Study to evaluate an $AS03_B$/oil-in-water emulsion-adjuvanted split-virion vs non-adjuvanted whole-virion H1N1 influenza vaccine in children

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

CS Waddington,[1]* N Andrews,[2] K Hoschler,[2] WT Walker,[3] C Oeser,[4] A Reiner,[1] T John,[1] S Wilkins,[5] M Casey,[3] PE Eccleston,[6] RJ Allen,[6] I Okike,[4] S Ladhani,[2,4] E Sheasby,[2] P Waight,[2] AC Collinson,[5] PT Heath,[4] A Finn,[6] SN Faust,[3] MD Snape,[1] E Miller[2] and AJ Pollard[1]

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

*Corresponding author

Executive summary

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Executive summary

Background

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

Objectives

Immunogenicity

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

Reactogenicity

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

Methods

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

Results

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

Conclusion

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

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

Trial registration

This trial was registered as ISRCTN89141709.

Publication

Waddington CS, Andrews N, Hoschler K, Walker WT, Oeser C, Reiner A, *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.

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The National Institute for Health Research

The National Institute for Health Research (NIHR) has been established as a part of the Government's strategy, 'Best Research for Best Health'. It provides the framework through which the research staff and research infrastructure of the NHS in England is positioned, maintained and managed as a national research facility.

The NIHR provides the NHS with the support it needs to conduct first-class research funded by the Government and its partners alongside high-quality patient care, education and training. Its aim is to support outstanding individuals (both leaders and collaborators), working in world-class facilities (both NHS and university), conducting leading-edge research focused on the needs of patients.

This themed issue of the *Health Technology Assessment* journal series contains a collection of research commissioned by the NIHR as part of the Department of Health's (DH) response to the H1N1 swine flu pandemic. The NIHR through the NIHR Evaluation Trials and Studies Coordinating Centre (NETSCC) commissioned a number of research projects looking into the treatment and management of H1N1 influenza.

NETSCC managed the pandemic flu research over a very short timescale in two ways. Firstly, it responded to urgent national research priority areas identified by the Scientific Advisory Group in Emergencies (SAGE). Secondly, a call for research proposals to inform policy and patient care in the current influenza pandemic was issued in June 2009. All research proposals went through a process of academic peer review by clinicians and methodologists as well as being reviewed by a specially convened NIHR Flu Commissioning Board.

The final reports from these projects have been peer reviewed by a number of independent expert referees before publication in this journal series.

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Reports are published in the HTA journal series if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reports in this themed issue were funded through the Cochrane Collaboration; the Health Services Research programme (HSR); the Health Technology Assessment programme (HTA); the Policy Research Programme (PRP); the Public Health Research programme (PHR); and the Service Delivery and Organisation Programme (SDO).

The Cochrane Collaboration is an international not-for-profit and independent organisation, dedicated to making up-to-date, accurate information about the effects of health care readily available worldwide. It produces and disseminates systematic reviews of health-care interventions and promotes the search for evidence in the form of clinical trials and other studies of interventions. Cochrane reviews and the Cochrane Central Register of Controlled Trials are published and updated in *The Cochrane Library* (www.cochranelibrary.com).

The HSR programme aims to lead to an increase in service quality and patient safety through better ways of planning and providing health services. It funds both primary research and evidence syntheses, depending on the availability of existing research and the most appropriate way of responding to important knowledge gaps.

The HTA programme produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The PRP provides the evidence base for policy development on public health and social care issues. It funds research in three main ways: 5-year programmes of research in 16 research units, a primary-care research centre, a public health research consortium, and a surveillance unit; programmes of interlinked studies on key policy initiatives; and single projects and literature reviews.

The PHR programme evaluates public health interventions, providing new knowledge on the benefits, costs, acceptability and wider impacts of non-NHS interventions intended to improve the health of the public and reduce inequalities in health. The scope of the programme is multi-disciplinary and broad, covering a range of interventions that improve public health.

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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. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the Department of Health.

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