Comparison of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza during the "PROTECT" phase of the pandemic response

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ABSTRACT

Objective: To compare the patient characteristics, clinical features and outcomes of adult patients hospitalised with pandemic (H1N1) 2009 influenza and seasonal influenza.

Design and setting: Retrospective medical record review of all patients admitted to Liverpool Hospital, Sydney, with laboratory-confirmed influenza from the initiation of the "PROTECT" phase of the pandemic response on 17 June until the end of our study period on 31 July 2009.

Main outcome measures: Severity of illness; requirement for admission to the intensive care unit (ICU) and/or invasive ventilation; mortality.

Results: Sixty-four adults were admitted to Liverpool Hospital with influenza, 48 with pandemic (H1N1) 2009 influenza and 16 with seasonal influenza. Thirteen patients were admitted to the ICU. Seven required invasive ventilation, with 2 patients requiring ongoing extracorporeal membrane oxygenation (ECMO). Five patients died (mortality rate, 8%) with two deaths occurring after the study period. Patients with pandemic (H1N1) 2009 influenza were younger and less likely to be immunocompromised than patients with seasonal influenza. However, the clinical features of pandemic (H1N1) 2009 influenza and seasonal influenza were similar.

Conclusions: Our findings show that the clinical course and outcomes of pandemic (H1N1) 2009 influenza virus are comparable to those of the current circulating seasonal influenza in Sydney. The high number of hospital admissions reflects a high incidence of disease in the community rather than an enhanced virulence of the novel pandemic influenza virus.

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In early April 2009, a novel influenza A virus was identified in Mexico and Southern California.[1] The subsequent rapid international spread and sustained community transmission in the Americas, Europe, New Zealand and Australia resulted in the World Health Organization escalating the pandemic influenza response to Phase 6 on 11 June 2009.[2]

The Australian Health Management Plan for Pandemic Influenza, which includes the ALERT, DELAY, CONTAIN, SUSTAIN, CONTROL and RECOVER phases of response,[3] was predicated on pandemic influenza causing high morbidity and mortality. However, pandemic (H1N1) 2009 influenza appeared to be causing milder disease. Cases of severe disease and deaths have been reported,[4] in particular, pregnant women could have severe disease.[5,6] A modified strategy, the "PROTECT" phase, was thus enacted on 17 June 2009.[7] It focused on identifying and treating infection in people with moderate to severe disease and those with certain risk factors (pregnancy and underlying chronic diseases), controlling outbreaks in institutions, and monitoring hospitalisation.[8]

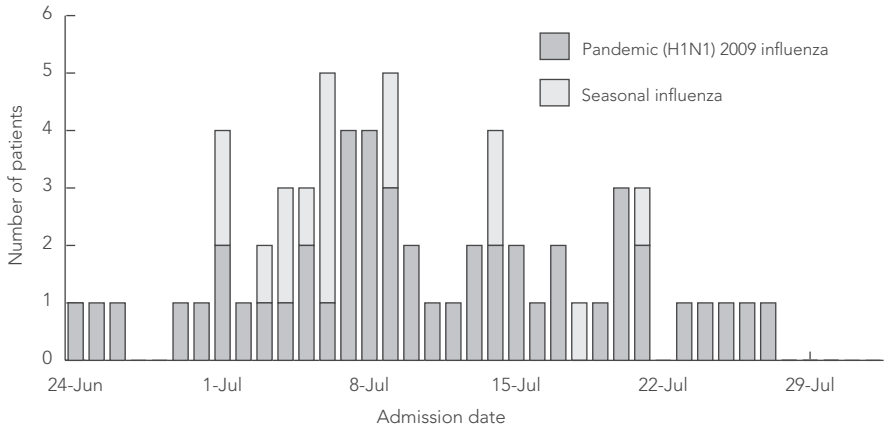
The PROTECT phase coincided with the start of the influenza season in Sydney, and the surge in hospital admissions of patients with pandemic (H1N1) 2009 influenza coincided with the expected surge in seasonal influenza. This situation allowed us to compare patient characteristics, clinical features and outcomes of infection with pandemic (H1N1) 2009 influenza and seasonal influenza. Part of this work was presented at the 14th Congress of the Asian Pacific Society of Respirology in Seoul, Korea, 14–18 November 2009 (Poster no. APSR 2009-594).

METHODS

We reviewed the medical records of all adult patients (aged 18 years and over) with a laboratory-confirmed diagnosis of influenza who were admitted to Liverpool Hospital, Sydney, from 17 June (the beginning of the PROTECT Phase) to 31 July 2009.

During this period, nose and/or throat swabs were collected from all patients admitted with an influenza-like illness. Following total nucleic acid extraction using the MagNA Pure System (Roche Diagnostics Australia, Sydney, NSW) influenza was confirmed by polymerase chain reaction using the Influenza 4 Easy-Plex

1 Admissions to Liverpool Hospital of 64 adults with confirmed seasonal and pandemic (H1N1) 2009 influenza during the "PROTECT" phase of the epidemic*



* The peak of both epidemics occurred around 8 July 2009.

assay kit (AusDiagnostics, Sydney, NSW). Subsequent typing was performed on all influenza A-positive isolates on the stored extract (–80°C) using the Influenza 6 Easy-Plex assay kit (AusDiagnostics, Sydney, NSW).

Demographic and clinical details were extracted from the clinical notes and electronic information system. These details included age, sex, place of residence, and presence of comorbid conditions or risk factors for possible severe illness (eg, obesity, diabetes, pregnancy and immunosuppression). The date of onset of presenting influenza-like illness symptoms (coryza, fever, cough, breathlessness, chest pain, sore throat, lethargy, myalgia, vomiting, diarrhoea and abdominal pain), clinical signs and laboratory results (including haematological, biochemical, serological, microbiological and arterial blood gas results with patients breathing room air) were also extracted. The clinical course, management directed by the attending physicians, and outcomes at discharge were similarly recorded.

Chest x-rays were reviewed and classified according to the type, pattern and extent of any abnormalities. The principal respiratory diagnosis was made after review of the complete record, with pneumonia defined as the presence of consistent radiological abnormalities and clinical signs.

Health-care-associated influenza was defined as onset of symptoms more than 4 days after admission, to correspond with the upper limit of influenza virus incubation.[9]

Statistical analysis

Continuous and categorical data were analysed with Microsoft Office Excel 2007 (Microsoft Corporation, Redmond, Wash, USA) and SPSS student version 16.0 (SPSS Inc, Chicago, Ill, USA) using two-sample *t* tests, Fisher's exact test, or adjusted or unadjusted χ^2 tests, as appropriate.

The study was approved by the Sydney South West Area Health Service, Human Research Ethics Committee (Project No. QA2009/047).

RESULTS

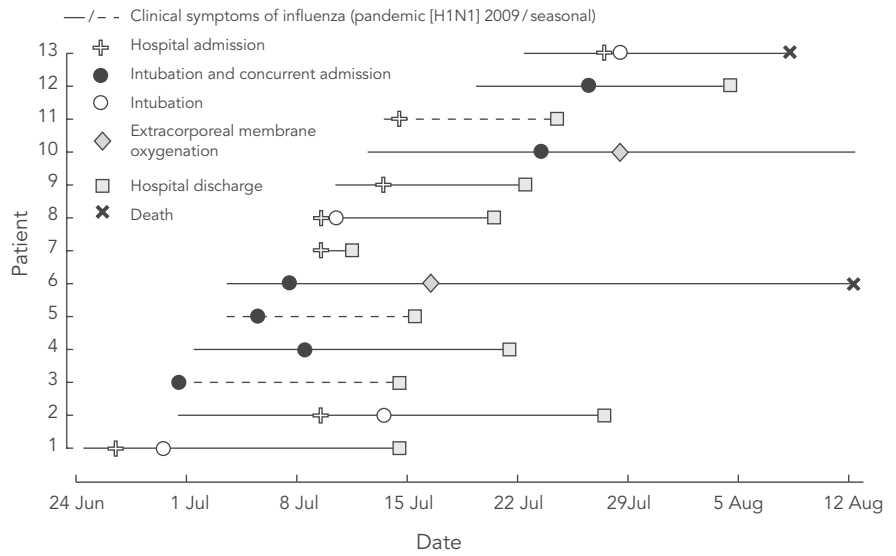
Sixty-five patients were admitted to Liverpool Hospital with a laboratory-confirmed diagnosis of influenza between 17 June and 31 July 2009. One of these patients had been admitted for ischaemic gut, and was excluded from the analysis because the patient did not have a concurrent influenza-like illness. Of the remaining 64 patients, 48 tested positive for pandemic (H1N1) 2009 influenza and the remaining 16 tested posi-

2 Demographic, clinical and laboratory features of the 64 patients admitted to Liverpool hospital with seasonal and pandemic (H1N1) 2009 influenza, 17 June to 31 July 2009

Patient features	Seasonal influenza	H1N1 2009 influenza
No. of patients	16	48
Mean age (years)	64	45*
No. female	13	30
Comorbid conditions		
None	6	21
Chronic obstructive pulmonary disease	4	9
Obesity	2	9
Diabetes	1	15
Immunocompromised	7	8*
Pregnancy related	1†	8‡
Community acquired	16	43
Health-care associated	0	5
Symptoms		
Fever	15	46
Cough	15	34
Dyspnoea	8	33
Lethargy	7	21
Myalgia	4	10
Sore throat	2	11
Vomiting and/or diarrhoea	5	23
Mean days from symptom onset to presentation (range)	4 (0–10)	4 (0–15)
Observations at presentation		
Febrile (temperature > 37.5° C)	10	38
Tachycardia (> 100 beats per min)	8	29
Hypotensive (blood pressure < 90 mmHg systolic or < 60 mmHg diastolic)	5	7
Tachypnoea (> 16 breaths per min)	15	44
Hypoxia (peripheral blood oxygen saturation < 95%)	9	29
Laboratory results		
Mean white blood cell count (cells × 10^9/L [range])	8.86 (0.1–20.7)	8.87 (1.1–27.6)
Nadir lymphocyte count (cells × 10^9/L [range])	0.68 (0–1.5)	0.66 (0.1–1.9)
Mean C-reactive protein concentration (mg/L [range])	134 (9–580)	104 (6–630)
Mean PaO_2 with patient breathing room air (mmHg [kPa])	61 (8.1)	72 (9.6)
Chest x-ray findings		
Normal	9	19
Abnormal	6	25
No chest x-ray	1	4
Diagnosis of pneumonia	6	21
Pneumonia severity index (range)	*135 (100–158)*	*92 (30–160)*
Non-pneumonic diagnosis	10	27
Treatment		
Oseltamivir or zanamivir	13	40
Antibiotics	15	43
Corticosteroids	10	13
Intensive care unit admission	3	10
Non-invasive or invasive ventilation	2	10
Extracorporeal membrane oxygenation	0	2
Mean days to defervescence (range)	2.6 (0–10)	3.2 (0–14)
Mean days in hospital (range)	7 (1–18)	8 (0–61)
Overall deaths	1	4§

PaO_2 = partial pressure of oxygen in arterial blood. * $P < 0.05$. † Patient in the second trimester of pregnancy. ‡ Of the eight patients, three were in the postpartum period, with two in the first, two in the second and one in the third trimester of pregnancy. § Of the five deaths, three occurred during the study period; the remaining two occurred on 8 and 12 August 2009. ◆

3 Clinical courses of 13 patients admitted to Liverpool Intensive Care Unit (ICU) with pandemic (H1N1) 2009 influenza and seasonal influenza, 17 June to 31 July 2009*



* As of 31 July 2009, three patients remained in the ICU, with two of these being treated with extracorporeal membrane oxygenation. ◆

tive for seasonal influenza A (11 for subtype H3 and five for untypeable non-pandemic [H1N1] 2009 influenza). The epidemic curve showed that the peak of the outbreak occurred around 8 July (Box 1). Five of the 64 cases of influenza (all pandemic [H1N1] 2009) were health-care associated.

Box 2 shows demographic characteristics and presenting features and outcomes for patients admitted with pandemic (H1N1) 2009 and seasonal influenza. Patients with pandemic (H1N1) 2009 influenza were significantly younger than those presenting with seasonal influenza (mean age, 45 years v 64 years; $P < 0.01$). Patients with seasonal influenza were more commonly immunosuppressed than patients with pandemic (H1N1) 2009 ($P < 0.05$). Although a relationship with pregnancy (patients in their postpartum period or pregnant) was more common in the pandemic (H1N1) 2009 group (eight patients v one patient with seasonal influenza), this difference did not reach statistical significance (Box 2).

Thirteen patients were admitted to the intensive care unit (ICU) — three with seasonal and 10 with pandemic (H1N1) 2009 influenza. The clinical course and hospitalisation of these patients is illustrated in Box 3. Of the three patients remaining in ICU, two died (patient 13 and patient 6 in Box 3 on 8 August and 12 August, respectively), with the remaining patient discharged alive from hospital on 23 September 2009.

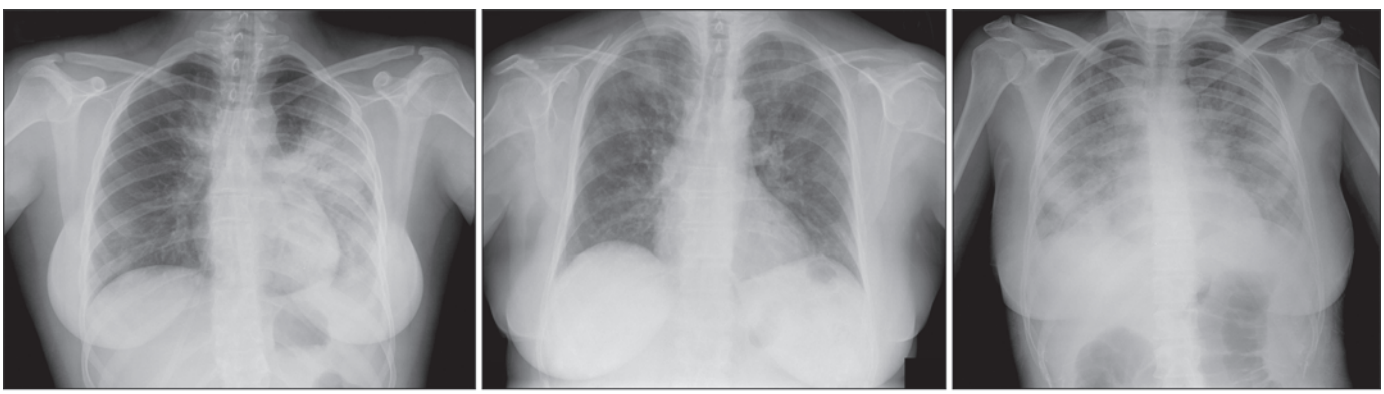
Box 2 shows that the mean duration of symptoms before presentation was 4 days, with fever, cough and dyspnoea being the most common symptoms in both groups. Similarly, there was no difference in the clinical signs between the two groups, with a diagnosis of pneumonia occurring in similar proportions of patients with seasonal and pandemic (H1N1) 2009 influenza.

Laboratory results showed no difference between the two groups in mean total white blood cell count, nadir lymphocyte count, C-reactive protein concentration, and mean partial pressure of arterial oxygen (patients breathing room air) at presentation. Forty-six patients had blood cultures and 12 had sputum cultures performed. Three patients had bacterial co-infections with *Streptococcus pneumoniae* and *Haemophilus influenzae* confirmed by blood culture, and methicillin-sensitive *Staphylococcus aureus* was isolated from one sputum culture.

Chest x-rays were taken of 59 of the 64 patients, and abnormalities were detected in 31 patients. Abnormal radiological features ranged from localised infiltrates to bilateral airspace consolidation (Box 4). Four patients had radiological abnormalities attributable to chronic lung conditions without evidence of concurrent pneumonia.

Fifty-three hospitalised patients were treated with a neuraminidase inhibitor and antibiotics. Corticosteroids were significantly more likely to be prescribed in the

4 Chest x-rays showing typical abnormalities found in patients hospitalised with influenza, 17 June to 31 July 2009



Patient with pandemic (H1N1) 2009 influenza showing airspace opacity in the left upper and left lower lobes and medial right upper zone.

Patient with pandemic (H1N1) 2009 influenza showing bilateral interstitial and airspace opacity.

Patient with seasonal influenza showing bilateral airspace opacity.

◆

seasonal influenza group compared with the pandemic (H1N1) 2009 group ($P < 0.05$; Box 2). However, all corticosteroid use was deemed to be for treatment of an underlying respiratory illness rather than influenza. Treatment response did not differ significantly between the two groups, and the overall mean time to defervescence was 2.6 days (range, 0–10 days) and mean number of days in hospital was 8 days (range, 0–61 days). Overall, there were five deaths (four in the pandemic (H1N1) 2009 group and one in the seasonal influenza group). Two deaths occurred in the ICU (see above).

DISCUSSION

A major strength of our study was that the epidemics of seasonal and pandemic (H1N1) 2009 influenza occurred concurrently, which allowed us to make a direct comparison. Our data show that there was no difference between the two groups except that patients admitted with pandemic (H1N1) 2009 influenza tended to be younger and less immunocompromised. The clinical, radiological and laboratory features at presentation were similar in both patient groups, as were the clinical course, management and outcomes. Our findings show that, for hospitalised patients, the clinical manifestations and severity of pandemic (H1N1) 2009 and seasonal influenza were similar. This suggests that the number of admissions to our hospital and ICU reflected the higher burden of disease in the community rather than a greater virulence of the novel pandemic influenza virus.

Significant morbidity and mortality from influenza in pregnant women during previous pandemics has been reported.[10,11] For seasonal influenza, the highest morbidity for pregnant women occurred in the third trimester.[12] There have been several reports that pregnant women are at increased risk of severe complications from pandemic (H1N1) 2009 influenza.[5,6] However, we were unable to demonstrate a difference in clinical severity between the seasonal and the pandemic viruses. The reliability of our estimate is limited by the small sample size, and a definitive answer to this question requires a multicentre study.

The clinical and epidemiological characteristics of 18 people hospitalised with pneumonia caused by pandemic (H1N1) 2009 influenza in Mexico City have been reported.[13] The age, presence of comorbid conditions, presenting symptoms, laboratory findings and clinical features were similar to those in our group. However, in the Mexican series the higher proportion of abnormalities on chest x-ray (all patients), the number of patients with severe disease requiring invasive ventilation (12), and the mortality rate (39%) differ from our series (mortality rate, 8%). This could reflect differing admission criteria and smaller numbers.

In conclusion, our study shows that the clinical disease caused by the novel pandemic (H1N1) 2009 influenza virus in humans is comparable to that caused by the current circulating seasonal influenza strains in Sydney. The number of patients with severe disease reflects the disease burden in the community resulting from the pandemic. Pregnant women are at risk of severe infection from influenza, but whether pandemic (H1N1) 2009 influenza is particularly virulent in pregnant women and those in their postpartum period requires further study. It remains unclear whether antiviral drugs alter the clinical course of severe influenza infection.

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COMPETING INTERESTS

None identified.

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