Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an $AS03_B$/oil-in-water emulsion-adjuvanted ($AS03_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children 6 months to 12 years of age

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Abstract

Open-label, randomised, parallel-group, multicentre study to evaluate the safety, tolerability and immunogenicity of an AS03$_B$/oil-in-water emulsion-adjuvanted (AS03$_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children 6 months to 12 years of age

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Objective: To evaluate the safety, tolerability and immunogenicity of an AS03$_B$/oil-in-water emulsion-adjuvanted (AS03$_B$) split-virion versus non-adjuvanted whole-virion H1N1 influenza vaccine in UK children aged 6 months to 12 years.
Design: Multicentre, randomised, head-to-head, open-label trial.
Setting: Five UK sites (Oxford, Bristol, Southampton, Exeter and London).
Participants: Children aged 6 months to < 13 years, for whom a parent or guardian had provided written informed consent and who were able to comply with study procedures, were eligible for inclusion.
Interventions: A tocopherol/oil-in-water emulsion-adjuvanted (AS03$_B$) egg culture-derived split-virion H1N1 vaccine and a non-adjuvanted cell culture-derived whole-virion vaccine, given as a two-dose schedule, 21 days apart, were compared. Participants were grouped into those aged 6 months to < 3 years (younger group) and 3 years to < 13 years of age (older group) and were randomised by study investigators (1 : 1 ratio) to receive one of the two vaccines. Vaccines were administered by intramuscular injection (deltoid or anterior-lateral thigh, depending on age and muscle bulk). Local reactions and systemic symptoms were collected for 1 week post immunisation, and serum was collected at baseline and after the second dose. To assess safety and tolerability, parents or guardians recorded the following information in diary cards from days 0–7 post vaccination: axillary temperature, injection site reactions, solicited and unsolicited systemic symptoms, and medications.
Main outcome measure: Comparison between vaccines of the percentage of participants demonstrating seroconversion by microneutralisation assay.
Results: Among 937 children receiving vaccine, per-protocol seroconversion rates were higher after the AS03$_B$-adjuvanted vaccine than after the whole-virion vaccine (98.2% vs 80.1% in children < 3 years, 99.1% vs 95.9% among those aged 3–12 years), as were severe local reactions (3.6% vs 0.0% in those under 5 years, 7.8% vs 1.1% in those aged 5–12 years), irritability in children < 5 years (46.7% vs 32.0%), and muscle pain in older children (28.9% vs 13.2%). The second dose of the adjuvanted vaccine was more reactogenic than

the first, especially for fever >38.0°C in those under 5 years of age (8.9% vs 22.4%).
Conclusion: The adjuvanted vaccine, although reactogenic, was more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.
Trial registration number: ISRCTN89141709

Contents

List of abbreviations

CI	confidence interval
EMEA	European Medicines Agency
GSK	GlaxoSmithKline
UK-SAGE	UK Scientific Advisory Group for Emergencies
WHO	World Health Organization
WHO-SAGE	WHO Strategic Advisory Group of Experts on Immunisation

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Children are a priority for vaccination in an influenza pandemic, but safety and immunogenicity data for new-generation adjuvanted and whole-virion vaccines are limited.

Objectives

Immunogenicity

- How does the percentage of children aged 6 months to 12 years of age with a fourfold rise in microneutralisation titres between the prevaccination sample and the sample taken 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- How does the percentage of children aged 6 months to 12 years of age with haemagglutination inhibition titres of ≥ 1 : 32 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- How does the percentage of children aged 6 months to 12 years of age with a fourfold rise in haemagglutination inhibition titres between the prevaccination sample and the sample taken 3 weeks after completion of a two-dose course of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine compare?
- What is the geometric mean fold rise in haemagglutination inhibition titres from baseline to 3 weeks after two doses of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine?
- What is the geometric mean haemagglutination inhibition titre 3 weeks after two doses of the non-adjuvanted, whole-virion vaccine and the $AS03_B$-adjuvanted split-virion vaccine?

Reactogenicity

- How does the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the 7 days following each dose of the non-adjuvanted, whole-virion and the $AS03_B$-adjuvanted split-virion vaccines compare?
- What percentage of children aged 6 months to 12 years of age experience non-febrile systemic reactions within the 7 days following each dose of the non-adjuvanted, whole-virion and the $AS03_B$-adjuvanted split-virion vaccine?

Methods

The safety, reactogenicity and immunogenicity of a tocopherol/oil-in-water emulsion-adjuvanted ($AS03_B$) egg culture-derived split-virion H1N1 vaccine and a non-adjuvanted cell culture-derived whole-virion vaccine, given as a two-dose schedule, 21 days apart, were compared in a randomised, open-label trial of children aged 6 months to 12 years of age. Local reactions and systemic symptoms were collected for 1 week post immunisation, and serum was collected at baseline and after the second dose.

Results

Among 937 children receiving vaccine, per-protocol seroconversion rates were higher after the $AS03_B$-adjuvanted vaccine than after the whole-virion vaccine (98.2% vs 80.1% in children < 3 years, 99.1% vs 95.9% among those aged 3–12 years), as were severe local reactions (3.6% vs 0.0% in those under 5 years, and 7.8% vs 1.1% in those aged 5–12 years), irritability in children < 5 years (46.7% vs 32.0%), and muscle pain in older children (28.9% vs 13.2%). The second dose of the adjuvanted vaccine was more reactogenic than the first especially for fever > 38.0°C in those under 5 years of age (8.9% vs 22.4%).

Conclusion

In this first direct comparison of an $AS03_B$-adjuvanted split-virion vaccine versus whole-virion non-adjuvanted H1N1 vaccine, the adjuvanted vaccine – while reactogenic – was

more immunogenic, especially in younger children, indicating the potential for improved immunogenicity of influenza vaccines in this age group.

Trial registration

This trial was registered as ISRCTN89141709.

Chapter 1
Introduction

The first illness caused by a new influenza A virus was confirmed in the UK on 27 April 2009. Since then, the virus has become much more common in both the UK and across the world, and the World Health Organization (WHO) declared a pandemic on 11 June 2009. Children have experienced pandemic influenza A(H1N1) infections at four times the rate of adults and are hospitalised more frequently.[1,2] Although most childhood disease has been mild, severe disease and deaths have occurred, mainly in those with comorbidities.[3–5] As children are also very effective transmitters of the virus,[6–8] they are a high-priority group for vaccination against pandemic influenza in many countries.[8–10]

In response to this pandemic, the WHO's Strategic Advisory Group of Experts on Immunisation (WHO-SAGE), held an extraordinary meeting on 7 July 2009 to consider the role for immunisation in the prevention of this disease.[11] The key recommendations of this report were:

- All countries should immunise their health-care workers as a first priority to protect the essential health infrastructure. As vaccines that are available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. WHO-SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15–49 years of age; healthy children; healthy adults of 50–64 years of age; and healthy adults of 65 years of age and above.
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement postmarketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and postmarketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.
- In view of the anticipated limited vaccine availability at a global level, and the potential need to protect against 'drifted' strains of virus, WHO-SAGE recommended that promoting production and use of vaccines, such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines, was important.
- As most of the production of the seasonal vaccine for the 2009–10 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, WHO-SAGE did not consider that there was a need to recommend a 'switch' from seasonal to pandemic vaccine production.

The UK Department of Health provided two H1N1 vaccines for the national immunisation programme: a split-virion, egg culture-derived $AS03_B$-adjuvanted vaccine, manufactured by GlaxoSmithKline (GSK) and a non-adjuvanted Vero cell culture-derived whole-virion vaccine manufactured by Baxter.[12] Both manufacturers initially gained marketing authorisation approval from the European Medicines Agency (EMEA) for a pandemic strain vaccine under the 'mock-up' dossier route, based on limited clinical trial data for a candidate H5N1 vaccine. These vaccines were modified to cover the novel influenza AH1N1 strain.

Novel adjuvants had not been routinely used in early childhood prior to this pandemic, but were believed to provide enhanced immunogenicity, particularly in infants in whom traditional influenza vaccines have limited efficacy,[9] and potentially allow antigenic sparing and induction of cross-clade immunity.[13–15]

Although whole-virion influenza vaccines have previously been associated with unacceptable reactogenicity rates,[16] H5N1 'mock-up' whole-virion vaccines were well tolerated,[17] and these vaccines avoid problems with egg-allergic individuals.[18] Use of cell culture for manufacture was expected

to shorten production times, by avoiding the bottleneck of supply of hens' eggs.[12,19]

Although substantial safety data regarding the use of trivalent seasonal split and subunit non-adjuvanted inactivated influenza vaccines in children existed, similar safety and efficacy data for novel H1N1 vaccines were lacking.[20–23] The need for comparative immunogenicity and reactogenicity data for these two products in children was identified by the UK Scientific Advisory Group for Emergencies (UK-SAGE) as a high priority to help guide national recommendations on which to use in a paediatric population.

This study was therefore conducted to compare the immunogenicity, reactogenicity and safety of the two H1N1 vaccines in children aged 6 months to 12 years in a multicentre, open-label, randomised head-to-head trial. Immunogenicity was assessed by both the haemagglutination inhibition assay and microneutralisation assay.

Chapter 2
Methods

Vaccines

Two novel H1N1 vaccines were compared: a split-virion, $AS03_B$-adjuvanted vaccine (GSK Vaccines, Rixensart, Belgium) and a non-adjuvanted whole-virion vaccine (Baxter Vaccines, Vienna, Austria).

The split-virion adjuvanted vaccine was constructed from the influenza A/California/07/2009 (H1N1) v-like strain antigen (New York Medical College x-179A), generated by classical reassortment in eggs, combining the *HA*, *NA* and *PB1* genes of influenza A/California/07/2009 (H1N1)v to the PR8 strain backbone.[23,24] Each dose (0.25 ml, one-half of the adult dose) contained 1.875 µg of haemagglutinin antigen and the oil-in-water emulsion-based adjuvant $AS03_B$ [containing squalene (5.345 mg), DL-α-tocopherol (5.93 mg) and polysorbate 80 (2.43 mg) and thiomersal], and was supplied as suspension and emulsion in multidose vials. Opened vials were used within 24 hours but not stored overnight.

The non-adjuvanted whole-virion vaccine derived from Vero cell culture was supplied in multidose vials. Opened vials were used within 3 hours; each dose (0.5 ml) contained 7.5 µg of haemagglutinin from influenza A/California/07/2009 (H1N1).

Study design

Between 26 September and 11 December 2009, we conducted an open-label, randomised, parallel-group, phase II study at five UK sites (Oxford, Bristol, Southampton, Exeter and London) in children aged 6 months to 12 years, comparing the safety, reactogenicity and immunogenicity of two novel H1N1 vaccines in a two-dose regimen.

The study was approved by the UK Medicines and Healthcare Products Regulatory Agency (EUDRACT 2009–014719–11), the Oxfordshire Ethics Committee (09/H0604/107) and the local NHS organisations by an expedited process.[25] The study was registered at ClinicalTrials.gov, and was conducted in accordance with the principles of the Declaration of Helsinki, the standards of Good Clinical Practice (as defined by the International Conference on Harmonisation) and UK regulatory requirements.

Recruitment was by media advertising and direct mailing. Children aged 6 months to < 13 years, for whom a parent or guardian had provided written informed consent and who were able to comply with study procedures, were eligible for inclusion. In addition, verbal assent was sought from participants aged 7 years and older. Those with laboratory-confirmed pandemic H1N1 influenza or with clinically diagnosed disease meriting antiviral treatment were excluded to target an immunologically naive population. For safety reasons, those with allergy to egg or any other vaccine components and coagulation defects were excluded. Other exclusions included those with significant immunocompromise, immunosuppressive therapy, recent receipt of blood products, intent to immunise with another H1N1 vaccine, or, participation in another clinical trial. Participants were grouped into those aged 6 months to < 3 years (younger group) and 3 years to < 13 years of age (older group). Participants were randomised by study investigators (1 : 1 ratio) to receive one of the two vaccines (randomisation group stratified for age group with block sizes of 10 and concealed until immunisation by opaque envelope generated by the Health Protection Agency). Vaccines were administered by intramuscular injection (deltoid or anterior-lateral thigh, depending on age and muscle bulk) at enrolment and at day 21 (± 7) days. Sera were collected at study days 0 and 21 (–7 to +14) after second vaccination.

Safety and tolerability assessments

From days 0–7 post vaccination, parents or guardians recorded axillary temperature, injection site reactions, solicited and unsolicited systemic symptoms, and medications (including antipyretics/analgesic use) in diary cards. Primary reactogenicity end points were frequency and severity of fever, tenderness, swelling and erythema post vaccination. Secondary end points were the frequency and severity of non-febrile

solicited systemic reactions or receipt of analgesic/antipyretic medication. Solicited systemic reactions were different in those under and over 5 years of age to reflect participants' ability to articulate symptoms. Erythema and swelling were graded by diameter as mild (1–24 mm), moderate (25–29 mm) or severe (≥ 50 mm). Other reactions were graded by effect on daily activity as none, mild (transient reaction, no limitation in activity), moderate (some limitation in activity) or severe (unable to perform normal activity) or by frequency/duration into none, mild, moderate and severe categories.

Medically significant adverse events (any ongoing solicited reaction or any event necessitating a doctor's visit or study withdrawal after day 7 post vaccination) were recorded on a diary card. Monitoring of adverse events of special interest, as recommended by the EMEA,[26] was undertaken (for full details, see Appendix 1, subappendix E).

All data from case report forms and participant diary cards were double-entered and verified on computer.

Assays

Antibody responses were measured by microneutralisation and haemagglutination inhibition assays on sera using standard methods[27,28] at the Centre for Infections, Health Protection Agency (UK). Assays were performed with the egg-grown NIBRG-121 reverse-genetics virus based on influenza A/California/07/2009 and A/Puerto Rico/8/34 (see Appendix 1).

The primary immunogenicity objective was a comparison between vaccines of the percentage of participants demonstrating seroconversion by the microneutralisation assay, with seroconversion defined as a fourfold rise to a titre of ≥ 1 : 40 from prevaccination to 3 weeks post second dose. A secondary objective based on the microneutralisation assay was a comparison between vaccines of the percentage with post-second-dose titres ≥ 1 : 40. Further secondary objectives based on the haemagglutination inhibition assay were comparisons between vaccines of the percentage with fourfold rises to titres ≥ 1 : 32 post second dose, the percentage with post-second-dose titres ≥ 1 : 32, geometric mean fold rises from baseline to post second dose, and geometric mean titres post second dose.

For microneutralisation assays, the initial dilution was 1 : 10 and the final dilution was 1 : 320, unless further dilutions were necessary to determine fourfold rises from baseline. For haemagglutination inhibition assays, the initial dilution was 1 : 8 and the final dilution was 1 : 16,384. For both assays, negative samples were assigned a value of one-half of the initial dilution. Sera were processed in 1 : 2 serial dilutions in duplicate and the geometric mean of each pair used.

Statistical analysis

With 200 participants in each age and vaccine group, the study had 80% power to detect differences of –14% to 12% around a 70% reactogenicity and seroconversion rate. Planned recruitment was up to 250 participants per group to allow for dropout and non-availability of sera.

Proportions with local or systemic reactions, and with seroconversion or titres above given thresholds, were calculated for each age and vaccine group. Comparisons between vaccines were made using a two-sided Fisher's exact test. For reactions, comparisons between doses were made using the sign test for paired data.

Geometric mean haemagglutination inhibition titres and fold rises were calculated for each age and vaccine group, along with 95% confidence intervals (CIs). Logged postvaccination haemagglutination inhibition titres were compared between vaccines using normal errors regression in a univariable model and then in a multivariable model adjusting for age, study site, sex, and interval from second vaccine dose to obtaining final serum sample. The interaction between age and vaccine was also investigated.

A planned interim analysis on the reactogenicity data from the first 500 participants was performed to provide rapid data to the UK Department of Health. The study site investigators remained blinded to the results of this analysis while visits were ongoing.

Data analysis was undertaken with STATA software, version 10. The level of statistical significance was 5%. The data were analysed per protocol. As planned, no intention-to-treat analyses were conducted, as < 10% of subjects would have been classified differently in such an analysis.

Summary of protocol changes

- Version 1.1 – increased sample size to 1000 participants, clarification of the role of the Data Monitoring Committee, procedures for vaccine labelling, specification of needle size for immunisation
- Version 1.2 – addition of an interim analysis of the safety data, change in indemnity information
- Version 2 – modification of serious adverse event reporting timelines and procedures, and addition of monitoring and reporting of adverse events of special interest
- Version 3 – addition of the possibility of using a half-adult dose of vaccine if that became the recommended dose; the suggested dose for the split-virion adjuvanted vaccine in children did become half of the adult dose before the trial commenced and therefore this was used; and the recommendation remained to use a full adult dose of the whole-virion vaccine.

Chapter 3
Results

Recruitment visits were attended by 949 participants, of whom 943 were enrolled and 937 included in the per-protocol analysis (*Figure 1* and *Table 1*). Overall, 913 participants received the second vaccine dose per protocol, at a mean interval of 20 days (range 14–28 days). Sera were obtained in 827 participants (88.2%) after the second vaccine dose as per protocol, at a mean interval of 20 days (range 14–35).

Safety and tolerability

Solicited reactions are shown in *Tables 2* and *3*.

The split-virion $AS03_B$-adjuvanted vaccine was associated with more frequent severe local reactions than the whole-virion vaccine after either dose in those aged over 5 years (dose 1, 7.2% vs 1.1%, $p = < 0.001$; dose 2, 8.5% vs 1.1%,

TABLE 1 *Baseline characteristics of study subjects, according to group*

	Age of participants			
	6 months to <3 years		**3–12 years**	
Characteristic	**Split-virion $AS03_B$-adjuvanted vaccine (*n* = 210)**	**Whole-virion (*n* = 229)**	**Split-virion $AS03_B$-adjuvanted vaccine (*n* = 254)**	**Whole-virion vaccine (*n* = 244)**
Race or ethnic group (no.)				
White	189	201	231	222
Indian	0	1	0	0
Pakistani	1	0	2	1
Asian other	1	2	1	0
Mixed ethnic group	14	19	9	10
Black African	1	3	3	3
Black Caribbean	2	0	3	1
Chinese	0	0	2	2
Other	2	3	3	5
Sex (no.)				
Male	116	123	131	121
Female	94	106	123	123
Previous seasonal influenza vaccine (no.)	5	5	22	28
Age (years/months)				
Median	23 months	23 months	82 months	84 months
Range	6–35 months	6–35 months	36–151 months	36–155 months
Site in the UK				
Bristol	44	46	41	42
Exeter	16	23	24	19
Oxford	70	79	66	59
Southampton	67	58	72	80
St George's	13	23	51	44

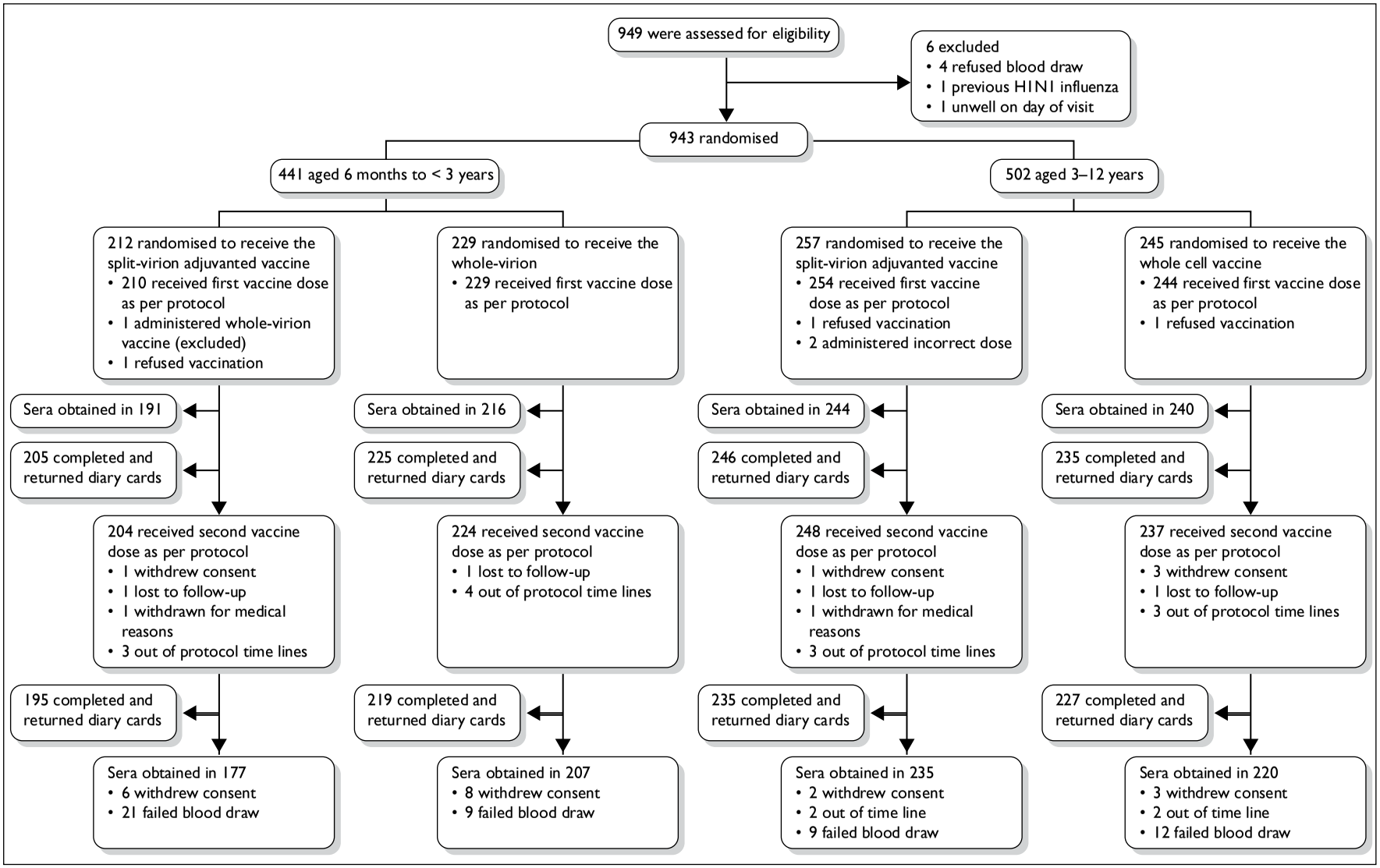

FIGURE 1 *Enrolment and follow-up of study participants.*

TABLE 2 *Local and systemic reactions in participants 6 months to < 5 years of age, by vaccine and dose*

		Vaccine			
		Split-virion AS03$_B$ adjuvanted		Whole-virion	
Measurement	**Level**	**Dose 1,[a] *n* (%)**	**Dose 2,[b] *n* (%)**	**Dose 1,[c] *n* (%)**	**Dose 2,[d] *n* (%)**
Pain	Mild	77 (28.5)	79 (31.1)	48 (17.2)	46 (17.0)
	Moderate	6 (2.2)	19 (7.5)	3 (1.1)	1 (0.4)
	Severe	2 (0.7)	2 (0.8)	0 (0)	0 (0)
	Any	85 (31.5)[e,f]	100 (39.4)[e,f]	51 (18.3)[e]	47 (17.3)[e]
Redness	1–24 mm	67 (24.8)	59 (23.2)	64 (22.9)	52 (19.2)
	25–49 mm	9 (3.3)	8 (3.1)	0 (0)	0 (0)
	≥ 50 mm	0 (0)	11 (4.3)	0 (0)	0 (0)
	Any	76 (28.1)	78 (30.7)[e]	64 (22.9)	52 (19.2)[e]
Swelling	1–24 mm	42 (15.6)	37 (14.6)	26 (9.3)	17 (6.3)
	25–49 mm	8 (3)	6 (2.4)	0 (0)	1 (0.4)
	≥ 50 mm	2 (0.7)	7 (2.8)	0 (0)	0 (0)
	Any	52 (19.3)[e]	50 (19.7)[e]	26 (9.3)[e]	18 (6.6)[e]
Any local reaction	Severe	4 (1.5)[f]	15 (5.9)[e,f]	0 (0)	0 (0)[e]
Decreased feeding	Mild	67 (24.8)	70 (27.6)	75 (26.9)	59 (21.8)
	Moderate	17 (6.3)	27 (10.6)	17 (6.1)	14 (5.2)
	Severe	5 (1.9)	6 (2.4)	2 (0.7)	8 (3)
	Any	89 (33)	103 (40.6)[e]	94 (33.7)	81 (29.9)[e]
Decreased activity	Mild	34 (12.6)	45 (17.7)	26 (9.3)	33 (12.2)
	Moderate	17 (6.3)	33 (13)	24 (8.6)	11 (4.1)
	Severe	4 (1.5)	3 (1.2)	2 (0.7)	3 (1.1)
	Any	55 (20.4)[f]	81 (31.9)[e,f]	52 (18.6)	47 (17.3)[e]
Increased irritability	Mild	89 (33)	84 (33.1)	64 (22.9)	45 (16.6)
	Moderate	28 (10.4)	34 (13.4)	28 (10)	26 (9.6)
	Severe	6 (2.2)	4 (1.6)	7 (2.5)	6 (2.2)
	Any	123 (45.6)[e]	122 (48)[e]	99(35.5)[e]	77 (28.4)[e]
Persistent crying	Mild	52 (19.3)	49 (19.3)	32 (11.5)	35 (12.9)
	Moderate	8 (3)	13 (5.1)	12 (4.3)	13 (4.8)
	Severe	1 (0.4)	1 (0.4)	2 (0.7)	1 (0.4)
	Any	61 (22.6)	63 (24.8)	46 (16.5)	49 (18.1)
Vomiting	Mild	28 (10.4)	28 (11)	29 (10.4)	26 (9.6)
	Moderate	6 (2.2)	5 (2)	3 (1.1)	3 (1.1)
	Severe	0 (0)	0 (0)	0 (0)	0 (0)
	Any	34 (12.6)	33 (13)	32 (11.5)	29 (10.7)
Diarrhoea	Mild	54 (20)	49 (19.3)	58 (20.8)	46 (17)
	Moderate	9 (3.3)	6 (2.4)	10 (3.6)	12 (4.4)
	Severe	3 (1.1)	3 (1.2)	3 (1.1)	4 (1.5)
	Any	66 (24.4)	58 (22.8)	71 (25.4)	62 (22.9)
Any symptoms	Severe	14 (5.2)	19 (7.5)	12 (4.3)	14 (5.2)
Fever	≥ 38°C	24 (8.9)[f]	57 (22.4)[e,f]	26 (9.3)	34 (12.5)[e]
GP visit for any reason	Any	14 (5.2)	14 (5.5)	11 (3.9)	16 (5.9)

continued

TABLE 2 *Local and systemic reactions in participants 6 months to < 5 years of age, by vaccine and dose (continued)*

Hospital visit for any reason	Any	1 (0.4)	0 (0)	0 (0)	1 (0.4)
Analgesic or antipyretic medication	Any	85 (31.5)[f]	111 (43.7)[e,f]	77 (27.6)	64 (23.6)[e]

a Total vaccinated, $n = 278$; diary cards available, per protocol, $n = 270$.
b Total vaccinated, $n = 275$; diary cards available, per protocol, $n = 254$.
c Total vaccinated, $n = 286$; diary cards available, per protocol, $n = 279$.
d Total vaccinated, $n = 285$; diary cards available, per protocol, $n = 271$.
e $p < 0.05$ for comparison between vaccines.
f $p < 0.05$ for comparison between doses.

TABLE 3 *Local and systemic reactions in participants 5–12 years of age by vaccine and dose*

		Split-virion AS03$_B$ adjuvanted		**Whole-virion**	
		Dose 1,[a] *n* (%)	**Dose 2,[b] *n* (%)**	**Dose 1,[c] *n* (%)**	**Dose 2,[d] *n* (%)**
Measurement	**Level**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Pain	Mild	89 (49.2)	78 (44.3)	68 (37.6)	65 (37.1)
	Moderate	44 (24.3)	43 (24.4)	4 (2.2)	8 (4.6)
	Severe	3 (1.7)	4 (2.3)	0 (0)	1 (0.6)
	Any	136 (75.1)[e]	125 (71)[e]	72 (39.8)[e]	74 (42.3)[e]
Redness	1–24 mm	41 (22.7)	40 (22.7)	38 (21)	34 (19.4)
	25–49 mm	8 (4.4)	8 (4.5)	3 (1.7)	4 (2.3)
	≥ 50 mm	7 (3.9)	9 (5.1)	0 (0)	0 (0)
	Any	56 (30.9)	57 (32.4)[e]	41 (22.7)	38 (21.7)[e]
Swelling	1–24 mm	24 (13.3)	28 (15.9)	21 (11.6)	24 (13.7)
	25–49 mm	9 (5)	6 (3.4)	2 (1.1)	1 (0.6)
	≥ 50 mm	8 (4.4)	5 (2.8)	2 (1.1)	1 (0.6)
	Any	41 (22.7)[e]	39 (22.2)	25 (13.8)[e]	26 (14.9)
Any local reaction	Severe	13 (7.2)[e]	15 (8.5)[e]	2 (1.1)[e]	2 (1.1)[e]
Loss of appetite	Mild	33 (18.2)	26 (14.8)	17 (9.4)	16 (9.1)
	Moderate	5 (2.8)	5 (2.8)	2 (1.1)	3 (1.7)
	Severe	4 (2.2)	2 (1.1)	2 (1.1)	1 (0.6)
	Any	42 (23.2)[e]	33 (18.8)	21 (11.6)[e]	20 (11.4)
Generally unwell	Mild	39 (21.5)	31 (17.6)	27 (14.9)	14 (8)
	Moderate	20 (11)	13 (7.4)	16 (8.8)	12 (6.9)
	Severe	3 (1.7)	2 (1.1)	2 (1.1)	0 (0)
	Any	62 (34.3)	46 (26.1)[e]	45 (24.9)[f]	26 (14.9)[e,f]

$p = 0.002$) and after dose 2 in those under 5 years (5.9% vs 0.0%, $p < 0.001$). There were also more systemic reactions among participants 6 months to < 5 years of age with more irritability after either dose (dose 1, 45.6% vs 35.5%; dose 2, 48% vs 28.4) and, after dose 2, more decreased feeding (40.6% vs 29.9%) and decreased activity (31.9% vs 17.3%).

Participants aged over 5 years experienced more muscle pain after either dose (dose 1, 32.6% vs 13.8%; dose 2, 25% vs 12.6%) and were more often generally unwell after dose 2 (26.1% vs 14.9%).

In younger children, dose 2 of the split-virion AS03$_B$-adjuvanted vaccine was more reactogenic

		Split-virion $AS03_B$ adjuvanted		Whole-virion	
		Dose 1,[a] *n* (%)	Dose 2,[b] *n* (%)	Dose 1,[c] *n* (%)	Dose 2,[d] *n* (%)
Measurement	**Level**	***n* (%)**	***n* (%)**	***n* (%)**	***n* (%)**
Headache	Mild	51 (28.2)	38 (21.6)	50 (27.6)	36 (20.6)
	Moderate	25 (13.8)	21 (11.9)	10 (5.5)	10 (5.7)
	Severe	1 (0.6)	1 (0.6)	1 (0.6)	0 (0)
	Any	77 (42.5)	60 (34.1)	61 (33.7)	46 (26.3)
Nausea/vomiting	Mild	30 (16.6)	25 (14.2)	20 (11)	15 (8.6)
	Moderate	4 (2.2)	1 (0.6)	1 (0.6)	0 (0)
	Severe	0 (0)	1 (0.6)	1 (0.6)	2 (1.1)
	Any	34 (18.8)	27 (15.3)	22 (12.2)	17 (9.7)
Diarrhoea	Mild	24 (13.3)	11 (6.3)	25 (13.8)	17 (9.7)
	Moderate	4 (2.2)	2 (1.1)	2 (1.1)	3 (1.7)
	Severe	0 (0)	1 (0.6)	0 (0)	1 (0.6)
	Any	28 (15.5)[f]	14 (8)[f]	27 (14.9)	21 (12)
Muscle pain	Mild	40 (22.1)	29 (16.5)	22 (12.2)	17 (9.7)
	Moderate	19 (10.5)	13 (7.4)	3 (1.7)	5 (2.9)
	Severe	0 (0)	2 (1.1)	0 (0)	0 (0)
	Any	59 (32.6)[e]	44 (25)[e]	25 (13.8)[e]	22 (12.6)[e]
Joint pain	Mild	17 (9.4)	15 (8.5)	19 (10.5)	13 (7.4)
	Moderate	3 (1.7)	3 (1.7)	4 (2.2)	2 (1.1)
	Severe	0 (0)	1 (0.6)	0 (0)	0 (0)
	Any	20 (11)	19 (10.8)	23 (12.7)	15 (8.6)
Any symptoms	Severe	5 (2.8)	5 (2.8)	3 (1.7)	2 (1.1)
Fever	≥ 38°C	14 (7.7)	11 (6.3)	6 (3.3)	5 (2.9)
GP visit for any reason		0 (0)	0 (0)	1 (0.6)	0 (0)
Hospital visit for any reason		66 (36.5)[e]	50 (28.4)[e]	40 (22.1)[e]	29 (16.6)[e]
Analgesic/ antipyretic medication	Any	66 (36.5)[e]	50 (28.4)[e]	40 (22.1)[e]	29 (16.6)[e]

a Total vaccinated, $n = 181$; number of diary cards available, per protocol, $n = 181$.
b Total vaccinated, $n = 188$; number of diary cards available, per protocol, $n = 176$.
c Total vaccinated, $n = 187$; number of diary cards available, per protocol, $n = 181$.
d Total vaccinated, $n = 185$; number of diary cards available, per protocol, $n = 175$.
e $p < 0.05$ for comparison between vaccines.
f $p < 0.05$ for comparison between doses.

than dose 1, with more fever ≥ 38°C (22.4% vs 8.9%, $p < 0.001$), local severe reactions (5.9% vs 1.5%, $p = 0.02$) and decreased activity (31.9% vs 20.4%, $p = < 0.001$). The second dose of the whole-virion vaccine was associated with decreased frequency of being generally unwell (14.9% vs 24.9%).

More recipients of the split-virion $AS03_B$-adjuvanted vaccine used antipyretic/analgesic medication after either dose of vaccine in the older participants (dose 1, 36.3% vs 22.1%; dose 2, 28.4% vs 16.6%) and after the second dose in younger participants (43.7% vs 23.6%, $p < 0.001$).

Adverse events

In participants receiving the split-virion adjuvanted vaccine, three adverse events of special interest occurred. One was an episode of reactive arthritis, in a participant aged 11 months, in the leg in which vaccine had been administered 2 days previously; this was considered possibly related. In brief, this participant became febrile to 39.1°C on the evening of vaccination. Two days later he was noted to be hesitant to weight bear on his right leg and was crawling unusually. Hospital review showed a well, afebrile child with a slightly erythematous and warm right knee with a reduced range of movement. There was no other obvious joint involvement and the vaccination site appeared normal. Blood tests were performed, including a C-reactive protein (1.00 mg/l) and white cell count (13.9×10^9), which were normal; throat swab and blood cultures were also taken, which showed no growth on either culture. Radiographs of both pelvis and right knee were normal. A diagnosis of reactive arthritis, possibly related to the vaccination, was made. The participant made a full recovery after 10 days. The second was a self-terminating generalised seizure 22 days post second vaccination in a participant aged 11 years 7 months with a previous history of possible seizure following head injury; this was considered unrelated to vaccination. The third was a possible seizure 20 days post second vaccination in a participant aged 12 years and 7 months, with a history of seizure following head injury; this was considered unrelated to vaccination.

In participants receiving the whole-virion vaccine, one adverse event of special interest occurred. This was a right focal seizure in a participant, aged 11 months, associated with fever, 9 days post second vaccination; this was considered unrelated to vaccination.

Five serious adverse events occurred, not in the category of adverse events of special interest and all considered unrelated to vaccination. In participants receiving the split-virion adjuvanted vaccine, these included an episode of exacerbation of asthma and an episode of tonsillitis with associated exacerbation of asthma; in participants receiving the whole-virion vaccine, these included an episode of exacerbation of asthma, a chest infection and vaccine failure with microbiologically confirmed influenza A(H1N1) 17 days post completion of vaccine course.

Immunogenicity

Prior to vaccination, 4.0% of participants (2.9% younger group, 5.0% older group) had microneutralisation titres ≥ 1 : 40, suggesting pre-existing immunity. Antibody responses are shown in *Tables 4–6* and *Figure 2*.

Seroconversion rates were higher with the split-virion $AS03_B$-adjuvanted vaccine than with the whole-virion unadjuvanted vaccine both by microneutralisation assay (younger group, 98.2% vs 80.1%, $p < 0.001$; older group, 99.1% vs 95.9%, $p = 0.03$) and haemagglutination inhibition assay (younger group, 99.4% vs 64.0%; older group, 98.7% vs 88.5%, $p = < 0.001$ for both groups). Compared with the whole-virion vaccine, the split-virion $AS03_B$-adjuvanted vaccine was associated with a higher percentage of participants with microneutralisation titres ≥ 1 : 40 (99.3% vs 88.5%, $p < 0.001$), a higher percentage with haemagglutination inhibition titre ≥ 1 : 32 (99.3% vs 78.2%, $p < 0.001$), higher geometric mean haemagglutination inhibition titres (411.0 vs 69.3) and greater geometric fold rise in haemagglutination inhibition titre from baseline (89.5 vs 15.0) ($p < 0.001$ for all comparisons). Although 95% CIs for the degree of pre-existing immunogenicity for the two groups overlapped, the 95% CIs did not overlap for post second dose immunogenicity results.

The multivariable analysis on logged haemagglutination inhibition titres showed a significant interaction between age and vaccine ($p < 0.001$), with 10.5-fold (95% CI 8.1 to 13.5) higher titres induced by the split-virion $AS03_B$-adjuvanted vaccine in the younger participants compared with 3.6-fold (95% CI 3.0 to 4.3) higher titres in older children. This difference in the age effect by vaccine was further evaluated by including age as a continuous variable in the multivariable model, which showed a 3% decrease in titre per year of age (95% CI 0.5 to 5, $p = 0.02$) for the split-virion adjuvanted vaccine and a 16% increase per year (95% CI 12 to 21, $p < 0.001$) for the whole-virion vaccine.

TABLE 4 *Seroconversion by microneutralisation titre*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n/N***	**% MN ≥ 1 : 40 (95% CI)**	***n/N***	**% MN ≥ 1 : 40 (95% CI)**	***n/N***	**% ≥ fourfold to ≥ 1 : 40 (95% CI)**
Whole-virion	< 3 years	9/216	4.2 (1.9–7.8)	166/206	80.6 (74.5–85.8)	157/196	80.1 (73.8–85.5)
	3–12 years	11/240	4.6 (2.3–8.1)	211/220	95.9 (92.4–98.1)	208/217	95.9 (92.4–98.1)
	All	20/456	4.4 (2.7–6.7)	377/426	88.5 (85.1–91.3)	365/413	88.4 (84.9–91.3)
Split-virion, $AS03_B$-adjuvanted	< 3 years	3/191	1.6 (0.3–4.5)	175/177	98.9 (96.0–99.9)	163/166	98.2 (94.8–99.6)
	3–12 years	13/244	5.3 (2.9–8.9)	234/235	99.6 (97.7–99.9)	226/228	99.1 (96.9–99.9)
	All	16/435	3.7 (2.1–5.9)	409/412	99.3 (97.9–99.8)	389/394	98.7 (97.1–99.6)

MN, microneutralisation.

TABLE 5 *Seroconversion by haemagglutination inhibition titre*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n/N***	**% HI ≥ 1 : 32 (95% CI)**	***n/N***	**% HI ≥ 1 : 32 (95% CI)**	***n/N***	**% ≥ fourfold to ≥ 1 : 32 (95% CI)**
Whole-virion	< 3 years	8/216	3.7 (1.6–7.2)	136/207	65.7 (58.8–72.1)	126/197	64.0 (56.8–70.7)
	3–12 years	7/240	2.9 (1.2–5.9)	198/220	90.0 (85.3–93.6)	192/217	88.5 (83.5–92.4)
	All	15/456	3.3 (1.9–5.4)	334/427	78.2 (74.0–82.0)	318/414	76.8 (72.4–80.8)
Split-virion, $AS03_B$-adjuvanted	< 3 years	3/191	1.6 (0.3–4.5)	174/175	99.4 (96.9–99.9)	163/164	99.4 (96.6–99.9)
	3–12 years	13/244	5.3 (2.9–8.9)	233/235	99.1 (97.0–99.9)	225/228	98.7 (96.2–99.7)
	All	16/435	3.7 (2.1–5.9)	407/410	99.3 (97.9–99.8)	388/392	99.0 (97.4–99.7)

HI, haemagglutination inhibition.

TABLE 6 *Haemagglutination inhibition geometric mean titres*

		Pre-vaccine		Post second dose		Fold rise	
Vaccine	**Age**	***n***	**GMT (95% CI)**	***n***	**GMT (95% CI)**	***n***	**GMT (95% CI)**
Whole-virion	< 3 years	216	4.6 (4.2–5.1)	207	44.0 (35.6–54.3)	197	9.5 (7.8–11.6)
	3–12 years	240	4.6 (4.2–4.9)	220	106.3 (90.2–125.3)	217	22.7 (19.3–26.8)
	All	456	4.6 (4.3–4.9)	427	69.3 (60.3–79.6)	414	15.0 (13.2–17.2)
Split-virion, $AS03_B$-adjuvanted	< 3 years	191	4.2 (4.0–4.5)	175	461.0 (409.0–519.6)	164	107.4 (93.9–122.9)
	3–12 years	244	4.8 (4.3–5.3)	235	377.3 (339.2–419.7)	228	78.5 (69.9–88.1)
	All	435	4.5 (4.3–4.8)	410	411.0 (379.4–445.2)	392	89.5 (81.9–97.8)

GMT, geometric mean titre.

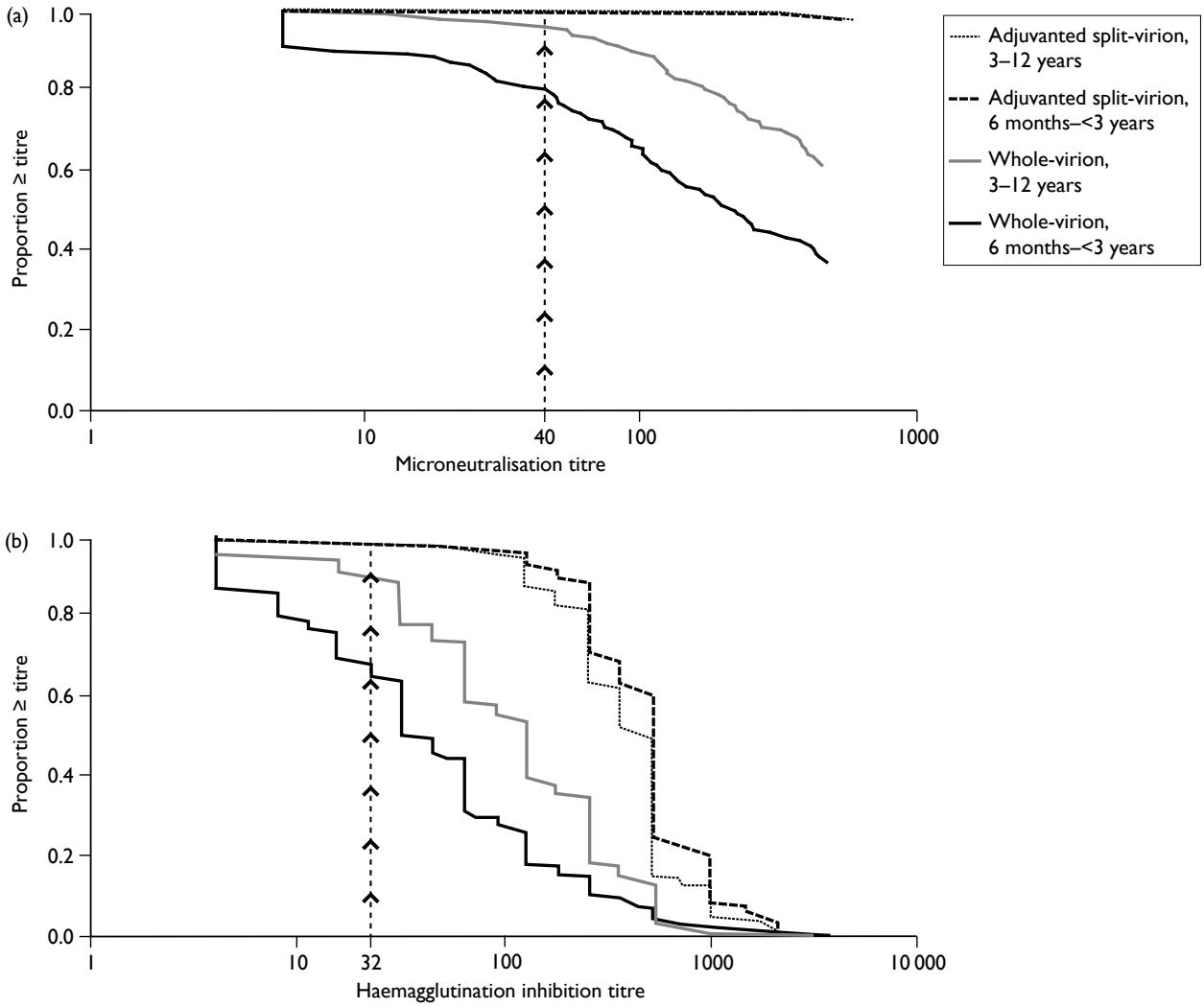

FIGURE 2 *Reverse cumulative distribution curves of antibody titres as measured by microneutralisation curves and haemagglutination inhibition assays by age group and vaccine. Arrows indicate seroprotection thresholds.*

Chapter 4
Discussion

This is the first paediatric head-to-head study of the GSK split-virion $AS03_B$-adjuvanted H1N1 pandemic vaccine and the Baxter whole-virion non-adjuvanted vaccine. The vaccine containing the novel adjuvant was more immunogenic than the whole-virion vaccine, especially in young children, but was also more reactogenic. Children with comorbidities are at increased risk of severe H1N1 disease, and for this reason we did not exclude children with pre-existing medical conditions (except immunodeficiency), making our findings relevant to the general paediatric population. A UK vaccination programme, principally using the adjuvanted split-virion vaccine[29] was announced in August 2009, initially targeting those with comorbidities,[30] but the programme was widened to all children aged 6 months to 5 years in December 2009 following a review of interim data from this study and other data.[29]

The haemagglutination inhibition assay is used extensively in the serological assessment of immunity to influenza viruses and as licensure criteria.[27,31–33] However, the haemagglutination inhibition assay measures only antibody directed to the receptor binding site, whereas the microneutralisation assay may be more sensitive, as it detects antibody directed at this and other antigenic sites in the virus,[31,34,35] and was therefore chosen as the primary immunogenicity end point.

Only 3.5% of participants had prevaccination antibody levels ≥ 1 : 32 by haemagglutination inhibition, suggestive of prior infection with the pandemic strain H1N1.[1] This was lower than that found in a recent serosurvey in England, which was conducted after the first wave, and may reflect geographical differences in exposure risk.[1] Moreover, we excluded children with a history of confirmed H1N1 disease or who had been treated for suspected infection. Follow-up took place during the second wave of the UK pandemic, but any boosting effect of natural infection would be expected to be similar between vaccine groups.

An important finding of this study was that the whole-virion vaccine showed a strong age-dependent response, with a 16% increase in immunogenicity per year with age. Similarly, the immunogenicity of both seasonal influenza vaccines[16] and other non-adjuvanted H1N1 vaccines[22] in young children is less than in older children and adults. New-generation adjuvants (such as MF59 and $AS03_B$) have been used to improve immunogenicity[13,14,35] and in *this study* the split-virion adjuvanted vaccine was highly immunogenic, even in young children, but was slightly less immunogenic in older children than in infants (3% per year with age), a pattern not previously described for inactivated vaccines.

Other H1N1 vaccines, including both adjuvanted and non-adjuvanted vaccines, are immunogenic in children but contain considerably more antigen than the split-virion adjuvanted vaccine used in this trial.[21,36,37] Antigen sparing is important in a pandemic setting where vaccine requirements exceed manufacturing capability.[38] Pre-pandemic H5N1 vaccine trials demonstrated the need for a two-dose regimen in immunologically naive individuals,[24] and two-dose regimens of several H1N1 vaccines are more immunogenic than single-dose regimens.[21,22,36] However, limited data have suggested that a single-dose regimen of the split-virion $AS03_B$-adjuvanted vaccine used in this trial may be sufficient to meet licensing criteria,[23,24] and the UK has recently recommended a single-dose regimen in healthy children.[29] When we were designing this study, a two-dose pandemic vaccine schedule was planned for children, and for this reason our pragmatic trial did not include a blood test after one dose to simplify the study in the face of the need for rapid recruitment. With the subsequent change to a single-dose regimen in the UK, our results would have been strengthened by addition of assessment of immunogenicity after a single dose. Furthermore, a comparison with a non-adjuvanted split-virion vaccine would be of interest but none was used in the UK during the 2009 H1N1 pandemic, and we limited the study to these two novel vaccines.

Even during interpandemic periods, children experience significant morbidity and mortality from influenza infection, and their role in virus transmission results in a much wider burden.[16] The favourable immunogenicity and reactogenicity

of the split-virion $AS03_B$-adjuvanted vaccine demonstrated in this study suggest that novel adjuvants may also have a role in seasonal influenza vaccines.

Whole-virion influenza vaccines have previously been associated with high reactogenicity rates.[16] This study provides the first data showing that a whole-virion H1N1 vaccine in children was well tolerated. Increased reactogenicity was seen with an MF59-adjuvanted H1N1 vaccine in children,[37] as well as in adult trials of oil-in-water adjuvanted vaccines.[13–15,23,35] The $AS03_B$-adjuvanted vaccine in this trial was similarly associated with more local reactions, and some increase in systemic reactions, compared with the whole-virion vaccine. The higher reactogenicity observed with the split-virion adjuvanted vaccine may influence parental uptake of the vaccine. No data on the parental feelings on the tolerability were collected, so the likely effective of this cannot be assessed. Our observed local and systemic reactogenicity rates were generally in keeping with data in the *Summary of Product Characteristics*.[23,24] However, although we found the rate of fever to be slightly higher in infants after the second dose compared to the first, these are one-half of the reported rate (43.1% of 51 infants).[24]

Chapter 5
Conclusions

This is the first direct comparison of two commercially available novel H1N1 vaccines. The split-virion AS03$_B$-adjuvanted vaccine was more immunogenic and induced high seroconversion rates in young children. These data provide important information to guide immunisation policy in an influenza pandemic and indicate the potential for improved immunogenicity of seasonal influenza vaccines in children.

Implications for health care, recommendations for research

Further studies evaluating the breadth and duration of the immune response to single- and two-dose regimens are needed, in particular the persistence of antibody and the degree of cross-clade protection. Our observation that the split-virion adjuvanted vaccine was slightly less immunogenic in older children than in infants (3% per year with age) is a pattern that is not previously described for inactivated vaccines. Further research is needed to see if this is a consistent finding with adjuvant use, and, if so, what the underlying mechanisms are. The role of adjuvants in seasonal influenza vaccines to provide enhanced immunogenicity in infants is also needed.

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Contributions of authors

Professor Andrew Pollard (Professor of Paediatric Infection and Immunity) contributed to the design of the study, participant enrolment, and data interpretation, and was chief investigator.

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Professor Elizabeth Miller (Head, Immunisation Department) was lead investigator, contributing to study design and data interpretation, and overseeing data management, statistical analysis and laboratory processing.

Dr Saul Faust (Senior Lecturer in Paediatric Immunology and Infectious Diseases) contributed to design of the study, participant enrolment and data interpretation, and was principal investigator at the Southampton site.

Professor Adam Finn (David Baum Professor of Paediatrics) contributed to design of the study, participant enrolment and data interpretation, and was principal investigator at the Bristol site.

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Amanda Reiner (Project Manager) and Tessa John (Clinical Team Lead, Paediatric Vaccine Research) were responsible for project management,

including coordination across sites, study logistics and preparation of regulatory submissions, as well as contributing to patient enrolment and data collection.

Polly Eccleston (Data Manager) contributed to data management.

Ruth Allen (Research Network Manager) contributed to project management at the Bristol and Exeter sites.

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Claire Waddington (Clinical Research Fellow, Vaccinology) drafted this report, which was subsequently reviewed by all authors, and contributed to design of the study, participant enrolment and data interpretation.

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References

1. Miller E, Hoschler K, Hardelid P, Stanford E, Andrews N, Zambon M. Incidence of 2009 pandemic influenza A H1N1 infection in England: a cross-sectional serological study. *Lancet* 2010;**375**:1100–8.

2. Health Protection Agency. *Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the secondwave*. HPA, UK; 2009 (updated 25 February 2010, cited 2010). URL: www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1258560552857

3. Centers for Disease Control and Prevention. Surveillance for paediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection – United States, April–August 2009. *MMWR Morb Mortal Wkly* 2009;**58**:941–7.

4. Centers for Disease Control and Prevention. Hospitalised patients with novel influenza A (H1N1) virus infection – California, April–May, 2009. *MMWR Morb Mortal Wkly Rep* 2009;**58**:536–41.

5. Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, *et al*. Hospitalised Patients with 2009 H1N1 Influenza in the United States, April-June 2009. *N Engl J Med* 2009;**360**:2605–15.

6. Kuehn BM. CDC names H1N1 vaccine priority groups. *JAMA* 2009;**302**(11):1157–8.

7. Glezen WP, Couch RB. Interpandemic influenza in the Houston area, 1974–76. *N Engl J Med* 1978;**298**:587–92.

8. Strategic Advisory Group of Experts on Immunisation. *Report of the extraordinary meeting on the influenza A (H1N1) 2009 pandemic*, 7 July 2009 (cited 25 February 2010). URL: www.who.int/wer/2009/wer8430.pdf

9. Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2008;**2**:CD004879.

10. Ferguson N. Poverty, death, and a future influenza pandemic. *Lancet* 2006;**368**:2187–8.

11. World Health Organization. *Pandemic (H1N1) 2009 briefing note 2: WHO recommendations on pandemic (H1N1) 2009 vaccines* (cited 17 July 2009). URL: www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/print.html

12. Barrett PN, Mundt W, Kistner O, Howard MK. Vero cell platform in vaccine production: moving towards cell culture-based viral vaccines. *Expert Rev Vaccines* 2009;**8**:607–18.

13. Chu DW, Hwang SJ, Lim FS, Oh HM, Thongcharoen P, Yang PC, *et al*. Immunogenicity and tolerability of an AS03(A)-adjuvanted prepandemic influenza vaccine: a phase III study in a large population of Asian adults. *Vaccine* 2009;**27**:7428–35.

14. Leroux-Roels I, Roman F, Forgus S, Maes C, De Boever F, Drame M, *et al*. Priming with AS03(A)-adjuvanted H5N1 influenza vaccine improves the kinetics, magnitude and durability of the immune response after a heterologous booster vaccination: an open non-randomised extension of a double-blind randomised primary study. *Vaccine* 2010;**28**:849–57.

15. Leroux-Roels I, Borkowski A, Vanwolleghem T, Drame M, Clement F, Hons E, *et al*. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. *Lancet* 2007;**370**:580–9.

16. Zangwill KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. *Pediatr Infect Dis J* 2004;**23**:189–97.

17. Ehrlich HJ, Muller M, Oh HM, Tambyah PA, Joukhadar C, Montomoli E, *et al*. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture. *N Engl J Med* 2008;**358**:2573–84.

18. Erlewyn-Lajeunesse M, Brathwaite N, Lucas JS, Warner JO. Recommendations for the administration of influenza vaccine in children allergic to egg. *BMJ* 2009;**339**:b3680.

19. Oxford JS, Manuguerra C, Kistner O, Linde A, Kunze M, Lange W, *et al*. A new European perspective of influenza pandemic planning with a particular focus on the role of mammalian cell culture vaccines. *Vaccine* 2005;**23**:5440–9.

20. Kelly H, Barr I. Large trials confirm immunogenicity of H1N1 vaccines. *Lancet* 2009;**75**:6–9.

21. Liang XF, Wang HQ, Wang JZ, Fang HH, Wu J, Zhu FC, *et al*. Safety and immunogenicity of 2009 pandemic influenza A H1N1 vaccines in China: a multicentre, double-blind, randomised, placebo-controlled trial. *Lancet* 2009;**375**:56–66.

22. Plennevaux E, Sheldon E, Blatter M, Reeves-Hoche MK, Denis M. Immune response after a single vaccination against 2009 influenza A H1N1 in USA: a preliminary report of two randomised controlled phase 2 trials. *Lancet* 2010;**375**:41–8.

23. Roman F, Vaman T, Gerlach B, Markendorf A, Gillard P, Devaster JM. Immunogenicity and safety in adults of one dose of influenza A H1N1v 2009 vaccine formulated with and without AS03(A)-adjuvant: preliminary report of an observer-blind, randomised trial. *Vaccine* Feb 17;**28**:1740–5.

24. European Medicines Agency (EMEA). *Pandemrix. Summary of Product Characteristics, approved by the European Commission on 22 December 2009*. GlaxoSmithKlein, Germany; 2009 (cited 25 February 2010). URL: www.ema.europa.eu/humandocs/PDFs/EPAR/pandemrix/D-H1N1%20single%20PDFs/SPC/emea-spc-h832pu17en.pdf

25. Pollard AJ, Reiner A, John T, Sheasby E, Snape M, Faust S, *et al*. Future of flu vaccines. Expediting clinical trials in a pandemic. *BMJ* 2009;**339**:b4652.

26. European Medicines Agency (EMEA). CHMP *Recommendations for the core risk management plan for influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context*. London, UK; 2008 (cited 25 February 2010). URL: www.ema.europa.eu/pdfs/human/pandemicinfluenza/4999308en.pdf

27. Rowe T, Abernathy RA, Hu-Primmer J, Thompson WW, Lu X, Lim W, *et al*. Detection of antibody to avian influenza A (H5N1) virus in human serum by using a combination of serological assays. *J Clin Microbiol* 1999;**37**(4):937–43.

28. Ellis JS, Zambon MC. Molecular analysis of an outbreak of influenza in the United Kingdom. *Eur J Epidemiol* 1997;**13**(4):369–72.

29. UK Department of Health. *A(H1N1) swine flu influenza: phase two of the vaccination programme; children over 6 months and under 5 years: dosage schedule update*, 2009 (cited 25 February 2010). URL: www.dh.gov.uk/en/Publicationsandstatistics/lettersandcirculars/Dearcolleagueletters/DH_110182

30. UK Department of Health. *Priority groups for the vaccination programme*. Department of Health, UK; 2009 (cited 25 February 2010). URL: www.dh.gov.uk/en/Publichealth/Flu/Sweineflu/InformationandGuidance/Vaccinationprogramme/DH_105455

31. Stephenson I, Heath A, Major D, Newman RW, Hoschler K, Junzi W, *et al*. Reproducibility of serological assays for influenza virus A (H5N1). *Emerg Infect Dis* 2009;**15**:1252–9.

32. US Food and Drug Administration. *Guidance for industry: clinical data needed to support the licensure of pandemic influenza vaccines*, 2007 (cited 25 February 2010). URL: www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074786.htm

33. European Medicines Agency (EMEA). *Guideline on influenza A vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier content*, 2007. URL: www.ema.europa.eu/pdfs/human/vwp/26349906enfin.pdf

34. Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, *et al*. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009;**361**:1945–52.

35. Clark TW, Pareek M, Hoschler K, Dillon H, Nicholson KG, Groth N, *et al*. Trial of influenza A (H1N1) 2009 monovalent MF59-adjuvanted vaccine: preliminary report. *N Engl J Med* 2009;**361**:2424–35.

36. Nolan T, McVernon J, Skeljo M, Richmond P, Wadia U, Lambert S, *et al*. Immunogenicity of a monovalent 2009 influenza A(H1N1) vaccine in infants and children: a randomised trial. *JAMA* 2009;**303**:37–46.

37. Arguedas A, Soley C, Lindert K. Responses to 2009 H1N1 vaccine in children 3 to 17 years of age. *N Engl J Med* 2009;**362**:370–2.

38. Collin N, de Radigues X. Vaccine production capacity for seasonal and pandemic (H1N1) 2009 influenza. *Vaccine* 2009;**27**:5184–6.

Appendix 1

Protocol, version 3, dated 25 September 2009

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Study Title: Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.

Internal Reference No: 2009/08 H1N1

Ethics Ref: 09 H0604/107

EudraCT Number: 2009-014719-11

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1. SYNOPSIS

Study Title	**Open Label, Randomized, Parallel-Group, Multi-Centre Study to Evaluate the Safety, Tolerability and Immunogenicity of Baxter H1N1 vaccine and GlaxoSmithKline H1N1 vaccine in children 6 months to 12 years of age.**
Internal ref. no.	2009/08 H1N1
Clinical Phase	Phase II
Trial Design	Open Label, Randomised
Trial Participants	Children aged 6 months to 12 years
Planned Sample Size	1000 participants
Follow-up duration	6 to 8 weeks
Planned Trial Period	12 weeks (for study visits)
Primary Objective	Immunogenicity • To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Reactogenicity • To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
Secondary Objectives	• To compare the percentage of children aged 6 months to 12 years of age with haemagglutination inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To compare the percentage of children aged 6 months

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	to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To determine the geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine • To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.
Primary Endpoint	Primary end points for the immunogenicity analysis will be defined as: • The percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. Primary endpoints for reactogenicity analysis

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	• Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
Secondary Endpoints	• Percentage of subjects with an HAI titre ≥ 1 in 32 • The percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean fold rises in MN titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine. • Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds). • Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds). • The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.
Investigational	Baxter Novel Influenza A H1N1 Whole Virus Vaccine

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Medicinal Products	(Celvapan) GlaxoSmithKline Novel Influenza A H1N1 Split Virion Vaccine (Pandemrix)

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2. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
CFI	Centre for Infections
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTRG	Clinical Trials & Research Governance, University of Oxford
EMEA	European Medicines Agency
GCP	Good Clinical Practice
GSK	GlaxoSmithKline
GP	General Practitioner
HAI	Haemaglutination Inhibition
HPA	Health Protection Agency
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IMP	Investigational Medicinal Product
IRB	Independent Review Board
MHRA	Medicines and Healthcare products Regulatory Agency
MN	Microneutralisation
NRES	National Research Ethics Service
OVG	Oxford Vaccine Group

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PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
RVU	Respiratory Virus Unit
SAE	Serious Adverse Event
SAGE	Strategic Advisory Group of Experts on Immunisation
SAR	Serious Adverse Reaction
SMPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSG	Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group
VRD	Virus Reference Department
WHO	World Health Organisation

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3. BACKGROUND AND RATIONALE

Two manufacturers, Baxter and GlaxoSmithKline, have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. These vaccines have now been modified to cover the novel influenza A H1N1 strain. The proposed study aims to assess the safety and immunogenicity of these two H1N1 vaccines when administered as two doses three weeks apart to children aged 6 months to 12 years of age.

The first illness caused by a new influenza A virus was confirmed in the United Kingdom on 27 April 2009. Since then the virus has become much more common in both the UK and across the world, and the World Health Organization (WHO) declared a pandemic on 11 June 2009. Internationally, human infections with the new virus have occurred in 120 countries including the UK (WHO). There have been more than 77,000 laboratory confirmed cases and 332 deaths globally. The actual number of cases of people infected with the new virus is likely to be much higher than these numbers suggest, as most cases are not tested. There have been 11,159 laboratory confirmed cases of new influenza A H1N1v in the United Kingdom, and 840 hospitalisations as of the 23rd July 2009[1].

In response to this pandemic the WHO's Strategic Advisory Group of Experts on Immunisation (SAGE), held an extraordinary meeting on 7th July 2009 to consider the role for immunisation in the prevention of this disease[2]. The full report is included as appendix A of this protocol, however the key recommendations were

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.
- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and

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post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.

- In view of the anticipated limited vaccine availability at global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

As children are recognised as being a high risk group for pandemic influenza, it is imperative to conduct a study comparing the immunogenicity and reactogenicity of the two vaccines likely to be available for use in the UK.

One vaccine, Celvapan, (manufactured by Baxter Vaccines) is a whole virus unadjuvanted vaccine, and the other, Pandemrix, (from GlaxoSmithKline vaccines (GSK)) is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the “mock-up” dossier route based on limited clinical trial data for a candidate H5N1 vaccine. As the influenza strain on which these vaccines are based has changed from H5N1 to H1N1, vaccine manufacturers have had to apply for a ‘variation’ to the marketing authorisation for these vaccines. There are however limited data on safety and immunogenicity in children.

Previous studies have suggested that whole virus vaccine may be better at inducing a protective immune response in children following a single dose than a subunit or split virion vaccine. Reactogenicity may also vary between the two vaccines. There are, however, limited data on the immunogenicity and reactogenicity of these vaccines in a paediatric population, particularly in children under 3 years of age. The need for comparative immunogenicity and reactogenicity data for these two products in children has therefore been identified by the UK Scientific Advisory Group for Emergencies (SAGE) as a high priority to help guide national recommendations on which to use in a paediatric population.

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Information that is available on the immunogenicity and reactogenicity of the H5N1 version of the GSK pandemic influenza vaccine in children between the ages of 3 and 9 years suggests that initial seroconversion rates following immunisation with 2 doses of a half adult dose of vaccine (0.25 mL) are comparable to those observed after immunisation with 2 doses of the full 'adult' dose (0.5mL). As fever rates were higher in the full dose than half dose group (for 3 to 5 year olds 36% versus 16%, respectively, had temperatures above 37.5 °C), consideration has been given to using the half dose of GSK vaccine in this study. However it has been decided to use a full dose in all age groups. This decision has been made on the basis of:

- evidence that in the 3 to 5 year age group the full dose of the H5N1 vaccine resulted in better persistence of protective antibodies to 6 months post-immunisation than the half dose
- evidence that the full dose also provides better cross-protection against antigenically drifted versions of the H5N1 vaccine than the half dose
- the suggestion that the higher fever rates were predominantly seen in the 6 to 9 year old age groups rather than the 3 to 5 year old age groups, suggesting that this may be more of a feature with increasing, rather than decreasing, age
- advice from the Department of Health that, based on the above evidence, they would anticipate using a full dose of Pandemrix in all age groups in the event of mass immunisation of children against 'swine flu', as this would be more likely to protect against a 'second wave' of pandemic influenza with an antigenically drifted virus. Therefore evidence on the full dose of vaccine would be most relevant to immunisation policy.

If, however, it became apparent prior to the start of this study that a half dose of either vaccine were to be recommended for routine use in children, then we would use a half dose of the relevant vaccine in this study.

Cases of Guillian-Barré syndrome, characterised by symmetric paralysis, have previously been attributed to influenza vaccination. The possible association with the influenza vaccine was initially suggested following the 1976-1977 A/ New Jersey (Swine 'flu) season, when relative risks between 4.0 and 7.6 in the 6 or 8 week period post vaccination were seen. Variation in the number of cases of Guillian-Barré syndrome from year to year and season to season are well recognised. An extensive study of all cases of Guillian-Barré syndrome recorded on the General Practice Research Database (total cases 989) in the period 1990-

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2005 found no association of Guillian-Barré syndrome with influenza vaccination. In the 90 day period after vaccination the relative risk of Guillian-Barré syndrome was calculated as 0.76. This is in contrast to the relative risk following an influenza-like illness, calculated at 7.35. The occurrence of Guillian-Barré syndrome related to vaccination as part of this study is considered very unlikely and indeed the vaccine may well protect against Guillian-Barré syndrome by preventing influenza itself.

This study aims to compare the immunogenicity, reactogenicity and safety of the two H1N1 vaccines in children aged 6 months to 12 years in a multi centre, open label, randomised head to head trial. Immunogenicity will be assessed by both Haemagglutination inhibition and microneutralisation. Although EMEA guidelines for licensure of influenza vaccine are based on HAI assays, the primary objective for this study is to determine the percentage of subjects with seroconversions (i.e., fourfold or greater increases in antibody titre) by MN, while determination of the proportion of subjects which show seroconversion by HI will be a secondary objective. The decision for the preference of MN titres over HI titres was made based on recently published observations by CDC[3] and results from the Health Protection Agency's own analysis, which showed that the MN assay generally yields higher titres and detected more seroconversions (i.e., fourfold or greater increases in antibody titres) to A/California/04/2009 than the HI assay (although both generally show high correlation).

In addition to the collection of serum samples for analysis of vaccine immunogenicity, with specific consent the cellular 'plug' remaining after centrifugation from participants in Oxford, London, and Southampton will be stored and sent (as applicable) to the Oxford Vaccine Group for DNA extraction. The DNA samples obtained in this study can then contribute to a DNA bank pooling samples from multiple different Oxford Vaccine Group studies. These DNA samples can be used for genome wide analysis of the genetic factors influencing the host response (immunogenicity and reactogenicity) to the vaccines received in the relevant studies. This DNA extraction and storage will only occur with the specific consent of participants, and DNA will not be analysed for any other purpose than to assess factors influencing the response to vaccines. Funding for the DNA analysis is independent to funding for this influenza immunogenicity and reactogenicity study. Similarly, where appropriate consent is given by Bristol and Exeter participants, genetic samples will be stored in the Bristol Research in Infection & Immunity Collaboration Tissue Bank and aliquots made available for genetic analysis relating to this and potentially other future studies.

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With appropriate consent, serum samples remaining after the analyses required for this study will be stored for use in future infection and immunity related research studies at the relevant study sites.

4. OBJECTIVES

4.1 Primary Objective

Immunogenicity

- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in microneutralisation (MN) titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

Reactogenicity

- To compare the percentage of children aged 6 months to 12 years of age experiencing fever and local reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine

4.2 Secondary Objectives

- To compare the percentage of children aged 6 months to 12 years of age with Haemagglutination Inhibition (HAI) titres of ≥ 1:32 three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To compare the percentage of children aged 6 months to 12 years of age with a four fold rise in HAI titres between the pre-vaccination sample and the sample taken three weeks after completion of a two dose course of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in HAI titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rise in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

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- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- To assess the percentage of children aged 6 months to 12 years of age experiencing non-febrile systemic reactions within the seven days following each dose of the Baxter and GSK H1N1 vaccine
- To investigate the effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines in a given individual.

5. TRIAL DESIGN

5.1 Summary of Trial Design

This is a multi centre, open-label, randomised, controlled study in 1000 children aged 6 months to 12 years.

A summary of the trial can be seen in table one:

Table One: Trial summary

	Day 0	Day 21 (3 weeks)	Day 42 (6 weeks)
Group A1 (N~250) 6mths - <3 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B1 (N~250) 6mths - <3 yrs GSK vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group A2 (N~250) ≥3 yrs – 12 yrs Baxter vaccine	Vaccination 1 Blood A	Vaccination 2	 Blood B
Group B2 (N~250) ≥3 yrs – 12 yrs	Vaccination 1	Vaccination 2	

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GSK vaccine	Blood A		Blood B

5.2 Study Procedures

It is predicted that 1000 total participants will be recruited across the UK, 500 in each of 2 age categories (6 months to <3 years and ≥3 years to 12 years). 250 participants within each age group will be randomly allocated to receive two doses of either the Baxter vaccine or the GlaxoSmithKline vaccine. A baseline blood test will be taken at enrolment and a further blood test at 6 weeks (3 weeks after the second vaccine dose) to determine immunogenicity of the vaccine. A diary card detailing local and systemic effects of the vaccine and any AEs, medications used to treat these AEs and SAEs will be completed by parents/ guardians for the first week after each immunisation, as will a memory aid card used to record solicited adverse events persisting after the first week following immunisation and any medically significant adverse events occurring

5.3 Primary and Secondary Endpoints/Outcome Measures

Primary end points for the immunogenicity analysis will be defined as:

- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose

Primary endpoints for reactogenicity analysis

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines

Secondary endpoints:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- The geometric mean fold rises in HAI titres from baseline to after three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- The geometric mean fold rises in MN titres from baseline to three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.

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- The geometric mean HAI and MN titres three weeks after 2 doses of the Baxter H1N1 vaccine and the GSK H1N1 vaccine.
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).
- The effect of genetic polymorphisms on the immunogenicity and reactogenicity of the H1N1 vaccines.

5.4 Trial Participants

5.4.1 Overall Description of Trial Participants

We intend to recruit 1000 total participants from across the UK, 500 in each of 2 age categories, 6 months to <3 years (i.e. to day before 3rd birthday) and ≥ 3 years to 12 years. 250 participants within each age group will be randomly allocated to receive the Baxter vaccine and 250 the GSK vaccine.

5.4.2 Inclusion Criteria

The participant must satisfy all the following criteria to be eligible for the study:

- baby or child aged between 6 months to 12 years of age (i.e. to day before 13th birthday).
- for whom a parent/legal guardian has given written informed consent after the nature of the study has been explained;
- available for all the visits scheduled in the study
- willingness to complete all study procedures

5.4.3 Exclusion Criteria

The potential participants may not enter the study if ANY of the following apply:

- History of any vaccine against novel influenza A strain H1N1 (based on verbal confirmation from parent/guardian);

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- Previous laboratory confirmed case of novel influenza A strain H1N1 or treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 (n.b. a child commenced on treatment with oseltamivir or zanamivir for novel influenza A strain H1N1 whose treatment was stopped following negative microbiological tests for H1N1 on nasals swabs would be allowed to enrol in the study].
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any H1N1 vaccine component;
- Current egg allergy
- Known or suspected impairment/alteration of the immune system
- Disorders of coagulation
- Immunosuppressive therapy, use of systemic corticosteroids for more than 1 week within the 3 months prior to enrolment
- Receipt of blood, blood products and/or plasma derivatives or any immunoglobulin preparation within 3 months prior to enrolment;
- Intent to immunize with any other vaccine(s) against novel influenza A strain H1N1 throughout the study period;
- Participation in another clinical trial of an investigational medical product
- Any condition which, in the opinion of the investigator, might interfere with the evaluation of the study objectives. Children with chronic, stable medical illnesses that do not result in immunosuppression (e.g. cerebral palsy, epilepsy, cystic fibrosis, congenital heart disease) will be allowed to participate in the study, unless these conditions will in some way interfere with the completion of study procedures. Children with conditions that may alter the immune response to vaccines (e.g. Trisomy 21) or will affect the ability to accurately describe adverse events (e.g. children over 5 years of age but with severe learning difficulties) will be excluded.

5.4.4 Temporary Exclusion Criteria

- Participants who have experienced fever (>38.0°C) within the previous 24 hours.
- Participants receiving another immunisation within 3 days prior to enrolment (21 days for any live vaccine), or planning to receive another vaccine within 7 days of enrolment.

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5.5 Expenses and Benefits

All participants will be reimbursed £10 for each study visit to cover travel expenses. These payments will be provided to participants at the conclusion of the third and final study visit (or following the scheduled date for this visit if this were not to be completed).

5.6 Study Procedures

5.6.1 Recruitment and pre screening

In order to recruit the required cohort of 1000 participants, several strategies may be employed:

Direct mail-out: This will involve obtaining names and addresses of children via the Child Health Computer database or sending information home from schools with other school mailings.

Direct email and web newsletter advertising via local school parent email databases

Direct email and web newsletter advertising the study in Hospitals and Universities in participating regions

Radio and local newspaper advertisement campaign: adverts will be placed on local radio/newspapers with brief details of the study and contact details for further information.

Radio/television interviews: Regional radio and television stations will be contacted to arrange an interview opportunity with one of the study investigators.

Display of posters advertising the study in hospitals, at doctor's surgery, schools and other public places.

Presentation of relevant information at suitable locations, e.g. information sessions in schools and nurseries.

Description of study and copy of information booklet on study site websites.

Once an expression of interest has been received by the study centres an appointment would be made for them to attend at the designated recruitment centre where informed consent would be taken and the first study visit would be carried out. In schools, separate informed consent sessions may be arranged for parents where this is required. Due to the number of participants to be enrolled within a short time frame, some study centres may choose not to have a formal pre-screening process. Instead, the inclusion and exclusion criteria will be made clear in the information letter made available to all families interested in

participating in this study, and families will be encouraged to make an appointment only if their child has no exclusion criteria.

5.6.2 Informed consent

At Visit 1, written and verbal versions of the participant information and informed consent will be presented to the participants' parent or legal guardian detailing no less than:

the exact nature of the study;

the implications and constraints of the protocol;

the known side effects and any risks involved in taking part.

It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The participant's parent or legal guardian will be allowed as much time as required to consider the information, and the opportunity to question the researcher, their GP or other independent parties to decide whether they will participate in the study. Written Informed Consent will be obtained by means of a dated signature of the person legally responsible for the participant and signature of the person who presented informed consent. A copy of the signed Informed Consent will be given to the participant's parent or legal guardian. The original signed form will be retained at the study site. The informed consent discussion will be conducted by a nurse or doctor who has been trained in the consent process. The written informed consent form and any other written information will be revised whenever important new information becomes available that may be relevant to the consent. Any revised written informed consent form and written study information will be submitted to an ethics committee for approval before use.

The participant's parent or legal guardian will be informed in a timely manner if new information becomes available that may affect the decision to participate in the clinical trial. The communication of this information will be documented.

5.6.3 Screening and eligibility assessment

Following the attainment of informed consent, potential participants will be assessed by a study doctor to determine whether the candidate satisfies the inclusion/ exclusion criteria and to aid in the analysis of data. This assessment will include:

- Demographics: The date of birth, ethnicity and gender.
- Medical History: Details of any significant medical history based on parental recall

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(including previous seasonal influenza vaccination, atopy and a personal or family history of seizures).

- Gestational age at birth (for participants under 1 year of age only).
- Concomitant Medication: All immunosuppressive medication and non-steroidal anti-inflammatory medications.
- Physical Examination
- Axillary temperature.

The details of this assessment will be recorded in the CRF. If the inclusion/ exclusion criteria are satisfied (including willingness to have a blood sample taken) and the informed written consent has been obtained the participant will be randomised to receive either the Baxter or the GlaxoSmithKline vaccine

5.6.4 Randomisation

Envelope randomisation will be generated by Nick Andrews or another statistician at the Health Protection Agency. The randomisation envelope will only be opened once the participant has demonstrated their willingness to have a blood test; at the point of randomisation the child will be considered enrolled into the study. The study will be open label, however the group to which they have been randomised will be concealed until after the point of enrolment.

5.6.5 Baseline assessments

1. Perform blood draw collecting up to 6 ml in the 6 month to 3 year age groups and10ml in the 3 – 12 year age groups.
2. Randomise participant to receive either the Baxter or GSK vaccine
3. Administer vaccination, as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or the study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Provide participant with study centre contact details (including 24 hour telephone advice line contact details for study staff member).
9. Instruct participant on notifying study centre of any serious adverse events/reactions.
10. Instruct participants to use antipyretics only to treat fever or other adverse reactions, rather than prophylactically.

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11. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record any ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
12. Schedule Visit 2, 21 days after Visit 1.

5.6.6 Subsequent assessments

Eligibility Check

The on-going eligibility of the participant will be reviewed at each visit. The participant's medical status will be assessed to detect:

1. any serious reaction related to the investigational vaccine
2. any further condition occurring which in the opinion of the investigator, might interfere with the evaluation of the study objectives.

Follow-up Phone Call

5-7 days after Visit 1

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the first administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 2

21 days (+/-7 days) after visit 1 date.

1. Obtain interim history and check eligibility criteria, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant
    c. newly prescribed vaccines
    d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

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2. Measure axillary temperature immediately prior to vaccination and record on CRF.
3. If the participant is still suitable for inclusion in the study, administer vaccination with either Baxter or GSK vaccine as per randomisation group.
4. Record vaccination details in participant's 'red book' and/or study vaccination card.
5. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.
6. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.
7. Fill out a notification to the participant's GP of the vaccine administered.
8. Ensure participant has study site contact details (including 24 hour emergency contact details for study staff member).
9. Instruct participant on notifying study site of any serious adverse events/reactions.
10. Provide participant's parent or legal guardian with a Diary Card to detail local and systemic effects and AEs in first seven days after immunisation and Memory Card to record ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.
11. Schedule Visit 3, 21 days after Visit 2.

Follow-up Phone Call

5-7 days after Visit 2

1. A follow-up phone call will be made to the participant's parent or legal guardian 7 days after the second administration of the study vaccine. This phone call will establish whether an SAE has occurred during the last 7 days.
2. Where an SAE has occurred that is deemed to need further review the information will be passed on to a nurse or medic from the study team who will phone the participant's parent or legal guardian to discuss further.
3. The phone call will also serve as a reminder to return the diary card and complete the memory card as appropriate.

Visit 3

21 days (- 7 days to + 14 days) after Visit 2

1. Obtain interim history, specifically assessing for:
    a. serious adverse events
    b. adverse events requiring a visit to a physician or emergency department or potentially leading to the withdrawal of the participant

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c. newly prescribed vaccines
d. any solicited AEs continuing on after day 7 post-immunisation or any medically significant AEs (as recorded in the memory aid card).

2. Perform blood draw collecting up to 6 ms in the 6 month to 3 year age groups and 10 mls in the 3 – 12 year age groups.

Every endeavour should be made to respect the timelines indicated above, however if a participant is not able to undertake a study visit within these timelines (e.g. due to intercurrent illness) then as long as the visit is able to be done in a reasonably timely manner they will not be excluded from the study. In particular, every effort should be made to complete the immunisation course once this has been commenced.

5.6.7 Blood sampling

The volume of blood samples obtained from infants less than 3 years of age will be up to 6 mL, the volume after 3 years of age will be up to 10 mL. If the initial attempt at venepuncture is unsuccessful, (i.e. less than 4 ml obtained), then, depending on the judgment of the staff member, assent will be sought from the parents and child (as appropriate according to age) to have a further attempt. Following the initial attempt at venepuncture, a parent may decline any of these further attempts and their child will still be eligible to remain in the study. A local anaesthetic cream (Ametop or Emla according to local practice at each site) or cold spray (ethyl chloride) will be applied for an appropriate period of time prior to each venepuncture. The parent/guardian will be provided with the anaesthetic cream and instructions for use prior to Visit 3 so that they can apply it to the child's skin in the appropriate amount of time prior to the visit.

5.6.8 Diary card for recording local and systemic side effects

The participant's parent or guardian will be instructed to complete a diary card to record daily temperatures and describe local and systemic symptoms, all adverse events (AEs), and usage of analgesic/antipyretic medication for seven days following each vaccination starting on the day of administration.

Upon completion of the diary cards (i.e. 7 days after administration of the study vaccine) they will be mailed by the participant's parent or guardian directly to the Health Protection Agency. Data Clarification Forms or annotated photocopies of the diary card will be sent to the study site by the Health Protection Agency when queries arise from the participant's diary card.

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These data queries will be resolved with the participant's parent or guardian when the participant attends for the second (V2) visit and the third (V3) visit.

5.6.9 Memory Card for recording visits to doctors and emergency departments

The participant's parent or guardian will be instructed to complete a memory card to record any visits to a doctor or emergency department from the eighth day after vaccination until the next study visit and any adverse events recorded in the diary card that are ongoing after day 7.

The memory card will be returned to the study site at the following study visit at which point the study staff will review the recorded information with the participant's parent or guardian and record this in the CRF.

5.7 Laboratory methods

Blood samples taken from participants will be stored at room temperature for up to 60 minutes, and then stored at between 2 to 8°C. Samples collected at each study site will be centrifuged at 3000 rpm for 10 minutes within 24 hours at the study site and separated into at least 2 aliquots for storage at or below -30°C. Aliquots will be shipped separately to the Centre for Infections Virus Reference Department (VRD) for testing. All samples will be analysed by microneutralisation (MN) and haemagglutination inhibition (HAI) with the NIBRG121 virus (rg virus based on ACalifornia/7/2009 (vH1N1) and A/Puerto Rico/8/34). Pre and post vaccination sera will be tested in parallel.

Microneutralisation (MN)

The microneutralisation assay will be performed in 96- well format according to previously described protocols and SOPs developed at the Respiratory Virus Unit (RVU).

Serum Pre-treatment

Elimination of complement (e.g. from Foetal Calf Serum in culture medium) will be achieved by incubation of study sera and appropriate quality control sera (provided and chosen according to test virus by the RVU; usually serum of ferret, sheep or human, with/without neutralization activity) at +56°C / 30min. This step will be performed simultaneously for all study samples and control sera.

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MN Test

The MN analysis with the NIBRG121 virus will be performed as follows: a 6-step, two-fold dilution series (covering titres 20 to 640) will be set up for each of the samples and control sera. After addition of a pre-titred virus (usually around 100x$TCID_{50}$ per well or 0.1-1 virus particle per cell) neutralisation will be performed by incubation of the virus/serum mixture at room temperature for 1h.

After neutralization, a suspension of MDCK cells will be added and the plates will be incubated for 16h at 37°C in a CO2 incubator. The remaining infectivity of virus after neutralisation is determined in an EIA format using a mAb to detect expression of viral nucleoprotein. The amount of nucleoprotein expression is determined photometrically (OD450) using a plate reader.

Reading

An Optical Density reading for each dilution step for each sample will be used to calculate the titre. The titre will be reported as the reciprocal dilution at which 50% of the virus is neutralized (e.g. titre of 100). The microneutralisation analysis will be performed in duplicate (in separate runs on 2 days) for each sample.

The two titres for each sample must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

Haemagglutination Inhibition (HAI)

The principle of the HAI test is based on the ability of specific anti-influenza antibodies to inhibit haemagglutination of red blood cells (RBC) by influenza virus haemagglutinin antigen (HA). The sera to be tested have to be previously treated to eliminate the non-specific inhibitors and the anti-species HAs. The experiment will be performed in accordance to protocols and SOPs established by RVU.

Serum Pre-treatment

Elimination of non-specific inhibitors will be achieved by incubation of the unknown serum samples and quality control sera (serum of ferret or human immunized with influenza virus) with neuraminidase (RDE II; 18 h / +36°C followed by heat-inactivation 1h / +56°C).

All samples (sera pre- and post-vaccination and controls) will be prepared simultaneously.

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HAI Test

For the HI analysis with the NIBRG121 virus samples and controls will be titrated in an 8-step, two-fold dilution series (covering titres 8 to 1024) and incubated with the haemagglutinin antigen suspension (previously titrated to adjust the dilution at 4 haemagglutination units/25 µL; 50% endpoint). The haemagglutinin antigen is not added to the well dedicated to the RDE quality control.

The mixture is incubated for 1 hour at room temperature and 25 µL of the 0.5% RBC suspension (turkey blood) are added. The reaction is left for 1/2 hour at room temperature before reading.

Reading

The serum titre is equal to the highest reciprocal dilution, which induces a complete inhibition of haemagglutination. The titre of each quality control serum is close to the previously assigned value (within one serial two-fold dilution limits).

The RBC controls (red blood cell suspension without antigen) and the RDE controls do not produce any agglutination.

Each serum sample is titrated in duplicate and individual titres will be reported (two for each sample). These must not differ by more than a two-fold serial dilution. In cases, where samples don't fall within this limit, a third analysis is performed and the two closest titres (which must be within a two-fold serial dilution) will be reported.

5.8 Definition of End of Trial

The end of trial is the date at which the processing of samples for the purposes of this study has been completed.

5.9 Discontinuation/ Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with treatment regimen or study requirements
- An adverse event which requires discontinuation of the study medication or results in inability to continue to comply with study procedures
- Consent withdrawn
- Lost to follow up

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Withdrawn participants will not be replaced.
Data generated from participants that later withdraw will still be included in the analysis on an intention to treat basis.
The reason for withdrawal will be recorded in the end of study CRF if the participant offers an explanation.
If the participant is withdrawn due to an adverse event, the investigator will arrange for follow-up visits or telephone calls until the adverse event has resolved or stabilised.

5.10 Source Data

Source documents are original documents and records from which participants' data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g., there is no other written or electronic record of data).
All documents will be stored safely in confidential conditions. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name.

6. TREATMENT OF TRIAL PARTICIPANTS

6.1 Description of Study Treatment

Baxter H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by Baxter Vaccines is a whole virus unadjuvanted vaccine with 7.5 µg of H1N1 virus per 0.5 ml dose. The H1N1 virus is grown in a vero cell culture. The vaccine is presented as a multidose vial (10 doses per vial).

GSK H1N1 vaccine
The novel Influenza A H1N1 Vaccine produced by GSK Vaccines is a split virion vaccine adjuvanted with an oil in water emulsion (ASO3) containing Squalene, Vitamin E- as immunostimulant and Tween 80 as surfactant. The vaccine also contains the preservative thiomersal. Each 0.5 ml dose contains 3.75 µg of H1N1 virus. The H1N1 virus is grown in an

egg cell culture and is presented in a multidose vial (10 doses per vial) to be reconstituted with the adjuvant (also in a multi-dose vial, 10 doses per vial) prior to administration.

If at the start of the trial there is clinical data or a recommendation from JCVI that supports the use of a half dose of either vaccine in children this will be used, however in the absence of any specific directive of this nature a full dose will be used (see section 3, background and rationale).

Both vaccines are to be administered intramuscularly via a 23 gauge, 25 mm needle into either the upper arm or thigh (if muscle bulk of the upper arm is insufficient). Vaccines should be administered into the non-dominant arm or thigh, ensuring consistency of limb administration between both doses of vaccine.

6.2 Storage of Study Vaccine

Prior to the commencement of the trial the Department of Health will supply the Baxter vaccine (Celvapan) to the Centre for Infections (CFI) which holds a GMP licence for re-labelling of IMPs. At CFI this vaccine will be relabelled for use in this clinical trial. They will then be shipped via cold chain to the trial sites using accredited couriers.
The GSK vaccine (Pandemrix) will be labelled for use in this clinical trial by GSK and shipped directly to the trial sites using accredited couriers.
The labels applied to these vaccines will include information on the study name/code, the CI and for 'clinical trial use only' and vial number.
The investigator (or delegate) will make an inventory and acknowledge receipt of all shipments of study medication/vaccine.
All vaccine supplies must be stored between +2 and +8°C. Vaccines that have been stored differently from the sponsor's recommendations must not be used unless the sponsor provides written authorization for use. In the event that the use cannot be authorized, vaccine supply must be replaced with fresh stock supplied by the sponsor.

6.3 Vaccine administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the study according to the procedures stipulated in this study protocol. All vaccines will be administered only by personnel who are qualified to perform that function under applicable local laws and regulations for the specific study site.
The vaccine must be visually inspected before use.

Study vaccines should not be administered to individuals with known hypersensitivity to any component of the vaccines.

Any axillary temperature ≥ 38°C or serious active infection is reason for delaying vaccination. Standard immunization practices should be observed and care should be taken to administer the injection intramuscularly. A 23 gauge, 25 mm needle is to be used for administration. As with all injectable vaccines, appropriate medical treatment and supervision should be readily available in case of rare anaphylactic reactions following administration of the study vaccine. Epinephrine 1:1000 should be available in case of any anaphylactic reactions. Care must be taken to ensure the vaccine is not injected into a blood vessel.

6.4 Vaccine compliance

The investigator will be responsible for adequate and accurate accounting of vaccine usage. The investigator or designee will administer the study vaccines only to individuals included in this study following the procedures set out in this study protocol. The date, dosage, and time of the vaccinations will be recorded. The investigator will track vaccines received, used and wasted and will retain all unused or expired products until the sponsor is satisfied that the vaccine accountability records are correct. Thereafter, all unused vaccines are to be destroyed at the investigational site. An overall summary of vaccines supplied, received, wasted, used and returned will be prepared at the conclusion of the study.

6.5 Adherence to randomisation list

The investigator or his designate will administer the vaccine as indicated on the randomization list for the individual subject. Adherence to the randomization will be verified by the Study Monitor by checking the vaccination records maintained in the investigator's study file.

6.6 Accountability of the Study Treatment

All vaccine doses will be accounted for within an accountability log. Unused vaccine at the end of the trial will be disposed of with written documentation describing this process.

6.7 Concomitant medication

Any immunosuppressant or non-steroidal anti-inflammatory medication taken at the time of enrolment into the study is to be recorded on the CRF.

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7. SAFETY REPORTING

7.1 Definitions

7.1.1 Adverse Event (AE)

An AE or adverse experience is:

Any untoward medical occurrence in a patient or clinical investigation participants administered a medicinal product, which does not necessarily have to have a causal relationship with this treatment (the study medication).

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of the study medication, whether or not considered related to the study medication.

7.1.2 Adverse Reaction (AR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal product" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

7.1.3 Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.4 Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death,

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- Is life-threatening, NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect.
- Other important medical events. NOTE: Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

7.1.5 Serious Adverse Reaction (SAR)

An adverse event (expected or unexpected) that is both serious and, in the opinion of the reporting investigator, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

7.1.6 Expected Serious Adverse Events/Reactions

No serious adverse events or reactions are expected. Extensive study of Guillian-Barré syndrome has demonstrated that there is no association between influenza vaccines and Guillian-Barré syndrome, and therefore Guillian-Barré syndrome is not expected to occur in this study.

7.1.7 Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable product information.

7.1.8 Adverse event of special interest (AESI)

Adverse events of special interest are those AEs recommended by the CHMP for inclusion as part of Risk Management Plans to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine (EMEA/359381/2009) and include: neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, and vaccination failure.

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7.1.9 Potentially Immune Mediated Diseases or pIMDs

Adverse events that constitute pIMDs are those diseases and conditions listed in Appendix E.

7.2 Reporting Procedures for All Adverse Events

In the seven days following vaccine administration the following solicited symptoms will be recorded by the participants parents/guardian in their study diary:

- injection site reactions (local tenderness, swelling or erythema)
- Fever ((≥ 38°C per axilla)
- Non febrile systemic reactions, i.e:
- reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).
- malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In addition parents/ guardians will be requested to record any other general symptoms in the 7 days post vaccination in the diary card.

These study diaries will be sent directly to the HPA for review by medical staff prior to transciption of the data to the study database. If clarification of any adverse events is required then the study staff at the relevant study site will be contacted.

At visit 2 and 3 medically significant adverse events (as recorded on the memory aid card) that have occurred in the period between the seven days after vaccination and the subsequent study visit (visit 2 or 3) will be recorded on the CRF, whether or not these are attributed to the study medication. Medically significant AEs will be defined as AEs requiring a physician visit, Emergency Department visit, or leading to a subject's withdrawal (with the exclusion of pre-planned visits and GP or emergency department visits for routine medical care). Adverse events solicited in the diary card that are ongoing after day 7 (as recorded in the memory aid card) will similarly be recorded in the CRF.

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The following information will be recorded for medically significant AEs: description, date of onset and end date, severity, assessment of relatedness to study medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of medically significant AEs to the study medication will be assessed by a medically qualified investigator according to the following criteria:

- Related - If the causal relationship between the IMP and the SAE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.
- Not related - If there is no causal relationship between the IMP and the SAE i.e. the event is caused by something other that the IMP e.g. underlying disease, a concomitant medication.

Verbal consent will be sought from participants to follow up all AEs considered related to the study medication, AEs leading to the participant's withdrawal from the study, AESIs, pIMD and pregnancies until resolution or the event is considered stable. If obtained this verbal consent will be documented in participant's case report form (CRF).

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment (see section 6.6). A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.
The rates of adverse events experienced by participants will be reviewed by a data monitoring committee (see section 10 below).

7.3 Reporting Procedures for Serious Adverse Events

All SAEs must be reported to the chief investigator or delegate for review within one working day of discovery or notification of the event. The chief investigator or delegate will then forward these on to CTRG and to the relevant vaccine manufacturer within 24 hours of receipt. All SAE information must be recorded on a signed SAE form and relayed to the chief investigator by fax or email. Additional information received for a case (follow-up or

corrections to the original case) need to be detailed on a new SAE form and faxed to the chief investigator or delegate for review and forwarding to the CTRG.

All serious adverse reactions (SAR's), AESIs and pIMDs will be reported on CIOMS 1 forms to the relevant manufacturer within 24 hours of any study staff becoming aware of these events. These events should also be reported as SAE's using the appropriate forms.

The CI will report all SUSARs to the MHRA, the Research Ethics Committee concerned and Host NHS Trusts. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will also inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.
In addition to the expedited reporting above, the CI shall submit once a year throughout the clinical trial or on request a safety report to the Competent Authority (MHRA in the UK), Ethics Committee, Host NHS Trust and sponsor.

The CTRG will ensure that all SAEs are reviewed by medical monitors on a weekly basis and at the next meeting of the Oxford Radcliffe Hospitals Trust / University of Oxford Trials Safety Group (TSG), who will meet at regular intervals and consider:

- Occurrence and nature of adverse events
- Whether additional information on adverse events is required
- Consider taking appropriate action where necessary to halt trials
- Act / advise on incidents occurring between meetings that require rapid assessment (e.g. SUSARs)

If deemed appropriate, the TSG will refer the SAEs experienced in the study to the data monitoring committee for review.

7.4 Reporting of Pregnancy

Although pregnancy tests will not be performed in this study due to the age range of the participants, if the investigators were to become aware of a study participant receiving a study vaccine within 30 days prior to pregnancy or during pregnancy, then they would inform the chief investigator or delegate, who will inform the sponsor, the ethics committee, the MHRA and the vaccine manufacturer of this occurrence.

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8. STATISTICS

8.1 Description of Statistical Methods

Immunogenicity

The following statistical parameters will be determined for each study group:

- Percentage of subjects with an HAI titre ≥ 1 in 32
- Percentage of subjects with a 4 fold rise in HAI titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Percentage of subjects with a 4 fold rise in MN titre between the pre-vaccination sample and sample taken 3 weeks after the second dose
- Geometric mean of pre-vaccination serum HAI titres
- Geometric mean of post-vaccination serum HAI titres
- Geometric mean of pre-vaccination serum MN titres
- Geometric mean of post-vaccination serum MN titres
- Geometric mean of the rise in HAI titres from pre- to post-immunisation
- Geometric mean of the rise in MN titres from pre- to post-immunisation

The above analyses will be performed on all participants in the Per-protocol (PP) immunogenicity population (see section 8.8). In addition, a sub-analysis will be performed on the participants in the PP population who were seronegative by for the relevant assay (MN or HAI) at enrolment.

In the event of HAI titres being negative at the initial dilution (1:8) an arbitrary value of 4 will be assigned for calculation of fold rise and GMTs, while for the MN assay (initial dilution 1:20) this value will be 10.

Reactogenicity

- Percentage of participants experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following each immunisation with the study vaccines
- Percentage of participants experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature (6 month to 5 year olds).

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- Percentage of participants experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 12 year olds).

In children aged under 5 years the severity of solicited systemic reactions will be graded according to the following criteria:

Reduced Feeding:

0 None	
1 Mild	Eating less than normal for 1-2 feeds
2 Moderate	Missed 1-2 feeds completely
3 Severe	Refused most or all feeds

Reduced Activity

0 None	
1 Mild	Less interested in surroundings, toys etc
2 Moderate	No interest in above and sleeping through feeds
3 Severe	Sleeping most of the time

Increased Irritability

0 None	
1 Mild	Continuously irritable for less than 1 hour
2 Moderate	Continuously irritable for 1 to less than 3 hours
3 Severe	Continuously irritable for 3 or more hours

Persistent Crying

0 None	
1 Mild	Cried continuously for less than 1 hour
2 Moderate	Cried continuously for 1 to less than 3 hours
3 Severe	Cried continuously for 3 or more hours

Vomiting

0 None	
1 Mild	1-2 episodes without interfering with routine

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2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material
3 Severe Multiple liquid stools without much solid material

In children aged 5 years or above the severity of solicited systemic events will be assessed on the following scale:

Generally unwell (malaise)
0 = No
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Headache
0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Vomiting
0 None
1 Mild 1-2 episodes without interfering with routine
2 Moderate Several episodes & cannot keep any food down
3 Severe: Frequent episodes & taking nothing by mouth

Diarrhoea
0 None
1 Mild More loose stools than usual
2 Moderate Frequent runny stools without much solid material

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3 Severe Multiple liquid stools without much solid material

Reduced feeding
0 None
1 Mild Eating less than normal for 1-2 meals
2 Moderate Missed 1-2 meals completely
3 Severe Refused most or all meals

Myalgia
0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Arthralgia

0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

In both age groups, local erythema and swelling will be classified as absent, less than 2.5 cm and greater than or equal to 2.5 cm, while local tenderness will be assessed on the following scale:

0 = None
1 = Mild (transient with no limitation on normal activity)
2 = Moderate (some limitation in daily activity)
3 = Severe (unable to perform normal daily activity).

Reactogenicity will be assessed by calculating the percentage of participants with solicited local reactions and fever in each group (i.e. the percentage of participants within each age group receiving each vaccine experiencing these reactions).The percentage of participants in

each group experiencing each of these reactions after each vaccine will be calculated, as will the percentage of participants in each group experiencing each reaction during the immunisation course. The percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course. As well as being calculated for each group, these percentages may also be calculated for all recipients of each vaccine (regardless of age group).

The percentage of participants experiencing non-febrile solicited adverse events (e.g. irritability or vomiting) will be calculated for recipients of each vaccine aged less than 5 years and for those aged 5 years and over. This will be calculated for participants experiencing each non-febrile solicited adverse event after each vaccine dose and during the whole immunisation course, and the percentage of participants experiencing any solicited local reaction or fever may also be calculated, both after each immunisation and during the whole vaccine course.

The number of subjects with reported serious adverse events up to 7 days after each vaccination and during the whole study will also be calculated, as will the number of participants with any adverse event in the first week after immunisation and any medically significant adverse event during the study.

In the event of one of the vaccines not being available at the start of this study, an alternative enrolment strategy will be conducted, in which participants are initially recruited to receive the available vaccine alone. This could be done at all sites or a selection of sites as appropriate, and enrolment for this phase would continue until one half of the participants due to receive that vaccine had been recruited (i.e. 125 in each age group). Recruitment to the study will then cease until both vaccines are available, at which time a revised randomisation (2:1) scheme will be employed, so that equal numbers of participants will have received each vaccine by the study's end.

8.2 The Number of Participants

With a sample size of 100-200 in each of two age groups for each vaccine the precision (95% CI) of estimates of percentages with adverse reactions or responding to vaccination is shown in the table below.

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	N=100	N=150	N=200
Observed %	95% CI*	95% CI	95%CI
0	0 to 4	0 to 2	0 to 2
10	5 to 18	6 to 16	6 to 15
20	13 to 29	14 to 27	15 to 26
30	21 to 40	23 to 38	24 to 37
40	30 to 50	32 to 48	33 to 47
50	40 to 60	42 to 58	43 to 57
60	50 to 70	52 to 68	53 to 67
70	60 to 79	62 to 77	63 to 76
80	71 to 87	73 to 86	74 to 85
90	82 to 95	84 to 94	85 to 94

*exact 95% CIs are shown

So precision is within +/- 10% for N=100, +/- 8% for N=150 and +/- 7% for N=200

Detectable differences in percentages between vaccines or age groups will be as follows (80% power, 5% significance level, N=100-200 per group compared)

	N=100		N=150		N=200	
True % in first group	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)	% in second group detectable (below)	% in second group detectable (above)

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0	-	9	-	6	-	5
10	0	26	2	22	3	21
20	6	39	8	35	10	33
30	13	50	16	46	18	44
40	21	61	24	57	26	54
50	30	70	33	67	36	64
60	39	79	43	76	46	74
70	50	87	54	84	56	82
80	61	94	65	92	67	90
90	74	100	77	98	79	97

So, for example, if one vaccine has a true local reaction rate of 10% in a given age group then a rate of 26% is detectable as different for the other vaccine with N=100 down to 21% for N=200. Similarly if one vaccine had a seroconversion rate of 70%, then it would be possible to detect a difference in seroconversion rates to the other vaccine if this value was below 56% or greater than 82%.

For comparison of geometric mean HI fold rises between vaccines or ages, the sample size of 200 will allow 1.34 fold differences to be detectable with 80% power at 5% significance. This uses an estimate of 0.45 for the log10 scale SD of post vaccination fold rises as seen with other influenza vaccines. For N=100 1.51 fold differences are detectable and for N=150 1.40 fold differences.

Based on these calculations a sample size of 200 per group has been chosen to optimise the power to detect a difference in the immunogenicity and reactogenicity of the two vaccines in the two age groups. Specifically, it was felt that a difference in seroconversion or local reaction/ fever rates of -14% and +12% around a (hypothetical) rate of 70% would be of

clinical importance, and that it would not be possible to this degree of variance with a smaller sample size.

In order to account for about 25% of participants not completing the study or not having blood samples obtained, the overall number of participants is therefore 1000. Due to the rapid nature of recruitment across multiple sites that is required for this study, it may not be possible to precisely match the number of participants to 1000; the actual figure enrolled may therefore be slightly higher or lower than this target figure. Recruitment is provisionally expected to be approximately 250 participants at 3 sites (Oxford, Southampton, and St. George's) and approximately 250 participants at 2 sites combined (Bristol and Exeter), however should it be required to optimise recruitment then it will be possible for any site to recruit more than the provisional number of participants.

If recruitment were to be lower than expected then the above calculations suggest that the immunogenicity and reactogenicity of the individual vaccines could still be assessed with reasonably narrow confidence intervals (e.g. +/- 10% for 100 participants in each group), however the ability to detect differences between the two groups would be reduced.

Withdrawn participants will not be replaced.

It is anticipated that some potential participants who will be allocated a participant number after completion of informed consent will not subsequently be enrolled or randomised (e.g. if an exclusion criterion is identified at medical assessment or the child is unwilling to have a blood sample taken). An excess of participant numbers will therefore be allocated for each study site to allow for this.

8.3 Interim analysis

An interim analysis may be performed when results of laboratory assays or adverse event rates are available on about 250 participants for each vaccine (i.e. half-way through). This analysis will consist of a descriptive analysis (proportions and 95% CI's) of the primary immunogenicity end point and a subset of safety end points (fever ≥ 38°C, local redness and swelling ≥ 2.5 cm). Continuation of recruitment will not be dependent on the results of this analysis, which is being performed due to the need for rapid data on these vaccines in children. An additional interim analysis, in which adverse event rates after the first dose of

vaccine are evaluated by study statistician's and/or the data monitoring committee, may be performed.

8.4 The Level of Statistical Significance

The level of statistical significance will be taken as 5%.

8.5 Criteria for the Termination of the Trial.

The study uses two vaccines produced by Baxter and GlaxoSmithKline. Both manufacturers have gained marketing authorisation approval from the EMEA for a pandemic strain vaccine under the "mock-up" dossier route based on limited clinical trial data for a candidate H5N1 vaccine. Trials of the mock up vaccines have been conducted in adults and there is some safety data of the use of the GSK H5N1 vaccine in children over 3 years of age. These trials have not reported significant safety concerns. The vaccines are similar to other influenza vaccines that have been licensed and used in children. It is unlikely that any safety issues should lead to termination of the trial, however the data monitoring committee will have the authority to recommend termination of the trial or for immunisation with either of the vaccines to be discontinued. In addition, the investigator has the right to discontinue this study at any time. If the clinical study is prematurely terminated, the investigator is to promptly inform the participants and should assure appropriate therapy and follow-up for the participants.

8.6 Procedure for Accounting for Missing, Unused, and Spurious Data.

The reason for missing data (consent withdrawn, lost to follow-up, removed from study due to serious side effects, death, or unable to obtain any laboratory results) will be indicated but missing data will not be imputed. Amount of missing data between the 2 groups and other demographic characteristics will be compared.

8.7 Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any additional analysis or deviation(s) from the analysis plan will be documented and updated according to the statistical standard operating procedure.

8.8 Inclusion in Analysis

The primary immunogenicity analyses will be conducted on a per-protocol (PP) population, consisting of all participants who completed the study and did not experience any significant protocol deviations. All participants in the PP population providing a blood sample following immunisation will be included in the PP immunogenicity analyses, with the exception of

analyses related to the fold rises from baselines, in which all participants in the PP population providing blood samples both before and after baseline will be included in the PP immunogenicity analyses.

An intention to treat (ITT) immunogenicity population will also be defined, consisting of all participants receiving an immunisation and providing a blood sample after immunisation. If the ITT immunogenicity population differs from the PP population by more than 10% then the measures of immunogenicity will also be calculated for the ITT immunogenicity population.

All data will be included up until the time that a participant is withdrawn from the study.

The population for safety analysis will include all those that received a study vaccine and provided any safety/reactogenicity data.

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Direct access will be granted to authorised representatives from the sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

10. QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

The study will be conducted in accordance with the current approved protocol, ICH GCP, relevant regulations and the study sites standard operating procedures.

Regular monitoring will be performed according to ICH GCP. Monitoring of this study will be conducted by freelance monitors in collaboration with the quality assurance manager of the Oxford Vaccine Group and local staff at each study centre. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures and an approved monitoring plan, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

A trial steering committee will be formed that will include, but not be limited to, the chief investigator, a statistician, a quality assurance manager and project manager.

A Data Monitoring Committee (DMC) will be convened that will primarily have responsibility for reviewing the adverse event rates and serious adverse events experienced by participants in this study. Due to the rapid nature of recruitment intended for this study, it is not anticipated that the DMC will be able to review immunogenicity data during the study itself. The DMC will be independent of the study team and will report to the trial steering

committee. The DMC will include, but not be limited to, a paediatric infectious disease specialist, a statistician and a consultant with expertise in public health.
This committee will be in addition to the trial safety group (TSG), who will provide review of serious adverse events as part of routine procedures for the CTRG.

11. ETHICS

11.1 Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

11.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

11.3 Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), regulatory authorities (MHRA in the UK), and host institution(s) for written approval.
The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

11.4 Participant Confidentiality

The trial staff will ensure that the participants' anonymity is maintained. With the exception of the study diary card (where the participant's first name only will be listed) and correspondence sent to the relevant child health computer department and general practitioner all documents leaving the study sites will refer to the participant by the study participant number/code, not by name. All documents will be stored securely and only accessible by trial staff and authorised personnel. The study will comply with the Data Protection Act which requires data to be anonymised as soon as it is practical to do so.

11.5 Compensation for harm

As study sponsor the University of Oxford will provide indemnity for harm arising as a result of the study protocol.

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The Government has already provided an indemnity to Baxter and GSK in relation to any claims arising out of the use of the vaccines purchased under the Advance Purchase Agreements (APA) with those companies, other than where the harm is due to a defect in manufacture. That indemnity covers the use of the vaccine in research projects, as the contractual indemnity provisions are not limited by reference to the circumstances in which the vaccines are used.

In relation to the liability of the sponsors and investigators taking part in the research projects, the usual insurance or indemnity arrangements will apply (for example, in relation to NHS bodies and staff, the NHS Indemnity and Clinical Negligence Scheme arrangements apply).

Exceptionally, given the nature of this study, as part of a wider government response to a major public health emergency, the Department will also offer a “no fault” compensation scheme to trial participants, in relation to serious injury of an enduring and disabling character caused by the vaccines which are the subject of the trials

12. DATA HANDLING AND RECORD KEEPING

Information on study participants will be recorded on hard copy case report forms (CRFs) held locally. CRFs will be supplied by CFI in packs and will include the following:

i. Subject contact details (to be retained locally)
ii. Inclusion and exclusion criteria
iii. Medical history
iv. Immunosuppressive or non-steroidal medication at study start
v. Each vaccination and each blood
vi. Post vaccination follow up at 3 weeks
vii. Study termination record for subjects completing per protocol and for earlier withdrawals
viii. Age specific diary cards for completion by parents
ix. Memory aid card for completion by parents

Each study site will be responsible for generating and retaining their own source documents if required.

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Each study participant will have a unique study number which will be allocated following the taking of informed consent. For each participant, sufficient labels with the same study number will be generated at CFI to label all CRFs, diary cards, vaccine vials and blood sample tubes.

In order to identify study staff who have completed each CRF, each site will have a signature sheet, including full name and initials a copy of which will be provided to CFI.

12.1 Data entry at CFI

The CRFs from each trial site will be photocopied locally and the copy sent to CFI with the original retained at the local site. The diary cards will be sent directly to CFI by the participant's parent or legal guardian. The diary cards will be photocopied at CFI and a copy will be sent to the local site to retain in the participant's study file. The only patient identifying information on the CRFs sent to CFI will be study number and participant initials. The only patient identifying information on the diary cards sent to CFI will be the participant's first name on the front page to aid parents who may have more than one child enrolled in the study, and the study number and participant initials. A study database will be constructed at CFI to record the information collected in the CRFs and diary cards. As the data is being entered, the CRFs and diary cards will be monitored. Study diaries will be reviewed by medical staff at the HPA prior to transciption of the data to the study database. If clarification of any adverse events is required or completion errors or omissions are noted then the study staff at the relevant study site will be contacted.

When completion errors or omissions are noted the study site will be notified of the entries requiring correction or clarification. The local investigator will make the correction on the CRFs, crossing out any incorrect information with a single line, and will sign and date the change on the original CRF which will be photocopied again and sent to CFI. On return of the photocopy to CFI the database will be updated accordingly and the photocopy filed with the initial photocopy. Corrections to the diary cards will be made via data clarification forms that will be sent to the study sites to resolve with the participant's parent or guardian on the subsequent study visit.

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If diaries have not been returned to CFI at the specified time, the local site will contact the parent and advise CFI of any outstanding diaries weekly by a spreadsheet return. This return will also list by subject number and initials any subject who has withdrawn from the study and complete the "end of study" CRF as appropriate.

Information from the CRFs will be double entered onto the data base at CFI by two independent data-entry staff. Verification routine will be done weekly and data inputting errors corrected.

12.2 Data locking

At the end of the study, the database will be locked and a data extract provided to the study statistician for analysis according to a pre-defined statistical analysis plan. Should an interim analysis be conducted then a dated copy of the database will be made and locked and the analysis conducted on a data extract of that locked database.

13. FINANCE AND INSURANCE

The involved parties will be insured, in accordance with the Clinical Trials regulations, against financial loss resulting from personal injury and/or other damages, which may arise as a consequence of this study. For details see contract agreements.

14. PUBLICATION POLICY

The Investigator will co-ordinate dissemination of data from this study. All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study will be reviewed by each sub-investigator prior to submission.

15. REFERENCES

1. Health Protection Agency Weekly National Influenza Report 23rd July 2009.
2. World Health Organisation Pandemic (H1N1) 2009 briefing note 2: WHO recommendations on pandemic (H1N1) 2009 vaccines, 2009.
3. Katz J, Hancock K, Veguilla V, Zhong W, Lu X, Sun H, et al. Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine. *Morbidity and Mortality Weekly Review* 2009;58(19):521 - 524.

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APPENDIX A: PANDEMIC (H1N1) 2009 BRIEFING NOTE 2. WHO RECOMMENDATIONS ON PANDEMIC (H1N1) 2009 VACCINES

13 JULY 2009 | GENEVA -- On 7 July 2009, the Strategic Advisory Group of Experts (SAGE) on Immunization held an extraordinary meeting in Geneva to discuss issues and make recommendations related to vaccine for the pandemic (H1N1) 2009.

SAGE reviewed the current pandemic situation, the current status of seasonal vaccine production and potential A (H1N1) vaccine production capacity, and considered potential options for vaccine use.

The experts identified three different objectives that countries could adopt as part of their pandemic vaccination strategy:

- protect the integrity of the health-care system and the country's critical infrastructure;
- reduce morbidity and mortality; and
- reduce transmission of the pandemic virus within communities.

Countries could use a variety of vaccine deployment strategies to reach these objectives but any strategy should reflect the country's epidemiological situation, resources and ability to access vaccine, to implement vaccination campaigns in the targeted groups, and to use other non-vaccine mitigation measures.

Although the severity of the pandemic is currently considered to be moderate with most patients experiencing uncomplicated, self-limited illness, some groups such as pregnant women and persons with asthma and other chronic conditions such as morbid obesity appear to be at increased risk for severe disease and death from infection.

Since the spread of the pandemic virus is considered unstoppable, vaccine will be needed in all countries. SAGE emphasized the importance of striving to achieve equity among countries to access vaccines developed in response to the pandemic (H1N1) 2009.

The following recommendations were provided to the WHO Director-General:

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be

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sufficient, a step-wise approach to vaccinate particular groups may be considered. SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions: pregnant women; those aged above 6 months with one of several chronic medical conditions; healthy young adults of 15 to 49 years of age; healthy children; healthy adults of 50 to 64 years of age; and healthy adults of 65 years of age and above.

- Since new technologies are involved in the production of some pandemic vaccines, which have not yet been extensively evaluated for their safety in certain population groups, it is very important to implement post-marketing surveillance of the highest possible quality. In addition, rapid sharing of the results of immunogenicity and post-marketing safety and effectiveness studies among the international community will be essential for allowing countries to make necessary adjustments to their vaccination policies.
- In view of the anticipated limited vaccine availability at a global level and the potential need to protect against "drifted" strains of virus, SAGE recommended that promoting production and use of vaccines such as those that are formulated with oil-in-water adjuvants and live attenuated influenza vaccines was important.
- As most of the production of the seasonal vaccine for the 2009-2010 influenza season in the northern hemisphere is almost complete and is therefore unlikely to affect production of pandemic vaccine, SAGE did not consider that there was a need to recommend a "switch" from seasonal to pandemic vaccine production.

WHO Director-General Dr Margaret Chan endorsed the above recommendations on 11 July 2009, recognizing that they were well adapted to the current pandemic situation. She also noted that the recommendations will need to be changed if and when new evidence becomes available.

SAGE was established by the WHO Director-General in 1999 as the principal advisory group to WHO for vaccines and immunization. It comprises 15 members who serve in their personal capacity and represent a broad range of disciplines from around the world in the fields such as epidemiology, public health, vaccinology, paediatrics, internal medicine, infectious diseases, immunology, drug regulation, programme management, immunisation delivery, and health-care administration.

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Additional participants in the SAGE meeting included members of the ad hoc policy advisory working group on influenza A (H1N1) vaccine, chairs of the regional technical advisory groups and external experts. Observers included industry representatives and regulators who did not take part in the recommendation process in order to avoid conflicts of interest.

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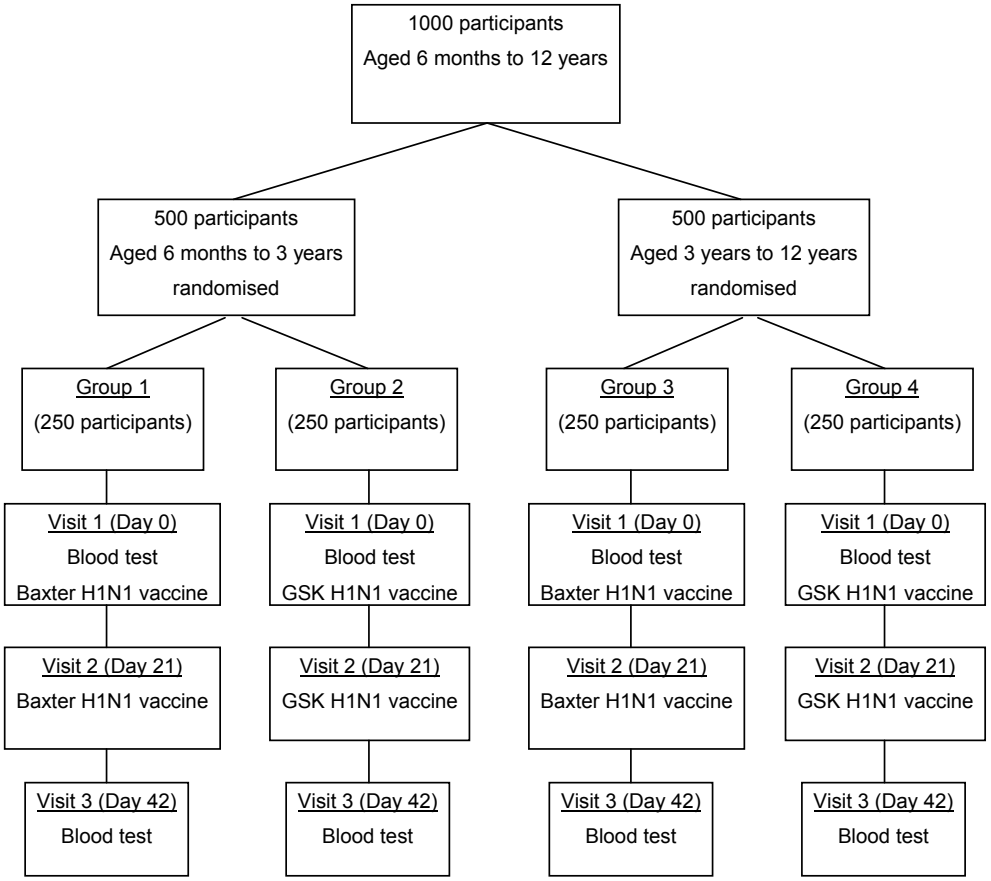
APPENDIX B: STUDY FLOW CHART



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APPENDIX C: STUDY TIMELINES

Stage	Timing (Planned start date 8th September, depending on vaccine availability and regulatory approval)
Visit 1	Week 1 to 3
Visit 2	Weeks 4 to 7
Visit 3	Weeks 7 to 12
Laboratory testing	Weeks 12 to 14
Analysis and initial report	Week 15
Completion of study for initial reporting	Week 15 (Week beginning 17th December if commence 8th September)

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APPENDIX D: STAFF PERSONNEL

CFI

Professor Elizabeth Miller:	Principal investigator for CFI site and overall trial co-ordinator
Nick Andrews:	Trial statistician
Liz Sheasby:	Quality Assurance at the CFI site
Pauline Kaye:	Trial data manager
Dr. Katja Hoschler:	Responsible for overseeing serological testing for the trial
Teresa Gibbs:	Senior administrator responsible for overseeing data entry and verification

OVG

Professor Andrew Pollard:	Chief investigator of study
Dr Matthew Snape:	Principal investigator for OVG site
Tessa John:	Clinical Team Leader at OVG site
Simon Kerridge:	Quality Assurance at the OVG site
Amanda Reiner:	Project Manager at OVG site

St George's Vaccine Institute

Dr Paul Heath:	Principal investigator at St George's site.
Dr Clarissa Oeser.	Research fellow
Dr Shamez Ladhani.	Consultant Paediatrician
Dr Ifeanyichukwu Okike:	Research Fellow

Bristol Children's Vaccine Centre

Professor Adam Finn:	Principal investigator at Bristol site
Dr Jolanta Bernatoniene:	Consultant paediatrician
Dr Edward Clarke:	Clinical Lecturer in Paediatric Infectious Diseases
Dr Ruth Allen:	Manager, Medicines for Children South West
Natalie Fineman:	MCRN Research Nurse team leader

Royal Devon and Exeter Hospital

Dr Andrew Collinson:	Principal Investigator at Royal Devon and Exeter

University of Southampton Wellcome Trust Clinical Research Facility

Dr Saul Faust:	Principal investigator at Southampton site

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APPENDIX E:

Immune Mediated Disorders (IMD)

Event Category	Immune-Mediated Disorder	MedDRA PT
Neuroinflammatory disorders	Cranial nerve disorders	Optic neuritis
		III nerve paralysis
		III nerve paresis
		IV nerve paralysis
		IV nerve paresis
		VI nerve paralysis
		Facial palsy
		Facial paresis
		VII nerve paralysis
		XI nerve paralysis
		Vagus nerve paralysis
		Acoustic nerve neuritis
		Glossopharyngeal nerve paralysis
		Trigeminal palsy
		Trigeminal nerve paresis
		Tongue paralysis
		Hypoglossal nerve paresis
		Anosmia
		Neuritis cranial
		Cranial neuropathy
		Paresis cranial nerve
		Cranial nerve paralysis
		Cranial nerve palsies multiple
	Multiple sclerosis	Multiple sclerosis
		Primary progressive multiple sclerosis
		Progressive multiple sclerosis
		Marburg's variant multiple sclerosis
		Secondary progressive multiple sclerosis
		Multiple sclerosis relapse
		Progressive relapsing multiple sclerosis
		Relapsing-remitting multiple sclerosis
	Demyelinating disease	Demyelination
		Leukoencephalomyelitis
		Acute disseminated encephalomyelitis
		Concentric sclerosis
		Neuromyelitis optica
		Chronic inflammatory demyelinating polyradiculoneuropathy
		Demyelinating polyneuropathy
	Transverse myelitis	Myelitis transverse
		Myelitis
	Guillain-Barré syndrome	Guillain-Barré syndrome
		Miller Fisher syndrome
	Myasthenia gravis	Myasthenia gravis
		Ocular myasthenia
	Encephalitis	Encephalitis
		Encephalomyelitis
		Encephalitis post immunisation

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Event Category	Immune-Mediated Disorder	MedDRA PT
		Encephalitis toxic
	Neuritis	Neuritis
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculopathy
		Radiculitis
		Radiculitis brachial
		Radiculitis cervical
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus
	Cutaneous lupus	Cutaneous lupus
	Sjogren's syndrome	Sjogren's syndrome
	Scleroderma	Scleroderma
		Systemic sclerosis
		CREST syndrome
		Morphoea
	Dermatomyositis	Dermatomyositis
	Polymyositis	Polymyositis
	Rheumatoid arthritis	Rheumatoid arthritis
		Juvenile arthritis
	Polymyalgia rheumatica	Polymyalgia rheumatica
	Reactive arthritis	Arthritis reactive
		Reiter's syndrome
	Psoriatic arthritis	Psoriatic arthropathy
	Ankylosing spondylitis	Ankylosing spondylitis
	Undifferentiated spondyloarthropathy	Spondyloarthropathy
	Mixed connective tissue disease	Mixed connective tissue disease
Gastrointestinal disorders	Crohn's disease	Crohn's disease
	Ulcerative colitis	Colitis ulcerative
	Ulcerative proctitis	Proctitis ulcerative
	Celiac disease	Coeliac disease
Metabolic disorders	Autoimmune thyroiditis	Autoimmune thyroiditis
	Hashimoto's thyroiditis	
	Grave's or Basedow's disease	Basedow's disease
	Insulin-dependent diabetes mellitus	Type 1 diabetes mellitus
	Addison's disease	Addison's disease
Skin disorders	Psoriasis	Psoriasis
	Vitiligo	Vitiligo
	Raynaud's phenomenon	Raynaud's phenomenon
	Erythema nodosum	Erythema nodosum
	Autoimmune bullous skin diseases	Pemphigus
		Pemphigoid
		Dermatitis herpetiformis
Other	Stevens-Johnson syndrome	Stevens-Johnson syndrome
		Erythema multiforme
		Toxic epidermal necrolysis

Date and Version No: 25/09/2009, version 3

Event Category	Immune-Mediated Disorder	MedDRA PT
	Autoimmune hemolytic anemia	Anemia heamolytic autoimmune
	Thrombocytopenias	Thrombocytopenia
		Autoimmune thrombocytopenia
		Idiopathic thrombocytopenic purpura
		Thrombocytopenic purpura
		Thrombotic thrombocytopenic purpura
	Antiphospholipid syndrome	Antiphospholipid syndrome
	Vasculitis	Vasculitis
		Diffuse vasculitis
		Leukocytoclastic vasculitis
		Behcet's syndrome
		Temporal arteritis
		Takayasu's arteritis
		Microscopic polyangiitis
		Polysrteritis nodosa
		Wegener's granulomatosis
		Allergic granulomatous angiitis
		Henoch-Schonlein purpura
		Kawasaki's disease
	Pernicious anemia	Pernicious anaemia
	Autoimmune hepatitis	Autoimmune hepatitis
	Primary biliary cirrhosis	Biliary cirrhosis primary
	Primary slerosisng cholangitis	Cholangitis sclerosing
	Autoimmune glomerulonephritis	Glomerulonephritis
	Autoimmune uveitis	Uveitis
	Autoimmune myocarditis	Autoimmune myocarditis
	Sarcoidosis	Sarcoidosis

Appendix 2

Information booklet

OXFORD VACCINE GROUP

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Information Booklet

You and your child are being invited to take part in a study of a vaccine against Influenza A H1N1 (swine flu). The study is being run by the Oxford Vaccine Group, part of the University of Oxford.

Before you decide whether to take part, it is important for you to understand what the study is about and what participation would involve. Please take time to read the information carefully, and discuss with others if you wish.

If anything is unclear or you would like further information please contact the study team – details below.

Thank you for taking the time to consider taking part in this study.

Contact Details

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Oxford
OX3 7LJ
Tel/Fax: 01865 857080
Email: ovg@paediatrics.ox.ac.uk

Dear Parent/Legal Guardian,

The Oxford Vaccine Group would like to invite your child to be in a study that will look at how well children respond to two new vaccines against H1N1 influenza (swine flu). This booklet outlines the study and what it would involve if your child were to take part. This study is being sponsored by the University of Oxford and is being conducted by a network of vaccine study centres in collaboration with the Health Protection Agency (HPA). Approval for this study has been gained from the Oxfordshire Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA).

What is this study about?

In the first half of this year a new strain of Influenza A H1N1 virus (known as 'swine flu' or 'Mexican flu') began to cause infections in humans. As this virus is very different from previously circulating influenza strains, few people have immunity to it and a global influenza pandemic has occurred. Fortunately most people who catch swine flu have a relatively mild illness, but a few people become very unwell and may even die. Many of these people have other underlying health conditions, such as heart or lung disease that put them at increased risk of severe disease.

Two new vaccines have been made against swine flu in response to the pandemic. These vaccines have been tested in adults, but there is less information on how well they work in children. This study will assess these two new vaccines in children aged between six months and twelve years. Participating children would receive two doses of swine flu vaccine and blood tests would be taken before and after vaccination to see how well the immune system responds. We will also look at any side effects of the two vaccines.

Taking part in this study is voluntary and if you do not want your child to participate he/she would still be eligible to receive a swine flu vaccine if it were to become available as part of a government immunisation program.

What does the study involve?

This study would consist of 3 visits each occurring 3 weeks apart over a 6 week period and would involve 2 vaccinations and 2 blood tests. These visits would be conducted at the Children's Hospital (John Radcliffe Hospital) in Oxford.

At the first visit, the study would be explained and you would be given the chance to ask any questions you may have. Before enrolment into the study, a doctor would examine your child and ask you some questions to ensure s/he was able to be included. Reasons that children would not be able to take part in the study include:

- Previous swine flu vaccination
- Previous swine flu infection (only if confirmed by laboratory testing or treated with oseltamivir ('Tamiflu') or zanamivir ('Relenza'))
- History of egg allergy or allergic reaction after previous vaccinations
- Problems with the immune system
- Coagulation disorders
- Receiving steroid tablets or syrup (e.g. for asthma) for more than 1 week within the previous 3 months (steroid inhalers or creams are allowed)
- Recent transfusion of blood or blood products (within the previous 3 months)
- Concurrent participation in another clinical trial
- Not being available for all the study visits

If your child was able to be enrolled, s/he would be allocated to one of two groups to decide which vaccine s/he would receive. The group allocation would be determined by a computer programme so that this would be decided by chance (similar to tossing a coin). Neither you nor the study team would be able to influence which group your child was allocated to.The vaccines would be given at the 1st and 2nd visit.

In order to assess the response to the vaccine each child would have 2 blood tests, one before the first vaccination and the second 3 weeks after the 2nd dose of vaccine. For each blood test we would take 6 to 10 mls of blood (one to two teaspoonfuls, depending on the age of your child). Local anaesthetic cream or cold spray would be used to minimise the discomfort of the blood test.

A diary card would be given to you after each vaccine visit. In this diary we would ask you to record daily temperatures and any reactions, such as injection site redness or swelling for 7 days after each immunisation. After this, we would ask that you to send the completed diary card to the Health Protection Agency using a pre-paid envelope. A

member of the study team will phone you after 7 days to ensure that your child is well and to remind you to post the diary card. A memory card would also be given to you after each vaccine visit. In this card we would ask you to record any reactions recorded in the diary card that are ongoing after day 7 and any visits to a doctor or emergency department until your next study visit.

In order to conduct this study as quickly as possible we plan to see many children over a short space of time. We would therefore ask you to come prepared to wait at various points during the visits. We will try to see you and your child as quickly as possible.

How many participants are there in the study?

A total of 1000 children will take part in this study; 500 aged 6 months to 3 years and 500 aged 3 to 12 years. Children will be recruited in Oxford, Bristol, Exeter, Southampton and South London.

What vaccines are going to be used in this study?

The two vaccines being assessed in this study are those that the UK government has arranged to be supplied for use if routine immunisation is recommended. One of these vaccines is made from an inactivated form of the whole swine flu virus, and is produced by the pharmaceutical company Baxter Vaccines. The other vaccine is known as a 'split virion' vaccine, meaning that it is made from a few key components of the virus, and is produced by the pharmaceutical company GlaxoSmithKline. This vaccine also contains an adjuvant called AS03 (an adjuvant is a substance designed to stimulate the immune system) and the preservative thiomersal.

The table below summarises the study design:

	Day 0	Day 21 (3 weeks)	Day 42 (6 weeks)
Group A	Baxter swine flu vaccine Blood test	Baxter swine flu vaccine	Blood test
Group B	GSK swine flu vaccine Blood test	GSK swine flu vaccine	Blood test

(Each group will have 250 children aged 6 months to 3 years and 250 children aged 3 to 12 years)

What happens if my child receives the vaccine that is not used by the government in the future?

As a result of this research the government may choose to use the vaccine that your child DID NOT receive. There may be several reasons why one of the vaccines is chosen over the other including vaccine cost, side effect frequency, response of the immune system and vaccine availability. We are expecting both vaccines to give sufficient protection and therefore don't anticipate your child requiring a further vaccine in the future. However, if your child would be better protected by receiving the other vaccine at a later date then there is no medical reason why s/he could not receive it.

Why does my child need two doses of the vaccine?

The information that we have from previous research shows that children's immune systems do not respond sufficiently after just one vaccine dose. It is expected that giving 2 doses 3 weeks apart will give the best immune response in children. Having a good immune response will be especially important if the virus changes in the future.

What are the advantages of taking part in the study?

The study provides the opportunity for your child to receive a swine flu vaccine whilst helping us to assess the response to the vaccine.

What are the risks and side effects of taking part in the study?

Both of the vaccines to be used in this study have been adapted from vaccines originally designed to protect against 'bird flu' (influenza A H5N1), and most of the information that we have about the vaccines to be used in the study comes from trials of the 'bird flu' versions of the vaccines. Over 600 adults have received the 'bird flu' form of the Baxter vaccine in clinical trials, but this vaccine has not been tested in children or adolescents under 18 years of age. Over 5,000 adults and 300 children aged 3 to 9 years have received various doses of the 'bird flu' version of the GSK vaccine in clinical trials. Both companies have started, or are about to start, studies of their 'swine flu' vaccines in children.

From the studies of the GSK 'bird flu' vaccine in children it is possible that approximately one third of children receiving the GSK 'swine flu' vaccine will have a fever over 37.5 °C, and that this fever may be above 39°C in approximately 1 in 10

children. In the 'bird flu' vaccine studies these fevers are short lived and were not associated with any complications such as febrile convulsions (a seizure associated with fever that does not have long term effects), but it is possible that complications such as these could rarely be seen following the 'swine flu' vaccine. As no studies of the Baxter 'bird flu' vaccine have been completed in children we do not know what the fever rates following this vaccine will be, but it is to be expected that some children receiving this vaccine will also develop a fever. We would therefore suggest that you have a supply of medicine against fever (such as paracetamol or ibuprofen) available for the first few days after immunisation.

Other reactions that may be observed are tenderness, redness, bruising, swelling, hardness or warmth at the injection site. Uncommon reactions are a change in eating habits, sleepiness, persistent crying, irritability, swelling of lymph nodes ('glands'), muscle pain or joint pain. Very rare (less than 1 in 1000) reactions seen in adults receiving the H5N1 vaccines include vomiting, diarrhoea, rash, cough and a congested nose. We expect these events to be generally mild and to resolve within a few days. Other very rare events that have been seen with routine flu vaccines include seizures and temporary bleeding disorders. In the past Guillian-Barré syndrome (a rare disorder of nerves) has been associated with flu vaccines but the relationship remains uncertain, with some studies suggesting a possible link but others not finding it. One large study in the UK found that influenza-like illness itself was associated with an increased risk of the Guillian-Barré syndrome but there was no link with the seasonal influenza vaccines, suggesting that vaccination might actually protect against the disorder by preventing flu.

Following the blood tests your child may experience temporary soreness and bruising. This discomfort will be minimised by the use of a local anaesthetic cream or cold spray.
In addition to the reactions listed above, there is a chance that an unexpected reaction may occur as these are new vaccines that are still being evaluated in children. We would therefore ask that you tell the study team about any changes in your child's health.

As with all vaccines there is the very small possibility of an allergic reaction. Your child would be observed for at least 20 minutes following the vaccine to monitor for any such reaction; all staff are trained and specifically equipped to respond to this unlikely event.

What happens to the blood samples?

Blood samples obtained in the study would be labelled with your child's study code and study number, but not their name. The blood sample would be stored in a freezer until the tests looking at your child's immune response had been performed. Blood samples would be tested for markers of immunity to the swine flu virus. With your specific permission we would use a small amount of blood to look at your child's DNA as part of a project looking at the influence of genetic factors on the response to vaccines. This would help us understand the body's response to immunisation. We would also ask your permission to store your child's blood samples, including DNA, for future research into infection and the immune system. The blood samples would only be used for research and would not be sold or used directly for commercial purposes. The use of blood for the genetic study and the storing of blood for future research are voluntary; you could choose not to take part in these aspects of the study and still take part in the swine flu vaccine study.

Is there someone I can contact during the study?

If your child were to take part in this study we would provide you with a 24-hour telephone number to enable you to contact one of our study team should you have any concerns.

Who else would be told about my child's involvement in the study?

Your child's participation would remain confidential and if the results of the study were published your child would not be identified. With your permission we would inform your GP and child health department that your child was enrolled in this study and that we had administered the swine flu vaccine. Any study records with your child's name and address would be held by the Oxford Vaccine Group. Your child's first name will also be on the front of the diary card and memory card that will be sent to the Health Protection Agency.

In order to ensure that the study is being conducted correctly, the following groups may inspect the study records and your child's medical records, without violating your child's confidentiality:

- Monitors hired to check that the study is being conducted to a high standard
- The Ethics Committee (EC) - A group that oversees the conduct of human research and assures the protection of patient rights and welfare.
- The Clinical Trials and Research Governance Office, University of Oxford, who are responsible for ensuring the appropriate conduct of the research on behalf of the research sponsor (the University of Oxford)
- The Medicines and Healthcare products Regulatory Agency (MHRA), who regulate all medicines and vaccines in the United Kingdom.

By signing the consent form for this study, you would be giving permission for these groups to look at your child's medical records; however they would not be able to remove any information that identified your child from the premises of the Oxford Vaccine Group.

Your child's study information, removed of any identifying information, may also be used for additional unanticipated medical and/or scientific research projects in the future. If you do not want this information used in this way, or have any questions about the use of your child's information in the study, please inform the study team.

What happens if I say 'no'?

Taking part in research is voluntary. If you decided not to participate, this would not affect your child's routine care in any way. You are also free to change your mind at any time without giving any reason. If you decide not to take part in this study you should follow any advice from your GP or the government regarding swine flu or swine flu vaccines.

What if I wish to complain?

If you have any cause to complain about any aspect of the way in which you have been approached or treated during the course of this study we suggest that you contact us or, alternatively, the University of Oxford Clinical Trials and Research Governance Office on 01865 743005.

What else do I need to know?

In the highly improbable event that your child would suffer any harm during the study, compensation for harm arising from the vaccines would be provided by the vaccine manufacturers. The University has arrangements in place to provide for harm arising from participation in the study that is not due to the vaccines themselves. Should any information become available during the course of the study that may affect your child's participation, you would be informed as soon as possible.

At the end of the study we would pay you a fee of £10 per visit to compensate you for any travel costs incurred as a result of taking part in the study. The study has been funded by a grant from the NIHR Health Technology Assessment programme.

So, in summary, what would happen if I decide to take part in the study?

- We would administer 2 doses of the influenza A H1N1 (swine flu) vaccine and take two 6 to 10 ml blood samples from your child over 3 visits each occurring 3 weeks apart.
- You would have 24-hour telephone access to our study team should you have any concerns following vaccination.

What do I do now?

Participation in this study is voluntary. If you are interested in taking part, please phone our appointment line on 01865 857080 to arrange a time to come to the Oxford Children's Hospital. If you agree for your child to take part in the study it will still be possible to change your mind at any point and withdraw. If you wish to discuss any element of the study further, then please contact us by telephone (01865 857420) or e-mail (*ovg@paediatrics.ox.ac.uk*). If you do decide to take part we would be grateful if you could bring along your child's health record (the 'red book') to your first visit.

Yours sincerely,

Professor Andrew Pollard
Professor of Paediatric Infection and Immunity
Honorary Consultant Paediatrician

Dr Matthew Snape
Consultant Vaccinologist
Honorary Consultant Paediatrician

Dr Claire Waddington
Clinical Research Fellow

Mrs Tessa John
Clinical Team Leader

Appendix 3
Consent form

Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital - Oxford OX3 7LJ
ovg@paediatrics.ox.ac.uk
Tel/Fax: 01865 857420

OXFORD VACCINE GROUP

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Consent Form

Child's full name:..... Participant code: |___| |___| |___|

If you agree with each statement please initial in each box below;

I confirm that I have read the *Information booklet Swine Flu (Novel Influenza A H1N1) Vaccine Study Version 3 dated 18th September 2009.* I have had the opportunity to consider the information, discuss the study, to ask questions and have had these answered satisfactorily. ☐

I understand that data collected during the study may be looked at by authorised individuals from the University of Oxford, MHRA, Health Protection Agency and study monitors where it is relevant to my taking part in this research. I permit these individuals access to my research records. ☐

I understand that I am free to withdraw my child from the study at any time, without having to give a reason for leaving and without affecting his/her medical care. ☐

I agree to you informing my GP and Child Health Department of my child's participation in this study. ☐

I agree to my child being examined by a study doctor as required for this study. ☐

I agree to my chid receiving two immunisations with a swine flu (novel influenza A H1N1) vaccine. ☐

I agree to you taking and storing blood samples from my child as required for this study. ☐

I agree that my child's medical records may be read by study investigators. ☐

I agree that some identifiable data such as my child's first name on the diary and memory cards, will be sent to the HPA. ☐

For children over 7 years of age:

The study has been discussed with my child and they are happy to participate. ☐

If all of the above are initialled, meaning "yes", then please continue:

I voluntarily agree to my child taking part in this study ☐

Please note that your child can still participate in this study whether or not you agree to the next statement:

I agree that blood from my child may be used for analysis of genetic factor related to vaccine reactions. ☐

I agree that any remaining blood from my child may be stored and used in future research related to vaccines and infectious diseases (with the exception of the Human Immunodeficiency Virus [HIV]). ☐

Name:.....

Relationship to Child: .....

Signature:..... Date: |___ ___| |___ ___| |___ ___|

Investigator/Study nurse's name (*please delete as appropriate*): .....

Signature: ..... Date: |___ ___| |___ ___| |___ ___|

Appendix 4

Child information sheet

Swine Flu (Novel Influenza A H1N1) Vaccine Study

•Swine Flu is a new disease that can make some people very sick. You might have seen it on the television or heard people talking about it

•Vaccines are special medicines that we give as an injection. They stop you becoming unwell. You will have had some injections when you were a baby and before you went to school but you might not remember this.

•A new vaccine has been made to stop people becoming unwell with Swine Flu.

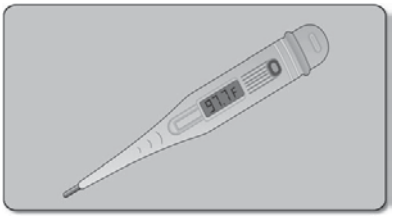
•We need to work out how well this new vaccine works and if it makes you feel unwell in any way. We would like you to help us do this.

•We would like to take a small amount of blood (about a teaspoonful) today.

•We will use a special (cream/spray) on your hand or elbow so that you won't feel the blood test, but you might have a little bruise afterwards. If you get upset when we are taking the blood you can ask us to stop and you won't be in trouble.

•We would then like to give you an injection to try and stop you getting Swine Flu.

•At home an adult will measure your temperature everyday for a week and write down if you feel unwell.



•To protect you from Swine Flu as much as possible we'd like you to come and see us again in 3 weeks time for another injection.

•To check that the injections have worked we'd like to see you one last time 3 weeks after the 2nd injection to do another blood test. We'd use special cream again so that it won't hurt.

•We have discussed this study with your mother/father/guardian. They are happy for us to do this, but we also want you to understand what we are doing and why we are doing it.

•You don't have to have this done as you are not poorly but it may stop you becoming unwell from Swine Flu and it will help us understand how the injections work.

•We will tell your doctor that you have taken part in the study, as well as the people who check on what vaccines children have been given

•We will not be telling anyone else about the study and you do not have to tell your friends and teachers at school unless you want to.

Thank you!

NHS National Institute for Health Research

Oxford Radcliffe Hospitals NHS Trust

Paediatric Infectious Diseases, Clinical Vaccine Research, Immunisation Education

Appendix 5
Diary cards

Swine Flu (Novel Influenza A H1N1) Vaccine Study

CHILDREN OVER 5 YEARS OF AGE DIARY

DIARY 1 / DIARY 2

7 DAY HEALTH DIARY

Study No:

First name: _____

Date of Vaccination: ____/_____/_____ Time of vaccination: _____

RIGHT / **LEFT** ARM

INSTRUCTIONS

Please note that Day 0 is the day of vaccination, Day 1 is the next day and so on. At about the same time each evening, please fill in the chart overleaf

HOW AND WHEN TO MEASURE YOUR CHILDS TEMPERATURE

Take the temperature under the arm (axillary)

Day 0 -6 hours after the injection / later that evening (6 - 8 pm)
Day 1 - 7 -Evening (6 - 8 pm)

Look at the vaccination site and measure the maximum width of any redness or swelling using the ruler and fill in the chart accordingly

GENERAL SYMPTOMS

*Please **circle** the appropriate number. If you child has symptoms then please evaluate the severity (mild, moderate or severe) of the symptom(s). Please complete each day.*

	Day 0 (Day of vaccine)		Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7		Please send in diary card now
Has your child been generally unwell? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	*If symptom was ongoing at day 7, document on memory aid card*
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had a headache? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child felt nauseous or vomited? 0 None 1 Mild - 1-2 episodes without interfering with routine 2 Moderate Several episodes and cannot keep any food down 3 Severe: Frequent episodes and taking nothing by mouth	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had <u>diarrhoea</u>? **0 None** **1 Mild –** More loose stools than usual **2 Moderate** – Frequent runny stools without much solid material **3 Severe** – Multiple liquid stools without much solid material	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child been eating less than usual/had a loss of appetite? **0 None** **1 Mild –** Eating less than normal for 1-2 meals **2 Moderate** Missed 1-2 meals completely **3 Severe** Refused most or all meals	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had muscle pain? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Has your child had joint pain? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	

VACCINE SITE SYMPTOMS: Please score any pain or tenderness at the injection site and measure any swelling or redness at the injection site.

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		
Has there been pain at the injection site? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	If symptom was ongoing at day 7, document on memory aid card
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
RIGHT / LEFT arm maximum swelling (mm)																	
RIGHT / LEFT arm maximum redness (mm)																	

TEMPERATURE

Day	Day 0 Evening	Day 1 Evening	Day 2 Evening	Day 3 Evening	Day 4 Evening	Day 5 Evening	Day 6 Evening	Day 7 Evening
Axillary (under arm) temperature**	°C	°C	°C	°C	°C	°C	°C	°C
Any medication for pain or temperature used?	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**
If medication used please specify name								

****TEMPERATURE (UNDER ARM):*** For an accurate temperature place the tip of the thermometer against the skin under the armpit and hold your child with his or her arm by their side closed for approximately 1 minute until the rapid beeps confirming that the temperature measurement is complete (see instruction leaflet enclosed with the thermometer for further information). On days 1 to 7, please measure your child's temperature at approximately the same time on each day.

If your child feels warm at any other time of day please record the date and time below:

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

If you need to see a doctor during the 7 day period following immunisation, please take this diary with you and tell the doctor about the study.

If your child is unwell at all, if you need to call a doctor or your child is seen by a doctor or is given any medicine then please write the details below:

Date	***Problem***	***Action taken*** (please circle answer)			***Medicine given***		
						(1st medicine)	(2nd medicine)
Start date: ___/___/___ Stop date: ___/___/___		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ___/___/___ Stop date: ___/___/___		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ___/___/___ Stop date: ___/___/___		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ___/___/___ Stop date: ___/___/___		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______
						(1st medicine)	(2nd medicine)
Start date: ___/___/___ Stop date: ___/___/___		Did you telephone a GP? Was your child seen by a GP? Seen by GP at Taken to hospital? **Admitted to hospital**	**Yes** **Yes** **Home/Surgery** **Yes** **Yes**	**No** **No** **No** **No**	Name: Start date: End date: Dosage:	______ ______ ______ ______	______ ______ ______ ______

If you, your doctor or anyone else needs advice regarding the study, he/she should contact:

H1N1 Study Team
Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Old Road, Headington
Oxford
OX3 7LJ

Tel: 01865 857080
Email: ovg@paediatrics.ox.ac.uk

24 hour emergency telephone number: 07699 785400

Thank you for taking the time to fill in this diary. We would be grateful if you would return it to us using the prepaid envelope provided.

If you have lost the envelope, we would be obliged if you would post it to:

The Clinical Trials Admin Team
Immunisation Department
Health Protection Agency
61 Colindale Avenue
London
NW9 5EQ

Swine Flu (Novel Influenza A H1N1) Vaccine Study

INFANTS AND CHILDREN UNDER 5 YEARS OF AGE DIARY

DIARY 1 / DIARY 2

7 DAY HEALTH DIARY

Study No:

First name: _____

Date of Vaccination: ____/_____/_____ Time of vaccination: _____

RIGHT / **LEFT** **ARM / LEG**

INSTRUCTIONS

Please note that Day 0 is the day of vaccination, Day 1 is the next day and so on. At about the same time each evening, please fill in the chart overleaf

HOW AND WHEN TO TAKE YOUR CHILDS TEMPERATURE

Take the temperature under the arm (axillary)

Day 0	-6 hours after the injection / later that evening (6 - 8 pm)
Day 1 - 7	-Evening (6 - 8 pm)

Look at the vaccination site and measure the maximum width of any redness or swelling using the ruler and fill in the chart accordingly

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GENERAL SYMPTOMS

*Please **circle** the appropriate number. If you child has symptoms then please evaluate the severity (mild, moderate or severe) of the symptom(s).*

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		***Please send in diary card now***
Has your child been feeding less than usual? 0 None 1 Mild – Eating less than normal for 1-2 feeds/meals 2 Moderate – Missed 1-2 feeds/meals completely 3 Severe – Refused most or all feeds/meals	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	***If symptom was ongoing at day 7, document on memory aid card***
Has your child been less active than usual? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child been more irritable than usual? 0 None 1 Mild – Continuously irritable for less than 1 hour 2 Moderate – Continuously irritable for 1 to less than 3 hours 3 Severe – Continuously irritable for 3 or more hours	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child cried persistently? 0 None 1 Mild – Cried continuously for less than 1 hour 2 Moderate – Cried continuously for 1 to less than 3 hours 3 Severe – Cried continuously for 3 or more hours	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child vomited? 0 None 1 Mild – 1-2 episodes without interfering with routine 2 Moderate – Several episodes & cannot keep any food down 3 Severe – Frequent episodes & taking nothing by mouth	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	
Has your child had diarrhoea? 0 None 1 Mild – More loose stools than usual 2 Moderate – Frequent runny stools without much solid material 3 Severe Multiple liquid stools without much solid material	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	0	1 2	

VACCINE SITE SYMPTOMS: Please score any pain or tenderness at the injection site and measure any swelling or redness at the injection site.

	Day 0 (Day of vaccine)		***Day 1***		***Day 2***		***Day 3***		***Day 4***		***Day 5***		***Day 6***		***Day 7***		
Has there been pain at the injection site? 0 None 1 Mild – transient with no limitation on normal activity 2 Moderate – some limitation in daily activity 3 Severe – unable to perform normal daily activity	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	If symptom was ongoing at day 7, document on memory aid card
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
RIGHT / LEFT arm maximum swelling (mm)																	
RIGHT / LEFT arm maximum redness (mm)																	

TEMPERATURE

Day	Day 0 Evening	Day 1 Evening	Day 2 Evening	Day 3 Evening	Day 4 Evening	Day 5 Evening	Day 6 Evening	Day 7 Evening
Axillary (under arm) temperature**	°C	°C	°C	°C	°C	°C	°C	°C
Any medication for pain or temperature used?	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**	**YES / NO**
If medication used please specify name								

*****TEMPERATURE (UNDER ARM):*** For an accurate temperature place the tip of the thermometer against the skin under the armpit and hold your child with his or her arm by their side closed for approximately 1 minute until the rapid beeps confirming that the temperature measurement is complete (see instruction leaflet enclosed with the thermometer for further information). On days 1 to 7, please measure your child's temperature at approximately the same time on each day.

If your child feels warm at any other time of day please record the date and time below:

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

_____°C ____/____/____ _____:_____ _____°C ____/____/____ _____:_____

If you need to see a doctor during the 7 day period following immunisation, please take this diary with you and tell the doctor about the study.

If your child is unwell at all, if you need to call a doctor or your child is seen by a doctor or is given any medicine then please write the details below and overleaf:

Date	***Problem***	***Action taken*** (please circle answer)			***Medicine given***		
						(1st medicine)	(2nd medicine)
Start date:		Did you telephone a GP?	**Yes**	**No**			
____/____/____		Was your child seen by a GP?	**Yes**	**No**	Name:	__________	__________
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	__________	__________
____/____/____		Taken to hospital?	**Yes**	**No**	End date:	__________	__________
		Admitted to hospital	**Yes**	**No**	Dosage:	__________	__________
						(1st medicine)	(2nd medicine)
Start date:		Did you telephone a GP?	**Yes**	**No**			
____/____/____		Was your child seen by a GP?	**Yes**	**No**	Name:	__________	__________
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	__________	__________
____/____/____		Taken to hospital?	**Yes**	**No**	End date:	__________	__________
		Admitted to hospital	**Yes**	**No**	Dosage:	__________	__________
						(1st medicine)	(2nd medicine)
Start date:		Did you telephone a GP?	**Yes**	**No**			
____/____/____		Was your child seen by a GP?	**Yes**	**No**	Name:	__________	__________
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	__________	__________
____/____/____		Taken to hospital?	**Yes**	**No**	End date:	__________	__________
		Admitted to hospital	**Yes**	**No**	Dosage:	__________	__________
						(1st medicine)	(2nd medicine)
Start date:		Did you telephone a GP?	**Yes**	**No**			
____/____/____		Was your child seen by a GP?	**Yes**	**No**	Name:	__________	__________
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	__________	__________
____/____/____		Taken to hospital?	**Yes**	**No**	End date:	__________	__________
		Admitted to hospital	**Yes**	**No**	Dosage:	__________	__________
						(1st medicine)	(2nd medicine)
Start date:		Did you telephone a GP?	**Yes**	**No**			
____/____/____		Was your child seen by a GP?	**Yes**	**No**	Name:	__________	__________
Stop date:		Seen by GP at	**Home/Surgery**		Start date:	__________	__________
____/____/____		Taken to hospital?	**Yes**	**No**	End date:	__________	__________
		Admitted to hospital	**Yes**	**No**	Dosage:	__________	__________

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London
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Appendix 6

Memory aid card

Swine Flu (Novel Influenza A H1N1) Vaccine Study

Memory Aid Card

Your child's next visit is scheduled for:
__ __ /__ __ /__ __ __ __ at __ __:__ __ hours

Child's first name:_____ **Child's Number:** _____

WHY DO I NEED TO COMPLETE THIS MEMORY CARD?

Dear Parent/Legal Guardian

Thank you very much for completing the diary card for the 7 days after your child was vaccinated. Please remember to return the diary card in the pre-paid envelope.

We would be grateful if you could fill in this memory card from 8 days after the vaccine until we see you at the next visit. We would like to know if any of the **symptoms that your child may have had after vaccination continued beyond day 7.** We would also like you to record any change in your child's health **that has led to your child being seen by a doctor or going to the Emergency Department (A&E).**

If your child needs hospitalisation for any reason or if you are concerned about your child's health, please contact the study team immediately

Our contact details are:
01865 857080 (Office hours)

24 hours advice number:
07703134238

Vaccine reactions continuing after day 7

Injection site reactions •tenderness •swelling •Redness	Start date(s) of reaction dd/mm	Stop date(s) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the reaction
				□No □Yes, specify:

General reactions •fever (≥ 38°C) •changing in feeding/ eating •reduced activity/ irritability/ generally unwell •vomiting or diarrhoea •For children <5 years: persistant crying •For children >5 years: muscle pain or joint pain	Start date(s) of reaction dd/mm	Stop date(s) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the reaction
				□No □Yes, specify:

SYMPTOMS/ILLNESSES requiring a visit to a doctor or emergency department (A&E)

Symptom / Illness	Start date (s) of reaction dd/mm	Stop date(S) of reaction dd/mm	Date(s) of doctor / Emergency Department visit (A&E)?	Medication(s) to treat the illness/ symptom
				□No □Yes, specify:

Reminder: Please bring this card with you to the next visit

Appendix 7

Recruitment poster

Children's Swine Flu Vaccine Study

The Oxford Vaccine Group is part of a network of 5 centres in the UK conducting a study of 2 new vaccines aimed at providing protection against Swine Flu.

We would like to invite you and your child to take part in this study.

If you are the parent of a child aged between 6 months and 12 years inclusive and want to find out more information please access the website via the web address below to view the information for parents:

www.swineflutrial.org

For further information or to talk to one of our team please contact the Oxford Vaccine Group on 01865 857080 or email ovg@paediatrics.ox.ac.uk