Original Article

Pandemic (H1N1) 2009: Clinical and Laboratory Findings of the First Fifty Cases in Singapore

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Abstract

Introduction: Since the first imported case on 26 May 2009, pandemic (H1N1) 2009 has spread from travellers and has resulted in sustained community transmission. Singapore began with a strict containment policy where all suspected and confirmed cases of pandemic (H1N1) 2009 were admitted for testing. We describe here the clinical and laboratory characteristics of the first 50 adult cases with confirmed pandemic (H1N1) 2009. Materials and Methods: A review was conducted of medical notes of adult patients with confirmed pandemic (H1N1) 2009 by polymerase chain reaction assay from combined nasal and throat swabs admitted to the Communicable Disease Centre, Tan Tock Seng Hospital. Results: From 26 May to 18 June 2009, 50 patients with a median age of 27 years old were admitted at a median of 3 days from illness onset. Half were male and all were travellers arriving in Singapore. Non-Singaporean citizens (38%) and other ethnic groups (40%) were over-represented. History of fever was reported in 90% and respiratory symptoms in 92%. Gastrointestinal symptoms were uncommon, present in 4% only. Temperatures on presentation of ≥38.0ºC, ≥37.8ºC and ≥37.5ºC were present in 48%, 56% and 76%, respectively. Only 46% of patients met the United States Centers for Disease Control and Prevention (US CDC) case definition of influenza-like illness (ILI). Clinical and laboratory findings were unremarkable for the majority. All cases were treated with oseltamivir and had uncomplicated recovery. Conclusion: Pandemic (H1N1) 2009 had mild clinical and laboratory findings in immunocompetent patients. Use of the US CDC ILI criteria alone would have detected less than half of confirmed cases.

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Key words: Emerging infections, Influenza, Outbreak containment

Introduction

On 24 April 2009, the World Health Organization (WHO) issued the first global alert on pandemic (H1N1) 2009.[1] Subsequent investigations revealed the emergence of a novel strain of influenza A with a mixture of avian, swine and human influenza genes.[2] From 27 April 2009, within days of the first WHO alert, Singapore began to actively screen and test symptomatic travellers arriving in Singapore. The first imported case was reported on 26 May 2009.[3] During the early phase of the pandemic, all suspected cases identified at border entry by thermal screening, or patients presenting with symptoms of acute respiratory illness (cough, sore throat or rhinorrhoea) and with history of travel, to polyclinics, general practitioners and direct self-referrals were tested and treated at the Communicable Disease Centre (CDC) 2, Tan Tock Seng Hospital (TTSH). Contacts of cases were also actively traced and screened. Confirmed cases of pandemic (H1N1) 2009 were hospitalised for observation until 2 consecutive combined nasal and throat swabs obtained 6 hours apart were found negative by polymerase chain reaction (PCR). This continued until July 2009 when community level transmission was evident and pandemic response moved to mitigation phase. Hospitalisation was then no longer required for all confirmed cases and diagnostic laboratory testing was not routinely performed.

During the containment phase, comprehensive testing of symptomatic travellers and contacts provided an opportunity to study this new disease in detail. In this paper, we describe the detailed epidemiological, clinical and laboratory findings of the first 50 adult cases with confirmed pandemic (H1N1) 2009 in Singapore. The first 10 cases had been briefly reported in an earlier paper.[3]

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Materials and Methods

This study retrospectively reviewed the first 50 consecutive adult cases of confirmed pandemic (H1N1) 2009 admitted to CDC 2, TTSH between 26 May 2009 and 18 June 2009.

A standardised data collection format was used, which included information on patient demographics, source of referral, travel and exposure history, comorbidity, signs and symptoms, and duration of illness prior to hospitalisation. Laboratory investigations conducted routinely for all patients on admission included full blood count, renal and liver function, C-reactive protein (CRP) and chest radiograph.

Laboratory diagnosis of pandemic (H1N1) 2009 was made by real-time reverse transcription PCR (RT-PCR) on combined nasal and throat specimens obtained using flocked swabs (Copan, Italy) at presentation to TTSH. Confirmation by the National Public Health Laboratory was with the use of 2 RT-PCR assays, partial sequencing of the matrix gene and viral culture.

During the containment phase, all confirmed cases were treated with oral oseltamivir 75 mg twice daily and hospitalised until 2 consecutive combined nasal and throat swabs obtained at least 6 hours apart were negative.

Chi-square test for trend was used to assess correlation between proportion of patients with particular symptoms and day of illness at presentation. Data were analysed by SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). The study was approved by the institutional review board of the National Healthcare Group.

Results

Table 1 presents the demographic and epidemiological features of the 50 cases. The median age of confirmed cases was 27 years (range, 16 to 56) with the majority of cases being in younger age groups (62% aged 16 to 29). Only 6 patients (12%) were aged 50 years and above and none were older than 60. Half of the patients were male. Three patients had comorbidities including 2 patients with asthma and 1 with Hodgkin's lymphoma in remission, but the majority (94%) had no significant comorbidities.

All 50 patients had recently travelled. Australia (34%) and the United States (24%) accounted for more than half of imported cases. Confirmed cases initially had returned from the United States. As the weeks progressed, subsequent cases returned from Australia and then from regional countries of the Philippines (12%), Thailand (2%) and Malaysia (2%). Other ethnic groups and non-Singaporeans were over-represented reflecting the travel-related nature of acquisition.

Community general practitioners referred approximately half (46%) of the patients overall. Airport general practitioners referred 18%, including those patients identified with elevated temperature on thermal screening. Direct self-referrals to TTSH contributed the remaining 36%.

The majority (78%) of patients presented to hospital between day 1 and day 4 of illness (median, 3 days; range, 1 to 11 days). The most common symptoms were self-reported fever in 90% and cough in 80% (Table 2).

Table 1. Demographics, Epidemiological History and Comorbidities

Age (y)	
Median (range)	27 (16 to 56)
Age groups (%)	
<20	18
20-29	44
30-39	16
40-49	10
≥50	12
Male gender (%)	50
Ethnicity (%)	
Chinese	42
Malay	8
Indian	10
Others	40
Nationality (%)	
Singaporean	62
Non-resident based in Singapore	14
Others	24
Travel history (%)*	
Australia	17
Canada	2
Philippines	10
Thailand	1
USA	12
Others	8
Source of referral (%)	
Airport general practitioner	18
Community general practitioner	46
Self-referral	36
Day of illness at presentation, median (range)	3 (1 to 11)
Risk factors for severe diseases (%)	
Significant comorbid conditions†	6
Age ≥50 years of significant comorbidities	14

* based on last port of departure (excluding transit locations)
† includes Hodgkin's lymphoma in remission x1, asthma x2

Table 2. Symptoms at Presentation

Day of illness at presentation (%)	
Day 1	14
Day 2	28
Day 3	22
Day 4	14
Day 5 or later	22
Respiratory tract symptoms (%)	
Cough	80
Sorethroat	48
Rhinorrhoea	50
Any of the above respiratory symptoms	92
Abdominal symptoms (%)	
Abdominal discomfort	4
Diarrhoea	2
Either of the above abdominal symptoms	4
Constitutional symptoms (%)	
Fever	90
Myalgia	18
Headache	24
Malaise/fatigue	8
Any of the above constitutional symptoms	92

Approximately half reported rhinorrhoea (50%) and sore throat (48%), with at least 1 respiratory symptom present in 92%. Gastrointestinal symptoms of abdominal discomfort and diarrhoea were uncommon and present in 4% only.

The mean temperature based on the highest recorded temperature at presentation to the Emergency Department (ED) was 38.0 ± 0.7ºC (± standard deviation, SD). However, documented temperature ≥38.0ºC was present only in 48%; temperature ≥37.8ºC and temperature ≥37.5ºC were present in 56% and 76%, respectively. Other than mild tachycardia, vital signs were within normal limits and all patients had oxygen saturations of 96% and above on room air. Lung examination was unremarkable for all patients, with the only physical findings being injected pharynx in 2 patients and a macular rash in 1 patient.

Laboratory investigations (Table 3) showed normal white blood cell count (WBC) for the majority (82%) of patients with only 3 patients having WBC above 11 x 10^9/L. Lymphopenia was common but not pronounced and thrombocytopenia of less than 150 x 10^9/L was present in only 4 patients. Marked transaminitis was also not present. One patient had CRP of more than 100 mg/L, but blood cultures performed were negative and the patient responded to antiviral therapy alone. Chest radiographs for all patients did not show any gross consolidation. All patients improved on antiviral therapy alone without clinical evidence of secondary bacterial infection.

Assessing the different sets of symptoms showed that respiratory symptoms of cough, sore throat and rhinorrhoea overlapped, but sore throat without cough occurred in only 6% of patients (Fig. 1A). For constitutional symptoms, self-reported fever was the predominant symptom and there were few additional patients with myalgia, headache, fatigue or malaise without self-reported fever (Fig. 1B). All patients had either self-reported fever or respiratory symptoms or both. Self-reported fever and cough were present in 74%, whilst self-reported fever with at least 1 respiratory symptom was present in 82% (Fig. 1C). No patient had constitutional symptoms of headache, myalgia, fatigue or malaise without self-reported fever or respiratory symptoms (Fig. 1C). Of interest, case definition of influenza-like illness (ILI) by the United States Centers for Disease Control and Prevention (US CDC) of either cough or sore throat or both and a given temperature ≥37.8ºC was present in only 46% of patients overall (Fig. 1D).[4]

A temperature of ≥37.8ºC at presentation was significantly more common if patients presented early in illness between day 1 and day 2 (71%) compared to day 5 or later (27%) (P <0.05) (Fig. 2). However, self-reported fever was present in the majority (81% to 94%) of patients regardless of day of presentation. In contrast, cough was reported with increasing frequency for those presenting later in their illness. All patients presenting on day 5 or later reported symptoms of cough compared with two-thirds of patients presenting on day 1 and day 2 (P <0.05). The proportion of patients meeting the US CDC ILI criteria was higher among those presenting earlier, 52% for patients presenting on day 1 and day 2 of illness, compared with 27% on day 5 or later.

Discussion

Since April 2009 when the initial outbreak was notified,[5] air travel has contributed to the spread of pandemic (H1N1) 2009 globally.[6] In Singapore, the initial cases were travellers from North America and Australasia followed by regional countries.[7]

The affected patients were young, with the majority aged below 50 years old with no comorbidities. Although healthier and younger individuals travelling for work and leisure may have accounted for this finding, other studies have consistently shown an increased incidence among the young.[8] The low incidence in people over 60 years of age is postulated to be due to partial immunity from protective antibodies to previous infections with H1N1 influenza viruses.[9]

Symptoms were predominantly of fever and cough, consistent with other studies[5,8] whereas constitutional

Table 3. Vital Signs and Laboratory Findings on Presentation

	Mean	Median	IQR	Min	Max
Vital signs					
Temperature (ºC)	38	37.9	37.5-38.4	36.7	39.5
Heart rate (beats per min)	106	106	94-116	70	196
SBP (mmHg)	114	115	102-126	82	154
DBP (mmHg)	71	72	62-79	70	196
SPO_2 (%)	98	98	97-98	96	100
Full blood count					
White cell count ($x10^9$/L)	7.1	6.6	5.2-8.8	3.6	14.7
Neutrophils (%)	67.2	69.9	60.2-74.8	36.7	86.6
Absolute neutrophil count ($x10^9$/L)	4.9	4.4	3.2-6.3	1.6	12.5
Lymphocytes, %	19.1	16.5	12.5-23.2	5.4	54.9
Absolute lymphocyte count ($x10^9$/L)	1.3	1.1	0.9-1.5	0.4	2.8
Platelets ($x10^9$/L)	239	232	186-284	109	394
Basic biochemistry					
Serum creatinine (umol/L)	79	75	65-93	51	119
ALT (U/L)	24	19	14-26	9	76
AST (U/L)*	26	24	21-29	9	56
C-reactive protein (mg/L)	17.1	11.2	6.4-18.1	0.3	102.7

* Based on 47 cases where AST was available

ALT: alanine transaminase; AST: aspartate transaminase; DBP: diastolic blood pressure; SBP: systolic blood pressure; SPO_2: oxygen saturation on room air

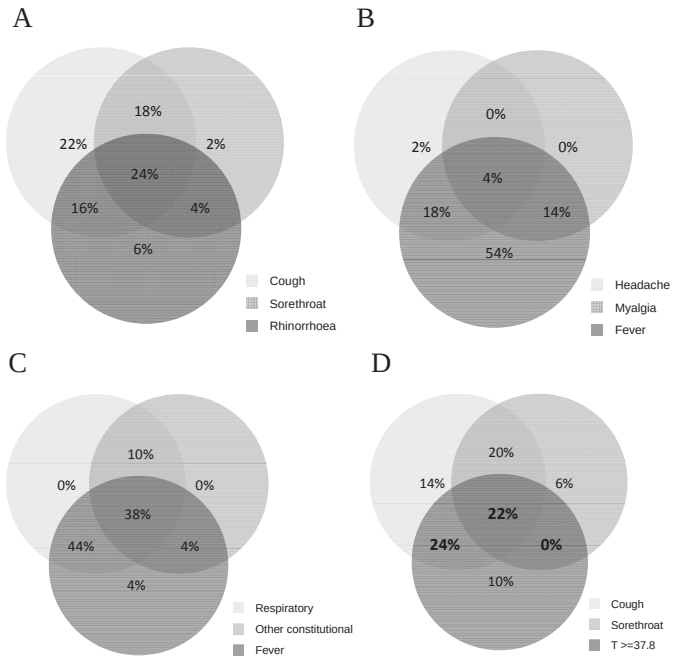

Fig. 1. Associations between different sets of symptoms. (A) Respiratory symptoms. (B) Constitutional symptoms. (C) Respiratory, fever and other constitutional symptoms (includes headache, myalgia, fatigue or malaise). (D) Complex of signs and symptoms which makes up US CDC influenza-like illness (ILI) criteria. In Figure D, the percentages in bold are the proportion of cases which would be classified as ILI.

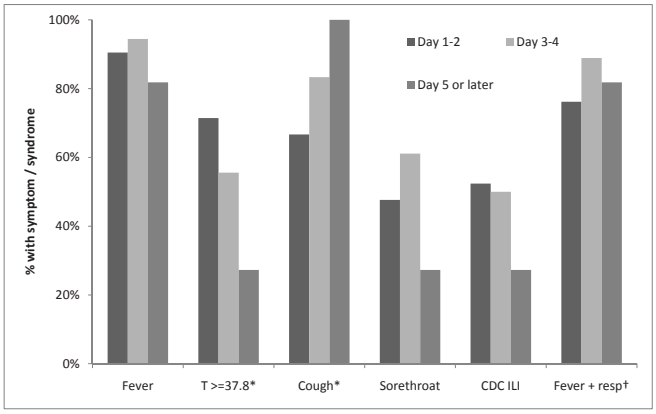

Fig. 2. Proportion with different symptoms or syndromes by day of illness at time of presentation.
Symptoms significant at P <0.05 by chi-square test for linear trend are marked with*.
† Fever and respiratory syndrome indicates cases who had self-reported fever and any of the respiratory symptoms.

symptoms did not feature prominently. Gastrointestinal symptoms were less common than the 22% to 27% reported in Mexico and the UK,[5,10] possibly as those reports included both paediatric and adult populations.[5,10] Clinical presentation of pandemic influenza (H1N1) 2009 was indistinguishable from seasonal influenza with similar proportions having symptoms of self-reported fever and

cough.[11] Of interest, less than half (46%) met the US CDC ILI case definition, largely because a documented temperature of ≥37.8ºC was absent in patients presenting in the later part of the illness.

The above results have several implications. Firstly, the results support the use of self-reported fever and respiratory symptoms to detect all possible cases, for example during airport screening and public health containment. In contrast, ILI case definition and documented fever would be more useful in surveillance, although this may be less reliable in cases presenting late in illness. Secondly, given that a large proportion of cases may have been missed by criteria using documented temperature, it was not surprising that containment measures would have at best delayed the entry of infectious cases into and subsequent transmission within the general community.

Delayed presentation to hospital with more than a third presenting after day 4 of illness onset despite heightened awareness and broad referral criteria is also of concern for public health authorities. Secondary attack rate for pandemic (H1N1) 2009 has been reported to range from 7% to 27%[12,13] even among those on oseltamivir prophylaxis.[13]

Findings of mild illness in immunocompetent patients with minimal physical, laboratory and radiographic findings are similar to an earlier report.[3] Severe illness has been associated with pregnancy, underlying disease and obesity[14,15] with case fatality rate (CFR) reported to vary from 0.1% to 5.1% in various countries.[16] Recovery was uncomplicated in all 50 patients, although viral shedding was 7 days or longer in approximately half despite treatment with oseltamivir.[17]

Previous studies have highlighted the devastating consequences of past influenza pandemics in Singapore.[18,19] Excess mortality secondary to seasonal influenza, particularly in the elderly has been well demonstrated.[20] Although seasonal influenza is recognised in the tropics, burden of disease is often underestimated. Indeed, enhanced surveillance of patients with acute febrile respiratory illness during the first week of the pandemic alert in Singapore, found that almost one-third had seasonal influenza.[21]

Measuring the frequency of complications in our population would have required a much larger sample size. However, the sample size of this study was limited by changes in pandemic response policy with an emphasis on outpatient care during the mitigation phase. Other limitations of this study include pre-defined criteria for screening people with fever, respiratory symptoms and recent travel, so that we may be underestimating the proportion of individuals with mild or unusual illness.

In summary, the first 50 confirmed pandemic influenza (H1N1) 2009 patients in Singapore were mild, possibly because the initial cases included mainly young adults, most of whom had no significant comorbidities. Symptoms were consistent with those reported for other strains of influenza, and physical findings and laboratory investigations were unremarkable.

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