Comparative community burden and severity of seasonal and pandemic influenza: results of the Flu Watch cohort study

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Summary

Background Assessment of the effect of influenza on populations, including risk of infection, illness if infected, illness severity, and consultation rates, is essential to inform future control and prevention. We aimed to compare the community burden and severity of seasonal and pandemic influenza across different age groups and study years and gain insight into the extent to which traditional surveillance underestimates this burden.

Methods Using preseason and postseason serology, weekly illness reporting, and RT-PCR identification of influenza from nasal swabs, we tracked the course of seasonal and pandemic influenza over five successive cohorts (England 2006–11; 5448 person-seasons' follow-up). We compared burden and severity of seasonal and pandemic strains. We weighted analyses to the age and regional structure of England to give nationally representative estimates. We compared symptom profiles over the first week of illness for different strains of PCR-confirmed influenza and non-influenza viruses using ordinal logistic regression with symptom severity grade as the outcome variable.

Findings Based on four-fold titre rises in strain-specific serology, on average influenza infected 18% (95% CI 16–22) of unvaccinated people each winter. Of those infected there were 69 respiratory illnesses per 100 person-influenza-seasons compared with 44 per 100 in those not infected with influenza. The age-adjusted attributable rate of illness if infected was 23 illnesses per 100 person-seasons (13–34), suggesting most influenza infections are asymptomatic. 25% (18–35) of all people with serologically confirmed infections had PCR-confirmed disease. 17% (10–26) of people with PCR-confirmed influenza had medically attended illness. These figures did not differ significantly when comparing pandemic with seasonal influenza. Of PCR-confirmed cases, people infected with the 2009 pandemic strain had markedly less severe symptoms than those infected with seasonal H3N2.

Interpretation Seasonal influenza and the 2009 pandemic strain were characterised by similar high rates of mainly asymptomatic infection with most symptomatic cases self-managing without medical consultation. In the community the 2009 pandemic strain caused milder symptoms than seasonal H3N2.

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See Comment page 430

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Introduction

Influenza causes roughly 250 000–500 000 deaths worldwide each year.[1] In the 20th century there were three influenza pandemics for which there are varying mortality estimates: 1918 A/H1N1 at least 20–40 million excess deaths, 1957 A/H2N2 about 4 million excess deaths, and 1968 A/H3N2 about 2 million excess deaths.[2–4] In 2009 a new pandemic virus,[5] influenza A(H1N1)pdm09, emerged in Mexico[6] and spread globally over 2009–10, causing an estimated 200 000 respiratory deaths and 83 000 cardiovascular deaths during the first 12 months of circulation.[7] WHO declared an end to the pandemic on Aug 10, 2010.[8] However, a further pandemic wave occurred in some European and other countries outside North America[9] in 2010–11 with reports of excess deaths in, for example, England.[10]

Internationally, influenza activity surveillance provides real-time information to inform prevention and control policy.[11] Surveillance focuses on cases seeking medical attention: the so-called tip of the iceberg of infection. Underestimation of the number of community cases leads to overestimates of severity.[12,13] Heightened concern during a pandemic can change patient consultation thresholds and clinician recording and investigation behaviour, thus distorting surveillance information.[14] Information on the community burden of influenza is key to informing control,[15] but is not routinely collected. For example, influenza transmission models, which are widely used to consider the efficacy and cost-effectiveness of vaccines, antivirals, and non-pharmaceutical countermeasures, depend on valid epidemiological estimates of the community occurrence of disease. The available data for periods of seasonal influenza are largely derived historically from household cohort studies of families with children in communities in the USA between 1948 and 1981,[16–19] and a more recent study from rural Vietnam.[20] There have also been some cohort studies reporting on the 2009 pandemic from Hong Kong, southeast Asia, and Mali[21–25] as well as

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several cross-sectional serosurveys from this period.[26] Case-ascertained household transmission studies can estimate the secondary attack proportion and effects of interventions within households; however, they are not designed to estimate community burden of influenza infection and disease.[27,28] The Flu Watch study is the first national community cohort study of influenza occurrence enrolling households with and without children, with the additional benefit of modern molecular diagnostic techniques.

We aimed to compare the community burden and severity of seasonal and pandemic influenza across different age groups and study years and gain insight into the extent to which traditional surveillance underestimates this burden. Our specific objectives were to measure the proportion of the population infected each season, the proportion of those infected who developed symptomatic disease attributable to influenza, the proportion who had detectable nasal shedding of influenza virus, the symptoms among those with confirmed influenza, and the proportion who were medically attended. During the pandemic we also aimed to measure the development of type-specific immunity to the pandemic strain.

Methods

Participants

We did a household-level community cohort study of acute respiratory illness and influenza infection, recruiting households across England (appendix). We followed up successive cohorts over the 2006–07, 2007–08, and 2008–09 periods of seasonal influenza circulation, and the first (spring and summer 2009), second (autumn and winter 2009), and third (winter 2010–11) waves of the pandemic. Households were recruited annually through written invitation sent to a random sample of people registered with 146 volunteer general practices as well as inviting previous participants (in 2008–11). In England, most of the population is registered with a general practice.[29] At baseline (October–December) and follow-up visits (May–July) of each year we collected blood samples for serological testing (willingness to provide samples was a condition of participation in adults, voluntary in children aged 5–15 years, and not requested in children younger than 5 years). Follow-up samples from spring 2009 acted as baseline specimens for individuals who continued to participate through the 2009–10 pandemic.

See Online for appendix

Participants gave written informed consent (proxy consent for children). The protocol was approved by the Oxford MultiCentre Research Ethics Committee. (06/Q1604/103).

Procedures

We collected demographic and medical history data at baseline and self-reported vaccination status at baseline and end of follow-up. Admissions to hospital and deaths during follow-up were recorded with the end of season follow-up questionnaire completed by the lead householder, with deaths among participants also being reported to the study by participating practices and directly by families. We minimised recall bias of illness through weekly telephone or online surveys to record any "cough, cold, sore throat, or flu-like illness" among household members. In addition to weekly surveys, participants were asked to complete detailed daily symptom diaries for the duration of any acute respiratory illness, including daily temperature measurement and reporting of several symptoms: feeling feverish, headache, having muscle aches, cough, sore throat, runny nose, blocked nose, and sneezing. Symptoms were allocated a numerical score on the basis of severity (0=absent, 1=mild, 2=moderate, 3=severe or for fever <37·8°C=0, 37·8–38·9°C=1, 39·0–39·9°C=2, ≥40°C=3). Review of participants' primary-care records was used to measure consultation behaviour in practices where a research nurse was available to extract the data. We asked participants to submit, by mail, nasal swabs on day 2 of any illness. These swabs were transported in viral transport medium and screened by RT-PCR for influenza A (subtypes H1, H3), influenza B, influenza A(H1N1)pdm09 (from 2009 onwards), and a panel of other respiratory viruses including respiratory syncytial virus, rhinovirus, coronavirus, adenovirus, human metapneumovirus, and parainfluenza virus with methods described elsewhere.[30,31] We measured serum antibody titres against circulating influenza strains (appendix) in baseline and follow-up samples with haemagglutination inhibition assay using standard methods.[32,33]

Outcomes

Key outcomes of interest were infection with influenza, defined as a four-fold titre rise in serum samples of unvaccinated individuals (but not in vaccinated individuals since both vaccination and natural infection lead to titre rises); occurrence of any acute respiratory illness (self-reported "cough, cold, sore throat, or flu-like illness"); occurrence of influenza-like illness, defined according to the US Centers for Disease Control and Prevention (CDC) definition of fever (temperature ≥37·8°C) and a cough or a sore throat in the absence of a known cause other than influenza;[34] occurrence of PCR-confirmed influenza; symptom severity over the first week of illness in PCR-confirmed cases; and consultation with primary care. During the pandemic additional outcomes included monitoring the development of immunity (defined as antibody titre to influenza A H1N1 pdm2009 of ≥32). In this analysis key predictors of interest are age, study year, and circulating strain of influenza. The study size was chosen to give accurate annual estimates of infection and disease rates such that a sample size of 800 per year would allow a 25% risk of infection to be estimated within 95% CIs of 22–25 and a 10% risk of influenza-like illness within 95% CIs of 8–12. The study was expanded in the pandemic to provide accurate real-time measures of influenza-like illness rates recruiting as many participants as was practically possible.

	November, 2006, to March, 2007	November, 2007, to March, 2008	November, 2008, to March, 2009	May, 2009, to September, 2009	October, 2009, to February, 2010	November, 2010, to March, 2011
GP practices/households/people	42/243/602	43/310/779	37/309/729	41/332/797	127/1460/3552	51/361/901
Age group, years						
0–4 (6%)	38 (6%)	42 (5 %)	37 (5%)	36 (5%)	179 (5 %)	45 (5%)
5–15 (11%)	87 (15%)	110 (14%)	99 (14%)	109 (14%)	501 (14%)	131 (15%)
16–44 (42%)	151 (25%)	258 (33%)	172 (24%)	192 (24%)	848 (24%)	206 (23%)
45–64 (25%)	203 (34%)	272 (35%)	267 (37%)	293 (37%)	1225 (35%)	344 (38%)
≥65 (16%)	123 (20%)	97 (13%)	154 (21%)	167 (21%)	799 (23%)	175 (19%)
Sex						
Male (49%)	281 (47%)	366 (47%)	340 (47%)	377 (47%)	1740 (49%)	455 (51%)
Female (51%)	321 (53%)	413 (53%)	389 (53%)	420 (53%)	1812 (51%)	446 (50%)
Region						
North (28%)	99 (17%)	89 (11%)	100 (14%)	106 (13%)	320 (9%)	115 (13%)
West Midlands (11%)	42 (7%)	96 (12%)	46 (6%)	53 (7%)	179 (5%)	53 (6%)
East and east Midlands (20%)	122 (20%)	120 (15%)	124 (17%)	118 (15%)	1456 (41%)	321 (36%)
London (15%)	28 (5%)	77 (10%)	26 (4%)	28 (4%)	270 (8%)	65 (7%)
Southeast (16%)	100 (17%)	117 (15%)	107 (15%)	155 (20%)	319 (9%)	110 (12%)
Southwest (10%)	211 (35%)	280 (36%)	326 (45%)	337 (42%)	1008 (28%)	237 (26%)
Vaccine						
Vaccinated	115 (19%)	130 (17%)	169 (23%)	0	157 (4%)	186 (21%)
Unvaccinated	462 (77%)	632 (81%)	527 (72%)	797 (100%)	3159 (89%)	715 (79%)
Unknown	25 (4%)	17 (2%)	33 (5%)	0	236 (7%)	0
IMD quintile						
1 (20%)	37 (6%)	39 (5%)	28 (4%)	18 (2%)	98 (3%)	29 (3%)
2 (20%)	88 (15%)	126 (16%)	91 (13%)	62 (8%)	310 (9%)	82 (9%)
3 (20%)	164 (27%)	235 (30%)	238 (33%)	146 (18%)	915 (26%)	221 (25%)
4 (20%)	162 (27%)	250 (32%)	187 (26%)	146 (18%)	938 (26%)	280 (31%)
5 (20%)	151 (25%)	129 (17%)	185 (25%)	425 (53%)	1291 (56%)	289 (32%)
Ethnic origin						
White (75%)	557 (98%)	733 (95%)	666 (99%)	730 (99%)	3306 (98%)	846 (98%)
Non-white (25%)	5 (2%)	35 (5%)	6 (1%)	7 (1%)	78 (2%)	19 (2%)

Percentages given alongside the categories are the national distributions. Data are n (%). IMD=Index of Multiple Deprivation.

Table 1: **Baseline characteristics**

Statistical analysis

Analyses were done in STATA version 12. Analyses of serological data were restricted to those with serological samples available (no children younger than 5 years had serological specimens). We weighted analyses to the age and regional structure of England to give nationally representative estimates. In this weighting, children younger than 15 years were considered as a single group, so measures of age-adjusted population rates of infection (but not of PCR-confirmed disease or illness) apply the rates in the 5–15 year age group to the 0–15 population. We did not weight on ethnic origin or social deprivation because there was no evidence of a strong association with infection or disease rates (data not shown) and small or zero numbers in some groups would have led to instability of weighted measures.

Participants were assumed not to have a respiratory illness in weeks with missing illness status reports. After excluding illnesses where PCR identified a non-influenza virus we plotted rates of respiratory illness, influenza-like illness, and PCR-confirmed influenza (per 100 000 person-weeks). We estimated the percentage of the population infected each season by calculating age and season-specific rates of serological infection and PCR-confirmed disease per 100 person-seasons. A person-season was defined as the time from the first PCR isolation of influenza in the cohort to the last isolation in any given season, rates therefore accounted for differential follow-up time during periods of influenza circulation. We did not undertake follow-up blood samples for serological testing for participants recruited before the first (spring/summer) pandemic wave until after the second (winter) wave had finished because we had not predicted separate summer and winter pandemic waves. Methods to derive infection rates in the first wave are described in the appendix.

We estimated the percentage of serological infections leading to illness by two independent methods. First, we calculated age-adjusted attributable rates of illness due to infection (subtracting rates of respiratory illness in non-seroconverters from those in seroconverters).[35] Sensitivity

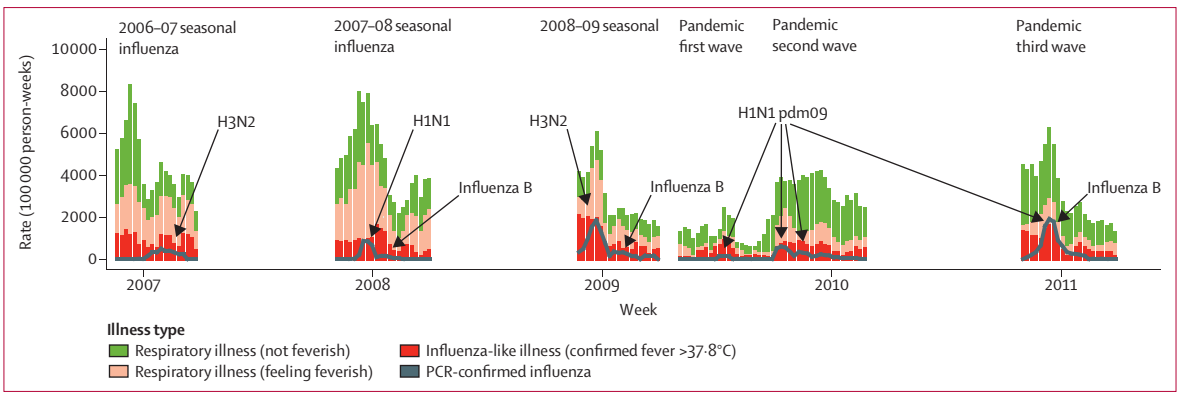

Figure 1: **Rates of illness or PCR-confirmed influenza standardised by age and region**
Rates of acute respiratory illness, influenza-like illness, and PCR-confirmed influenza per 100 000 person-weeks. Excludes illnesses known to be due to non-influenza viruses.

analyses inflated these adjusted attributable rates to account for the recorded level of under-reporting (based on the proportion of expected weekly illness status reports received during periods of influenza circulation). Second, we measured the proportion of unvaccinated sero-converters with PCR-confirmed influenza.

We compared symptom profiles (an ordered categorical variable) over the first week of illness for different strains of PCR-confirmed influenza and non-influenza viruses using ordinal logistic regression with symptom severity grade as the outcome variable, adjusting for age group and strain type and accounting for repeated measures in individuals using robust standard errors (Stata ologit commands with cluster option).

Role of the funding source

The sponsors had no role in study design, collection analysis, interpretation of data, or writing of the report. ACH, EBF, and ERCM had access to the raw data. The corresponding author had full access to all data and final responsibility to submit for publication.

Results

Roughly 10% of invited households agreed to participate (appendix). Table 1 presents the comparison of unweighted cohort demographics with those of the England population showing good geographical spread but under-representation of young adults; people living in socially deprived areas, north England, west Midlands, and London; and people of non-white ethnic origin.

Person follow-up time (118158 person-weeks, 5448 person-seasons), illness-status reports (102 300: 86·6% of follow-up weeks), nasal swab submissions (2941; 88·3% of 3332 illnesses recorded during periods of influenza circulation), and influenza virus detection results are given in the appendix. There were 3295 paired sera (81% of eligible adults and 27% of eligible children aged 5–15 years, in whom blood tests were optional). Of these 2737 (83 %) were in unvaccinated individuals.

The highest rates of influenza-like illness and PCR-confirmed influenza were during the epidemic of H3N2 in 2008–09 before the pandemic and in the 2010–11 third pandemic wave. Compared with other seasons, illness rates in the first pandemic wave were low (figure 1).

The dominant circulating strain was influenza A H3N2 in 2006–07, seasonal A H1N1 in 2007–08, A H3N2 in 2008–09, and A(H1N1)pdm09 in 2009–10 and 2010–11. Influenza B circulated in 2007–08 and 2008–09 when it peaked after the main influenza A outbreak. In 2010–11 the influenza B peak coincided with the third wave of A(H1N1)pdm09. On average, based on rates per 100 person-seasons, PCR-confirmed influenza was identified in 4% (95% CI 3–5) of the cohort each winter: 3% (2–5) during prepandemic seasons and 5% (4–6) during pandemic winter seasons. Highest rates were in the third pandemic wave when 9% (6–13) had PCR-confirmed disease (6% influenza A and 3% influenza B) and in the 2008–09 season when 6% (4–10) had PCR-confirmed disease (5% influenza A and 2% influenza B). In all seasons most PCR-confirmed cases were influenza A, although influenza B was important in 2007–08, 2008–09, and 2010–11.

Risk of PCR-confirmed disease tended to decrease with increasing age (figure 2, appendix). For influenza A this age dependence was most apparent during the H3N2 epidemic of 2008–09 and the 2009–10 second wave of the H1N1 pandemic when children had significantly higher rates of PCR-confirmed disease and serological infection with influenza A than older adults (appendix). For influenza B, children had significantly higher rates of PCR-confirmed disease than adults in 2008–09 and 2010–11 seasons (appendix). The 2010–11 third wave of the H1N1 pandemic was unusual in having markedly higher rates of influenza A in young adults than any other season. PCR-confirmed influenza was very rare in people older than 65 years in all seasons.

On average, based on rates per 100 person-seasons, influenza infected 18% (95% CI 16–22) of the unvaccinated population each winter season: 19% (15–24) during prepandemic seasons and 18% (14–22) during the pandemic. The highest infection rate (27%, 22–34; 24% influenza A, 2% influenza B) was in the season

preceding the pandemic (2008–09) and then in the 2010–11 third pandemic wave (22%, 17–28; 18 influenza A, 5% influenza B).

Infection rates were typically highest in children aged 5–15 years (not measured in younger children) and decreased with age (figure 2, appendix). This age-dependence was most apparent during the 2009 first pandemic wave when children aged 5–15 years was the only age group with measurable risk of infection: 26% (0–58). Age dependence of influenza A was also strong during the 2009–10 second wave of the pandemic when children had significantly higher rates of serological infection with influenza A than older adults (appendix). The 2010–11 third pandemic wave was the only season when young adults aged 16–44 years had the highest risk of infection: 34% (26–46). During periods of seasonal influenza A age dependence was strongest during the H3N2 epidemic of 2008–09 (appendix). Children also had significantly higher rates of influenza B infection than older adults in 2008–09 (appendix).

Most infections were asymptomatic. 192 respiratory illnesses including 70 influenza-like illnesses were reported from 327 participants with serological evidence of infection over 280 person-seasons of follow-up (69 respiratory illnesses, 25 influenza-like illnesses per 100 person-seasons). There were 623 respiratory illnesses including 95 influenza-like illnesses reported from 1742 participants with no serological evidence of infection over 1423 person-seasons of follow-up (44 respiratory illnesses, seven influenza-like illnesses per 100 person-seasons). The rate of respiratory illness attributable to influenza (age-adjusted incidence rate difference)[35] was 23 respiratory illnesses

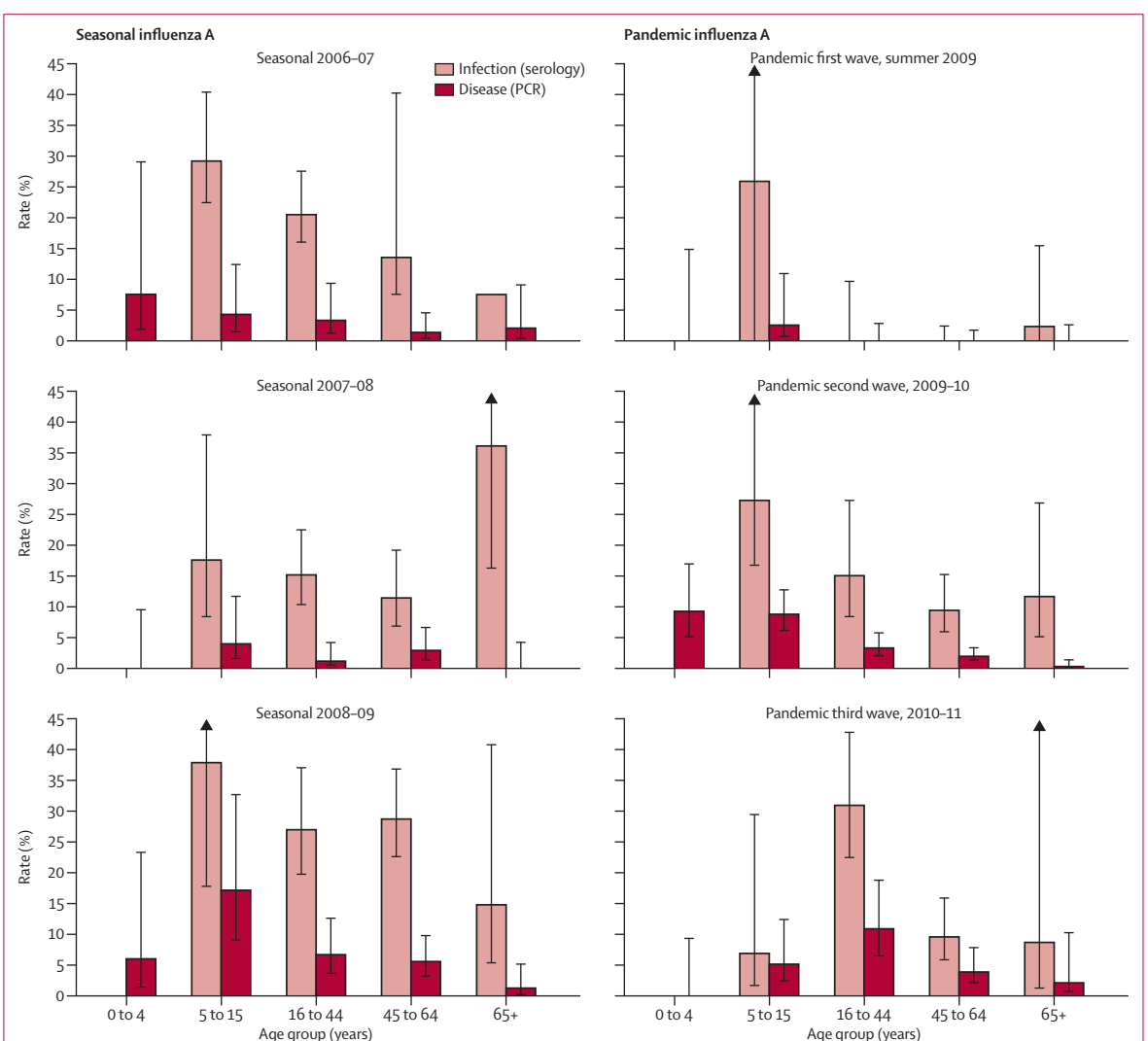

Figure 2: **Rates of seasonal and pandemic influenza A infection and PCR-confirmed disease**
Rates of infection established through seroconversion (four-fold titre rises in unvaccinated individuals) and rates of disease established through PCR-confirmation per 100 person-seasons (95% CIs).

	Fever	Feverish	Headache	Muscle ache	Sore throat	Cough	Runny nose	Sneeze	Blocked nose
A(H1N1)pdm09* (n=102)	1	1	1	1	1	1	1	1	1
H3N2 (n=35)	1·09 (0·61–1·95); 0·774	2·22 (1·33–3·71); 0·002	2·72 (1·60–4·63); <0·001	4·15 (2·36–7·27); <0·001	1·51 (0·90–2·54); 0·118	1·34 (0·82–2·18); 0·245	3·18 (2·12–4·77); <0·001	2·95 (1·88–4·62); <0·001	2·39 (1·46–3·93); 0·001
H1N1 (n=10)	0·27 (0·09–0·87); 0·027	0·59 (0·28–1·25); 0·172	1·53 (1·83–2·81); 0·173	1·23 (0·49–3·08); 0·653	2·29 (1·13–4·60); 0·020	0·85 (0·47–1·54); 0·584	2·26 (1·24–4·10); 0·007	1·74 (1·00–3·02); 0·05	1·76 (0·96–3·23); 0·068
Influenza B (n=35)	1·56 (0·87–2·80); 0·134	1·94 (1·08–3·47); 0·026	1·27 (0·72–2·25); 0·411	1·79 (0·91–3·52); 0·094	1·32 (0·73–2·37); 0·694	0·69 (0·35–1·37); 0·290	1·01 (0·59–1·72); 0·972	1·0 (0·56–1·78); 0·990	2·02 (1·14–3·58); 0·017
Non-influenza (n=385)	0·34 (0·22–0·53); <0·001	0·51 (0·36–0·72); <0·001	1·02 (0·74–1·41); 0·905	0·66 (0·44–0·98); 0·040	1·07 (0·76–1·50); 0·694	0·56 (0·40–0·77); <0·001	1·95 (1·45–2·62); <0·001	1·50 (1·11–2·05); 0·009	1·93 (1·14–3·58); 0·017
0–15 years* (n=189)	1	1	1	1	1	1	1	1	1
16–44 years (n=147)	0·25 (0·15–0·41); <0·001	0·95 (0·66–1·39); 0·803	1·32 (0·95–1·85); 0·098	1·48 (0·98–2·22); 0·06	1·60 (1·16–2·20); 0·005	0·68 (0·50–0·94); 0·019	0·91 (0·68–1·20); 0·0503	1·28 (0·96–1·70); 0·09	1·18 (0·85–1·63); 0·323
45–64 years (n=195)	0·31 (0·20–0·50); <0·001	1·55 (1·11–2·18); 0·010	1·22 (0·89–1·67); 0·219	1·75 (1·18–2·59); 0·005	1·35 (0·99–1·87); 0·056	0·81 (0·60–1·08); 1·045	0·82 (0·63–1·07); 0·148	1·15 (0·87–1·52); 0·324	0·97 (0·71–1·32); 0·826
≥65 years (n=70)	0·135 (0·07–0·28); <0·001	1·09 (0·67–1·78); 0·726	0·97 (0·64–1·47); 0·888	1·67 (0·94–2·97); 0·08	1·12 (0·75–1·68); 0·569	1·22 (0·84–1·76); 0·0294	1·08 (0·74–1·58); 0·678	2·10 (1·36–2·96); <0·001	0·88 (0·54–1·42); 0·595

Data are adjusted OR (95% CI); p value (across the categories of the symptom severity scale, assuming proportional odds). Numbers in the left-hand column refer to the number of PCR-confirmed cases across all years with information on daily symptoms. ORs are mutually adjusted for age and strain type. OR=odds ratio. *Baseline group for comparisons.

Table 2: **Comparative symptom severity for different strains of influenza and non-influenza viruses and different age groups**

(95% CI 13–34) including 18 influenza-like illnesses per 100 person-seasons (95% CI 12–24). There was insufficient power to test the hypothesis that the asymptomatic proportion varied by age or strain type. Sensitivity analyses adjusting for the fact that 85% of illness status reports were returned during periods of influenza circulation gave estimates of the rate of respiratory illness or influenza-like illness attributable to infection of 27 respiratory illnesses and 21 influenza-like illnesses per 100 person-seasons, respectively. These estimates of infections leading to disease are similar to the 25% (18–35) of people with serological infections who had PCR-confirmed influenza from nasal swabs. PCR-confirmation levels seemed to be lower in adults aged 65 years or older (9%, 95% CI 1–60) and for influenza B infections (5%, 1–28), although this was not statistically significant.

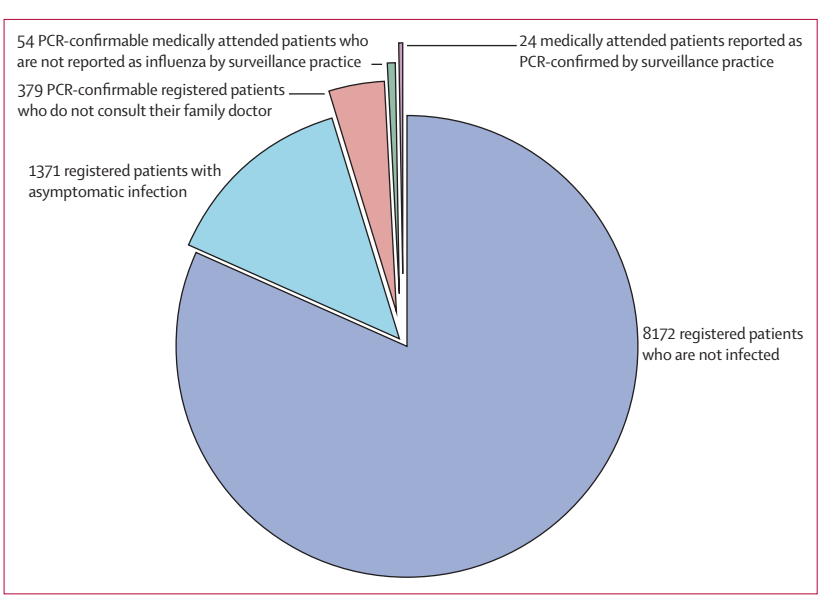

Figure 3: **Number of expected events in a surveillance practice serving a population of 10 000 people**
Data for a typical influenza season.

Only a minority of people with PCR-confirmed influenza had fever with a temperature greater than 37·8°C and so met the CDC definition of influenza-like illness (110/238; 46%, 95% CI 40–53). Symptoms of A(H1N1)pdm09 were milder than those of H3N2 (appendix). Detailed daily symptom diaries were available on 567 participants with PCR-confirmed respiratory illnesses (102 A[H1N1]pdm09, 35 H3N2, ten H1N1, 35 influenza B, 385 non-influenza viruses). Symptoms of influenza A(H1N1)pdm09 were milder than those of H3N2 for feeling feverish, headache, muscle ache, runny nose, sneezing, and blocked nose (table 2). Symptoms of A(H1N1)pdm09 were significantly more severe than those of non-influenza viruses for fever, feeling feverish, muscle aches, and cough, but significantly less severe than non-influenza viruses for runny nose, sneezing, and blocked nose (table 2). Children were significantly more likely than adults to have fever (table 2).

Most people with PCR-confirmed influenza did not consult and among those who did, influenza or influenza-

like illness was rarely recorded in medical notes. Medical record review of 93 PCR-confirmed influenza cases across all seasons and of 459 episodes of influenza-like illness showed that 16 of 93 people with PCR-confirmed influenza (17%, 10–26) and 96 of 459 people with episodes of influenza-like illness (21%, 17–25) consulted their family doctor. Of the 96 patients consulting with influenza-like illness only eight (8%, 4–16) had influenza or influenza-like illness recorded in their medical record. Of the people with respiratory illness, those younger than 5 years were most likely to have a medical consultation (appendix).

Of 133 PCR-confirmed cases of influenza, with data available from end of season surveys, there was one admission to hospital potentially attributable to influenza (febrile convulsions in a child younger than 5 years within 2 weeks of a positive swab for influenza A H1N1 pdm2009). There were no deaths among these 133 PCR-confirmed cases. This single admission gives a maximum estimated hospitalisation rate of 0·75% (95% CI 0·02–4·19). Of 226 seroconverters to influenza, with data available from end of season surveys, there were two admissions to hospital that were potentially attributable to influenza: one in a young adult with a four-fold titre rise to influenza A H1N1 pdm2009 admitted with a chest infection in the winter of 2010–11 and one in an individual aged 45–64 years with a four-fold rise in titre to influenza B admitted with pneumonia during the winter of 2010–11. These two admissions give a maximum estimated hospitalisation rate for serological infection of 0·88% (95% CI 0·11–3·19). This compares with three respiratory hospitalisations in 1730 participants who did not have a four-fold titre rise (0·17%, 95% CI 0·04–0·51). There were two respiratory deaths in the cohort, both of which occurred in vaccinated participants older than 65 years during the 2008–09 winter season; one was partly attributable to chest infection and the other was attributable to pneumonia. It is not possible to infer whether or not influenza contributed because there were no nasal swab samples and post mortem serum samples were not sought.

Primary-care-based surveillance greatly underestimated the extent of infection and illness in the community (figure 3). Under ascertainment was lower during the summer wave of the pandemic. The rate of PCR-confirmed influenza across all winter seasons was on average 22-times higher (95% CI 17–28) than rates of PCR-confirmed disease from the Royal College of General Practitioners Sentinel Influenza-Like Illness/Virological Surveillance Scheme.[36] During the pandemic summer wave the rate was only three-times higher.

In children aged 5–15 years, protective antibodies were mainly acquired as a result of natural infection over the first and second pandemic wave, in young adults (16–44 years) protective antibody levels increased mainly as a result of natural infection in the second and third wave, in people older than 45 years protective antibodies were mainly acquired as a result of vaccination during the second and third waves (figure 4).

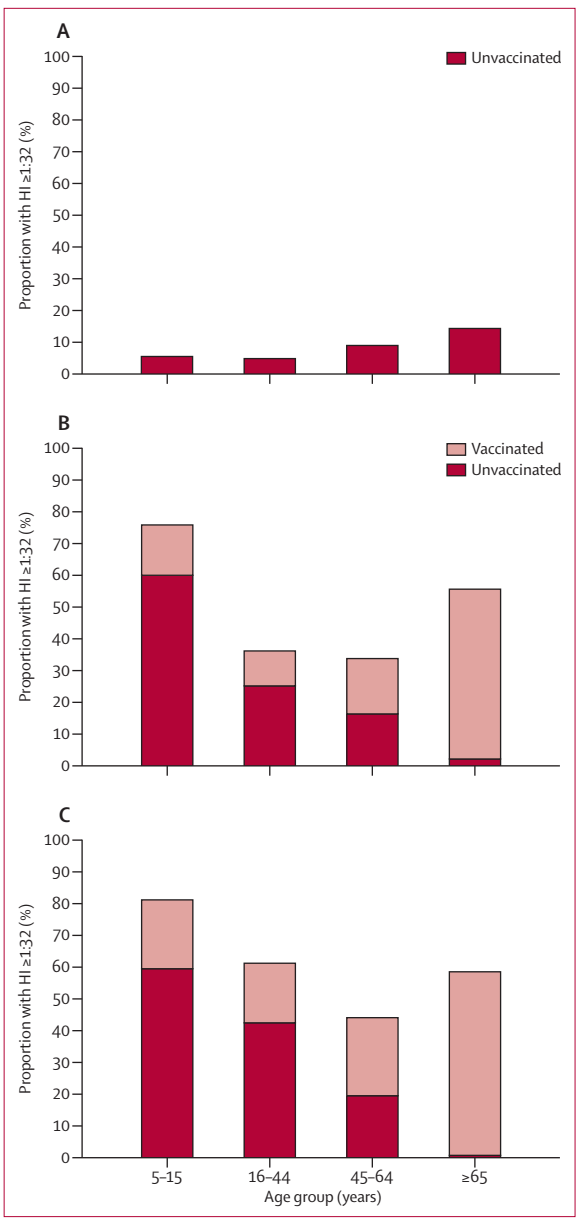

Figure 4: **Immune profiles to influenza A(H1N1)pdm09 before each influenza season.**
Profiles before first wave (no vaccine; A), after second wave and before third wave (B), and after third wave (C). HI=haemagglutinin inhibition.

Discussion

Flu Watch is one of the largest and most comprehensive studies of its type since the 1980s (panel).[19] Through providing reliable information on the epidemiology and burden of seasonal and pandemic influenza we hope to inform future decisions on seasonal disease control and pandemic planning. For example, better measures of community disease burden will increase the validity of population models that are widely used to infer the efficacy and cost-effectiveness of countermeasures such as use of antivirals, vaccines, and behavioural

Panel: **Research in context**

Systematic review

We searched published work to address four key questions relevant to our study: what proportion of the population have influenza infection each influenza season, what proportion of infections lead to illness, what are the symptom profiles and severity of these illnesses, and what proportion of these illnesses lead to consultation? We reviewed historical community cohort studies of respiratory infections such as the Tecumseh study,[18] the methods of which were adapted for the Flu Watch study. These studies are summarised elsewhere.[19] We also reviewed findings from more recent cohort studies using similar designs.[20–23] We then did three separate systematic literature searches in Embase, Global Health, and Medline databases (up to Aug 13, 2013) to identify community-level cohort studies of influenza with PCR or serological confirmation (search terms in appendix).

To identify work relevant to establishing population-level influenza infection rates, we reviewed a recent review and meta-analysis of age-specific cumulative incidence for the 2009 influenza pandemic.[26] We also searched published work for community-level cohort studies of influenza that collected paired sera (search terms in appendix). Studies were included in this review if they were community-level cohorts but excluded if they only focused on subsections of the population.

To add to the work identified above, we did a further two systematic literature searches in the same databases to identify relevant community-level prospective cohort studies that had PCR confirmation of influenza illnesses (search terms in appendix). Studies were included if they were community-level cohorts with prospective follow-up of respiratory illnesses with swabbing for PCR confirmation of influenza. Studies were excluded if they only focused on subsections of the population or if they only did PCRs on a subset of illnesses (ie, only consulting illnesses or only those meeting a case definition which would exclude less severe influenza).

Interpretation

Our rates of infection and disease were similar to those found in historical cohort studies and in more recent, mostly pandemic, studies.[18–20] Our finding that a high proportion of infections were asymptomatic was consistent with other research.[35] Influenza A H3N2 has previously been reported as causing more severe symptoms than Influenza A H1N1.[35] Others have also reported that a high proportion of people with influenza-like illness do not seek medical attention.[14]

interventions. On average influenza infected 18% of unvaccinated people each winter. Up to three-quarters of infections were asymptomatic and about a quarter of infections had PCR-confirmed disease. 17% of people with PCR-confirmed disease had medically attended illness. These data did not vary significantly when comparing pandemic with seasonal influenza. People infected with the 2009 pandemic strain had markedly less severe symptoms than those infected with seasonal H3N2.

The study covers six influenza seasons, including seasonal and pandemic periods, but the variable nature of influenza means that we cannot exclude substantially more severe periods of both seasonal and pandemic influenza in the future. The study was limited by the difficulty in obtaining a fully representative sample because, although selection was random, acceptance rates were low. Weighted analyses ensured results represented the age and regional structure of the country. Weighted analyses of overall population rates of infection (but not illness or disease) assume the level of infection recorded in children younger than five years were similar to those in those aged 5–16 years. However, because children younger than 5 years represent only about 6% of the UK population the lack of serological analysis in this group will not have made a major difference to overall reported rates. Our estimates of infection in people older than 65 years are limited to unvaccinated individuals because we cannot reliably infer infection from titre rises in vaccinated people.

Differences in volunteers such as propensity to consult if ill and uptake of interventions might affect findings. Participants were generally highly diligent at completing weekly illness reports and submitting nasal swabs during illness (>85% completion). That the proportion of infections judged symptomatic was very similar using two independent methods (proportion of seroconverters PCR-confirmed and attributable-rate of respiratory illness in seroconverters compared with non-seroconverters)[35] suggests that the low proportion with PCR-confirmed disease is not simply a matter of low test sensitivity. Nasal swabs have similar sensitivity to the gold-standard nasopharyngeal aspirates.[37,38] Self-taken swabs have similar sensitivity to those taken by health-care workers.[39] The extent of postal delay is not associated with likelihood of PCR positivity for influenza.[40] After adjusting for time from symptom onset to swab date, a recent comparison showed similar levels of viral detection and viral load in primary-care samples from patients with influenza-like illness to those in postally submitted samples from patients consulting the National Pandemic Flu Service.[41] Because of the high level of completion of weekly illness status reports, adjusting our attributable rates for the recorded level of under-reporting made minimal difference to our conclusions on the proportion of infections leading to illness. The attributable-rate method might underestimate the proportion of infections leading to illness if having influenza reduces the risk of other respiratory infections through viral interference,[42] but we did not identify any evidence of this in our data.

Reported cases of influenza represent the tip of a large clinical and subclinical iceberg that is mainly invisible to routine surveillance systems (figure 3). Surveillance does not aim to capture the totality of community cases, but low ascertainment means that changes in consultation and reporting behaviour during periods of increased concern can make interpretation of trends highly problematic. It is also likely that propensity to consult if ill might vary by country, making international comparisons difficult. Our findings show this during the summer wave of the pandemic, where comparison of disease rates with national surveillance suggest a much higher proportion of cases were identified with surveillance than at other times. This greater identification probably represents an increase in propensity for people to consult and be reported during periods of increased national concern; however, because only two confirmed cases were identified in the study

during this summer period we cannot test this directly. From a population perspective there was little difference in burden of disease in the 2009 pandemic compared with seasonal influenza periods. Both seasonal and pandemic infections were common, especially in children, but most infection was asymptomatic and most symptomatic cases did not consult. The symptoms associated with 2009 pandemic influenza were substantially milder than those of seasonal H3N2. The completeness of return of weekly illness status reports did not alter during the pandemic, suggesting that change in reporting to the study was not a source of bias (appendix). Hospitalisation and death rates were very low with insufficient events to establish if this varied by strain type.

After the high attack rates during the 2009–10 pandemic, WHO advised that the virus had largely run its course.[8] Despite this, a further wave of A(H1N1)pdm09 infection was noted across Europe in 2010–11.[9] In England this wave was associated with an upwards age shift in infected people admitted to hospital (median age 35 years during the 2010–11 winter compared with 20 years over the 2009–10 pandemic period) and pressure on intensive care.[43] We did not identify any evidence of increased symptom severity in the third wave, but there was a marked increase in the number of cases in young adults. This upwards age shift is probably explained by the fact that before this third wave, protective antibody titres were present in about three-quarters of children, but only about a third of working-age adults. However, it remains unclear why young adults were not more affected during earlier waves. The higher numbers of deaths and admissions noted nationally during the pandemic third wave were therefore probably due to increased numbers of cases in young adults rather than, as reported by others, increased severity.[44] The occurrence of a third wave in the pandemic reinforces the value of investing in vaccine development even if vaccines are unlikely to be available sufficiently early to alter the course of early waves.

The proportion of serologically confirmed infections that are asymptomatic is an often neglected variable, which is an important component of severity. Our finding that only 23% (95% CI 13–34) of infections are symptomatic is lower than is sometimes assumed, but is consistent with findings from other studies of seasonal influenza[35] and human challenge studies.[45] Measurement of the proportion of serologically confirmed infections that are asymptomatic should be an early priority for any emerging infection of pandemic potential. This provides an additional index of severity complementing population level data on admission to hospital and deaths. Our study was limited by our inability to identify virus shedding during asymptomatic infection because this would have needed frequent regular nasal swabbing throughout follow-up. Comparison of symptom profiles in community cases of an emerging infection with those noted with other viruses can also provide important information on severity, complementing population level data on numbers of admissions to hospital and deaths.

Application of consistent methods across periods of seasonal and pandemic influenza has allowed assessment of the 2009 pandemic in context. Although A(H1N1) pdm09 infected most children and a high proportion of unvaccinated adults of all ages over three pandemic waves, infection and disease rates were similar to or lower than prepandemic periods. Symptoms due to infection with the 2009 pandemic strain were milder than those with seasonal influenza strains. Our findings are consistent with the very low case-fatality rates recorded during the pandemic. Whereas overall, pandemic illnesses were mild there was a shift in the age distribution of deaths leading to an increase in years of life lost during the 2009 pandemic compared with some seasonal periods.[7] Despite its mild nature, the 2009 pandemic caused enormous international concern, expense, and disruption. We need to prepare for how to respond to both mild and severe pandemics. To do this we need more refined assessments of severity, including community studies to guide control measures early in the course of a pandemic and inform a proportionate response.

Contributors

ACH is the principal investigator of the Flu Watch study. He conceived the idea for and designed the original seasonal influenza study and the pandemic extension in discussion with JMW, AMJ, and MZ. AB, WJE, AMcM, JSN-V-T, IN, JMW, AMJ, and MZ were coapplicants on the seasonal and pandemic grants, members of the steering group, and contributors to study design. AC, NF, and RP were coapplicants for the pandemic extension and joined the steering group in 2009, contributing to the design of the pandemic phase. EBF, JK, and ERCM also contributed to the study design. Data collection was led by Flu Watch project managers JK (2006–08) and GH (2008–11). EBF, AB, LW, ERCM, and FBW also contributed to data collection. EBF, Flu Watch statistician 2008–11, led the data management with contributions from JK, MSCL, ERCM, and FBW. ACH and EBF led the development of the overall analytical strategy with contributions from all steering group members as well as NG, ERCM, and FT. AB and MZ led the laboratory analysis with contributions from LW. AC was the statistical adviser for the study. FT also contributed statistical advice. ACH and EBF analysed the data. All steering group members and EBF, LW, NG, JK, MSCL, and ERCM contributed to interpretation of the findings. ACH wrote the report with contributions from EBF and AB and input on drafts from all authors. Literature search was done by ACH and EBF. Tables and figures were created by ACH, EBF, and ERCM.

Declaration of interests

JSN-V-T has served on speaker bureaus for, served as a consultant to, and received grants and support for travel from Roche and GSK, but all personal remuneration stopped in Sept, 2010. He also received support for travel from Roche. IN was funded by GSK as chief investigator on a prospective, observational, multicentre, cohort, post-authorisation safety study of GlaxoSmithKline Biologicals A/California/7/2009 (H1N1) v-like pandemic vaccine adjuvanted with AS03. This study was part of the Medicines and Healthcare products Regulatory Agency's procedures for approval of the vaccination from 2009 to 2011. MZ has received funding from vaccine companies (Sanofi, Novartis, CSL, Baxter, GSK) and Roche for antiviral work. AMJçs been a Governor of the Wellcome Trust since 2011. ACH, WJE, NF, JSN-V-T, RP, JMW, and MZ have served on UK national advisory committees relevant to planning and response for seasonal and pandemic influenza. Authors not specifically mentioned declare that they have no competing interests.

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