Original Article

Risk Factors for Complicated Influenza A (H1N1) 2009 Disease in Children

Chia Yin Chong, [1]*MBBS, M Med, FRCPCH*, Natalie WH Tan, [1]*MBBS, MRCPCH (UK)*, Anita Menon, [1]*MBBCh BAO , MRCPCH*, Koh Cheng Thoon, [1]*MBBS, MRCPCH (UK)*, Nancy WS Tee, [2]*MBBS, FRCPA*, Sheng Fu, [3]*MBBS, PhD*

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.

Ann Acad Med Singapore 2013;42:232-6

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-assortment 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 1000 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-confirmed cases in accordance with the World Health Organization's (WHO) recommendations.[8,9] This study examines the risk factors associated with complicated disease among Singapore children with confirmed pandemic influenza A (H1N1) 2009 infection.

Using these risk factors, the authors hope to be able to rationalise which children needed early treatment with oseltamivir (OSV) during an emerging influenza epidemic when there are limited OSV stocks. The authors wished to establish that without any high-risk factors, children below a cut-off age of either less than 2 or 5 years were needed to take OSV for the influenza illness. Children younger than 5 years of age have previously had the highest risk of hospitalisation following influenza A (H1N1) infection (Relative risk 3.3, compared to the general population).[10] In adults older than 16 years old in Australia, a similar case control study found that pregnancy, immune suppression, pre-existing lung disease, asthma , heart disease, diabetes , smoking were risk factors for hospitalisation from pandemic (H1N1) 2009.[11]

Materials and Methods

All children below 17 years of age with pandemic influenza A (H1N1) 2009 infection who were 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.

Results

We enrolled 143 children in this study, consisting of 48 cases and 95 controls, giving a ratio of 1 : 2 cases versus controls. Cases were complicated by: asthma exacerbation (n = 11, 22.9%), viral gastritis or gastroenteritis requiring intravenous (IV) fluids (n = 9, 18.75%), pneumonia (n = 8, 16.67%), bronchiolitis or bronchitis (n = 8, 16.67%), febrile seizures (n = 3, 6.25%), severe myalgia (n = 2, 4.16%), and 1 each for lung atelectasis, croup, febrile delirium, poor perfusion and mottling, poor feeding requiring intravenous (IV) fluids, mesenteric adenitis and rash resembling scarlet fever.

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

Table 1. Univariate Comparison of Cases and Controls

	Cases (n = 48)	Controls (n = 95)	Odds ratio (95% CI)	*P* value
Age (years)				
Mean	7.3	9.9		0.002
Median	6.8	10.3		
Range	2 months to 16 years	6 months to 16.9 years		
Age, n (%)				
<1 year	4 (8.3)	1 (1.1)	8.5 (0.9 to 76.9)	0.044
<2 years	8 (16.7)	3 (3.3)	6.1 (1.5 to 24.4)	0.007
<5 years	16 (33.3)	19 (20.0)	2.0 (0.9 to 4.4)	0.08 (NS)
5 to 16 years	32 (66.7)	76 (80.0)		
Male, n (%)	28 (58.3)	51 (53.7)	0.8 (0.4 to 1.7)	0.598 (NS)
Race, n (%)				
Chinese	15 (31.3)	43 (45.3)		0.053 (NS)
Malay	14 (29.2)	12 (12.6)		
Indian	7 (14.6)	9 (9.5)		
Others	12 (25.0)	31 (32.6)		
Nationality, n (%)				
Singaporean	33 (68.8)	66 (69.5)	1.0 (0.5 to 2.2)	0.929 (NS)
Foreigner	15 (31.3)	29 (30.5)		
Significant Comorbidities				
Asthma	10 (20.8)	8 (8.4)		
Neurologic disorders	2 (4.2)	0		
Obesity	1 (2.1)	3 (3.2)		
Cardiac disease	1 (2.1)	0		
Diabetes mellitus and Grave's disease	1 (2.1)	0		
Obesity and asthma	2 (4.2)	0		
Cancer and obesity	1 (2.1)	0		
Total, n (%)	18 (37.5)	11 (11.6)	4.6 (1.9 to 10.8)	<0.0001

NS: not significant

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

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.[13] 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 the high number of foreigners who were tourists or transit passengers or were foreign-born residents in Singapore and sent to KKH for isolation.[16] Ninety-five patients (66.4%) reported overseas travel. In a local publication, there were 3 distinct waves of importation of H1N1-2009: US, followed by Australia followed by Southeast Asia.[16]

Well-known complications of influenza in children include febrile seizures, bronchiolitis, bronchitis, pneumonia (viral and bacterial) and otitis media.[17] The risk factors for complicated disease in children in this cohort included age under 2 years old. We did not detect a higher complication rate among those under 5 years of age. This is likely because the study was underpowered but there was a trend towards children <5 years of age getting more complicated disease. Hospitalisation rates during this pandemic were highest among children <10 years (60.6 per 100,000 population) and older children aged 10 to 19 years (46.1 per 100,000 population) compared to the elderly >60 years old (26.1 per 100,000).[16] In the USA, the risk for severe complications from seasonal influenza is highest among children younger than 2 years of age.[18] The hospitalisation rates are highest in the age group under 2 years of age and 12 times higher than those 5 to 17 years old and without high-risk conditions.[18] This has implications for the empiric use of OSV in the later stages of the epidemic as it means that those under 2 years old should routinely be given OSV if they have an influenza-like illness. This is consistent with the latest Infectious Disease Society of America guidelines that states that unvaccinated children 12 to 24 months of age should be considered for antiviral therapy.[19] For patients between 2 to 5 years of age, OSV may be given if they have 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.[2,23,24] 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).[2] 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

1. Centers for Disease Control and Prevention. Outbreak of Swine-origin Influenza A (H1N1) Virus infections- Mexico, March- April 2009. MMWR Morb Mortal Wkly Rep 2009;58:467-70.
2. World Health Organization. Human infection with new influenza A (H1N1) virus: clinical observations from Mexico and other affected countries, May 2009. Wkly Epidemiologic Record 2009;84:185-9.
3. Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. N Engl J Med 2009;360:2605-15.
4. World Health Organization. Global alert and response (GAR). Pandemic (H1N1) 2009 – update 61. Avaliable at: http://www.who.int/csr/don/2009_08_12/en/index.html Accessed 25 April 2013.
5. Liang M, Lye D C, Chen M I, Chow A, Krishnan P, Seow E, et al. New Influenza A (H1N1) 2009 in Singapore: the first ten adult imported cases. Singapore Med J 2009;50:581-3.
6. Tay J, Ng YF, Cutter J, James L. Influenza A (H1N1-2009) pandemic in Singapore- public health control measures implemented and lessons learnt. Ann Acad Med Singapore 2010;39:313-24.
7. Harper SA, Fukuda K, Uyeki TM, Cox NJ, Bridges CB. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2005;54:1-40.
8. Ministry of Health, Singapore. Managing Influenza A (H1N1-2009). Available at: http://www.moh.gov.sg/mohcorp/pressrelesases.aspx?id=22488). Accessed 25 April 2013.
9. World Health Organization: Changes in reporting requirements for pandemic (H1N1) 2009 virus infection. Pandemic (H1N1) 2009 briefing note 3. Available at: http:// www.who.int/ csr/disease/swineflu/h1n1_surveillance_20090710. Accessed 25 April 2013.
10. Van Kerkhove MD, Vandermaele KAH, Shinde V, Jaramillo-Gutierrez G, Koukounari A, Donelly CA, et al. Risk factors for severe outcomes following 2009 Influenza A (H1N1) Infection: A global pooled analysis. Plos Medicine 2011;8: e1001053.
11. Ward KA, Spokes PJ, McAnulty JM. Case-control study of risk factors for hospitalization caused by pandemic (H1N1) 2009. Emerg Infect Dis 2011;17:1409-16.
12. Population Trends 2009. Singapore: Department of Statistics, Ministry of Trade & Industry, Republic of Singapore. Available at: www.singstat.gov.sg/pubn/popn/population2009.pdf. Accessed 25 April 2013.
13. Doraisingham S, Goh KT, Ling AE, Yu M. Influenza surveillance in Singapore 1972-86. Bull World Health Organ 1988;66:57-63.
14. Chew FT, Doraisingham S, Ling AE, Kumarasinghe G, Lee BW. Seasonal trends of viral respiratory tract infections in the tropics. Epidemiol Infect 1998;121:121-8.
15. Ministry of Health, Singapore. An outbreak of influenza-like illness in a primary school. Epidemiol News Bulletin 2008;34:50-3.
16. Ministry of Health, Singapore. Outbreak of pandemic influenza A (H1N1-2009) in Singapore, May – September 2009. Epidemiol News Bulletin 2009;35:39-48.
17. Matheson NJ, Harnden A, Perera R, Sheikh A, Symmonds-Abrahams M. Neuraminidase inhibitors for preventing and treating influenza in children. Cochrane database Syst Rev 2007, Issue 1. Art No.: CD002744. DOI: 10.1002/14651858. CD0027744.pub2.
18. Izurieta HS, Thompson WW, Kramarz P, Shay DK, Davis RL, DeStefano F, et al. Influenza and the rates of hospitalization for respiratory disease amongst infants and young children. N Engl J Med 2000;342:232-9.
19. Harper SA, Bradley JS, Englund JA, File TM, Gravenstein S, Hayden FG, et al. Seasonal influenza in adults and children- Diagnosis, treatment, chemoprophylaxis and institutional outbreak management: Clinical practice guidelines of the Infectious Diseases Society of America. Clin Infect Dis 2009;48:1003-32.
20. Centers for Disease Control and Prevention. Antiviral agents for the treatment and chemoprophylaxis of influenza-recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2011;60:1-25.
21. Darwood FS, Fiore A, Kamimoto L, Bramley A, Reingold A, Gershman K, et al. Burden of seasonal influenza hospitalization in children, United States 2003 to 2008. J Pediatr 2010;157:808-14.
22. Pattermore PK. Johnston SL, Bardin PG. Viruses as precipitants of asthma symptoms. I. Epidemiology. Clin Exp Allergy 1992;22:325-36.
23. Centers for Disease Control and Prevention. Intensive-care patients with severe novel influenza A (H1N1) virus infection- Michigan, June 2009. MMWR Morbid Mortal Wkly Rep 2009;58:749-52.
24. Vailant L, La Ruche G, Tarantola A, Barboza P, for the epidemic intelligence team at InVS. Epidemiology of fatal cases associated with pandemic H1N1 Influenza 2009. Euro Surveill 2009;14:pii=19309.
25. Whitley RJ, Haydfen FG, Reisinger DS, Young N, Dutkowski R, Ipe D, et al. Oral oseltamivir treatment of influenza in children. Pediatr Infect Dis J 2001;20:127-33.
26. Peters PH, Moscona A, Schulman KL, Barr CE. Study of the impact of oseltamivir on the risk for pneumonia and other outcomes of influenza, 2000-2005. Medscape J Med 2008;10:131.