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

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Executive summary

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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.

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Publication

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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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