participant or participant's parent or legally acceptable representative. A subset of the participants, who had at least one non-missing data for at least one solicited symptom, was asked to be a part of the reactogenicity cohort. Diary cards for assessment of reactogenicity were provided to participants in the reactogenicity cohort.

Participants were classified according to their risk of complications from influenza infection according to the definitions of the UK Department of Health:[13] immunocompromised, at risk, or healthy participants. Immunocompromised participants were those who reported immunosuppression at the administration of the first dose of vaccine. At risk participants were participants who were not classified as immunocompromised and reported any of the following conditions at the administration of the first dose: spleen dysfunction ~~(absent or defective splenic function)~~ or asplenia (defective or absent splenic function, respectively); chronic respiratory disease, including asthma; chronic neurological diseases and neurodevelopmental disorders; chronic renal disease; chronic liver disease; metabolic disease; immune system disorders; chronic haematological disorders; or gastrointestinal disorders. Pre-existing conditions were ~~self-~~reported by the participants ~~during~~at the time of enrol~~l~~ment ~~first study visits~~ based on medical history. All other participants were classified as healthy participants.

Criteria for evaluation

The primary endpoint was MAEs occurring within 31 days (D0–D30) after any dose. The secondary endpoints were solicited local (pain, redness, swelling) and general (children <5 years: fever, irritability, drowsiness, loss of appetite; participants ≥5 years: fever, headache, fatigue, gastrointestinal symptoms, joint pain, muscle ache, shivering, sweating) AEs self-reported during a 7 day follow-up period (D0–D6) after any dose, and SAEs and AESIs occurring within 181 days (D0–D180) after any dose. As recommended by the CHMP, the safety database was searched for all AESIs corresponding to the recommended preferred terms (PTs) or narrow Standardised Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs).[10] Potential cases were identified according to available case definitions such as those developed by the Brighton Collaboration (http://www.brightoncollaboration.org) or medical judgment. A medically qualified person evaluated all cases reported for diagnosis ascertainment to identify confirmed cases of interest among all the potential cases identified. The medical evaluation of diagnosis certainty had three possible outcomes for each potential case:

- Diagnosis confirmed (confirmed AESI),
- Reported without sufficient information to conclude on diagnosis certainty, or
- Diagnosis excluded (non-AESI).

Cases with a confirmed diagnosis and cases reported without sufficient information to conclude on diagnosis certainty were included in the Observed-to-Expected (O/E) analyses of AESIs, with the exception of two cases of anaphylactic shock that were related to concomitant medications.

The investigators ~~classified~~assessed some of the ~~adverse events~~AEs as possibly related to the vaccination and~~-~~ general descriptive information ~~will be provided~~ on these related AEs is provided here. However to increase sensitivity ~~to be more sensitive~~ all main analyses included all reported AEs, irrespective whether or not they were considered vaccination-related, as per investigator's assessment~~ie whether initially labelled as related or not~~.

Statistical analysis

The sample size was determined based on the recommendations of the EMA for post-authorisation evaluation of medicines for human use.[10] The target population consisted of at least 9000 participants vaccinated according to the national vaccination programme at participating general practices. According to the EMA power estimations, "a total sample size of 9000 participants would be able to rule out at 95% confidence events [MAEs, SAEs and AESIs] occurring with a frequency of 1 per 3000 if no event is observed (provided that the event occur in all age categories)".

~~The software used for the statistical analyses was SAS (Statistical Analysis System) version 9.2.~~

Demographics characteristics were summarised by descriptive statistics. The incidence of solicited AEs in the reactogenicity subset, and the proportion of unsolicited AEs, SAEs, MAEs and AESIs in the total vaccinated cohort were calculated along with the associated 95% confidence intervals (CIs) using an exact method. MAEs, SAEs and AESI were categorised according to the MedDRA PT. Missing data was not replaced for the analysis of solicited

symptoms. Analysis of MAEs, SAEs and AESIs included all vaccinated participants, and participants that did not report the event were considered as participants without the event. Incidences were computed for the overall population, per age group, risk groups and for pregnancy status. The following age groups were considered for the analysis: < 2 years ~~(70 23 months)~~, 2-4 years, 5-9 years, 10-17 years, 18-44 years, 45-60 years, and >60 years.

Observed-to-expected analyses were performed for AESIs and fatalities. In order to take the age distribution of the study population into account, an age-stratified expected number of cases was calculated. The observed incidences for AESIs within 31 and 181 days following the first dose were compared to expected incidences available for convulsion,[15] optic neuritis,[16] Bell's palsy,[17] GBS,[18] and Multiple Sclerosis for demyelination.[19] The expected rate was age-stratified and the standardised incidence ratio (SIR) was calculated as observed/expected. SIR was presented by age group and overall, with 95% CIs based on the CI of the numerator. As only one case of GBS was identified in a male single male participant, the observed number of cases was compared to the expected number of cases for males only. Expected mortality rates were retrieved from the Office for National Statistics, UK.[20] The standardised mortality ratio (SMR) was calculated for the follow-up periods of 31 and 181 days after each dose as observed incidence rate (IR) divided by expected IR. SMR was presented by age group and overall, with 95% CIs based on the CI of the numerator. The date of the event was defined as the date of death and not the date of onset of the associated AE. For any participants that were lost to follow-up, a request was sent to the National Health Service (NHS) Information Centre Medical Research Department in order to identify any fatality that was not recorded.

The software used for all statistical analyses was SAS (Statistical Analysis System) version 9.2.

RESULTS

Demographics

From the MRC GPRF, 120 English general practices were asked to partake in the study. Of these, 87 general practices participated and these were largely distributed throughout England. A total of 9215 participants were enrolled and data for analysis was available on 9143 participants (Study cohort). Further, 72 participants were eliminated for not complying fully with the written informed consent process. The mean (± SD) age of the study cohort was 54.7 ± 20.2 years (range ~~<1~~7 months to 97 years) and 51.1% were female (Table 1~~Table 1~~). The majority (80.8%) of participants were in the non-immunocompromised and at risk group, 6.3% were immunocompromised and 12.8% were healthy participants. 94.4% (N=8633/9143) of the participants completed the 6 month follow-up. Reasons for non-completion of the study are detailed in Figure 1~~Figure 1~~Figure 1.

Reactogenicity

~~682 participants (52.8% females) were included T~~in the reactogenicity analysis included 682 participants (52.8% females) (Table 1~~Table 1~~Table 1). Overall, the most frequently reported solicited local AE was injection site pain (children ≤17 years: 79.5%, adults: 78.3%) followed by injection site redness (children: 49.6%, adults: 19.8%) for both age groups (Figure 2~~Figure 2~~A). The median duration of local symptoms ranged between 2 and 5 days for any symptom. In children, incidence of local symptoms was higher in at risk participants than healthy children, especially for swelling (43.4% [32.1–55.3] vs. 19.5% [8.8–34.9]) (Table 2~~Table 2~~). In adults,

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local pain was more frequently reported by healthy participants (80.0%) and participants at risk (78.5%) than immunocompromised participants (73.0%). Local redness (27.0%) and swelling (21.6%) were more frequently reported in immunocompromised participants than in healthy participants or participants at risk (Table 2~~Table 2~~). The median duration of local symptoms was somewhat longer in immunocompromised participants (4.0–4.5 days) compared to healthy participants (2.0–3.0 days) and participants at risk (3.0 days).

In children <5 years of age, irritability was the most common solicited general AE (61.8%; Figure 2~~Figure 2~~B). Most solicited general AEs were reported more often for children aged <5 years that were considered healthy compared to those at risk (Table 2~~Table 2~~). Myalgia (muscle aches) was the most common solicited general AE in children aged 5–17 years (61.9%) and adults aged >17 years (46.9%). The overall proportion of participants with Grade 3 solicited symptoms did not exceed 7.7%. In children aged 5–17 years, most symptoms were commonly observed in at risk children, except for fever which was more frequently observed in healthy children (28.6% vs. 14.3%) and for joint pain for which there was no difference between the groups (28.6% in both groups). In adults, the reactogenicity profile was generally highest in the immunocompromised participants compared to the healthy participants and participants at risk (Table 2~~Table 2~~). In all age groups, the median duration of a grade 3 solicited general symptoms ranged between 1–2 days.

MAEs, SAEs and AESIs

At least one MAE was reported by investigators for 13.3% (1219/9143) of participants within the 31-day post-vaccination period (Table 3~~Table 3~~). The most frequently reported MAEs were

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associated with “infections and infestations”. Lower and upper respiratory tract infections were the most frequently reported event PTs. A higher proportion of MAEs (any symptom) were reported in the immunocompromised participants (18.5%) compared to at risk (13.0%) and healthy (13.3%) participants. One hundred and fifty four participants experienced a~~A~~t least one MAE ~~with causal relationship to vaccination (as~~ assessed by investigators as possibly related to vaccination~~) was reported for 154 participants~~, with the most frequently reported event PTs being:l~~-~~ower ~~and upper~~ respiratory tract infections ~~being the most frequently reported event PTs~~ (1~~2~~6/9143) and upper respiratory tract infection (10/9143) and cough (10/9143). ~~Per age group, the most frequently reported PTs were: conjunctivitis (8.82%, 3/34) and lower respiratory tract infection (8.82%, 3/34) in the <2 years group; upper respiratory tract infection (8.96%, 12/134) in the 2–4 years and in 5–9 years groups (2.20%, 4/182); asthma (1.25%, 4/319) and oropharyngeal pain (1.25%, 4/319) in the 10–17 years group; upper respiratory tract infection (1.28%, 22/1717) in the 18–44 years group; and lower respiratory tract infection (0.96%, 23/2391) in the 45–60 years and in the >60 years age groups (1.42%, 62/4365).~~

At least one SAE was reported for 4.5% (411/9143) of participants in the study cohort during the 181-day post-vaccination period with pneumonia (16 cases), lower respiratory tract infections (13 cases) and asthma (13 cases) the most frequently reported event PTs (Table 4~~Table 4~~). Of these, 1.2% (113/9143) of participants reported at least one SAE during the 31-day post-vaccination period, with lower respiratory tract infection (0.07%, 6/9143) the most frequently reported event PT. Eleven participants experienced a~~A~~t least one SAE assessed by investigators as possibly related to vaccination, with asthma/asthmatic crisis being the most frequently reported event PTs (3/9143)~~with a causal relationship with the vaccination was reported for 11 participants~~.

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During the 181-day post-vaccination period, 22 participants reported ~~at least one~~26 potential AESI. ~~The most frequently reported AESI was convulsion: 11 episodes of convulsion occurring in 8 participants.~~ After medical review, only 18 AESIs (including confirmed cases and cases for which there was insufficient information confirm the certainty of diagnosis) ~~experienced by~~in 14 participants ~~met the criteria to be~~were considered for the Observed-to-expected *(O/E)* analyses (Table 5~~Table 5~~~~Table 5~~). 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 most frequently reported AESI was convulsion: 11 episodes of convulsion occurring in 8 participants. For participants with more than one episode of convulsion, only the first occurrence after vaccination was included in the analyses. AESIs not included in analyse~~is~~ were: 2 cases of anaphylactic reaction experienced by 2 participants, which ~~were related to concomitant medication~~occurred at 69 and 145 days after vaccination, and were causally associated to other medications (~~i.e.~~ atracurium besylate in one case and terbinafine in the other case); 1 case of polymyalgia rheumatica which was~~ere~~ ~~excluded as~~not associated with vasculitis, and 5 cases of circulatory collapse in 45 elderly participants. These 5 cases~~ which~~ were excluded as anaphylaxis, as ~~these events~~they were assessed by the investigators as being associated to the patients'~~their~~ coexisting cardiovascular diseases. ~~.~~

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There were 53 deaths (0.58%) reported during the entire study period, with an additional three cases retrieved from the NHS Information Centre Medical Research Department. In particular, 41 deaths occurred during the 181-day period after vaccination, one additional case was retrieved from the NHS Information Centre Medical Research Department, corresponding to an incidence mortality rate of 940 per 100,000 person*years (95% CI: 675–1275). None of the fatalities reported (40 cases) were considered by the investigator as related to vaccination, while the one

additional fatality was assessed by a GlaxoSmithKline safety physician who considered that there was no reasonable possibility that the fatal event was related to vaccination, but rather related to the participant's medical conditions. 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.

Observed-to-expected (O/E) analyses

The observed number of fatalities was below the expected number of fatalities (SMR: 0.45; [95% CI: 0.32–0.61]). There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction. According to the O/E analysis, incidence of AESI was higher than expected for two AESIs. The first AESI wa~~i~~s neuritis, for which a single case occurred within 30 days (SI~~M~~R: 65.51 [1.66–365.01]). This event was not considered serious. 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 ~~of~~ in the ~~on~~ left hand and was diagnosed with neuritis (not specified otherwise). No clinical details or relevant diagnostic test results were provided by investigator. The second AESI wa~~i~~s convulsions with two cases reported within the 30 days (3.84 [0.47–13.89]), but was only significant for the 181 day interval (2.65 [1.14–5.22]).

DISCUSSION

Statement of principal findings

This prospective observational study was set-up in time to enrol the first participant when the mass vaccination campaign began in the UK. Overall target recruitment was exceeded for both the study cohort and the reactogenicity cohort. Only a limited number of participants were lost to follow-up (<6%). The solicited adverse events reported were primarily common local and general symptoms: injection site-related AEs, irritability in young children and muscle aches in older children and adults. MAEs were reported for 1219 participants during the 31 day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events anticipated to be reported by the populations under study particularly during the winter season: i.e. respiratory tract infections. The observed number of fatalities was below the expected number of fatalities. There were no reports suggestive of non-infectious encephalitis and vaccination failure, and no confirmed reports of vasculitis or vaccine-related anaphylactic reaction were received.

Confirmed cases of AESIs were rare (0.15%). The observed number of Bell's palsy, GBS and demyelination was below the expected number. The observed number of convulsions was higher than expected for the 181 day interval, but not for the 31-day interval; the lack of temporal association with vaccination is reassuring. The observed number of neuritis cases was higher than expected for the 30 day-interval, considering that only one case was retrieved. This event occurred in a non-immunocompromised at risk 86 years old male with no relevant past medical history. On day of vaccination the subject experienced neck stiffness and paraesthesias of his left hand. No clinical details or relevant diagnostic test results were provided and the final diagnosis

was neuritis. In general, the O/E analysis was overly sensitive, as both, prevalent cases and cases reported without sufficient information to conclude on diagnosis certainty were included. Furthermore, no correction for the multiplicity of comparisons was done.

Strengths and weaknesses of the study

General practices are the primary contact point for persons in the UK to access the National Health Service. The general practices were able to provide an almost complete overview of all medical events that occurred throughout the study,[14] so an almost complete ascertainment of the safety profile of the AS03 adjuvanted H1N1 (2009) pandemic influenza vaccine is the main strength of this study. A second strength of this study was the number of participants (i.e. over 9000) enrolled, which exceeded the sample size recommended by EMA for pharmacovigilance activities concerning pandemic vaccines.[10] Nevertheless, there are some limitations in this study. Firstly, no sample size estimations of the number of participants that should have been enrolled in each risk group (immunocompromised, at risk, and healthy participants) were performed. Thus it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes such as reactogenicity and MAEs in the general UK population. Additionally, the majority of participants involved in the study (81%) were classified as at risk according to the definitions of the UK Department of Health[13] and consequently enrolled in at risk group, resulting in a sample structure that differ from the general population. Second, a related limitation of this study is that the sample size may not be large enough for the assessment of the potential for the vaccine to be associated with rare adverse events such as autoimmune diseases. Another limitation is that there was no comparator group,

so proportions of observed outcomes were compared with the available background rates from the general population derived from literature.

Strengths and weaknesses of the study in relation to other studies

The reactogenicity and safety profiles of healthy participants were generally comparable to those observed in other trials on the H1N1 pandemic[7,21,22-24,26] and H5N1 prepandemic[8] vaccines. However, in the <5 years group, all general symptoms tended to be higher when compared to an H1N1 pandemic vaccine clinical trial (for example, irritability 46.2% vs. 61.8% in this study).[25,2] Also in the <5 years group, drowsiness and irritability tended to be higher when compared to an H1N1 pandemic vaccine[23,6] and an H5N1 prepandemic vaccine clinical trial (for instance drowsiness 24.5% vs. 38.2% and irritability 36.7% vs. 61.8%).[24,7]

There were 18 AESIs reported with the most common being 11 episodes of convulsions in eight participants. Five of these participants had a medical history of convulsion or epilepsy and, according to the study's investigators the convulsive episode was triggered by other possible causes (e.g. trauma~~tism~~, acute infection, alcohol consumption or lack of compliance with treatment). Febrile convulsion was only reported in one participant, a healthy 8 months old female. The remaining participants experienced a first convulsive episode occurring 38 days and 123 days respectively after vaccination, with no apparent cause. The incidence of convulsions, in particular febrile convulsions, has recently received much attention after an increased incidence of severe febrile convulsions in young children led to the suspension of the 2010 seasonal influenza vaccination program in Western Australia.[25,8] Further investigation into the cause of these convulsions showed that it was due to vaccination with one particular brand of trivalent

seasonal influenza vaccine and not associated with prior vaccination with the seasonal influenza or 2009 H1N1 pandemic vaccine.[26,9] Indeed, a recent study did not demonstrate an association between an increased risk of convulsions and vaccination with seasonal trivalent influenza vaccines (over a 10-year surveillance period) or the AS03-adjuvanted pandemic H1N1 vaccine in 2009–2010.[30,27]

Another AESI of particular interest is demyelination. Some forms of demyelination attack the central nervous system (the main example being multiple sclerosis), while others affect the peripheral nervous system (the main example being Guillain-Barré syndrome, which was analysed separately as AESI). There was one case of GBS reported in this study diagnosed as a possible mild GBS, occurring 106 days after vaccination in a 78 years old non-immunocompromised and at risk male who had a pre-existing medical condition of polyneuropathy (not otherwise specified). A previous mass vaccination campaign that ended in 1976 against swine influenza in the US was suspended due to the significantly increased rate of GBS in adults of all ages.[28,31] Although no increased risk of GBS following influenza vaccination was detected during the two subsequent seasonal influenza seasons,[29,32,33,30] the incidences of GBS and similar AEs following mass vaccination campaigns are still a concern. While a systemic review of meta-analysis of clinical trials assessing the effectiveness of the pandemic influenza A/H1N1 2009 vaccine did not detect any cases of GBS following vaccination,[31,4] a preliminary analysis by the Centers for Disease Control in the US suggested a significant association between the 2009 H1N1 vaccination and GBS.[32,5] Recent studies performed in several European countries reported no increased risk of GBS with pandemic influenza A/H1N1 2009 vaccine.[33,6,34,7] It has been a matter of debate whether vaccination may have the potential to exacerbate pre-existing relaxing-remitting conditions such as multiple sclerosis. This study was not adequately powered

to rule out a clinically relevant association between the 2009 H1N1 vaccination and a pre-existing relaxing-remitting condition. In our study, there was one participant who had a pre-existing secondary progressive multiple sclerosis that experienced a possible aggravation or flare-up occurring 62 days after vaccination. Multiple sclerosis relapse has been considered when assessing the evidence of a possible association with influenza vaccines. Clinical studies with cohorts of multiple sclerosis patients generally concluded that influenza vaccination did not appear to be associated with an increased risk of multiple sclerosis relapse.[3~~5~~8-41~~3~~8]

Conclusions

This study has shown that the 2009 pandemic influenza vaccine adjuvanted with the AS03 Adjuvant System ~~was~~ showed~~generally well tolerated in all age and risk groups studied with~~ clinically acceptable reactogenicity and safety profiles in all age and risk groups studied~~.~~. There were~~as~~ limited safety data available regarding the safety of this vaccine in both children and adults before the outbreak of the pandemic. Thus, the experience acquired with this vaccine will be of benefit for the development of future vaccines against pandemic influenza outbreaks.

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Contributorship: Vincent Bauchau, Irwin Nazareth and Dominique Rosillon conceived and designed the study. Irwin Nazareth acquired the data. All authors conceived the paper. François Haguinet carried out statistical analysis. Dominique Rosillon participated in the statistical analysis. All authors participated in the analysis and interpretation of the data. All authors were involved in the drafting of the article or revising it critically for important intellectual content, and final approval of the manuscript. All authors had full access to the data and had final responsibility to submit for publication. Claire Marie Seymour and Adriana Rusu (XPE Pharma & Science) provided writing assistance on behalf of GlaxoSmithKline Vaccines Biologicals and Géraldine Drevon (CRO MSource) provided editorial assistance and manuscript coordination. Vincent Bauchau is guarantor.

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Ethical approval: All participants provided written informed consent before taking part. The study protocol and informed consent forms were reviewed and approved by a national Independent Ethics Committee.

Data sharing statement: Consent was not obtained from the participants but the presented data are depersonalised and risk of identification is low. No additional data available.

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TABLES

Table 1: **Demographic characteristics of the study cohort and the reactogenicity cohort**

Characteristic at vaccination	Study Cohort (N=9143)	Reactogenicity Cohort (N=682)
Age (years)		
Mean ± SD	54.7 ± 20.22	47.5 ± 24.27
Median (min–max)	60.0 (0–97)	54.0 (0–88)
Age groups	**n(%)**	**n(%)**
~~0–1~~<2 years*	34 (0.4)	14 (2.1~~0~~)
2–4 years	134 (1.5)	47 (6.9)
5–9 years	182 (2.0)	31 (4.5)
10–17 years	319 (3.5)	35 (5.1)
18–44 years	1717 (18.8)	125 (18.3)
45–60 years	2391 (26.2~~+~~)	168 (24.6)
>60 years	4365 (47.7)	262 (38.4)
Gender	**n(%)**	**n(%)**
Female	4672 (51.1)	360 (52.8)
Male	4471 (48.9)	322 (47.2)
Risk Group ~~(~~†	**n(%)**	**n(%)**
Healthy	1170 (12.8)	117 (17.2)
Immunocompromised	579 (6.3)	39 (5.7)
Non-immunocompromised & at risk	7392 (80.9)	526 (77.1)

Max=maximum; min=minimum; N=number of participants in the cohort; SD=standard deviation; n(%)= number (percentage) of participant in the category

*The <2 years age group included participants ~~0~~7~~–~~23 months of age

†Information regarding risk group was missing for two participants in the Study Cohort

Table 2: Proportion (%) of participants with solicited local and general adverse events (AEs) reported within the 7-day post-vaccination period (Reactogenicity cohort N=682).

	Children (≤17 years)			Adults (>17 years)		
	ImmunoComp	At Risk	Healthy	Immunocomp	At Risk	Healthy
	N=0	N=76	N=41	N=37	N=424	N=70
Pain		82.9 (72.5–90.6)	73.2 (57.1–85.8)	73.0 (55.9–86.2)	78.5 (74.3–82.4)	80.0 (68.7–88.6)
Grade 3		10.5 (4.7–19.7)	2.4 (0.1–12.9)	2.7 (0.1–14.2)	3.1 (1.6–5.2)	5.7 (1.6–14.0)
Redness		53.9 (42.1–65.5)	41.5 (26.3–57.9)	27.0 (13.8–44.1)	20.5 (16.8–24.7)	11.4 (5.1–21.3)
Grade 3		11.8 (5.6–21.3)	0 (0–8.6)	10.8 (3.0–25.4)	1.7 (0.7–3.4)	0 (0–5.1)
Swelling		43.4 (32.1–55.3)	19.5 (8.8–34.9)	21.6 (9.8–38.2)	16.7 (13.3–20.6)	17.1 (9.2–28.0)
Grade 3		9.2 (3.8–18.1)	0 (0–8.6)	5.4 (0.7–18.2)	0.5 (0.1–1.7)	4.3 (0.9–12.0)

	Children (<5 years)		Children (5–17 years)		Adults (>17 years)		
	At Risk	Healthy	At Risk	Healthy	Immunocomp	At Risk	Healthy
All General (N)	28	27	49	14	38	431	70
Drowsiness	28.6 (13.2–48.7)	48.1 (28.7–68.1)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Irritability	57.1 (37.2–75.5)	66.7 (46.0–83.5)					
Grade 3	7.1 (0.9–23.5)	7.4 (0.9–24.3)					
Loss of appetite	39.3 (21.5–59.4)	37.0 (19.4–57.6)					
Grade 3	3.6 (0.1–18.3)	7.4 (0.9–24.3)					
Fever	10.7 (2.3–28.2)	22.2 (8.6–42.3)	14.3 (5.9–27.2)	28.6 (8.4–58.1)	5.3 (0.6–17.7)	2.1 (1.0–3.9)	4.3 (0.9–12.0)
Grade 3	0 (0–12.3)	3.7 (0.1–19.0)	2.0 (1.0–10.9)	0 (0–23.2)	0 (0–9.3)	0.5 (0.1–1.7)	0 (0–5.1)
Fatigue			46.9 (32.5–61.7)	35.7 (12.8–64.9)	55.3 (38.3–71.4)	32.7 (28.3–37.4)	40.0 (28.5–52.4)

Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	7.9 (1.7–21.4)	1.9 (0.8–3.6)	7.1 (2.4–15.9)
Gastrointestinal	24.5 (13.3–38.9)	21.4 (4.7–50.8)	31.6 (17.5–48.7)	15.8 (12.5–19.6)	20.0 (11.4–31.3)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.4 (0.5–3.0)	5.7 (1.6–14.0)
Headache	44.9 (30.7–59.8)	28.6 (8.4–58.1)	39.5 (24.0–56.6)	34.3 (29.9–39.0)	41.4 (29.8–53.8)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	5.3 (0.6–17.7)	1.2 (0.4–2.7)	5.7 (1.6–14.0)
Joint pain	28.6 (16.6–43.3)	28.6 (8.4–58.17)	44.7 (28.6–61.7)	26.0 (21.9–30.4)	28.6 (18.4–40.6)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	0 (0–9.3)	1.9 (0.8–3.6)	5.7 (1.6–14.0)
Muscle aches	65.3 (50.4–78.3)	50.0 (23.0–77.0)	65.8 (48.6–80.4)	43.9 (39.1–48.7)	55.7 (43.3–67.6)
Grade 3	6.1 (1.3–16.9)	0 (0–23.2)	7.9 (1.7–21.4)	2.1 (1.0–3.9)	5.7 (1.6–14.0)
Shivering	28.6 (16.6–43.3)	14.3 (1.8–42.8)	36.8 (21.8–54.0)	15.3 (12.0–19.1)	17.1 (9.2–28.0)
Grade 3	4.1 (0.5–14.0)	0 (0–23.2)	2.6 (0.1–13.8)	1.6 (0.7–3.3)	2.9 (0.3–9.9)
Sweating	20.4 (10.2–34.3)	7.1 (0.2–33.9)	21.1 (9.6–37.3)	11.4 (8.5–14.8)	15.7 (8.1–26.4)
Grade 3	0 (0–7.3)	0 (0–23.2)	0 (0–9.3)	1.4 (0.5–3.0)	1.4 (0–7.7)

%(95% CI)=percentage of participants reporting the event with exact 95% confidence limit (lower limit–upper limit); N=number of participants in the cohort;

Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F).

Grade 3 redness was defined as being >50 mm, grade 3 swelling was > 50 mm and Grade 3 fever was >39°C.

Table 3: Most frequently reported (≥9 cases) medically attended adverse events (MAEs) within the 31-day post-vaccination period

Medically Attended Events (MAEs)[†]	ImmunoComp	At risk	Healthy	Total*
	N= 579	**N**= 7392	**N**= 1170	**N**= 9143
	n (%)	**n (%)**	**n (%)**	**n (%)**
At least one MAE	107 (18.5)	958 (13.0)	154 (13.2)	1219 (13.3)
Lower respiratory tract infection	12 (2.1)	94 (1.3)	4 (0.3)	110 (1.2)
Upper respiratory tract infection	5 (0.9)	56 (0.8)	14 (1.2)	75 (0.8)
Cough	5 (0.9)	49 (0.7)	6 (0.5)	60 (0.7)
Urinary tract infection	5 (0.9)	36 (0.5)	12 (1.0)	53 (0.6)
Asthma	1 (0.2)	39 (0.5)	1 (0.1)	41 (0.5)
Back pain	2 (0.4)	25 (0.3)	2 (0.2)	29 (0.3)
Abdominal pain	4 (0.7)	20 (0.3)	2 (0.2)	26 (0.3)
Diarrhoea	2 (0.4)	17 (0.2)	2 (0.2)	21 (0.2)
Arthralgia	0	16 (0.2)	4 (0.3)	20 (0.2)
Oropharyngeal pain	2 (0.4)	16 (0.2)	2 (0.2)	20 (0.2)
Chronic obstructive pulmonary disease	0	18 (0.2)	0	18 (0.2)
Conjunctivitis	1 (0.2)	13 (0.2)	3 (0.3)	17 (0.2)
Headache	2 (0.4)	10 (0.1~~2~~)	5 (0.4)	17 (0.2)
Dyspnoea	5 (0.9)	9 (0.1)	3 (0.3)	17 (0.2)
Rash	0	16 (0.2)	1 (0.1)	17 (0.2)
Herpes zoster	1 (0.2)	13 (0.2)	2 (0.2)	16 (0.2)
Chest pain	1 (0.2~~1~~)	13 (0.2)	1 (0.1)	15 (0.2)
Sinusitis	0	10 (0.1)	5 (0.4)	15 (0.2)
Pain in extremity	3 (0.5)	10 (0.1)	2 (0.2)	15 (0.2)
Otitis externa	0	13 (0.2)	1 (0.1)	14 (0.2)
Dizziness	0	11 (0.2)	3 (0.3)	14 (0.2)
Dyspepsia	0	11 (0.2)	2 (0.2)	13 (0.1)
Vomiting	2 (0.4)	8 (0.1)	2 (0.2)	12 (0.1)
Pyrexia	0	7 (0.1)	4 (0.3)	11 (0.1)
Bronchitis	2 (0.4)	6 (0.1)	2 (0.2)	10 (0.1)
Cellulitis	2 (0.4)	7 (0.1)	1 (0.1)	10 (0.1)
Pharyngitis	3 (0.5)	5 (0.1)	2 (0.2)	10 (0.1)
Musculoskeletal chest pain	1 (0.2)	9 (0.1)	0	10 (0.1)
Influenza-like illness	3 (0.5)	6 (0.1)	0	9 (0.1)
Fall	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)
Wheezing	1 (0.2)	7 (0.1)	1 (0.1)	9 (0.1)

Immunocomp=participants identified as immunocompromised on study initiation; N=number of participants in the cohort; n (%)=number of participants reporting the event (percentage);
[†]MAEs were defined as events leading to an otherwise unscheduled visit to or from medical personnel for any reason, including emergency room visits. If a MAE led to hospitalization (or met any other SAE criteria), it was to be reported as a SAE.

*Information regarding risk group was missing for two participants

Table 4: Most frequently reported (≥5 cases) serious adverse events (SAEs) during the 181-day post-vaccination period (N=9143)

Serious Adverse Event (SAE)	Total[†] n (%)	Time from previous vaccination dose to SAE (range in days)
At least one SAE	411 (4.50)	
Pneumonia	16 (0.17)	30–178
Lower respiratory tract infection	13 (0.14)	6–171
Asthma	13 (0.14)	1–170
Chest pain	10 (0.11)	3–180
Urinary tract infection	9 (0.10)	14–147
Chronic obstructive pulmonary disease	8 (0.09)	5–172
Myocardial infarction	7 (0.08)	17–148
Acute coronary syndrome	6 (0.07)	55–172
Atrial fibrillation	6 (0.07)	1–157
Abdominal pain	6 (0.07)	<1–74
Vomiting	6 (0.07)	<1–176
Transient ischaemic attack	6 (0.07)	2–173
Cholecystitis	5 (0.05)	43–118
Bronchopneumonia	5 (0.05)	1–103
Sepsis	5 (0.05)	12–172
Radius fracture	5 (0.05)	66–156
Colon cancer	5 (0.05)	1–84
Pulmonary embolism	5 (0.05)	11–157

[†] n (%)=number of participants reporting the event (percentage)

Table 5. Adverse events of special interest (AESIs) reported within the 181-day post-vaccination period (N=9143)

Adverse Events of Special Interest (AESIs)†	n (%)	SIR [95% CI]
At least one AESI	14 (0.15)	
Convulsions	8 (0.09)	2.65 [1.14–5.22]
Non-febrile convulsions	7 (0.08)	
Febrile convulsion	1 (0.01)	
Bell's Palsy	3 (0.03)	2.70 [0.56–7.89]
Guillain-Barré syndrome	1 (0.01)	18.11 [0.46–100.89]
Neuritis	1 (0.01)	11.46 [0.29–63.85]
Demyelination	1 (0.01)	4.88 [0.12–27.17]

95% CI=95% confidence interval (lower limit–upper limit); n (%)=number of participants reporting event (percentage), more than one event could be reported for a participant; SIR = standardised incidence ratio

† The Adverse Events of Special Interest (AESI) for this study were: Anaphylactic reaction, Bell's palsy, convulsions, demyelination, Guillain-Barré syndrome, neuritis, non-infectious encephalitis, vaccination failure, vasculitis

FIGURES

Figure Legends

Figure 1

Flow diagram depicting the completion of study contact points with the reasons for discontinuation. Participants with contacts not performed for other reasons could have had following contacts. If only one dose of vaccine was given, Contact 2 was considered "Missing confirmed".

Figure 2

Solicited local (A) and general (B) adverse events reported during a 7-day follow-up period after any dose (Reactogenicity cohort N=682).

The general symptoms of drowsiness, irritability and loss of appetite were only assessed in children <5 years while fatigue, gastrointestinal, headache, joint pain, muscle aches, shivering and sweating were assessed in children aged 5–17 years and in adults. Fever was defined as an oral or axillary temperature of ≥37.5°C (99.5°F) or a rectal temperature of ≥38.0°C (100.4°F). Data are shown as percentage of participants reporting the symptom with 95% confidence interval.

Figure 1

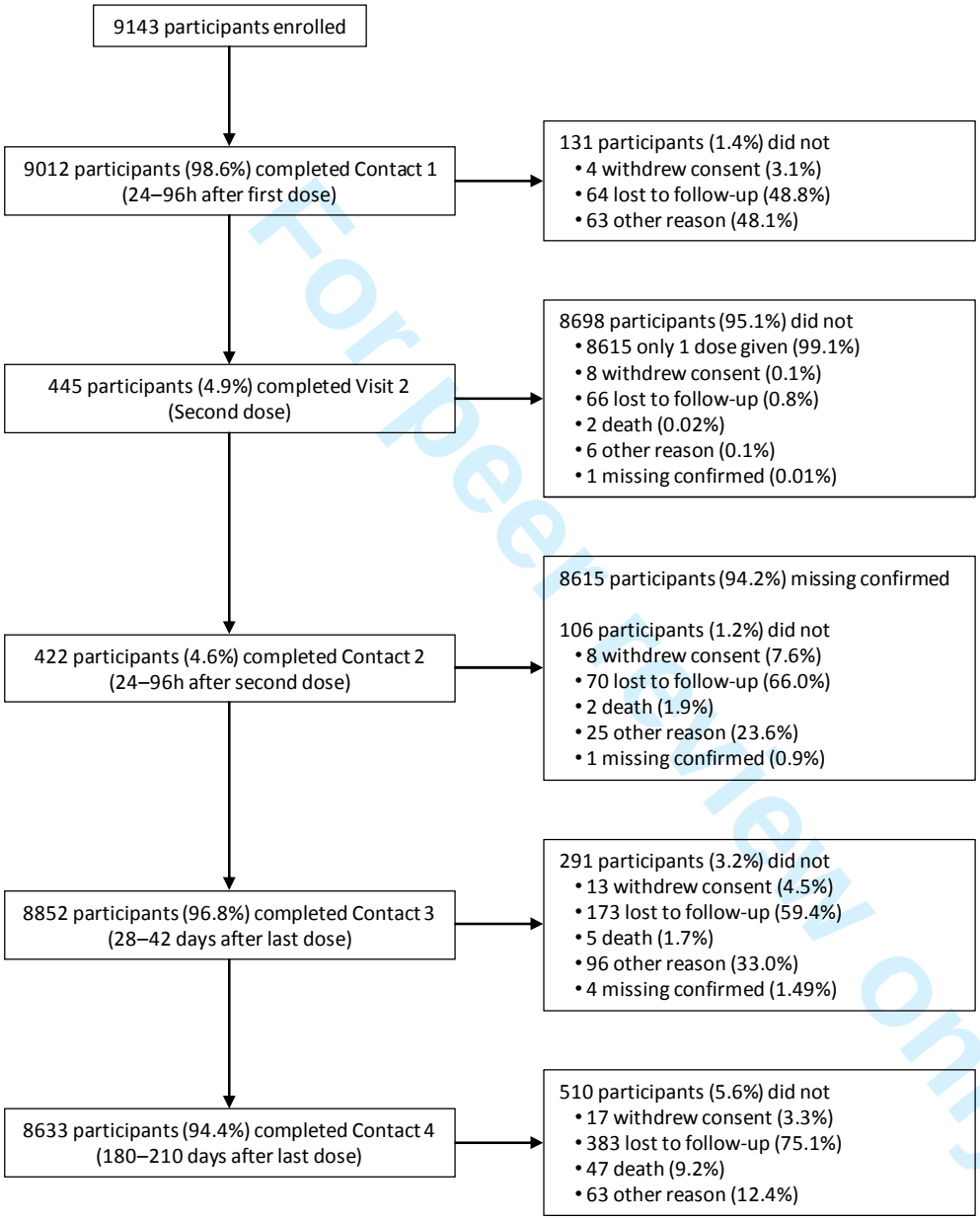
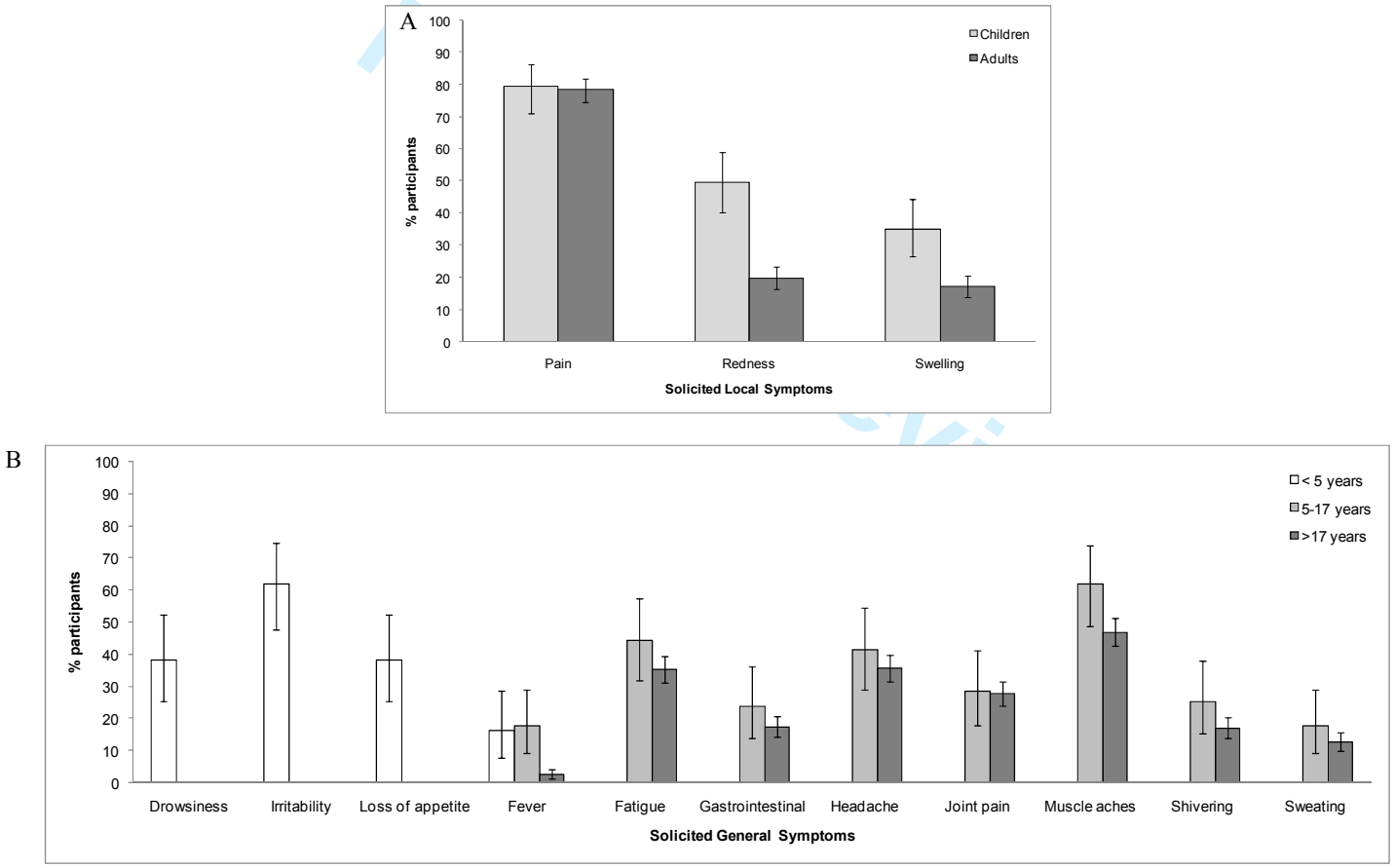


Figure 2


A
100
90
80
70
60
50
40
30
20
10
0
% participants
Children
Adults
Pain
Redness
Swelling
Solicited Local Symptoms
B
100
90
80
70
60
50
40
30
20
10
0
% participants
< 5 years
5-17 years
>17 years
Drowsiness
Irritability
Loss of appetite
Fever
Fatigue
Gastrointestinal
Headache
Joint pain
Muscle aches
Shivering
Sweating
Solicited General Symptoms

Title Page

Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study

Irwin Nazareth *professor of primary care & population health*[1], Fernanda Tavares *Therapeutic Area Safety Head*[2], Dominique Rosillon[2], François Haguinet *biostatistician*[2], Vincent Bauchau *senior epidemiologist*[2]

ABSTRACT

Objectives: To assess the safety of an AS03-adjuvanted split virion H1N1 (2009) vaccine in persons vaccinated during the national pandemic influenza vaccination campaign in the United Kingdom.

Design: Prospective, cohort, observational, post-authorisation safety study.

Setting: 87 general practices forming part of the Medical Research Council General Practice Research Framework and widely distributed throughout England.

Participants: 9143 men and women who received at least one dose of the AS03-adjuvanted H1N1 pandemic vaccine during the national pandemic influenza vaccination campaign in the United Kingdom were enrolled. 94% completed the 6-month follow-up. Exclusion criteria were previous vaccination with any other H1N1 pandemic vaccine before study enrolment and any child in care.

Primary and secondary outcome measures: Medically attended events (MAEs) occurring within 31 days after any dose, serious adverse events (SAEs), and adverse events of special interest (AESI) following vaccination were collected for all participants, Solicited AEs were assessed in a subset of participants (reactogenicity subset).

Results: MAEs were reported in 1219 and SAEs in 113 participants during the 31-day post-vaccination period. The most frequently reported MAEs and SAEs were consistent with events expected to be reported during the winter season in this population: lower respiratory tract infections, asthma and pneumonia. The most commonly reported solicited AEs were irritability in young children aged <5 years (61.8%) and muscle aches in children age 5–17 years (61.9%) and adults (46.9%). Eighteen AESIs experienced by 14 subjects met the criteria to be considered for the observed-to-expected analyses. AESIs above the expected number were neuritis (1 case

within 31 days) and convulsions (8 cases within 181 days). There were 41 deaths during the 181-day period after vaccination, fewer than expected.

Conclusions: These results indicate that the AS03-adjuvanted H1N1 pandemic vaccine was generally well tolerated with a clinically acceptable reactogenicity and safety profile.

Trial registration: ClinicalTrials.gov, NCT00996853

SUMMARY

Article focus

- The outbreak of the H1N1 (2009) influenza pandemic led to vaccination of high risk groups with novel pandemic vaccines targeting the A/California/7/2009 (H1N1)v-like strain. Limited data about the clinical safety of these novel vaccines were available.
- In this paper we report the results of a post-authorisation safety study designed as a pharmacovigilance activity to evaluate safety endpoints related to the H1N1 pandemic vaccination.

Key messages

- The Most frequently reported medically-attended events and serious adverse events were consistent with events expected to be reported during the winter season.
- The observed number of adverse events of special interest —Bell's palsy, Guillain-Barré syndrome and demyelination— were below the expected number.
- The AS03-adjuvanted H1N1 (2009) vaccine was generally well-tolerated in the age and risk groups studied, with clinically acceptable reactogenicity and safety profiles.

Strengths and limitations of this study

- General practices, the primary point of contact for persons in the UK to access the National Health Service, were able to provide an extensive overview of the safety profile of the AS03-adjuvanted H1N1 pandemic influenza vaccine.

- Sample size was not estimated for each risk group (immunocompromised, at risk or healthy participants). Thus, it is difficult to ascertain whether the analysis reported here was sufficiently powered to adequately assess safety outcomes in the general UK population.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No		Recommendation
Title and abstract	1	✓	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
			(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction			
Background/rationale	2		Explain the scientific background and rationale for the investigation being reported
Objectives	3		State specific objectives, including any prespecified hypotheses
Methods			
Study design	4	✓	Present key elements of study design early in the paper
Setting	5	✓	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6		(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls
		✓	*Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
			(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7		Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	✓	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	N	Describe any efforts to address potential sources of bias
Study size	10	✓	Explain how the study size was arrived at
Quantitative variables	11	✓	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	✓	(*a*) Describe all statistical methods, including those used to control for confounding
		✓	(*b*) Describe any methods used to examine subgroups and interactions
			(*c*) Explain how missing data were addressed
			(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed
		N	*Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		X	(*e*) Describe any sensitivity analyses

Continued on next page

Results			
Participants	13*		(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
			(b) Give reasons for non-participation at each stage
			(c) Consider use of a flow diagram
Descriptive data	14*	✓	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		✓	(b) Indicate number of participants with missing data for each variable of interest
			(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*		*Cohort study*—Report numbers of outcome events or summary measures over time
			Case-control study—Report numbers in each exposure category, or summary measures of exposure
		✓	*Cross-sectional study*—Report numbers of outcome events or summary measures
Main results	16	✓	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		✓	(*b*) Report category boundaries when continuous variables were categorized
		N	(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	✓	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion			
Key results	18	✓	Summarise key results with reference to study objectives
Limitations	19	✓	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	✓	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	✓	Discuss the generalisability (external validity) of the study results
Other information			
Funding	22	✓	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Response to reviewers:

Title: **Safety of AS03-adjuvanted split-virion H1N1 (2009) pandemic influenza vaccine: a prospective cohort study**

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.

Figure 1

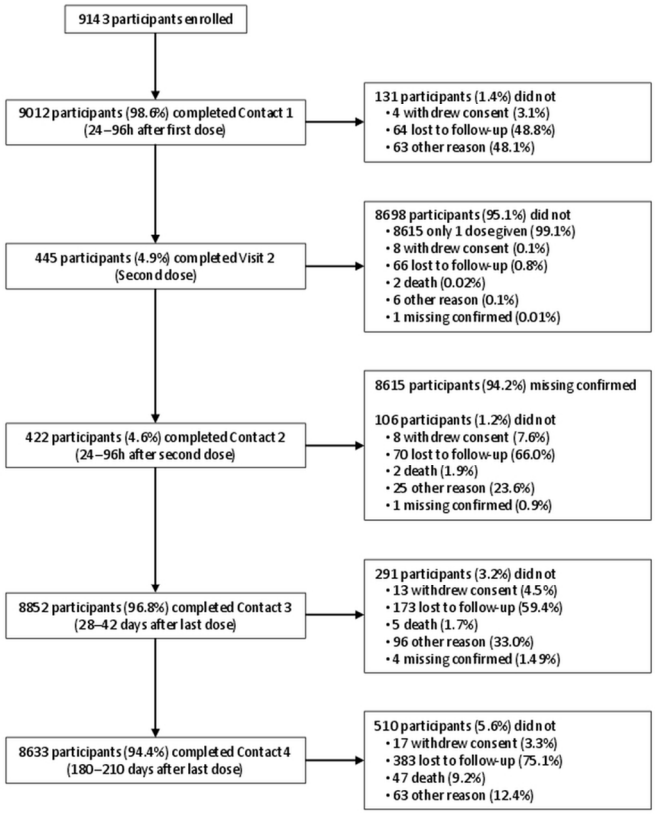


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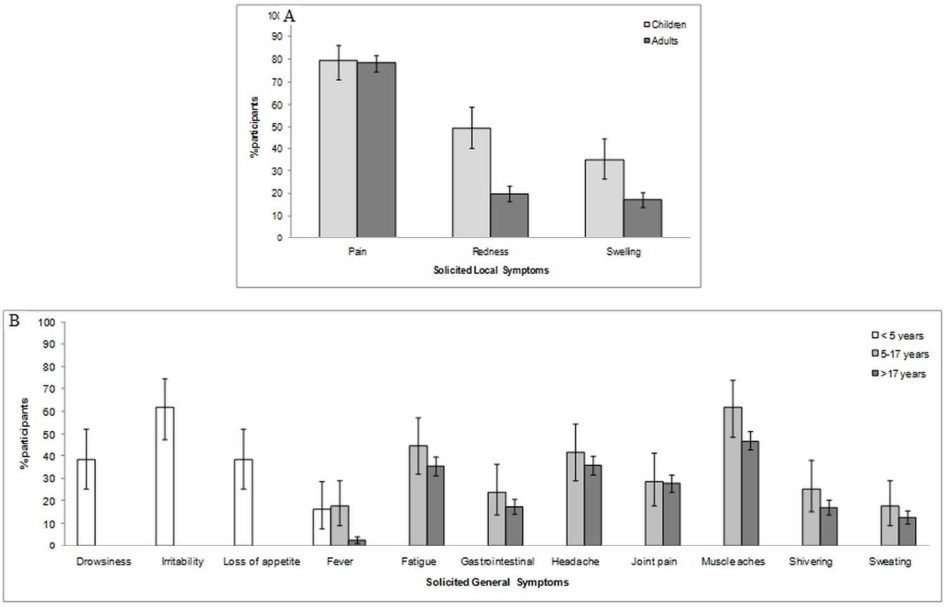
Figure 2



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