Assessment of baseline age-specific antibody prevalence and incidence of infection

Assessment of baseline age-specific antibody prevalence and incidence of infection to novel influenza A/H1N1 2009

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Executive summary

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Executive summary

Background

Serological studies investigating infection with influenza H1N1 2009 virus enhance understanding of its transmission dynamics and the likely impact of interventions, and provide insight into the nature of immunity to influenza. Timely seroepidemiological surveys provide information on the age-specific incidence of infection. Such information is essential for deriving the true denominator for markers of severity, such as case fatality and hospitalisation rates, and for estimating key transmission parameters, such as the average number of secondary cases generated from a single index case, known as the reproduction number (R). These data are essential for planning national intervention policies for vaccines, antiviral drugs and other public health measures taken to minimise the impact of a pandemic.

Objectives

Studies were designed to provide an assessment of pre-pandemic baseline immunity in the population and the prevalence of antibody in the population after the first and second waves, and thereby deduce incidence of infection during successive waves of the pandemic. The specific objectives were to document:

1. the prevalence of cross-reactive antibodies to H1N1 2009 by age group
2. the age-specific incidence of infection by month as the pandemic progressed, by measuring increases in the proportion of individuals with antibodies to H1N1 2009 by age.

Methods

Serum panels collected from a variety of sources within the English health system before, during and after the pandemic waves in the UK, were assembled and tested with serological assays to provide an assessment of influenza H1N1 2009-specific protective antibody. Residual aliquots of samples submitted to 16 microbiology laboratories in eight regions in England in defined age groups in 2008 and stored by the Health Protection Agency (HPA) serological surveillance programme were used to document age-stratified prevalence of antibodies to H1N1 2009 prior to the arrival of the pandemic in the UK. For timely measurement of the monthly incidence of infection with H1N1 2009 between August 2009 and April 2010, the microbiology serum collections were supplemented by collection of residual sera from chemical pathology laboratories in England. Incidence in sequential months during the pandemic was estimated from changes in prevalence between time points and also by a likelihood-based method. Development of sensitive and specific assays for measuring antibodies to H1N1 2009 in humans poses technical challenges of virus selection and characterisation, development of reagents and assay validation. Haemagglutination inhibition (HI) and microneutralisation (MN) assays were developed and used by the HPA to document the prevalence of baseline cross-reactive antibodies in the population prior to the arrival of pandemic strain in the UK, and to investigate the penetration of H1N1 2009 in the population after the first and second waves. Data from this serological analysis have been compared with virological incidence data derived from laboratory confirmation of acute infections and other measures of virological and clinical surveillance during the pandemic to synthesise an accurate picture of the effect on different age groups across England, and thereby help to refine the initial estimates of the impact of the pandemic.

Results

Results from the baseline prevalence survey showed that 29.8% (95% CI 25.7 to 34.3) of persons born before 1940 had pre-existing cross-reactive functional antibodies capable of neutralising A/H1N1 2009. The most susceptible groups in the population were the younger age groups, which had the lowest pre-existing antibody; for example, only 6.1% (95% CI 4.1 to 9.1) of persons born after 1989 had HI titres of $\geq 1:32$. The prediction of immunological protection derived from serological

analysis was consistent with the observed highest influenza-like illness consultation rates in the population aged < 15 years and the impact of school closure in interrupting transmission in the early stages of the pandemic. These observations are consistent with observations from previous pandemics in 1918, 1957 and 1968 – that the major impact of influenza pandemics is on younger age groups, with a pattern of morbidity/mortality that is distinct from seasonal influenza epidemics.

Serological studies confirm that case estimates derived from statistical models that depend on assessment of clinical presentation of disease underestimated the extent of pandemic virus penetration in the population by a factor of about 10-fold in the first wave of infection, largely due to an overestimate of the proportion of individuals with symptomatic H1N1 2009 who consulted a health-care professional. This propensity to consult is likely to have reduced even further in the second wave. Analysis of serology by region confirms that there were geographical differences in the timing of the major pandemic waves. London had a big first wave among the 5- to 14-year age group with the rest of the country reducing the gap in seroprevalence after the second wave. Cumulative incidence in London remained higher throughout the pandemic in each age group.

By the end of the second wave it is estimated that around 70% of school-aged children in London had been infected, and approximately 60% of children of the same age in other regions.

Research recommendations

- The authors consider that investment in seroepidemiological studies for seasonal influenza would improve understanding of its epidemiology and the impact of vaccination. Investing in infrastructure for storage and investigation of alternative modalities of collection, such as dried blood spots, would enable more rapid execution of research to inform the management of future epidemics.
- Collaboration between the devolved administrations in the UK in the preparation of pandemic plans to ensure a common approach to generating comparable seroepidemiological data.
- Detailed analysis of surveillance data from the H1N1 2009 pandemic to ensure legacy systems, which can provide information about propensity to consult, are developed for use in seasonal influenza.
- Development of more rapid serological assays that can measure recent infection in a single acute sample and do not require collection of convalescent sera.
- Further research into key cross-reacting antibodies, their genesis, and implications for immunity in older people.
- Further snapshot of population immunity at regular intervals during the next 5 years to track the waning of immunity to pandemic influenza in the affected ages and investigate the interplay with immunity arising from seasonal circulating viruses.
- Further development of statistical methods, such as likelihood-based estimation, which can facilitate the rapid interpretation of serological data for 'real-time' model parameterisation.

Implications for the NHS

- The current low levels of susceptibility to the H1N1 2009 virus in the population of England after the second wave, imply that there has been sufficient infection of susceptibles in the population such that a third wave of infection in the 2010–11 influenza season is not to be expected, although sporadic cases of H1N1 are likely to continue to occur, some of which may arise in particular risk groups and be associated with severe illness. This interpretation would be consistent with the HPA real-time model that correctly predicted that the second wave would peak in early November 2009.
- Continued virological surveillance of influenza is essential during the 2010–11 season to ensure early identification of any drifted variants or continued adaptation of virus that may be associated with severe illness.
- Measurement of the HI and MN titres to any drifted strains in sera generated by infection or vaccination with the H1N1 2009 virus would be essential for the rapid assessment of the potential for a third wave of infection.
- Further investment in pandemic preparation within the NHS is required to ensure that robust mechanisms for serosurveillance in different sectors of acute care delivery are in place and can be rapidly activated.

Conclusions

Serological analysis of appropriately structured, age-stratified and geographically representative samples can provide an immense amount of information to set in context other measures of pandemic impact in a population and provide the most accurate measures of population exposures. National scale seroepidemiology studies require cross-agency coordination, multidisciplinary working and considerable scientific resource.

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Publication

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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.

Criteria for inclusion in the HTA journal series

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.

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.

The SDO programme commissions research evidence that improves practice in relation to the organisation and delivery of health care. It also builds research capability and capacity amongst those who manage, organise and deliver services – improving their understanding of the research literature and how to use research evidence.

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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