Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia

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ABSTRACT

Objective: To describe the case characteristics and outcomes of patients hospitalised with pandemic (H1N1) 2009 influenza infection during the first 2 months of the epidemic.

Design, participants and setting: Prospective case series of 112 patients admitted to seven hospitals in Melbourne with laboratory-confirmed pandemic (H1N1) 2009 influenza between 1 May and 17 July 2009.

Main outcome measures: Details of case characteristics, risk factors for severe disease, treatment and clinical course.

Results: Of 112 hospitalised patients, most presented with cough (88%) and/or fever (82%), but several (4%) had neither symptom. A quarter of female patients (15) were pregnant or in the post-partum period. Patients presenting with multifocal changes on chest x-ray had significantly longer hospital lengths of stay, and were more likely to require intensive care unit admission. Thirty patients required admission to an intensive care unit, and three died during their acute illness. The median length of intensive care admission was 10.5 days (interquartile range, 5–16 days).

Conclusions: This study highlights risk factors for severe disease, particularly pregnancy. Clinical and public health planning for upcoming influenza seasons should take into account the spectrum and severity of clinical infection demonstrated in this report, and the need to concentrate resources effectively in high-risk patient groups.

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The novel influenza virus, pandemic (H1N1) 2009 influenza (or "swine flu") has spread rapidly since it was first reported in California on 15 April 2009, and in a returned traveller in Australia on 9 May 2009.[1] During the early phase of the pandemic, a particularly large number of infections were confirmed in Victoria, making it the location with the greatest density of infections worldwide.[2]

Seasonal influenza is associated with considerable morbidity and mortality, accounting for about 2100 hospitalisations in Australia annually.[3] Early reports pertaining to pandemic (H1N1) 2009 influenza suggested high mortality in younger, previously well patients;[4,5] however, subsequent reports have noted a lower mortality. Among the first 553 confirmed cases in California, 30 affected patients had been admitted to hospital, and none had died.[6] Other reports found that around half of patients admitted to hospital had traditional risk factors for severe seasonal influenza infection, and that of 22 hospitalised patients with confirmed pandemic (H1N1) 2009 influenza infections, two had died.[7,8]

We reviewed the clinical characteristics of adult patients admitted to seven Melbourne hospitals at the beginning of the outbreak to inform public health planning and pandemic preparedness, particularly for northern hemisphere countries during the approaching seasonal influenza period.

METHODS

All eight public (non-paediatric) hospitals in Melbourne that had infectious diseases physicians were contacted and invited to participate. Patients admitted to participating hospitals between 1 May and 17 July 2009 were eligible for inclusion if they had laboratory-confirmed infection with pandemic (H1N1) 2009 influenza. Admission data were collected using a standardised case report form. The case report form included demographic information, information about comorbid conditions and potential sources of infection, and clinical information about symptoms, treatment and patients' progress in hospital. Length of stay data were collected for total time in hospital as well as time spent in intensive care units (ICUs). Data for six patients in this series have been reported in an earlier brief communication.[9]

Risk factors, including asthma, renal disease, diabetes mellitus, chronic obstructive pulmonary disease and ischaemic heart disease were defined from prior documentation or self-reported history. Obesity was defined as a body mass index of $>30\,m/kg,^2$ and fever as a temperature over 38°C.

Testing for pandemic (H1N1) 2009 influenza was performed at the Victorian Infectious Diseases Reference Laboratory, a statewide service. Testing for influenza A viruses involved RNA extraction from clinical material, followed by reverse transcription. Complementary DNA was amplified using a 7500 Fast Real-Time PCR [polymerase chain reaction] System (Applied Biosystems, Melbourne, Vic), incorporating primers and probe that targeted the matrix gene of influenza type A viruses, including the novel (swine lineage) H1N1 virus. Samples that tested positive in this assay were confirmed as positive or negative for the swine influenza virus in a second real-time PCR assay incorporating primers and probe specific for the haemagglutinin gene of that virus.[10]

Descriptive statistical analysis was performed on aggregated data, and intergroup comparisons were made with χ^2 analysis or Fisher's exact test for categorical variables and the Mann–Whitney test for continuous variables. The level of statistical significance was defined as $P<0.05$ on a two-tailed test. Aggregate data are reported as mean values unless otherwise specified.

The research ethics committee at each participating hospital approved patient enrolment as a quality assurance project. Data were collected and stored at each individual hospital, with de-identified and aggregated data reported centrally for analysis.

RESULTS

Of the eight hospitals invited to participate, one declined. The seven participating hospitals consisted of four tertiary hospitals, two peripheral hospitals and one specialist oncology centre. These hospitals admitted most of the patients hospitalised in Melbourne with pandemic (H1N1) 2009 influ-

1 Demographic characteristics and comorbid conditions of the first 112 patients admitted to participating hospitals with pandemic (H1N1) 2009 influenza

Demographic characteristics	Finding
Median age in years (range)	42 (15–79)
Age > 65 years	13 (12%)
Female	60 (54%)
Smoking	29 (26%)
Heavy alcohol intake	10 (9%)
Comorbid conditions	
Asthma	35 (31%)
Diabetes	20 (18%)
Immunosuppressive medications	18 (16%)
Oral steroid use	12 (11%)
For haematological malignancy	9 (8%)
For solid malignancy	5 (4%)
For prior organ transplantation	4 (4%)
Pregnancy	15 (13%)
Malignancy	14 (13%)
Obesity	8 (7%)
Chronic renal disease	7 (6%)
Ischaemic heart disease	6 (5%)
Chronic obstructive pulmonary disease	6 (5%)
No risk factors for severe disease	24 (21%)

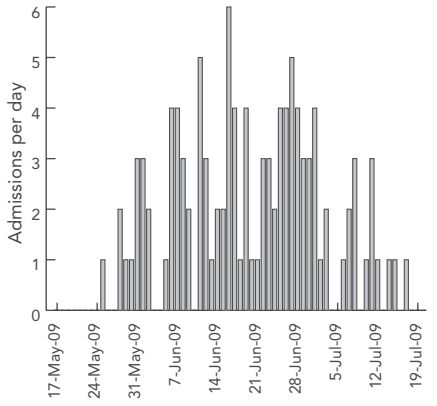
enza infection, although the exact proportion is unknown.

Demographic characteristics and the comorbid conditions of the first 112 patients hospitalised with pandemic (H1N1) 2009 influenza are shown in Box 1.

Most hospitalised patients (86; 77%) did not have a clearly identifiable exposure history to a patient with influenza-like illness or known pandemic (H1N1) 2009 influenza infection. Of the 26 patients who identified an exposure, 18 patients (16%) had been exposed through a household contact, four (4%) through a community contact and one (1%) through a school contact, while three patients (3%) were thought to have been infected in a hospital. No infections were believed to have been acquired overseas.

Box 2 shows the daily admissions of patients with confirmed pandemic (H1N1) 2009 influenza infection at the participating hospitals. An apparent peak of 4–6 admissions per day was noted between 12 and 28 June (peak, 16 June), with a decline in admissions thereafter.

2 Number of daily admissions to participating hospitals of patients with confirmed pandemic (H1N1) 2009 influenza, 1 May to 31 July 2009



Clinical and radiological features at the time of initial presentation are shown in Box 3. Box 4 shows the spectrum of illness observed in patients admitted to participating hospitals with pandemic (H1N1) 2009 influenza; these included some unusual complications, such as febrile seizures (three patients), rhabdomyolysis (one), myocarditis (one) and Guillain–Barré syndrome (one). Other non-respiratory presentations included preterm labour, syncope, lethargy, abdominal pain and diarrhoea.

At the time of or during hospitalisation, 93 patients (83%) were prescribed an antiviral agent. All 93 patients received 75 mg oseltamivir twice daily, while one patient received both oseltamivir and zanamivir. Antiviral therapy was initiated at a median time of 3 days (interquartile range [IQR], 2–5 days) after the onset of the first symptom, with fever persisting for a median of 1 day (IQR, 0–1 days) after initiation of treatment. The median length of stay of all hospitalised patients was 4 days (IQR, 3–8 days).

Thirty patients (27%) were admitted to an ICU. Patients remained in an ICU for a median of 7 days (IQR, 3–14 days), and this group had a median total hospital length of stay of 10.5 days (IQR, 5–16 days). Nine patients remained in hospital at the time of writing this report, with five patients remaining in an ICU. Three patients died during the study period, all during or following an ICU admission.

3 Symptoms and radiological findings in the first 112 patients admitted to participating hospitals with pandemic (H1N1) 2009 influenza

Symptoms	No. (%)
Cough	99 (88%)
Fever	92 (82%)
Fatigue	66 (59%)
Dyspnoea	57 (51%)
Myalgia	54 (48%)
Sore throat	44 (39%)
Coryza	37 (33%)
Diarrhoea	14 (13%)
Fever with cough or sore throat	91 (81%)
Radiological abnormalities	
Multifocal changes	30 (27%)
Unifocal changes	20 (18%)
Normal	56 (50%)
Pleural effusion	4 (4%)
Not performed	6 (6%)

There were 24 patients without identified risk factors; these patients had a lower median age (28 years) and shorter median length of stay (3 days; IQR, 2–4 days). Twelve of these patients were current smokers, 23 met the clinical case definition for influenza, and four required ICU admission (16.7% v 29.5% of patients with identified risk factors; $P < 0.01$). None of the 24 patients without risk factors died.

There were 30 patients with multifocal changes on initial chest x-ray (Box 3), and these patients appeared to have worse in-hospital outcomes. When compared with patients who had normal findings on initial

4 Spectrum of illness observed in the first 112 patients admitted to participating hospitals with pandemic (H1N1) 2009 influenza

- Classical "influenza-like illness" with fever, cough and dyspnoea
- Secondary bacterial pneumonia following influenza-like illness
- Afebrile exacerbation of chronic obstructive pulmonary disease
- Premature labour due to influenza
- Increased frequency of seizures in a patient with known epilepsy
- Rhabdomyolysis
- Guillain–Barré syndrome
- Myocarditis ◆

chest x-ray, those with multifocal changes were more likely to require ICU admission (odds ratio, 5.2; 95% CI, 1.9–13.9). Mean hospital length of stay in this group was 10.7 days versus 5.1 days in patients with unifocal or no changes on initial chest x-ray ($P < 0.001$). Finally, each of the three patients who died had multifocal changes on initial chest x-ray.

DISCUSSION

This is the largest series of patients hospitalised with pandemic (H1N1) 2009 influenza reported to date, and the first during a regular influenza season. It highlights the spectrum of severe disease experienced in hospitalised patients infected with pandemic (H1N1) 2009 influenza, particularly in pregnant women. Although this pandemic influenza has been portrayed as a less virulent infection than early reports suggested, our report shows that some patients continue to experience significant morbidity.

The characteristics of admitted patients in this series differ in important ways from both the early North American experience of pandemic (H1N1) 2009 influenza and what would be expected from seasonal influenza. While the initial cases in California and Mexico were predominantly in young patients without defined comorbid risk factors, our series included patients of advanced age and with malignancy and chronic lung disease, who would normally be considered at high risk of acquiring seasonal influenza.

Most patients presented with a history of cough (88%) and/or fever (82%), while other symptoms occurred in around half or fewer of admitted patients. These features were not universal, and 4% of patients did not have fever, cough or sore throat before they were admitted. Diarrhoea, reported as a prominent symptom in early North American reports, occurred in only 13% of cases. Overall, 91 patients (81%) met the clinical case definition of fever with either cough or sore throat.

The high proportion of pregnant women in our cohort is particularly striking — a quarter of all women hospitalised with pandemic (H1N1) 2009 influenza were pregnant or in the post-partum period. This does not appear to reflect an admission bias, with a third of pregnant patients requiring ICU admission during the period of hospitalisation.

Although it is difficult to compare these findings directly with those expected in the case of seasonal influenza,[11] of the 112 patients in our series, 30 required admission to an intensive care or high dependency unit, and three died during their acute illness; this severity of illness considerably exceeds that which would be expected during a regular influenza season. Our findings highlight the significant illness and burden of disease that may be associated with pandemic (H1N1) 2009 influenza infections. When taken together with the additional resources required for infection control and isolation practices, our findings indicate that pandemic (H1N1) 2009 influenza has the potential to provide a significant additional burden on hospitals in affected areas.

Our study is limited by incomplete coverage of Melbourne hospitals, with an emphasis on adult tertiary referral centres. This may have resulted in a referral bias of more severe cases than might be admitted in smaller peripheral centres. Our analysis was performed early in the outbreak, and may have underestimated mortality as patients may have died after the conclusion of the study period. By comparison, as of the end of September 2009, there have been 24 deaths in Victoria of a total of 178 deaths nationally attributed to pandemic (H1N1) 2009 influenza.

Overall, most cases occurred in patients with recognised risk factors for severe influenza, with an overrepresentation of pregnant women. A significant proportion of patients in this series required intensive care support. These findings have significant implications for future pandemic planning, and particularly highlight the need to concentrate resources effectively in high-risk patient groups.

COMPETING INTERESTS

None identified.

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REFERENCES

1 Centers for Disease Control and Prevention (US). Swine influenza (H1N1) infection in two children — Southern California, March–April 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58: 400-402.
2 State Government of Victoria, Australia, Department of Health. H1N1 influenza 09 (human swine flu). http://humanswineflu.health.vic.gov.au/ (accessed Jul 2009).
3 Brotherton J, Wang H, Schaffer A. Vaccine preventable diseases and vaccination coverage in Australia 2003 to 2005. *Commun Dis Intell* 2007; 31 (2 Suppl): 1-50.
4 Schanzer DL, Langley JM, Tam TW. Co-morbidities associated with influenza-attributed mortality, 1994–2000, Canada. *Vaccine* 2008; 26: 4697-4703.
5 Centers for Disease Control and Prevention (US). Outbreak of swine-origin influenza A (H1N1) virus infection — Mexico, March–April 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58: 467-470.
6 Centers for Disease Control and Prevention (US). Hospitalized patients with novel influenza A (H1N1) virus infection — California, April–May 2009. *MMWR Morb Mortal Wkly Rep* 2009; 58: 536-546.
7 Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med* 2009; 361 : 680-689. Epub 2009 Jun 29.
8 Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009; 360: 2605-2615.
9 Kaufman MA, Duke GJ, McGain F, et al. Life-threatening respiratory failure from H1N1 influenza 09 (human swine influenza). *Med J Aust*, 2009; 191: 154-156.
10 World Health Organization. CDC protocol of real-time RTPCR for swine flu influenza A(H1N1). 28 April 2009, revision 1 (30 April 2009). http://www.who.int/csr/resources/publications/swineflu/CDCrealtimeRTPCRprotocol_20090428.pdf (accessed Oct 2009).
11 Kelly H, Grant KA, Williams S, et al. Epidemiological characteristics of pandemic influenza H1N1 2009 and seasonal influenza infection. *Med J Aust* 2009; 191: 146-149.

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