Abstract

Introduction: Singapore had its first case of pandemic influenza A (H1N1) 2009 on 26 May 2009. As of 3 August 2009, 440 children with confirmed H1N1 were admitted to KK Women’s and Children’s Hospital (KKH). Materials and Methods: This is a retrospective case control study of children admitted from 26 May 2009 to 19 July 2009 with H1N1 infection. Cases and controls were first differentiated by whether they were complicated or non-complicated in nature, and subsequently analysed with regards to possible independent risk factors. Results: We analysed 143 admitted children; 48 cases and 95 controls (1 : 2 ratio). Significant comorbidity was found in 20.3% (n = 29) of patients with the majority having asthma (n = 18, 12.6 %) followed by obesity (n = 7, 4.9%). Binary logistic regression analysis showed risk factors for complicated disease were comorbidity (adjusted OR 6.0, 95% CI, 2.5 to 14.6, \( P < 0.0001 \)) and age <2 years (adjusted OR 9.8, 95% CI, 2.4 to 40, \( P = 0.001 \)). Age less than 5 years was not found to be a risk factor. Conclusion: In the early stages of an evolving influenza epidemic when oseltamivir stocks are low, oseltamivir treatment for influenza can be streamlined and offered to those at highest risk who are under 2 years old or have significant comorbidity to prevent complicated disease.


Key words: Children, Complications, Influenza A H1N1, Risk factors

Introduction

In March and April 2009, Mexico started experiencing an epidemic of influenza-like illness and on 17 April 2009, the novel strain of influenza A (H1N1) was identified.\(^1,2\) This virus appears to have resulted from genetic re-arrangement of influenza viruses from swine, avian and human sources.\(^3\) As of 6 August 2009, the virus was in 6 continents, with 177,457 laboratory-confirmed cases and 1462 deaths worldwide.\(^4\) The first influenza A H1N1 case was detected in Singapore on 26 May 2009 in a young returning traveller from North America.\(^5\) As of 21 July 2009, Singapore had more than 100 confirmed cases with 1 fatality, and it had spread into the community.

Between 26 May and 3 August 2009, 611 children with confirmed influenza A (H1N1) 2009 presented to our hospital, of which 440 were admitted and 171 were treated as outpatients. At the start of the pandemic, all suspected children presenting to KK Women’s and Children’s Hospital (KKH) were admitted into single isolation rooms under the “containment strategy”.\(^6\) The definition of patients with suspected influenza A (H1N1) 2009 were presence of fever and any 2 symptoms of runny nose, cough or sore throat and a positive travel history to countries that were experiencing epidemics. All suspected patients were tested by nasopharyngeal (NP) swabs for influenza A (H1N1) 2009 by polymerase chain reaction (PCR) and treated with oseltamivir if they were positive. They could only be discharged if they had 2 consecutive negative PCR tests on the NP swabs. By 26 June 2009, patients were discharged home if they fulfilled the home quarantine criteria and were willing to have a video-camera installed in their home. These home quarantine criteria were the absence of high-risk factors for complicated influenza illness, pregnancy...

\(^1\)Department of Paediatric Medicine, KK Women’s and Children’s Hospital
\(^2\)Department of Pathology and Laboratory Medicine, KK Women’s and Children’s Hospital
\(^3\)Division of Medicine, KK Women’s and Children’s Hospital

Address for Correspondence: Dr Chong Chia Yin, Department of Paediatric Medicine, KK Women’s and Children’s Hospital, 100 Bukit Timah Road, Singapore 229899.

Email: Chong.Chia.Yin@kkh.com.sg
or immunosuppression among household contacts and
the availability of a separate bedroom with an attached
restroom to isolate the patient. High-risk factors for
complicated disease were: asthma or chronic lung disease,
cardiovascular disease, immunosuppression, cancer, renal
disease, haemoglobinopathies, chronic metabolic disease
including diabetes mellitus, diseases requiring long-term,
salicyclates e.g. Kawasaki disease and neurologic disease
that compromises respiratory function or the handling
of respiratory secretions or that can increase the risk of
aspiration.7 By 25 June 2009, only patients who warranted
admission based on clinical indications were admitted.
When the total number of infected patients surpassed
1000 in Singapore on 8 July 2009, Singapore adopted a
“mitigation” strategy in an attempt to focus on treating those
with severe disease.6 The Ministry of Health, Singapore
stopped reporting the daily number of laboratory-con
firmed pandemic in
fluenza A (H1N1) 2009.11

Results
The mean age of the cases were younger compared to the
controls (7.3 years vs 9.9 years, \(P = 0.002\)). There were 79
males and 64 females, giving a male: female ratio of 1.23 : 1.
The vast majority were Singaporeans (n = 99, 69.2%) with 44
(30.8%) foreigners. The ethnic distribution was as follows:
Chinese 58 (40.6%), Malay 26 (18.2%), Indian 16 (11.2%),
other races 43 (30.1%). In contrast, the racial distribution
of the Singapore population in 2009 was: Chinese 74.2%,
Malay 13.4%, Indian 9.2% and others 3.2%.12

Significant comorbidity (at least 1 or more) was found in
20.3% (n = 29) of patients. The comorbidities are listed in
Table 1. Asthma was considered a significant underlying

Materials and Methods
All children below 17 years of age with pandemic influenza
A (H1N1) 2009 infection or admitted to KKH were
included in this study. This is a retrospective case-control
study of 1 : 2 ratio between cases (n = 48) and controls
(n = 95). Cases were defined by being pandemic H1N1
positive and having complicated illness. Complications
were defined as invasive bacterial infection, neurologic
symptoms, severe dehydration, exacerbation of chronic
disease and any disease requiring admission to hospital.

Therefore, cases were included from admissions between
26 May and 19 July 2009. Controls were pandemic H1N1
positive patients who were admitted solely for isolation
purposes and who only had upper respiratory tract infection
and were included from admissions between 26 May and 26
June 2009. Patients were confirmed as pandemic influenza
A (H1N1) 2009 positive if they were positive on influenza
A (H1N1) 2009 PCR. Data captured included patient
demographics, biophysical parameters, complications,
symptoms and signs and comorbidity. Results of bacterial
cultures and radiologic imaging were captured if they had
complicated illness.

Methods for PCR: A real time RT-PCR assay was set up
on the Rotor-Gene Q (Qiagen, Germany) using primers
and probe that target the haemagglutinin gene of Influenza
A H1N1 (2009). The primers and probe were selected
according to published pandemic influenza A (H1N1) 2009
sequences and optimised by the National Public Health
Laboratory, Singapore.

Statistical analysis was performed using the SPSS
statistical software program. Chi square tests, as well as
Fisher’s exact tests were used for categorical data, and t-test
for continuous data. Binary logistic regression analysis
was used to examine risk factors that were significant in
the univariate analysis. Forward stepwise regression was
used for identifying the optimum variables for the model.
\(P\) values <0.05 were considered statistically significant at.
This study was approved by the Singhealth Institutional
Review Board under an expedited review and approval
was obtained for waiver of consent.

Materials and Methods
All children below 17 years of age with pandemic influenza
A (H1N1) 2009 infection who were admitted to KKH were
enrolled in this study. This is a retrospective case-control
study of 1 : 2 ratio between cases (n = 48) and controls
(n = 95). Cases were defined by being pandemic H1N1
positive and having complicated illness. Complications
were defined as invasive bacterial infection, neurologic
symptoms, severe dehydration, exacerbation of chronic
disease and any disease requiring admission to hospital.

Therefore, cases were included from admissions between
26 May and 19 July 2009. Controls were pandemic H1N1
positive patients who were admitted solely for isolation
purposes and who only had upper respiratory tract infection

and were included from admissions between 26 May and 26
June 2009. Patients were confirmed as pandemic influenza
A (H1N1) 2009 positive if they were positive on influenza
A (H1N1) 2009 PCR. Data captured included patient
demographics, biophysical parameters, complications,
symptoms and signs and comorbidity. Results of bacterial
cultures and radiologic imaging were captured if they had
complicated illness.
illness if the patient had at least persistent asthma and not episodic (infrequent or frequent episodic) asthma. All of the obese patients fulfilled CDC criteria >95th percentile on CDC growth charts for body mass index-for-age. In addition, weight-for-height percentages using Singapore growth charts in the obese children ranged from 140% to more than 180%.

In our cohort, presumptive bacterial complications occurred in 10 patients (7%) including 8 cases of presumptive bacterial pneumonia (5.6%), 1 mesenteric adenitis that resembled acute appendicitis and 1 with scarlet-fever like rash and pharyngitis that responded to antibiotics. Among the 8 children with pneumonia, 4 had bronchopneumonia, 2 had lobar pneumonia and 2 had pneumonitis confirmed on chest radiograph. One child had underlying complex cyanotic congenital heart disease and another child had spastic quadriplegic cerebral palsy with tracheostomy. Only 1 of the 8 patients with pneumonia had a positive tracheostomy culture for *P. aeruginosa*. The other 7 had no bacteria isolated. The child with spastic quadriplegic cerebral palsy with tracheostomy required high dependency (HD) care for continuous positive airway pressure, while another child with no significant underlying comorbidity also required HD care for severe wheezing and respiratory distress.

Univariate comparison of cases and controls is shown in Table 1. The most significant risk factors were age and presence of comorbidity. By univariate analysis, age <1 year was associated with a statistically significant risk for complicated disease (Odds Ratio [OR] 8.5, *P* = 0.044). However this was more significant for age <2 years old (OR 6.1, *P* = 0.007). Age <5 years old was not found to be a statistically significant risk factor for complicated disease (OR 2.0, *P* = 0.08). The presence of comorbidities was a statistically significant risk factor for complicated disease (OR 4.6, *P* <0.0001). Binary logistic regression analysis

<table>
<thead>
<tr>
<th>Table 1. Univariate Comparison of Cases and Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n = 48)</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Range</td>
</tr>
<tr>
<td>Age, n (%)</td>
</tr>
<tr>
<td>&lt;1 year</td>
</tr>
<tr>
<td>&lt;2 years</td>
</tr>
<tr>
<td>&lt;5 years</td>
</tr>
<tr>
<td>5 to 16 years</td>
</tr>
<tr>
<td>Male, n (%)</td>
</tr>
<tr>
<td>Chinese</td>
</tr>
<tr>
<td>Malay</td>
</tr>
<tr>
<td>Indian</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>Nationality, n (%)</td>
</tr>
<tr>
<td>Singaporean</td>
</tr>
<tr>
<td>Foreigner</td>
</tr>
<tr>
<td>Significant Comorbidities</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Neurologic disorders</td>
</tr>
<tr>
<td>Obesity</td>
</tr>
<tr>
<td>Cardiac disease</td>
</tr>
<tr>
<td>Diabetes mellitus and Grave’s disease</td>
</tr>
<tr>
<td>Obesity and asthma</td>
</tr>
<tr>
<td>Cancer and obesity</td>
</tr>
<tr>
<td>Total, n (%)</td>
</tr>
</tbody>
</table>

NS: not significant
was done using factors of significant comorbidity and age groups of <2 years and ≥2 years old. After logistic regression, the only significant risk factors for complicated disease were the presence of comorbidity (adjusted OR 6.0, 95% CI, 2.5 to 14.6, P < 0.0001) and age <2 years old (adjusted OR 9.8, 95% CI, 2.4 to 40, P = 0.001).

There were no fatalities in this early stage of the epidemic. All patients were treated with OSV for 5 days regardless of their age or presence of comorbidity. The mean time for the start of OSV from the onset of symptoms was 3.2 days in cases versus 2.5 days in controls (P = 0.066, not significant). The mean time for the start of OSV from the onset of fever was 2.2 days in cases vs 2.0 days in controls (P = 0.578, not significant). The patients’ caregivers (usually the mothers) were given OSV prophylaxis for 10 days. There were no major side effects of oseltamivir observed in infants or children based on passive surveillance.

Discussion

In Singapore, Influenza A is reported year round with 2 peaks between the period of April to July and the period of November to January. This seasonal increase seems to coincide with the southern and northern hemisphere winter influenza seasons respectively.14 Influenza A H1N1 and H3N2 usually co-circulate with H3 being predominant in recent years in Singapore. In one primary school outbreak in January 2008, all 3 influenza strains (A-H1N1, A-H3N2 and B) were detected in the school concurrently.15 The start of the outbreak in May 2009 coincided with our regular seasonal influenza peak but was the result of spread from travelers who had been to countries that were experiencing pandemic influenza A (H1N1) outbreaks. The skewed distribution of patients of other races in our study was due to a concurrent comorbidity. However, this study is too small to extrapolate that those between 2 and 5 years who present with an influenza-like illness should not be given empiric OSV if they do not have any comorbidities.

Children with the following medical conditions are known to be at increased risk for complicated influenza disease: asthma, cardiovascular disease, pulmonary disease, immunosuppression, cancer, renal disease, haemoglobinopathies, neurologic disease that compromises respiratory function and diabetes mellitus.19,20 In 1 study of laboratory-confirmed seasonal influenza hospitalizations in children, 40% had at least 1 chronic high-risk medical condition.21 In prospective studies of children with asthma who are infected with influenza, the reported incidence of exacerbations has varied widely from 7% to 86%.22 Therefore during influenza epidemics, children with underlying asthma need to be more closely monitored as they have higher chances of developing complicated disease. Patients with asthma and influenza-like illness should also be given empiric OSV during the epidemic.

Obesity was also seen in 7 (4.9%) patients with 3 of them having concurrent comorbidities of asthma (n = 2, 1.4%) and cancer (n = 1, 0.7%). It has been suggested that morbid obesity is a risk factor for complicated disease from pandemic influenza A(H1N1) 2009 infection.23,24 However the number of obese patients in this study was too small to show any association with complicated influenza disease. The obese patients had the following complications: asthma exacerbation (n = 2), bronchitis (n = 1) and lung atelectasis (n = 1). The 3 remaining obese patients had upper respiratory tract infection only.

OSV has been shown to reduce the incidence of complications requiring antibiotic use by 40% and overall antibiotic usage rate by 24% in children with laboratory-confirmed influenza.25 In another study in children ≤12 years, OSV treatment reduced the risk of pneumonia by 53%, other respiratory illness by 28% and otitis media and its complications by 39%.26 Early use of OSV can make a difference in outcome. In the 27 fatal cases in Mexico, the median time from onset of symptoms to initiation of
antiviral therapy was 8 days (range, 1 to 26 days). All of our patients were treated with OSV early at an average of 2.1 days from onset of symptoms; this may have contributed to the absence of deaths among children in the early part of the epidemic.

Conclusion

The risk factors for complicated Influenza A (H1N1) 2009 disease were age <2 years old (OR 6.1, P = 0.007) and the presence of comorbidity (OR 4.6, P <0.0001). Children with underlying comorbidity or who are aged under 2 years old should be given empiric OSV as therapy early when they present with influenza-like illness during an influenza epidemic to prevent complicated disease. However, patients who are 2 to 5 years with no comorbidity need not receive OSV in the same situation, although our study was underpowered for this.

REFERENCES

5. Liang M, Lye D C, Chen M I, Chow A, Krishnan P, Seow E, et al. New influenza A (H1N1) 2009 disease were age <2 years old (OR 6.1, P = 0.007) and the presence of comorbidity (OR 4.6, P <0.0001). Children with underlying comorbidity or who are aged under 2 years old should be given empiric OSV as therapy early when they present with influenza-like illness during an influenza epidemic to prevent complicated disease. However, patients who are 2 to 5 years with no comorbidity need not receive OSV in the same situation, although our study was underpowered for this.