Clinical and laboratory features distinguishing pandemic H1N1 influenza-related pneumonia from interpandemic community-acquired pneumonia in adults

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ABSTRACT

Background Early identification of patients with H1N1 influenza-related pneumonia is desirable for the early instigation of antiviral agents. A study was undertaken to investigate whether adults admitted to hospital with H1N1 influenza-related pneumonia could be distinguished clinically from patients with non-H1N1 community-acquired pneumonia (CAP).

Methods Between May 2009 and January 2010, clinical and epidemiological data of patients with confirmed H1N1 influenza infection admitted to 75 hospitals in the UK were collected by the Influenza Clinical Information Network (FLU-CIN). Adults with H1N1 influenza-related pneumonia were identified and compared with a prospective study cohort of adults with CAP hospitalised between September 2008 and June 2010, excluding those admitted during the period of the pandemic.

Results Of 1046 adults with confirmed H1N1 influenza infection in the FLU-CIN cohort, 254 (25%) had H1N1 influenza-related pneumonia on admission to hospital. In-hospital mortality of these patients was 11.4% compared with 14.0% in patients with inter-pandemic CAP (n=648). A multivariate logistic regression model was generated by assigning one point for each of five clinical criteria: age ≤65 years, mental orientation, temperature ≥38°C, leucocyte count $\leq 12\times10^9$/l and bilateral radiographic consolidation. A score of 4 or 5 predicted H1N1 influenza-related pneumonia with a positive likelihood ratio of 9.0. A score of 0 or 1 had a positive likelihood ratio of 75.7 for excluding it.

Conclusion There are substantial clinical differences between H1N1 influenza-related pneumonia and inter-pandemic CAP. A model based on five simple clinical criteria enables the early identification of adults admitted with H1N1 influenza-related pneumonia.

INTRODUCTION

In March 2009 the first cases of a novel strain of influenza A virus of swine origin were reported in Mexico[1] and, within 3 months, global spread led to declaration of a pandemic by the World Health Organization (WHO). While most cases of pandemic influenza H1N1 infection have been mild or subclinical,[2–4] some patients experienced severe illness from H1N1 influenza infection and others severe influenza-related complications.[5 6]

Pneumonia is one of the commonest and most important complications of influenza infection. Influenza virus causes primary viral pneumonia, and secondary bacterial infections are also recognised.[7 8] In contemporary cohorts of patients admitted with inter-pandemic community acquired pneumonia (CAP), influenza is frequently found as a co-pathogen alongside other respiratory pathogens such as *Streptococcus pneumoniae*.[9–12] Studies of the 1918–19 influenza pandemic have suggested that the majority of influenza-related deaths during that period were caused by secondary bacterial pneumonia.[13] More recently, in hospitalised patients with confirmed H1N1 influenza infection, radiological evidence of pneumonia was observed in 18–66% of patients.[14–17] In addition, although not necessarily the cause of death, pneumonia was found in the majority of fatal cases at post-mortem examination.[18 19] Overall, fewer than 30% of H1N1 influenza-related pneumonia cases have evidence of bacterial co-infection,[20–22] suggesting that primary viral pneumonia is often important.

Early identification of patients with H1N1 influenza-related pneumonia may enable the early administration of antiviral agents with possible improved outcomes.[23] However, there are few data relating to the clinical differentiation of H1N1 influenza-related pneumonia from inter-pandemic CAP. The aims of the current study were (1) to compare and contrast the clinical features of adult patients admitted with CAP versus H1N1 influenza-related pneumonia and (2) to develop a model that identifies H1N1 influenza-related pneumonia using simple clinical criteria.

METHODS

Study patients

H1N1 influenza-related pneumonia cohort (H1N1 cohort)

Between May 2009 and January 2010, the Influenza Clinical Information Network (FLU-CIN) collected clinical and epidemiological data on patients admitted to UK hospitals with confirmed H1N1 influenza infection. Seventy-five hospitals in 31 cities or towns were included. The details of data collection and the overall findings from the first wave of the 2009 pandemic have been described elsewhere.[24] H1N1 influenza infection

was diagnosed by a positive polymerase chain reaction (PCR) result from respiratory samples obtained via a nasopharyngeal swab or bronchoalveolar lavage performed during the admission episode. Data collected included demography, clinical observations, clinical course, laboratory and radiological test results and outcome. The current study cohort comprised adults (aged ≥16 years) whose admission chest x-rays met one of the following criteria:

1. Chest x-ray report clearly suggestive of pneumonia.[25]
2. Chest x-ray report showed acute infiltrates but no consolidation.
3. No chest x-ray report available but x-ray documented in the clinical notes as being in keeping with pneumonia (n=24).

Patients who had acquired H1N1 influenza infection while in hospital or had been transferred to a study site from another hospital (eg, for extracorporeal membrane oxygenation therapy) were excluded.

Non-H1N1 influenza CAP cohort (CAP cohort)

Between September 2008 and June 2010, consecutive adult patients (aged ≥16 years) admitted to a large UK teaching hospital trust (Nottingham University Hospitals NHS trust) with CAP were prospectively recruited as part of a population-based observational cohort study. Patients were included if they had at least one acute symptom in keeping with a lower respiratory tract infection (breathlessness, cough, sputum production or fever), had new infiltrates on a chest x-ray and were treated by the admitting team for CAP. Patients were excluded if they had been admitted to hospital in the preceding 10 days, had tuberculosis, or had post-obstructive pneumonia due to lung cancer. Participants were identified by study investigators on a daily basis from the acute admitting medical wards and enrolled following informed consent. All patients were managed in a similar manner according to trust CAP guidelines at the discretion of the attending clinician. For the purposes of this analysis and to ensure inclusion of only cases without H1N1 influenza infection, participants were excluded if admitted during the period of H1N1 influenza circulation in Nottingham (between 30 April 2009 and 10 February 2010—this interval comprising all cases of H1N1 influenza infection in the Nottingham area based on local Health Protection Agency data (unpublished)).

Statistical methods

Data were analysed using SPSS Version 16.0. Continuously distributed variables were compared between H1N1 and CAP cohorts using the Student's t test if data were normally distributed and the Mann–Whitney U test if non-normally distributed. Categorical data were compared using Pearson χ^2. In order to derive a clinical diagnostic model for H1N1 influenza-related pneumonia, continuously distributed variables were re-categorised into binary variables based on thresholds derived from established acute severity scores (CURB-65 score,[26] Pneumonia Severity Index,[27] Surviving Sepsis Campaign[28]) and univariate analysis using χ^2 allowed calculation of odds ratios with 95% confidence intervals. Variables for inclusion in the final model were selected using automatic stepwise regression with both forwards (selection) and backwards (deletion) variants. The efficacy of the model for predicting H1N1 influenza-related pneumonia was then assessed by calculating the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve.

RESULTS

Patient characteristics

Of 1046 adults with confirmed H1N1 influenza infection in the FLU-CIN cohort, 266 (25.4%) had evidence of either radiographic consolidation or other infiltrates consistent with acute infection. Twelve patients were transferred in from hospitals outside the study area or developed influenza infection while already an inpatient, leaving a study cohort of 254 patients (H1N1 cohort). The comparator group comprised 648 patients with inter-pandemic CAP (CAP cohort). The patient characteristics are summarised in table 1 and the relative age distribution of both cohorts is shown in figure 1. Despite having similar in-hospital mortality (H1N1 cohort 11.4%; CAP cohort 14.0%), the two groups differed substantially. The median age of patients in the H1N1 cohort was 42 years compared with 75 years in the CAP cohort ($p<0.001$). The most common comorbid illnesses in the H1N1 cohort were asthma (25.2%) and diabetes mellitus (9.8%) compared with chronic obstructive pulmonary disease (COPD) (26.1%) and diabetes mellitus (15.4%) in the CAP cohort. In the H1N1 cohort, 9.4% of patients had ≥3 comorbid illnesses compared with 11.9% of controls. In addition, patients in the H1N1 cohort were more likely to be febrile, tachycardic, have bilateral radiographic abnormalities and have lower leucocyte counts and levels of C-reactive protein. Confusion, comorbidity and blood urea levels were higher among patients in the CAP cohort. Within the H1N1 cohort, 11 (4.3%) were pregnant and 21 (8.3%) were obese. The value of the CURB-65 score in predicting inpatient mortality was assessed by calculating the AUC for ROC curves for each group; the AUC for the H1N1 cohort was 0.650 compared with 0.741 for the CAP cohort.

Derivation of a clinical model for the diagnosis of H1N1 influenza-related pneumonia

Nine categorical variables were found to be associated with H1N1 influenza-related pneumonia on univariate analysis (table 2). Two of these variables (C-reactive protein and albumin) were excluded from the derivation of the diagnostic prediction model because they are not routinely performed on admission in all hospitals for acutely ill patients. In a logistic regression model, five of the seven variables were found to be statistically significant at the 5% level (table 3). These variables remained statistically significant using both forwards and backwards stepwise regression models. The resulting 5-point score generated a ROC curve AUC of 0.873 (based on 858 data points). The derived score stratifies patients into three risk groups for H1N1 influenza-related pneumonia as shown in table 4. In order to assess the impact of age on the discriminant model, a further analysis was undertaken with age excluded from the logistic regression analysis, leaving the four variables of bilateral radiographic consolidation, mental orientation, leucocyte count $\leq 12\times10^9$/l and temperature ≥38°C. The resulting ORs were 3.0 (95% CI 2.0 to 4.4), 6.3 (95% CI 3.5 to 11.5), 9.4 (95% CI 6.3 to 14.3) and 2.6 (95% CI 1.8 to 3.8), respectively. The ROC curve AUC for this model was 0.806. Use of age ≤65 years as a single binary predictor gave an AUC of 0.794.

C-reactive protein and albumin were excluded from the initial logistic regression analysis in order to maximise clinical utility of the algorithm. When both variables were included as part of a multivariate analysis for exploratory purposes (H1N1 cohort, n=123; CAP cohort, n=456), only albumin ≤30 g/dl was statistically significant at the 5% level (OR 1.9; 95% CI 1.1 to 3.5). The five previously described variables of age ≤65 years, bilateral radiographic consolidation, mental orientation, leucocyte count $\leq 12\times10^9$/l and temperature ≥38°C remained statistically significant within the model.

As the age profiles of the two cohorts were significantly different and age may be a surrogate for other confounding factors, a secondary analysis was undertaken including only

Table 1 Clinical characteristics of patients with H1N1 influenza-related pneumonia compared with community-acquired pneumonia (CAP)

Characteristic	H1N1 cohort (n=254)	CAP cohort (n=648)	p Value
Demographics			
Age (years)	42 (29–54)	75 (61–84)	<0.001
Male	109 (42.9%)	367 (56.6%)	<0.001
Admission observations			
Temperature (°C), mean (95% CI)	38.1 (37.9 to 38.2) (n=245)	37.5 (37.4 to 37.6) (n=644)	<0.001
Pulse (/min)	110 (97–120) (n=244)	100 (86–115) (n=646)	<0.001
SBP (mm Hg), mean (95% CI)	125 (123 to 128) (n=243)	126 (124 to 129) (n=646)	0.61
Respiratory rate (/min)	24 (19–28) (n=240)	22 (18–28) (n=646)	0.14
Confusion	18 (7.1%)	182 (28.1%)	<0.001
Outcome			
Critical care admission	88 (34.6%)	83 (12.8%)	<0.001
LOS for survivors (days)	6 (3–11) (n=206)	8 (4–14) (n=553)	0.003
Inpatient death	29 (11.4%)	91 (14.0%)	0.296
Investigations			
Bilateral consolidation	89 (39.0% of 228)	129 (19.9%)	<0.001
White cell count ($\times 10^9$/l)	7.6 (5.4–11.3) (n=239)	14.5 (10.5–19.9) (n=646)	<0.001
Urea (mmol/l)	4.7 (3.3–6.9) (n=232)	7.9 (5.5–12.6) (n=647)	<0.001
C-reactive protein (mg/l)	85 (34–199) (n=184)	148 (61–248) (n=602)	<0.001
Albumin (g/dl)	34 (30–40) (n=177)	31 (27–35) (n=488)	<0.001
Symptoms			
Productive cough	147 (57.9%)	287 (58.7% of 489*)	0.83
Dyspnoea	151 (59.4%)	428 (87.5% of 489*)	<0.001
Comorbidity			
Asthma	64 (25.2%)	57 (8.8%)	<0.001
COPD	24 (9.4%)	169 (26.1%)	<0.001
CCF	1 (0.4%)	46 (7.1%)	<0.001
Diabetes mellitus	25 (9.8%)	100 (15.4%)	0.029
Charlson index, mean (95% CI)	1.11 (0.94 to 1.27)	1.33 (1.23 to 1.44)	0.023

Values are median (IQR) or n (%) of patients unless otherwise stated. Normally distributed data are reported as means with 95% CI and non-normally distributed data as medians with interquartile range.
*Data not given for patients with confusion.
CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; CCF, congestive cardiac failure; LOS, length of hospital stay; SBP, systolic blood pressure.

those patients aged <65 years (H1N1 cohort, n=228; CAP cohort, n=200). Within this subgroup, median age remained significantly different (39 years vs 50 years; p<0.001). In a logistic regression analysis, leucocyte count ≤12×10^9/l (OR 10.1, 95% CI 6.1 to 16.7), age ≤50 years (OR 2.7, 95% CI 1.6 to 4.4), bilateral radiographic change (OR 2.5, 95% CI 1.5 to 4.4) and temperature ≥38°C (OR 2.1, 95% CI 1.3 to 3.4) were the only significant contributors to the final model. Using this model to predict H1N1 influenza-related pneumonia, the AUC for the ROC curve was 0.789.

A model to distinguish H1N1 influenza-related pneumonia based solely on physiological and radiological variables available rapidly in the emergency department (ie, excluding laboratory results) is shown in the online supplement.

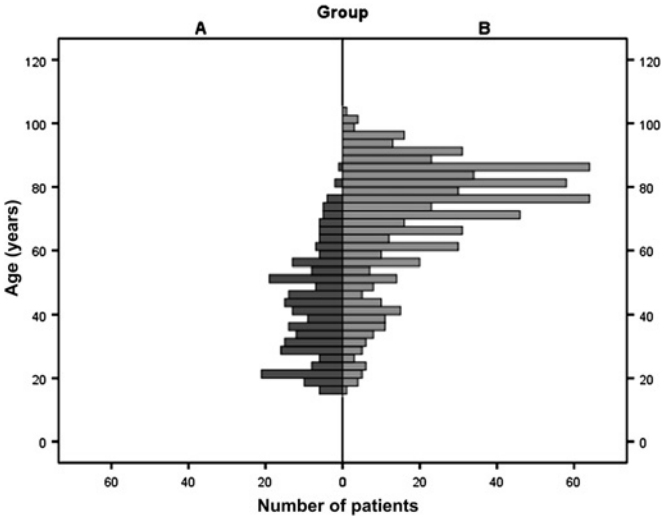

Figure 1 Age distribution of patients with H1N1 influenza-related pneumonia (group A) compared with community-acquired pneumonia (group B).

DISCUSSION

To our knowledge, this is the first study to highlight the clinical differences between inter-pandemic CAP and H1N1

Table 2 Univariate association between selected clinical characteristics and presence of H1N1 infection

Characteristic	H1N1 cohort	CAP cohort	OR	95% CI	p Value
Age ≤65 years	228/254	200/648	19.6	12.7 to 30.3	<0.001
White cell count ≤12×10^9/l	189/239	222/646	7.2	5.1 to 10.3	<0.001
Oriented in time/place/person	236/254	466/648	5.1	3.1 to 8.5	<0.001
Urea <7 mmol/l	175/232	270/647	4.3	3.1 to 6.0	<0.001
Temperature ≥38°C	142/245	232/644	2.5	1.8 to 3.3	<0.001
Bilateral x-ray change	89/228	129/648	2.6	1.9 to 3.6	<0.001
CRP ≤50 mg/l	67/184	126/602	2.2	1.5 to 3.1	<0.001
Albumin ≤30 g/dl	44/177	189/488	1.9	1.3 to 2.8	0.001
Female sex	145/254	281/648	1.7	1.3 to 2.3	0.001
Pulse ≥125/min	45/244	107/646	1.1	0.8 to 1.7	0.51

CAP, community-acquired pneumonia; CRP, C-reactive protein.

Table 3 Multivariate analysis of variables associated with H1N1 influenza-related pneumonia

Characteristic	Odds ratio	95% CI	p Value
Age ≤65 years	12.7	7.2 to 22.2	<0.001
White cell count ≤12×10^9/l	9.7	6.1 to 15.6	<0.001
Bilateral radiographic change	3.3	2.1 to 5.4	<0.001
Oriented in time/place/person	2.6	1.2 to 5.3	0.012
Temperature ≥38°C	1.9	1.3 to 3.0	0.003
Female sex	1.4	0.9 to 2.2	0.09
Urea <7 mmol/l	1.4	0.8 to 2.3	0.214

Complete data on all seven variables were available in 205 patients in the H1N1 cohort and 642 patients in the community-acquired pneumonia cohort.

influenza-related pneumonia. Patients with H1N1 influenza-related pneumonia were significantly younger than patients with CAP, reflecting the epidemiology of H1N1 influenza infection globally.[2 14 24 29 30] This may relate to previous exposure of older persons to pre-2009 H1N1 influenza viruses conferring some immunity.[31–33] In future years, as the virus evolves, the epidemiology of H1N1 infection may alter to affect older persons to a greater extent. Such a shift would also impact on the age distribution of patients developing H1N1 influenza-related pneumonia with potentially important consequences on resultant morbidity and mortality. Studies of CAP conducted in inter-pandemic years demonstrate an association between extremes of age or frailty and influenza or viral infection.[10 11]

Lower levels of C-reactive protein and leucocytes were observed in patients with H1N1 influenza-related pneumonia. This finding is consistent with reports from studies of inter-pandemic influenza-related pneumonia of relatively low leucocyte, neutrophil and C-reactive protein levels.[10–12] These markers of inflammation are driven mainly by bacterial infections, and the predominance of primary viral pneumonia as opposed to secondary bacterial pneumonia in H1N1 influenza-related pneumonia may therefore partially account for this observation.[16 34] Despite the lower levels of C-reactive protein and leucocytes, patients with H1N1 influenza-related pneumonia had higher levels of fever than patients with CAP. This may be related to high levels of production of proinflammatory cytokines, particularly interleukin 6,[35] with reduced innate and adaptive responses to *S pneumoniae* seen with pandemic H1N1 influenza.[36] It may also partially reflect the relative inability of older subjects to mount a febrile response to serious infection.[37]

A diagnostic prediction model was derived from five simple clinical criteria—age ≤65 years, presence of bilateral radiographic consolidation, absence of confusion as measured by orientation in time, place or person, leucocyte count ≤12×10^9/l and temperature ≥38°C. Assigning one point for each clinical criterion present, a score of 4 or 5 gave a positive likelihood ratio of 9.0 for predicting H1N1 influenza-related pneumonia, while a score of 0 or 1 gave a positive likelihood ratio of 75.7 for excluding H1N1 influenza-related pneumonia. Although age is by far the single strongest predictor (OR 19.6), its predictive value is inferior to the proposed model comprising five variables. When age was removed from the proposed model, the remaining four variables—bilateral radiographic consolidation, mental orientation, leucocyte count ≤12×10^9/l and temperature ≥38°C—retained their significance as independent predictors of H1N1 influenza-related pneumonia, attesting to their importance within the model. This model is applicable at the time of admission when a diagnosis of CAP is determined and would be useful in aiding the early diagnosis of patients with H1N1 influenza-related pneumonia as well as management decisions relating to infection control and the instigation of early empirical antiviral therapy. Although the efficacy of antiviral agents in the treatment of patients hospitalised with influenza-related pneumonia is not scientifically proven,[38] evidence from observational studies in hospital settings suggests that early antiviral use does improve clinical outcomes.[14 23 39 40]

Currently, this diagnostic prediction model can only be advocated for H1N1 influenza-related pneumonia. It should not be applied to other viral pneumonias without further validation. Similarly, should pandemic influenza A/H1N1 2009 evolve and affect older persons more widely, the predictive value of the model is likely to be altered.

Disease severity assessment is crucial in the management of patients with pneumonia. The CURB-65 severity assessment score has been validated for use in predicting 30-day mortality in patients with CAP[26] and was advocated as potentially useful in patients with influenza-related pneumonia.[41 42] However, this study suggests that, in patients with H1N1 influenza-related pneumonia, the CURB-65 score does not perform so well. This difference may be due to a combination of features including the lower age distribution and comorbidity profile of patients with H1N1 influenza-related pneumonia and differences in the inflammatory response to H1N1 influenza infection.[43] Further study of the prognostic factors relevant to H1N1 influenza-related pneumonia is warranted.

Study limitations

The main limitation to this study is that the CAP cohort was not collected contemporaneously with the H1N1 cohort and, while the latter patients were distributed nationally, patients in the CAP cohort were recruited from a single study centre. Patients in the CAP cohort were prospectively enrolled as part of a population-based cohort study involving all patients hospitalised with CAP in the Nottingham area (catchment population 750 000). Nottingham has a record of conducting large cohort studies of CAP.[44–47] The age and demographics of this CAP study cohort mirror the demographics of patients with CAP described in a recently completed national multicentre audit of CAP organised by the British Thoracic Society (unpublished data). These factors support the view that the CAP cohort is representative of patients admitted to hospital with CAP.

Patients recruited to the FLU-CIN cohort were identified following testing for H1N1 influenza on the basis of clinical suspicion rather than rigorously applied testing criteria. Nevertheless, the FLU-CIN cohort is similar to other large published H1N1 influenza cohorts in terms of clinical features and rates of pneumonia (22–37%) and critical care admission (13–25%).[14 48 49 17] These observations suggest that the FLU-CIN cohort is indeed representative of patients hospitalised with H1N1 infection in the UK and is not biased in relation to patients with influenza-related pneumonia or patients with severe disease.

Table 4 Proportions of patients identified with H1N1 influenza-related pneumonia according to the diagnostic prediction model

Score*	0	1	2	3	4	5
Proportion with H1N1 pneumonia	0/55 (0%)	1/171 (0.6%)	24/250 (9.6%)	65/214 (30.3%)	95/133 (71.4%)	31/35 (88.6%)

*One point for the presence of each of: age ≤65 years, white cell count ≤12×10^9/l, bilateral radiographic change, oriented in time/place/person and temperature ≥38°C.

All patients with H1N1 influenza-related pneumonia had laboratory-confirmed pandemic H1N1 influenza infection so misclassification is eliminated. In contrast, it remains possible that the CAP cohort may have contained patients in whom the precipitating cause of pneumonia was influenza, despite the exclusion of patients admitted with CAP during the period when pandemic H1N1 influenza was circulating in the study catchment population. The inclusion of some individuals with influenza-related pneumonia within the CAP cohort would tend towards increasing the similarities between the two groups thereby producing underestimates of any differences.

CONCLUSIONS

H1N1 influenza-related pneumonia differs substantially from inter-pandemic CAP. A diagnostic prediction model based on the five clinical features of age (≤65 years), leucocyte count ($\leq 12\times10^9$/l), bilateral radiographic change, temperature (≥38°C) and mental orientation (time/person/place) allows the early discrimination of H1N1 influenza-related pneumonia from CAP following hospital admission and confers confidence to the instigation of early empirical antiviral therapy.

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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. SJB has received consultancy fees from GlaxoSmithKline and Baxter. MGS and BB are advisors to the Department of Health, England. PJMO is a member of the European Scientific Working Group on Influenza (ESWI) which is funded by the pharmaceutical industry. 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. WSL has received an unrestricted educational grant from Wyeth (now Pfizer).

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. Full ethical approval was obtained from the Nottingham Research Ethics Committee for the conduct of the CAP cohort study.

Contributors All authors were involved with designing the study, interpreting and analysing the 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 PM. SG collected data for FLU-CIN and the CAP cohort. TB and PM analysed the data. TB and WSL 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.

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