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 decreased 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.

Key messages

What is the key question?
► What factors influenced severe outcomes in patients admitted to hospital with pandemic influenza, and were there differences between the first and second waves in the UK in terms of clinical epidemiology and management?

What is the bottom line?
► In addition to underlying chronic illnesses and specific clinical characteristics (pneumonia, dyspnoea, raised C-reactive protein), delayed hospital admission was also an important risk factor for severe outcome (which itself followed a W-shaped distribution by age).
► Among patients admitted, there was evidence that use of antivirals in the community declined in the second pandemic wave, whereas prescribing of antibiotics increased substantially.

Why read on?
► This large study provides detailed insights into the pattern of hospital admission for pandemic influenza in the UK, including variations by ethnicity, age and recorded obesity; it also reveals that, despite widespread availability, antiviral treatment was usually not started before admission to hospital in contrast to the prescribing of antibiotics.

surveillance of hospitalised cases.[3] Having already documented the first wave of the pandemic (May—September 2009),[3] this paper presents an analysis across the first and second pandemic waves.

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

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

transcribed PCR were included; no other selection criteria were applied. FLU-CIN was an 'emergency' initiative with a purposive sampling frame based on 13 sentinel hospitals situated in five clinical 'hubs' in Nottingham, Leicester, London, Sheffield and Liverpool, with contributions from a further 45 non-sentinel hospitals in England and 17 in Scotland, Wales and Northern Ireland. This included five children's hospitals and five tertiary respiratory referral centres (three with facilities for Extra Corporeal Membrane Oxygenation).[i] Participating hospitals were requested to notify all cases of confirmed pandemic H1N1 infection.

Descriptive analyses considered demographic data, pre-existing comorbidities recorded in case notes, pregnancy, physician-defined obesity, clinical parameters and clinical management details. Paediatric data were described as abnormal when values lay outside two standard deviations of normal ranges for respiratory rate, heart rate and blood pressure, adjusting for age, sex and temperature (heart rate only).[3 4] We examined total and weighted comorbidity burden (the latter using Charlson's comorbidity index).[5 6]

Using logistic regression (Wald tests) we investigated differences by pandemic wave and identified risk factors for severe outcomes. The split between first and second waves was defined using national surveillance data (first wave: to 31 August 2009; second wave: from 1 September 2009).[7] 'Severe outcome' was defined as admission to level 2 (high dependency unit) or level 3 (intensive care unit) facilities,[ii] and/or death. Age was treated as a categorical variable for univariate analyses. The lowest age band (<1 year) was used as a reference for the comparison of the two waves as the purpose was to compare distributions between waves. However, for the analyses of severe outcome, the age band of 16−24 years (least risk category) was used as the reference because we could not assume a linear relationship between age and severe outcome. Continuous variables such as serum C-reactive protein (CRP) levels were coded categorically to facilitate clinical interpretation.[8 9] A multivariable regression analysis was conducted for statistically significant variables (p≤0.05) identified during univariate analyses. Two separate models were constructed to examine potential predictors of severe outcome: model 1 included patient characteristics (demographic characteristics and pre-existing comorbidities) while model 2 included clinical characteristics (symptoms, findings of clinical examination and investigations). Both models were then restricted to include only the variables that were significantly associated with an increased risk, and receiver operating characteristics (ROC) curves were plotted to explore the prediction of severe outcome. In essence, the predictive ability of the final model for severe outcome was calculated by assigning each patient an unweighted score of '1' for every risk factor present, and calculating sensitivity and specificity for each cut-off value. All analyses were conducted using Stata, V.11.

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

	n (%)	UK population comparison, %	Pre-pandemic hospital data, acute respiratory infections,* %
Sex†			
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	4.6
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
Ethnicity§			
White	630 (41.5)	92.1	83.3
Mixed	11 (0.7)	1.2	1.9
Asian/Asian British	249 (16.4)	4.0	8.7
Black/black British	129 (8.5)	2.0	3.4
Chinese and other	121 (8.0)	0.8	2.7

*Hospital 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.
†Census 2001 data for comparison of sex (KS01 tables) were obtained from the Office for National Statistics (ONS) (http://www.statistics.gov.uk).
‡Demographic data on age distribution based on 2009 mid-year population estimates (ONS).
§Ethnicity 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%).

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

[ii]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 multi-organ failure—intensive care unit.

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.
¶5.6% 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 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 (12 502 100).

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.[iii] 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=0.361) or number of comorbidities (median 0 vs 1; p=0.023). However, radiological pneumonia (unadjusted OR 1.83; 95% CI 1.27 to 2.63) 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 843 (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 843 (14.0%); unadjusted OR 3.09; 95% CI 2.21 to 4.33). Of the 87 patients (38.3%) 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, 234 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

[iii]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.

Figure 1 Frequency of presenting symptoms in adults and children (<16 years) hospitalised with pandemic H1N1 infection during the 2009–2010 pandemic.
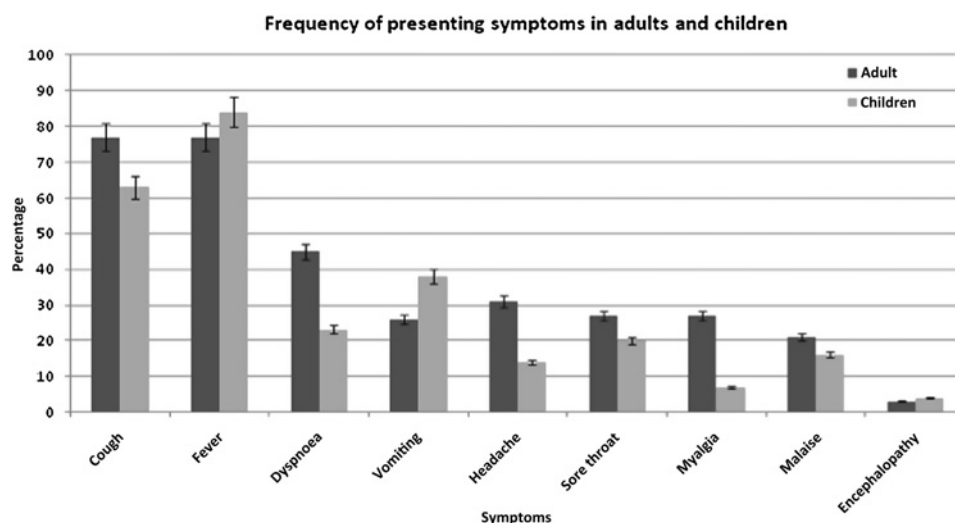
years) were admitted during the second wave, and the proportion of people from non-white ethnic groups also declined significantly (becoming similar to that seen during seasonal influenza activity). But higher proportions of patients presented with dyspnoea, altered consciousness and CRP levels ≥31 mg/litre. Hospital stays <2 days' duration were 33% less likely in the second wave (unadjusted OR 0.67; 95% CI 0.52 to 0.88), but the likelihoods of delayed admission (unadjusted OR 1.93; 95% CI 1.42 to 2.63), and needing level 2/3 care (unadjusted OR 1.76; 95% CI 1.31 to 2.37) were both higher, although there were no apparent differences in mortality. The frequency of prescribing of pre-hospital antiviral drugs decreased from 13.3% to 10.0% between the first and second waves, respectively (p=0.048), whereas the use of pre-hospital antibiotics increased from 13.6% to 21.6% (p<0.001).

Factors associated with severe outcome
Univariate analysis
The risk of severe outcome varied by age band and was generally highest in the youngest children (age <1 year) and those aged 45 years and over (table 4). However, a further sensitivity analysis using quinquennial age bands showed an increased risk in children under 1 year, those aged 31–40 and older adults (age >50 years), following a W-shaped distribution (figure 2). An increased risk of severe outcome was associated with specific comorbidities (pre-existing chronic lung disease (excluding asthma and chronic obstructive pulmonary disease (COPD)), neurological disorders and cardiovascular disease); but there was no relation to total comorbidity burden. Recorded obesity was also associated with increased risk. In contrast, pre-existing asthma was associated with significantly decreased risk of severe outcome. No significant association was observed between pregnancy and severe outcome (unadjusted OR 0.92; 95% CI 0.47 to 1.83).[iv]

Dyspnoea, altered consciousness, levels of CRP ≥100 mg/litre, need for supplemental oxygen or intravenous fluid replacement on admission were all associated with an increased risk of severe outcome, as was the use of pre-admission antibiotics. Radiologically confirmed pneumonia was strongly associated with severe outcome.

[iv]Comparator restricted to non-pregnant women aged 16–44 years in the FLU-CIN cohort.

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, nonlinear 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 1.30 to 2.66, respectively). Figure 3 shows the ROC curves and area under curve values for the two resulting models with only the independent predictors of increased risk. In the case of model 1 a new variable representing the age group 55–64 years was created to construct the ROC curve, to allow for the nonlinear increase in risk observed with age.

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)	
16–24	106 (17.6)	139 (15.1)	0.62 (0.39 to 0.99)	
25–34	87 (14.5)	155 (16.9)	0.85 (0.53 to 1.35)	
35–44	72 (12.0)	123 (13.4)	0.81 (0.50 to 1.31)	
45–54	59 (9.8)	109 (11.9)	0.88 (0.54 to 1.44)	
55–64	33 (5.5)	82 (8.9)	1.18 (0.68 to 2.06)	
≥65	29 (4.8)	46 (5.0)	0.75 (0.41 to 1.38)	
p Value			p trend=0.010	
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			<0.001	<0.001
Neurological disorders	45 (7.5)	42 (4.6)	0.59 (0.38 to 0.91)	0.60 (0.39 to 0.92)
p Value			0.018	0.020
Radiological pneumonia	79 (13.1)	175 (19.0)	1.55 (1.16 to 2.07)	1.41 (1.04 to 1.90)
p Value			0.003	0.025
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			p trend <0.001	P trend <0.001
Altered consciousness	21 (3.5)	53 (5.8)	1.69 (1.01 to 2.83)	1.72 (1.03 to 2.89)
p Value			0.046	0.040
Dyspnoea	191 (31.8)	384 (41.8)	1.54 (1.24 to 1.91)	1.46 (1.17 to 1.82)
p Value			<0.001	0.001
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			<0.001	<0.001
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			0.048	0.049
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			<0.001	<0.001
Required supplemental oxygen on admission	154 (25.6)	281 (30.6)	1.28 (1.02 to 1.61)	1.21 (0.96 to 1.53)
p Value			0.037	0.104
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			0.003	0.002
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)	165 (18.0)	—	—
p Value			<0.001	<0.001
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	69 (11.5)	117 (12.7)	—	—
p Value			0.003	0.012
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			<0.001	0.001
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			<0.001	<0.001

*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.

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				
No	114 (42.5)	729 (58.2)	1.00	
Yes	47 (17.5)	180 (14.4)	1.67 (1.15 to 2.43)	0.008
Missing	107 (39.9)	343 (27.4)	−	
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.

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.[10] 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)[10] 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.[11] 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 overrepresented 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 overrepresented. 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,[12] and in Canada and the Netherlands in 2009.[13 14] This phenomenon may be related to antigenic similarity between 1918-like and 2009 viruses,[15] and immune complex-mediated disease in some middle-aged adults.[16]

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

Figure 2 Unadjusted OR of severe outcome by age (OR and 95% CI) for patients hospitalised with pandemic H1N1 infection during the 2009—2010 pandemic. Severe outcome defined as admission to high dependency (level 2) or intensive (level 3) care facilities, and/or death.
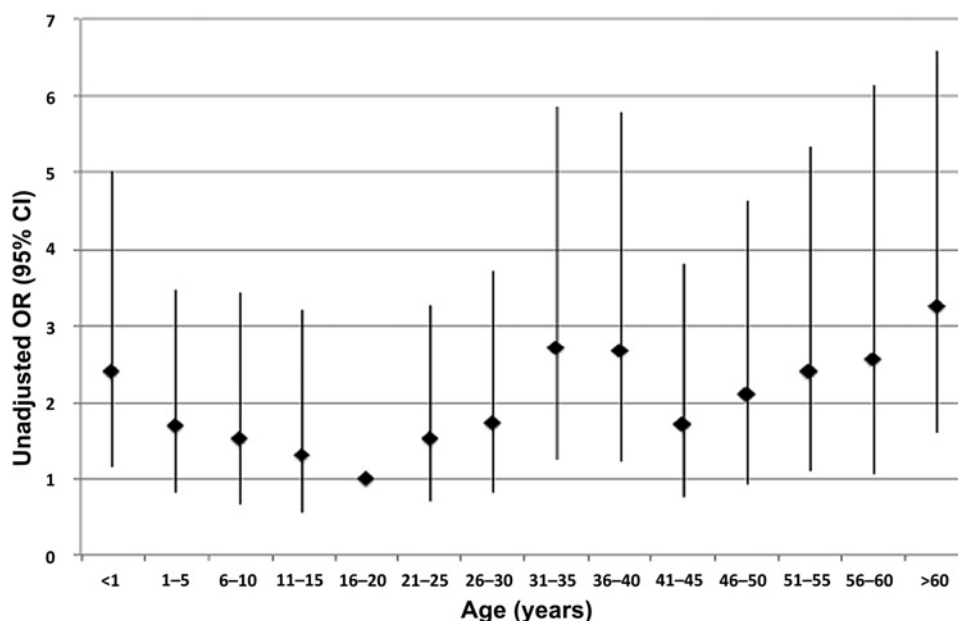
previously healthy. People with pre-existing neurological disease and chronic pulmonary disease (other than asthma or COPD), and those with physician-defined obesity were at increased risk of severe outcomes as observed worldwide.[17–23] Although 65% of patients recorded as obese had one or more underlying comorbidities, after adjustment, this remained an independent risk factor, possibly explained by respiratory compromise or a pro-inflammatory state.[24 25]

The most common comorbidity was asthma, which was associated with a decreased risk of severe outcome and is consistent with other reports.[17 18 22] Possible explanations include a lower threshold for admission[26] 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 and influenza-related pneumonia, as noted elsewhere.[17 18 23 27]

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.[28]

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) (≥100 vs <100)	3.78 (2.41 to 5.94)	<0.001

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

Figure 3 Receiver operating curves (ROCs) for model 1 (patient characteristics predicting severe outcomes in pandemic influenza) and model 2 (clinical parameters predicting severe outcomes in pandemic influenza) for patients hospitalised with pandemic H1N1 infection during the 2009—2010 pandemic.
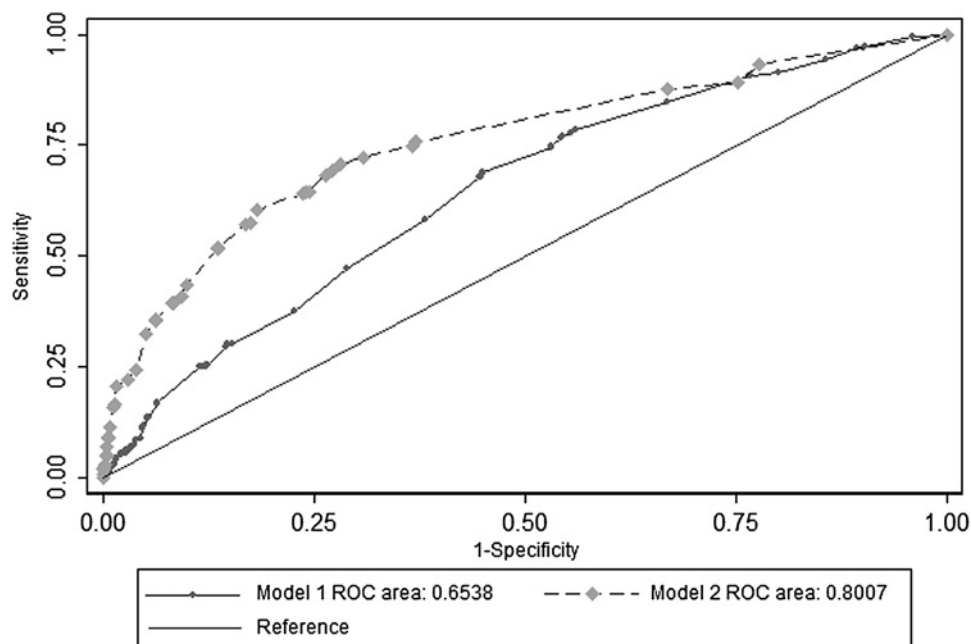
Comparison of ROC curves for Model 1 (patient characteristics) and Model 2 (clinical parameters)

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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