EDITOR'S CHOICE

Risk factors for hospitalisation and poor outcome with pandemic A/H1N1 influenza: United Kingdom first wave (May–September 2009)

J S Nguyen-Van-Tam,[1] P J M Openshaw,[2] A Hashim,[1] E M Gadd,[3] W S Lim,[4] M G Semple,[5] R C Read,[6] B L Taylor,[7] S J Brett,[8] J McMenamin,[9] J E Enstone,[1] C Armstrong,[3] K G Nicholson,[10] on behalf of the Influenza Clinical Information Network (FLU-CIN)

► Supplementary figures are published online only. To view these files please visit the journal online (http://thorax.bmj.com).

For numbered affiliations see end of article.

Correspondence to
Professor J Nguyen-Van-Tam, Division of Epidemiology and Public Health, University of Nottingham, Clinical Sciences Building, City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; jvt@nottingham.ac.uk

Received 14 January 2010
Accepted 21 April 2010

ABSTRACT

Background During the first wave of pandemic H1N1 influenza in 2009, most cases outside North America occurred in the UK. The clinical characteristics of UK patients hospitalised with pandemic H1N1 infection and risk factors for severe outcome are described.

Methods A case note-based investigation was performed of patients admitted with confirmed pandemic H1N1 infection.

Results From 27 April to 30 September 2009, 631 cases from 55 hospitals were investigated. 13% were admitted to a high dependency or intensive care unit and 5% died; 36% were aged <16 years and 5% were aged ≥65 years. Non-white and pregnant patients were over-represented. 45% of patients had at least one underlying condition, mainly asthma, and 13% received antiviral drugs before admission. Of 349 with documented chest x-rays on admission, 29% had evidence of pneumonia, but bacterial co-infection was uncommon. Multivariate analyses showed that physician-recorded obesity on admission and pulmonary conditions other than asthma or chronic obstructive pulmonary disease (COPD) were associated with a severe outcome, as were radiologically-confirmed pneumonia and a raised C-reactive protein (CRP) level (≥100 mg/l). 59% of all in-hospital deaths occurred in previously healthy people.

Conclusions Pandemic H1N1 infection causes disease requiring hospitalisation of previously fit individuals as well as those with underlying conditions. An abnormal chest x-ray or a raised CRP level, especially in patients who are recorded as obese or who have pulmonary conditions other than asthma or COPD, indicate a potentially serious outcome. These findings support the use of pandemic vaccine in pregnant women, children <5 years of age and those with chronic lung disease.

INTRODUCTION

On 11 June 2009 the World Health Organization announced the first influenza pandemic of the 21st century.[1 2] While most pandemic H1N1 infections were mild or subclinical, the case fatality rate was 0.1–0.7%.[3 4] Early reports suggested a case hospitalisation rate of 2–8%,[5–9] later moderated to approximately 1% in view of under-ascertainment of mild cases.[10] Although atypical, patients with severe disease imposed a considerable burden on hospital systems. Hospitalisation due to pandemic H1N1 infection was most common in children, teenagers and younger adults. At least half had underlying medical conditions.[1 2 8–12] Relatively few studies have examined the risk factors associated with a severe outcome.[7 13]

METHODS

Data collection

The Influenza Clinical Information Network (FLU-CIN) surveillance network was established by the Department of Health in England on 11 May 2009. Clinical data were collected from 55 hospitals in 20 cities or towns (see figure 1 in online supplement). Trained FLU-CIN data collectors gathered information from the case notes of patients hospitalised with pandemic H1N1 infection without pre-selection. All patients had acute respiratory illness and pandemic H1N1 infection confirmed by real-time reverse-transcriptase PCR. Diagnostic tests were performed as dictated by clinical management.

Data were extracted using a standard form that included demographic characteristics, past medical history, prehospital medication, clinical presentation, care timelines, initial assessment (emergency department and/or acute medical unit), investigations and care escalation from levels 0 to 3,[i] discharge and death. Since height and weight are not uniformly recorded in UK hospital notes, obesity based on physicians' observations was captured when recorded on admission.

Analysis of data

Anonymised data were analysed using STATA Version 10 (StataCorp). χ^2 or Fisher exact tests were used to assess differences in proportions and the Mann–Whitney test was used for continuous variables. The demographic data were compared with those of the combined populations of London, East Midlands and Northern Ireland because these areas provided >75% of the FLU-CIN cases. As

[i] Level 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 multiorgan failure (intensive care unit).

paediatric normal reference ranges for respiratory rate and blood pressure vary with age, and heart rate also varies with body temperature, abnormal values in children (aged <16 years) were defined after appropriate adjustment.[14–17]

Univariate analysis was performed using logistic regression to identify factors affecting the risk of requiring enhanced care (levels 2 or 3) or death in hospital (or both) as a combined measure of severe outcome. Unadjusted odds ratios (Wald test) and 95% CIs were computed. A multivariable regression technique was applied using all statistically significant variables identified during univariate analysis, including exploration for robustness and interactions using likelihood ratio tests. Age (continuous variable) was forced into each model, being an a priori confounder for comorbid conditions and case fatality. Two separate models were constructed—one for demography, comorbidities and clinical characteristics and one for selected investigations and other prognostic indicators. Where continuous variables (eg, serum C-reactive protein (CRP)) were found to be significant, these were converted into categorical variables to facilitate clinical interpretation. A peripheral oxygen saturation threshold of 94% (breathing air) was selected based on British Thoracic Society recommendations for the instigation of supplemental oxygen therapy.[18]

RESULTS

A total of 631 hospitalised cases with H1N1 infection (226 children, 405 adults; median age 23 years; range 3 months–90 years) admitted between 27 April and 30 September 2009 are described. The onset of illness, available for 522 patients, occurred from April 25 to September 29 (see figure 2 in online supplement). Most cases were non-white (table 1) and the distribution of age and ethnicity differed substantially from the source population. Of the 631 patients, 284 (45% overall; 34% children and 51% adults) had one or more underlying medical conditions (table 2), of which asthma was most common in children (16%) and adults (31%). Of 159 subjects with asthma, 88 (55%) regularly used oral or inhaled steroids. Twenty-seven patients were pregnant, representing 4% of total admissions and 18% of admissions among women aged 16–44 years (table 2). Two, 13 and 8 pregnancies were in the first, second and third trimesters, respectively (missing data, n=4), and 8 (30%) had one or more underlying medical conditions. Obesity was recorded on admission in 8 (2%) of 405 adults; no child was noted to be obese.

Preadmission care

The median interval between onset of illness and admission recorded for 522 cases was 2 days (range 0–33; interquartile range 0–24). It was shorter in children than in adults (1 day vs 2 days, p<0.001) but was unaffected by comorbid conditions (median 2 vs 2 days; p=0.42). Twenty children (9%) and 62 adults (15%) received antiviral drugs before admission (p=0.02). Preadmission antiviral drugs were given to 35 patients (12%) with comorbidity and to 47 patients (14%) without comorbidity (p=0.80).

Clinical presentation, treatment and outcome

Patients presented most frequently with fever (71%), cough (68%), breathlessness (36%), headache (27%), sore throat (23%) and nausea or vomiting (22%) in adults; and fever (74%), cough (50%) and nausea or vomiting (27%) in children. Overall, 11% presented with diarrhoea, which was almost twice as common in white ethnic groups (15.4% vs 8.1%; p=0.008) in both adults (16% vs 9%) and children (14% vs 7%).

Table 1 Demographic characteristics of 631 UK patients hospitalised with pandemic H1N1 infection during the first pandemic wave compared with source population data

	n (%)	Population comparison* (%)
Sex: female	320 (51)	51.3
Age (years)		
<1	42 (7)	1.2
1–4	59 (9)	5.2
5–15	125 (20)	14.2
16–24	114 (18)	11.7
25–34	83 (13)	16.9
35–44	75 (12)	15.4
45–54	68 (11)	12.3
55–64	32 (5)	9.4
65–74	22 (3)	7.3
>75	11 (2)	6.4
Ethnicity†		
White	202 (38)	81.9
Mixed	7 (1)	2.1
Asian/Asian British	169 (31)	8.0
Black/Black British	100 (19)	6.3
Chinese and other	59 (11)	1.7

Data are number (%) unless otherwise indicated.
*Data for comparison of sex, age structure and ethnicity (London, East Midlands and Northern Ireland combined) were obtained from the Office for National Statistics (www.statistics.gov.uk) and Northern Ireland Statistics and Research Agency (www.nisra.gov.uk): National Census 2001 data: KS01 sex, KS02 age structure, KS06 ethnicity and corresponding census area statistics (CAS) data: UV03, UV04 and UV09 (available on Neighbourhood Statistics and www.nomis.co.uk) for further subdivisional data.
†Information on ethnicity was unavailable for 94 cases; assessments of ethnicity are based on 537 cases.

Upon presentation, 63% of children and 87% of adults had tachycardia and 30% of children and 33% of adults had tachypnoea (table 3). About half had fever (≥38°C); 16% of children and 24% of adults had a peripheral oxygen saturation of <94% breathing air, and 13% of children and 24% of adults had systolic hypotension. Alanine aminotransferase was raised in 19% of children and 34% of adults. Increased levels of CRP of <100 mg/l occurred in 19% of children and 31% of adults; increases of ≥100 mg/l occurred in 8% of children and 18% of adults. Eighteen patients (3%) presented with symptoms of encephalitis (new behavioural change, meningism, focal signs, seizures or confusion), one of whom died. Twenty-nine patients (5%) presented with muscle weakness or tenderness suggestive of myositis, of whom one died.

Pneumonia

Chest radiographic results were recorded in the notes in 349 cases (106 children, 243 adults), of which 37 children (35%) and 65 adults (27%) had findings consistent with pneumonia. Thirty-seven of 65 adults had sufficient data to derive a CURB65 score of 0, 1 and 2 in 15 (41%), 17 (46%) and 5 (14%) cases, respectively. The median age of patients with pneumonia was 26 years; 46 (45%) had one or more underlying medical conditions, 4 were pregnant and 2 were obese. Initial arterial blood gas analysis readings (while breathing room air) were available from 34 patients with pneumonia; 1/23 (4%) with an arterial oxygen tension ≥8 kPa died compared with 3/11 (27%) with an initial reading <8 kPa (p=0.085).

The occurrence of radiological pneumonia was unrelated to the presence of underlying medical conditions (p=0.09). Of the 102 cases with radiological pneumonia, 14 (6 children) had received preadmission antiviral drugs (14%) compared with 28/247 (11%) patients (2 children) without pneumonia on the chest x-ray (p=0.53). The median length of stay for patients with

Table 2 Prehospital comorbidity in 631 patients hospitalised with pandemic H1N1 infection during the first pandemic wave compared with national prevalence data

	Children (n=226)	Adults (n=405)	All admissions (n=631)	Background prevalence* (%)
No. of comorbidities†				
0	149 (66)	198 (49)	347 (55)	–
1	66 (29)	138 (34)	204 (32)	–
≥2	11 (5)	69 (17)	80 (13)	–
Comorbidity				
Cardiovascular disease	5 (2)	64 (16)	69 (11)	3.5
Pulmonary disease				
COPD	0 (0)	25 (6)	25 (4)	1.5
Asthma	35 (16)	124 (31)	159 (25)	5.9
Other pulmonary disease	8 (3)	13 (3)	21 (3)	-
Diabetes	3 (1)	48 (12)	51 (8)	4.1
Other metabolic disease	4 (2)	2 (<1)	6 (1)	-
Neurological disease	9 (4)	10 (3)	19 (3)	-
Cerebrovascular disease	0 (0)	3 (<1)	3 (<1)	1.7
Obesity recorded on admission	0 (0)	8 (2)	8 (1)	8.1‡
Pregnancy	0 (0)	27 (7)§	27 (4)	6.2¶

Data are number (%) unless otherwise indicated.
*National prevalence data on comorbidity were obtained from the Quality and Outcomes Framework (QOF) primary care data for 2009 (www.qof.ac.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 portion of the table.
‡National prevalence data on obesity based on QOF obesity registers defined as body mass index ≥30 kg/m^2.
§27 pregnancies represent 7% of all adults but 18% of women aged 16–44 years in the study.
¶6.2% of females aged 15–44 years estimated to be pregnant in source population: in addition to 207 474 live births in London, East Midlands and Northern Ireland in 2008, we assumed that 4% of females aged 15–44 years experienced miscarriage or abortion in the same time period (119 668). To calculate the prevalence of pregnancy we took 9/12 of annual live births (assuming 9-month duration of pregnancy) and 3/12 of miscarriages/abortions (assuming 3-month duration), divided by the total female population aged 15–44 years.
COPD, chronic obstructive pulmonary disease.

pneumonia was 6 days compared with 3 days for patients without pneumonia (p=0.0001). Thirty-seven of 102 patients (36%) required level 2 (n=6) or level 3 (n=31) care, 21 (21%) underwent mechanical ventilation (intubated) and 12 (12%) died, of whom 11 were ventilated. Mortality in cases with radiographic pneumonia was significantly higher than in cases without (OR 4.57, 95% CI 1.71 to 12.18; p=0.0008). Four cases of pneumonia (4%) had positive bacteriological findings. Two children with severe developmental delay and extreme prematurity, respectively, grew methicillin-resistant *Staphylococcus aureus* (MRSA) and one adult grew *Streptococcus pneumoniae* in sputum; all three died. One adult had *S aureus* bacteraemia and survived.

Inpatient treatment

After admission, antiviral drugs were prescribed to 474 patients (75%) and 366 (58%) received antibiotics. One hundred and forty-seven of 157 cases (93%) who did not receive an antiviral drug in hospital did not receive an antiviral agent before hospitalisation. One hundred and fourteen patients (18%) received steroids as an acute intervention; of these, 71 had underlying asthma, 57 of whom were previously maintained on steroids. The 43 patients without asthma treated in hospital with steroids included 13 with COPD or other chronic lung disease on long-term steroids; 7 on steroids for other long-term conditions (eg, myeloma); 8 with sudden deterioration (of whom 4 were pregnant or recently post-partum); 5 with wheeze on admission; 2 obese patients; 2 with suspected new asthma; and 1 suspected allergic reaction (the reason for steroid treatment was unclear in 5 cases).

Length of stay

The median length of hospital stay was 3 days in children (range 1–32; interquartile range 1–28) and 4 days in adults (range 1–41; interquartile range 1–29; p=0.004); it was unaffected by comorbidity or treatment with antiviral drugs before hospitalisation.

Deaths, severity criteria and requirement for critical care

Overall, 85 of the 631 cases (14%) had a severe outcome. Eighty patients received level 2 (n=27) or level 3 (n=53) care and 29 died. The recorded case fatality rate was 4.6%, 3.5% in children and 5.2% in adults (likelihood ratio=1.5, p=0.34). Seventeen of the 29 fatalities (59%) were previously healthy. The median age of those who died was 49 years in adults and 7 years in children. There were no significant differences in use of level 2 or level 3 care with age; however, the in-hospital case fatality rate increased with age (<5 years (3%), 5–15 years (4%), 16–44 years (3.7%), 45–64 years (9%), ≥65 years (6.0%)) and was significantly higher in patients aged ≥45 years (3.6% vs 8.3%; p=0.02). Twenty-five patients (31%) died while in level 2 or level 3 care. A further two deaths occurred on standard wards (a patient with metastatic carcinoma and another with severe chronic lung disease), one in the emergency room (after 4 h resuscitation) and one after transfer to another hospital (no subsequent information). Of cases receiving level 2 or level 3 care, those who died received a median of 10 days care at this level whereas survivors received 3 days of care (p=0.001). No patients were declined level 2 or level 3 care for non-clinical reasons during the study period.

Recipients of antiviral drugs before admission were less likely to require level 2 or level 3 care (8/82 (9.8%) vs 72/549 (13%); likelihood ratio=0.72, p=0.394) or to die (2/82 (2.4%) vs 27/549 (4.9%); likelihood ratio=0.48, p=0.31) than non-recipients, but both trends were non-significant. Two of 27 pregnant women (7%) died in hospital while in level 3 care; four others (15%) received level 2 (n=1) or level 3 (n=3) care and survived.

Table 4 shows the association between admission variables and severe outcome. Altered conscious level, dyspnoea, requirements for intravenous fluids or supplementary oxygen, radiologically-confirmed pneumonia and CRP levels ≥100 mg/l were each associated with a severe outcome, as were obesity recorded on admission and chronic pulmonary disease other than asthma or COPD (eg, cystic fibrosis, fibrosing alveolitis and congenital lung defects). In a multivariable model of demography, comorbidities and clinical characteristics, obesity recorded on admission and pulmonary conditions other than asthma or COPD were found to be associated with a severe outcome (table 5). An additional multivariable analysis of selected investigations and possible prognostic indicators showed that radiologically-confirmed pneumonia and a CRP level ≥100 mg/l were independently significant (table 5). The addition of further variables did not significantly alter either model.

DISCUSSION

The strengths of this study include confirmation by standardised PCR criteria, relatively few missing data and a setting in which hospitalisation and management of cases is driven by national guidelines.[19] Reported cases were followed up without selection. Except in Scotland, the acquisition of cases closely mirrored the national epidemic curve geographically and temporally, with most occurring in Greater London, the English Midlands and

Table 3 Presenting signs and initial investigations and the percentage that were abnormal in patients hospitalised with pandemic H1N1 infection during the first pandemic wave

Observations	n	Mean	Range	Interquartile range	Level of abnormality	%
Temperature (°C)						
Children	183	38.0	35.3–41.4	36.0–40.1	37.1–37.9	22
					≥38.0	50
Adults	344	39.0	35.1–40.2	35.9–40.3	37.1–37.9	24
					≥38.0	53
Pulse (rate/min)						
Children	97	137	54–240	89–184	> Normal*	63
Adults	218	107	54–184	62–155	>85	87
Pulse (respirations/min)						
Children	94	37	18–98	20–66	> Normal	30
Adults	205	23	10–44	14–40	>30	33
Systolic BP (mmHg)						
Children	32	106	83–126	93–119	< Normal	13
Adults	216	125	68–191	84–185	<110	24
Diastolic BP (mmHg)						
Children	33	60	39–90	42–77	< Normal	36
Adults	217	71	32–121	43–100	<65	32
C-reactive protein (mg/l)						
Children	98	60	1–322	4–146	31–99	19
					≥100	8
Adults	208	57	1–322	1.5–274	31–99	31
					≥100	18
White cell count ($\times 10^9$/l)						
Adults and children	425	9.0	1.1–38.0	1.1–32.9	>11.0	17
Children	102	44	3–163	19–82	>195	0
Adults	285	91	5–800	7–611	>200	3
Urea (μmol/l)						
Children	104	7.2	0.6–106	1.1–40	>6.4	14
Adults	286	7.3	0.9–130	1.5–56	>6.7	18
Alanine transaminase (IU/l)						
Children	70	42.7	2–393	7–177	>40	19
Adults	179	36.3	8–167	10–127	>35	34
Spo_2 (%, breathing room air)						
Children	175	95.9	54–100	80–100	<94%	16
Adults	334	95.1	66–100	60–100	<94%	24

*See Methods for derivation of abnormal values in children.
Spo_2, peripheral oxygen saturation.

Northern Ireland (see figures 1 and 2 in the online supplement). Overall, 12% of patients required high dependency or intensive care and 4.6% died; the mortality among those requiring enhanced care was 31%.

The median age of cases was 23 years and 46% had risk factors for seasonal influenza complications. In relation to the source population, hospitalisations were highest in those aged <5 years and lowest in those aged ≥55 years, consistent with the age-specific prevalence of cross-reacting antibodies.[20] Similar to other reports,[13] mortality was significantly higher above 44 years of age.

Over one-half of all admissions and 59% of all in-hospital deaths occurred in previously healthy people. In contrast, Donaldson *et al* found that 36% of patients who died had no (19%) or only mild (17%) underlying illnesses.[21] The principal comorbidity was asthma (in adults and children). About 45% of hospitalised patients with asthma with pandemic H1N1 infection did not routinely use inhaled or oral steroids, suggesting that pandemic influenza vaccine (H1N1) might be beneficial for all patients with asthma rather than just those with more severe disease.

Pregnancy substantially increases the risks for severe respiratory illness and excess deaths during pandemics and seasonal influenza,[22] and in our series pregnant women comprised 18% of admissions among women aged 16–44 years compared with an expected prevalence of 6% in the source population. These findings suggest that pregnant women are about three times more likely to be admitted to hospital with H1N1 infection than non-pregnant women of similar age and confirm the importance of vaccinating pregnant women, which may also protect their newborn infant.[23]

Obesity has been previously identified as a risk factor for severe pandemic H1N1 infection.[13 24 25] Obesity recorded on admission was identified as an independent risk factor for a severe outcome. This observation possibly reflects that gross (as opposed to mild) obesity is more likely to be recorded by physicians in case notes and the lack of reserve respiratory capacity in such individuals.

Univariate analyses showed that patients with a severe outcome were more likely to be recorded as obese and to have pulmonary disease other than asthma or COPD (eg, cystic fibrosis, fibrosing alveolitis and congenital lung defects), altered consciousness level, shortness of breath, radiologically-confirmed pneumonia, CRP level ≥100 mg/l, peripheral oxygen saturation of <94% on air or to have required supplemental oxygen or intravenous fluids on admission than those managed on standard wards. These findings are similar to those of previous studies[7 13] and highlight the importance of regular monitoring

Table 4 Analysis of comorbidity, demography, clinical characteristics and selected investigations as risk factors for severe outcome in patients hospitalised with pandemic H1N1 infection during the first pandemic wave

	People affected by condition or feature (number with severe outcome)	Likelihood ratio (95% CI)	p Value
Age (years)	–	1.01* (0.99 to 1.02)	0.089
Asthma	159 (18)	0.77 (0.44 to 1.34)	0.360
COPD	25 (6)	2.10 (0.81 to 5.43)	0.123
Chronic pulmonary conditions, excluding asthma or COPD	21 (7)	3.41 (1.33 to 8.71)	0.010
Cardiovascular disease	69 (12)	1.41 (0.72 to 2.75)	0.314
Diabetes	51 (7)	1.02 (0.44 to 2.35)	0.956
Neurological disorders	19 (3)	1.21 (0.34 to 4.25)	0.764
Hepatic disease	7 (2)	2.60 (0.49 to 13.65)	0.257
Obesity recorded on admission	8 (4)	6.96 (1.46 to 27.28)	0.008
Smoker (current and former)‡	103 (16)	1.01 (0.53 to 1.91)	0.972
Pregnancy	27 (6)	1.87 (0.73 to 4.77)	0.190
White ethnicity† ‡	202 (29)	1.08 (0.65 to 1.78)	0.764
Altered conscious level	10 (6)	1.11 (1.04 to 1.17)	0.001
Dyspnoea	181 (44)	1.32 (1.81 to 1.49)	0.001
Heart rate (abnormal)†	198 (31)	1.62 (0.80 to 3.30)	0.180
Respiratory rate (abnormal)†	89 (16)	1.78 (0.89 to 3.56)	0.102
Required supplemental oxygen on admission	99 (33)	4.51 (2.72 to 7.40)	0.001
Intravenous fluid replacement on admission	145 (28)	1.76 (1.07 to 2.89)	0.005
Radiologically-confirmed pneumonia	102 (37)	5.28 (2.95 to 9.47)	0.001
CRP ≥100 mg/l†	46 (16)	4.41 (2.14 to 9.10)	0.001
Spo_2 <94% on air†	107 (31)	3.60 (2.17 to 6.27)	0.001

*Reflects a 1% increase in risk of severe outcome for each additional year of age.
†Information about smoking history was documented for 216 cases; ethnicity was recorded for 537 cases; heart rate, with corrections for temperature, was available for 512 cases; respiratory rate was recorded for 470 cases; chest radiography findings were recorded for 349 cases; CRP levels were recorded for 306 cases; Spo_2 data were recorded for 252 cases.
‡45 severe outcomes among 335 non-white patients.
COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; Spo_2, peripheral oxygen saturation.

for dyspnoea and peripheral oxygen saturation. Multivariable analysis of clinical features revealed that obesity recorded on admission and pulmonary conditions other than asthma or COPD remained significant clinical risk factors for a severe outcome. In addition, radiologically-confirmed pneumonia and CRP levels ≥100 mg/l were independently associated with a severe outcome. In general, CRP levels are higher in patients with bacterial infections than in those with non-bacterial infections, and high levels are associated with mortality.[26] Our findings should alert physicians to the possibility of very high CRP levels in patients with pandemic H1N1 infection and its potential seriousness. In our study, 29% of patients with chest x-rays had findings consistent with pneumonia. The median duration of stay of these patients was twice as long as those without pneumonia, and mortality in cases with radiographic pneumonia was several fold higher than for the whole case series (12% vs 4.6%). Bacterial co-infections were less commonly reported than in other case series,[27 28] although we did not access autopsy data.[29]

Table 5 Results of logistic regression analyses of (A) demography, comorbidities and clinical characteristics and (B) selected investigations and other possible prognostic indicators for critical care requirement or death in hospital

	Odds ratio (95% CI)	p Value
(A) Clinical conditions*		
Obesity recorded on admission	6.08 (1.45 to 25.37)	0.013
Chronic respiratory disease other than asthma or COPD	3.17 (1.22 to 8.24)	0.018
(B) Other clinical parameters†		
Radiologically-confirmed pneumonia	4.97 (2.09 to 11.81)	0.001
C-reactive protein >100 mg/l	3.06 (1.20 to 7.81)	0.019

*Multivariable analysis of demography, comorbidities and clinical characteristics was constructed based on observations from 631 cases.
†A separate multivariable analysis was constructed for selected investigations and other possible prognostic indicators based on observations from 193 cases.
COPD, chronic obstructive pulmonary disease.

Higher rates of severe pandemic H1N1 infection have been reported in indigenous or disadvantaged populations,[24 30 31] as also occurred during 1918–19.[32] In our study, the number of Asian and black people who were admitted exceeded population estimates of ethnic profile 3–4-fold. The reasons for this excess are unclear, but could include language barriers affecting consulting behaviour or treatment access, overcrowding, household size and genetic susceptibility.

Fewer than one-sixth of all children and adults in this case series, including those with underlying medical risk factors for complications, received antiviral drugs before admission; this requires further investigation. In this case series, 25% were not prescribed antiviral drugs during the admission for reasons that are unclear; in most cases (93%) they did not receive an antiviral drug before hospital admission either. While the median interval between illness onset and hospital admission was just 1 day in children and 2 days in adults, 28% of children and 23% of adults in our study were apyrexial on admission, while just over half had a fever of ≥38°C. Such findings question the appropriateness of specifying fever of at least 38°C as part of the clinical case definition in current diagnostic, treatment and infection control algorithms.

The median length of stay in hospital was 3 days in children and 4 days in adults, which was unaffected by comorbidity or the use of antiviral drugs before admission. While cases that received antiviral drugs before admission were less likely to require high dependency or intensive care and were 50% less likely to die in hospital, neither trend was significant. A number of other studies now suggest that early treatment with oseltamivir may reduce the likelihood of hospitalisation and death due to pandemic H1N1 influenza.[33–35]

Conclusions

While most patients with pandemic H1N1 influenza experience mild disease, 12% of those admitted to hospital require high dependency or intensive care, about 30% have radiographic pneumonia and 5% die. Pandemic H1N1 influenza should be considered in the differential diagnosis of any respiratory illness while the pandemic virus is circulating in the community; fever ≥38°C is a poor discriminator. Patients admitted to hospital with illness compatible with influenza should have a chest x-ray on admission and should be actively monitored for altered level of consciousness, dyspnoea and low peripheral oxygen saturation. An abnormal chest x-ray or raised CRP level—especially in patients who are observed to be obese, have pulmonary conditions other than asthma or COPD or are pregnant—may suggest a potentially serious outcome. Our findings support the use of H1N1 pandemic vaccine in pregnant women, children aged <5 years and those with chronic lung disease as a priority, including patients with asthma, regardless of severity.

Author affiliations
[1]Division of Epidemiology and Public Health, University of Nottingham, Nottingham, UK
[2]Centre for Respiratory Infections, National Heart and Lung Institute, Imperial College, London, UK
[3]Department of Health, Skipton House, London, UK
[4]Department of Respiratory Medicine, Nottingham University Hospitals NHS Trust, Nottingham, UK
[5]School of Reproductive and Developmental Medicine, University of Liverpool, Liverpool, UK
[6]Department of Infection and Immunity, University of Sheffield, Royal Hallamshire Hospital, Sheffield, UK
[7]Department of Critical Care, Portsmouth Hospitals NHS Trust, Portsmouth, UK
[8]Centre for Peri-operative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, London, UK
[9]Health Protection Scotland, NHS National Services, Glasgow, UK
[10]Infectious Diseases Unit, University Hospitals of Leicester NHS Trust, Leicester Royal Infirmary, Leicester, UK

Acknowledgements The authors gratefully acknowledge individuals who helped identify cases and collated clinical data: Alison Booth, Margaret Charlesworth, Sarah Rodenhurst, Angela Ballard and Alison Holmes at Imperial College Healthcare NHS Trust, London, UK; Sally Batham, Phayre Parkinson, Tracy Kumar and Aiden Dunphy at the University Hospitals of Leicester NHS Trust, Leicester, UK; Anne Tunbridge, Patty Hempsall, Joyce Linskill, Aimee Turner and Eric Moulds at Sheffield University Hospitals NHS Trust, Sheffield, UK; Elvina White, Elaine Scott, Jennifer Cater, Erica Sergi and Helen Hill at Alder Hey Children's Hospital NHS Foundation Trust, Liverpool, UK; Deborah Fleetwood, Lorna Roche, Sarah Dyas and Maria Boswell at the Royal Liverpool and Broadgreen University Hospital's Trust, Liverpool, UK; Gillian Vernon, Gillian Houghton, Heather Longworth and Angela Kerrigan at Liverpool Women's Hospital, Liverpool, UK; Sonia Greenwood, Gemma Thompson, Emily Jarvis, Tom Bewick and Charlotte Minter at the Nottingham University Hospitals NHS Trust, Nottingham, UK; Kristina Lum Kin, Jacqueline Daglish, Sam Hayton and Gemma Slinn at Birmingham Children's Hospital, Birmingham, UK; Michelle Lacey at Quality Improvement Scotland; Karen Duffy, Anne Gordon and Kevin Rooney at Greater Glasgow and Clyde NHS Hospitals, Scotland; Brian Smyth and Cathriona Kearns from the National Public Health Agency, Northern Ireland for identifying cases and facilitating data collection; Teresa Cunningham at the Southern Trust and Leslie Boydell at the Belfast Trust for facilitating data collection; Alemayehu Amberbir, Safaa Al-Badri, Baraa Mahgoob and Nachi Arunachalam at the University of Nottingham for data entry and obtaining background population data; also Graham Watson for database development and support. They also thank Professor Sir Gordon Duff, Co-Chair of the Scientific Advisory Group for Emergencies, and Professor Dame Sally Davies and Professor Janet Darbyshire, who Co-Chair the Influenza Clinical Information Network Strategy Group, for their support and constructive remarks; Dr Shona Kelly of the University of Nottingham for help in developing the initial data collection tool; and Dr Barbara A Bannister of the Department of Health, England and Dr Patrick O'Brien of University College London Hospitals NHS Foundation Trust for assistance in further developing the data set. The authors thank the Chief Executive Officers, clinicians, virologists and managers, too numerous to mention, who were active in notifying cases to FLU-CIN. SJB and PJMO wish to acknowledge the support of the UK NIHR Biomedical Research Centre scheme.

Funding Funding was received from the Department of Health, London and from the Scottish Government Chief Medical Officer and Public Health Directorate (funding for Scottish centre only).

Competing interests JSN-V-T has received funding to attend influenza related meetings, lecture and consultancy fees and research funding from several influenza antiviral drug and vaccine manufacturers and is a former employee of SmithKline Beecham plc (now GlaxoSmithKline), Roche Products Ltd and Sanofi-Pasteur MSD. PJMO is a member of the European Scientific Working Group on Influenza (ESWI) which is funded by the pharmaceutical industry. EMG and CA are employees of the Department of Health, England. WSL has received research funding from Wyeth. MGS is an advisor to the Department of Health, England. SJB has received consultancy fees from GlaxoSmithKline and Baxter. JEE has received consultancy fees from GlaxoSmithKline and performed paid work for the Department of Health, England. KGN has received H5 avian influenza vaccines from Novartis and H1N1 pandemic influenza vaccines from GlaxoSmithKline and Baxter to facilitate MRC and NIHR-funded trials. He has received consultancy fees from Novartis and GlaxoSmithKline and lecture fees from Baxter. A colleague of KGN at the University Hospitals of Leicester NHS Trust was principal investigator and recipient of research funding from Roche on antiviral resistance and from Novartis on pandemic H1N1 vaccines.

Ethics approval Before starting this study, 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.

Contributors All authors were involved with designing the study and interpreted and analysed data and contributed to the report and approved the final version. JEE trained FLU-CIN data collectors, coordinated data collection, collated the data and oversaw data entry with JSN-V-T and AH. AH analysed the data. MGS adjusted the paediatric data for age and temperature. JSN-V-T and KGN wrote the report with assistance from all co-authors and are guarantors. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of their respective employers.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Perez-Padilla R,** de la Rosa-Zamboni D, Ponce de Leon S, *et al*. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009;**361**:680–9.
2. **Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team.** Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009;**360**:2605–15. [Erratum: N Engl J Med 2009;361:102.]
3. **Garske T,** Legrand J, Donnelly CA, *et al*. Assessing the severity of the novel influenza A/H1N1 pandemic. *BMJ* 2009;**339**:b2840.
4. **Vaillant L,** La Ruche G, Tarantola A, *et al*. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. *Euro Surveill* 2009;**14**:pii=19309. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19309 (accessed 19 Oct 2009).
5. **Health Protection Agency**, Health Protection Scotland, National Public Health Service for Wales, HPA Northern Ireland Swine Influenza Investigation Teams. Epidemiology of new influenza A (H1N1) virus infection, United Kingdom, April–June 2009. *Euro Surveill* 2009;**14**:pii=19232. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19232 (accessed 19 Oct 2009).
6. **Gilsdorf A,** Poggensee G. Working Group Pandemic Influenza A(H1N1)v. Influenza A (H1N1)v in Germany: the first 10,000 cases. *Euro Surveill* 2009;**14**:pii=19318. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19318 (accessed 19 Oct 2009).
7. **Jain S,** Kamimoto L, Bramley AM, *et al*. Hospitalized patients with 2009 H1N1 influenza in the United States, April–June 2009. *N Engl J Med* 2009;**361**:1935–44.
8. **Centers for Disease Control and Prevention.** Hospitalized patients with novel influenza A (H1N1) virus infection—California, April–May, 2009. *MMWR Morb Mortal Wkly Rep* 2009;**58**:536–41.
9. **Anon.** Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. *Wkly Epidemiol Rec* 2009;**84**:185–9.
10. **Anon.** Human infection with new influenza A (H1N1) virus: clinical observations in hospitalized patients, Americas, July 2009 — update. *Wkly Epidemiol Rec* 2009;**84**:305–8.

11. **Jamieson DJ,** Honein MA, Rasmussen SA, *et al*. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet* 2009;**374**:451—8.
12. **Denholm JT,** Gordon CL, Johnson PD, *et al*. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. *Med J Aust* 2010;**192**:1—3.
13. **Louie JK,** Acosta M, Winter K, *et al*. Factors associated with death or hospitalization due to pandemic 2009 influenza A(H1N1) infection in California. *JAMA* 2009;**302**:1896—902.
14. **Rusconi F,** Castagneto M, Gagliardi L, *et al*. Reference values for respiratory rate in the first 3 years of life. *Pediatrics* 1994;**94**:350—5.
15. **Wallis LA,** Healy M, Undy MB, *et al*. Age related reference ranges for respiration rate and heart rate from 4 to 16 years. *Arch Dis Child* 2005;**90**:1117—21.
16. **American Heart Association in collaboration with International Liaison Committee on Resuscitation.** Guidelines 2000 for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2000;**102**(Suppl):I1—I384.
17. **Thompson M,** Harnden A, Perera R, *et al*. Deriving temperature and age appropriate heart rate centiles for children with acute infections. *Arch Dis Child* 2009;**94**:361—5.
18. **O'Driscoll BR,** Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008;**63**(Suppl 6):vi1—68. [Erratum: Thorax 2009;64:91].
19. **British Infection Society**, British Thoracic Society, Health Protection Agency. Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic. Provisional guidelines from the British Infection Society, British Thoracic Society and Health Protection Agency in collaboration with the Department of Health. *Thorax* 2007;**62**(Suppl 1):1—46.
20. **Hancock K,** Veguilla V, Lu X, *et al*. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. *N Engl J Med* 2009;**361**:1945—52.
21. **Donaldson LJ,** Rutter PD, Ellis BM, *et al*. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. *BMJ* 2009;**339**:b5213.
22. **Fiore AE,** Shay DK, Broder K, *et al*. Prevention and control of seasonal influenza with vaccines: Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. *MMWR* Recomm Rep 2009 July 31/58(Early Release);1—52. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr58e0724a1.htm (accessed 18 Nov 2009).
23. **Zaman K,** Roy E, Arifeen SE, *et al*. Effectiveness of maternal influenza immunization in mothers and infants. *N Engl J Med* 2008;**359**:1555—64.
24. **Kumar A,** Zarychanski R, Pinto R, *et al*. Critically ill patients with 2009 influenza A (H1N1) infection in Canada. *JAMA* 2009;**302**:1872—9.
25. **Centers for Disease Control and Prevention.** Intensive-care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *MMWR Morb Mortal Wkly Rep* 2009;**58**:749—52.
26. **Keshet R,** Boursi B, Maoz R, *et al*. Diagnostic and prognostic significance of serum C-reactive protein levels in patients admitted to the department of medicine. *Am J Med Sci* 2009;**337**:248—55.
27. **Estenssoro E,** Rios FG, Apeztegula C, *et al*. Pandemic 2009 influenza A(H1N1) in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med* 2010. [Epub 2010 Mar 4].
28. **Centers for Disease Control and Prevention.** Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection—United States, April —August 2009. *MMWR Morb Mortal Wkly Rep* 2009;**58**:941—7.
29. **Centers for Disease Control and Prevention.** Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) virus infection—United States, May—August 2009. *MMWR Morb Mortal Wkly Rep* 2009;**58**:1071—4.
30. **The ANZIC Influenza Investigators.** Critical care services and 2009 H1N1 influenza in Australia and New Zealand. *N Engl J Med* 2009;**361**:1925—34.
31. **Baker MG,** Wilson N, Huang QS, *et al*. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. *Euro Surveill* 2009;**14**:1—6. http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19319 (accessed 14 Jan 2010).
32. **Rice GW,** Palmer E. Pandemic influenza in Japan, 1918-19: mortality patterns and official responses. *J Jpn Stud* 1993;**19**:389—420.
33. **Falagas ME,** Vouloumanou EK, Baskouta E, *et al*. Treatment options for 2009 H1N1 influenza: evaluation of the published evidence. *Int J Antimicrob Agents* 2010;**35**:421—30.
34. **Institut de Veille Sanitaire.** Intérêt d'un traitement précoce par antiviral pour réduire la sévérité et la mortalité par grippe A(H1N1)2009: données issues de la surveillance des formes graves. *[French]*. http://www.invs.sante.fr/surveillance/grippe_dossier/docs_professionnels/antiviraux_grippe_a_h1n1_211209.pdf (accessed 25 Mar 2010).
35. **Zarychanski R,** Stuart TL, Kumar A. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) infection. *CMAJ* 2010;**182**:257—64.