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Clinical and epidemiological profile of patients with severe H1N1/09 pandemic influenza in Australia and New Zealand: an observational cohort study

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ABSTRACT

Background: Pandemic influenza H1N1/09 emerged in April 2009 and spread widely in Australia and New Zealand. Although an unprecedented number of cases required intensive care, comparative community-based studies with seasonal influenza strains have not shown any significant differences in clinical symptoms or severity.

Methods: The authors performed active surveillance on confirmed influenza-related admissions and compared the clinical profile of patients with pandemic H1N1/09 influenza and patients with seasonal influenza at eight hospitals in Australia and one hospital in New Zealand.

Results: During the 1 July and 30 November 2009, 560 patients with confirmed influenza were admitted, of which 478 had H1N1/09, and 82 had other seasonal strains. Patients with H1N1/09 influenza were younger, were more likely to have fever and were more likely to be pregnant but less likely to have chronic obstructive pulmonary disease and ischaemic heart disease than patients with seasonal strains. Other clinical features and comorbidities were reported in similar proportions. Admission to intensive care was required in 22% of patients with H1N1/09 influenza and 12% in patients with other strains. Hospital mortality was 5% in patients with H1N1 influenza.

Conclusions: The clinical features of H1N1/09 influenza and seasonal strains were similar in hospitalised patients. A higher proportion of patients had comorbidities than had been reported in community-based studies. Although the overall mortality was similar, the authors found evidence that H1N1/09 caused severe disease in a higher proportion of hospitalised patients.

ARTICLE SUMMARY

Article focus

- We performed an observational study of patients with H1N1/09 and seasonal strains of influenza in 2009, based on active surveillance at nine sentinel hospitals.
- We explored differences between patients with H1N1/09 influenza infection and those with seasonal influenza infections.

Key messages

- This study found that the clinical features of H1N1/09 influenza were similar in hospitalised patients, similar to previous community-based studies.
- The finding that H1N1/09 influenza was associated with more severe disease reconciles apparently contradictory data suggesting no differences in community studies, but unprecedented use of critical care services.

BACKGROUND

Pandemic influenza H1N1/09 emerged in late April 2009 and was the predominant influenza strain globally in 2009/2010.[1] The first imported cases in Australia and New Zealand were reported in mid-April and early May 2009, and spread widely, coinciding with the southern winter in June. The few comparative studies of the clinical features of H1N1/09 influenza and other seasonal strains suggest that clinical features are generally similar. However, the large comparative studies were community-based, and analysis of hospital-based studies was limited by the small numbers of patients.[2–6] A recent study from Western Australia concluded that the severity of illness, assessed by rates of hospitalisation and hospital length of stay, was similar.[5] In contrast, intensive care units in Australia and New Zealand reported an increased demand for resources; while this may in part have been due to high numbers of community cases, there was also unprecedented use of extracorporeal

ARTICLE SUMMARY

Strengths and limitations of this study

- This surveillance system was rapidly established, and initial data collection was retrospective from the medical record where symptoms were not always well documented. Despite high levels of awareness in medical staff, clinical testing criteria were operating during the period of the study and were likely to bias the proportion of patients reporting fever and respiratory symptoms. Nucleic-acid detection using PCR is regarded as the gold standard for diagnosis, but our experience with discordant results on repeated testing suggested that it may not be completely sensitive. This study does not encompass the full duration of the epidemic which was waning in several states (notably Victoria and New South Wales) at the commencement of the study period. Although several hospitals provided maternity and paediatric services, these patient groups are likely to be under-represented in this series. The population served by the sentinel hospitals is not known, and thus we were not able to establish a disease incidence rate.
- This large study captured all admissions with influenza at multiple hospitals across Australia and New Zealand. All cases were confirmed by nucleic acid detection with clinical details collected by research staff.

membrane oxygenation (ECMO) in a small number of patients.[7 8]

We initiated active surveillance for patients hospitalised with influenza and pneumonia at nine hospitals in Australia and New Zealand to define the spectrum of disease associated with severe influenza. In this study, we aimed to explore differences in risk factors, clinical features and outcome between patients with H1N1/09 influenza and other seasonal strains of influenza.

METHODS

We conducted active surveillance in eight hospitals in Australia and one hospital in New Zealand for laboratory-confirmed influenza from 1 July 2009 to 31 November 2009. This formed part of a real-time hospital-based surveillance system (Influenza Complications Alert Network; FluCAN) for influenza and community-acquired pneumonia.[9] Data collection was retrospective from July 1 until early August 2009 and prospective subsequently. Patients were identified from lists of admissions and/or laboratory results, and included if they had laboratory-confirmed influenza. Site investigators audited 10% of records selected at random. Study sites included large regional and metropolitan hospitals (but did not include specialty paediatric or obstetric hospitals) in six of the eight Australian states and territories and in Hamilton, New Zealand. Data were collected on standardised clinical record forms. In all study sites, influenza was diagnosed using nucleic-acid detection from respiratory samples, with subtyping performed at a reference laboratory for each state. While we did not record seasonal subtypes, previous studies have reported that of the 414 seasonal influenza strains typed in Australia between January and December 2009, 67% were subtype A/H3, 28% were subtype A/H1N1, and 5% were influenza B.[10]

We defined severe obesity as a body mass index of $>35\ kg/m^2$. Indigenous status, smoking and symptoms were self-reported. Pneumonia was defined as the presence of respiratory symptoms consistent with pneumonia together with radiological evidence of consolidation reported by a radiologist or site investigator. Diabetes, asthma, chronic obstructive pulmonary disease, chronic liver disease, chronic neurological disease and chronic renal disease were recorded as comorbidities if these diagnoses were documented in the patient notes. Immunosuppression was defined as oral steroid use or other immunosuppressive medication, organ transplantation, HIV infection or cancer chemotherapy. The length of stay included the time from admission to the sentinel hospital (not including time spent at other hospitals where patients were transferred from other hospitals) to discharge (including hospital-in-the-home services, but not including time in other hospitals if patients were transferred for further care).

Continuous measures were compared using the Mann–Whitney U test, and categorical variables using the χ^2 test or Fisher exact test as appropriate. Multivariate logistic regression models examining risk factors for intensive-care unit (ICU) admission were constructed using backwards selection (with a p value threshold of 0.1 for selection of variables). Analyses included only patients where data were ascertained (denominator data are provided in tables).

Ethical approval to perform this study was obtained at all sites; consent was sought to follow-up patients after 30 days by telephone. This study was supported by the Australian National Health and Medical Research Council; the funder did not have a role in study design, analysis or interpretation.

RESULTS

Between 1 July 2009 and 30 November 2009, 560 patients were admitted to the sentinel hospitals with laboratory-confirmed influenza. Of these, 478 (85%) of patients had infection with H1N1/09, and 82 (15%) had infection with seasonal influenza strains (all other strains of influenza A). The number of cases varied by site; 47 (8.4%) cases were reported in Victorian sites, 37 (6.6%) in New South Wales, 108 (19%) in Queensland, 158 (28%) in West Australia, 101 (18%) in South Australia, 85 (15%) in Tasmania and 24 (4.2%) in New Zealand.

The median age of patients admitted was 48 years (IQR 30, 59 years), and 288 (51%) were female. Patients with H1N1/09 influenza were younger, and a higher proportion were female (table 1). There were 82 (16%) indigenous patients of the 546 patients where ethnic status was known; this included 65 Australian Aboriginal people, 10 Torres Strait Islanders (one of whom was both Aboriginal and a Torres Strait Islander) and eight Maori

Table 1 Demographics characteristics in patients with H1N1 influenza and other seasonal strains

	H1N1/09	Other strains	p Value
No	478	82	
Age (median; IQR)	47 (29 to 58)	58 (38 to 74)	0.06
Female	258 (54%)	30 (37%)	0.004
Indigenous			
ATSI: Aboriginal and Torres Strait Islander (Australia)	68/453 (15%)	7/71 (10%)	0.28
Maori (NZ)	4/13 (31%)	4/9 (44%)	0.62
Nosocomial	23 (4.8%)	4 (4.9%)	1.00
Healthcare worker	13/459 (2.8%)	1 (1.3%)	0.7

people. Fourteen admissions (2.6%) were healthcare workers. The source of infection was known in 130 (223%) cases, was from the household in 76 cases, involved nosocomial infection in 27 cases and was reported to follow interstate or overseas travel in 27 cases.

Risk factors

The most common reported comorbidities included asthma (28%), chronic obstructive pulmonary disease (COPD) (17%), immunosuppression (17%) and diabetes (18%). In the 424 patients where smoking status was recorded, 30% were current smokers and 24% were past smokers. In the 322 patients where an estimate of height and weight was documented, 23% were severely obese. A higher proportion of patients with H1N1/09 influenza were pregnant, and a lower proportion of patients had COPD and ischaemic heart disease than those with seasonal influenza (table 2).

In the 216 patients with asthma or COPD, 68 (31%) had radiologically confirmed pneumonia (compared with 39% in patients without asthma or COPD, p=0.07), and 15% were admitted to ICU (compared with 23% in other patients, p=0.015). The 30-day mortality of patients with asthma or COPD was 4%.

Clinical features

The reason for admission was recorded in 541 patients; this included respiratory disease in 470 (86%) patients, non-respiratory complications (including obstetric complications and exacerbation of underlying medical problems) in 47 (9%) and other reasons in 24 cases. The largest group of patients presented to outpatients, emergency departments or hospital-based 'flu clinics' (n=249, 44%). Other sources of referral were smaller hospitals for further management (n=115, 21%) and general practitioners (n=80, 14%).

Presenting symptoms could not be ascertained for all patients, but where reported, cough was the most common symptom (92%); fever was present in only 80% of patients. Fever and sore throat were reported in a higher proportion of patients with H1N1/09 influenza compared with patients with other strains (table 3). Fever with one respiratory symptom (cough, nasal congestion, sore throat or rhinorrhoea) was present in 410 of the 557 patients (76%) where any of these symptoms were ascertained.

Table 2 Risk factors in patients with H1N1 influenza and other seasonal strains

	H1N1/09	Other strains	p Value
Smoking			
Current	109/363 (30%)	18/61 (30%)	0.1
Past	82 (23%)	21/61 (34%)	
Non-smoker	172 (47%)	22/61 (36%)	
Asthma	137/470 (29%)	17/80 (21%)	0.17
Chronic obstructive pulmonary disease	73/468 (16%)	20/80 (25%)	0.05
Diabetes	82/475 (17%)	16/81 (20%)	0.63
Pregnancy*	43/256* (9.5%)	2/30* (2.5%)	0.046
Liver disease	29/474 (4.9%)	4/81 (6.2%)	0.80
Immunosuppressed	80/473 (17%)	12/80 (15%)	0.74
Current malignancy	43/473 (9%)	13/80 (16%)	0.69
Congestive cardiac failure	31/472 (6.6%)	8/80 (10%)	0.24
Ischaemic heart disease	45/473 (9.7%)	17/81 (21%)	0.006
Severe obesity	68/276 (25%)	7/46 (15%)	0.19
Chronic neurological disease	52 (11%)	8/81 (10%)	0.84
Chronic renal disease	33/472 (7.0%)	7/81 (8.6%)	0.64

*Expressed as proportion of female patients.

Table 3 Clinical and diagnostic features in patients with H1N1 influenza and other seasonal strains

	H1N1/09	Other strains	p Value
Fever	383/470 (81%)	57/80 (71%)	0.04
Nasal congestion	45/339 (13%)	6/46 (14%)	1.0
Rhinorrhoea	114/358 (32%)	15/51 (29%)	0.87
Sore throat	162/382 (42%)	15/53 (28%)	0.05
Cough	420/458 (92%)	70/76 (93%)	1.0
Chest pain	137/413 (33%)	22/69 (32%)	0.89
Dyspnoea	323/452 (71%)	55/74 (74%)	0.67
Myalgia	188/375 (50%)	27/59 (46%)	0.57
Diarrhoea	58/394 (15%)	11/69 (16%)	0.85
Consolidation on chest x-ray	167/478 (35%)	37/82 (45%)	0.08
Positive blood culture	12/251 (5%) (*E coli* 1, *S aureus* 7, *S pneumoniae* 3, *E faecium* 1)	3/40 (8%) (*Enterobacter cloacae* 1, *S aureus* 1, *S pneumoniae* 1)	0.44
Positive sputum culture	19/145 (13%) (*Ps aeruginosa* 8, *S pneumoniae* 4, *H. influenzae* 4, *E coli* 1, *Moraxella* 1, *Serratia* 1)	5/19 (26%) (*H. influenzae* 2, *Klebsiella* 1, *Ps. aeruginosa* 1, *S pneumoniae* 1)	0.15

Pneumonia and secondary bacterial infection

Of the 560 patients with influenza, 204 (36%) had radiologically confirmed consolidation. Symptoms more common in patients with pneumonia included fever (86% vs 76%, p<0.001) and dyspnoea (83%, vs 65%, p<0.001). Cough (95% vs 90%), diarrhoea (18% vs 13%) and chest pain (35% vs 32%) were reported in similar proportions in patients with and without pneumonia. Asthma (23% vs 30%, p=0.06) was less common in patients with pneumonia; similar proportions reported COPD, diabetes, immunosuppression, cardiac failure or ischaemic heart disease. Independent clinical predictors of pneumonia included fever (OR 1.7, 95% CI 1.1 to 2.8), dyspnoea (OR 2.9, 95% CI 1.9 to 4.6); a history of asthma (OR 0.53, 95% CI 0.35 to 0.82) was protective against pneumonia. Pneumonia was less common in patients with H1N1/09 (35%) than other seasonal strains (45%, p=0.08), although this difference was not statistically significant.

Blood cultures were taken in 291 patients, and a significant pathogen was isolated in 15 patients and included *Staphylcoccus aureus* (n=8), pneumococcus (n=4), *Escherichia coli* (n=1) and *Enterobacter* sp (n=1). Sputum cultures were taken in 164 patients with pneumonia; significant pathogens isolated included *Pseudomonas* spp (n=9), *Haemophilus influenzae* (n=6), pneumococcus (n=5), *Moraxella catarrhalis*, *Serratia* sp and *Klebsiella* sp (all n=1). Positive cultures were reported in similar proportions in patients with H1N1/09 influenza compared with those with other strains (table 1). A higher proportion of patients with H1N1/09 influenza received antiviral therapy; similar proportions received antibiotics.

Intensive-care admission

A higher proportion of patients with H1N1/09 influenza required admission to intensive care (table 4). Of the 116 patients admitted to ICU, 111 required ventilatory support (including 28 patients requiring non-invasive ventilation, 79 requiring invasive ventilation and four requiring ECMO). Vasopressor and/or inotropic support was required in 60 patients.

On univariate analysis, factors associated with ICU admission included older age, pregnancy, liver disease

Table 4 Management and outcome in patients with H1N1 influenza and other seasonal strains

	H1N1/09	Other strains	p Value
Oseltamivir	384/472 (81%)	42/77 (55%)	<0.001
Zanamavir	6/441 (1%)	1/73 (1%)	1.0
Any antibiotics	381/469 (81%)	71/80 (89%)	0.10
Intensive-care-unit admission	106/478 (22%)	10/82 (12%)	0.03
Intensive-care-unit interventions			
Extracorporeal membrane oxygenation	4 (4%)	0	1.0
Mechanical ventilation	72 (68%)	7 (70%)	1.0
Non-invasive ventilation	26 (25%)	2 (20%)	1.0
Vasopressor	53 (50%)	5 (50%)	1.0
Hospital length of stay (IQR)	5 days (2 to 10 days)	4 days (2 to 9 days)	0.44
Hospital mortality	26 (5%)	0	0.02
30 day mortality	30 (6%)	3 (4%)	0.35

Table 5 Factors associated with intensive-care-unit admission

	Univariate OR		Multivariate-adjusted OR	p Value
Age (per decade)	0.90 (0.81 to 1.00)	0.05		
Sex				
Female	1 (referent)	0.26		
Male	0.79 (0.52 to 1.2)			
Influenza strain				
H1N1/09	2.1 (1.0 to 4.1)	0.04	1.9 (0.9 to 4.0)	0.08
Other strain	1			
Radiologically confirmed pneumonia	6.7 (4.2 to 10.5)	<0.001	NI (in causal pathway)	
Smoking			NI (missing data)	
Non-smoker	1			
Current	0.87 (0.50 to 1.4)	0.61		
Past	0.51 (0.26 to 0.97)	0.04		
Asthma	0.62 (0.38 to 1.03)	0.07		
Chronic obstructive pulmonary disease	0.48 (0.25 to 0.94)	0.03	0.54 (0.27 to 1.07)	0.08
Diabetes	0.91 (0.53 to 1.59)	0.76		
Pregnancy	2.6 (1.3 to 4.9)	0.004	2.5 (1.3 to 4.8)	0.007
Liver disease	2.3 (1.1 to 4.9)	0.03	2.8 (1.3 to 5.9)	0.008
Immunosuppression	0.92 (0.53 to 1.6)	0.78		
Current malignancy	0.92 (0.46 to 1.84)	0.82		
Cardiac failure	0.83 (0.36 to 1.9)	0.74		
Ischaemic heart disease	0.54 (0.25 to 1.2)	0.13		
Obesity	1.9 (1.1 to 3.2)	0.03	NI	
Chronic neurological disease	0.40 (0.17 to 0.97)	0.12		
Chronic renal disease	1.3 (0.63 to 2.8)	0.46		

NI, not included in final model owing to the high proportion of missing data. Hosmer–Lemeshow goodness-of-fit statistic for final model, p=0.82.
NI, not included in final model.

and obesity (table 5). Patients with pneumonia commonly required admission to ICU; 41% of patients with pneumonia required ICU, compared with 8% of patients with no radiological evidence of consolidation. On multivariate analysis, liver disease and pregnancy were independently associated with ICU admission. Obesity was not included in the multivariate model owing to missing data, but in the 81 patients admitted to ICU where body weight was assessed, 26 patients (32%) were obese.

Outcome

The median duration of admission was 5 days (IQR 2, 10 days) and was similar for patients with H1N1/09 influenza and other seasonal strains (table 4). For patients admitted to ICU, the median duration of hospital admission was 14 days (IQR 7, 25 days). The in-hospital mortality was higher in patients with H1N1/09 influenza (5%) than in patients with other influenza strains (no deaths), but the 30-day mortality was similar (6% vs 4%).

DISCUSSION

This study compares the clinical features and outcomes of hospitalised patients with pandemic H1N1/09 influenza and those with seasonal strains at nine hospitals in Australia and New Zealand. A study comparing community patients with seasonal and pandemic H1N1/09 influenza in Western Australia found similar hospitalisation rates, hospital length of stay and comorbidities, and concluded that the clinical severity of disease of pandemic H1N1/09 influenza was similar to that of seasonal influenza.[5] Although case series of patients with H1N1/09 influenza may provide some information on clinical features,[11–13] comparisons with previously published literature are difficult to interpret owing to differences in health-seeking behaviour, and policies regarding diagnostics, hospital admission and treatment.

Similar to other studies, we found that patients with H1N1 influenza were younger, were more likely to report fever but had otherwise similar symptoms and comorbidities to patients with other influenza strains.[5 6 14] Differences between this study of hospitalised patients and other community-based studies are likely to reflect the severity of illness; cough and dyspnoea were more common and rhinorrhoea less common.[3 5] Differences in comorbidities are difficult to compare with other studies owing to differences in definitions, but in general comorbidities, particularly current smoking, renal disease and obesity appeared to be more common in hospitalised patients.[5] Consistent with previous hospital studies,[6] we also found obesity to be more common in patients with H1N1 influenza, although ascertainment of these data was incomplete. We found pregnancy and liver disease to occur in a higher proportion of patients with H1N1/09 influenza (and to be risk factors for ICU admission) and ischaemic heart disease and COPD to occur in a lower proportion. The differences in comorbdities may in part reflect the younger age of patients with H1N1/09 infection.

Importantly, we found some evidence that the severity of illness was greater in patients hospitalised with H1N1/09 influenza compared with those hospitalised with seasonal influenza. Patients with H1N1/09 influenza were more likely to require ICU admission, although after adjusting for underlying risk factors, this difference was no longer statistically significant. The proportion of patients requiring ICU was similar to that reported in other Australian series[4 12] but much higher than in a series reported in Hong Kong.[6] This is unlikely to represent differences in ICU admission criteria, as over 70% patients required ventilation or ECMO. A higher proportion of patients with H1N1/09 influenza required mechanical ventilation and ECMO; the in-hospital mortality (but not 30 day mortality) was higher.

Our findings highlight the importance of lower-respiratory-tract involvement, regardless of strain, as a marker of severity of disease, with 40% of patients with consolidation requiring admission to intensive care. Radiological evidence of pneumonia or pneumonitis was found in similar proportions of patients with H1N1 influenza and other influenza strains. Although bacterial pneumonia is notoriously underdiagnosed using blood and sputum culture, in the majority of patients no bacterial pathogens were identified This is consistent with previous studies suggesting that bacterial pneumonia following H1N1/09 influenza is less common than viral pneumonitis.[15] We found COPD to be negatively associated with ICU admission. Potential explanations include differing admission policies for ICU in patients with pre-existing respiratory compromise and a lower threshold for admission to hospital for patients with viral exacerbations of COPD; the latter is supported by the lower proportion of patients with asthma requiring ICU admission.

There were several limitations to this study. This surveillance system was rapidly established, and the initial data collection was retrospective from the medical record where symptoms were not always well documented. Despite high levels of awareness in medical staff, clinical testing criteria were operating during the period of the study,[16] and were likely to bias the proportion of patients reporting fever and respiratory symptoms. Thus, the clinical syndrome of influenza-like illness is likely to be less sensitive than that described here. Nucleic-acid detection using PCR is regarded as the gold standard for diagnosis, but our experience with discordant results on repeated testing suggested that it may not be completely sensitive. This has implications for surveillance systems and for infection-control measures in hospitalised patients. This study does not encompass the full duration of the epidemic which was waning in several states (notably Victoria and New South Wales) at the commencement of the study period.[9 17 18] Although several hospitals provided maternity and paediatric services, these patient groups are likely to be under-represented in this series. Despite this, we are confident that the admissions to sentinel hospitals are representative of patients admitted elsewhere, as the characteristics of the patients in this report are comparable with national surveillance data.[9] However, the population served by the sentinel hospitals is not known, and thus we were not able to establish an incidence rate of infection which has been calculated elsewhere.[19]

CONCLUSION

H1N1/09 influenza was the predominant strain of influenza in hospitalised patients; the younger profile of patients reflected widespread population susceptibility. A higher proportion of patients with H1N1/09 influenza were obese, were pregnant but had lower rates of COPD and ischaemic heart disease compared with patients with other influenza strains. In reconciling community-based studies that have not found any differences in severity with the experience of intensive care units, patients requiring hospitalisation with H1N1/09 were more likely to require admission to intensive care than those with infection with other strains. The case death of patients hospitalised with influenza was around 5% with a 30-day mortality similar in patients with H1N1/09 influenza and seasonal strains.

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Competing interests AC is an investigator for a study of vaccine safety funded by CSL Ltd.

Ethics approval This study was conducted by approval of the Australian National University.

Contributors TK (chair), SDB, SGAB, RJH, MH, LI, CJ, PT, GS, GW and RW-B were all members of the Thoracic Society of Australia and New Zealand Swine Flu task force who supervised the data collection at each site. They designed the study in conjunction with PMK, AR and ACC, and the group obtained funding to perform the study. ACC analysed the data and drafted the manuscript. All authors assisted with the interpretation of findings and revised the manuscript.

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Notes