Population-level susceptibility, severity and spread of pandemic influenza: design of, and initial results from, a pre-pandemic and hibernating pandemic phase study using cross-sectional data from the Health Survey for England (HSE)

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Scientific summary

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Background

Assessing the severity and spread of a novel influenza strain at the start of a pandemic is critical for informing a targeted and proportional response. It requires understanding of the community burden of infection and disease, which can be determined only through community-level studies. However, rapidly initiating such studies at the start of a pandemic is difficult.

Our experience from the 2009 pandemic showed that recruiting community cohorts through primary care introduced substantial delays. These delays related to the need to recruit and train multiple general practitioner practices and the need to obtain appropriate ethical/research and development approvals for each of these sites. The research project described here was specifically designed to overcome these barriers so that we can measure the key parameters very rapidly in the event of a pandemic.

Aims and objectives

The study aims to establish an efficient system allowing real-time assessment of population susceptibility, spread of infection and clinical attack rates in the event of a pandemic. Specific objectives are to:

1. develop the Health Survey for England (HSE) as a tool for rapid population-based surveys of influenza infection and influenza-like illness rates
2. provide monthly measures of numbers of cases infected and weekly updates on numbers of influenza-like illnesses during the first two infection waves of a pandemic, to act as denominators for national estimates of case fatality and hospitalisation rates
3. assess spread of the novel influenza strain geographically, by age and through time.

Methods

This research project has two components: a pre-pandemic component (currently running) designed to develop and assess a system to monitor population susceptibility, severity and spread of pandemic influenza, and a pandemic component designed to be triggered rapidly in the event of an influenza pandemic.

The monitoring system is designed as a series of cross-sectional serological prevalence studies with retrospective ascertainment of vaccination and respiratory illness history in conjunction with the HSE. The HSE is a series of annual surveys, which have monitored the nation's health since 1991. All HSE surveys involve a stratified random probability sample of private households in England. There are two parts to the HSE surveys: an interview visit, during which a trained interviewer collects information on health and health-related behaviours, and measures height and weight, and, later, a nurse visit, during which additional information, measurements and biological samples are collected.

The system that we have designed simply adds a small number of additional pandemic-related questions for all participants to answer and an extra blood sample (for those aged $\geq$ 16 years) for serological testing to the nurse visit.

The project is broken down into four phases:

- *Phase 1*: retrospective validation of 2010 population-level influenza-like illness rates derived from the 2010 HSE by comparison with illness rates from the Flu Watch study (a concurrently running household-level community cohort study of influenza).
- *Phase 2*: pilot of specimen and data collection alongside the 2012 HSE and development of automated analysis and reporting of influenza-like illness and infection rates.
- *Phase 3*: holding phase during which the project is ethically approved each year but triggered only in the event of a pandemic.
- *Phase 4*: real-time monitoring through the first two infection waves of a pandemic using the methods developed in phase 2 in order to provide rapid estimates of severity and spread, and to monitor any changes to these estimates through the pandemic.

Phase 1

In response to the pandemic, we included a special 'swine flu' section in the 2010 HSE survey, in which we asked participants about influenza vaccination uptake and timing, and influenza-like illness, including timing, duration of sick leave and treatment. The availability of prospectively collected illness data from the Flu Watch study and the retrospectively collected data from the 2010 HSE provided an opportunity to compare these two approaches to monitoring levels of disease. Monthly and seasonal age-specific rates of illness and proportion vaccinated were calculated in both data sources and compared.

Phase 2

This phase has piloted the collection of specimens and data on recent illness and vaccination from the 2012 HSE and the transfer of these data and specimens to University College London Hospital (UCLH) for further analysis. Serological protocols and assays are under development, as is the automated analysis and reporting of age-specific rates of influenza-like illness and monthly estimates of the age-specific proportion of the population with protective antibodies accounting for vaccination (for those aged $\geq$ 16 years) and the proportion vaccinated. Using these data we can estimate the number of infections nationally, which can be used as a denominator by Public Health England (PHE), and the research community, in calculations of the case fatality proportion and rates of hospitalisation (both measures of severity).

Phase 3

Included within each annual HSE planning round and ethics application is the ability to trigger – in the event of a pandemic threat – the collection of an additional 5-ml blood specimen and data on vaccination, and recent respiratory illness history. This will enable rapid roll-out of the system previously described.

Phase 4

In the event of a pandemic, the collection and transfer of specimens and data can be triggered within 1 working week. We will use the automated analytical routines developed in phase 2, continually, to either directly estimate or provide the denominators necessary to estimate pandemic severity, susceptibility and spread throughout the course of the pandemic. Reports will be sent fortnightly to PHE and findings will be presented to key decision-makers through the researchers' positions on government advisory committees and links with key policy-makers.

Results

Phase 1

The rates of reported illness during the first two waves of the 2009 pandemic in the HSE greatly underestimated the community burden as measured by the Flu Watch study. The patterns of influenza-like illness rates by age and time were broadly comparable to Flu Watch. The extent of underestimation in the HSE data was greatest for youngest (0–4 years) and oldest (≥ 65 years) age groups, and in those interviewed later in the survey year compared with those interviewed closer to the pandemic.

Uptake of any influenza vaccine in the HSE was 17% in children aged 0–4 years in the unadjusted analysis, but owing to the relatively small number in this age group the confidence intervals (CIs) were wide (3% to 59%). The CI for this estimate includes both the national pandemic vaccine uptake estimate of 24% for children aged 6 months to < 5 years and the Flu Watch estimate of 40% in the 0- to 4-year age group. The HSE estimate in the older adults aged ≥ 65 years was 63% (95% CI 48% to 76%) in unadjusted analysis, again similar to the national average of 72%. The HSE CIs also overlap with the Flu Watch confidence intervals in that age group (point estimate 81%, 95% CI 44% to 96%).

The vaccine uptake time trends between Flu Watch and HSE were very similar and the difference between the HSE adjusted and non-adjusted estimates were almost identical.

Phases 2 and 3

Illness data and serological samples from 2018 participants were collected in the 2012–13 HSE and transferred to UCLH. In the 2013 HSE and onwards, this project was included in the annual HSE ethics and planning rounds.

Conclusions

The HSE's underestimation of illness rates during the first two waves of the pandemic is probably due to recall bias and the limitation of being able to report only one illness when multiple illnesses per season can occur. The multiple illness issue may explain the more extreme underestimation in the youngest age group (who are more likely to have multiple illnesses in a season). The recall bias issue may explain the more pronounced underestimation in the oldest age groups, as their illnesses tend to be milder than younger adults. The CIs for the youngest and oldest age groups were also widest and therefore the estimates were the least precise. Changes to the illness questions (reporting only recent illnesses) and data collection methods (asking about illnesses during the pandemic and not months later) in the 2012 HSE and in the event of a pandemic should help minimise the under-ascertainment issue. The HSE vaccine uptake estimates and timing were similar to national and Flu Watch estimates, and did not seem to be affected by recall bias to the same extent as the illness questions. Additionally, the unadjusted and adjusted HSE estimates were very close, indicating that unadjusted analyses (necessary during a pandemic because of survey weights not being available) would yield reasonable estimates.

We have demonstrated the feasibility of efficiently collecting large-scale representative population-level data and blood samples in real time during an influenza season, and we have established mechanisms to rapidly trigger this system in the event of a pandemic. Ongoing preparatory work includes protocols for development and roll-out of serological assays for a novel influenza virus, and automated processes for data analysis and reporting. Our phase 1 work has also demonstrated the importance of minimising recall bias in illness reporting, and the ability to estimate vaccination uptake through unadjusted analyses of HSE data. The authors are additionally considering the possibility of inviting HSE participants to participate in a follow-on prospective cohort study with self-swabbing for virological confirmation. This could potentially provide more accurate measurements of disease incidence than a cross-sectional study, and greatly enhance the interpretability of the otherwise non-specific respiratory illness data.

Study registration

This observational study is registered as ISRCTN80214280.

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This report

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