Clinical and epidemiological profile of patients with severe H1N1/09 pandemic influenza in Australia and New Zealand: a 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 significant differences in clinical symptoms or severity.

Methods: We 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 8 hospitals in Australia and 1 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 hospitalized patients. A higher proportion of patients had comorbidities than had been reported in community-based studies. Although overall mortality was similar, we found evidence that H1N1/09 caused severe disease in a higher proportion of hospitalized patients.

Article focus

- We performed an observational study of patients with H1N1/09 and seasonal strains of influenza in 2009, based on active surveillance at 9 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 hospitalized 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.

Strengths and limitations

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.

Background

Pandemic influenza H1N1/09 emerged in late April, 2009 and was the predominant influenza strain globally in 2009/10 (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 were limited by small numbers of patients (2-6). The recent study from Western Australia concluded that the severity of illness, assessed by rates of hospitalization 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 membrane oxygenation (ECMO) in a small number of patients (7, 8).

We initiated active surveillance for patients hospitalized 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 July 1, 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 (Kelly P et al, in press). 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 speciality paediatric or obstetric hospitals) in 6 of the 8 Australian states and territories and in Hamilton, New Zealand. Data was collected on standardized 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 of the 414 seasonal influenza strains typed in Australia between January and December, 2009, 67% was subtype A/H3, 28% was subtype A/H1N1 and 5% influenza B (9).

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, human immunodeficiency virus 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 chi-squared test or Fisher's exact test as appropriate. Multivariate logistic regression models examining risk factors for 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 TSI) and 8 Maori 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%), 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 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 to 39% in patients without asthma or COPD, p=0.07) and 15% were admitted to ICU (compared to 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 only present in 80% of patients. Fever and sore throat were reported in a higher proportion of patients with H1N1/09 influenza compared to 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.

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), dyspnoea (83%, vs 65%, p<0.001). Cough (95% vs 90%), diarrhea (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, 2.8), dyspnoea (OR 2.9, 95% CI: 1.9, 4.6); a history of asthma (OR 0.53, 95% CI: 0.35, 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, *Klebsiella* sp (all n=1). Positive cultures were reported in similar proportions in patients with H1N1/09 influenza compared to 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 4 requiring extracorporeal membrane oxygenation). Vasopressor and/or inotropic support was required in 60 patients.

On univariate analysis, factors associated with ICU admission included older age, pregnancy, liver disease and obesity (table 5). Patients with pneumonia commonly required admission to ICU; 41% of patients with pneumonia required ICU, compared to 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 due 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). In-hospital mortality was higher in patients with H1N1/09 influenza (5%) than in patients with other influenza strains (no deaths), but 30 day mortality was similar (6% vs 4%).

Discussion

This study compares the clinical features and outcomes of hospitalized patients with pandemic H1N1/09 influenza and those with seasonal strains at 9 hospitals in Australia and New Zealand. A study comparing community patients with seasonal and pandemic H1N1/09 influenza in Western Australia found similar hospitalization 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 (10-12),

comparisons with previously published literature are difficult to interpret due to differences in health-seeking behavior, 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, 13). Differences between this study of hospitalized 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 due to differences in definitions, but in general comorbidities, particularly current smoking, renal disease and obesity appeared to be more common in hospitalized 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 were incomplete. We found pregnancy and liver disease to occur in a higher proportion of patients with H1N1/09 influenza (and were risk factors for ICU admission), and ischaemic heart disease and COPD to occur in a lower proportion. The differences in co-morbdities 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 hospitalized with H1N1/09 influenza compared to those hospitalized 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, 11) 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; 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 under-diagnosed 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 (14). 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 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 (15), 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 hospitalized 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, 16, 17). 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 to national surveillance data (9) (Kelly P, Med J Aust, in press). 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 (18).

Conclusion

H1N1/09 influenza was the predominant strain of influenza in hospitalized 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 to 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 hospitalization with H1N1/09 were more likely to require admission to intensive care than those with infection with other strains. The case fatality of patients hospitalized with influenza was around 5% with 30 day mortality similar in patients with H1N1/09 influenza and seasonal strains.

Role of authors: Tom Kotsimbos (Chair), Simon Bowler, Simon Brown, Robert Hancox, Mark Holmes, Louis Irving, Christine Jenkins, Phillip Thompson, Graham Simpson, Grant Waterer, Richard Wood-Baker were all members of the TSANZ Swine Flu task force who supervised data collection at each site. They designed the study in conjunction with Paul Kelly, Anna Reynolds and Allen Cheng and the group obtained funding to perform the study. Allen Cheng analyzed the data and drafted the manuscript. All authors assisted with the interpretation of findings and revised the manuscript.

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References

1. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009 Jun 18;360(25):2605-15.

2. Crum-Cianflone NF, Blair PJ, Faix D, Arnold J, Echols S, Sherman SS, et al. Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (swine origin) influenza A virus among United States military beneficiaries. Clin Infect Dis. 2009 Dec 15;49(12):1801-10.

3. Ong AK, Chen MI, Lin L, Tan AS, Nwe NW, Barkham T, et al. Improving the clinical diagnosis of influenza--a comparative analysis of new influenza A (H1N1) cases. PLoS One. 2009;4(12):e8453.

4. Chang YS, van Hal SJ, Spencer PM, Gosbell IB, Collett PW. Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the "PROTECT" phase of the pandemic response. Med J Aust. 2010 Jan 18;192(2):90-3.

5. Carcione D, Giele C, Dowse GK, Mak DB, Goggin L, Kwan K, et al. Comparison of Pandemic (H1N1) 2009 and Seasonal Influenza, Western Australia, 2009. Emerg Infect Dis. 2010 Sep;16(9):1388-95.

6. To KK, Wong SS, Li IW, Hung IF, Tse H, Woo PC, et al. Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection. Postgrad Med J. 2010 Aug 5.

7. Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009 Nov 12;361(20):1925-34.

8. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009 Nov 4;302(17):1888-95.

9. DoHA. Australian Influenza Surveillance Summary Report: 4 December 2009 [http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/18D06BAC4644C98DCA25763E00823442/$File/ozflu-no30-2009.pdf]. Journal [serial on the Internet]. 2009 Date; 30.

10. CDC. Hospitalized Patients with Novel Influenza A (H1N1) Virus Infection --- California, April--May, 2009. MMWR Morb Mortal Wkly Rep. 2009 May 22;58(19):536-41.

11. Denholm JT, Gordon CL, Johnson PD, Hewagama SS, Stuart RL, Aboltins C, et al. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. Med J Aust. 2010 Jan 18;192(2):84-6.

12. WHO. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Weekly Epidemiological Record. 2009;84(21):185-6.

13. Kelly HA, Grant KA, Williams S, Fielding J, Smith D. Epidemiological characteristics of pandemic influenza H1N1 2009 and seasonal influenza infection. Med J Aust. 2009 Aug 3;191(3):146-9.

14. CDC. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. MMWR Morb Mortal Wkly Rep. 2009 Oct 2;58(38):1071-4.

15. Cheng AC, Dwyer DE, Kotsimbos AT, Starr M, Korman TM, Buttery JP, et al. Summary of the Australasian Society for Infectious Diseases and the Thoracic Society of Australia and New Zealand guidelines: treatment and prevention of H1N1 influenza 09 (human swine influenza) with antiviral agents. Med J Aust. 2009 Aug 3;191(3):142-5.

16. Kelly HA, Mercer GN, Fielding JE, Dowse GK, Glass K, Carcione D, et al. Pandemic (H1N1) 2009 influenza community transmission was established in one australian state when the virus was first identified in North America. PLoS One. 2010;5(6):e11341.

17. Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. Euro Surveill. 2009 Aug 6;14(31).

18. Kelly H, Mercer G, Cheng A. Quantifying the risk of pandemic influenza in pregnancy and Indigenous people in Australia in 2009. Euro Surveill. 2009;14(50).

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

	H1N1/09	Other strains	
Number	478	82	
Age (median; IQR)	47 (29, 58)	58 (38, 74)	P=0.06
Female	258 (54%)	30 (37%)	P=0.004
Indigenous ATSI (Australia) Maori (NZ)	 68/453 (15%) 4/13 (31%)	 7/71 (10%) 4/9 (44%)	 P=0.28 p=0.62
Nosocomial	23 (4.8%)	4 (4.9%)	P=1.00
Health care worker	13/459 (2.8%)	1 (1.3%)	P=0.7

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

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

Chronic renal disease	33/472 (7.0%)	7/81 (8.6%)	P=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	
Fever	383/470 (81%)	57/80 (71%)	P=0.04
Nasal congestion	45/339 (13%)	6/46 (14%)	P=1.0
Rhinorrhoea	114/358 (32%)	15/51 (29%)	P=0.87
Sore throat	162/382 (42%)	15/53 (28%)	P=0.05
Cough	420/458 (92%)	70/76 (93%)	P=1.0
Chest pain	137/413 (33%)	22/69 (32%)	P=0.89
Dyspnoea	323/452 (71%)	55/74 (74%)	P=0.67
Myalgia	188/375 (50%)	27/59 (46%)	P=0.57
Diarrhoea	58/394 (15%)	11/69 (16%)	P=0.85
Consolidation on CXR	167/478 (35%)	37/82 (45%)	P=0.08
Positive BC	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)	P=0.44
Positive sputum culture	19/145 (13%) (*Ps. aeruginosa* 8,	5/19 (26%) (*H. influenzae* 2,	P=0.15

	S.pneumoniae 4,*H. influenzae* 4, *E. coli* 1, *Moraxella* 1, *Serratia* 1)	*Klebsiella* 1, *Ps. aeruginosa* 1, *S.pneumoniae* 1)	

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

	H1N1/09	Other strains	
Oseltamivir	384/472 (81%)	42/77 (55%)	P<0.001
Zanamavir	6/441 (1%)	1/73 (1%)	P=1.0
Any antibiotics	381/469 (81%)	71/80 (89%)	P=0.10
ICU admission	106/478 (22%)	10/82 (12%)	P=0.03
ICU interventions • ECMO • MV • NIV • Vasopressor	 4 (4%) 72 (68%) 26 (25%) 53 (50%)	 0 7 (70%) 2 (20%) 5 (50%)	 P=1.0 P=1.0 P=1.0 P=1.0
Hospital length of stay (IQR)	5 days (2,10 days)	4 days (2, 9 days)	P=0.44
Hospital mortality	26 (5%)	0	P=0.02
30 day mortality	30 (6%)	3 (4%)	P=0.35

Table 5: Factors associated with ICU admission

	Univariate OR		Multivariate adjusted OR	
Age (per decade)	0.90 (0.81, 1.00)	0.05		
Sex • Female • Male	 1 (referent) 0.79 (0.52, 1.2)	 0.26		
Influenza strain • H1N1/09 • Other strain	 2.1 (1.0, 4.1) 1	 0.04	 1.9 (0.9, 4.0)	 0.08
Radiologically confirmed pneumonia	6.7 (4.2, 10.5)	<0.001	Not included	
Smoking • Non-smoker • Current • Past	 1 0.87 (0.50, 1.4) 0.51 (0.26, 0.97)	 0.61 0.04	NI	
Asthma	0.62 (0.38, 1.03)	0.07		
COPD	0.48 (0.25, 0.94)	0.03	0.54 (0.27, 1.07)	0.08
Diabetes	0.91 (0.53, 1.59)	0.76		

Pregnancy	2.6 (1.3, 4.9)	0.004	2.5 (1.3, 4.8)	0.007
Liver disease	2.3 (1.1, 4.9)	0.03	2.8 (1.3, 5.9)	0.008
Immunosuppression	0.92 (0.53, 1.6)	0.78		
Current malignancy	0.92 (0.46, 1.84)	0.82		
Cardiac failure	0.83 (0.36, 1.9)	0.74		
Ischaemic heart disease	0.54 (0.25, 1.2)	0.13		
Obesity	1.9 (1.1, 3.2)	0.03	NI	
Chronic neurological disease	0.40 (0.17, 0.97)	0.12		
Chronic renal disease	1.3 (0.63, 2.8)	0.46		

NI: not included in final model due to high proportion of missing data. Hosmer-Lemeshow goodness of fit statistic for final model p=0.82

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	20-24
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25
		(*b*) Report category boundaries when continuous variables were categorized	25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Clinical and epidemiological profile of patients with severe H1N1/09 pandemic influenza in Australia and New Zealand: a 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 significant differences in clinical symptoms or severity.

Methods: We 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 8 hospitals in Australia and 1 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 hospitalized patients. A higher proportion of patients had comorbidities than had been reported in community-based studies. Although overall mortality was similar, we found evidence that H1N1/09 caused severe disease in a higher proportion of hospitalized patients.

Article focus

- We performed an observational study of patients with H1N1/09 and seasonal strains of influenza in 2009, based on active surveillance at 9 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 hospitalized 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.

Strengths and limitations

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.

Background

Pandemic influenza H1N1/09 emerged in late April, 2009 and was the predominant influenza strain globally in 2009/10 (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 were limited by small numbers of patients (2-6). The recent study from Western Australia concluded that the severity of illness, assessed by rates of hospitalization 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 membrane oxygenation (ECMO) in a small number of patients (7, 8).

We initiated active surveillance for patients hospitalized 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 July 1, 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 (Kelly P et al, in press). 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 speciality paediatric or obstetric hospitals) in 6 of the 8 Australian states and territories and in Hamilton, New Zealand. Data was collected on standardized 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 of the 414 seasonal influenza strains typed in Australia between January and December, 2009, 67% was subtype A/H3, 28% was subtype A/H1N1 and 5% influenza B (9).

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, human immunodeficiency virus 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 chi-squared test or Fisher's exact test as appropriate. Multivariate logistic regression models examining risk factors for 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 TSI) and 8 Maori 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%), 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 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 to 39% in patients without asthma or COPD, p=0.07) and 15% were admitted to ICU (compared to 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 only present in 80% of patients. Fever and sore throat were reported in a higher proportion of patients with H1N1/09 influenza compared to 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.

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), dyspnoea (83%, vs 65%, p<0.001). Cough (95% vs 90%), diarrhea (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, 2.8), dyspnoea (OR 2.9, 95% CI: 1.9, 4.6); a history of asthma (OR 0.53, 95% CI: 0.35, 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, *Klebsiella* sp (all n=1). Positive cultures were reported in similar proportions in patients with H1N1/09 influenza compared to 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 4 requiring extracorporeal membrane oxygenation). Vasopressor and/or inotropic support was required in 60 patients.

On univariate analysis, factors associated with ICU admission included older age, pregnancy, liver disease and obesity (table 5). Patients with pneumonia commonly required admission to ICU; 41% of patients with pneumonia required ICU, compared to 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 due 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). In-hospital mortality was higher in patients with H1N1/09 influenza (5%) than in patients with other influenza strains (no deaths), but 30 day mortality was similar (6% vs 4%).

Discussion

This study compares the clinical features and outcomes of hospitalized patients with pandemic H1N1/09 influenza and those with seasonal strains at 9 hospitals in Australia and New Zealand. A study comparing community patients with seasonal and pandemic H1N1/09 influenza in Western Australia found similar hospitalization 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 (10-12),

comparisons with previously published literature are difficult to interpret due to differences in health-seeking behavior, 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, 13). Differences between this study of hospitalized 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 due to differences in definitions, but in general comorbidities, particularly current smoking, renal disease and obesity appeared to be more common in hospitalized 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 were incomplete. We found pregnancy and liver disease to occur in a higher proportion of patients with H1N1/09 influenza (and were risk factors for ICU admission), and ischaemic heart disease and COPD to occur in a lower proportion. The differences in co-morbdities 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 hospitalized with H1N1/09 influenza compared to those hospitalized 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, 11) 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; 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 under-diagnosed 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 (14). 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 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 (15), 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 hospitalized 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, 16, 17). 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 to national surveillance data (9) (Kelly P, Med J Aust, in press). 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 (18).

Conclusion

H1N1/09 influenza was the predominant strain of influenza in hospitalized 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 to 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 hospitalization with H1N1/09 were more likely to require admission to intensive care than those with infection with other strains. The case fatality of patients hospitalized with influenza was around 5% with 30 day mortality similar in patients with H1N1/09 influenza and seasonal strains.

Role of authors: Tom Kotsimbos (Chair), Simon Bowler, Simon Brown, Robert Hancox, Mark Holmes, Louis Irving, Christine Jenkins, Phillip Thompson, Graham Simpson, Grant Waterer, Richard Wood-Baker were all members of the TSANZ Swine Flu task force who supervised data collection at each site. They designed the study in conjunction with Paul Kelly, Anna Reynolds and Allen Cheng and the group obtained funding to perform the study. Allen Cheng analyzed the data and drafted the manuscript. All authors assisted with the interpretation of findings and revised the manuscript.

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References

1. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med. 2009 Jun 18;360(25):2605-15.

2. Crum-Cianflone NF, Blair PJ, Faix D, Arnold J, Echols S, Sherman SS, et al. Clinical and epidemiologic characteristics of an outbreak of novel H1N1 (swine origin) influenza A virus among United States military beneficiaries. Clin Infect Dis. 2009 Dec 15;49(12):1801-10.

3. Ong AK, Chen MI, Lin L, Tan AS, Nwe NW, Barkham T, et al. Improving the clinical diagnosis of influenza--a comparative analysis of new influenza A (H1N1) cases. PLoS One. 2009;4(12):e8453.

4. Chang YS, van Hal SJ, Spencer PM, Gosbell IB, Collett PW. Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the "PROTECT" phase of the pandemic response. Med J Aust. 2010 Jan 18;192(2):90-3.

5. Carcione D, Giele C, Dowse GK, Mak DB, Goggin L, Kwan K, et al. Comparison of Pandemic (H1N1) 2009 and Seasonal Influenza, Western Australia, 2009. Emerg Infect Dis. 2010 Sep;16(9):1388-95.

6. To KK, Wong SS, Li IW, Hung IF, Tse H, Woo PC, et al. Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection. Postgrad Med J. 2010 Aug 5.

7. Webb SA, Pettila V, Seppelt I, Bellomo R, Bailey M, Cooper DJ, et al. Critical care services and 2009 H1N1 influenza in Australia and New Zealand. N Engl J Med. 2009 Nov 12;361(20):1925-34.

8. Davies A, Jones D, Bailey M, Beca J, Bellomo R, Blackwell N, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009 Nov 4;302(17):1888-95.

9. DoHA. Australian Influenza Surveillance Summary Report: 4 December 2009 [http://www.healthemergency.gov.au/internet/healthemergency/publishing.nsf/Content/18D06BAC4644C98DCA25763E00823442/$File/ozflu-no30-2009.pdf]. Journal [serial on the Internet]. 2009 Date; 30.

10. CDC. Hospitalized Patients with Novel Influenza A (H1N1) Virus Infection --- California, April--May, 2009. MMWR Morb Mortal Wkly Rep. 2009 May 22;58(19):536-41.

11. Denholm JT, Gordon CL, Johnson PD, Hewagama SS, Stuart RL, Aboltins C, et al. Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia. Med J Aust. 2010 Jan 18;192(2):84-6.

12. WHO. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Weekly Epidemiological Record. 2009;84(21):185-6.

13. Kelly HA, Grant KA, Williams S, Fielding J, Smith D. Epidemiological characteristics of pandemic influenza H1N1 2009 and seasonal influenza infection. Med J Aust. 2009 Aug 3;191(3):146-9.

14. CDC. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1) - United States, May-August 2009. MMWR Morb Mortal Wkly Rep. 2009 Oct 2;58(38):1071-4.

15. Cheng AC, Dwyer DE, Kotsimbos AT, Starr M, Korman TM, Buttery JP, et al. Summary of the Australasian Society for Infectious Diseases and the Thoracic Society of Australia and New Zealand guidelines: treatment and prevention of H1N1 influenza 09 (human swine influenza) with antiviral agents. Med J Aust. 2009 Aug 3;191(3):142-5.

16. Kelly HA, Mercer GN, Fielding JE, Dowse GK, Glass K, Carcione D, et al. Pandemic (H1N1) 2009 influenza community transmission was established in one australian state when the virus was first identified in North America. PLoS One. 2010;5(6):e11341.

17. Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. Euro Surveill. 2009 Aug 6;14(31).

18. Kelly H, Mercer G, Cheng A. Quantifying the risk of pandemic influenza in pregnancy and Indigenous people in Australia in 2009. Euro Surveill. 2009;14(50).

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

	H1N1/09	Other strains	
Number	478	82	
Age (median; IQR)	47 (29, 58)	58 (38, 74)	P=0.06
Female	258 (54%)	30 (37%)	P=0.004
Indigenous ATSI (Australia) Maori (NZ)	 68/453 (15%) 4/13 (31%)	 7/71 (10%) 4/9 (44%)	 P=0.28 p=0.62
Nosocomial	23 (4.8%)	4 (4.9%)	P=1.00
Health care worker	13/459 (2.8%)	1 (1.3%)	P=0.7

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

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

Chronic renal disease	33/472 (7.0%)	7/81 (8.6%)	P=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	
Fever	383/470 (81%)	57/80 (71%)	P=0.04
Nasal congestion	45/339 (13%)	6/46 (14%)	P=1.0
Rhinorrhoea	114/358 (32%)	15/51 (29%)	P=0.87
Sore throat	162/382 (42%)	15/53 (28%)	P=0.05
Cough	420/458 (92%)	70/76 (93%)	P=1.0
Chest pain	137/413 (33%)	22/69 (32%)	P=0.89
Dyspnoea	323/452 (71%)	55/74 (74%)	P=0.67
Myalgia	188/375 (50%)	27/59 (46%)	P=0.57
Diarrhoea	58/394 (15%)	11/69 (16%)	P=0.85
Consolidation on CXR	167/478 (35%)	37/82 (45%)	P=0.08
Positive BC	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)	P=0.44
Positive sputum culture	19/145 (13%) (*Ps. aeruginosa* 8,	5/19 (26%) (*H. influenzae* 2,	P=0.15

	S.pneumoniae 4,*H. influenzae* 4, *E. coli* 1, *Moraxella* 1, *Serratia* 1)	*Klebsiella* 1, *Ps. aeruginosa* 1, *S.pneumoniae* 1)	

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

	H1N1/09	Other strains	
Oseltamivir	384/472 (81%)	42/77 (55%)	P<0.001
Zanamavir	6/441 (1%)	1/73 (1%)	P=1.0
Any antibiotics	381/469 (81%)	71/80 (89%)	P=0.10
ICU admission	106/478 (22%)	10/82 (12%)	P=0.03
ICU interventions • ECMO • MV • NIV • Vasopressor	 4 (4%) 72 (68%) 26 (25%) 53 (50%)	 0 7 (70%) 2 (20%) 5 (50%)	 P=1.0 P=1.0 P=1.0 P=1.0
Hospital length of stay (IQR)	5 days (2,10 days)	4 days (2, 9 days)	P=0.44
Hospital mortality	26 (5%)	0	P=0.02
30 day mortality	30 (6%)	3 (4%)	P=0.35

Table 5: Factors associated with ICU admission

	Univariate OR		Multivariate adjusted OR	
Age (per decade)	0.90 (0.81, 1.00)	0.05		
Sex • Female • Male	 1 (referent) 0.79 (0.52, 1.2)	 0.26		
Influenza strain • H1N1/09 • Other strain	 2.1 (1.0, 4.1) 1	 0.04	 1.9 (0.9, 4.0)	 0.08
Radiologically confirmed pneumonia	6.7 (4.2, 10.5)	<0.001	Not included	
Smoking • Non-smoker • Current • Past	 1 0.87 (0.50, 1.4) 0.51 (0.26, 0.97)	 0.61 0.04	NI	
Asthma	0.62 (0.38, 1.03)	0.07		
COPD	0.48 (0.25, 0.94)	0.03	0.54 (0.27, 1.07)	0.08
Diabetes	0.91 (0.53, 1.59)	0.76		

Pregnancy	2.6 (1.3, 4.9)	0.004	2.5 (1.3, 4.8)	0.007
Liver disease	2.3 (1.1, 4.9)	0.03	2.8 (1.3, 5.9)	0.008
Immunosuppression	0.92 (0.53, 1.6)	0.78		
Current malignancy	0.92 (0.46, 1.84)	0.82		
Cardiac failure	0.83 (0.36, 1.9)	0.74		
Ischaemic heart disease	0.54 (0.25, 1.2)	0.13		
Obesity	1.9 (1.1, 3.2)	0.03	NI	
Chronic neurological disease	0.40 (0.17, 0.97)	0.12		
Chronic renal disease	1.3 (0.63, 2.8)	0.46		

NI: not included in final model due to high proportion of missing data. Hosmer-Lemeshow goodness of fit statistic for final model p=0.82

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	7
Objectives	3	State specific objectives, including any pre-specified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	7-8
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*8*
Bias	9	Describe any efforts to address potential sources of bias	8-9
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	9
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	n/a

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	20-24
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	12
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	25
		(*b*) Report category boundaries when continuous variables were categorized	25
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	11
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	11
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.