New influenza A (H1N1) 2009 in Singapore: the first ten adult imported cases

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ABSTRACT

Introduction: Since late March 2009, a novel influenza H1N1 strain emerged in humans in Mexico and the United States. It has rapidly spread to many countries on different continents, prompting unprecedented activation of pandemic preparedness plans. Singapore has adopted a containment strategy with active screening of febrile travellers with respiratory symptoms from affected countries since April 27, 2009.

Methods: All cases with new influenza A (H1N1) confirmed on polymerase chain reaction assay on combined nasal and throat swabs and who were admitted to the Communicable Disease Centre, were included in a prospective evaluation of clinical characteristics of new influenza A (H1N1).

Results: From May 26 to June 3, 2009, there were ten patients with a mean age of 27.6 years, seven of whom were female. All but one travelled from the United States, six of whom travelled from New York; the last one travelled from the Philippines. Clinical illness developed within a mean of 1.4 days after arrival in Singapore, and presentation to the emergency department at a mean of 2.7 days from illness onset. Fever occurred in 90 percent, cough 70 percent, coryza 40 percent, sore throat and myalgia/arthralgia 30 percent; none had diarrhoea. The fever lasted a mean of 2.1 days. All were treated with oseltamivir. The clinical course was uncomplicated in all cases.

Conclusion: Clinical features of new influenza A (H1N1) appeared mild, and ran an uncomplicated course in immunocompetent patients.

Keywords: containment, H1N1 virus, influenza A virus, pandemic, swine influenza

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INTRODUCTION

Since April 26, 2009 when the first case of new influenza A (H1N1) 2009 was notified to the World Health Organisation (WHO), it has spread to 74 countries, with 29,669 cumulative cases and 145 deaths with a case-fatality ratio of 0.5% (as of June 12, 2009).[1] As of June 10, 2009, local transmission was noted in 20 countries with death in four countries. In Asia, cases have been reported from Japan, China, South Korea, Taiwan, Hong Kong and India, and the Southeast Asian countries of Singapore, Malaysia, Thailand, Vietnam and the Philippines. In Asia and Southeast Asia, local transmission has thus far been documented in Japan, China, South Korea, Taiwan, India, Singapore, Thailand, Vietnam and the Philippines. Singapore started screening febrile travellers with respiratory symptoms from affected countries for the new influenza A (H1N1) since April 27, 2009, and the first case was detected on May 26, 2009. We present the epidemiology, clinical illness and treatment outcome of the first ten cases, diagnosed and treated at Communicable Disease Centre (CDC) 2, Tan Tock Seng Hospital (TTSH), Singapore, which is the designated screening centre for new influenza A (H1N1).

METHODS

All confirmed cases of new influenza A (H1N1) treated at TTSH, Singapore, from April 27, 2009 and who were admitted to the Communicable Disease Centre were included in a prospective evaluation of the clinical and virological characteristics of their infection. Baseline and daily clinical data, including demographical, travel and exposure history, comorbidity, symptoms and signs, were collected until discharge. On admission, all patients had full blood count, renal and liver functions, and C-reactive protein assayed, as well as chest radiography done. Virological study included serial sampling of the nose and throat to examine viral shedding. Laboratory diagnosis of new influenza A (H1N1) was made by probe-based polymerase chain reaction (PCR) on combined nasal and throat swabs and confirmed with sequencing of the M gene (in-house method, National Public Health Laboratory, Singapore).

All confirmed patients with new influenza A (H1N1) were admitted to a single isolation room with negative pressure ventilation in CDC 2, TTSH, and all healthcare workers donned N95 masks, gowns and gloves on entering

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Table I. Selected clinical and virological data, and travel history of the first ten adult confirmed new influenza A (H1N1) patients.

Case	Age (years), gender	Travel (country of origin)	Travel dates*	Illness onset*	ED visit date*	Day of illness started on oseltamivir	Days of fever	Days of viral shedding†	Unwell on board aircraft
1	22, F	USA, New York City	14–24 May	26 May	26 May	1	2	11	Yes
2	43, F	USA, San Francisco via Manila	14–26 May	26 May	27 May	1	2	3	Yes
3	28, M	USA, Chicago via Hong Kong	16–25 May	25 May	27 May	3	3	3	No
4	28, F	USA, North Carolina/ Honolulu via Tokyo	13–26 May	26 May	27 May	3	5	3	Yes
5	21, F	USA, Vermont/New York City via Tokyo	13–29 May	30 May	30 May	1	2	5	No
6	36, M	Philippines, Manila	18–29 May	29 May	1 June	4	4	7	No
7	29, M	USA, Chicago/Detroit/ New York City via Frankfurt	14 May – 1 June	26 May	1 June	7	1	8	Yes
8	19, F	USA, New York City via Tokyo	Singaporean student residing in the USA, arrived 28 May	1 June	2 June	2	1	1	No
9	32, F	USA, New York City via Frankfurt	23–30 May	1 June	3 June	3	–	4	No
10	18, F	USA, Atlanta/New York City via Frankfurt	USA resident, arrived 30 May	2 June	3 June	2	1	4	No

F: female; M: male; ED: emergency department; *dates refer to year 2009; † from the first day of hospitalisation to the time of writing (9 June 2009).

the isolation room. Criteria for discharge required two successive influenza PCR negative results from combined nasal and throat swabs taken at least six hours apart. Follow-up was planned for 2–4 weeks after discharge. The study was approved by the institutional review board of the National Healthcare Group.

RESULTS

The ten patients treated at CDC 2, TTSH, from May 26 to June 3, 2009 are profiled in Table I. Mean age was 27.6 (range 18–43) years, and seven were female. Six were Singaporean; there were two Americans, one Australian, and one Filipino. While all were travellers, seven resided in Singapore, two in the United States, and one in Australia. One patient had lymphoma in remission for four years, and the others had no comorbidity.

Notably, all but one patient travelled from the United States, and six of the nine travelled from New York. The remaining one patient travelled from Manila, Philippines. They developed symptoms within a mean of 1.4 (range –7 to 5) days of arrival in Singapore. Of interest, four patients were referred by their general practitioners, two by the airport medical clinic and the remaining patients presented themselves to hospitals, as a result of symptomatic illness. Notably, four patients were symptomatic while on board their flight.

All but four patients presented within the first two days of illness; two presented on Day 3, one on Day 4 and the last on Day 7 (but within one day of arrival in Singapore). Presentation to emergency department took place at a mean of 2.7 (range 1–7) days from illness onset. Fever was reported in 90%, cough 70%, coryza 40%, and sore throat 30%. Myalgia and arthralgia were noted in 30%, and none reported diarrhoea. Temperature ≥ 37.5°C, 37.8°C and 38°C was noted in 80%, 60% and 60%, respectively, at presentation in the emergency department. After admission to the ward, temperature ≥ 37.5°C, 37.8°C and 38°C was noted in 80%, 70% and 70%, respectively. Physical examination findings were unremarkable in all patients. Fever lasted a mean of 2.1 (range 0–5) days.

Leucocytosis was noted in 30%, with a mean leucocyte count of 7.8 (range 5.1–14.7) $\times$ 10^3/uL. Neutrophilia occurred in 40%, with a mean neutrophil count of 5.8 (range 2.8–12.5) $\times$ 10^3/uL, and lymphopenia in 50%, with a mean lymphocyte count 1.10 (range 0.56–1.75) $\times$ 10^3/uL. The mean C-reactive protein was 20 (range 7–57) mg/L. Renal and liver function tests, and chest radiographs were normal in all patients. Viral shedding (from the first day of hospitalisation) from combined nasal and throat swabs as detected by PCR lasted a mean of 4.9 (range 1–11) days.

All patients were treated with oseltamivir, according to the policy from Ministry of Health (MOH), Singapore (MOH circular 27/2009). At the time of writing, eight patients have been discharged and two patients remain in hospital. All remaining patients in hospital are well and have recovered from their acute respiratory illness.

DISCUSSION

Since the middle of March 2009, infections with the new influenza A (H1N1) strain started to occur in Mexico, and the first two cases in the United States occurred in late March 2009, although they were not confirmed until April 15, 2009.[2] The rapid global spread testifies to the influence of international air travel on influenza.[3] Based on data from Mexico, this new influenza A (H1N1) is estimated to have a case-fatality ratio of 0.6% and reproductive number between 1.4 and 1.6; notably, the clinical attack rate was 61% in children < 15 years vs. 29% in adults ≥ 15 years.[4] Of the eight influenza genes in this novel virus, six belonged to the North American swine lineage and two from the Eurasian swine.[5]

From April 15 to May 5, 2009, there were 642 confirmed cases in 41 states in the United States; 60% were < 18 years. Fever occurred in 94%, cough 92%, sore throat 66% and diarrhoea 25%; notably, 36 were hospitalised, of which 12 of 22 with available data had underlying conditions which put them at risk of influenza complications.[5] From April 24 to May 11, 2009, there were 98 confirmed cases in Spain, with a mean age of 24 years and 51% were male. Notably, 78% had returned from Mexico and 36% developed symptoms during the return flight.[6] Fever occurred in 96%, cough 95% and diarrhoea 41%; there was no death.[6] From April 27 to May 11, 2009, 65 cases were confirmed in the United Kingdom, of whom 24 returned from Mexico and five from the United States. Fever occurred in 94%, sore throat 82% and diarrhoea 28%.[7] There was no death, but three were hospitalised, two for investigation and one for secondary pneumonia.[7] Fewer of our patients had cough (70%) and sore throat (30%), and none had diarrhoea, compared with the larger reported case series.

Of interest, while reported fever was noted in 90%, temperature > 38°C was noted only in 70% and temperature > 37.5°C in 80%. This is not an unusual finding as fever was reported only in 37% of influenza A (H1N1), 41% of influenza A (H3N2) and 8% of influenza B cases, among healthy volunteers challenged with wild-type influenza virus.[8] In addition, symptomatic infection occurred in 70% only. Another study during a seasonal influenza epidemic in Glasgow estimated that between 28% and 59% of serologically- proven acute influenza infections in healthcare workers were sub-clinical.[9]

Our first patient had detectable virus in a combined nasal and throat swab up till Day 11 from illness onset, after completion of five days of oseltamivir and resolution of fever and respiratory symptoms. Two other patients still had detectable virus in combined nasal and throat swabs by PCR on Days 7 and 8 of their illness, one of whom was only treated with oseltamivir when he presented on Day 4 of his illness. While the reported mean duration of viral shedding was 4.8 days, several studies reported viral shedding on Days 8–10 in 20%–30%.[8] Since this new virus has been shown to be sensitive to oseltamivir,[5] our observation that some patients had prolonged viral shedding is intriguing. This may be due to a more sensitive influenza PCR assay compared with viral culture, but it may also suggest the possibility of a more prolonged viral shedding from this new influenza A (H1N1), a potentially longer duration of infectivity, and possibility of the emergence of drug resistance to oseltamivir. Further studies are underway to delineate these concerns.

Of eight patients who arrived in Singapore on a return flight, all were overseas for a mean duration of 13 (range 8–19) days. Five developed illness within two days of arrival, two on Day 3, one on Day 4 and the last on Day 6 of arrival (one patient became ill prior to travel and arrival in Singapore). This raises the possibility of their being infected at the airport where they boarded the aircraft, or during the flight, given that the incubation period of influenza ranges from one to four days.[10] In conclusion, we describe the epidemiological and clinical features of the first ten confirmed new influenza A (H1N1) patients in Singapore, in whom the infection appeared mild and uncomplicated. To date, there have been no secondary cases among the primary contacts of these ten patients, and no evidence of sustained community transmission in Singapore.

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