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P de Whalley,[1]* W Walker,[2] MD Snape,[1] C Oeser,[3] M Casey,[2] P Moulsdale,[4] C Harrill,[5] N Andrews,[6] K Hoschler,[6] B Thompson,[1] C Jones,[1] J Chalk,[1] S Kerridge,[1] R Tomlinson,[5] PT Heath,[3] A Finn,[4] S Faust,[2] E Miller[6] and AJ Pollard[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK
[2]University of Southampton Wellcome Trust Clinical Research Facility and Division of Infection, Inflammation and Immunity, Southampton, UK
[3]St George's Vaccine Institute, St George's, University of London, London, UK
[4]Bristol Children's Vaccine Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK
[5]Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[6]Centre for Infections, Health Protection Agency, London, UK

*Corresponding author

Declaration of competing interests: Vaccines used in the original study were manufactured by GlaxoSmithKline and Baxter, both of which donated the vaccine, but had no role in study planning or conduct. The vaccine used in this follow-on study was manufactured by GlaxoSmithKline, from whom it was purchased. AJP, AF, PTH and SF act as chief or principal investigators for clinical trials conducted on behalf of their respective NHS trusts and/or universities, sponsored by vaccine manufacturers, but receive no personal payments from them. KH has been an investigator for clinical trials sponsored by vaccine manufacturers, but received no personal payments from them. AJP, AF, PTH and SF have participated in advisory boards for vaccine manufacturers, but receive no personal payments for this work. MDS, PTH, SF, KH and AF have received financial assistance from vaccine manufacturers to attend conferences. All grants and honoraria are paid into accounts within the respective NHS trusts or universities, or to independent charities.

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The research reported in this issue of the journal was commissioned by the HTA programme as project number 10/111/01. The contractual start date was in November 2010. The draft report began editorial review in May 2011 and was accepted for publication in August 2011. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A 1-year follow-on study from a randomised, head-to-head, multicentre, open-label study of two pandemic influenza vaccines in children

P de Whalley,[1]* W Walker,[2] MD Snape,[1] C Oeser,[3] M Casey,[2] P Moulsdale,[4] C Harrill,[5] N Andrews,[6] K Hoschler,[6] B Thompson,[1] C Jones,[1] J Chalk,[1] S Kerridge,[1] R Tomlinson,[5] PT Heath,[3] A Finn,[4] S Faust,[2] E Miller[6] and AJ Pollard[1]

[1]Oxford Vaccine Group, Department of Paediatrics, University of Oxford, Oxford, UK
[2]University of Southampton Wellcome Trust Clinical Research Facility and Division of Infection, Inflammation and Immunity, Southampton, UK
[3]St George's Vaccine Institute, St George's, University of London, London, UK
[4]Bristol Children's Vaccine Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK
[5]Royal Devon and Exeter NHS Foundation Trust, Exeter, UK
[6]Centre for Infections, Health Protection Agency, London, UK

*Corresponding author

Introduction: Pandemic influenza A H1N1 infections occurred worldwide from 2009. Children were particularly vulnerable. Novel vaccines were used during the pandemic.
Objective: To assess the persistence of antibody to H1N1 influenza 1 year after children aged 6 months to 12 years had been immunised with two doses of either a non-adjuvanted whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine; and also to assess the immunogenicity and reactogenicity in this population of a single dose of 2010–11 trivalent seasonal influenza vaccine.
Design: Multicentre, open-label, follow-on from randomised, head-to-head trial.
Setting: Five UK sites (Southampton, Oxford, Bristol, London and Exeter).
Participants: Children who completed last year's head-to-head randomised study were invited to participate. Children who had subsequently received a further dose of H1N1 vaccine, or who had already received a dose of 2010–11 trivalent seasonal influenza vaccine, were excluded.
Interventions: In the previous study, children were randomised (in a 1:1 ratio) to receive two doses, 21 days apart, of either a non-adjuvanted whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine. In this follow-on study, a blood sample was taken to assess the persistence of antibody 1 year later, followed by administration of one 0.5 ml-dose of trivalent seasonal influenza vaccine. A second blood sample was taken 3 weeks later.
Main outcome measures: Comparison between vaccines of the percentage of participants with a microneutralisation (MN) titre ≥1:40 and a haemagglutination titre ≥1:32, 1 year after vaccination. Immunogenicity of the trivalent seasonal influenza vaccine was assessed 3 weeks after vaccination by both the MN and the haemagglutination inhibition (HI) titres. Reactogenicity data were recorded for 7 days after vaccination.
Results: A total of 323 children were enrolled and 318 were included in the analysis of the

persistence of antibody. One year after receipt of whole-virion vaccine, the MN titre was ≥1:40 in 32.4% of those vaccinated when <3 years old and in 65.9% of those vaccinated when ≥3 years old; the HI titre was ≥1:32 in 63.2% and 79.1% of children in the respective age groups. One year after receipt of the adjuvanted vaccine, the MN titre was ≥1:40 in 100% of those vaccinated when <3 years old and in 96.9% of those vaccinated when ≥3 years old; the HI titre was ≥1:32 in 98.4% and 96.9% of children in the respective age groups. Three hundred and two children were given trivalent seasonal influenza vaccination. Three weeks later, sera were obtained from 282 children; 100% had an MN titre ≥1:40 and HI titre ≥1:32. Trivalent seasonal influenza vaccine was well tolerated, although in children <5 years old, fever ≥38 °C was reported in 13.6% of those who had previously received whole-virion vaccine, and in 18.3% of those who had received adjuvanted vaccine.

Conclusions: Nearly all children who received two doses of $AS03_B$-adjuvanted split-virion pandemic H1N1 influenza vaccine had titres of antibody deemed protective (HI titre ≥1:32, MN titre ≥1:40) 1 year later. Children who received two doses of whole-virion vaccine had lower titres, although many were above the putative protective thresholds. One year after either pandemic vaccine, the 2010–11 trivalent seasonal influenza vaccine produced a marked serological response to the H1N1 component of the vaccine and was well tolerated. We propose to investigate whether or not previous receipt of monovalent influenza vaccines affected serological response to the H3N2 and B components of the 2010–11 seasonal influenza vaccine, using stored sera.

Trial registration: ClinicalTrials.gov NCT01239537.

Funding: The National Institute for Health Research Health Technology Assessment programme.

Contents

List of abbreviations

CI	confidence interval
HI	haemagglutination inhibition
MN	microneutralisation

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 in the UK were offered the pandemic H1N1 influenza vaccine in the 2009–10 influenza season. Given that the pandemic influenza A/California/07/2009 (H1N1) virus continued to circulate in 2010–11, clinicians and parents required information on whether or not these children were still protected from this virus. Information was also required on how well the children responded to a dose of 2010–11 trivalent seasonal influenza vaccine, which contained the pandemic H1N1 strain.

In a previous study [Waddington *et al.* 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. *Health Technol Assess* 2010;**14**(46):1–130], we compared two monovalent pandemic influenza vaccines given to children aged 6 months to 12 years between September and December 2009. They received two doses, 3 weeks apart, of either a non-adjuvanted, whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted, split-virion H1N1 influenza vaccine. The $AS03_B$-adjuvanted vaccine produced a more marked immune response, particularly in the children < 3 years old, although it resulted in more injection-site reactions and fever.

In this study, we followed up these children 1 year later, to determine the persistence of antibody and response to the 2010–11 trivalent seasonal influenza vaccine.

Objectives

1. To assess the persistence of antibody to H1N1 influenza [measured using microneutralisation (MN) and haemagglutination inhibition (HI) titres], 1 year after children aged 6 months to 12 years were immunised with two doses of either a non-adjuvanted whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine.
2. To assess the immune response to a single dose of 2010–11 trivalent seasonal influenza vaccine in these children.
3. To assess symptoms occurring within the first week after receipt of the trivalent seasonal influenza vaccine, including fever, local and systemic reactions and medical consultations.
4. To record specific adverse events of special interest occurring since receipt of the pandemic H1N1 influenza vaccine.
5. To store sera from children who received pandemic H1N1 influenza vaccine in the 2009–10 influenza season. If a drifted strain of H1N1 were to emerge in the future, these sera would enable rapid determination of cross-protection.

Methods

In the original study (Waddington *et al.* 2010), 943 children aged between 6 months and 12 years were recruited at five UK sites (Southampton, Oxford, Bristol, London and Exeter). They were randomised (1 : 1 ratio) to receive two doses, 21 days apart, of either a non-adjuvanted whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine.

Children who completed the original study were invited to participate in this follow-on study, although those who had subsequently received a further dose of H1N1 vaccine, or who had already received a dose of 2010–11 trivalent seasonal influenza vaccine, were excluded. At the first study visit, a blood sample was taken to assess the persistence of immunity. A single dose of trivalent seasonal influenza vaccine was given by intramuscular injection (into the deltoid muscle). A second blood sample was taken 3 weeks later. A diary card was used to record the following information daily for the first 7 days after vaccination: axillary temperature, injection-site reactions, systemic symptoms and antipyretic medication. Medical consultations were also recorded. MN and HI titres were measured in the laboratories of the Health Protection Agency (London, UK). A MN titre ≥ 1:40, or an HI titre ≥ 1:32, was considered to be indicative of serological protection against disease.

Results

A total of 323 children were enrolled in the study, and 318 were included in the analysis of the persistence of antibody. One year after receipt of the whole-virion vaccine, the MN titre was ≥ 1 : 40 in 32.4% of those vaccinated when < 3 years old, and in 65.9% of those vaccinated when ≥ 3 years old; the HI titre was ≥ 1 : 32 in 63.2% and 79.1% of children in the respective age groups. One year after receipt of the $AS03_B$-adjuvanted vaccine, the MN titre was ≥ 1 : 40 in 100% of those vaccinated when < 3 years old and in 96.9% of those vaccinated when ≥ 3 years old; the HI titre was ≥ 1 : 32 in 98.4% and 96.9% of children in the respective age groups.

A total of 302 children were given 2010–11 trivalent seasonal influenza vaccination. Three weeks later, sufficient blood for analysis was obtained from 282; 100% had MN titres of ≥ 1 : 40 and HI titres of ≥ 1 : 32. The HI geometric mean titre was more than 10-fold greater than it had been immediately before receipt of the trivalent seasonal influenza vaccine. The vaccine was well tolerated, although in children < 5 years old, a fever of ≥ 38 °C was reported in 13.6% who had previously received the whole-virion vaccine, and in 18.3% of children who had received the $AS03_B$-adjuvanted vaccine. Redness and injection-site symptoms graded as severe were reported significantly more frequently in children < 5 years old who had previously received the $AS03_B$-adjuvanted vaccine than in those children who had been given the whole-virion vaccine.

Conclusions

Nearly all children who received two doses of $AS03_B$-adjuvanted split-virion pandemic H1N1 influenza vaccine had titres of antibody deemed protective (HI titre ≥ 1 : 32, MN titre ≥ 1 : 40) 1 year later. Children who received two doses of whole-virion vaccine had lower titres, but many still had titres above the putative protective thresholds.

A single dose of 2010–11 trivalent seasonal influenza vaccine produced a marked serological response to the H1N1 component of the vaccine in children who had received either of the monovalent pandemic influenza vaccines 1 year earlier. It was generally well tolerated, although a febrile response (≥ 38°C) occurred in 13–18% of children < 5 years old.

Implications for health care

Children who were given monovalent pandemic influenza vaccines still had protective titres of antibody 1 year later, although antibody persistence beyond 1 year remains unknown. In these children, administration of a trivalent vaccine, containing the pandemic strain as one component, effectively boosted antibody titre and was well tolerated.

Recommendations for future research

The inclusion of the $AS03_B$ adjuvant has resulted in an antigen-sparing vaccine producing a marked antibody response, which persists 1 year after vaccination. The inclusion of this adjuvant in future seasonal influenza vaccines might enhance their immunogenicity, particularly in children < 3 years old, and this warrants further investigation. It would be interesting to assess whether or not previous receipt of the $AS03_B$-adjuvanted pandemic vaccine affected the serological response to the other two strains in the 2010–11 seasonal influenza vaccine. We propose to investigate this using stored serum.

Assessment of total duration of effective immunity after vaccination with both $AS03_B$-adjuvanted and whole-virion pandemic influenza vaccines will require further studies. It would be useful to assess the persistence of immunity after a single dose of these vaccines. There should be continuing surveillance of the long-term safety profile of these novel vaccines. Further elucidation of the correlation between MN titre and protection from disease is required.

Trial registration

This trial was registered at ClinicalTrials.gov (NCT01239537). The previous randomised trial was registered as ISRTCN89141709.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1

Introduction

In 2009, a novel influenza A H1N1 strain (A/California/07/2009), first reported in Mexico, spread rapidly around the globe.[1,2] In the UK, the first cases were confirmed on 27 April 2009[3] and the World Health Organization declared a global pandemic on 11 June 2009.[4] The UK experienced two waves of infection in 2009, peaking in July and October.[5] There was a further resurgence of infection during the 2010–11 influenza season, peaking in late December 2010 and early January 2011.[6]

Before the pandemic, children were less likely to possess protective antibody than adults and during the pandemic they experienced higher rates of infection.[7,8] In England, between 26 June 2009 and 22 March 2010, there were 70 deaths attributable to H1N1 influenza in those aged < 18 years.[9] Children also effectively transmit the virus.[10] For these reasons, children have been identified as a high-priority group for vaccination against pandemic influenza.[11]

In 2009, the UK Government purchased two monovalent H1N1 vaccines: an $AS03_B$-adjuvanted, split-virion vaccine, derived from egg culture (Pandemrix®, GlaxoSmithKline, Rixensart, Belgium), and a non-adjuvanted, whole-virion vaccine, derived from Vero cell culture (Celvapan®, Baxter, Vienna, Austria). The $AS03_B$-adjuvanted vaccine was the predominant vaccine used for immunisation of both children and adults. Initially, from late October 2009, two doses of vaccine at least 3 weeks apart were offered to children > 6 months old who were in the clinical risk groups defining eligibility for seasonal influenza vaccine.[12] In the second phase of the vaccination programme, announced in November 2009, monovalent H1N1 vaccine was offered to all children from 6 months to 5 years of age, because of the frequency of hospital admission in this age group.[13] A single-dose regimen for immunocompetent children was adopted from December 2010.[14] By 31 March 2010, the overall uptake of the vaccine in this age group was 23.6% in England and 44.6% in Scotland.[5]

The trivalent seasonal influenza vaccines used in the 2010–11 influenza season included the A/California/07/2009 (H1N1) strain.[15] These vaccines were offered to children in clinical risk groups only.

There are no previous reports of the persistence of antibody in children following vaccination for pandemic H1N1 influenza,[16] and no previous data on the immunogenicity and reactogenicity of trivalent seasonal influenza vaccine given to those who have previously received pandemic H1N1 influenza vaccine. This information is important in assisting the formulation of vaccination policy. Knowledge of the persistence of antibody following vaccination is also valuable in the construction of disease transmission models, which are an important component of the UK's pandemic influenza plan.[8]

In an earlier study, conducted between September and December 2009, we compared the immunogenicity and reactogenicity of the two monovalent pandemic H1N1 influenza vaccines used in the UK, an $AS03_B$-adjuvanted, split-virion vaccine and a non-adjuvanted, whole-virion vaccine.[17,18] Eight hundred and ninety-four children, aged from 6 months to 12 years, completed this study. The $AS03_B$-adjuvanted vaccine was significantly more immunogenic than the non-adjuvanted vaccine, particularly in children < 3 years of age. For this age group, the seroconversion rate was 98.2% in those children who received the $AS03_B$-adjuvanted vaccine,

compared with 80.1% in recipients of the non-adjuvanted vaccine ($p < 0.001$). Seroconversion was defined as a fourfold rise in the microneutralisation (MN) titre to a value of ≥ 1 : 40, from before the first dose to 3 weeks after the second dose of vaccine. The $AS03_B$-adjuvanted vaccine was also more reactogenic, with more local and systemic symptoms reported in the week following vaccination.

The present study followed up this cohort of children, 1 year later. The persistence of antibody was assessed by both MN and haemagglutination inhibition (HI) assays. A single dose of trivalent seasonal influenza vaccine was given and antibody titres were assessed 3 weeks later.

The study also provided an opportunity to monitor the long-term safety of the novel pandemic influenza vaccines and to store sera from children who received them. This could be particularly useful should a drifted strain of the virus emerge in the future, as it would allow rapid assessment of cross-protection. The sera are stored at the individual study sites.

Chapter 2

Methods

Participants

In the original study, children aged 6 months to 12 years were recruited by five UK sites (Southampton, Oxford, Bristol, London and Exeter). They were randomised (in a 1 : 1 ratio, with assignment by sequentially numbered, identical, opaque sealed envelopes) to receive two doses, 21 days apart, of either a non-adjuvanted whole-virion H1N1 influenza vaccine or an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine. Children who completed the original study were invited to participate in this follow-on study, although those who had subsequently received a further dose of the H1N1 vaccine owing to an insufficient response to the original two doses of vaccine were excluded, as were those who had already received a dose of the 2010–11 trivalent seasonal influenza vaccine. Other exclusion criteria were severe allergic reaction following previous vaccination, suspected unexpected severe adverse reaction in the original study, current egg allergy, impaired immunity, receipt of blood products or > 1 week of systemic steroid treatment within the last 3 months, or participation in another clinical trial. Written informed consent was obtained from a parent or guardian, and verbal assent was sought from children aged ≥ 7 years. Enrolment took place in November and December 2010.

Study design

This was a multicentre, open-label, phase IV study, following on from a randomised trial. At the first study visit, a blood sample was taken to assess the persistence of antibody. A single dose of trivalent seasonal influenza vaccine was given by intramuscular injection (into the deltoid muscle). A second blood sample was taken 21 days later (protocol time window 14–35 days). For those who wanted to participate in the study, but who did not wish to receive the trivalent seasonal influenza vaccine, an option was available to consent to only the first blood test.

The study was approved by the UK Medicines and Healthcare products Regulatory Agency (EudraCT number 2010-022817-24), the Oxfordshire Research Ethics Committee A (10/H0604/81) and the local NHS organisations. The study was registered at ClinicalTrials.gov (NCT01239537).

Vaccines

The original study compared two novel H1N1 vaccines: a non-adjuvanted whole-virion H1N1 influenza vaccine (Celvapan) and an $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine (Pandemrix).

The non-adjuvanted, whole-virion vaccine was derived from Vero cell culture. Each dose (0.5 ml) contained 7.5 µg of haemagglutinin from influenza A/California/07/2009 (H1N1).

The $AS03_B$-adjuvanted split-virion H1N1 influenza vaccine was derived from egg culture. Each dose (0.25 ml, half the adult dose) contained 1.875 µg of the haemagglutinin antigen and the

oil-in-water emulsion-based adjuvant $AS03_B$ (containing 5.345 mg of squalene, 5.39 mg of DL-α-tocopherol, 2.43 mg of polysorbate 80 and thiomersal).

The present study used the 2010–11 trivalent seasonal influenza vaccine (Fluarix®, GlaxoSmithKline, Rixensart, Belgium). This contained an inactivated, split-virion influenza virus, propagated in fertilised hens' eggs. Each 0.5-ml dose contained 15 µg of haemagglutinin for each of the three influenza strains [A/California/07/2009 (H1N1) derived strain (NYMC X-181), A/Perth/16/2009 (H3N2)-like strain (NYMC X-187, derived from A/Victoria/210/2009) and B/Brisbane/60/2008].

Laboratory analysis

Microneutralisation and haemagglutination assays were performed at the Centre for Infections, Health Protection Agency (London, UK), using previously described methods.[8] Sera were processed in 1 : 2 serial dilutions. For MN assays, the initial dilution was 1 : 10 and the final dilution 1 : 5120. For HI assays, the initial dilution was 1 : 8 and the final dilution 1 : 16,384.

Safety and reactogenicity assessments

Adverse events of special interest, defined by the European Medicines Agency[19] (see *Appendix 1* for further details), that had occurred in the year since receipt of the monovalent pandemic influenza vaccine were recorded.

For 7 days after receipt of the trivalent seasonal influenza vaccine, the following information was recorded in a diary card: daily axillary temperature, injection-site reactions, systemic symptoms and the use of antipyretic medication. Different systemic symptoms were solicited for children aged < 5 years than for older children, to accommodate their limited ability to articulate symptoms. All medical consultations occurring between receipt of the trivalent seasonal influenza vaccine and the second study visit were recorded.

Statistical analysis

For antibody persistence, data were analysed according to vaccine received, following a predetermined statistical plan. For response to trivalent seasonal vaccine, a modified intention-to-treat analysis was performed.

To enable an unbiased assessment of the persistence of antibody, a random sample of participants excluded owing to receipt of a third dose were included in the analysis, assuming that their (low) antibody titre was unchanged from its value after two doses of vaccine in the original study.[17,18] The number in this random sample was determined proportionately (the proportion of participants excluded owing to receipt of a third dose who were in the selected sample was equal to the proportion of participants in the original study who enrolled in the follow-on study).

For analysis, HI titres of < 8 were given a value of 4, MN titres of < 10 were given a value of 5 and MN titres of > 5120 were given a value of 10,240.

Comparisons between groups were made using Fisher's exact test. Geometric means were compared using normal error regression on logged titres.

Additional analyses, examining the effect of different variables, were performed using multivariable logistic and normal error regression.

Statistical significance was set at 5%. Analysis was performed in Stata 10.0 (StataCorp LP, College Station, TX, USA).

Chapter 3

Results

Participants

Figure 1 shows the flow diagram for study participants. Eight hundred and ninety-four children completed the original study. Of these, 115 could not be contacted, 49 were excluded and 407 elected not to take part in the follow-on study; 323 children enrolled in the follow-on study (36.1% of those completing the original study). Of these, 19 consented to one blood test only (but not to trivalent seasonal influenza vaccination); 290 children attended the second study visit.

Persistence of antibody

Of the 323 participants enrolled, 15 were excluded from the persistence analysis (five did not have antibody assay results after the second dose of pandemic influenza vaccine in the original study and 10 had insufficient blood for the follow-on assay).

After the original study,[17,18] 28 children received a third dose of pandemic influenza vaccine, owing to both the MN and HI titres being below the protective threshold after two doses. These children were excluded from the follow-on study, as this study was designed to assess the persistence of antibody after two doses of the pandemic vaccine (not three). This introduced a potential bias, because poor responders to the vaccine in the original study were excluded.[17,18] In order to account for this, and to try to obtain an unbiased assessment of the persistence of antibody in a population representative of the participants in the original study, 10 of these 28 (36%), selected randomly, were included in the persistence analysis. They were not enrolled in (and therefore did not have a blood test in) the follow-on study, but it was assumed that their titres remained unchanged from the low values recorded after the second dose of pandemic influenza vaccine in the original study. Hence, a total of 318 children were included in the persistence analysis. *Table 1* shows the demographic characteristics of these children.

Four groups were considered in the analysis, defined by the type of pandemic influenza vaccine received in the original study[17,18] ($AS03_B$-adjuvanted or whole-virion) and age at receipt of the first dose of pandemic vaccine (< 3 years or ≥ 3 years).

The median interval from the second dose of pandemic influenza vaccine in the original study to the blood draw to assess the persistence of antibody was 392 days (range 365–413 days). The median interval from the antibody assay after the second dose of pandemic influenza vaccine in the original study to the blood draw to assess the persistence of antibody was 371 days (range 347–399 days).

Table 2 shows the number (and percentage) of children with an MN titre ≥ 1 : 40 at 3 weeks and at 1 year after the second dose of pandemic influenza vaccine. *Table 3* shows the MN geometric mean titre 1 year after the second dose of pandemic influenza vaccine. It was not possible to calculate a valid geometric mean titre for MN at 3 weeks after the second dose of the pandemic influenza vaccine because the upper limit of the MN titre measured in the original study was 1 : 320, and the MN titre was > 1 : 320 for many participants.

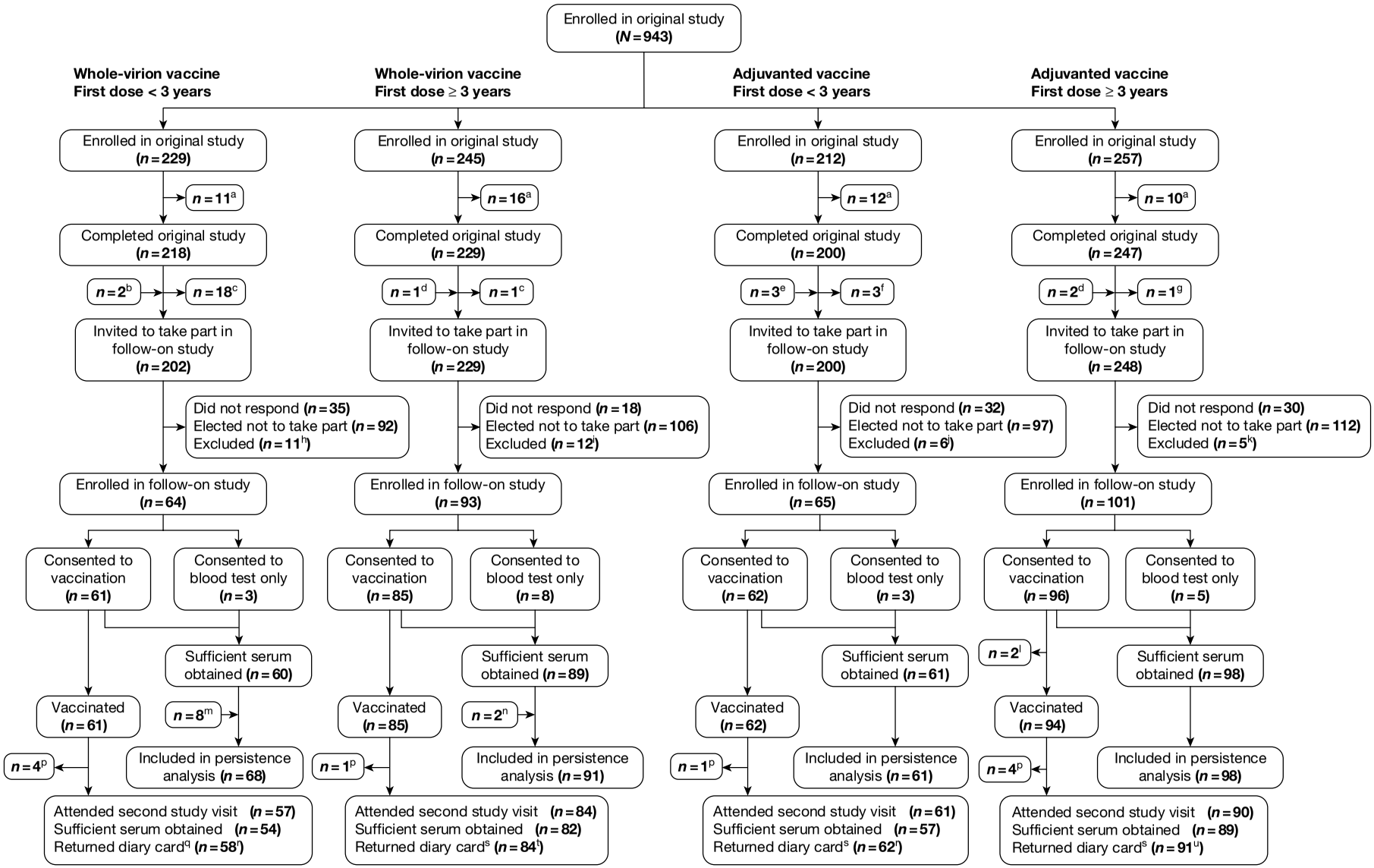
Enrolled in original study (N = 943)
Whole-virion vaccine First dose < 3 years
Whole-virion vaccine First dose ≥ 3 years
Adjuvanted vaccine First dose < 3 years
Adjuvanted vaccine First dose ≥ 3 years
Enrolled in original study (n = 229)
Enrolled in original study (n = 245)
Enrolled in original study (n = 212)
Enrolled in original study (n = 257)
n = 11[a]
n = 16[a]
n = 12[a]
n = 10[a]
Completed original study (n = 218)
Completed original study (n = 229)
Completed original study (n = 200)
Completed original study (n = 247)
n = 2[b]
n = 18[c]
n = 1[d]
n = 1[c]
n = 3[e]
n = 3[f]
n = 2[d]
n = 1[g]
Invited to take part in follow-on study (n = 202)
Invited to take part in follow-on study (n = 229)
Invited to take part in follow-on study (n = 200)
Invited to take part in follow-on study (n = 248)
Did not respond (n = 35)
Elected not to take part (n = 92)
Excluded (n = 11[h])
Did not respond (n = 18)
Elected not to take part (n = 106)
Excluded (n = 12[i])
Did not respond (n = 32)
Elected not to take part (n = 97)
Excluded (n = 6[j])
Did not respond (n = 30)
Elected not to take part (n = 112)
Excluded (n = 5[k])
Enrolled in follow-on study (n = 64)
Enrolled in follow-on study (n = 93)
Enrolled in follow-on study (n = 65)
Enrolled in follow-on study (n = 101)
Consented to vaccination (n = 61)
Consented to blood test only (n = 3)
Consented to vaccination (n = 85)
Consented to blood test only (n = 8)
Consented to vaccination (n = 62)
Consented to blood test only (n = 3)
Consented to vaccination (n = 96)
Consented to blood test only (n = 5)
Sufficient serum obtained (n = 60)
Sufficient serum obtained (n = 89)
Sufficient serum obtained (n = 61)
n = 2[l]
Sufficient serum obtained (n = 98)
Vaccinated (n = 61)
n = 8[m]
Vaccinated (n = 85)
n = 2[n]
Vaccinated (n = 62)
Vaccinated (n = 94)
n = 4[p]
Included in persistence analysis (n = 68)
n = 1[p]
Included in persistence analysis (n = 91)
n = 1[p]
Included in persistence analysis (n = 61)
n = 4[p]
Included in persistence analysis (n = 98)
Attended second study visit (n = 57)
Sufficient serum obtained (n = 54)
Returned diary card[q] (n = 58[r])
Attended second study visit (n = 84)
Sufficient serum obtained (n = 82)
Returned diary card[s] (n = 84[t])
Attended second study visit (n = 61)
Sufficient serum obtained (n = 57)
Returned diary card[s] (n = 62[r])
Attended second study visit (n = 90)
Sufficient serum obtained (n = 89)
Returned diary card[s] (n = 91[u])

FIGURE 1 Flow diagram of participants. [a]Did not complete the original study. [b]One invited in error; one randomised to receive the adjuvanted vaccine, but was given the whole-virion vaccine. [c]Did not fulfil the inclusion criteria because was known to have received a third dose of the vaccine. [d]Invited in error, as did not complete the original study. [e]Two invited in error; one vaccinated just before third birthday, but assigned to the ≥3 years group in the original study in error. [f]One invited in error; one did not fulfil inclusion criteria, owing to suspected unexpected severe adverse reaction in original study. One randomised to receive the adjuvanted vaccine, but was given the whole-virion vaccine. [g]One vaccinated just before third birthday, but assigned to the ≥3 years group in the original study in error. [h]Eight found to have received a third dose of pandemic influenza vaccine; two had already received 2010–11 seasonal influenza vaccine; one had received another vaccine in the exclusion period. [i]Three found to have received a third dose of pandemic influenza vaccine; nine had already received the 2010–11 seasonal influenza vaccine. [j]Two had already received the 2010–11 seasonal influenza vaccine; two were too unwell to participate; one was taking part in another clinical trial of an investigation medical product; one was inadvertently excluded in error. [k]Five had already received the 2010–11 seasonal influenza vaccine. [l]Withdrew after consenting to vaccination but before receiving the vaccine. [m]Eight extras, randomly chosen from those excluded owing to receipt of a third dose of pandemic influenza vaccine, to reduce bias in persistence analysis. [n]Two extras, randomly chosen from those excluded owing to receipt of a third dose of pandemic influenza vaccine, to reduce bias in persistence analysis. [p]Withdrew after vaccination but before the second study visit. [q]Includes two diary cards returned by participants who withdrew after vaccination. [r]All diary cards for children <5 years old. [s]Includes one diary card returned by a participant who withdrew after vaccination. [t]Eight diary cards for children <5 years old, 76 diary cards for children ≥5 years old. [u]Nine diary cards for children <5 years old and 82 diary cards for children ≥5 years old.

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TABLE 1 Demographic characteristics of the 318 participants included in the persistence analysis

		Group				
		Whole-virion vaccine		Adjuvanted vaccine		
		First dose <3 years	First dose ≥3 years	First dose <3 years	First dose ≥3 years	All
Site	Bristol	6	16	7	8	37
	Exeter	8	3	2	9	22
	Oxford	24	27	17	28	96
	Southampton	26	32	31	36	125
	St George's, London	4	13	4	17	38
Gender	Male	31	39	31	52	153
	Female	37	52	30	46	165
Age at original pandemic vaccination	Median months (range)	21 (6–35)	97 (37–155)	24 (6–35)	91 (36–150)	51 (6–155)
Ethnicity	White	60	86	60	91	297
	Indian	0	0	0	0	0
	Pakistani	0	1	0	1	2
	Asian – other	0	0	0	0	0
	Mixed	8	1	1	2	12
	Black African	0	0	0	0	0
	Black Caribbean	0	0	0	2	2
	Chinese	0	2	0	1	3
	Other	0	1	0	1	2
Received previous seasonal vaccine		2	6	1	4	13
Interval from blood sample taken after second dose of pandemic vaccine to persistence blood assay	Median days (range)	359 (347–364)	371 (351–384)	361 (350–399)	371 (351–384)	371 (347–399)
Interval from second dose of pandemic vaccine to persistence blood assay	Median days (range)	375 (365–396)	392 (369–405)	380 (365–413)	392 (372–405)	392 (365–413)

TABLE 2 Persistence of antibody assessed by number (and percentage) of participants with an MN titre ≥1:40 at 3 weeks and at 1 year after the second dose of pandemic influenza vaccine

Group	*n*/*N*, percentage (95% CI) with MN titre ≥1:40, 3 weeks after second pandemic vaccine dose	*n*/*N*, percentage (95% CI) with MN titre ≥1:40, 1 year after second pandemic vaccine dose
Whole-virion vaccine		
6 months to <3 years	56/68, 82.4% (71.2% to 90.5%)	22/68, 32.4% (21.5% to 44.8%)[a]
3–12 years	86/91, 94.5% (87.6% to 98.2%)	60/91, 65.9% (55.3% to 75.5%)[a]
Both age groups	142/159, 89.3% (83.4% to 93.6%)	82/159, 51.6% (43.5% to 59.6%)[a]
Adjuvanted vaccine		
6 months to <3 years	61/61, 100% (94.1% to 100%)	61/61, 100% (94.1% to 100%)[a]
3–12 years	98/98, 100% (96.3% to 100%)	95/98, 96.9% (91.3% to 99.4%)[a]
Both age groups	159/159, 100% (97.7% to 100%)	156/159, 98.1% (94.6% to 99.6%)[a]

CI, confidence interval.
a $p<0.001$ comparing the whole-virion group with the corresponding adjuvanted group.

TABLE 3 Persistence of antibody assessed by the MN geometric mean titre at 1 year after the second dose of pandemic influenza vaccine

Group	MN GMT (95% CI), 1 year after second pandemic vaccine dose
Whole-virion vaccine	
6 months to < 3 years	33.6 (23.8 to 47.5)[a]
3–12 years	66.9 (53.1 to 84.2)[a]
Both age groups	49.8 (40.7 to 61.0)[a]
Adjuvanted vaccine	
6 months to < 3 years	411.9 (332.5 to 510.2)[a]
3–12 years	287.6 (230.5 to 358.9)[a]
Both age groups	330.1 (281.3 to 387.4)[a]

CI, confidence interval; GMT, geometric mean titre.
a $p < 0.001$ comparing the whole-virion group with the corresponding adjuvanted group.

Table 4 shows the number (and percentage) of participants with an HI titre ≥ 1 : 32 at 3 weeks and at 1 year after the second dose of pandemic influenza vaccine. *Table 5* shows the HI geometric mean titre at these time points. *Table 6* shows the distribution of fold changes in the HI titre (change from HI titre 3 weeks after the second dose of pandemic influenza vaccine to HI titre 1 year after vaccination).

Figure 2 shows reverse cumulative distribution curves for HI and MN titres, at 3 weeks and at 1 year after receipt of a monovalent pandemic influenza vaccine, analysed according to vaccine given and age at first dose.

The unexpected finding that the HI geometric mean titre was greater 1 year after vaccination than at 3 weeks after vaccination in children who had been given the whole-virion vaccine when < 3 years old prompted further analysis of the changes in titres in whole-virion vaccine recipients. *Tables 7–9* compare those whose HI titre was ≥ 1 : 32 at 3 weeks after two doses of whole-virion vaccine with those whose HI titre was < 1 : 32 at this time point. For these two subgroups, *Table 7* shows the HI geometric mean titre at 3 weeks and at 1 year after the second dose of the whole-virion vaccine, *Table 8* shows the distribution of fold changes in the HI titre (change from HI titre 3 weeks after the second dose of pandemic influenza vaccine to HI titre 1 year after vaccination) and *Table 9* shows the numbers and percentages with HI titres of ≥ 1 : 32 at 1 year after vaccination. *Table 10* compares those recipients of the whole-virion vaccine whose MN titre was ≥ 1 : 40 at 3 weeks after vaccination with those whose MN titre was < 1 : 40, showing numbers and percentages with MN titre ≥ 1 : 40 at 1 year after vaccination.

An additional analysis of the persistence of antibody, modelling the logged HI and MN titres 1 year after pandemic influenza vaccination, is shown in *Tables 11* and *12*. The variables considered were pandemic vaccine received, age at first dose (< 3 years or ≥ 3 years), gender, whether or not seasonal influenza vaccine had been previously given, interval between post-vaccination blood draw in the original study and the first blood draw in the follow-on study, and study site. Gender and receipt of previous seasonal influenza vaccine did not have a statistically significant effect and these variables are not shown in the tables. *Table 11* shows the fold effect on HI and MN titres 1 year after pandemic influenza vaccination. *Table 12* shows the fold effect on HI titres 1 year after pandemic influenza vaccination, including the HI titre recorded 3 weeks after pandemic vaccination as a covariate.

TABLE 4 Persistence of antibody assessed by the number (and percentage) of participants with an HI titre ≥1:32, at 3 weeks and at 1 year after the second dose of pandemic influenza vaccine

Group	*n/N*, percentage (95% CI) with HI titre ≥1:32, 3 weeks after second pandemic vaccine dose	*n/N*, percentage (95% CI) with HI titre ≥1:32, 1 year after second pandemic vaccine dose
Whole-virion vaccine		
6 months to <3 years	40/68, 58.8% (46.2% to 70.6%)	43/68, 63.2% (50.7% to 74.6%)[a]
3–12 years	82/91, 90.1% (82.1% to 95.4%)	72/91, 79.1% (69.3% to 86.9%)[a]
Both age groups	122/159, 76.7% (69.4% to 83.1%)	115/159, 72.3% (64.7% to 79.1%)[a]
Adjuvanted vaccine		
6 months to <3 years	61/61, 100% (94.1 to 100%)	60/61, 98.4% (91.2 to 100%)[a]
3–12 years	98/98, 100% (96.3 to 100%)	95/98, 96.9% (91.3 to 99.4%)[a]
Both age groups	159/159, 100% (97.7 to 100%)	155/159, 97.5% (93.7 to 99.3%)[a]

CI, confidence interval.
a $p<0.001$ comparing the whole-virion group with the corresponding adjuvanted group.

TABLE 5 Persistence of antibody, assessed by the HI geometric mean titre, at 3 weeks and at 1 year after the second dose of pandemic influenza vaccine

Group	*n*	HI GMT (95% CI), 3 weeks after second pandemic vaccine dose	HI GMT (95% CI), 1 year after second pandemic vaccine dose	Fold change
Whole-virion vaccine				
6 months to <3 years	68	35.6 (24.8 to 51.2)	40.0 (27.9 to 57.6)[a]	1.12 (0.78 to 1.61)[a]
3 to 12 years	91	110.8 (85.9 to 142.7)	49.8 (39.0 to 63.5)[a]	0.45 (0.35 to 0.58)[a]
Both age groups	159	68.2 (54.3 to 85.6)	45.4 (36.9 to 55.8)[a]	0.67 (0.53 to 0.83)[a]
Adjuvanted vaccine				
6 months to <3 years	61	520.8 (442.7 to 612.6)	157.9 (125.8 to 198.3)[a]	0.30 (0.24 to 0.38)[a]
3 to 12 years	98	455.6 (395.9 to 524.3)	129.8 (105.7 to 159.5)[a]	0.28 (0.23 to 0.35)[a]
Both age groups	159	479.6 (431.4 to 533.2)	140.0 (120.1 to 163.1)[a]	0.29 (0.25 to 0.34)[a]

CI, confidence interval; GMT, geometric mean titre.
a $p<0.001$ comparing the whole-virion group with the corresponding adjuvanted group.

TABLE 6 Distribution of fold changes in the HI titre (change from HI titre 3 weeks after the second dose of pandemic influenza vaccine to HI titre 1 year after vaccination)

Group	≥8-fold drop	4- to 7.9-fold drop	2- to 3.9-fold drop	<2-fold change	2- to 3.9-fold rise	4- to 7.9-fold rise	≥8-fold rise
Whole-virion vaccine							
6 months to <3 years	4	9	12	20	8	5	10
3–12 years	18	22	19	19	8	2	3
Adjuvanted vaccine							
6 months to <3 years	10	20	20	8	3	0	0
3–12 years	21	34	28	12	1	1	1

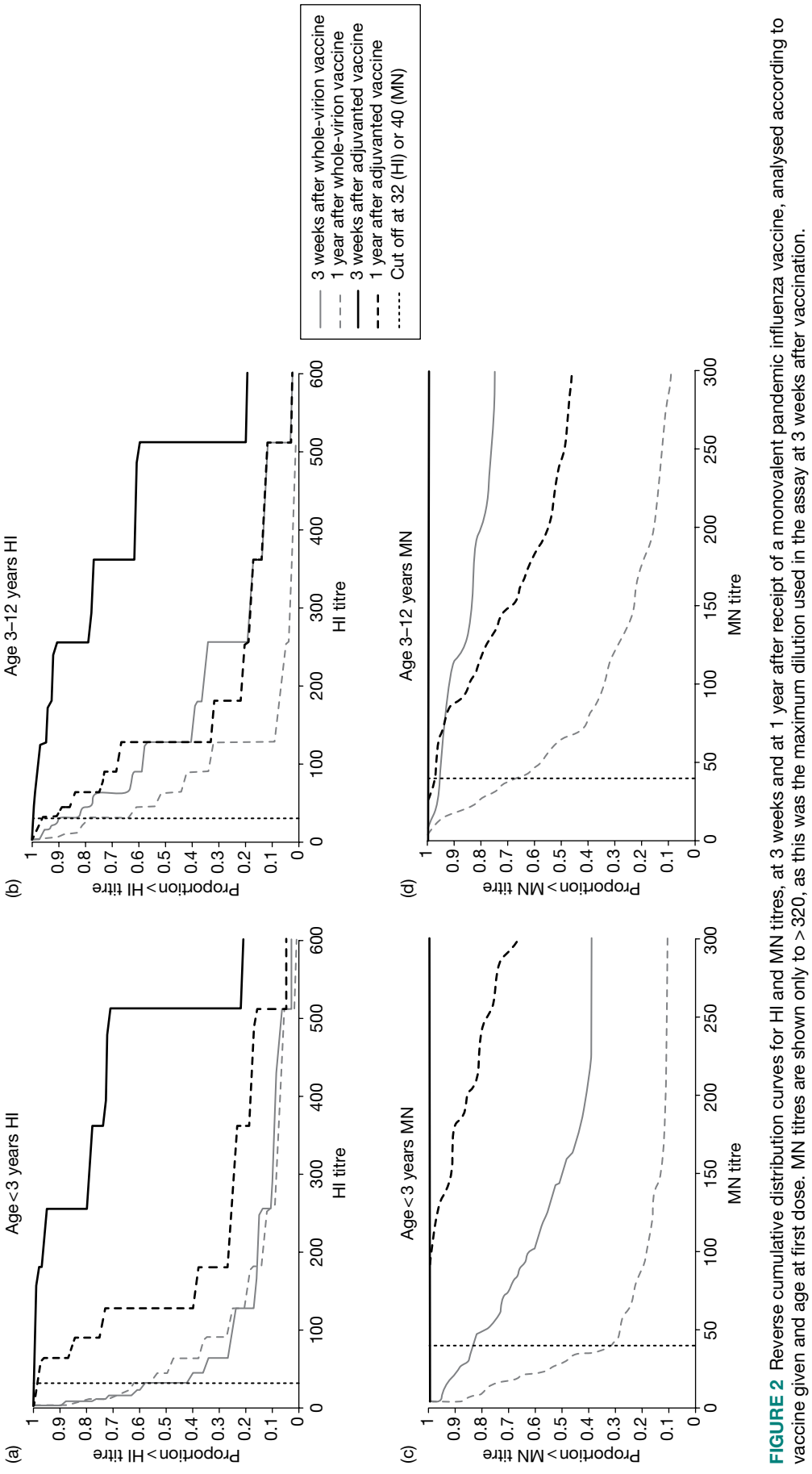

FIGURE 2 Reverse cumulative distribution curves for HI and MN titres, at 3 weeks and at 1 year after receipt of a monovalent pandemic influenza vaccine, analysed according to vaccine given and age at first dose. MN titres are shown only to > 320, as this was the maximum dilution used in the assay at 3 weeks after vaccination.

TABLE 7 Further analysis of recipients of the whole-virion vaccine, comparing those children who had an HI titre ≥1:32 with those who had an HI titre <1:32 at 3 weeks after vaccination, showing the HI geometric mean titre at 3 weeks and at 1 year after the second dose of the whole-virion vaccine

Group, age at first dose	*n*	HI GMT (95% CI), 3 weeks after second pandemic vaccine dose	HI GMT (95% CI), 1 year after second pandemic vaccine dose	Fold change (95% CI)
HI titre ≥ 1:32				
6 months to 3 years	40	95 (67 to 135)	73 (41 to 109)	0.76 (0.48 to 1.20)
3–12 years	82	145 (118 to 177)	56 (44 to 71)	0.39 (0.31 to 0.49)
All ages	122	126 (106 to 151)	61 (50 to 75)	0.48 (0.39 to 0.60)
HI titre <1:32				
6 months to 3 years	28	9 (7 to 11)	19 (10 to 30)	1.95 (1.11 to 3.43)
3–12 years	9	10 (5 to 18)	17 (5 to 52)	1.71 (0.54 to 5.40)
All ages	37	9 (7 to 11)	19 (11 to 27)	1.89 (1.17 to 3.06)

CI, confidence interval; GMT, geometric mean titre.

TABLE 8 Further analysis of recipients of the whole-virion vaccine, comparing those children who had an HI titre ≥1:32 with those who had an HI titre <1:32 at 3 weeks after vaccination, showing distribution of fold changes in the HI titre (change from HI titre 3 weeks after the second dose of pandemic influenza vaccine to HI titre 1 year after vaccination)

Group, age at first dose	≥8-fold drop	4- to 7.9-fold drop	2- to 3.9-fold drop	<2-fold change	2- to 3.9-fold rise	4- to 7.9-fold rise	≥8-fold rise
HI titre ≥ 1:32							
6 months to 3 years	4	7	9	8	6	2	4
3–12 years	18	21	18	16	7	0	2
HI titre <1:32							
6 months to 3 years	0	1	3	12	2	3	6
3–12 years	0	1	1	3	1	2	1

TABLE 9 Further analysis of recipients of the whole-virion vaccine, comparing those children who had an HI titre ≥1:32 with those who had an HI titre <1:32 at 3 weeks after vaccination, showing numbers and percentages with an HI titre ≥1:32 at 1 year after vaccination

Group, age at first dose	*n*/*N*, percentage (95% CI) with HI titre ≥1:32, 1 year after vaccination
HI titre ≥ 1:32	
6 months to 3 years	32/40, 80% (64.4% to 90.9%)
3–12 years	68/82, 82.9% (73% to 90.3%)
All ages	100/122, 82.0% (74% to 88.3%)
HI titre <1:32	
6 months to 3 years	11/28, 39.3 (21.5% to 59.4%)
3–12 years	4/9, 44.4% (13.7% to 78.8%)
All ages	15/37, 40.5% (24.8% to 57.9%)

CI, confidence interval.

TABLE 10 Further analysis of recipients of the whole-virion vaccine, comparing those who had an MN titre ≥ 1 : 40 with those who had an MN titre < 1 : 40 at 3 weeks after vaccination, showing numbers and percentages with an MN titre ≥ 1 : 40 at 1 year after vaccination

Group, age at first dose	*n*/*N*, percentage (95% CI) with MN titre ≥ 1 : 40, 1 year after vaccination
MN titre ≥ 1 : 40	
6 months to 3 years	21/56, 37.5% (24.9% to 51.5%)
3–12 years	60/86, 69.8% (58.9% to 79.2%)
All ages	81/142, 57.0% (48.5% to 65.3%)
MN titre < 1 : 40	
6 months to 3 years	1/12, 8.3% (0.2% to 38.5%)
3–12 years	0/5, 0% (0% to 52.2%)
All ages	1/17, 5.9% (0.1% to 28.7%)

CI, confidence interval.

TABLE 11 Additional analysis of the persistence of antibody, modelling the logged HI and MN titres 1 year after the pandemic influenza vaccination

		HI		MN	
Variable	**Level**	**Fold effect (95% CI)**	***p*-value**	**Fold effect (95% CI)**	***p*-value**
Age	< 3 years	Baseline		Baseline	
	≥ 3 years	1.16 (0.86 to 1.56)	0.33	1.10 (0.81 to 1.49)	0.54
Vaccine	Whole-virion	Baseline		Baseline	
	Adjuvanted	3.10 (2.41 to 3.98)	< 0.001	6.63 (5.14 to 8.55)	< 0.001
Interval since blood draw for original post-vaccination titre	Effect per week	0.86 (0.75 to 0.99)	0.03	1.06 (0.92 to 1.22)	0.39
Site	Bristol	Baseline		Baseline	
	Exeter	0.27 (0.14 to 0.49)	< 0.001	0.37 (0.20 to 0.69)	0.002
	Oxford	0.88 (0.57 to 1.34)	0.54	0.79 (0.51 to 1.23)	0.30
	Southampton	1.01 (0.67 to 1.53)	0.95	0.77 (0.50 to 1.18)	0.23
	St George's, London	1.26 (0.74 to 2.13)	0.40	0.69 (0.40 to 1.19)	0.18

CI, confidence interval.

Safety of pandemic influenza vaccines

There were no reports of clinically significant adverse events related to the original pandemic influenza vaccination in any of the 323 children enrolled {0/157 [95% confidence interval (CI) 0% to 2.3%] in the whole-virion vaccine group and 0/166 (95% CI 0% to 2.2%) in the $AS03_B$-adjuvanted vaccine group}. Clinically significant adverse events were determined by the investigators, from medical history given by the parents, and included hospitalisations, influenza-like episodes, febrile convulsions and adverse events of special interest.

TABLE 12 Additional analysis of the persistence of antibody, modelling the logged HI titres 1 year after the pandemic influenza vaccination, including the HI titre 3 weeks after vaccination as a covariate

Variable	Level	Fold effect (95% CI)	*p*-value
HI titre 3 weeks after vaccination	Per 2.7-fold change	1.57 (1.41 to 1.75)	< 0.001
Age	< 3 years	Baseline	
	≥ 3 years	0.96 (0.73 to 1.26)	0.78
Vaccine	Whole-virion	Baseline	
	Adjuvanted	1.29 (0.95 to 1.75)	0.10
Interval since blood draw for original post-vaccination titre	Effect per week	0.83 (0.74 to 0.94)	0.004
Site	Bristol	Baseline	
	Exeter	0.44 (0.25 to 0.78)	0.005
	Oxford	0.87 (0.59 to 1.28)	0.48
	Southampton	1.11 (0.76 to 1.63)	0.57
	St George's, London	1.40 (0.86 to 2.25)	0.17

CI, confidence interval.

Immunogenicity of trivalent seasonal influenza vaccine

A total of 302 children received the 2010–11 trivalent seasonal influenza vaccine in the follow-on study. *Table 13* shows the demographic characteristics of these children. After vaccination, sufficient blood for analysis was obtained from 282 of these children. MN and HI titres for the H1N1 component of the vaccine were measured.

The median interval from vaccination to post-vaccination blood sampling was 21 days (range 11–44 days). For nine children, this interval was outside the range of 14–28 days (and for two of these children the interval was outside the range of 14–35 days). These children were included in the modified intention-to-treat analysis.

Table 14 shows the number (and percentage) of children with an MN titre ≥ 1 : 40 immediately before and 3 weeks after receipt of the seasonal influenza vaccine. A valid MN geometric mean titre could not be calculated, as titration was not performed beyond 1 : 5120 and the MN titre after vaccination was > 1 : 5120 for many participants.

Table 15 shows the number (and the percentage) of participants with an HI titre ≥ 1 : 32, immediately before and 3 weeks after receipt of the seasonal influenza vaccine. *Table 16* shows the HI geometric mean titres at these time points.

Figure 3 shows reverse cumulative distribution curves for HI and MN titres immediately before and at 3 weeks after receipt of the trivalent seasonal influenza vaccine, analysed according to pandemic vaccine previously given and age at first dose.

Table 17 shows the additional analysis, modelling HI titres 3 weeks after receipt of the trivalent seasonal influenza vaccine, split according to pandemic vaccine previously received. The variables of gender, previous receipt of seasonal influenza vaccine, interval from vaccination to blood assay and study site had no statistically significant effect. There was no age effect for the whole-virion vaccine group, but children given the $AS03_B$-adjuvanted vaccine before 3 years of age had a significantly greater fold rise in HI titre in response to the trivalent influenza vaccine than did

TABLE 13 Demographic characteristics of the 302 participants given seasonal influenza vaccine

		Group				
		Whole-virion vaccine		Adjuvanted vaccine		
		First dose <3 years	First dose ≥3 years	First dose <3 years	First dose ≥3 years	All
Site	Bristol	5	16	7	8	36
	Exeter	4	5	4	6	19
	Oxford	26	25	17	27	95
	Southampton	25	28	30	36	119
	St George's, London	1	11	4	17	33
Gender	Male	30	38	32	48	148
	Female	31	47	30	46	154
Age at seasonal influenza vaccination	Median months (range)	37 (19–48)	112 (52–169)	37 (18–49)	105 (50–164)	67 (18–169)
Ethnicity	White	53	80	61	87	281
	Indian	0	0	0	0	0
	Pakistani	0	1	0	1	2
	Asian–other	0	0	0	0	0
	Mixed	8	1	1	2	12
	Black African	0	0	0	0	0
	Black Caribbean	0	0	0	2	2
	Chinese	0	2	0	1	3
	Other	0	1	0	1	2
Received previous seasonal vaccine		2	6	1	4	13
Interval from vaccination to blood assay	<14 days	0	0	0	1	1
	14–28 days	53	83	60	88	284
	>28 days	3	2	1	2	8

TABLE 14 Response to the trivalent seasonal influenza vaccine, assessed by the number (and percentage) of participants with an MN titre ≥1:40, immediately before and 3 weeks after vaccination

Group	*n*/N, percentage (95% CI) with MN titre ≥1:40 before vaccine	*n*/*N*, percentage (95% CI) with MN titre ≥1:40, 3 weeks after vaccine	*n*/*N*, percentage (95% CI) with ≥4-fold rise in MN titre
Whole-virion vaccine			
6 months to <3 years	21/60, 35.0% (23.1% to 48.4%)	54/54, 100% (93.4% to 100%)	51/53, 96.2% (87% to 99.5%)
3–12 years	52/81, 64.2% (52.8% to 74.6%)	82/82, 100% (95.6% to 100%)	77/78, 98.7% (93.1% to 100%)
Both age groups	73/141, 51.8% (43.2% to 60.3%)	136/136, 100% (97.3% to 100%)	128/131, 97.7% (93.5% to 99.5%)
Adjuvanted vaccine			
6 months to <3 years	60/60, 100% (94% to 100%)	57/57, 100% (93.7% to 100%)	56/56, 100% (93.6% to 100%)
3–12 years	91/93, 97.8% (92.4% to 99.7%)	89/89, 100% (95.9% to 100%)	82/88, 93.2% (85.7% to 97.5%)
Both age groups	151/153, 98.7% (95.4% to 99.8%)	146/146, 100% (97.5% to 100%)	138/144, 95.8% (91.2% to 98.5%)

children who had received the $AS03_B$–adjuvanted vaccine when ≥3 years old. HI titre 3 weeks after pandemic vaccination had a statistically significant effect on the response to the trivalent influenza vaccine, whereas HI titre immediately before giving the trivalent influenza vaccine did not.

TABLE 15 Response to the trivalent seasonal influenza vaccine, assessed by the number (and percentage) of participants with an HI titre ≥1:32, immediately before and 3 weeks after vaccination

Group	*n*/*N*, percentage (95% CI) with HI titre ≥1:32 before vaccine	*n*/*N*, percentage (95% CI) with HI titre ≥1:32, 3 weeks after vaccine	*n*/*N*, percentage (95% CI) with ≥4-fold rise in HI titre
Whole-virion vaccine			
6 months to <3 years	42/60, 70.0% (56.8% to 81.2%)	54/54, 100% (93.4% to 100%)	43/53, 81.1% (68% to 90.6%)
3–12 years	64/81, 79.0% (68.5% to 87.3%)	82/82, 100% (95.6% to 100%)	73/78, 93.6% (85.7% to 97.9%)
Both age groups	106/141, 75.2% (67.2% to 82.1%)	136/136, 100% (97.3% to 100%)	116/131, 88.5% (81.8 % to 93.4%)
Adjuvanted vaccine			
6 months to <3 years	59/60, 98.3% (91.1% to 100%)	57/57, 100% (93.7% to 100%)	52/56, 92.9% (82.7% to 98%)
3– 12 years	90/93, 96.8% (90.9% to 99.3%)	89/89, 100% (95.9% to 100%)	76/88, 86.4% (77.4% to 92.8%)
Both age groups	149/153, 97.4% (93.4% to 99.3%)	146/146, 100% (97.5% to 100%)	128/144, 88.9% (82.6% to 93.5%)

TABLE 16 Response to the trivalent seasonal influenza vaccine, assessed by the HI geometric mean titre, immediately before and 3 weeks after vaccination

Group	HI GMT (95% CI) before vaccine	HI GMT (95% CI) 3 weeks after vaccine	Fold change
Whole-virion vaccine			
6 months to <3 years	50.2 (34.0 to 74.2)	661.9 (524.9 to 834.6)[a]	12.6 (8.3 to 19.1)
3 to 12 years	49.7 (38.6 to 64.1)	846.6 (733.0 to 977.9)[a]	16.7 (12.8 to 21.7)
Both age groups	49.9 (40.1 to 62.1)	767.8 (676.6 to 871.3)[a]	14.9 (11.8 to 18.7)
Adjuvanted vaccine			
6 months to <3 years	159.4 (127.5 to 199.3)	2611.9 (2238.1 to 3048.0)[a]	16.2 (12.2 to 21.4)
3 to 12 years	131.4 (105.9 to 163.0)	1425.8 (1244.9 to 1632.9)[a]	10.7 (8.5 to 13.7)
Both age groups	141.7 (121.2 to 165.8)	1805.9 (1614.3 to 2020.3)[a]	12.6 (10.5 to 15.1)

GMT, geometric mean titre.
a $p<0.001$ comparing the whole-virion group with the corresponding adjuvanted group

TABLE 17 Additional analysis, modelling HI titres 3 weeks after receipt of the trivalent seasonal influenza vaccine

		Whole-virion vaccine		Adjuvanted vaccine	
Variable	**Level**	**Fold effect (95% CI)**	***p*-value**	**Fold effect (95% CI)**	***p*-value**
HI titre 3 weeks after pandemic vaccination	Per 2.7-fold change	1.30 (1.18 to 1.43)	<0.001	1.30 (1.10 to 1.53)	0.002
HI titre before trivalent seasonal influenza vaccine	Per 2.7-fold change	1.03 (0.93 to 1.13)	0.60	1.06 (0.96 to 1.18)	0.26
Age	<3 years	Baseline		Baseline	
	≥3 years	0.95 (0.73 to 1.25)	0.73	0.60 (0.49 to 0.74)	<0.001
Site	Bristol	Baseline		Baseline	
	Exeter	1.04 (0.53 to 2.03)	0.91	1.51 (0.89 to 2.55)	0.13
	Oxford	0.96 (0.66 to 1.38)	0.82	1.04 (0.73 to 1.47)	0.85
	Southampton	1.33 (0.92 to 1.91)	0.13	1.20 (0.85 to 1.69)	0.29
	St George's, London	1.13 (0.68 to 1.89)	0.64	0.91 (0.61 to 1.36)	0.65

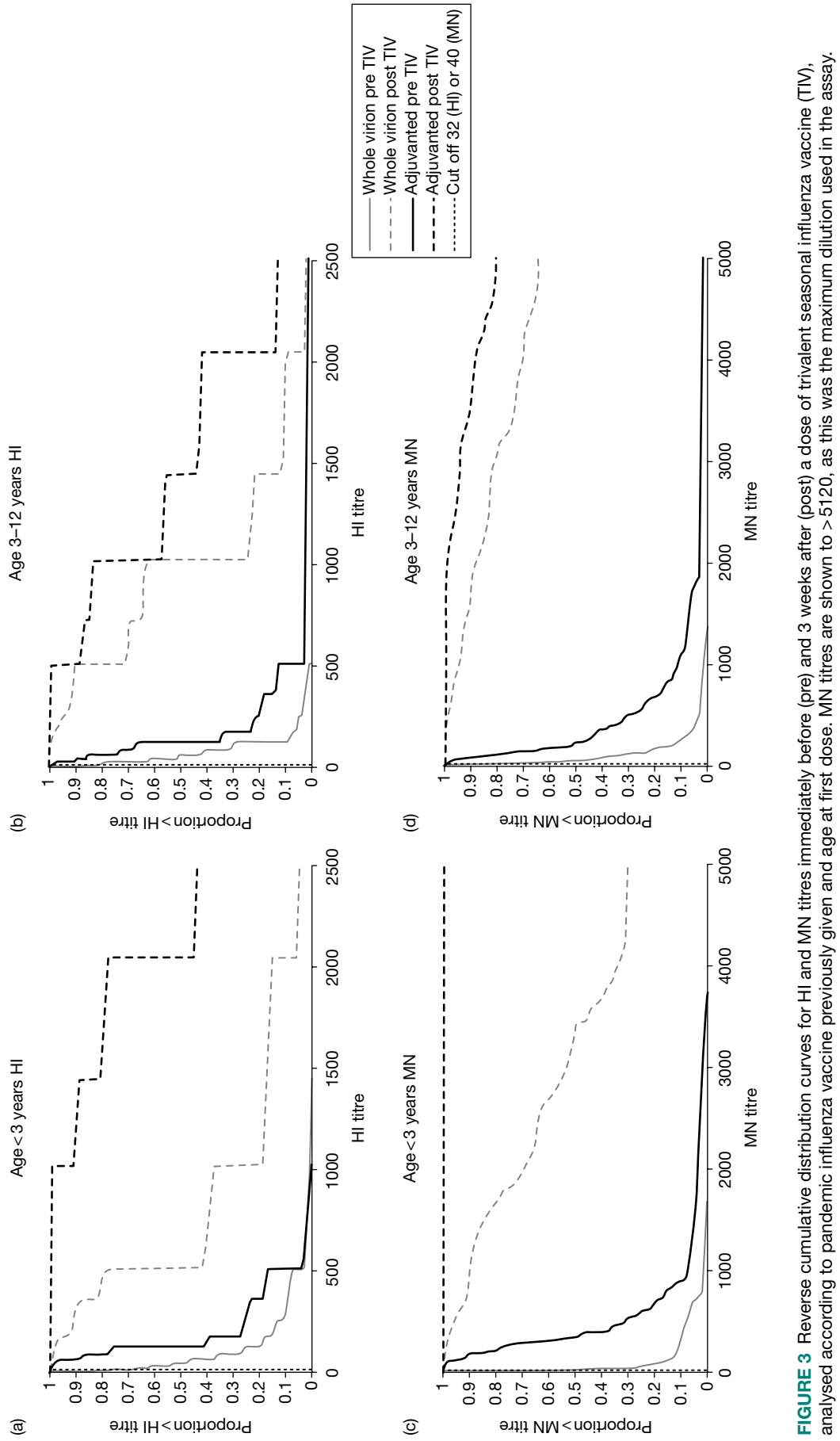

FIGURE 3 Reverse cumulative distribution curves for HI and MN titres immediately before (pre) and 3 weeks after (post) a dose of trivalent seasonal influenza vaccine (TIV), analysed according to pandemic influenza vaccine previously given and age at first dose. MN titres are shown to > 5120, as this was the maximum dilution used in the assay.

Reactogenicity of trivalent seasonal influenza vaccine

Diary cards were returned by 295 out of the 302 children who received the trivalent seasonal influenza vaccine. Diary cards were completed during the 5 days after vaccination and most were returned at the second study visit. Five children who were vaccinated, but then withdrew from the study before their second visit returned diary cards.

Between vaccination and completion of (or withdrawal from) the study, there were no serious adverse events.

Table 18 shows local reactions reported by children < 5 years old. *Table 19* shows local reactions reported by children ≥ 5 years old.

Table 20 shows systemic reactions reported by children < 5 years old. *Table 21* shows local reactions reported by children ≥ 5 years old.

Table 22 shows local reactions, severe systemic symptoms and fever ≥ 38 °C reported by children across both age groups.

Redness and severe local symptoms were reported more frequently in the children < 5 years old who had previously received the $AS03_B$-adjuvanted pandemic influenza vaccine than in those children who had been given the whole-virion vaccine ($p < 0.05$). For all other solicited local and systemic symptoms, there was no statistically significant difference between the whole-virion and the $AS03_B$-adjuvanted groups.

The relationship between reactogenicity and immune response was examined using logged HI titres in the multivariable model. *Table 23* shows the effects of fever and severe local reactions on HI titre 3 weeks after trivalent seasonal influenza vaccination. Fever and severe local reactions were both associated with a greater HI titre response to the trivalent seasonal influenza vaccine in children who had previously received the $AS03_B$-adjuvanted pandemic influenza vaccine, but not in those who had been given the whole-virion vaccine. No effect was seen for injection-site redness.

TABLE 18 Local reactions after the trivalent seasonal influenza vaccination in children < 5 years old.

Pandemic vaccine received in original study		Whole-virion vaccine		Adjuvanted vaccine	
Total vaccinated		*N* = 69		*N* = 72	
Number of diary cards available		*n* = 66		*n* = 71	
Measurement	**Level**	**Number**	**Percentage (95% CI)**	**Number**	**Percentage (95% CI)**
Pain	Mild	25	37.9% (26.2% to 50.7%)	24	33.8% (23% to 46%)
	Moderate	1	1.5% (0% to 8.2%)	7	9.9% (4.1% to 19.3%)
	Severe	0	0% (0% to 5.4%)	0	0% (0% to 5.1%)
	Any	26	39.4% (27.6% to 52.2%)	31	43.7% (31.9% to 56%)
Redness	1–24 mm	15	22.7% (13.3% to 34.7%)	16	22.5% (13.5% to 34%)
	25–49 mm	1	1.5% (0% to 8.2%)	3	4.2% (0.9% to 11.9%)
	≥ 50 mm	0	0% (0% to 5.4%)[a]	10	14.1% (7% to 24.4%)[a]
	Any	16	24.2% (14.5% to 36.4%)[a]	29	40.8% (29.3% to 53.2%)[a]
Swelling	1–24 mm	10	15.2% (7.5% to 26.1%)	10	14.1% (7% to 24.4%)
	25–49 mm	2	3% (0.4% to 10.5%)	3	4.2% (0.9% to 11.9%)
	≥ 50 mm	1	1.5% (0% to 8.2%)	5	7% (2.3% to 15.7%)
	Any	13	19.7% (10.9% to 31.3%)	18	25.4% (15.8% to 37.1%)
Any local	Severe	1	1.5% (0% to 8.2%)[a]	10	14.1% (7% to 24.4%)[a]

a $p < 0.05$ for comparison between vaccines.

TABLE 19 Local reactions after the trivalent seasonal influenza vaccination in children ≥ 5 years old

Pandemic vaccine received in original study		Whole-virion vaccine		Adjuvanted vaccine	
Total vaccinated		*N* = 77		*N* = 84	
Number of diary cards available		*n* = 76		*n* = 82	
Measurement	**Level**	**Number**	**Percentage (95% CI)**	**Number**	**Percentage (95% CI)**
Pain	Mild	34	44.7% (33.3% to 56.6%)	42	51.2% (39.9% to 62.4%)
	Moderate	16	21.1% (12.5% to 31.9%)	19	23.2% (14.6% to 33.8%)
	Severe	1	1.3% (0% to 7.1%)	1	1.2% (0% to 6.6%)
	Any	51	67.1% (55.4% to 77.5%)	62	75.6% (64.9% to 84.4%)
Redness	1–24 mm	19	25% (15.8% to 36.3%)	22	26.8% (17.6% to 37.8%)
	25–49 mm	3	3.9% (0.8% to 11.1%)	7	8.5% (3.5% to 16.8%)
	≥ 50 mm	1	1.3% (0% to 7.1%)	7	8.5% (3.5% to 16.8%)
	Any	23	30.3% (20.2% to 41.9%)	36	43.9% (33% to 55.3%)
Swelling	1–24 mm	18	23.7% (14.7% to 34.8%)	18	22% (13.6% to 32.5%)
	25–49 mm	2	2.6% (0.3% to 9.2%)	6	7.3% (2.7% to 15.2%)
	≥ 50 mm	0	0% (0% to 4.7%)	1	1.2% (0% to 6.6%)
	Any	20	26.3% (16.9% to 37.7%)	25	30.5% (20.8% to 41.6%)
Any local	Severe	2	2.6% (0.3% to 9.2%)	8	9.8% (4.3% to 18.3%)

a $p < 0.05$ for comparison between vaccines. No statistically significant differences seen.

TABLE 20 Systemic reactions after trivalent seasonal influenza vaccination in children < 5 years old

Group		Whole-virion vaccine		Adjuvanted vaccine	
Total vaccinated		*N* = 69		*N* = 72	
Number of diary cards available		*n* = 66		*n* = 71	
Measurement	**Level**	**Number**	**Percentage (95% CI)**	**Number**	**Percentage (95% CI)**
Decreased feeding	Mild	14	21.2% (12.1% to 33%)	10	14.1% (7% to 24.4%)
	Moderate	8	12.1% (5.4% to 22.5%)	8	11.3% (5% to 21%)
	Severe	1	1.5% (0% to 8.2%)	4	5.6% (1.6% to 13.8%)
	Any	23	34.8% (23.5% to 47.6%)	22	31% (20.5% to 43.1%)
Decreased activity	Mild	12	18.2% (9.8% to 29.6%)	14	19.7% (11.2% to 30.9%)
	Moderate	6	9.1% (3.4% to 18.7%)	7	9.9% (4.1% to 19.3%)
	Severe	2	3% (0.4% to 10.5%)	3	4.2% (0.9% to 11.9%)
	Any	20	30.3% (19.6% to 42.9%)	24	33.8% (23% to 46%)
Increased irritability	Mild	18	27.3% (17% to 39.6%)	15	21.1% (12.3% to 32.4%)
	Moderate	5	7.6% (2.5% to 16.8%)	14	19.7% (11.2% to 30.9%)
	Severe	4	6.1% (1.7% to 14.8%)	2	2.8% (0.3% to 9.8%)
	Any	27	40.9% (29% to 53.7%)	31	43.7% (31.9% to 56%)
Persistent crying	Mild	18	27.3% (17% to 39.6%)	15	21.1% (12.3% to 32.4%)
	Moderate	5	7.6% (2.5% to 16.8%)	14	19.7% (11.2% to 30.9%)
	Severe	4	6.1% (1.7% to 14.8%)	2	2.8% (0.3% to 9.8%)
	Any	27	40.9% (29% to 53.7%)	31	43.7% (31.9% to 56%)
Vomiting	Mild	7	10.6% (4.4% to 20.6%)	3	4.2% (0.9% to 11.9%)
	Moderate	1	1.5% (0% to 8.2%)	1	1.4% (0% to 7.6%)
	Severe	1	1.5% (0% to 8.2%)	1	1.4% (0% to 7.6%)
	Any	9	13.6% (6.4% to 24.3%)	5	7% (2.3% to 15.7%)
Diarrhoea	Mild	11	16.7% (8.6% to 27.9%)	11	15.5% (8% to 26%)
	Moderate	3	4.5% (0.9% to 12.7%)	2	2.8% (0.3% to 9.8%)
	Severe	1	1.5% (0% to 8.2%)	0	0% (0% to 5.1%)
	Any	15	22.7% (13.3% to 34.7%)	13	18.3% (10.1% to 29.3%)
Any severe systemic symptoms		5	7.6% (2.5% to 16.8%)	5	7% (2.3% to 15.7%)
Fever ≥ 38 °C		9	13.6% (6.4% to 24.3%)	13	18.3% (10.1% to 29.3%)

TABLE 21 Systemic reactions after the trivalent seasonal influenza vaccination in children ≥5 years old

Group		Whole-virion vaccine		Adjuvanted vaccine	
Total vaccinated		*N*=77		*N*=84	
Number of diary cards available		*n*=76		*n*=82	
Measurement	**Level**	**Number**	**Percentage (95% CI)**	**Number**	**Percentage (95% CI)**
Loss of appetite	Mild	8	10.5% (4.7% to 19.7%)	10	12.2% (6% to 21.3%)
	Moderate	0	0% (0% to 4.7%)	0	0% (0% to 4.4%)
	Severe	0	0% (0% to 4.7%)	0	0% (0% to 4.4%)
	Any	8	10.5% (4.7% to 19.7%)	10	12.2% (6% to 21.3%)
Generally unwell	Mild	9	11.8% (5.6% to 21.3%)	13	15.9% (8.7% to 25.6%)
	Moderate	7	9.2% (3.8% to 18.1%)	14	17.1% (9.7% to 27%)
	Severe	2	2.6% (0.3% to 9.2%)	2	2.4% (0.3% to 8.5%)
	Any	18	23.7% (14.7% to 34.8%)	29	35.4% (25.1% to 46.7%)
Headache	Mild	17	22.4% (13.6% to 33.4%)	15	18.3% (10.6% to 28.4%)
	Moderate	3	3.9% (0.8% to 11.1%)	9	11% (5.1% to 19.8%)
	Severe	1	1.3% (0% to 7.1%)	1	1.2% (0% to 6.6%)
	Any	21	27.6% (18% to 39.1%)	25	30.5% (20.8% to 41.6%)
Nausea/vomiting	Mild	9	11.8% (5.6% to 21.3%)	13	15.9% (8.7% to 25.6%)
	Moderate	1	1.3% (0% to 7.1%)	1	1.2% (0% to 6.6%)
	Severe	0	0% (0% to 4.7%)	0	0% (0% to 4.4%)
	Any	10	13.2% (6.5% to 22.9%)	14	17.1% (9.7% to 27%)
Diarrhoea	Mild	5	6.6% (2.2% to 14.7%)	9	11% (5.1% to 19.8%)
	Moderate	1	1.3% (0% to 7.1%)	1	1.2% (0% to 6.6%)
	Severe	0	0% (0% to 4.7%)	0	0% (0% to 4.4%)
	Any	6	7.9% (3% to 16.4%)	10	12.2% (6% to 21.3%)
Muscle pain	Mild	15	19.7% (11.5% to 30.5%)	21	25.6% (16.6% to 36.4%)
	Moderate	5	6.6% (2.2% to 14.7%)	10	12.2% (6% to 21.3%)
	Severe	1	1.3% (0% to 7.1%)	0	0% (0% to 4.4%)
	Any	21	27.6% (18% to 39.1%)	31	37.8% (27.3% to 49.2%)
Joint pain	Mild	9	11.8% (5.6% to 21.3%)	7	8.5% (3.5% to 16.8%)
	Moderate	2	2.6% (0.3% to 9.2%)	3	3.7% (0.8% to 10.3%)
	Severe	1	1.3% (0% to 7.1%)	0	0% (0% to 4.4%)
	Any	12	15.8% (8.4% to 26%)	10	12.2% (6% to 21.3%)
Any severe systemic symptoms		2	2.6% (0.3% to 9.2%)	2	2.4% (0.3% to 8.5%)
Fever ≥38 °C		1	1.3% (0% to 7.1%)	1	1.2% (0% to 6.6%)

TABLE 22 Local and systemic reactions after the trivalent seasonal influenza vaccination, both age groups combined

Pandemic vaccine received in original study		Whole-virion vaccine		Adjuvanted vaccine	
Total vaccinated		*N* = 146		*N* = 156	
Number of diary cards available		*n* = 142		*n* = 153	
Measurement	**Level**	**Number**	**Percentage (95% CI)**	**Number**	**Percentage (95% CI)**
Pain	Mild	59	41.5% (33.3% to 50.1%)	66	43.1% (35.2% to 51.4%)
	Moderate	17	12% (7.1% to 18.5%)	26	17% (11.4% to 23.9%)
	Severe	1	0.7% (0% to 3.9%)	1	0.7% (0% to 3.6%)
	Any	77	54.2% (45.7% to 62.6%)	93	60.8% (52.6% to 68.6%)
Redness	1–24 mm	34	23.9% (17.2% to 31.8%)	38	24.8% (18.2% to 32.5%)
	25–49 mm	4	2.8% (0.8% to 7.1%)	10	6.5% (3.2% to 11.7%)
	≥ 50 mm	1	0.7% (0% to 3.9%)[a]	17	11.1% (6.6% to 17.2%)[a]
	Any	39	27.5% (20.3% to 35.6%)[a]	65	42.5% (34.5% to 50.7%)[a]
Swelling	1–24 mm	28	19.7% (13.5% to 27.2%)	28	18.3% (12.5% to 25.4%)
	25–49 mm	4	2.8% (0.8% to 7.1%)	9	5.9% (2.7% to 10.9%)
	≥ 50 mm	1	0.7% (0% to 3.9%)	6	3.9% (1.5% to 8.3%)
	Any	33	23.2% (16.6% to 31.1%)	43	28.1% (21.1% to 35.9%)
Any local	Severe	3	2.1% (0.4% to 6%)[a]	18	11.8% (7.1% to 18%)[a]
Any symptoms	Severe	7	4.9% (2% to 9.9%)	7	4.6% (1.9% to 9.2%)
Fever	≥ 38 °C	10	7% (3.4% to 12.6%)	14	9.2% (5.1% to 14.9%)

a $p < 0.05$ for comparison between vaccines.

TABLE 23 Relationship between reactogenicity and immune response. Effects of fever and severe local reactions on HI titre 3 weeks after trivalent seasonal influenza vaccination

		Whole-virion vaccine		Adjuvanted vaccine	
Variable	**Level**	**Fold effect (95% CI)**	***p*-value**	**Fold effect (95% CI)**	***p*-value**
Fever	≥ 38 °C	0.78 (0.42 to 1.43)	0.41	1.60 (1.06 to 2.42)	0.03
Severe local	Yes	1.28 (0.30 to 5.39)	0.73	1.92 (1.24 to 2.98)	0.004

Chapter 4

Discussion

Response to monovalent pandemic influenza vaccine

Nearly all children who received two doses of the $AS03_B$-adjuvanted split-virion H1N1 monovalent pandemic influenza vaccine had antibody titres deemed protective (HI titre ≥ 1 : 32, MN titre ≥ 1 : 40) 1 year later. Children who received two doses of the whole-virion vaccine had lower titres than recipients of the $AS03_B$-adjuvanted vaccine, both at 3 weeks after vaccination and at 1 year later.

One year after receipt of the $AS03_B$-adjuvanted vaccine, the HI geometric mean titre had waned to about 30% of the baseline titre recorded 3 weeks after vaccination. Although $AS03_B$-adjuvanted vaccine recipients had a greater percentage drop in HI geometric mean titre than children who had been given the whole-virion vaccine, their higher titres 3 weeks after vaccination led to higher titres 1 year later. A similar waning of antibody occurs after the trivalent influenza vaccine – in one study of children < 2 years old, the time taken for antibody to decay to one-half of the post-vaccination titre was calculated to be approximately 126 days for H1N1 and 258 days for H3N2.[20]

In the group of children who received the whole-virion vaccine at < 3 years of age, an unexpected finding was that the HI geometric mean titre was higher at 1 year than at 3 weeks after vaccination. In this group of children, one-third (23 out of 68) had a more than twofold rise in HI titre, with 10 out of 68 having a more than eightfold rise in titre (see *Table 6*). This might be due to asymptomatic natural boosting of antibody following encounter with the virus. Alternatively, it might be due to the occurrence of symptomatic influenza infection (vaccine failure). These children did not report influenza-like illness in the year since receiving the pandemic influenza vaccine, indicating that natural boosting by asymptomatic exposure to the virus is the likely explanation. Subclinical infection with the virus was widespread – a seroepidemiological study in England indicated that many more children were infected during the first wave of 2009 pandemic H1N1 infection than had been estimated from surveillance of clinical cases.[8] We postulated that children with a low HI titre after vaccination were susceptible to asymptomatic infection, with consequent natural antibody boosting, whereas those with high HI titres after vaccination were unlikely to become infected. Further analysis of our results showed that children who had a poor HI titre response to the whole-virion vaccine were those most likely to have a higher HI titre 1 year later. The subgroup of children (of all ages) who had an HI titre < 1 : 32 at 3 weeks after receiving the whole-virion vaccine had a greater geometric mean titre at 1 year than at 3 weeks after vaccination (see *Table 7*), suggesting that some of them may have had subclinical infection in the intervening period. By contrast, the subgroup who had an HI titre ≥ 1 : 32 at 3 weeks after receiving the whole-virion vaccine, had a lower geometric mean titre 1 year after vaccination, indicative of waning antibody.

Our additional analysis of the persistence of antibody, modelling the HI and MN titres 1 year after pandemic influenza vaccination (see *Tables 11* and *12*), found that children from the Exeter site had statistically significantly lower HI titres 1 year after pandemic influenza vaccination than children at other sites, even allowing for their lower titres 3 weeks after vaccination. The explanation for these findings is unclear. One hypothesis might be that children in Exeter were

less exposed to the virus than children at other sites, therefore having less pre-vaccination natural priming and less post-vaccination natural boosting. However, this hypothesis is not supported by serological evidence. Although it is known that influenza infection rates were highest during the second wave of the pandemic in two large metropolitan areas in England, London and the West Midlands, in other English regions rates did not differ from one another significantly.[8] Another hypothesis might be that the vaccines given in Exeter somehow differed from those given at the other sites. However, the batch numbers did not differ between sites and the Exeter vaccines were not subject to undue temperature deviation.

One year after receiving the whole-virion vaccine, fewer children had an MN titre ≥ 1 : 40 than had an HI titre ≥ 1 : 32, particularly in the younger age group. The HI titre specifically measures antibodies directed against the receptor-binding site of viral haemagglutinin, whereas the MN titre measures a broader range of neutralising antibodies.[21] It is currently unknown which antibody classes are predominantly detected by HI and MN assays, but experience with other sera which show discordance between HI and MN titres suggests that, in addition to detecting different antibody targets, the two tests might detect different antibody classes. This has been observed when comparing results from an HI assay with a single radial haemolysis technique – the latter appears unable to detect immunoglobulin A.[21] Expressed antibody class might affect the level of clinical protection. The HI assay is widely regarded as a surrogate measure for protection and is the assay used for licensure of influenza vaccines.[23,24] Correlation between MN titre and protection is less well documented. The threshold MN titre of 1 : 40 used in our analysis is speculative and was chosen because it is approximately fourfold greater than the MN titre observed in populations that have not been exposed to the virus or vaccinated against it.

Our findings in children are comparable with the results of a study of these two vaccines in adults, which also found the $AS03_B$-adjuvanted vaccine to be more immunogenic than the whole-virion vaccine.[25] Both vaccines were found to be statistically significantly more immunogenic in adults from 18 to 44 years of age than in older individuals. This study assessed the persistence of antibody 6 months after vaccination. In the 18- to 44-year-old group, 6 months after a two-dose regimen, 98% of the $AS03_B$-adjuvanted vaccine recipients had an HI titre ≥ 1 : 40, compared with 78% of the whole-virion vaccine recipients. In these adults, 6 months after vaccination, the HI geometric mean titre had declined to 41% of its post-vaccination value in those given the $AS03_B$-adjuvanted vaccine and to 90% of the post-vaccination geometric mean titre in those given the whole-virion vaccine.

Vaccine effectiveness, assessed shortly after vaccination, for the $AS03_B$-adjuvanted vaccine given to clinical risk groups in England was 77% (95% CI 11% to 94%) in children < 10 years old and 100% (95% CI 80% to 100%) in 10 to 24-year-olds, but considerably lower in older adults.[26] The vaccine was effective in preventing confirmed cases of pandemic H1N1 influenza infection from 7 days after vaccination.[27] A recent report provided estimates of the effectiveness of vaccination in preventing confirmed influenza A (H1N1) 2009 infection in the UK in the 2010–11 season.[28] The adjusted vaccine effectiveness was 34% (95% CI –10% to 60%) if vaccinated only with monovalent pandemic influenza vaccine during the 2009–10 season, 46% (95% CI 7% to 69%) if vaccinated only with trivalent influenza vaccine in the 2010–11 season and 63% (95% CI 37% to 78%) if vaccinated in both seasons. These data accord with our serological findings of waning antibody titre 1 year after receipt of a monovalent pandemic influenza vaccine, and also with our observation of effective boosting of antibody after a dose of the 2010–11 trivalent influenza vaccine.

Another oil-in-water adjuvant containing squalene, MF59, has been used in the formulation of influenza vaccines (Fluad® and Focetria®; Novartis, Marburg, Germany). Two doses of MF59-adjuvanted trivalent influenza vaccine given to children aged from 16 to 48 months resulted in

higher HI titres, both at 3 weeks and at 1 year after vaccination, than in children given two doses of non-adjuvanted trivalent seasonal influenza vaccine.[29] An MF59-adjuvanted monovalent pandemic H1N1 influenza vaccine given to 101 children (two-thirds of whom were born at gestational age < 36 weeks) from 6 to 23 months of age, resulted in an HI titre ≥ 1 : 40 in 94% after one dose, and 100% after two doses.[30] Antibody titres induced by a single dose of either $AS03_B$- or MF59-adjuvanted monovalent pandemic H1N1 influenza vaccine in immunocompetent children (from 6 months to 18 years old) were similar to HI and MN titres in unvaccinated children after natural infection.[31]

None of the 323 children enrolled in our study reported clinically significant adverse events related to vaccination with either of the novel pandemic influenza vaccines, although the study was clearly too small to detect very rare adverse reactions. An increase in the incidence of narcolepsy in 4- to 19-year-old children and adolescents was recently reported in Finland, which appears to be associated with previous receipt of the $AS03_B$-adjuvanted pandemic influenza vaccine.[32] This possible association has now also been reported in Sweden, France and Ireland, and is being investigated further.[33] Squalene-based adjuvants have been associated with autoimmune diseases in newborn rats.[34,35]

Response to trivalent seasonal influenza vaccine

Our data show that the 2010–11 trivalent seasonal influenza vaccine, given to children who had received the pandemic influenza vaccine 1 year earlier, produced a marked serological response to the H1N1 component of the vaccine. All children in the study had an HI titre ≥ 1 : 32 and an MN titre ≥ 1 : 40 3 weeks after a dose of trivalent seasonal influenza vaccine. Nearly all had at least a fourfold rise in MN titre and most had at least a fourfold rise in HI titre. All groups showed at least a 10-fold increase in HI geometric mean titre from a high baseline. This is similar to the fold increase in HI geometric mean titre seen after the first dose of trivalent influenza vaccine in children who have not previously received an influenza vaccine, although in these children the baseline titre was low.[36,37]

The additional analysis, modelling HI titres 3 weeks after receipt of the trivalent seasonal influenza vaccine (see *Table 17*), indicated that the HI titre 3 weeks after pandemic vaccination had a statistically significant effect on response to the trivalent influenza vaccine, but the HI titre immediately before giving the trivalent influenza vaccine did not. This might indicate that individuals who had a strong serological response to the monovalent pandemic influenza vaccine also tended to have a similar response to the trivalent seasonal influenza vaccine.

The trivalent seasonal influenza vaccine was well tolerated in this population of children. No serious adverse events occurred in the 3 weeks after vaccination. Reactogenicity to the trivalent seasonal influenza vaccine in our study was similar to that reported when trivalent vaccine was given to children who had not previously received an influenza vaccine.[36–38] In our study, redness and local reactions graded as severe were statistically significantly more frequent in children who had originally been given the $AS03_B$-adjuvanted pandemic vaccine at < 3 years of age than in those who had received the whole-virion vaccine. In young children, previous receipt of an $AS03_B$-adjuvanted vaccine seems to enhance local response to a dose of a non-adjuvanted vaccine given 1 year later. Our multivariable model indicated that fever and severe local reactions occurring after trivalent seasonal influenza vaccination were both associated with a greater serological response to the vaccine in children who had previously received the $AS03_B$-adjuvanted pandemic influenza vaccine, but not in those who had previously been given the whole-virion vaccine (see *Table 23*). The mechanisms by which oil-in-water adjuvants mediate their immunological effects remain poorly understood.[39]

After the trivalent vaccine, fever ≥ 38 °C was more commonly seen in children < 5 years old than in older children. It occurred in 18.3% of < 5 year old children who had previously received the $AS03_B$-adjuvanted pandemic vaccine and in 13.6% of those who had received the whole-virion vaccine, but in only around 1% of older children. In our study, children < 5 years old developed post-vaccination fever more frequently than the rate reported in one study of influenza vaccine naive children < 3 years old who were given their first dose of trivalent influenza vaccine, and in whom 4/65 developed a fever ≥ 38 °C.[40] In Australia, an increase in the incidence of febrile convulsions occurred in children < 5 years old shortly after being given 2010 seasonal influenza vaccine.[41] This was subsequently found to be associated with one brand of vaccine (Fluvax®; CSL Biotherapies, Parkville, VIC, Australia), but not with the other brands of trivalent vaccine being used in Australia.[42] Similarly, in the USA, an increased risk of febrile convulsions has been reported with Fluzone® (Sanofi Pasteur, Swiftwater, PA, USA).[43] No child in our study experienced a febrile convulsion after the trivalent seasonal influenza vaccine.

Study limitations

This study investigates the persistence of putative protective antibody levels. It does not examine vaccine effectiveness.

The recruitment rate for our follow-on study, 36% of those completing the original study, was lower than anticipated (between 40% and 60%), which slightly reduced the power of the study to detect differences between groups. This was in part due to the need to complete recruitment to the study rapidly, prior to the start of the 2010–11 influenza season. The original study recruited participants at a time of very high media and public interest in pandemic influenza. The follow-on study recruited during a quiescent phase, with relatively few new cases, when there was a much lower level of public interest.

One limitation of our study is that a two-dose regimen of pandemic influenza vaccine was used. Our original study was designed when a two-dose schedule was planned for children. However, the majority of children in the UK vaccinated with pandemic influenza vaccine during the 2009–10 campaign were only given one dose. It is likely that these vaccinated children will have somewhat lower residual antibody titres than the children in our study. Our original study did not investigate the serological response after just one dose of pandemic vaccine. In young adults, the HI geometric mean titre was 30% higher 3 weeks after a second dose of $AS03_B$-adjuvanted vaccine, and 23% higher after a second dose of whole-virion vaccine, than 3 weeks after a single dose of vaccine.[24]

The addition of a control group, comprising children not previously vaccinated with pandemic influenza vaccine, would have strengthened the study design. This would have enabled direct comparison of antibody levels in children who had received the pandemic vaccines with children who had not, providing more robust data about the serological effects of the vaccines. A control group was not included because of time and budget limitations.

Chapter 5

Conclusions

Nearly all children who received two doses of the $AS03_B$-adjuvanted split-virion pandemic H1N1 influenza vaccine had putative protective titres of antibody (HI titre ≥ 1 : 32, MN titre ≥ 1 : 40) 1 year later, although titres had waned. Children who received two doses of the whole-virion vaccine had lower titres, but many still had titres above the putative protective thresholds.

In children who had received either pandemic influenza vaccine 1 year earlier, the 2010–11 trivalent seasonal influenza vaccine produced a marked serological response to the H1N1 component of the vaccine.

Implications for health care

Children given two doses of pandemic influenza vaccines still have putative protective titres of antibody 1 year later, although persistence beyond 1 year remains unknown. In these children, administration of the trivalent vaccine, containing the pandemic strain as one component, effectively boosts antibody titre with an acceptable reactogenicity profile. The study provides serological evidence that a two-dose regimen of the $AS03_B$-adjuvanted pandemic influenza vaccine may be sufficient to maintain protection across two waves of the same strain of virus.

Recommendations for future research

The inclusion of $AS03_B$ adjuvant has resulted in an antigen-sparing vaccine producing a marked antibody response, which persists a year after vaccination. The inclusion of this adjuvant in future seasonal influenza vaccines might enhance immunogenicity, particularly in children < 3 years old, and this warrants further investigation. It would be interesting to assess whether or not previous receipt of the $AS03_B$-adjuvanted pandemic vaccine affected the serological response to the other two strains in the 2010–11 seasonal influenza vaccine. We propose to investigate this using stored serum. Further research is required to gain greater understanding of the immune response to $AS03_B$ adjuvant at a cellular level.

Assessment of the total duration of effective immunity after vaccination with either $AS03_B$-adjuvanted or whole-virion pandemic influenza vaccines will require further study. It would be useful to assess the persistence of antibody after a single dose of these vaccines. There should be continuing surveillance of the long-term safety profile of these novel vaccines, especially in view of recent concerns regarding an association with narcolepsy in some countries. It is still unknown why two particular brands of trivalent seasonal influenza vaccine appeared to increase the risk of febrile convulsions in children < 5 years old in Australia and the USA, whereas other brands have not been implicated. It would be valuable to obtain further information on vaccine effectiveness, derived from cohort studies. Another priority should be the elucidation of the correlation between MN titre and protection from disease.

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Contribution of authors

Dr Philip de Whalley (Clinical Research Fellow) contributed to design of the study, preparation of regulatory submissions, participant enrolment, data collection and interpretation. He drafted this report which has been reviewed by all the authors.

Dr Woolf Walker (Wellcome Trust Clinical Research Fellow, Paediatrics) contributed to the design of the study, participant enrolment and data interpretation.

Dr Matthew Snape (Consultant Paediatrician and Vaccinologist) contributed to the design of the study, preparation of regulatory submissions, participant enrolment and data interpretation. He was the principal investigator at the Oxford site.

Dr Clarissa Oeser (Clinical Research Fellow, Vaccines) contributed to participant enrolment and data collection.

Michelle Casey (Senior Research Nurse) contributed to participant enrolment and data collection.

Phoebe Moulsdale (Clinical Research Nurse) contributed to participant enrolment and data collection.

Caroline Harrill (Clinical Research Nurse) contributed to participant enrolment and data collection.

Nick Andrews (Senior Statistician) was responsible for statistical analysis and contributed to the design of the study and to data interpretation.

Katja Hoschler (Advanced Healthcare Scientist/Clinical Scientist) was responsible for laboratory analysis.

Ben Thompson (Project Manager) was responsible for project management and contributed to preparation of regulatory submissions.

Claire Jones (Postdoctoral Research Assistant) contributed to project management and was the laboratory liaison.

Jem Chalk (Software Developer/Computer Officer) was responsible for the computer database and contributed to data collection and analysis.

Simon Kerridge (Quality Assurance Manager) was responsible for data monitoring.

Dr Richard Tomlinson (Consultant Paediatrician) contributed to participant enrolment. He was the principal investigator at the Exeter site.

Dr Paul Heath (Executive Officer Paediatric Studies, Reader and Honorary Consultant Paediatrician) contributed to the design of the study, participant enrolment and data interpretation. He was the principal investigator at the St George's, London site.

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

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

Professor Elizabeth Miller (Head, Immunisation Department) contributed to the design of the study.

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

Publication

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Appendix 1

Protocol

Study Title:

A multi-centre, open-label, clinical, phase 4 trial, following on from a head-to-head comparison study of two H1N1 influenza vaccines in children, to compare firstly, the persistence of antibody against the A/California/7/2009 (H1N1) virus and secondly the immunogenicity and reactogenicity of one dose of a non-adjuvanted trivalent seasonal influenza vaccine, in children who had received a two-dose immunisation regimen of Celvapan or Pandemrix.

Short title:

Swine Flu (Influenza A H1N1) Follow on Vaccine Study

Internal Reference No: OVG 2010/03

Ethics Ref: OxREC A 10/H0604/81

EudraCT Number: 2010-022817-24

Date and Version No: 27th October 2010, Version 2

Investigators:	Andrew Pollard (Oxford) (Chief Investigator)
	Liz Miller (Health Protection Agency)
	Paul Heath (St Georges, London)
	Adam Finn (Bristol)
	Saul Faust (Southampton)
	Richard Tomlinson (Devon and Exeter)
	Matthew Snape (Oxford)
Sponsoring Institution	University of Oxford
Funder:	Department of Health
Signature	
	28/10/10

Sites/Centres:

Oxford Vaccine Group
Centre for Clinical Vaccinology and Tropical Medicine
Churchill Hospital
Oxford, OX3 7LJ
01865 857420

Health Protection Agency
Centre for Infections
61 Colindale Avenue
London
NW9 5EQ

University of Southampton Wellcome Trust Clinical Research Facility, Southampton University Hospitals NHS Trust, Tremona Road, Southampton, SO16 6YD.
023 8079 4989

St Georges Vaccine Institute
St Georges, University of London
Cranmer Terrace
London SW17 ORE

Bristol Children's Vaccine Centre
UBHT Education Centre
Upper Maudlin Street
Bristol
BS2 8AE

Royal Devon and Exeter NHS Foundation Trust
Barrack Road
Exeter
EX2 5DW

SYNOPSIS

Study Title	**A multi-centre, open-label, clinical, phase 4 trial, following on from a head-to-head comparison study of two H1N1 influenza vaccines in children, to compare firstly, the persistence of antibody against the A/California/7/2009 (H1N1) virus and secondly the immunogenicity and reactogenicity of one dose of a non-adjuvanted trivalent seasonal influenza vaccine, in children who had received either a two-dose immunisation regimen of Celvapan or Pandemrix**
Short Study Title	Head-to-head comparison of two H1N1 swine influenza vaccines in children aged 6 months to 12 years - an extension study
Internal ref. no.	OVG 2010/03
Clinical Phase	Phase IV
Trial Design	Follow-on study from a randomised control trial
Trial Participants	Children aged approximately 17 months to 14 years and 2 month
Planned Sample Size	Approximately 560
Planned Trial Period	October 2010 – March 2011
Primary Objectives	**1. Persistence of microneutralising antibody titres against H1N1v** To compare the percentage of children with microneutralisation (MN) titres ≥ 1:40, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix. **2. Immunogenicity of trivalent seasonal influenza vaccine** To compare the percentage of children who seroconvert and have a post-vaccination MN titre ≥1:40 or HI titre ≥1:32 (H1N1 strain) or who were seropositive at pre-vaccination and have a 4-fold increase in titre, following one dose of a non-adjuvanted seasonal trivalent influenza vaccine, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

	3. Reactogenicity of trivalent seasonal influenza vaccine To compare the percentage of children experiencing fever, local reactions and non-febrile systemic reactions within the 7 days following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix[a].
Secondary Objectives	**Persistence of antibody titres to H1N1v** To compare the percentage of children with HI titre ≥ 1:32 and the geometric mean HI and MN titres 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix. **Long-term safety monitoring of Pandemrix and Celvapan** Specific adverse events (influenza-like illnesses (ILI)[b], hospitalisations, febrile convulsions, autoimmunity[c] and adverse events of special interest (AESIs[d]) will be assessed in all participants. **To store serum** For future testing of the immunogenicity of trivalent seasonal influenza vaccine for H3N2 and B strains, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix. Also, should a drifted H1N1 strain emerge next season, this would provide a valuable source of sera to assess cross protection.

[a] The age of study participants will be 11-15 months older than in the original study.
[b] ILI defined, as per the Center for Disease Control and Prevention (CDC) definition, as "temperature of ≥37.8 °C and either cough or sore throat in the absence of a known cause other than influenza" (see reference 2).
[c] See Appendix E
[d] Neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain–Barré syndrome, Bell's palsy, demyelinating disorders, vaccination failure and narcolepsy – see section 8.1.10

	T cell Responses To study the T cell responses to internal influenza antigens and haemagglutinin (pandemic H1) **Genetics** To identify genes that are differently expressed following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.
Primary Endpoints	**1. Persistence of MICRONEUTRALISING antibody titres against H1N1v** The percentage of children with microneutralisation (MN) titres ≥ 1:40, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix **2. Immunogenicity of trivalent seasonal influenza vaccine** The percentage of children who seroconvert and have a post-vaccination MN titre ≥1:40 or HI titre ≥1:32 (H1N1 strain) or who were seropositive at pre-vaccination and have a 4- fold increase in titre, following one dose of a non-adjuvanted seasonal trivalent influenza vaccine, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix **3. Reactogenicity of trivalent seasonal influenza vaccine** The percentage of children experiencing fever, local reactions and non-febrile systemic reactions within the 7 days following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.
Secondary Endpoints	**1. Persistence of antibody titres to H1N1v** The percentage of children with HI titre ≥ 1:32 and the geometric mean HI and MN titres in children 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix

	2. Long-term safety monitoring of Pandemrix and Celvapan Specific adverse events (influenza-like illnesses (ILI), hospitalisations, febrile convulsions, autoimmunity and adverse events of special interest (AESIs) will be assessed in all participants. **3. T cell Responses** The T cell responses to internal influenza antigens and haemagglutinin (pandemic H1) **4. Genetics** The identification of genes differentially expressed in response to vaccination with the seasonal influenza strain.
Investigational Medicinal Products	Non-adjuvanted seasonal trivalent influenza vaccine - Fluarix® (GlaxoSmithKline Biologicals, Dresden, Germany)

1. ABBREVIATIONS

AE	Adverse event
AR	Adverse reaction
AESI	Adverse Event of Special Interest
CFI	Centre for Infections
CHMP	Committee for Medicinal Products for Human Use
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
HI	Haemaglutination Inhibition
HPA	Health Protection Agency
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference of Harmonisation

ILI	Influenza Like Illness
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
PI	Principal Investigator
PIL	Participant/ Patient Information Leaflet
R&D	NHS Trust R&D Department
RBC	Red blood cells
RDE	Receptor Destroying Enzyme
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

2. BACKGROUND

The first cases of pandemic influenza A (H1N1) 2009 infection were seen in Veracruz, Mexico, in March 2009 and spread rapidly, leading the World Health Organization to declare it the first global pandemic of this century on 11th June 2009. (3, 4) It is thought to have been responsible for 16226 deaths globally as of 21st February 2010.(5)

Children have been identified as a high priority group for immunization during a pandemic influenza outbreak for some time. This is for several reasons; they are effective vectors for disease transmission and have four times higher rates of infection and are hospitalized more frequently than adults.(6-8) This is due, at least in part, to the fact that children had no measurable previous immunity to pandemic H1N1 infection prior to the outbreak, even if in receipt of previous seasonal influenza vaccine.(9)

The UK Government purchased two pandemic influenza vaccines, Celvapan, a non-adjuvanted whole virion vaccine made by Baxter (Vienna, Austria) and Pandemrix™, an $AS03_B$/oil-in-water emulsion-adjuvanted ($AS03_B$) split-virion vaccine made by GlaxoSmithKline Biologicals (Rixensart, Belgium). For the UK national vaccination program the AS03-adjuvanted vaccine was used as the first line. The national vaccination program in children switched from including only high-risk children to all children under 5 years of age in November 2009, when a single dose schedule was also adopted.

In previous influenza pandemics, for example the Spanish Influenza pandemic of 1918, there have been significant second and third waves of pandemic influenza infection in subsequent influenza seasons.(10) It is uncertain which influenza viruses will be prevalent in the Northern Hemisphere in the 2010-2011 influenza season but there is significant concern over the likely reemergence of the A/California/7/2009 (H1N1) virus, the 2009 pandemic influenza strain, as the predominant cause of influenza infection. This is illustrated by the fact that the WHO have recently released their recommendation for which virus strains should be included in trivalent seasonal influenza vaccines for this period, and this includes the A/California/7/2009 virus (H1N1).(11) There are no published data, at present, assessing persistence of seroprotection against the A/California/7/2009 (H1N1) virus for any vaccines.

The immunogenicity and reactogenicity of seasonal influenza vaccines following previous use of adjuvanted or unadjuvanted pandemic influenza H1N1 vaccines are unknown. On 23rd March 2010 the Australian Government suspended routine immunization of children 5 years of age and under due to a suspected increase in febrile convulsion rates using trivalent unadjuvanted seasonal influenza vaccine (12) (13). A national evaluation of cases of fever with convulsions in young children following seasonal flu vaccination initially found no pattern of increased incidence of this side effect, other than higher numbers in Western Australia

(13), although more detailed analysis has now demonstrated similar small increases in the rate of febrile convulsions across all Australian jurisdictions (14). Almost all these additional reactions were caused by Fluvax® or Fluvax® Junior, manufactured by CSL, with an estimated rate of febrile convulsions with these vaccines of up to 9 in 1000 doses compared to less than 1 in 1000 estimated for Influvac® and Panvax® (14). On 1st June 2010 the suspension of the Australian paediatric seasonal influenza immunisation programme was confirmed until further notice (14).

3. RATIONALE FOR FOLLOW-ON STUDY

In Autumn 2009 we undertook a study assessing the safety and immunogenicity of a two-dose schedule of the two Influenza A (H1N1) vaccines purchased by the UK Government, the non-adjuvanted whole virion vaccine and the ASO3-adjuvanted split-virion, in children aged 6 months to 12 years of age. 937 children completed the study by protocol and the main findings were that the adjuvanted vaccine, while reactogenic, was more immunogenic especially in younger children (seroconversion in children under 3 years of age was 98.2% vs. 80.1%, p=0.001) (15).

Following events in Australia (13, 14), and regardless of the formal investigation outcome, it is imperative to study the reactogenicity of UK seasonal influenza vaccines in children who had previously received immunization with adjuvanted H1N1 vaccines. It would be particularly important to gain early information on the fever rates in young children in order to assess whether these are higher than expected and carry a potential risk of febrile convulsions.

It is also important to determine the immunogenicity of trivalent seasonal influenza vaccine in children previously given univalent pandemic influenza vaccine. There is emerging data that different priming strategies with adjuvanted or non-adjuvanted vaccines may lead to considerable differences in the response to subsequent influenza vaccines. In the head to head paediatric study (15) unpublished analyses show significantly lower immunogenicity in children who had received seasonal influenza vaccines in the past, despite the receipt of two doses of either Pandemrix or Celvepan. In addition, unpublished data from a manufacturer study suggests a negative effect of two doses of Pandemrix on immune responses to subsequent seasonal vaccine when given 3 weeks after the second dose (personal communication to E Miller from MHRA). Alternatively, as shown with pandemic H5N1 influenza vaccine, there may be a significant booster response to a subsequent dose following priming 6 or 14 months previously. (16) (17). However, this has not been demonstrated with either Pandemrix or Celvapan, and it is unknown how previous

vaccination with these vaccines will affect the immunogenicity of the H1N1 component of an unadjuvanted trivalent seasonal influenza vaccine given a year later.

We therefore propose a follow-on study to compare firstly, the persistence of antibody against the A/California/7/2009 (H1N1) virus after the use of these novel H1N1 influenza vaccines and secondly the immunogenicity and reactogenicity of one dose of a non-adjuvanted trivalent seasonal influenza vaccine in children, after receiving a two-dose immunisation regimen of either Pandemrix or Celvapan.

In previous pandemics, there have been further waves of infection in the subsequent influenza seasons, particularly when the pandemic strain has drifted antigenically. It is important therefore to study the persistence of antibody against pandemic influenza A (H1N1) infection in children, particularly those for whom seasonal influenza vaccine will not be recommended next year. Should a drifted H1N1 strain emerge next season, sera from children vaccinated in 2009 with the A/California/7/2009(H1N1) strain could be used to assess the likely cross protection to such a drifted strain. The existence of this unique cohort of almost 1000 children will allow information on antibody persistence to be generated for both the non-adjuvanted whole virion vaccine (Celvapan) or the ASO3-adjuvanted split-virion vaccine (Pandemrix) and would provide a valuable source of sera to assess cross protection in the event of emergence of a drifted strain.

We therefore propose a follow-on study to compare firstly, the persistence of antibody against the A/California/7/2009 (H1N1) virus after the use of these novel H1N1 influenza vaccines and secondly the immunogenicity and reactogenicity of one dose of a nonadjuvanted trivalent seasonal influenza vaccine in children, after receiving a two-dose immunisation regimen of either Pandemrix or Celvapan.

This follow-on study will also provide an important opportunity to provide data on the long term safety of the Pandemrix and Celvapan vaccines prior to enrolment in the follow-on study.

The study will use a non-adjuvanted trivalent seasonal influenza vaccine, Fluarix® (GlaxoSmithKline Biologicals, Dresden, Germany). It is approved by the EMEA for prophylaxis of influenza in all ages and has been marketed since 1987. It has consistently been shown to meet or exceed the regulatory criteria for immunogenicity against the three strains H1N1, H3N2 and B, and has a good safety profile.(18) Although the option of receiving this vaccine (and having a blood test to assess the immune response to this vaccine) will be offered to all participants in the study, participants (or parents/ guardians, on the participant's behalf) may decline to receive this vaccine and the second blood test. These

participants would still be eligible to take part in the study for the first blood test assessing the persistence of antibody from the original study.

Persistence of seroprotection will be assessed by both haemagglutination inhibition (HI) and microneutralisation (MN). Although EMEA guidelines for licensure of influenza vaccine are based on HI assays, the primary objective for this study uses MN titres as its measure. The decision for the preference of MN titres over HI titres was made based on recently published observations by the Centers for Disease Control and Prevention (CDC)(19, 20) and results from the Health Protection Agency's own analysis, which showed that the MN assay generally yields higher titres and detected more seroconversions to A/California/04/2009 than the HI assay (although both generally show high correlation). We therefore used MN titres as the primary outcome measure in the original NIHR funded study (Clinicaltrials.gov registration number: NCT00980850).(1)

The cellular immune response to influenza immunisation will be assessed in children where sufficient blood is available and local laboratory facilities permit. Elispot assays will be carried out using PBMCs isolated from the blood to determine the T cell response to internal influenza antigens, and haemagglutinin (pandemic H1, seasonal H1 and seasonal H3). Exploratory flow cytometry assays may also be used to determine whether the T cells are CD4+ or CD8+, and to examine cytokine secretion.

RNA expression profiles pre and post vaccination will be scrutinised in 20 participants in each group to elucidate genes that are differentially expressed in response to immunisation. This analysis could highlight genes of particular importance in vaccine responses. Furthermore, comparisons between RNA profiles and correlates of vaccine immunity may identify profiles which could be useful 'biomarkers' of vaccine induced cellular and humoral immunity in future studies.

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 objectives

1. Persistence of microneutralising antibody titres against H1N1v

To compare the percentage of children with microneutralisation (MN) titres ≥ 1:40, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

2. Immunogenicity of trivalent seasonal influenza vaccine

To compare the percentage of children who seroconvert and have a post-vaccination MN titre ≥1:40 or HI titre ≥1:32 (H1N1 strain) or who were seropositive at pre-vaccination and have a 4- fold increase in titre, following one dose of a non-adjuvanted seasonal trivalent influenza vaccine, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

3. Reactogenicity of trivalent seasonal influenza vaccine

To compare the percentage of children experiencing fever, local reactions and non-febrile systemic reactions within the 7 days following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

4.2 Secondary objectives

Persistence of antibody titres to H1N1v

To compare the percentage of children with HI titre ≥ 1: 32 and the geometric mean HI and MN titres 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

Long-term safety monitoring of Pandemrix and Celvapan

Specific adverse events (influenza-like illnesses (ILI)[e], hospitalisations, febrile convulsions, autoimmunity[f] and adverse events of special interest (AESI's[g]) will be assessed in all participants.

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[e] ILI defined, as per the Center for Disease Control and Prevention (CDC) definition, as "temperature of ≥37.8 °C and either cough or sore throat in the absence of a known cause other than influenza" (see reference 2).
[f] See Appendix E

To store serum

For future testing of the immunogenicity of trivalent seasonal influenza vaccine for H3N2 and B strains, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix. Also, should a drifted H1N1 strain emerge next season, this would provide a valuable source of sera to assess cross protection.

T cell Responses

To study the T cell responses to internal influenza antigens and haemagglutinin (pandemic H1).

Genetics

To identify genes that are differently expressed following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

5. TRIAL DESIGN

5.1 Summary of trial design

This is a follow-on, multi-centre, open-label, clinical, phase 4 trial to investigate:

a) The persistence of antibody against the A/California/7/2009 (H1N1) virus, 11-15 months after receiving a two-dose immunisation regimen of either a non-adjuvanted H1N1 vaccine (Celvapan, group 1) or the ASO3-adjuvanted H1N1 vaccine (Pandemrix, group 2).

b) The immunogenicity and reactogenicity of one dose of a non-adjuvanted seasonal trivalent influenza vaccine, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan (group 1) or Pandemrix (group 2).

The original NIHR funded study (NCT00980850)(1) evaluating the safety, tolerability and immunogenicity of the Celvapan (non-adjuvanted H1N1 vaccine) and Pandemrix (ASO3-adjuvanted H1N1 vaccine) in children was carried out in Autumn 2009.

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[g] Neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, vaccination failure and narcolepsy – see section 8.1.10

A summary of the follow-on trial can be seen in the study flowchart (Table 1).

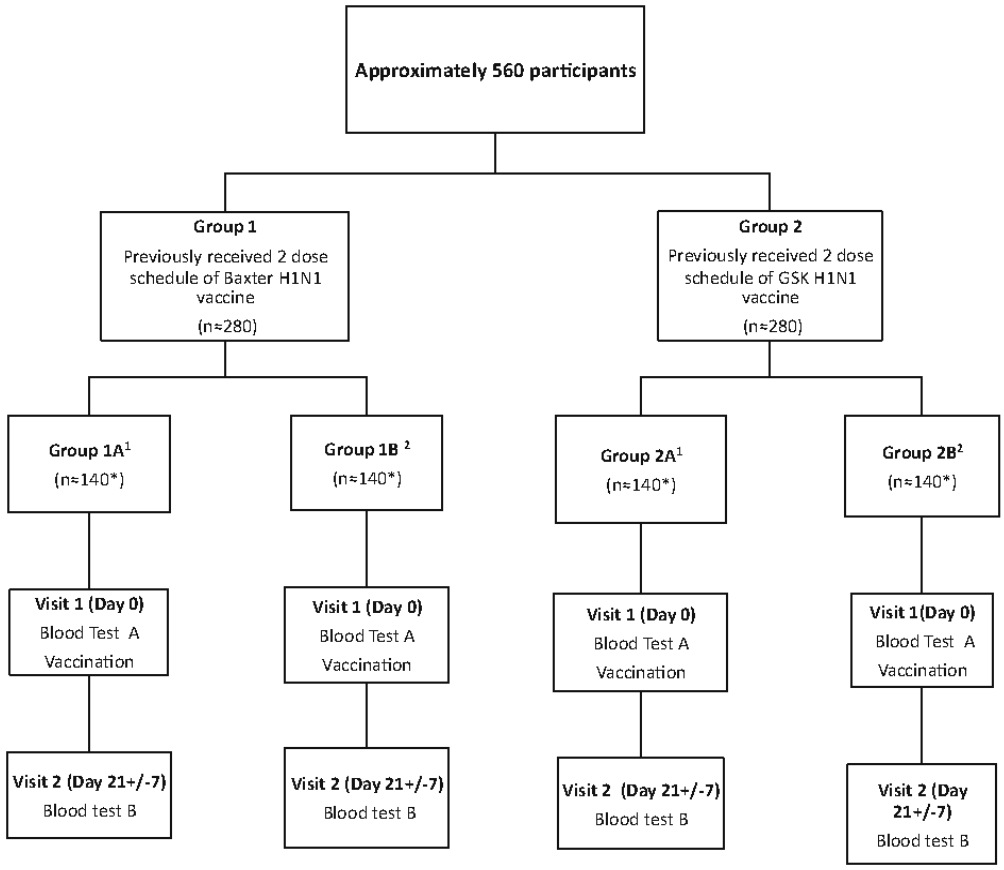

Table 1.

Group 1A and 2A: Aged between 6 months & 3 years old in original study. Group 1B and 2B: Aged between 3 & 12 years old in original study[h] Based on recruiting 66% of those who took part in original H1N1v vaccine study, see section 9.2 (sample sizes) for further details. Participants will be given the option of having a blood test alone at visit 1, or a blood test, immunisation with seasonal flu vaccine and second blood test at visit 2.

The children in groups 1 & 2 will be divided into two age groups (subgroups A & B) based on the age groups they were in during the original study (NCT00980850)(1), see footnote[h].

Table 1 shows groups and relationship of sample points. Blood A, taken at enrolment, will be used both to demonstrate persistence of antibody against the A/California/7/2009 (H1N1) virus and, for those participants receiving immunisation and a second blood test, as a baseline measurement to compare to Blood B. Blood B will be used to determine immunogenicity of a non-adjuvanted seasonal trivalent influenza vaccine in the different groups of children.

[h] The original study (See reference 1) divided the groups into those under and over 3 years of age. In this extension study we will use the original cohort of patients, 11-15 months after the initial immunisation.

5.2 Primary and secondary endpoints/outcome measures

5.2.1 Primary endpoints

1. Persistence of MICRONEUTRALISING antibody titres against H1N1v

The percentage of children with microneutralisation (MN) titres ≥ 1:40, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

2. Immunogenicity of trivalent seasonal influenza vaccine

The percentage of children who seroconvert and have a post-vaccination MN titre ≥1:40 or HI titre ≥1:32 (H1N1 strain) or who were seropositive at pre-vaccination and have a 4- fold increase in titre, following one dose of a non-adjuvanted seasonal trivalent influenza vaccine, 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

3. Reactogenicity of trivalent seasonal influenza vaccine

The percentage of children experiencing fever, local reactions and non-febrile systemic reactions within the 7 days following one dose of a non-adjuvanted seasonal trivalent influenza vaccine 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix**.**

5.2.2 Secondary endpoints

Persistence of antibody titres to H1N1v

The percentage of children with HI titre ≥ 1: 32 and the geometric mean HI and MN titres in children 11-15 months after receiving a two-dose immunisation regimen of either Celvapan or Pandemrix.

Long-term safety monitoring of Pandemrix and Celvapan

Specific adverse events (influenza-like illnesses (ILI), hospitalisations, febrile convulsions, autoimmunity and adverse events of special interest (AESIs) will be assessed in all participants.

T cell Responses

The T cell responses to internal influenza antigens and haemagglutinin (pandemic H1).

Genetics

The identification of genes differentially expressed in response to vaccination with the seasonal influenza strain.

5.3 Trial participants

5.3.1 Overall description of trial participants

We intend to recruit all interested participants who completed the original NIHR funded study (NCT00980850)(1) (n=937) into groups 1 & 2 outlined in table one above. It is anticipated that approximately 66% of these participants are likely to take part in this follow-on study; therefore the study population for groups 1 & 2 is likely to be approximately 560 children, refer to section 9.2 - sample sizes for further details. As the option of only having a blood sample taken at visit 1 will be made available to participants in this study, there will be two cohorts of participants: the 'persistence' cohort (consenting to the baseline blood test alone) and the 'booster' cohort (consenting to the baseline blood test, seasonal influenza vaccine and post-immunisation blood test).

5.3.2 Inclusion criteria

The participants must have completed the original NIHR funded study (NCT00980850)(1) comparing Celvapan with Pandemrix at one of the study sites participating in this follow-on study.

All participants must satisfy all the following criteria to be eligible for the study:

A parent/legal guardian has given written informed consent after the nature of the study has been explained;

Willingness to either

a) undertake a blood test at visit 1 ('persistence' cohort)

b) complete all study procedures ('booster' cohort)

5.3.3 Exclusion criteria

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

- Participant(s) in original study (NCT00980850)(1) who had a suspected unexpected serious adverse reaction (SUSAR).

- Participants in the original study (NCT00980850)(1) who did not receive two doses of H1N1 influenza vaccine
- Participants in original study (NCT00980850)(1) who received a third dose of H1N1 influenza vaccine due to an inadequate response to two doses.
- History of severe allergic reaction after previous vaccinations or hypersensitivity to any seasonal influenza 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
- Previous receipt of, or intent to immunize with, any other seasonal influenza vaccine(s) throughout the 2010/2011 influenza season.
- 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.

5.3.4 Temporary exclusion criteria

(Applicable to 'booster' cohort only.)

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

5.4 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 their final study visit (or following the scheduled date for this visit if this were not to be completed).
- Participants will potentially benefit by being offered immunisation with the seasonal influenza vaccine, for which they may not have been entitled if not taking part in the study. This year it will cover pandemic influenza A (H1N1) infection.

5.5 Study procedures

Participants will either have a single blood test taken at visit 1 (persistence cohort) or have a blood test and a dose of a non-adjuvanted seasonal trivalent influenza vaccine administered on visit 1, followed by a second blood test approximately 3 weeks later ('booster cohort'). For the latter cohort a diary card detailing local and systemic effects of the vaccine, any AEs and any medications used to treat these AEs and SAEs will be completed by parents/ guardians for the first week after first immunisation. For the remaining 2 weeks before the subsequent visit (visit 2) the diary card will then be used to record solicited adverse events persisting after the first week following immunisation and any medically significant adverse events occurring.

5.5.1 Recruitment and pre screening

Parents/guardians of participants who completed the original NIHR funded study (NCT00980850)(1) at the sites participating in this follow on study will be sent an invitation letter (by post or e-mail), or contacted by telephone, informing them that we are conducting a follow-on trial. At some centres, at the end of the original study, participant's families were informed of the possibility that they would be approached for a 'follow-on' study, and the opportunity to opt out of this provided. No one expressed that they would not be happy to be approach for this follow-on study. The invitation letter will invite them to take part and direct them to a specifically designed website. The website will allow the parents/guardians of participants to pre-screen themselves and register interest in taking part. Sites will have the option to telephone the parents/guardians of participants prior to sending out reminder cards, or to send out reminder cards without a prior telephone call. If used, reminder cards will be sent two to four weeks after the original invitation.

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.

5.5.2 Informed consent

A participant information sheet (in either paper or electronic form) will be provided to the participant's parent or legal guardian. At visit 1, a verbal version of the participant information will be presented to the participant's 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.

In addition to informed consent from the parent/legal guardian, for participation in the study assent will also be sought and documented for those aged over 7 years before any study specific procedures are performed

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.

5.5.3 Screening and eligibility assessment

On arrival at visit 1, prior to gaining full written consent for the trial, if verbal consent is given a local anaesthetic (Ametop or Emla) according to local practice at each site) will be applied to the candidate. This will be done for the families' convenience to save them time during the visit as, to be effective, the local anaesthetic cream, dependent on brand, needs to be applied for at least 30 minutes prior to venepuncture. This is the same procedure as took place in the original NIHR funded study (NCT00980850)(1) so participants will already understand the reason for this.

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: This will include history of asthma and details of any influenza-like illnesses (ILI), hospitalisations, febrile convulsions, autoimmunity and adverse events of special interest (AESI's)
- Concomitant Medication: All immunosuppressive medication and non-steroidal anti-inflammatory medications.
- Physical Examination.
- Axillary temperature (booster cohort only)

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 enrolled.

5.5.4 Baseline assessments

1. Perform blood draw collecting up to 7 ml in children under 3 years of age in the current study and 10ml in children ≥ 3 years of age[i].
2. Administer vaccination with a non-adjuvanted seasonal trivalent influenza vaccine. For all children administer 0.5 ml of vaccine.*
3. Record vaccination details in participant's 'red book' and/or the study vaccination card.*

[i] As opposed to the age group they were enrolled into in the original study.

4. Observe the participant for at least 20 minutes after vaccination for any immediate reactions.*
5. Fill out an 'unscheduled vaccination' form for the participant's Primary Care Trust.*
6. Fill out a notification to the participant's GP of the vaccine administered.*
7. Provide participant with study centre contact details (including 24 hour telephone advice line contact details for study staff member).
8. Instruct participant on notifying study centre of any serious adverse events/reactions.*
9. Instruct participants to use antipyretics only to treat fever or other adverse reactions, rather than prophylactically.*
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 any ongoing solicited reactions or doctor's visit/visit to Emergency Department from day 8 to the next visit.*
11. Provide the parent/guardian with local anaesthetic cream (Ametop or Emla according to local practice at each site) and instructions for use prior to visit 2 so that they can apply it to the child's skin in the appropriate amount of time prior to the visit.*
12. Schedule Visit 2, 21 (-7/+14) days after Visit 1.*

* Applicable to 'booster' cohort only

Visit 2

(Booster cohort only)

21 days (-7/+14 days) after visit 1 date.

1. If no local anaesthetic cream (Ametop or Emla according to local practice at each site) has been applied by parents prior to arrival then apply now.
2. Review diary card and 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 diary card).

3. Perform blood draw collecting up to 7 ml in children under 3 years of age in the current study and 10ml in children ≥ 3 years of age[j].

4. Give Feedback form and reply paid envelope to parents, to be returned anonymously.

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 (determined on an individual case basis by the clinical study team).

5.5.5 Blood sampling

The volume of blood samples obtained from infants less than 3 years of age will be up to 7 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. For children in the booster cohort the parent/guardian will be provided with the anaesthetic cream and instructions for use prior to Visit 2 so that they can apply it to the child's skin in the appropriate amount of time prior to the visit.

Wherever possible (depending on the volume of blood obtained from the participant), a minimum of 4ml of blood should be available for serological analysis. For children in the booster cohort (for whom it is anticipated that blood would be available following immunisation with seasonal influenza vaccine) additional T cell or RNA analyses may be performed at local sites according to blood volume and local capacity (see Table 2).

[j] As opposed to the age group they were enrolled into in the original study.

	Serology only	Serology and T cells* and/or RNA analysis**
4 – 7 ml obtained	All into serology	NA
≥7 ml obtained	All into serology tube	At least 4 ml for serology tube 3 ml into Heparinised tube (if T cell analysis being performed). 2.5 ml into PAX tube (if RNA analysis being performed)

Table 2: Allocation of blood samples at bedside.

* Approximately 100 participants will have T cell analyses performed at the Oxford site.

** At least 20 participants in each group will have RNA analyses performed.

Allocation into the serology only, serology and T cells or serology and RNA analysis subsets will depend on blood volume obtained at V1, local capacity and other logistical considerations (time and day of sampling etc). Enrolment into the T cell and RNA analysis groups is to be allocated and monitored locally (e.g. by controlling the number of T cell and RNA blood tube 'packs' distributed and used).

5.5.6 Diary card for recording local and systemic side effects

For the Booster cohort 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. They will be asked to bring the completed diary cards to visit 2. If the parents forget to bring the diary card they will be given a stamped addressed envelope in order to post the diary card back to the study site as soon as possible. The research staff will review the diary cards with the parents/ guardians at this visit and any discrepancies clarified at this time. The diary cards will be entered by site staff onto the study electronic database. Data clarification will occur at the local site, contacting the participant's parent or guardian where necessary.

5.5.7 Follow-up of sub-optimal vaccine responses.

Participants found to have MN titres below 1:40 or HI titres below 1:32 for Influenza A H1N1 will be offered an additional dose of the seasonal flu vaccine, to be arranged by the study sites. This will not form part of the study evaluations.

5.6 Laboratory methods

5.6.1 Serological analysis

Blood samples taken from participants will be stored at room temperature for up to 60 minutes, and then stored at 2ºC to 8ºC. 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 two aliquots for storage at or below -30ºC. One aliquot will be shipped to the Centre for Infections Virus Reference Department (VRD) for testing, the other aliquot should remain at the study site for storage. All samples will be analysed by microneutralisation (MN) and hemagglutination inhibition (HI) with the NIBRG121 virus (rg virus based on A California/7/2009 (vH1N1).

- **Microneutralisation (MN)**

  The Microneutralisation assay will only be performed for the analysis of serological responses to the pandemic H1N1 strain.

  A protocol has already been set up in the laboratory and data from the initial paediatric vaccine study shows that this assay is more sensitive (i.e. detects more 4-fold increases and generally higher GMTs) than the HI when analyzing seroresponses after vaccination with pandemic monovalent vaccine. However, MN is not routinely used for analysis of seasonal vaccines for several reasons:

  There is no defined correlate of protection for the MN, whereas such values are defined for HI and SRH. Secondly, this test is technically more demanding and time consuming than the HI. Lastly, the cross-reactivity between strains of currently circulating (seasonal) viruses and resulting pre-existing immunity complicates the development of specific and sensitive MN protocols and potentially confuses interpretation of results from vaccine trials.

  The Microneutralisation assay for measurement of responses to pandemic H1N1 influenza will be performed in 96- well format according to previously described protocols (20) and SOPs developed at RVU.

  - ***Serum pre-treatment***

Elimination of complement (e.g. from Fetal Calf Serum in culture medium) will be performed by incubation of study sera and appropriate quality control sera (provided and chosen according to test virus by 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.

- ***MN Test***

The MN analysis with the NIBRG121 virus will be performed as follows: A two-fold dilution series 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. We will routinely perform a 6-step dilution (covering titres 20 to 640), but will determine endpoint titres for each sample by further titrating those specimen that show titres> 640.

After neutralization, a suspension of MDCK cells will be added and the plates will be incubated for 16h at 37oC 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 OD 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.

- **Hemagglutination inhibition (HI)**

All sera will be analysed by HI using A/California/7/2009 (H1N1)-like virus (NIBRG121).The principle of the HI test is based on the ability of specific anti-influenza antibodies to inhibit hemagglutination of red blood cells (RBC) by influenza virus 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 SOP's established by RVU.

- ***Serum pre-treatment***

  Elimination of non-specific inhibitors will be performed 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).

  Preparation will be performed simultaneously for serum obtained pre- and post-vaccination.

- ***HI Test***

  For the HI analysis virus samples will be titrated in an 8-step two-fold dilution series, starting at a 1:8 dilution of serum sample (or quality control sera) and incubated with the HA antigen suspension (previously titrated to adjust the dilution at 4 HAU (Hemagglutination units)/25 µL; 50% endpoint). The HA 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 ½ hour for the turkey blood and 1h for the guinea pig blood at room temperature before reading.

- ***Reading***

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

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

Each serum sample is titrated in duplicate and individual titers 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.

- ***Reporting***

The collaborator(s) will receive results for both assays in form of an Excel table by email.

5.6.2 Assays of cellular immunity

Where sufficient blood is available (≥7ml, see Table 2), and depending on local facilities, Elispot assays will be carried out using PBMCs isolated from the blood to determine the T cell response to internal influenza antigens, and haemagglutinin from pandemic H1,seasonal H1 and seasonal H3. Exploratory flow cytometry assays may also be used to determine whether the T cells are CD4+ or CD8+, and to examine cytokine secretion

5.6.3 Genetics

In at least 20 participants in each group at the Oxford site, at the point of venepuncture, 2.5ml of the 7-10ml whole blood sample will be drawn into a PAXgene vacutainer and gently inverted. These samples will then be stable at room temperature and should be transported to the laboratory with 24 hours. The site laboratory will freeze these samples at -20°C to -70°C until time of RNA extraction and analysis. Allocation into the subgroup for this analysis is outlined in section 6.5.5.

5.7 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.

5.8 Discontinuation/ withdrawal of participants from study treatment

Notwithstanding the participant's being enrolled into the 'persistence' or 'booster' cohorts, each participant has the right to withdraw study at any time. The investigators recognise the need to respect the intention to treat population as much as possible, therefore will endeavor to keep consenting participants in the trial, according to their selected cohorts, as much as

reasonably possible. However, an 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

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.

5.9 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 (i.e., 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

The study will use a non-adjuvanted trivalent seasonal influenza vaccine, Fluarix®. It is approved by the EMEA for prophylaxis of influenza in all ages and has been marketed since 1987. It has consistently been shown to meet or exceed the regulatory criteria for immunogenicity against the three strains H1N1, H3N2 and B, have a good safety profile.(14) This season's influenza vaccine will include the A/California/7/2009 virus.

All children in the booster cohort will receive 0.5ml of vaccine.

The vaccine will be administered intramuscularly via a 23 gauge, 25 mm needle into the non-dominant upper arm.

6.2 Storage of study vaccine

The non-adjuvanted seasonal trivalent influenza vaccine will be supplied directly to the study sites by the manufacturer GlaxoSmithKline. As per MHRA advice, no clinical trial labels will be used. 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 manufacturer's recommendations must not be used unless the manufacturer 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 manufacturer.

6.3 Vaccine administration

The investigator will be responsible for the administration of the vaccine to subjects enrolled into the booster cohort 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 sponsor 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 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.

6.6 Concomitant medication

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

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 Medically significant adverse event

All adverse reactions taking place between Visit 1 and Visit 2 requiring medical consultation with the General Practitioner, Emergency Department, or leading to a subject's withdrawal (excluding pre-planned visits and GP or Emergency Department visits for routine medical care) will be considered to be medically significant adverse events. Adverse events solicited in the diary card that are ongoing after day 7 (as recorded in the diary card provided) will similarly be recorded in the CRF.

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.

7.1.4 Unexpected adverse reactions

An adverse reaction, the nature or severity of which is not consistent with the summary of product characteristics.

7.1.5 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.

7.1.6 Serious adverse event (SAE)

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

- Results in death,
- 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 including febrile convulsions. 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.

7.1.7 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.

7.1.8 Expected serious adverse events/reactions

No serious adverse events or reactions are expected.

7.1.9 Suspected unexpected serious adverse reaction (SUSAR)

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

7.1.10 Adverse event of special interest (AESI)

When taking the medical history adverse events of special interest that have occurred since participation in the original study will be determined. AESIs are those AEs previously recommended by the CHMP (Committee of Medicinal Products for Human Use) for inclusion as part of Risk Management Plans to be submitted with the Marketing Authorisation

Application for a Pandemic Influenza Vaccine (EMEA/359381/2009), i.e.: neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, and vaccination failure. AESI's are therefore only relevant for long term follow up from vaccine received in original study. In light of EMEA review of the relationship between Pandemrix and narcolepsy announced in August 2010, narcolepsy will also be considered an AESI.

7.1.11 Potentially immune mediated diseases (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 participant's 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 (17 month to day before 5th birthday).
  - malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication (5 to 14 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.

They will be asked to bring the completed diary cards to visit 2. The research staff will review the diary cards with the parents/ guardians at this visit and any discrepancies clarified at this time. Medically significant adverse events that have occurred in the period between visit 1 and visit 2 will be recorded on the CRF, whether or not these are attributed to the study medication. Adverse events solicited that are ongoing after day 7 will similarly be recorded in the CRF. The diary cards will be entered by site staff onto the study electronic database. Data clarification will occur at the local site, contacting the participant's parent or guardian where 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 11 below).

7.3 Reporting procedures for serious adverse events (SAEs)

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.

The CI will report all SUSARs to the sponsor, 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.

8. STATISTICS

8.1 Description of statistical methods

8.1.1 Dealing with those revaccinated due to being negative after two doses

Those revaccinated will be excluded from recruitment, but for persistence a random sample will be selected for inclusion and it will be assumed that their HI and MN titre would have remained the same as it was after two doses. The proportion selected will be set to be equal to the proportion of those who were not boosted who were recruited, this will enable an unbiased estimate of persistence to be calculated post vaccination.

8.1.2 Demographics

Demographic data (age, sex, study site, time since immunisation) will be tabulated for all participants (persistence and booster cohorts) and separately for these two cohorts.

8.1.3 Persistence

For persistence the following end points are used:

- HI seropositive: persistence titre >= 1 in 32
- HI geometric mean: persistence geometric mean calculated from logged antibody titres
- MN seropositive: persistence titre >= 1 in 40
- MN geometric mean: persistence geometric mean calculated from logged antibody titres– only if at least 80% non censored at the upper end

Each of these end points will be calculated for each group with 95% confidence intervals. Titres below the assay limits will be given a value of half the limit.

The proportions seropositive in groups 1 and 2 will be compared using Fisher's exact test both overall and by age group (A and B, corresponding to age less than 3 years or greater than/equal to three years in the original study). Geometric means will be compared between groups 1 and 2 by normal errors regression on logged antibody titres.

The above endpoints will be calculated for all participants (persistence and booster cohorts) and separately for the persistence and booster cohorts, with comparisons in these measures between the two cohorts made to ensure that the booster cohort is representative of the overall study population with regard to these endpoints.

Additional persistence analyses

For groups 1 and 2 proportions positive and logged antibody titres will be modelled in more detail to look at the effect of variables such as sex, study site, age at vaccination, time since vaccination, post second dose vaccination titre, pre first dose titre, previous seasonal influenza vaccination, interval between vaccine doses. The decline from post second dose can be modelled using the paired data by looking at the geometric mean fold change post primary to 9 months.

For both groups the effect of adjusting for age, sex, study site, and previous seasonal vaccination will be investigated using multivariable logistic and normal errors regression.

8.1.4 Long term safety

Long term safety assessments for groups 1 and 2 will be estimated as proportions with 95% CI's and compared between groups using Fisher's exact test.

8.1.5 Immunogenicity of trivalent seasonal vaccine

For these analysis the following definitions are used:

- HI seropositive: post vaccination titre >= 1 in 32
- HI seroresponse: post vaccination titre has at least a 4 fold rise from pre-vaccination and is >= 1:32
- HI geometric mean: post vaccination geometric mean calculated from logged antibody titres
- HI geometric mean fold rise: pre to post vaccination calculated from logged antibody titres
- MN seropositive: post vaccination titre >= 1:40
- MN seroresponse: post vaccination titre has at least a 4 fold rise from pre-vaccination and is >= 1:40
- MN geometric mean: post vaccination geometric mean calculated from logged antibody titres – only if at least 80% non censored at the upper end.
- MN geometric mean fold rise: pre to post vaccination calculated from logged antibody titres – only if at least 80% non censored at the upper end

Each of these end points will be calculated for each group with 95% confidence intervals. Titres below the assay limits will be given a value of half the limit.

Comparisons between groups 1 and 2 (and within age strata A and B) will be performed using Fisher's exact test. Post vaccination geometric mean HI and MN titres will be calculated.

Additional Immunogenicity of trivalent seasonal vaccine analysis

For groups 1 and 2 the effect of post second pandemic vaccine dose titres on post trivalent seasonal vaccine responses will be examined in multivariable models.

Other covariates will include age, sex, prevaccination titre, time to blood, study site, previous seasonal influenza vaccination and time since vaccination.

8.1.6 Safety of trivalent seasonal vaccine

End points for safety are as follows:

- Proportion with each local / systemic reaction from the diary card within 7 days post vaccination. These will be shown according to severity where the most severe level reached within the 7 days is used, see appendix A for full list of reactogenicity data being collected on diary cards.

95% confidence intervals will be calculated with stratification by age <5 years and ≥5 years (age in *current* study) for each group.

Comparisons of groups will be by Fisher's exact test using any severity and severe as the outcomes. Comparisons will be performed within age strata (<5, 5+ years of age in *current* study) and overall for redness, swelling, tenderness and fever.

8.2 Sample size

Based on the number of individuals who received two doses in the head to head trial and on possible recruitments rates the approximate numbers available in each group are shown below using the age splits of <3 / 3+ years and <5 / 5+ years (<3/ 3+ is the age range as per participant's age in the original study which will be used for immunogenicity analysis and <5/5+ is the age range at the time of the current study for the reactogenicity analysis).

	Recruitment rate				
Age	40%	50%	60%	66%	70%
<3	90	110	130	140	150
3+	100	120	140	160	170
total	190	230	270	300	320

	Recruitment rate				
Age	40%	50%	60%	66%	70%
<5	90	115	140	150	165
5+	90	115	140	150	165
total	180	230	280	300	330

8.2.1 Sample size tables

The scenarios of 50% and 66% recruitment will be considered for a reaction rate of 10% and for proportions positive of 50% (persistence) and 80% (post vaccination).

Table: Precision of estimates: 95% CIs around various percentages and sample sizes

	Percentage		
Sample Size	10%	50%	80%
90	5%-18%	39%-61%	70%-88%
100	5%-18%	40%-60%	71%-87%
110	5%-17%	40%-60%	71%-87%
120	5%-17%	41%-59%	72%-87%
140	6%-16%	41%-59%	72%-86%
160	6%-16%	42%-58%	73%-86%
180	6%-15%	42%-58%	73%-86%
230	6%-15%	43%-57%	74%-85%
300	7%-14%	44%-56%	75%-84%

So the proposed sample sizes enable reactions or proportions positive to be estimated to within between +/-5% to +/-10% depending on the observed percentage, recruitment rate and group being considered.

Table: Detectable differences - 66% recruitment scenario

Comparison	Percentage in first group	Percentage detectable as different below	Percentage detectable as different above
Group 1 (N=140) v 2 (N=140) age <3 (at time of original study)	10% 50% 80%	2% 33% 64%	23% 67% 92%
Group 1 (N=160) v 2 (N=160) age >=3 (at time of original study)	10% 50% 80%	2% 34% 65%	22% 66% 92%

Table: Detectable differences - 50% recruitment scenario

Comparison	Percentage in first group	Percentage detectable as different below	Percentage detectable as different above
Group 1 (N=110) v 2 (N=110) age <3 (at time of original study)	10% 50% 80%	1% 31% 62%	25% 69% 94%
Group 1 (N=120) v 2 (N=120) age >=3 (at time of original study)	10% 50% 80%	1% 31% 63%	24% 69% 93%

For the primary hypothesis comparing persistence in each age group 50% in one group would be detectable as different from about 67% in the other group. After vaccination 80% would be detectable as different from 92%. For other comparisons slightly larger differences are detectable.

8.3 The level of statistical significance

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

8.4 Criteria for the termination of the trial

The study uses the non-adjuvanted trivalent seasonal influenza vaccine, Fluarix®. It is approved by the EMEA for prophylaxis of influenza in all ages and has been marketed since 1987. It has consistently been shown to meet or exceed the regulatory criteria for immunogenicity against the three strains H1N1, H3N2 and B and to have a good safety profile. 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. 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.

8.5 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 four groups and other demographic characteristics will be compared.

8.6 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.

8.7 Study datasets

8.7.1 For persistence

All individuals recruited and with a blood sample taken at visit 1.

8.7.2 For immunogenicity of trivalent seasonal vaccine

Modified ITT: All individuals enrolled into the booster cohort vaccinated and with a post vaccination blood sample taken. This is the primary analysis for this objective

Per Protocol: All individuals vaccinated and with a post vaccination blood sample taken and with no major protocol deviations.

8.7.3 For safety of trivalent seasonal vaccine

Modified ITT: All individuals vaccinated and with at least one safety result.

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. 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 and the sponsor 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

In the very unlikely event that a participant suffered any harm during the duration of the trial, compensation for harm arising from the study vaccine would be provided by the vaccine manufacturer.

The sponsor will provide compensation from harm arising from participation in the study that is not due to the study treatment.

Negligent Harm: Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Non-Negligent Harm: Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the Research Subjects' participation in the trial for which the University is the Research Sponsor will be covered by the University of Oxford.

12. DATA HANDLING AND RECORD KEEPING

The Chief Investigator will have ultimate responsibility for management of data with responsibility for delegating the receiving, entering, cleaning, querying, analysing and storing all data that accrues from the study.

All study files (paper and electronic) with demographic and clinical details on the participants will be kept in a locked research office at each participating study centre. The study details will subsequently be entered on to a computer with an electronic database protected by a password. All blood samples will be identified by study number and study initials.

Information on study participants will be recorded on hard copy case report forms (CRFs) held locally to be entered into a web based electronic CRF (eCRF, OpenClinica™ database stored on a secure University of Oxford server). The eCRFs will include the following:

i. Subject contact details (to be retained locally)

ii. Inclusion and exclusion criteria

iii. Medical history

iv. Immunosuppressive treatment at study start

v. Each vaccination and each blood test

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

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

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 (by Oxford Vaccine Group and Health Protection Agency) to label all CRFs, diary cards, vaccine vials and blood sample tubes.

12.1 Web based eCRF

The investigators will enter the data into the volunteers' CRFs, which will be in a paper and/or electronic format (using an OpenClinica™ database stored on a secure University of Oxford server). As above, this includes safety data, laboratory data (both clinical and immunological) and outcome data. Data is entered in a web browser on PCs in the trial site building and then transferred to the OpenClinica Database by encrypted (Https) transfer.

OpenClinica is clinical trials software for electronic data capture (EDC) and clinical data management (CDM) which enables compliance with regulatory guidelines such as 21 CFR Part 11.

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.

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.

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APPENDIX A: Safety Data

Reactogenicity Data Collected in Diary Cards

- Percentage of children experiencing each of fever (≥ 38°C per axilla), local tenderness, local swelling or local erythema within the 7 days following one immunisation with the non-adjuvanted seasonal trivalent influenza vaccine in.
- Percentage of children experiencing each of: reduced feeding, reduced activity, irritability, persistent crying, vomiting or diarrhoea, receiving medication for pain or temperature within the 7 days following one immunisation with the non-adjuvanted seasonal trivalent influenza vaccine. (17 month to 5 year olds).
- Percentage of children experiencing each of: malaise, headache, nausea/ vomiting, diarrhoea, reduced appetite, muscle pain or joint pain, receiving analgesic/ antipyretic medication within the 7 days following one immunisation with the non-adjuvanted seasonal trivalent influenza vaccine (5 to 14 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

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

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).

APPENDIX B: Study timelines

Stage	Timing (Planned start date - second week in November (13th), depending on vaccine availability and regulatory approval)
Visit 1	Week 1 to 3
Visit 2	Weeks 3 to 7
Laboratory testing	Weeks 7 to 14
Analysis and initial report	Week 15 - 18
Completion of study for initial reporting	Week 18 (21st March 2011, if commence 13th November 2010)

APPENDIX C: STUDY 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
Ben Thompson:	Project Manager at OVG site
Philip de Whalley:	Research Fellow

Jenner Institute

Dr Sarah Gilbert:	Cellular immune response analysis

University of Southampton Wellcome Trust Clinical Research Facility

Dr Saul Faust:	Principal investigator at Southampton site
Dr Woolf Walker	Research Fellow
Michelle Casey	Senior Paediatric Research Sister
Emma Lim	Research Fellow

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
Dr Stephan Kohlhoff	Consultant Paediatrician
Nigel Butter	Research Nurse

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 Richard Tomlinson:	Principal Investigator at Royal Devon and Exeter

APPENDIX D: IMD

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

Event Category	Immune-Mediated Disorder	MedDRA PT
		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
		Encephalitis toxic
	Neuritis	Neuritis
		Cervical neuritis
		Mononeuritis
		Mononeuropathy multiplex
		Brachial plexopathy
		Radiculopathy
		Radiculitis
		Radiculitis brachial

Event Category	Immune-Mediated Disorder	MedDRA PT
		Radiculitis cervical
Musculoskeletal disorders	Systemic lupus erythematosus	Systemic lupus erythematosus
	Cutaneous lupus	Cutaneous lupus
	Sjögren'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

Event Category	Immune-Mediated Disorder	MedDRA PT
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
	Autoimmune haemolytic anaemia	Anemia haemolytic 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

Event Category	Immune-Mediated Disorder	MedDRA PT
	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

Follow on study of two swine 'flu vaccines in children

INFORMATION BOOKLET

You and your child are being invited to take part in a follow-on study to the Influenza A H1N1 (swine 'flu) vaccine trial of last year. 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 participating in this study.

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

Dear Parent/Legal Guardian,

Last year your child took part in a study comparing two different vaccines against Influenza A H1N1 (swine 'flu). We would like to thank you once again for taking part in this important study.

The Oxford Vaccine Group would now like to invite you and your child to participate in a follow-on study. This new study aims to find out how well the antibodies in your child's blood to the swine 'flu vaccine given last year have lasted. We would also like to assess your child's response to this year's "seasonal" 'flu vaccine, however you could still take part in the study even if you did not want your child to receive this. Just like last year, we will also monitor the side effects of the vaccine given. We would also like to ask you some questions about your child's health since we saw you last.

This booklet provides information about the follow-on study and what it would involve if your child were to take part. The 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). This study has been approved by the Oxfordshire Research Ethics Committee and the Medicines and Healthcare products Regulatory Agency (MHRA) and is funded by the Department of Health.

What is this study about?

In 2009 the World Health Organization (WHO) declared the Influenza A H1N1 (swine 'flu) outbreak the first global pandemic of this century. It is thought to have been responsible for 16,226 deaths globally as of 21st February 2010. We know from previous influenza outbreaks that the number of cases also tends to increase during the winter season of the years after a pandemic. There is concern that last year's pandemic influenza strain will return this winter and it has, therefore, been included in WHO's recommendations for seasonal influenza vaccine combinations. This study will assess the duration of the immune response to the H1N1 influenza vaccines given last year, and how children will respond to this year's seasonal trivalent influenza vaccine (which includes the H1N1 strain). Participating children would receive one dose of a licensed seasonal influenza vaccine and blood tests would be taken before and after vaccination. As in the original study, we would also ask you to complete a diary card to monitor any side-effects of the vaccine.

Taking part in this study is voluntary and, if you do not want your child to participate, you do not have to do anything.

What does the study involve?

The study consists of 2 visits occurring 3 weeks apart and involves 1 vaccination 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 <u>not</u> be able to take part in the study include:

- Having already received the seasonal influenza vaccine this autumn/winter
- History of egg allergy or allergic reaction after receiving the Influenza A H1N1 vaccine

- Problems with the immune system
- Bleeding 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
- Recent or current participation in another clinical trial
- Not being available for the study visits
- If they did not receive two doses of swine 'flu vaccine in last year's study
- If a third dose of the swine 'flu vaccine had been given (due to an inadequate response to the first two doses) in last year's study.

If your child was enrolled we would ask about any health problems since we saw them last and take a blood test to assess how well the immune response to the previous Influenza A H1N1 vaccine has lasted. If you were happy for your child to receive the seasonal influenza vaccine, we would give this, and a second blood test would be taken around 3 weeks later. For each blood test we would take 7 to 10 mls of blood (approximately 1½ to 2 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.

After the first visit, a diary card would be given to you to record daily temperatures and any reactions, such as redness or swelling at the injection site for 7 days. We would also ask you to record any visits to a doctor or the hospital from the time of vaccination until the second visit. We will collect the diary card at the second visit.

If you do not wish your child to receive the seasonal influenza vaccine, then it is still possible to take part in the study. In this case, we would take one blood test (to assess how well immunity from last year's vaccination has lasted).

How many participants are there in the study?

937 children in Oxford, Bristol, Exeter, Southampton and South London completed the original study and we hope that as many as possible would be able to take part in this follow-on study.

Which vaccine is going to be used in this study?

The study will use a licensed seasonal influenza vaccine, Fluarix® (produced by GlaxoSmithKline Biologicals, Dresden, Germany), which is designed to provide protection against three influenza strains: A H1N1, A H3N2 and B.

The table below summarises the study design; it is possible for participants to just have the blood test at Day 0 if that was preferred:

Day 0	Day 21 (3 weeks)
- Blood test - Seasonal influenza vaccine	- Blood test

What are the advantages of taking part in the study?

The study provides the opportunity for your child to receive the seasonal 'flu vaccine. This is not routinely given to healthy children in this country, although it is routine in some other countries and it may help provide protection against the strains of flu most likely to be circulating this winter, including swine 'flu. At the end of the study we will also be able to tell you whether your child is protected against influenza A H1N1 and will contact the families of those children who have not mounted a full response to the Influenza A H1N1 component of the vaccine. We will offer to arrange an additional dose of the seasonal 'flu vaccine for these children.

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

The trivalent seasonal influenza vaccine (Fluarix) is approved by the European Medicines Agency for prevention of influenza in all ages and has been available for use since 1987. It has consistently been shown to provide satisfactory immune responses against the influenza strains included in the vaccine, and has been shown to be safe. This vaccine does not contain live influenza virus and therefore cannot cause an influenza infection. Like all medicines, this vaccine may cause side effects in some individuals. More common side-effects (1-10% of those vaccinated) include headaches, sweating, muscle and joint pain, fever, feeling generally unwell, shivering, fatigue and local reactions (e.g. redness, swelling, pain, bruising and hardness). These events are generally mild and resolve within a few days. Very rare side-effects include an itchy rash (urticaria), blood vessel inflammation (vasculitis) which may result in skin rashes and in very rare cases temporary kidney problems, neurological disorders (e.g. Guillain-Barre syndrome), temporary reduction in the number of blood components (platelets) which can result in excessive bruising or bleeding (transient thrombocytopenia) and temporary swelling of the lymph nodes (glands) in the neck, armpits or groin. An increased risk of fever fits (febrile convulsions) following seasonal 'flu vaccine in children who had previously received a swine flu vaccine, has recently been described in Australia. This occurred in up to 9 in 1000 recipients (0.9%) of a particular influenza vaccine compared with a rate of less than 1 in 1000 (0.1%) with other seasonal 'flu vaccines. The vaccines used in Australia were different vaccines from those used in this study or the one your child took part in last year.

Finally, as with all vaccines there is the very small possibility of a severe allergic reaction (anaphylaxis). Your child would, therefore, be observed for at least 20 minutes after the vaccine is given; 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, and would be tested for the immune response to the swine 'flu virus. We would also ask your permission to use any remaining blood samples anonymously for future studies of immunity to infection. The stored blood samples will be anonymised before any further tests are performed so that it will not be possible to link the results of these extra tests back to your child. You will be asked to consent specifically for the storage of blood samples; if you are not happy for the samples to be stored and used for any other tests then you do not have to check this box on the consent form and it will not prevent you from taking part in the study. In this case your samples will be destroyed after testing for the influenza vaccine responses. Your

decision regarding the blood sample will not affect your child's participation in the influenza vaccine aspect of the study.

Also, for approximately 40 participants we will be asking for consent to use a small amount of the blood taken to study how your child's genetic code is 'read' when your child's immune system is responding to the influenza vaccine. As with the stored blood these genetic samples will be anonymised prior to testing, and if you did not want your child's blood to be tested in this way then you do not have to consent for this and can still take part in the main study. It is possible that blood samples or anonymised data may be sent outside the European Union for analysis.

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. 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 trivalent seasonal influenza vaccine. Any study records with your child's name and address would be held by the Oxford Vaccine Group only. Your child's first name will also be on the front of the diary card. We also plan to publish the results in a medical journal which will be accessible to the public, but will not contain any information that might allow children who took part to be identified by those reading it. At the end of the study, we will also write to all participating families to summarise the overall findings

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 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, 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, you should follow any advice from your GP or the government regarding influenza 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 on 01865 857420 (*ovg@paediatrics.ox.ac.uk)* 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 vaccine would be provided by the vaccine manufacturers. The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. NHS indemnity operates in respect of the clinical treatment with which you are provided.

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 will give you a "Feedback form", which you can fill in and return to us in a prepaid envelope. This is to give you the chance to tell us what you think we did well and whether you think there was anything we could do better in future. You will not be asked to write your name on this form, so we will not know who returned it.

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.

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

We would take a blood sample and collect relevant medical information.

If you are happy for your child to receive the seasonal influenza vaccine, we would also:

- Give one dose of this vaccine
- Collect a second blood sample, three weeks later
- Give you a diary card to record any possible side-effects after the vaccine
- Provide 24 hour telephone access to our study team, to discuss any concerns you may have following the vaccination.

What do I do now?

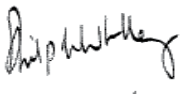
Participation in this study is voluntary. Please remember that you can withdraw your child from the study at any time without giving a reason. If you are interested in taking part, please visit the study website

http://www.paediatrics.ox.ac.uk/ovg/swineflu/, email us on (*ovg@paediatrics.ox.ac.uk*) or phone our appointment line on 01865 857420 to arrange a time to attend the Oxford Children's Hospital. Please remember to bring your child's health record (the 'red book') to your first visit. If you wish to discuss any element of the study further, then please contact us by e-mail (*ovg@paediatrics.ox.ac.uk*) or telephone 01865 857420.

Yours sincerely

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

Dr Matthew Snape
Consultant Vaccinologist
Honorary Consultant Paediatrician



Dr Philip De Whalley
Clinical Research Fellow

Mrs Tessa John
Clinical Team Leader

Appendix 3

Consent form

Follow on study of two swine 'flu vaccines in children – Consent Form

Child's full name:..... Study number: |____| |____| |____| |____|

If you agree with the statement, please initial the box next to it

I confirm that I have read the *Information booklet Influenza A H1N1 (Swine Flu) Vaccine Follow on Study Version 2 dated 26th October 2010.* 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, ORH NHS Trust and study monitors, where it is relevant to my child taking part in this research. I permit these individuals access to my child's research records. ☐

I understand that blood samples and data collected during the study may be sent outside the European Union ☐

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 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. ☐

Please initial ONLY ONE of the following statements:

EITHER I voluntarily agree to my child having one blood test ☐

OR I voluntarily agree to my child having one blood test and one dose of seasonal influenza vaccine, followed by a second blood test ☐

For children over 7 years of age:
The study has been discussed with my child and they are happy to participate. ☐

Please note that your child can still participate in the study whether or not you agree to the following statements:

I agree that a genetic sample from my child may be stored and analysed to help understand how my child's immune system responds to vaccines. ☐

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

Diary card for children under 5 years of age

Follow on study of two swine flu vaccines in children

CHILDREN UNDER 5 YEARS OF AGE 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

DOI: 10.3310/hta15450

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***		***If symptom was ongoing at day 7, please record the date this symptom resolved below***
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	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 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	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 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	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 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	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 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	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 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	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***		***If symptom was ongoing at day 7, please record the date this symptom resolved below***
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	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Maximum swelling (mm)																	
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 ____/____/____ _____:_____

If you need to see a doctor before the 2nd study visit, 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***		
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 No** **Yes No** **Home/Surgery** **Yes No** **Yes 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 No** **Yes No** **Home/Surgery** **Yes No** **Yes 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 No** **Yes No** **Home/Surgery** **Yes No** **Yes 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 No** **Yes No** **Home/Surgery** **Yes No** **Yes 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 No** **Yes No** **Home/Surgery** **Yes No** **Yes No**	Name: Start date: End date: Dosage:	(1st medicine) ____________ ____________ ____________ ____________	(2nd medicine) ____________ ____________ ____________ ____________

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 857420
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 bring it with you to your next visit.

Appendix 5

Diary card for children over 5 years of age

CHILDREN OVER 5 YEARS OF AGE 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***		***If symptom was ongoing at day 7, please record the date this symptom resolved below***
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	
	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 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	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***		***If symptom was ongoing at day 7, please record the date this symptom resolved below***
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	
	2	3	2	3	2	3	2	3	2	3	2	3	2	3	2	3	
Maximum swelling (mm)																	
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 ___/___/___ ____ : ____

DOI: 10.3310/hta15450

If you need to see a doctor before the 2nd study visit, 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***		
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:	(1st medicine) __________ __________ __________ __________	(2nd medicine) __________ __________ __________ __________

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 857420
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 bring it with you to your next visit.

Health Technology Assessment programme

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Director, Clinical Trials Research
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Professor of Old Age Psychiatry,
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Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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Principal Research Officer, Policy Research Programme, Department of Health

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Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Policy Research Programme, Department of Health

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Dr Simon Wright,
GP Partner, Walkden Medical Centre, Manchester

Observers

Dr Kay Pattison,
Senior NIHR Programme Manager, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Health Services and Public Health Services Board, Medical Research Council

Professor Tom Walley, CBE,
Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool

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Trust

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Learning, Peninsula Medical
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Professor of Public Health,
Division of Health in the
Community, University of
Warwick, Coventry

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GP Appraiser and Codirector,
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NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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