ORIGINAL ARTICLE

Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009–2010 in the UK

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ABSTRACT

Background Although generally mild, the 2009–2010 influenza A/H1N1 pandemic caused two major surges in hospital admissions in the UK. The characteristics of patients admitted during successive waves are described.

Methods Data were systematically obtained on 1520 patients admitted to 75 UK hospitals between May 2009 and January 2010. Multivariable analyses identified factors predictive of severe outcome.

Results Patients aged 5–54 years were over-represented compared with winter seasonal admissions for acute respiratory infection, as were non-white ethnic groups (first wave only). In the second wave patients were less likely to be school age than in the first wave, but their condition was more likely to be severe on presentation to hospital and they were more likely to have delayed admission. Overall, 45% had comorbid conditions, 16.5% required high dependency (level 2) or critical (level 3) care and 5.3% died. As in 1918, 1919, the likelihood of severe outcome by age followed a W-shaped distribution. Pre-admission antiviral drug use increased from 13.3% to 10% between the first and second waves (p=0.048), while antibiotic prescribing increased from 13.6% to 21.6% (p<0.001). Independent predictors of severe outcome were age 55–64 years, chronic lung disease (non-asthma, non-chronic obstructive pulmonary disease), neurological disease, recorded obesity, delayed admission (>5 days after illness onset), pneumonia, C-reactive protein ≥100 mg/litre, and the need for supplemental oxygen or intravenous fluid replacement on admission.

Conclusions There were demographic, ethnic and clinical differences between patients admitted with pandemic H1N1 infection and those hospitalised during seasonal influenza activity. Despite national policies favouring use of antiviral drugs, few patients received these before admission and many were given antibiotics.

INTRODUCTION

On 11 June 2009, WHO announced an influenza pandemic after a novel strain of influenza A virus emerged and spread worldwide.1 2 In the UK the Influenza Clinical Information Network (FLU-CIN) was established in May 2009 to undertake clinical surveillance of hospitalised cases.3 Having already documented the first wave of the pandemic (May–September 2009),2 this paper presents an analysis across the first and second pandemic waves.

METHODS

As previously described,3 trained FLU-CIN staff extracted demographic and clinical data from hospital case notes and electronic records. Patients with pandemic influenza A/H1N1 2009 infection (‘pandemic H1N1’) confirmed by real-time reverse
Respiratory infection

RESULTS

Overview

Data were obtained on 1520 patients with confirmed pandemic H1N1 infection. Illness onset occurred from 25 April 2009 to 26 January 2010 (online supplementary figure 1). The median length of hospital stay was 3 days (IQR 2–6). One in six (16.5%) patients needed admission to high dependency (4.1%) or intensive care (12.4%) units (respectively level 2 and level 3 care) and the in-hospital case death rate was 5.3% (children 0–15 years: 3.8%; adults 16–64 years: 5.6%; older people >65 years: 10.7%; first wave: 5.0%; second wave: 5.4%).

Patient characteristics

Table 1 summarises socio-demographic characteristics; the median age was 26 years (IQR 9–44). There were higher proportions of patients in age bands 0–4 (17%) and 16–34 (32%) compared with the general population. However, compared with pre-pandemic hospital admissions for acute respiratory infection (ARI) during the immediately preceding influenza active winter period (November 2008–March 2009), there was an inverse age distribution with fewer patients in age bands 0–4 and ≥65 and substantially higher proportions in age bands from 5 to 54. Among women, 20.8% were pregnant compared with an estimated national prevalence of pregnancy 5.6% in the female population aged 15–44 years (table 2). There was an over-representation of non-white ethnic groups in the FLU-CIN cohort compared with the UK general population and ARI admissions during the previous winter. More than half of all

Table 1 Demographic characteristics of 1520 UK patients hospitalised with pandemic H1N1 infection during the 2009–2010 pandemic compared with source population and pre-pandemic hospital data on acute respiratory infection admissions

| Ethnicity | Sex | Patient characteristics | UK population comparison, % | Pre-pandemic hospital data, acute respiratory infections, % |
|-----------|-----|-------------------------|-----------------------------|----------------------------------------------------------|
|           | n (%) |                           |                             |                                                          |
| White     |       |                           |                             |                                                          |
| Men       | 720 (47.4) | 48.7 | 50.4 |                         |
| Women     | 800 (52.6) | 51.3 | 49.6 |                         |
| Age (years) |       |                           |                             |                                                          |
| <1        | 121 (8.0) | 1.3 | 14.7 |                         |
| 1–4       | 138 (9.1) | 4.8 | 12.6 |                         |
| 5–15      | 221 (14.5) | 12.6 | 4.8 |                         |
| 16–24     | 245 (16.1) | 12.1 | 2.5 |                         |
| 25–34     | 242 (15.9) | 12.9 | 3.3 |                         |
| 35–44     | 195 (12.8) | 14.6 | 4.8 |                         |
| 45–54     | 168 (11.0) | 13.5 | 5.4 |                         |
| 55–64     | 115 (7.6) | 11.8 | 7.9 |                         |
| 65–74     | 55 (3.6) | 8.5 | 11.0 |                         |
| >75       | 20 (1.3) | 7.8 | 33.2 |                         |
| Mixed     |       |                           |                             |                                                          |
| Asian/Asian British | 249 (16.4) | 4.0 | 8.7 |                         |
| Black/black British | 128 (8.5) | 2.0 | 3.4 |                         |
| Chinese and other | 121 (8.0) | 0.8 | 2.7 |                         |

1Children's hospitals and tertiary referral centres were not mutually exclusive; one of three extracorporeal membrane oxygenation centres was a children’s hospital.

2Level 0: patients whose care needs can be met through normal ward care; level 1: patients at risk of deteriorating or recently relocated from higher levels of care whose needs can be met on an acute ward with additional advice and support from the critical care team; level 2: patients requiring more detailed observation or intervention, including support for a single failing organ system and those 'stepping down' from higher levels of care—high dependency unit; level 3: patients requiring advanced respiratory support alone or basic respiratory support together with support of at least two organ systems. This includes all complex patients requiring support for multi-organ failure—intensive care unit.

3Hospital Episodes Statistics data: primary discharge codes relating to possible influenza admissions (J06, J10, J11, J13-22) were considered for the pre-pandemic influenza active period November 2008–March 2009.

4Census 2001 data for comparison of sex (KS01 tables) were obtained from the Office for National Statistics (ONS) (http://www.statistics.gov.uk).

5Demographic data on age distribution based on 2009 mid-year population estimates (ONS).

6Ethnicity data from ONS (Census 2001 data, 2001 data from the General Register Office for Scotland and Northern Ireland Statistics and Research Agency). Missing data for 380 (25%).
admitted patients (55.1%) did not have any recorded pre-existing comorbidity at the time of admission (table 2).

## Preadmission care

The mean interval between symptom onset and admission to hospital was 2 days (median 2 days; IQR 1–4). ‘Delayed admission’ was defined as an interval of ≥5 days between symptom onset and presentation at hospital.14 After excluding missing data (n=450), 227 of 1070 patients (21.2%) had a delayed admission. Prior to admission, 417 of 1520 patients (27.4%) consulted a general practitioner (GP) with influenza-like symptoms. Patients who experienced delayed admission were not significantly different to ‘early’ admissions in relation to age (median 27.0 years vs 25.0 years; p=0.56) or number of comorbidities (median 0 vs 1; p=0.25). However, radiological pneumonia (unadjusted OR 1.35; 95% CI 1.27 to 2.65) and severe outcome (unadjusted OR 1.67, 95% CI 1.15 to 2.43) were associated with delayed admission. Pre-admission GP consultation was significantly associated with delayed admission (unadjusted OR 2.09; 95% CI 1.41 to 3.11). Pre-admission antiviral drugs and antibiotics had been given to 172 (11.3%) and 280 (18.4%) of the cohort, respectively. There was no difference in pre-admission antiviral use between early and delayed admissions (96 of 845 (11.4%) vs 25 of 227 (11.0%), respectively) but a threefold increase in the likelihood of receiving pre-admission antibiotics in patients with delayed admission (76 of 227 (33.4%) vs 118 of 845 (14.0%); unadjusted OR 3.09, 95% CI 2.21 to 4.35). Of the 87 patients (58.3%) with delayed admission who had also seen a GP, 8 (9.2%) were prescribed antiviral drugs in contrast to 50 (57.5%) prescribed antibiotics.

There were 987 cases admitted prior to 23 October 2009 who would not have had the opportunity to be vaccinated or to have seroconverted (even if vaccinated) prior to illness onset. In the remaining 533 patients, 2009 seasonal and pandemic vaccination was recorded in only 21 and 12 instances, respectively.

## Clinical presentation and results of early investigations

The most common presenting symptoms upon admission in adults and children are summarised in figure 1. Online supplementary table 1 summarises vital signs on admission and early investigations for the FLU-CIN cohort.

### Pneumonia

There were 239 (15.7%) pneumonia cases on the basis of radiological reports. A manual review of unreported chest x-ray findings recorded in the case notes (by an unblinded respiratory physician) found 15 additional cases that could be classified as pneumonia based on documentation of acute pulmonary infiltrates and bilateral changes, giving a total of 254 (16.7%) radiological pneumonia cases in the FLU-CIN cohort. The median age of patients with pneumonia was 42 years (IQR 29–54) compared with 23 years (IQR 7–41) for non-pneumonia patients (p<0.001). Of pneumonia cases, 27% had been prescribed pre-admission antibiotics whereas only 13% had been prescribed pre-admission antiviral drugs. From 2087 specimens including 941 nose/throat swabs, 503 blood cultures, 253 urine, 70 stool and 195 sputum specimens taken, the following bacteria were identified: Staphylococcus aureus (n=7), Streptococcus pneumoniae (n=5), Escherichia coli (n=5), Haemophilus influenzae (n=5), Pseudomonas aeruginosa (n=2), Klebsiella spp. (n=1), coagulase-negative staphylococci (n=1) and mixed bacterial flora (n=11).

## Differences by pandemic wave

These data are summarised in table 3. Significantly lower proportions of school-age children and young adults (age 5–24

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**Table 2** Pre-admission comorbidity in 1520 patients hospitalised with pandemic H1N1 infection during the 2009–2010 pandemic compared with national prevalence data

| Underlying medical conditions | Children (<16 years), n = 480 (31.6%), n (%) | Adults, n = 1040 (68.4%), n (%) | All admissions, n = 1520, n (%) | Background, prevalence in the general population, % |
|------------------------------|---------------------------------------------|---------------------------------|---------------------------------|-----------------------------------------------|
| No. of comorbidities†        |                                             |                                 |                                 |                                               |
| 0                            | 346 (72.1)                                  | 492 (47.3)                      | 838 (55.1)                      |                                               |
| 1                            | 115 (23.9)                                  | 394 (37.9)                      | 509 (33.5)                      |                                               |
| 2 or more                    | 19 (4.0)                                    | 154 (14.8)                      | 173 (11.4)                      |                                               |
| Comorbidity                  |                                             |                                 |                                 |                                               |
| Cardiovascular disease       | 20 (4.2)                                    | 168 (16.2)                      | 188 (12.4)                      | 3.5                                           |
| Pulmonary disease            |                                             |                                 |                                 |                                               |
| COPD                         | 0 (0.0)                                     | 83 (8.0)                        | 83 (5.5)                        | 1.5                                           |
| Asthma                       | 71 (14.8)                                   | 314 (30.2)                      | 385 (25.3)                      | 5.9                                           |
| Other pulmonary disease      | 16 (3.3)                                    | 20 (2.0)                        | 36 (2.4)                        |                                               |
| Diabetes                     | 6 (1.3)                                     | 96 (9.2)                        | 102 (6.7)                       | 4.1                                           |
| Other metabolic disease      | 8 (1.7)                                     | 4 (0.4)                         | 12 (0.8)                        |                                               |
| Neurological disease         | 36 (7.5)                                    | 51 (5.0)                        | 87 (5.7)                        |                                               |
| Cerebrovascular disease      | 0 (0.0)                                     | 5 (0.5)                         | 5 (0.5)                         | 1.7                                           |
| Obesity recorded on admission‡ | 3 (0.6)                                    | 46 (4.4)                        | 49 (3.2)                        | 8.1‡                                          |
| Pregnancy                   | 1                                           | 82 (20.3)§                      | 83 (20.8)§                      | 5.6‡                                          |

*National prevalence data on comorbidity were obtained from the Quality and Outcomes Framework (QOF) primary care data for 2009 (http://www.qof.ic.nhs.uk) and are based on all ages, except for pregnancy.
†Recorded obesity and pregnancy are excluded from the number of comorbidities in the upper part of table 2.
‡National prevalence data on obesity based on QOF obesity registers, defined as body mass index ≥30.
§Percentage of pregnancies shown represents proportion in women aged 16–44.

15.6% of women aged 15–44 estimated to be pregnant in source population: in addition to 761 934 live births in the UK in 2008 (Office of National Statistics, General Register Office for Scotland and Northern Ireland Statistics and Research Agency) we assumed that 4% of women aged 15–44 years experienced a miscarriage or abortion in the same time period (500 084). To calculate the prevalence of pregnancy we took 8/12 of annual live births (assuming 8-month duration of pregnancy) and 3/12 of miscarriages/abortions (assuming 3-month duration), divided by the total female population aged 15–44 years (12 502 100).

*All admissions, n = 1520; n (%) = number of patients with the condition as a proportion of all admissions; adults, n = 1040; n (%) = number of patients with the condition as a proportion of all adults admissions; children, n = 480; n (%) = number of patients with the condition as a proportion of all children admissions.

**Table 3** Vital signs on admission

- Median age of patients with pneumonia was 42 years (IQR 29–54) compared with 23 years (IQR 7–41) for non-pneumonia patients (p<0.001).
- Of pneumonia cases, 27% had been prescribed pre-admission antibiotics whereas only 13% had been prescribed pre-admission antiviral drugs. From 2087 specimens including 941 nose/throat swabs, 503 blood cultures, 253 urine, 70 stool and 195 sputum specimens taken, the following bacteria were identified: Staphylococcus aureus (n=7), Streptococcus pneumoniae (n=5), Escherichia coli (n=5), Haemophilus influenzae (n=5), Pseudomonas aeruginosa (n=2), Klebsiella spp. (n=1), coagulase-negative staphylococci (n=1) and mixed bacterial flora (n=11).

**The term ‘delayed admission’ defines the interval between symptom onset and admission as ≥5 days, but does not carry any imputation that the delay in all cases was undesirable or clinically suboptimal.**
Demographic and comorbid independent predictors of severe outcome

Model 1 considered patient characteristics (socio-demographic and comorbidities) that could predict severe outcome: age, asthma, cardiovascular disease, chronic lung disease (non-asthma, non-COPD) and neurological disorders (table 5). We observed statistically significant increased risks associated with the age band 55–64 years (adjusted OR 2.08; 95% CI 1.16 to 3.74), pre-existing lung disease (excluding asthma and COPD) (adjusted OR 2.40; 95% CI 1.17 to 4.93), neurological disorders (adjusted OR 2.59; 95% CI 1.62 to 4.15) and recorded obesity (adjusted OR 2.22; 95% CI 1.18 to 4.18). Pre-existing asthma was associated with reduced likelihood of severe outcome (adjusted OR 0.49; 95% CI 0.34 to 0.70). In view of the complex, non-linear relationship between age and severe outcome, model 1 was also analysed excluding age, with similar findings (online supplementary table 2).

Clinical parameters independently predictive of severe outcome

Model 2 included delayed admission because this had a significant effect on severe outcomes in the univariate analysis (table 6). Radiologically confirmed pneumonia (adjusted OR 1.83; 95% CI 1.27 to 2.64), delayed admission (adjusted OR 1.67; 95% CI 1.09 to 2.56), altered consciousness on presentation (adjusted OR 6.53; 95% CI 3.73 to 11.41) and CRP levels ≥100 mg/litre (adjusted OR 3.78; 95% CI 2.41 to 5.94) were independently associated with severe outcomes as was a need for supplemental oxygen or intravenous fluid replacement on admission (adjusted OR 4.34; 95% CI 3.09 to 6.08) and adjusted OR 1.86; 95% CI 0.70 to 2.56), altered consciousness on presentation (adjusted OR 2.40; 95% CI 1.17 to 4.93), neurological disorders (adjusted OR 2.59; 95% CI 1.62 to 4.15) and recorded obesity (adjusted OR 2.22; 95% CI 1.18 to 4.18). Pre-existing asthma was associated with reduced likelihood of severe outcome (adjusted OR 0.49; 95% CI 0.34 to 0.70). In view of the complex, non-linear relationship between age and severe outcome, model 1 was also analysed excluding age, with similar findings (online supplementary table 2).

DISCUSSION

Although limited to severe influenza cases requiring hospitalisation, these data provide important information on predictors of severe outcomes and the impact of clinical management. They also suggest potential for improvement in the community management of pandemic influenza that might influence disease progression. Hospitals were asked to notify all cases with
### Table 3 Comparative analysis of comorbidity, demography, clinical characteristics and selected investigations in first wave versus second wave for patients hospitalised with pandemic H1N1 infection during the 2009–2010 pandemic (n=1520)

| Patient characteristic                  | First wave, n=601 (39.5%), n (%) | Second wave, n=919 (60.5%), n (%) | Unadjusted OR* (95% CI) | Age-adjusted OR (95% CI) |
|----------------------------------------|----------------------------------|----------------------------------|-------------------------|-------------------------|
| **Age (years)**                        |                                  |                                  |                         |                         |
| <1                                     | 39 (6.5)                         | 82 (8.9)                         | 1.00 (reference)        |                         |
| 1–4                                    | 60 (10.0)                        | 78 (8.5)                         | 0.62 (0.37 to 1.03)     |                         |
| 5–15                                   | 116 (19.3)                       | 105 (11.4)                       | 0.43 (0.27 to 0.68)     | 0.39 (0.27 to 0.68)     |
| 16–24                                  | 106 (17.6)                       | 139 (15.1)                       | 0.62 (0.39 to 0.99)     | 0.62 (0.39 to 0.99)     |
| 25–34                                  | 87 (14.5)                        | 155 (16.9)                       | 0.85 (0.53 to 1.35)     | 0.98 (0.62 to 1.56)     |
| 35–44                                  | 72 (12.0)                        | 123 (13.4)                       | 0.81 (0.50 to 1.31)     | 0.81 (0.50 to 1.31)     |
| 45–54                                  | 59 (9.8)                         | 109 (11.9)                       | 0.88 (0.54 to 1.44)     | 0.88 (0.54 to 1.44)     |
| 55–64                                  | 33 (5.5)                         | 82 (8.9)                         | 1.18 (0.68 to 2.06)     | 1.18 (0.68 to 2.06)     |
| ≥65                                    | 29 (4.8)                         | 46 (5.0)                         | 0.75 (0.41 to 1.38)     | 0.75 (0.41 to 1.38)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Ethnicity**                          |                                  |                                  |                         |                         |
| White                                  | 180 (30.0)                       | 450 (49.0)                       | 1.00                    | 1.00                    |
| Other                                  | 337 (56.1)                       | 173 (18.8)                       | 0.21 (0.16 to 0.26)     | 0.21 (0.16 to 0.27)     |
| Missing                                | 84 (14.0)                        | 296 (32.2)                       |                         |                         |
| **p Value**                            |                                  |                                  |                         |                         |
| **Neurological disorders**             |                                  |                                  |                         |                         |
|                                       | 45 (7.5)                         | 42 (4.6)                         | 0.59 (0.38 to 0.91)     | 0.60 (0.39 to 0.92)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Radiological pneumonia**             |                                  |                                  |                         |                         |
|                                       | 79 (13.1)                        | 175 (19.0)                       | 1.55 (1.16 to 2.07)     | 1.41 (1.04 to 1.90)     |
| **C-reactive protein (mg/litre)**      |                                  |                                  |                         |                         |
| ≤30                                    | 171 (28.5)                       | 222 (24.2)                       | 1.00                    | 1.00                    |
| 31–99                                   | 91 (15.1)                        | 171 (18.6)                       | 1.45 (1.05 to 2.00)     | 1.39 (0.99 to 1.93)     |
| 100                                     | 40 (6.7)                         | 122 (13.3)                       | 2.35 (1.56 to 3.54)     | 2.22 (1.46 to 3.39)     |
| Missing                                 | 299 (49.8)                       | 404 (44.0)                       |                         |                         |
| **p Value**                            |                                  |                                  |                         |                         |
| **Altered consciousness**              |                                  |                                  |                         |                         |
|                                       | 21 (3.5)                         | 53 (5.8)                         | 1.69 (1.01 to 2.83)     | 1.72 (1.03 to 2.89)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Dyspnoea**                           |                                  |                                  |                         |                         |
|                                       | 191 (31.8)                       | 384 (41.8)                       | 1.54 (1.24 to 1.91)     | 1.46 (1.17 to 1.82)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Pre-admission antibiotics**          |                                  |                                  |                         |                         |
|                                       | 82 (13.6)                        | 198 (21.6)                       | 1.74 (1.31 to 2.30)     | 1.69 (1.27 to 2.24)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Pre-admission antiviral drugs**      |                                  |                                  |                         |                         |
|                                       | 80 (13.3)                        | 92 (10.0)                        | 0.72 (0.53 to 0.99)     | 0.73 (0.53 to 1.00)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Delayed admission**                  |                                  |                                  |                         |                         |
| No                                     | 420 (69.9)                       | 423 (46.0)                       | 1.00                    | 1.00                    |
| Yes                                    | 77 (12.8)                        | 150 (16.3)                       | 1.93 (1.42 to 2.63)     | 1.91 (1.41 to 2.60)     |
| Missing                                | 104 (17.3)                       | 346 (37.6)                       |                         |                         |
| **p Value**                            |                                  |                                  |                         |                         |
| **Required supplemental oxygen on admission** | 154 (25.6)                       | 238 (30.6)                       | 1.28 (1.02 to 1.61)     | 1.21 (0.96 to 1.53)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Intravenous fluid replacement on admission** | 179 (29.8)                       | 211 (23.0)                       | 0.70 (0.56 to 0.89)     | 0.70 (0.55 to 0.88)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Oxygen saturation <94% on air**      |                                  |                                  |                         |                         |
| No                                     | 61 (10.2)                        | 315 (34.3)                       | 1.00                    | 1.00                    |
| Yes                                    | 178 (29.6)                       | 439 (47.8)                       | 0.48 (0.35 to 0.66)     | 0.49 (0.35 to 0.68)     |
| Missing                                | 362 (60.2)                       | 164 (18.4)                       |                         |                         |
| **p Value**                            |                                  |                                  |                         |                         |
| **Length of hospital stay**            |                                  |                                  |                         |                         |
| <2 days                                 | 137 (22.8)                       | 152 (16.5)                       | 1.00                    | 1.00                    |
| ≥2 days                                 | 395 (65.7)                       | 650 (70.7)                       | 1.48 (1.14 to 1.93)     | 1.41 (1.08 to 1.84)     |
| Missing                                | 68 (11.5)                        | 117 (12.7)                       |                         |                         |
| **p Value**                            |                                  |                                  |                         |                         |
| **Adverse outcomes (death or level 2 or 3 admission)** | 80 (13.3)                       | 188 (20.5)                       | 1.67 (1.26 to 2.23)     | 1.64 (1.23 to 2.18)     |
| **p Value**                            |                                  |                                  |                         |                         |
| **Level 2 or 3 admission**             |                                  |                                  |                         |                         |
|                                       | 72 (12.0)                        | 178 (19.4)                       | 1.76 (1.31 to 2.37)     | 1.73 (1.29 to 2.33)     |
| **p Value**                            |                                  |                                  |                         |                         |

*All comparisons are second wave compared with first wave.

No statistically significant differences were found by pandemic wave in the following patient characteristics: sex; comorbidities such as asthma, chronic obstructive pulmonary disease (COPD) and chronic pulmonary conditions other than asthma or COPD, hepatic disease, cardiovascular disease, diabetes, hypertension, immunocompromised status, or total comorbidity burden; recorded obesity, smoking status, pregnancy, inpatient treatment with antivirals or antibiotics; and mortality.

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confirmed pandemic H1N1 and cases were followed up without selection. Nevertheless, the inclusion of several children’s hospitals and tertiary respiratory referral centres may alter the representativeness of our findings and case ascertainment may not have been complete in all centres.

Our analysis identified that only 11% of the FLU-CIN cohort had been prescribed pre-admission antiviral drugs despite a national policy for making them widely available. The significant decline in use of antiviral drugs between first and second waves (despite the opening of the National Pandemic Flu Service in late July 2009) and the concomitant increase in the frequency of antibiotic use suggest that GPs may have reverted to the use of antibiotics rather than antivirals during the second wave. However, very few (<3%) bacterial infections were confirmed in the cohort. These data also imply that affordable, specific and sensitive near-patient tests for influenza could, in future, offer a significant advance to influenza management strategies by informing the appropriate use of antiviral drugs. One in five admissions were delayed and such patients were more likely to suffer a severe outcome, as reported elsewhere.

Patients with delayed admission were not different in terms of age or comorbidities. However, without access to primary care data, we cannot determine whether such patients could have been identified for earlier admission or treatment.

The age bands 0–4 and 16–34 years were markedly over-represented in the FLU-CIN cohort compared with the UK general population. However, in comparison to winter seasonal admissions for ARI, the age bands from 5 to 54 years were over-represented. There was also an over-representation of non-white ethnic groups compared with the source population and in relation to ARI admissions during seasonal influenza activity (first wave only), but no differences in progression to severe outcome were noted. The association between severe outcome and age was nonlinear, with infants <1 year and the over 50s showing an increased risk. Moreover, figure 2 describes a W-shaped distribution, as seen in the severe pandemic of 1918 and in Canada and the Netherlands in 2009. This phenomenon may be related to antigenic similarity between 1918-like and 2009 viruses and immune complex-mediated disease in some middle-aged adults.

Over half of patients had no pre-existing comorbidity and about 41% of in-hospital deaths occurred in those who were

### Table 4 Analysis of comorbidity, demography, clinical characteristics, care pathway and selected investigations as risk factors for severe outcomes (level 2 or 3 admission and/or death) in patients hospitalised with pandemic H1N1 infection during the 2009–2010 pandemic (n=1520)

| Patient characteristic | Cases (severe outcomes), n=268 (17.6%), n (%) | Controls, n=1252 (82.4%), n (%) | Unadjusted OR (95% CI) | p Value |
|------------------------|-----------------------------------------------|---------------------------------|------------------------|---------|
| Age (years)            |                                               |                                 |                        |         |
| <1                     | 25 (9.3)                                      | 96 (7.7)                        | 1.87 (1.04 to 3.34)    | 0.036   |
| 1–4                    | 23 (8.6)                                      | 115 (9.2)                       | 1.43 (0.80 to 2.58)    | 0.231   |
| 5–15                   | 29 (10.8)                                     | 192 (15.3)                      | 1.08 (0.63 to 1.87)    | 0.776   |
| 16–24                  | 30 (11.2)                                     | 215 (17.2)                      | 1.00 (reference)       |         |
| 25–34                  | 44 (16.4)                                     | 198 (15.8)                      | 1.59 (0.96 to 2.63)    | 0.070   |
| 35–44                  | 37 (13.8)                                     | 158 (12.6)                      | 1.68 (0.99 to 2.83)    | 0.053   |
| 45–54                  | 33 (12.3)                                     | 135 (10.8)                      | 1.75 (1.02 to 3.00)    | 0.042   |
| 55–64                  | 30 (11.2)                                     | 85 (6.8)                        | 2.53 (1.44 to 4.45)    | 0.001   |
| ≥65                    | 17 (6.3)                                      | 58 (4.6)                        | 2.10 (1.08 to 4.07)    | 0.028   |
| Asthma                 | 43 (16.0)                                     | 342 (27.3)                      | 0.51 (0.36 to 0.72)    | <0.001  |
| Chronic pulmonary conditions excluding asthma or COPD | 12 (4.5)                     | 24 (1.9)                        | 2.40 (1.18 to 4.86)    | 0.015   |
| Neurological disorders | 31 (11.6)                                     | 56 (4.5)                        | 2.79 (1.76 to 4.43)    | <0.001  |
| Cardiovascular disease | 50 (18.7)                                     | 138 (11.0)                      | 1.85 (1.30 to 2.64)    | 0.001   |
| Radiological Pneumonia | 94 (35.1)                                     | 160 (12.8)                      | 3.69 (2.73 to 4.98)    | <0.001  |
| C-reactive protein (mg/litre) |                                          |                                 |                        |         |
| ≤30                    | 38 (14.2)                                     | 355 (28.4)                      | 1.00                   |         |
| 31–99                  | 41 (15.3)                                     | 221 (17.7)                      | 1.73 (1.08 to 2.78)    | 0.022   |
| ≥100                   | 73 (27.2)                                     | 89 (7.1)                        | 7.66 (4.86 to 12.09)   | <0.001  |
| Missing                | 116 (43.3)                                    | 587 (46.9)                      |                        |         |
| Recorded obese         | 17 (6.3)                                      | 32 (2.6)                        | 2.58 (1.41 to 4.72)    | 0.002   |
| Altered consciousness  | 40 (14.9)                                     | 34 (2.7)                        | 6.28 (3.89 to 10.14)   | <0.001  |
| Dyspnoea               | 141 (52.7)                                    | 434 (34.7)                      | 2.09 (1.60 to 2.73)    | <0.001  |
| Pre-admission antibiotics | 74 (27.6)                              | 206 (16.5)                      | 1.94 (1.43 to 2.63)    | <0.001  |
| Required supplemental oxygen on admission | 163 (60.8) | 272 (21.7) | 5.59 (4.23 to 7.40) | <0.001 |
| Intravenous fluid replacement on admission | 93 (34.7) | 297 (23.7) | 1.71 (1.29 to 2.27) | <0.001 |
| Delayed admission      |                                               |                                 |                        |         |
| Yes                    | 114 (42.5)                                    | 729 (58.2)                      | 1.00                   |         |
| No                     | 47 (17.5)                                     | 180 (14.4)                      | 1.67 (1.15 to 2.43)    | 0.008   |
| Missing                | 107 (39.9)                                    | 243 (19.4)                      |                        |         |
| Length of hospital stay |                                               |                                 |                        |         |
| <2 days                | 5 (1.9)                                       | 284 (22.7)                      | 1.00                   |         |
| ≥2 days                | 170 (63.4)                                    | 875 (69.9)                      | 11.04 (4.49 to 27.12)  | <0.001  |
| Missing                | 93 (34.7)                                     | 93 (7.4)                        |                        |         |
| In-hospital antibiotic therapy | 235 (87.7) | 1020 (81.5) | 1.62 (1.10 to 2.40) | 0.016 |

No statistically significant association was observed between severe outcomes (level 2 or 3 admission or death) and the following patient characteristics: sex, ethnicity; comorbidities such as chronic obstructive pulmonary disease (COPD), hepatic disease, diabetes, hypertension, immunocompromised status or total comorbidity burden; smoking status, pregnancy, pre-admission antiviral use, oxygen saturation <94% on air; and inpatient treatment with antivirals.
previously healthy. People with pre-existing neurological disease and chronic pulmonary disease (other than asthma or COPD), and those with physician-defined obesity were at increased risk of severe outcomes as observed worldwide. Although 65% of patients recorded as obese had one or more underlying comorbidities, after adjustment, this remained an independent risk factor, possibly explained by respiratory compromise or a pro-inflammatory state.

The most common comorbidity was asthma, which was associated with a decreased risk of severe outcome and is consistent with other reports. Possible explanations include a lower threshold for admission or earlier admission (patients with asthma were significantly less likely to have a delayed admission compared with those without asthma; unadjusted OR 0.68, 95% CI 0.48 to 0.96). Lastly, it is possible that corticosteroid administration as part of asthma management protected patients with asthma from severe outcomes. These hypotheses are discussed in more detail in a subsequent manuscript.

All of the following were independent predictors of severe outcome:

- Altered consciousness
- Need for supplemental oxygen or intravenous fluid replacement at admission
- CRP $>$ 100 mg/litre

Comparing pandemic waves, we found a 33% decreased likelihood of a length of stay < 2 days, higher proportions of dyspnoea, altered consciousness and raised CRP; and a higher likelihood of delayed admission and of needing level 2 or 3 care, but lower levels of pre-admission antiviral use in the second wave. Together, these data may reflect greater confidence among GPs and receiving physicians to manage milder cases at home, and a lower perceived benefit from antiviral drugs for milder cases. In addition, in-hospital mortality appeared unchanged between waves and we found no statistically significant differences in the factors influencing severe outcomes by wave. However, other work suggests that case death rate increased from 0.015% to 0.025% between the first and second waves in the UK.

Table 5 Multivariable analysis: Patient characteristics independently predictive of severe outcomes in pandemic influenza during the 2009–2010 pandemic (n=1520)

| Patient characteristic                | Adjusted* OR (95% CI) | p Value |
|---------------------------------------|-----------------------|---------|
| Socio-demographic characteristics     |                       |         |
| Age (years)                           |                       |         |
| <1                                    | 1.60 (0.88 to 2.90)   | 0.123   |
| 1–4                                   | 1.20 (0.66 to 2.19)   | 0.545   |
| 5–15                                  | 0.91 (0.52 to 1.59)   | 0.740   |
| 16–24                                 | 1.00 (reference)      | —       |
| 25–34                                 | 1.60 (0.96 to 2.66)   | 0.071   |
| 35–44                                 | 1.47 (0.86 to 2.52)   | 0.164   |
| 45–54                                 | 1.46 (0.84 to 2.56)   | 0.183   |
| 55–64                                 | 2.08 (1.16 to 3.74)   | 0.014   |
| ≥65                                   | 1.45 (0.71 to 2.93)   | 0.308   |
| Underlying comorbidities              |                       |         |
| Asthma                                | 0.49 (0.34 to 0.70)   | <0.001  |
| Cardiovascular disease                | 1.43 (0.96 to 2.13)   | 0.075   |
| Other lung disease excluding COPD and asthma | 2.40 (1.17 to 4.93)   | 0.018   |
| Neurological disorders                | 2.59 (1.62 to 4.15)   | <0.001  |
| Recorded obesity                      | 2.22 (1.18 to 4.18)   | 0.013   |

*Each variable has been adjusted for all other variables in the model.

COPD, chronic obstructive pulmonary disease.

Table 6 Multivariable analysis: clinical parameters independently predictive of severe outcomes in pandemic influenza during the 2009–2010 pandemic (n=1520)

| Clinical parameter                     | Adjusted* OR (95% CI) | p Value |
|---------------------------------------|-----------------------|---------|
| Delayed admission                      | 1.67 (1.09 to 2.56)   | 0.019   |
| Radiologically confirmed pneumonia    | 1.83 (1.27 to 2.64)   | 0.001   |
| Presenting symptoms                   |                       |         |
| Dyspnoea                               | 1.22 (0.88 to 1.67)   | 0.231   |
| Altered consciousness                  | 6.53 (3.73 to 11.41)  | <0.001  |
| Required supplemental oxygen on admission | 4.34 (3.09 to 6.08)   | <0.001  |
| Intravenous fluid replacement on admission | 1.86 (1.30 to 2.66)   | 0.001   |
| Clinical parameters                   |                       |         |
| C-reactive protein (mg/dl)             | 3.78 (2.41 to 5.94)   | <0.001  |

*Each variable has been adjusted for all other variables in the model.
Data from the ROC analysis suggest that patient characteristics in model 1 (age 55–64 years, lung disease other than asthma or COPD, neurological disorders, recorded obesity) were not good predictors of severe outcomes (ROC area under the curve 0.65). This was probably because the combination of these variables is too rare to serve as a generic prediction rule. However, the clinical parameters in model 2 proved better predictors of severe outcomes with a ROC area under the curve value of 0.80 (delayed admission, pneumonia, altered consciousness, the need for supplemental oxygen or intravenous fluid on admission, CRP levels ≥100 mg/litre). It is, of course, arguable whether any model based on hospital observations has any use unless earlier intervention would be possible. However, patients with markers of potential severity on admission could be earmarked for early review by specialised respiratory physicians and intensivists. The next step would be to conduct a formal, prospective, head-to-head comparison of our algorithm with other triage tools.29

CONCLUSIONS

During the H1N1 pandemic in the UK in 2009–2010, among hospitalised patients, independent predictors of severe outcomes were increasing age, pre-existing chronic lung disease (excluding asthma or COPD), neurological disease and recorded obesity, but asthma was associated with decreased risk. Additional independent predictors of severe outcome were delayed admission, dyspnoea, radiographical pneumonia, altered consciousness, need for supplemental oxygen or intravenous fluid replacement on admission and CRP levels ≥100 mg/litre. The age-related risk of severe outcome followed a W-shaped distribution similar to that described for mortality in the 1918–1919 pandemic. An increase in the proportion of non-white patients compared with ARI admissions during seasonal influenza activity, seen in the first pandemic wave, was not maintained during the second wave. In-patient mortality rates were unchanged between waves but the threshold for admission probably increased during the second wave.

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Contributors All authors were involved with designing the study, interpreting and analysing the data, contributing to the article and approving the final version. JEE trained FLU-CIN data collectors, coordinated data collection, collated the data and oversaw data entry with JSN-V-T. PRM analysed the data. MGS adjusted the paediatric data for age and temperature. PRM, MGS, WSL and JSN-V-T wrote the article with the assistance of all co-authors and JSN-V-T acts as guarantor. The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of their respective employers.

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Ethics approval Before commencement, FLU-CIN procedures were reviewed by the Ethics and Confidentiality Committee of the National Information Governance Board for Health and Social Care in England and approved for collection, storage and use of personal data for surveillance purposes.

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Data sharing statement The collection of data for the FLU-CIN database has been publicly funded and, as a public good, will be made available for new research purposes on a case-by-case basis. In general, only anonymised data will be supplied to researchers, except where the law permits the processing of identifiable data. Ownership and oversight of data access and use resides with the Pandemic Influenza Preparedness Team at the Department of Health, England. Any requests for access to FLU-CIN data should be made to Department of Health via the corresponding author, Prof JS Nguyen-Van-Tam.

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