Institution: The University of Oxford

Unit of Assessment: 1

Title of case study:

PREVENTING THE SPREAD OF H1N1: IMMUNISATION TRIALS IN UK CHILDREN

Summary of the impact:

Clinical Trials undertaken by the Oxford Vaccine Group led to the recommended immunisation of three million UK children during the 2009 H1N1 influenza pandemic. This research was also used to inform World Health Organization (WHO) global policy. The 2009 H1N1 influenza pandemic, or "Swine Flu", was first identified in April 2009 and declared a pandemic by the WHO in June 2009. After acquiring two novel flu vaccines for the 2009 H1N1 influenza virus, the UK government approached the Oxford Vaccine Group to provide paediatric data on the safety of each vaccine. Rapidly recruiting 943 children to the study, the Group delivered essential data to the Department of Health prior to the onset of the winter influenza season. In August 2010, the WHO declared the H1N1 pandemic over.

Underpinning research:

The 2009 H1N1 influenza pandemic was a devastating world health crisis. It claimed the lives of over 294,500 people globally between 2009 and 2010.

In autumn 2009, just months after H1N1 flu was declared a pandemic, two novel influenza A H1N1 vaccines were supplied to the United Kingdom prior to the winter influenza season. Both vaccines differed in crucial aspects from the standard 'seasonal' influenza vaccines used each season. One, known as the 'split-virion' vaccine (Pandemrix), was the first licensed vaccine to contain a new adjuvant (AS03B), while the other (Celvapan) was made from an inactivated version of the whole virus, rather than virus sub-units. Both vaccines were designed to improve immunogenicity, but potentially would increase the rates of adverse reactions. Due to the urgent need for effective vaccines against the H1N1 virus, both Pandemrix and Celvapan had been licensed for use without having ever been administered to children – one of the highest risk groups and primary transmitters of influenza infection. Accordingly, the UK Scientific Advisory Group for Emergencies (UK-SAGE) identified an urgent need to obtain paediatric data on the immunogenicity and reactogenicity and other adverse effects of these vaccines before the expected influenza season in December. This was judged a national priority.

In view of its extensive experience with paediatric vaccine studies the University of Oxford's Oxford Vaccine Group was approached to lead an urgent clinical trial to provide essential data on the safety and efficiency of these vaccines in children. With protocol development, ethical, NHS and regulatory approval all 'fast-tracked', recruitment of the first participant came in late September – just five weeks after provisional funding approval was granted[1].

Five weeks later 943 children aged between six months and 12 years were recruited across five sites. Children received two doses of either the split-virion or whole-virion vaccine, and blood tests were taken prior to and three weeks after the immunisation course. Parents mailed diaries recording immunisation reactions to study sites to allow rapid acquisition of these data. Crucially, by mid-November the study team provided the Department of Health with an interim analysis demonstrating that both vaccines were well tolerated by most children. Immunisation with either vaccine induced antibody levels above the correlates of protection in most children, however the split-virion vaccine was the more immunogenic. In children under 3 years of age antibody concentrations were over ten times higher following immunisation with the split-virion vaccine than

the whole-virion vaccine[2, 3]. Surprisingly, children previously immunised with seasonal influenza vaccines had a lower response to the 'swine-flu' vaccines than influenza vaccine-naïve participants[4].

The following year the NIHR funded a 'follow-on' study, demonstrating that 98% of children receiving the split-virion vaccine maintained Influenza A H1N1 antibodies above the threshold of protection one year after immunisation, compared with only 51% of children receiving the whole-virion vaccine[5,6]. This showed that the administration of a seasonal influenza vaccine was safe and immunogenic and confirmed the superiority of the Pandemrix vaccine.

References to the research:

1. Pollard AJ et, al. Expediting clinical trials in a pandemic. *BMJ.* 2009; **339**: 1099 – 1100. doi:10.1136/bmj.b4652 ***Letter outlining the benefit of an expedited approval process in obtaining rapid data in an influenza pandemic.***

2. Waddington CS et, al. Safety and immunogenicity of AS03B adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study. *BMJ* 2010; **340**:c2649. doi:10.1136/bmj:c2649 ***Manuscript reporting results of the head to head pandemic influenza vaccine study. This article has been cited 67 times in the 2 years since publication (source Harzing's Publish or Perish).***

3. Waddington C 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**:1-130. doi:10.3310/hta14460-01 ***Extended report on the head to head pandemic influenza vaccine study included in themed H1N1 influenza and Pandemic flu publication by NIHR HTA.***

4. Andrews NJ et, al. Predictors of immune response and reactogenicity to AS03B-adjuvanted split virion and non-adjuvanted whole virion H1N1 pandemic influenza vaccines. *Vaccine.* 2011; **29**: 7913-9. doi:10.1016/jvaccine.2011.08.076 ***Additional analysis of predictors of immunogenicity in the influenza vaccine study.***

5. Walker WT et, al. H1N1 antibody persistence 1 year after immunization with an adjuvanted or whole-virion pandemic vaccine and immunogenicity and reactogenicity of subsequent seasonal influenza vaccine: a multicenter follow-on study. Clin. Infect Dis. 2012 (Epub Jan 19 ahead of print). doi:10.1093/cid/cir905. ***Manuscript reporting results of the 'follow-on' study.***

6. de Whalley P et, al. A 1-year follow-on study from a randomized, head-to-head, multicenter, open-label study of two pandemic influenza vaccines in children *Health Technology Assessment*. 2011; **15**:1 – 128. doi:10.3310/hta15450 ***Extended report of results from the 'follow-on' study.***

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Details of the impact:

In the autumn of 2009 public health officials in the United Kingdom were faced with an emerging influenza A H1N1 pandemic with the potential to overwhelm the NHS. One of the most effective methods of controlling the pandemic was likely to be immunisation of children (the 'super-spreaders' of influenza), however there was an almost complete absence of paediatric data on the two vaccines available in the UK[7].

The Oxford Vaccine Group's rapid provision of reactogenicity and immunogenicity data on the two novel Influenza A H1N1 vaccines to the Joint Committee for Immunisation and Vaccination (JCVI) and Department of Health therefore had a profound impact on the immunisation policy for the 2009-2010 influenza A H1N1 pandemic. Specifically, data from an interim analysis on the rates of systemic and local reactions to immunisation were provided to the JCVI in mid-November, and gave reassurance that concerns regarding theoretical risks of high rates of febrile convulsions with these vaccines were unfounded[8,9].

These data were a key element in this committee's subsequent recommendation to the Department of Health that an influenza vaccine be offered to all children less than 5 years of age[10]. By February 2010, 518,000 children had received an influenza A H1N1 vaccine, with immunisation uptake rates in children varying from 23.6% in England to 44.6% in Scotland[11]. Almost all of these received the split-virion vaccine, with the whole-virion vaccine being reserved for those with an egg allergy.

Although it is not possible to precisely determine the effect of the immunisation campaign on reducing childhood disease and community spread of the influenza A H1N1 virus, a single dose of the split-virion vaccine was found to be 77% (95% C.I. 11% to 94%) effective in preventing influenza infection in children aged 0- 9 years[12]. While 70 children died as a result of influenza A H1N1 between June 2009 and March 2010 in England[13], only two of these had been immunised, however, as deaths occurred within 48 hours of immunisation these were not considered vaccine failures. It is arguable that without the expedited influenza A H1N1 study, immunisation rates in children would have been considerably lower with a resultant increase in the paediatric disease burden.

The study received extensive coverage in local and national media[14, 15, 16], and its high media profile provided very public evidence that determining the side-effect profile of the vaccines was an important aspect of the Department of Health's pandemic influenza strategy. Data on vaccine reactogenicity and immunogenicity was important not only in informing the national immunisation strategy, but also in providing an evidence base for clinicians in their discussions regarding immunisation with parents. As a result of this research parents could be reassured that rates of fever after a single dose of split-virus vaccine were low, and that no unexpected reactions had been observed.

Sources to corroborate the impact:

7. Scientific Advisory Group for Emergencies (SAGE), Swine Flu. Minutes of meeting held on 20th May 2009 [online]. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_126077.pdf [Accessed 20th June 2013]. ***Items 3 and 4 of these minutes relate SAGE's assessment of the lack of data on the use of the pandemic influenza vaccines in children, and the urgent need to obtain reactogencity data on the novel vaccines as a research priority. NB archived but still available by clicking on link to the UK Government Web archive.***

8. Joint Committee on Vaccination and Immunisation (JCVI). Minute of meeting head on 8th October 2009 [online]. Available at: http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_108833.pdf [Accessed 20th Junes 2013] ***Point 24 of these minutes relates the ongoing attention paid to the paediatric Influenza A H1N1 vaccine study by the JCVI.***

9. JCVI updated advice on H1N1v vaccination. 8 December 2009 [online] Available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@ab/documents/digitalasset/dh_109839.pdf. [Accessed 20th June 2013] ***This advice from the JCVI to the Department of Health recommends use of a single dose spilt virus vaccine (Pandemrix) for children.***

Evidence cited in support of this includes 'preliminary data on the reactogenicity of H1N1v vaccine from a paediatric trial coordinated by the Health Protection Agency'. This refers to the head to head study led by the Oxford Vaccine Group – data on reactogenicity was collated and analysed by the Health Protection Agency.

10. Department of Health Pandemic H1N1 (2009) influenza- letter from Chief Medical Officer, Sir Liam Donaldson (27th January 2010). [online] Available at http://webarchive.nationalarchives.gov.uk/20130107105354/http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_111598.pdf [Accessed 20th June 2013]***This letter from the Chief Medical Officer was distributed to all health professionals in the UK, and outlines the ongoing influenza immunisation policy (including routine immunisation of children aged 6 months to 5 years), as well as referencing data on the comparative immunogenicity of the two vaccines obtained, in part, from the OVG influenza vaccine study.***

11. Health Protection Agency. Epidemiological report of pandemic (H1N1) 2009 in the UK. October 2010 [online]. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1284475321350 [Accessed 20thJune 2013]. ***Page 45 of this report outlines immunisation uptake.***

12. Andrews N, Wright, O, Yung CF, Miller E. Age –specific effectiveness of an oil-in-water adjuvanted pandemic (H1N1) 2009 vaccine against confirmed infection in high risk groups in England. *J. Infect. Dis*; **203**:32 – 39 (2011). Doi:10:1093/in fdis/jiq014.***This manuscript provides an estimate of effectiveness of immunisation against pandemic influenza A H1N1 in children.***

13. Sachedina N, Donaldson LJ. Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. The Lancet; **376**: 1846 – 52 (2010). doi:10.1016/S0140-6736(10)61195-6 ***This manuscript, co-authored by the then chief medical officer, reports the numbers of childhood deaths from pandemic influenza.***

14. BBC news 'Babies will test swine flu jabs' [online]. 23rd September 2009 Available at: http://news.bbc.co.uk/1/hi/england/8271813.stm [Accessed 20th June 2013] ***BBC media report announcing the impending pandemic influenza vaccine study, evidence of the high public profile of the study and providing public reassurance that collecting data on the safety of these vaccines was a Department of Health Priority.***

15. BBC news 'UK children receive swine flu jab' [online] 29th September 2009 Available at http://news.bbc.co.uk/1/hi/uk/8279826.stm [Accessed 20th June 2013]. ***Further media report on the pandemic influenza vaccine study, which followed the first weekend of recruitment. This was accompanied by television interviews with participating parents.***

16. The Guardian 'Children respond well to swine flu vaccines, trial shows' 28th May 2010 [online] . Available at: http://www.guardian.co.uk/world/2010/may/28/children-swine-flu-vaccine-trial [Accessed 20th June 2013]. ***Print media report on the final publication of study results.***