Original Article

An Epidemiological Study of 1348 Cases of Pandemic H1N1 Influenza Admitted to Singapore Hospitals from July to September 2009

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Abstract

Introduction: We reviewed the epidemiological features of 1348 hospitalised cases of influenza A (H1N1-2009) [pandemic H1N1] infection in Singapore reported between 15 July and 28 September 2009. Materials and Methods: Data on the demographic and epidemiological characteristics of hospitalised patients with confirmed pandemic H1N1 infection were collected from all restructured and private hospitals in Singapore using a standard template and were analysed retrospectively. Results: Of the 1348 cases, 92 were classified as severely ill (i.e. were admitted to an intensive care unit and/or who died). Of these severely ill cases, 50 (54.3%) required mechanical ventilation. While overall hospitalisation rates were highest in the 0 to 11 months age group, the incidence of severely ill cases was highest in patients aged 65 years and older. Fifty per cent of all hospitalised cases and 28% of all severely ill cases did not have any underlying medical conditions. The following factors were found to be independently associated with a higher likelihood of severe illness: older age and the presence of the following comorbidities: neuromuscular disorders, epilepsy and obesity. Conclusion: Between 15 July and 28 September 2009, pandemic H1N1 infection caused significant illness requiring hospitalisation, as well as intensive care and mechanical ventilation in some cases. There were 18 deaths from pandemic H1N1 during this period, which corresponded to a case-fatality rate of 7 deaths for every 100,000 cases of pandemic H1N1.

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Introduction

On 17 April 2009, the US Centers for Disease Control (CDC) determined that febrile respiratory illness occurring in 2 children residing in adjacent counties in southern California was caused by a novel influenza A (H1N1) virus.[1] The virus is thought to be a re-assortment of 4 known strains of influenza A virus subtype H1N1: one that circulates in humans, one that circulates in birds, and two endemic in pigs.[2] The virus may have had its origins in Mexico, where surveillance had picked up an increasing number of cases of influenza-like illness beginning in March 2009.[3] The virus spread rapidly worldwide, causing the World Health Organization (WHO) to declare a Phase 6 global influenza pandemic on 11 June 2009.[4] As of 17 January 2010, more than 209 countries and overseas territories or communities have reported laboratory confirmed cases of pandemic influenza H1N1 2009, including at least 14,142 deaths.[5]

Singapore has a colour-coded response system to an influenza pandemic threat, which moves progressively from green through yellow, orange, red and black. Alert green represents the lowest level of threat, while alert black implies a severe pandemic.[6] The changes in Singapore's and WHO's alert status in response to the Influenza A(H1N1-2009) are shown in Table 1.

The first case of influenza A (H1N1) [pandemic H1N1] in Singapore was detected on 26 May 2009 in a returning traveller, 1 month after WHO's announcement of the novel virus outbreak on 24 April 2009. Singapore's control measures to ameliorate the impact of the influenza pandemic could be broadly grouped into 2 phases: containment and mitigation. Containment strategies were put in place to delay the onset of community spread of the infection. One of the strategies during the containment phase was mandatory hospitalisation and isolation of all confirmed

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Table 1. Dates of Changes in Singapore's and WHO's Influenza Pandemic Alert

Date	Change in alert status	Comments
27 April 2009	WHO pandemic alert raised from Phase 3 to Phase 4[7]	There is sustained human-to-human transmission capable of causing community-level outbreaks, and a significant increase in risk of a pandemic.[8]
28 April 2009	Singapore raised its alert status from green to yellow[9]	Infection control measures in healthcare institutions were stepped up. Temperature screening for and restriction of visitors to hospitals, and temperature screening at border checkpoints were implemented.[9]
29 April 2009	WHO pandemic alert raised from Phase 4 to Phase 5[7]	Human-to-human spread of the virus into at least 2 countries in 1 WHO region. Pandemic threat is imminent.[8]
30 April 2009	Singapore raised its alert status from yellow to orange[10]	Infection control measures in hospitals were further tightened. Other measures were also introduced, including routine temperature screening in schools, workplaces and other public venues, and home quarantine for a period of 7 days for travellers from Mexico.[10]
11 May 2009	Singapore lowered its alert status from orange to yellow[11]	The alert status was lowered because the virus appeared milder than originally feared. Routine temperature screening in schools, workplaces and other public venues was discontinued.[11]
11 June 2009	WHO declares an influenza pandemic (phase 6)[7]	Occurrence of community level outbreaks in at least one other country in a different WHO region in addition to the criteria defined in Phase 5.[8]

cases of pandemic H1N1, regardless of severity of disease. As the number of epidemiologically unlinked cases in the community increased in late June, there was a shift towards measures aimed at mitigating the severity of the disease instead of curtailing its spread. Hospitalisation of all cases was no longer required and only recommended when clinically indicated. This report presents the epidemiological features of the 1348 clinically-indicated hospitalised cases of laboratory-confirmed pandemic H1N1 infection in Singapore and analysis of risk factors associated with severe infection and death.

Materials and Methods

We retrospectively studied the demographic and epidemiological characteristics of hospitalised patients with confirmed pandemic H1N1 infection reported between 15 July and 28 September 2009. Patients were identified through reports of all confirmed cases from the 6 restructured hospitals (Singapore General Hospital, Tan Tock Seng Hospital, Alexandra Hospital, National University Hospital, KK Women's and Children's Hospital and Changi General Hospital), and 6 private hospitals (Mount Elizabeth Hospital, Gleneagles Hospital, Mount Alvernia Hospital, East Shore Hospital, Thompson Medical Centre and Raffles Hospital) in Singapore. In mid-July 2009, hospitals were asked to report all cases of laboratory confirmed pandemic H1N1 admitted for clinical indications only. Cases admitted for reasons of quarantine were not included in this dataset.

Data were collected using a standard template and included age, gender and ethnicity of patients, comorbidities, pregnancy, dates of onset of symptoms, dates of admission to and discharge from hospital, dates of admission to and discharge from the intensive care unit (ICU) where applicable, oseltamivir administration, the use of mechanical ventilation, and clinical outcomes. The duration of stay in hospital, the duration of treatment in ICU, the duration between onset of symptoms and admission to hospital, and the duration between onset of symptoms and oseltamivir administration were calculated. Population-based age-specific hospitalisation rates, ICU admission rates and mortality rates were calculated using the 2009 mid-year Singapore population.[12]

Data were also collected on the hospital admitting diagnosis. Some cases with respiratory ailments were reported to have more than one admission diagnosis. In these instances, the major admission diagnosis was assigned to the case based on the following hierarchy: acute respiratory distress syndrome (ARDS), pneumonia, chronic obstructive pulmonary disease (COPD) or asthma, upper respiratory tract infection (URTI), fever, and other diagnoses. Thus, a case with admission diagnoses of ARDS and pneumonia was assigned an admission diagnosis of ARDS, and a case with admission diagnoses of pneumonia, COPD and fever was assigned an admission diagnosis of pneumonia.

Influenza A (H1N1 2009) infection was confirmed by reverse transcription polymerase chain reaction (RT-PCR) assays. At the start of the outbreak in Singapore, the National Public Health Laboratory (NPHL) and 4 diagnostic laboratories tested their methods on positive controls received from WHO. The assays used were developed based on sequence information updated on the US CDC and National Center for Infectious Diseases websites, and were either in-house assays or the published CDC method. To ensure accuracy, each diagnostic laboratory was required to

send the first 15 positive samples to NPHL for confirmation, before the results were reported to the attending physician. Thereafter, each laboratory was able to confirm pandemic H1N1 positive cases independently.

Data were analysed for 3 groups of patients: (i) all hospitalised patients with pandemic H1N1 infection, (ii) severely ill patients with pandemic H1N1 infection and (iii) deaths related to pandemic H1N1 infection. Severely ill patients were defined as patients with pandemic H1N1 infection who required admission to ICU and/or deaths related to pandemic H1N1 infection.

Descriptive data were presented as counts and percentages for categorical variables and as medians and interquartile range (IQR) for continuous variables. Age and gender adjustments for each of the major ethnic groups were done using the direct method with the 2009 mid-year Singapore population as the base population. Differences between the age-gender-standardised hospitalisation rates of the 3 ethnic groups were computed and tested for statistical significance using the Z-test.[13]

For all variables, data were analysed using available data; no assumptions were made regarding missing data. Continuous variables were compared using the Wilcoxon rank sum test, and discrete variables were compared using Fisher's exact tests. Multivariate logistic regression analysis was performed to identify factors associated with severity of illness. The Kaplan-Meier method was used to investigate the survival of severely ill cases. Survival time was computed from date of onset of severe illness to date of the event. The onset of severe illness was defined as the date of admission to ICU or the date of admission to hospital for those who were not admitted to ICU, and an event was defined as death related to pandemic H1N1 infection. The patients who were discharged from ICU alive were censored at 28 days. The log rank test was used to identify the factors associated with the survival of severely ill cases. Statistical significance was taken as P <0.05 level. The statistical analyses were performed using the statistical software SAS version 9.1 (SAS Institute Inc, Cary, North Carolina).

Results

All Hospitalised Cases

A total of 1348 hospitalised cases of laboratory confirmed Influenza A (H1N1-2009) in Singapore were reported to the Ministry of Health between 15 July and 28 September 2009. The median age of hospitalised cases was 25 years (IQR, 12-50), with an overall male-to-female ratio of 1:1.04. Hospitalisation rates (per 100,000 population) were highest in the 0 to 11 months age group (119.9 per 100,000) and second highest in children aged 1 to 4 years (56.7 per 100,000). Of the 1217 cases who were Singapore residents, Malays had the highest hospitalisation rate among the three major ethnic groups in Singapore (Table 2). The age-gender-adjusted hospitalisation rate was significantly higher among the Malays (76.3 per 100,000) compared to Indians (53.2 per 100,000) (P <0.0001), and was also significantly higher among Indians compared to Chinese (22.1 per 100,000) (P <0.0001).

Information on the hospital admission diagnosis was available for 1249 of the hospitalised cases. Of the 1249 cases, 37% were admitted for a diagnosis of either pneumonia, exacerbation of asthma or COPD and 21% were admitted with a diagnosis of URTI. Other admitting diagnoses included gastrointestinal, cardiovascular or renal causes in the absence of fever or respiratory tract symptoms (Table 3).

Among the 1348 hospitalised cases, 679 (50%) had one or more underlying medical conditions. There were 258 cases (19%) with asthma, 169 (13%) with diabetes, 83 (6%) with cardiac diseases, 71 (5%) with renal disease, and 42 cases (3%) with autoimmune disease (Table 4). Of 805 cases aged 20 years and above and 543 cases aged less than 20 years, 544 (68%) and 135 (25%) had one or more

Table 2. Demographic Characteristics of 1348 Hospitalised Patients including 92 Severely Ill Patients Associated with Influenza A (H1N1-2009) Infection in Singapore

	All hospitalised patients			Severely ill patients		
Characteristic	**No.**	**%**	**Incidence rate per 100,000 population**	**No.**	**%**	**Incidence rate per 100,000 population**
Overall	1348	100	27.0	92	100	1.8
Age group						
0-11 months	46	3	119.9	1	1	2.6
1-4	101	8	56.7	3	3	1.7
5-14	247	18	48.8	10	11	2.0
15-19	149	11	47.7	2	2	0.6
20-49	465	35	16.5	39	42	1.4
50-64	240	18	30.9	25	27	3.2
65+	100	7	27.4	12	13	3.3
Sex						
Female	691	51	29.0	46	50	1.9
Male	657	49	25.2	46	50	1.8
Ethnic group						
Singapore residents						
Chinese	599	44	21.6	43	47	1.6
Malay	390	29	78.0	26	28	5.2
Indian	175	13	50.9	12	13	3.5
Others	53	4	44.2	2	2	1.7
Foreigners	131	10	10.4	9	10	0.7

Table 3. Major Hospital Admission Diagnosis/Symptom Among Hospitalised Cases of Influenza A (H1N1-2009)*

	All patients	Severely ill cases†	Non-severe cases
Hospital admission Diagnosis/symptom	N (%)	N (%)	N (%)
Pneumonia	320 (26)	39 (44)	281 (24)
Upper respiratory tract infection	261 (21)	6 (7)	255 (22)
Exacerbation of asthma	130 (10)	4 (4)	126 (11)
Exacerbation of COPD	15 (1)	2 (2)	13 (1)
Acute respiratory distress syndrome	4 (0.3)	4 (4)	0 (0)
Fever[1]	177 (14)	3 (3)	174 (15)
Gastrointestinal causes/symptoms[2]	32 (3)	1 (1)	31 (3)
Cardiovascular diseases/symptoms[2]	30 (2)	4 (4)	26 (2)
Renal causes/ symptoms[2]	17 (1)	2 (2)	15 (1)
Seizure[2]	17 (1)	5 (6)	12 (1)
Reasons related to pregnancy[3]	19 (2)	0 (0)	19 (1)
Others[4]	227 (18)	19 (21)	208 (18)
Total	1249	89	1160

* Information on clinical indication for admission was only available for 1249 of 1348 cases.

† Severely ill cases refer to those admitted to ICU and/or those who died from cause(s) related to pandemic H1N1.

a Fever or febrile fit, but excluding all cases with a respiratory tract diagnosis. Among the severe cases, none were admitted with a diagnosis of febrile fit.

b These categories include admission diagnoses/symptoms without fever or a respiratory tract diagnosis

c This category excludes admission diagnoses/symptoms in any of the other categories, and includes the following categories: (i) pre-term labour, (ii) poorly controlled hypertension in pregnancy, (iii) Braxton-Hicks contractions, (iv) vomiting in pregnancy, (iv) admission for delivery.

d Includes admitting diagnoses/symptoms of dengue, sepsis, diabetic ketoacidosis, poor feeding, deterioration of mental status or GCS, functional decline, social reasons. Among the severe cases, none were admitted with a diagnosis of dengue, poor feeding or for social reasons.

Percentages may not total 100% due to rounding

underlying medical conditions respectively. Asthma was the most common comorbidity present in both persons aged 20 years and above and those below 20 years. Diabetes, hypertension, hyperlipidaemia, cardiac and cerebrovascular disease were observed more commonly in cases aged 20 years and above.

The median duration of onset of symptoms to admission to hospital was 2 days (IQR, 1-4). As of 11 February 2010, 1 of the 1348 patients was still hospitalised. Of the 1347

Table 4. Characteristics of 1348 Hospitalised Cases of Influenza A (H1N1-2009)

	All patients (n = 1348)	Severely ill cases* (n = 92)	Non-severe cases (n = 1256)	*P*†
Age - year (median, IQR)	25 (12-50)	44 (23.5-53.5)	24 (12-49)	<0.0001
Male gender (no, %)	657 (49%)	46 (50%)	611 (49%)	0.8295
Duration from onset to hospital admissions‡- days (median, IQR)	2 (1-4)	3 (1-5)	2 (1-4)	0.1107
Co-morbid condition (no, %§)				
Asthma	258 (19%)	9 (10%)	249 (20%)	0.0188
COPD	30 (2%)	3 (3%)	27 (2%)	0.4536
DM	169 (13%)	20 (22%)	149 (12%)	0.0088
Cardiac diseases[a]	83 (6%)	10 (11%)	73 (6%)	0.0678
IHD	49 (4%)	5 (5%)	44 (4%)	
CCF	16 (1%)	1 (1%)	15 (1%)	
Other cardiac diseases	30 (2%)	5 (5%)	25 (2%)	
Cerebrovascular diseases	21 (2%)	4 (4%)	17 (1%)	0.0496
Renal diseases	71 (5%)	9 (10%)	62 (5%)	0.0529
Immunosuppression[b]	70 (5%)	7 (8%)	63 (5%)	0.3235
Malignancy	54 (4%)	6 (7%)	48 (4%)	0.2611
Pregnancy	46 (3%)	2 (2%)	44 (4%)	0.7652
Autoimmune diseases	42 (3%)	3 (3%)	39 (3%)	0.7611
Epilepsy	27 (2%)	7 (8%)	20 (1%)	0.0016
Obesity	13 (1%)	4 (4%)	9 (1%)	0.0090
Neuromuscular disorders	12 (1%)	7 (8%)	5 (0.4%)	<0.0001
Hypertension	217 (16%)	25 (27%)	192 (15%)	0.0048
Hyperlipidaemia	109 (8%)	9 (10%)	100 (8%)	0.5502
Anaemia	34 (3%)	4 (4%)	30 (2%)	0.2854
One or more of the above	679 (50%)	66 (72%)	613 (49%)	<0.0001

* Severely ill cases refer to those admitted to ICU and/or those who died from an influenza A (H1N1-2009) related cause.

† The *P* values refer to the bivariate comparisons between severely ill and non-severe patients.

‡ Excludes those who developed symptoms after their hospital admissions.

§ A patient may be listed with more than one comorbid condition

a Excludes hypertension

b Includes the following categories (i) history of organ transplant, (ii) on chemotherapy, (iii) on immunosuppressive treatment, (iv) on steroid treatment for autoimmune disease, (v) patients who were labelled as immunosuppressed

patients who were either discharged from hospital or who died, the median length of hospital stay was 3 days (IQR, 2-5) with 90% of patients staying 8 days or less in hospital.

Severely Ill Cases Among Hospitalised Cases of Influenza A (H1N1-2009)

Of the 1348 patients, 92 (6.8 %) were considered to be severely ill (i.e. cases that required ICU care or died). Eighty-eight out of the 92 cases were admitted to ICU; 4 cases died but were not admitted to ICU. The median age of the severe cases was 44 years (IQR, 23.5-53.5), and 46 (50%) were male. The proportion of severely ill cases and the incidence of severely ill cases per 100,000 population were highest in patients aged 65 years and older, and next highest in those over 60 years. Among Singapore residents, the age-gender-adjusted hospitalisation rate of severely ill cases was highest in Malays (5.5 per 100,000) followed by Indians (4.1 per 100,000) and Chinese (1.5 per 100,000). Overall, Chinese had a significantly lower age-gender-adjusted hospitalisation rate of severely ill cases compared to Malays (P <0.0001) and Indians (P <0.001). The age-gender-adjusted hospitalisation rate of severely ill cases among the Malays was not significantly higher than that of the Indians (P = 0.360).

Information on hospital admission diagnosis was available for 89 of the 92 severe cases. Of the 89 cases, 44% were admitted for pneumonia, and another 7% for either an exacerbation of asthma or COPD (Table 3). All 5 severely ill cases admitted with a diagnosis of seizure were below 20 years of age. There were 4 cases (4%) admitted with a diagnosis of ARDS.

Sixty-six (72%) of the 92 severely ill cases had one or more underlying medical conditions, including diabetes in 20 cases (22%), asthma in 9 cases (10%), COPD in 3 cases (3%), epilepsy in 7 cases (8%), obesity in 4 cases (4%), and a neuromuscular disease in 7 cases (8%) (Table 4). Neuromuscular conditions among the severe cases included myasthenia gravis (1 case), Duchenne muscular dystrophy (1 case), neurodevelopmental delay (1 case), Parkinson's disease (1 case), Leigh's syndrome, (2 cases), and amyotrophic lateral sclerosis (1 case).

One severely ill case developed symptoms related to pandemic H1N1 during her hospital stay. Of the other 91 severely ill cases, the median duration from onset of symptoms to hospital admission was 3 days (IQR, 1-5). Information on oseltamivir administration was available in 78 severely ill cases. The median duration between onset of symptoms and oseltamivir administration was 3 days (IQR, 2-6).

Of the 92 severely ill cases, 26 (28%) did not have any comorbidities. The median age of these 26 cases was 29 years (IQR, 21-45) and 13 of these cases (50%) were male. Eleven cases (42%) were admitted with a diagnosis of pneumonia, 3 cases (12%) with URTI, and 2 cases (8%) had a diagnosis of ARDS on admission to hospital. There were 2 cases aged 2 years and below: a 3-month-old male and a 2-year-old male. Both cases presented at hospital with seizures, were admitted to ICU for observation for 1 and 2 days respectively, and were subsequently discharged from hospital.

As of 12 February 2010, 1 of the 92 cases was still in ICU. Among the 91 severely ill patients who had either been discharged from hospital or died, the median length of stay in hospital was 9 days (IQR, 5-18), and the median length of ICU stay was 4 days (IQR, 2-8). Fifty cases (54.3%) required mechanical ventilation. The median age of the 50 ventilated patients was 44 years (IQR, 31-53), and 24 (48%) were male. The median length of stay in hospital and ICU stay for ventilated patients was 10.5 days (IQR, 6-23) and 7 days (IQR, 3-11) respectively. The median length of stay in hospital and ICU stay for severely ill patients who were not ventilated was 7 days (IQR, 6-23) and 2 days (IQR, 1-4) respectively.

Information on the occurrence of ARDS was available in 79 out of the 92 severely ill cases. ARDS occurred in 16 cases, 9 of whom were female. The median age of the 16 cases was 38 years (IQR, 32-47.5). The median duration from onset of symptoms to the development of ARDS was 6 days (IQR, 4.5-8). One or more comorbidities were present in 11 cases (69%) and included: diabetes (5 cases), malignancy (2 cases), immunosuppression (2 cases), asthma (1 case) and obesity (1 case). Six of the 16 cases (38%) with ARDS died.

Influenza A (H1N1-2009) Deaths

Among the 92 severe cases, 18 patients died. The median age of patients who died was 50 years (IQR, 36-68). Ten of the deaths (56%) were male. Fifteen were Singapore residents with 10 of Chinese ethnicity, 2 Malays and 3 Indians.

Among the 18 pandemic H1N1 related deaths, the median duration between onset of symptoms and hospital admission was 4 days (IQR, 1-5) and the median length of stay in hospital was 4.5 days (IQR, 2-8). Of the 14 cases who were admitted to ICU, the median length of stay in ICU was 3.5 days (IQR, 2-8). Information on oseltamivir administration was available for 17 cases. Among these 17 cases, the median duration between onset of symptoms and oseltamivir administration was 4 days (IQR, 2-7).

Of the 18 death cases, 2 cases had a history of neuromuscular disease, 2 had underlying malignancy, and 1 patient was reported as obese. Of the 2 cases with a history of neuromuscular disease, 1 had Parkinson's disease and the other had amyotrophic lateral sclerosis. The 2 cases with underlying malignancy included a 34-year-old female with acute myeloid leukaemia on chemotherapy, and a

7-year-old male with acute lymphocytic leukaemia who had completed chemotherapy the day prior to admission.

Four of the 18 deaths (22%) did not have any underlying medical conditions. All of them were female with a median age of 37 years with the youngest 28 years old and the oldest 95 years old. Among the 4 cases, the median duration between onset of symptoms and hospital admission was 6 days (IQR, 4.5-10.5) and the median duration between onset of symptoms and oseltamivir administration was 6.5 days (IQR, 5.5-10.5).

Comparative Analyses

Comparison between severely ill and non-severe hospitalised patients showed that patients who were severely ill were more likely to be older (P <0.0001) and to have an underlying comorbid condition (P <0.0001). Severely ill cases were significantly more likely to have underlying comorbidities of diabetes, cerebrovascular diseases, epilepsy, neuromuscular disorders, hypertension and obesity (Table 4). We examined the hypothesis that severity of illness was related to a delay in seeking medical care; however, the duration from onset of symptoms to hospital admission did not differ significantly between the 2 groups (P = 0.1107).

Comparison between severely ill patients who required ventilator support and those who did not require ventilator support showed that patients requiring ventilator support had a longer stay in ICU (P <0.0001). Patients requiring ventilator support were also more likely to have diabetes (P = 0.0442), and less likely to have cerebrovascular disease (P = 0.0401) as underlying comorbidities. Ventilated and non-ventilated severely ill patients did not differ significantly with respect to age, gender, ethnicity, length of hospital stay, and the presence of other underlying comorbidities.

Multivariate analysis showed that the following factors were independently associated with a higher likelihood of severe illness: older age (P = 0.0006) and the presence of the following comorbidities: neuromuscular disorders (P <0.0001), epilepsy (P = 0.0003) and obesity (P = 0.0024). Multivariate analysis also showed that there were significantly fewer cases of asthma in the severely ill group than in the non-severely ill group (P = 0.0220) (Table 5).

Survival of Severe Cases

The cumulative proportion of the severely ill patients with pandemic H1N1 surviving till 7 days from onset of severe illness was 86%, while the proportion surviving till 14 days from onset of severe illness was 82%. Among the severe cases, the survival of patients aged 64 and below was significantly better than those aged 65 and above (P = 0.0214). There was no statistical difference in the survival between those with and without comorbidities (P = 0.5364) and between those who were administered oseltamivir within 2 days and more than 2 days after the onset of illness (P = 0.8250) . The analysis also did not reveal any statistical difference in the survival between those with and without each individual comorbidity.

Table 5. Multivariate Logistic Regression Analysis for Factors Associated with Severity of Illness

Attribute	Odds ratio	95% confidence interval		*P*	
Age	1.02	1.01	1.04	0.0006	*
Gender F vs M	0.91	0.57	1.46	0.6982	
Asthma	0.45	0.22	0.92	0.0296	*
COPD	0.79	0.21	2.91	0.7213	
Diabetes	1.39	0.72	2.69	0.3240	
Cardiac diseases	0.93	0.40	2.16	0.8686	
Cerebrovascular diseases	1.69	0.45	6.36	0.4350	
Renal diseases	1.34	0.57	3.11	0.5030	
Immunosuppression	1.27	0.50	3.26	0.6164	
Malignancy	1.42	0.54	3.78	0.4803	
Pregnancy	0.94	0.22	4.11	0.9356	
Autoimmune diseases	0.60	0.16	2.22	0.4445	
Epilepsy	6.22	2.29	16.90	0.0003	*
obesity	7.06	2.00	24.95	0.0024	*
Neuromuscular disorders	17.81	4.97	63.85	<.0001	*
Hypertension	1.15	0.59	2.23	0.6873	
Hyperlipidaemia	0.56	0.25	1.30	0.1783	
Anaemia	1.55	0.50	4.76	0.4447	

*P value <0.05

Discussion

This report presents the available epidemiological characteristics of 1348 hospitalised cases of pandemic H1N1 infection between 15 July and 28 September 2009. The incidence rate of hospitalisations and of ICU admissions due to influenza A (H1N1-2009) between 15 July and 28 September was estimated to be 27 and 1.8 per 100,000 inhabitants, respectively. The mortality rate over the same period due to pandemic H1N1 over the same period was estimated to be 0.37 per 100,000 inhabitants. It was estimated that between 12 July and 26 September, a total of 245,000 cases of pandemic H1N1 were treated at outpatient clinics in Singapore.[14] This corresponded to approximately 600 hospitalisations for every 100,000 cases of pandemic H1N1 and a case-fatality rate of 7 deaths for every 100,000 cases of pandemic H1N1.

Our study found that, among Singapore residents, the age-gender-adjusted hospitalisation rates and rates of severe

illness were significantly lower among ethnic Chinese compared to both Malays and Indians. These differences in incidence may be due to a difference in the prevalence of risk factors among ethnic groups or may represent variations in susceptibility to the infection. The proportion of hospitalised cases was highest in children aged 0 to 5 years, but the proportion of severe cases was highest among those over 50 years. Although relatively few H1N1 infections occurred among patients older than 65 years, this age group was at significantly increased risk for severe disease.

The diagnosis on admission to hospital was either a respiratory tract disease or fever in about 70% of patients. However, pandemic H1N1 infection also occurred in the setting of a variety of other admitting diagnoses/symptoms, and in the absence of fever or respiratory tract symptoms. This may suggest that pandemic H1N1 influenza infection may exacerbate conditions or occasionally present atypically.

We found neuromuscular disease, epilepsy and obesity to be independently associated with a higher likelihood of severe illness. The underlying mechanism for these risk factors is not well understood, and it is possible that these factors may be confounded by other factors not identified in this study. Nonetheless, these associations have been observed in recent reports[15-17] and may serve to inform physicians of the need for early and aggressive treatment in these groups of patients.

We also found a significantly smaller proportion of patients with a history of asthma among the severely ill group compared to the non-severe group, particularly in persons aged 20 years and above. There is no apparent biologically plausible explanation for this observation. It is possible that through prior experience of asthmatic attacks, patients/guardians of patients with asthma seek treatment early in the event of an asthmatic exacerbation, which may also have allowed for early and effective treatment of pandemic H1N1.

Both older age and the presence of underlying medical conditions were found to be factors associated with increased severity of illness. However, only age was found to be associated with mortality. The median age of patients increased progressively along the continuum of all patients hospitalised, those severely ill, and those who died. Although there was a higher proportion of patients with one or more underlying comorbidities among severely ill cases compared with all hospitalised cases (72% vs 50%), the proportions were similar for severely ill cases and those who died (78% vs 72%).

There are some limitations to this study related to both data collection and data analysis. With respect to data collection, it is possible that there may have been some cases of pandemic H1N1 infection during the study period that had not been reported, and thus were not captured in this study. Secondly, there is a possibility of reporting bias. Despite the use of a standardised data collection template, not all information was captured for all cases; there is also the possibility that some data fields that were reported may have been incomplete. The study was limited by the information reported as the authors did not have direct access to case notes for the majority of the cases. Thus, it was also not possible to verify the information reported or to obtain detailed clinical information. Thirdly, the hospitals were asked to report their cases from 15 July 2009 onwards, and data for this study were censored on 28 September. Therefore, the hospitalisation admission rates reported were possibly underestimated. However, any variation in estimates is likely to be small as community biosurveillance of influenza in Singapore showed that the proportion of Influenza A(H1N1-2009) among all respiratory samples began to rise in early July, peaked in early August, and subsequently declined to low levels in late September. Fourthly, we did not collect data on the number of days for which patients were ventilated, a measure which would be useful in healthcare planning for future outbreaks of a similar nature. With respect to data analysis, one limitation was that since exact body mass index (BMI) values were not available, the association between the degree of obesity and severity of illness could not be ascertained. Secondly, we recognised that severely ill patients who required ventilator support might differ from severely ill patients who did not require ventilator support. Patients who required ventilator support had a significantly longer length of stay in ICU compared to those who did not require ventilator support, a finding that is not unexpected. The occurrence of diabetes and cerebrovascular disease as underlying comorbidities also differed in these 2 groups, but this finding was only weakly significant and may have been a chance occurrence. The 2 groups did not differ significantly on age, gender, ethnicity, length of hospital stay and the presence of other comorbidities. It is therefore likely that analysing ventilated and non-ventilated severely ill patients as one group did not distort the findings or result in the loss of significant information. Thirdly, we recognised that risk factors associated with severe illness may be different for adults and children, and therefore attempted to perform separate analyses for hospitalised cases aged below 20 years and for those aged 20 years and above. However, the number of cases, particularly among severely ill cases aged below 20 years, was insufficient to obtain robust estimates separately for these 2 age groups.

In our study, 88 cases (6.5%) were admitted to an intensive care unit. There were 18 deaths which represented 1.3% of all hospitalised cases and 19.6% of all severely ill cases. Webb et al[16] studied 722 patients in Australia and New

Zealand with confirmed pandemic H1N1 infection who were admitted to ICU over a 3-month period. Of these 722 patients, 103 (14.3%) died. Jain et al[17] reported on 272 patients hospitalised in the United States who tested positive for pandemic H1N1, of whom 25% were admitted to an ICU and 7% died. Studies conducted in Mexico and Canada have reported a 60- and 90-day mortality among critically ill patients with pandemic H1N1 infection of 41.4% and 17.3% respectively.[18,19]

Data on the clinical and epidemiologic features of pandemic H1N1 are still emerging. Recently published studies on the characteristics of hospitalised and critically ill pandemic H1N1 cases have made varying observations on the epidemiology of the disease.[15-19] While the varied epidemiological findings of different studies may be due to differences in case definitions, duration of study, study design and/or the limitations of each study, these findings may also be real and attributable to geographical factors or to a unique risk profile of distinct population groups within a country.

In conclusion, this study presents the epidemiological features of a large number of hospitalised patients with pandemic H1N1 infection, including demographic features of patients, hospital admission diagnosis, comorbidities, length of stay in hospital and length of stay in ICU. In addition, this study utilises the data to derive population-based hospitalisation and ICU admission rates. Factors such as changes in the virulence and/or transmissibility of the virus, and widespread availability and utilisation of an effective vaccine against the virus may mean that epidemiological and clinical patterns of future waves of the pandemic may differ markedly from the first wave. With this caveat and bearing in mind the possible limitations of the study, the information presented in this study may provide a basis for generating hypotheses for further epidemiological studies, and possibly for decision-making and planning for healthcare utilisation during future pandemics.

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