A randomised comparison of a two-dose regimen of Baxter and GSK H1N1 pandemic vaccines

A randomised, partially observer-blind, multicentre, head-to-head comparison of a two-dose regimen of Baxter and GlaxoSmithKline H1N1 pandemic vaccines, administered 21 days apart

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Executive summary

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Executive summary

Background

Vaccination is potentially the most effective means of mitigating pandemic influenza. Trials of H5, H7 and H9 vaccines were carried out during the last decade in response to an epizootic of H5 influenza and transmissions of H5, H7 and H9 influenza to man. Despite differences between these trials in vaccine formulation and assays used to assess immunogenicity, general conclusions from the data led in 2009 to the purchase by the UK Department of Health (DH) of whole-virion (WV) H1N1 vaccine and a squalene-containing, split-virion vaccine in response to the H1N1 pandemic. Both formulations had been investigated as H5 vaccine in trials involving thousands of people, but they had not been compared head to head. It was unclear whether they would be equally immunogenic or tolerated equally well.

Objectives

To evaluate the immunogenicity of a two-dose schedule of Baxter cell-cultured, non-adjuvanted, WV H1N1 vaccine, and GlaxoSmithKline $AS03_A$-adjuvanted, split-virion H1N1 vaccine, with respect to the EU Committee for Human Medicinal Products for Human Use (CHMP) and the US Food and Drug Administration (FDA) licensing criteria.

Setting

Three teaching hospitals in the UK (Leicester Royal Infirmary, Leicester; Nottingham City Hospital, Nottingham; and Royal Hallamshire Hospital, Sheffield).

Participants

Three hundred and forty-seven subjects were identified and randomised to receive $AS03_A$-adjuvanted split-virion H1N1 or WV vaccine in age groups [≥18–44 years ($n = 140$); ≥45–64 years ($n = 136$) and ≥65 years ($n = 71$)].

Interventions

Vaccine was administered by intramuscular (IM) injection into the deltoid muscle of the non-dominant arm. One hundred and seventy-five randomised subjects were allocated $AS03_A$-adjuvanted split-virion H1N1 vaccine; 169 subjects had a second dose of the same vaccine 21 days later. One hundred and seventy-two subjects were allocated WV vaccine; 171 subjects had a second dose of the same vaccine 21 days later. Serum samples for antibody measurements were collected on days 0 (before the first vaccination), 7, 14, 21 (before the second vaccination), 28, 35, 42 and 180. Subjects were observed for local and systemic reactions for 30 minutes after each injection, and for the next 7 days they recorded, in self-completed diaries, the severity of solicited local (pain, bruising, erythema and swelling) and systemic symptoms (chills, malaise, muscle aches, nausea and headache), oral temperature and use of analgesic medications.

Main outcome measurements

Vaccine immunogenicity using the CHMP and the FDA licensing criteria. Antibody titres were measured using haemagglutination inhibition (HI) and microneutralisation (MN) assays at baseline and 7, 14 and 21 days after each vaccination and at day 180. The three immunogenicity criteria end points were the seroprotection rate, the seroconversion rate and the mean-fold titre elevation.

Results

Both vaccine doses were given in 340 subjects (98%). Data from 680 (99%) of 687 issued diary cards were returned. Sera were obtained from 340 (98.0%), 333 (96.0%), 341 (98.3%), 331 (95.4%), 329 (94.8%) and 332 (95.7%) subjects on days 7, 14, 21, 28, 35 and 42, respectively. Three hundred and forty-six and 345 subjects were included

in the safety and immunogenicity analyses. Prevaccination antibody was detected by HI (titre ≥1 : 8) and MN (titre ≥1 : 10) in 14% and 31% of subjects, respectively. Among the 298 (85.9%) subjects without baseline antibody on HI assay, a titre of ≥1 : 40 (seroprotection) was achieved after a single dose of $AS03_A$-adjuvanted split-virion and WV vaccine by day 21 in 93.0% and 65.5%, respectively, of subjects between 18 and 44 years, 76.4% and 36.1% of subjects aged between 45 and 64 years, and 53.1% and 30.0% of subjects ≥65 years. Among all 347 subjects, ignoring baseline antibody status, a titre of ≥1 : 40 was achieved after a single dose of $AS03_A$-adjuvanted split-virion and WV vaccine by day 21 in 94.0% and 71.4%, respectively, of subjects aged between 18 and 44 years, 77.3% and 38.8% of subjects aged between 45 and 64 years, and 51.4% and 32.4% of subjects aged ≥65 years. The age-adjusted odds ratio (OR) for adjuvanted vaccine compared with WV vaccine, in terms of seroprotection, was 4.42 [95% confidence interval (CI) 2.63 to 7.44, $p < 0.001$]. Among all 347 subjects, one dose of adjuvanted vaccine satisfied all three CHMP criteria. One and two doses of WV vaccine satisfied two criteria. Among all subjects, seroprotection rates increased significantly from day 21 levels following the second dose of adjuvanted vaccine (18–44 years, from 94% to 100%; 45–64 years, from 77.3% to 90.8%; ≥65 years, from 51.4% to 80.6%; all ages, from 78.2% to 92.1%), but not after WV vaccine (18–44 years, from 71.4% to 77.6%; 45–64 years, from 38.8% to 45.3%; ≥65 years, from 32.4% to 47.1%; all subjects, from 50.9% to 58.8%). At day 42, the age-adjusted OR for adjuvanted split-virion compared with WV vaccine, in terms of seroprotection, was 11.21 (95% CI 5.80 to 21.64, $p < 0.001$). Among all 347 subjects, seroprotection was attained more rapidly with adjuvanted split-virion vaccine than the WV vaccine with seroprotection occurring in 52.9%, 79.4%, and 78.2% of subjects of all ages on days 7, 14 and 21, respectively, after the first dose of adjuvanted split-virion vaccine, and in 27.1%, 47.6%, and 50.9%, respectively, after WV vaccine. In all subjects, seroprotection was significantly increased at 6 months on adjuvanted split-virion vaccine (82.5%) compared with WV vaccine (59.4%) and the age-adjusted OR was 4.29 (95% CI 2.43 to 7.56, $p < 0.001$). Age-related decline in antibody response occurred after both doses of both vaccines, even 6 months after vaccination. WV vaccine was associated with fewer local and systemic reactions than $AS03_A$-adjuvanted vaccine. The most frequent solicited local event was pain, reported by 28% and 76% of subjects after either dose of WV or adjuvanted split-virion vaccine, respectively (OR 7.71, 95% CI 4.48 to 13.24, $p < 0.0001$). The most common systemic event was myalgia, reported by 24% and 49% of subjects after either dose of WV or adjuvanted vaccine (OR 2.99, 95% CI 1.86 to 4.80, $p < 0.0001$).

Conclusions

The $AS03_A$-adjuvanted split-virion 2009 H1N1 vaccine is more immunogenic and provides greater antigen-sparing capacity than the WV 2009 H1N1 vaccine. The adjuvanted vaccine satisfies more CHMP criteria than the WV vaccine. Seroprotection is attained more rapidly with adjuvanted split-virion vaccine than WV vaccine. A second dose of adjuvanted split-virion vaccine increases seroprotection rates more than WV vaccine. The WV vaccine is associated with fewer local and systemic reactions than the adjuvanted vaccine, but, as judged by our findings, the adjuvanted split-virion vaccine is better overall. A single-dose strategy provides potentially greater public health benefits than delivery of two doses to one-half of the population, but a two-dose strategy should be considered for the elderly.

Implications for the NHS

The decision by the DH to purchase and distribute AS03-adjuvanted split-virion vaccine as the key vaccine for adults and to implement the national immunisation programme using a one-dose regimen was justified by the findings in this study. However, a two-dose regimen with AS03-adjuvanted split-virion vaccine should be considered for the elderly due to improved seroprotection rates after the second dose. The study identified differences between vaccines in the frequency of self-reported symptoms, but the majority of symptoms after either formulation were described as mild or moderate, and there was extremely high uptake of the second dose of the more immunogenic and more reactogenic AS03-adjuvanted split-virion vaccine. Many vaccinees had antibody levels associated with protection at 6 months, indicating that pandemic vaccination has the potential to provide durable immunity, possibly extending through successive pandemic waves of the same virus. Vaccination should remain the mainstay of plans to mitigate pandemic influenza. Manufacturers and regulators should strive to accelerate vaccine production and licensure, and the NHS needs to increase vaccine uptake.

Recommendations for future research

Pandemic H1N1 is still circulating globally and is likely to undergo antigenic drift in the near future. Further analyses of sera collected during this study are required to establish whether either vaccine is associated with a broad immune response capable of offering protection against drift variants. A profound age-related response to vaccination was identified in this study with lower antibody responses occurring with increasing age. Neither vaccine could completely compensate for this age-related decline in immunogenicity, which may be attributable to immunosenescence and possibly previous encounters with ancestral virus or vaccines. Further work on understanding the aetiology and enhancing immune responses to influenza vaccine in the over-45-year-olds is required. Work should also be carried out to establish whether the immunostimulatory effects and reactogenicity of oil-in-water adjuvants can be disentangled. A striking feature of this pandemic was the excellent antibody response of young adults to a single dose of vaccine, which contrasts with the experience from studies of H5, H7 and H9 vaccines. Work that provides a clearer understanding of why a two-dose strategy appears necessary against these avian strains might lead to better vaccines to mitigate a future pandemic.

Trial registration

This study is registered as ISRCTN92328241.

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The National Institute for Health Research

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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 or, in the case of this national priority, the NIHR, 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).

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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.

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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' reports and would like to thank the referees for their constructive comments on the five draft documents. 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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