KK Women's and Children's Hospital
SingHealth

Influenza in hospitalized children in Singapore: a tropical country

Chia Yin Chong[1], Cherie Gan[2], Thio ST [1], Natalie Tan[1],Chee Fu Yung[1], Nancy Tee [3], Lin C[4], Raymond Lin[4], Koh Cheng Thoon[1]
Infectious Disease , Department of Paediatrics[1], National University of Singapore[2], Department of Pathology and Laboratory Medicine[3], KK Women's & Children's Hospital, National Public Health Laboratory, Ministry of Health [4]

Introduction and Purpose

In Singapore, Influenza A is reported year round with 2 peaks between April to July and November to January.[1] This seasonal increase seems to coincide with the southern and northern hemisphere winter influenza seasons respectively. KK Women's and Children's Hospital (KKH) is a tertiary and secondary level hospital with 830 beds. In our previous study, risk factors for complicated influenza A (H1N1) pandemic 2009 disease in children were comorbidity and age < 2 years.[2]

This was a retrospective study of hospitalized children with influenza at KKH admitted from January 2013- December 2014 to determine if similar risk factors prevailed. The aim of this study was to compare patient characteristics and risk factors between influenza A and B and between cases admitted to ICU and high dependency units with controls admitted to the general wards.

Methods

Influenza patients were identified by a positive polymerase chain reaction (PCR) or immunoflourescence antigen from nasopharyngeal swabs. Serotyping of influenza isolates was done at the National Public Health Laboratory, Ministry of Health. Clinical characteristics were derived from patient demographic data and chart reviews. We defined cases as severe disease requiring Intensive Care Unit (ICU) or High Dependency Unit (HD) admission and controls were patients admitted to the general ward. Statistics were derived using SPSS 19.0; the student t-test was used to compare continuous data and chi square test for nominal data with a significant p value of <0.05. For binary logistic regression, all the risk factors that were significant in univariate analysis were entered into multivariate analysis using the forward conditional method.

Results

- There were a total of 1272 patients with a median age of 37 months (IQR 13-76 months); males constituted 56.5%. Distribution by race: Chinese 646 (50.8%), Malay 384 (30.2%), Indian 149 (11.7%), other 93 (7.3%). Nosocomial acquisition occurred in 2.4% (n=30) of cases.
- Influenza A constituted 76.3% with serotype H3N2 (54.5%), H1N1 (18.%), untypeable 5.4%. Influenza B constituted 22.9% with serotypes: Yamagata (16.3%), Victoria (5.7%). There was 1 patient who had both influenza A H1N1-2009 and B Yamagata.
- Compared to Influenza B, Influenza A patients were younger, had a higher rate of seizures at presentation and had higher white blood cell count
- There were 56 (4.4%) cases admitted to ICU/ HD and 1216 (95.6%) controls. There were 3 unrelated deaths (0.2%) due to: Acute necrotizing encephalitis, invasive pneumococcal disease and decompensated liver failure in a patient with underlying biliary atresia post- Kasai procedure.

Table 1. Comparison of clinical characteristics between influenza A and B

Characteristic	Influenza A (n=978) (%)	Influenza B (n=297) (%)	P value	Odds ratio (95% CI)
Mean age (months)	46.0 ± 46.2	70.2 ± 50.2	< 0.001	
Diarrhoea at presentation	87 (8.9)	45 (15.2)	0.002	0.54 (0.4-0.8)
Seizures at presentation	153 (15.6)	21 (7.1)	< 0.001	2.4 (1.5-3.9)
Underlying Asthma/Lung disease	77 (7.9)	34 (11.4)	0.049	0.65 (0.4-1.0)
Any Developmental Delay	40 (4.1)	22 (7.4)	0.018	0.53 (0.3-0.9)
Neurologic disease	58 (5.9)	21 (7.1)	0.46	
Highest white blood cell count x 10 9/L (SD)	8.2 ± 7.6	5.5 ± 5.2	0.015	
Outcome : Full recovery	975 (99.7)	293 (98.7)	0.79	
Death/ sequelae	3 (0.3)	1 (0.3)		

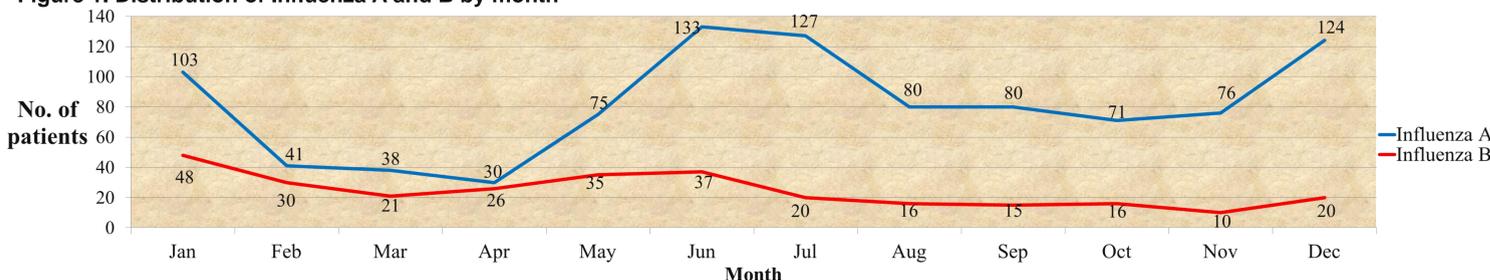**Figure 1. Distribution of Influenza A and B by month**

Table 2. Univariate analysis of risk factors between cases admitted to ICU/ High dependency unit vs controls admitted to general wards

Characteristic	Cases (n=56) (%)	Controls (n=1216) (%)	P value	Odds ratio (95% CI)
Mean Age (months)	85.3 ± 61.7	50.0 ± 46.9	< 0.001	
Age < 2 yr	11 (19.6)	475 (39.1)	0.003	0.4 (0.2-0.75)
Age > 5 yr	30 (53.5)	384 (31.6)	0.001	2.5 (1.5-4.3)
Male gender	34 (60.7)	685 (56.3)	0.52	
Nosocomial	10 (17.8)	21 (1.7)	<0.001	12.4 (5.5-27.8)
Any comorbidity	28 (50)	247 (20.3)	< 0.001	3.9 (2.3-6.7)
Seizures on presentation	17 (30.4)	157 (12.9)	< 0.001	2.9 (1.6-5.3)
Seizure history	13 (23.2)	49 (4.3)	< 0.001	7.2 (3.6-14.3)
Neurologic disease	18 (32.1)	61 (5.0)	< 0.001	9.0 (4.8-16.6)
Asthma & lung disease	7(12.5)	104 (8.6)	0.3	
Cardiac disease	7(12.5)	62 (5.1)	0.017	2.7 (1.2-6.1)
Hemoglobinopathy	4 (7.1)	31 (2.5)	0.04	2.9 (1.0-8.6)
Prematurity	7 (12.5)	57 (4.7)	0.009	2.9 (1.3-6.7)
Gastroesophageal reflux	6 (10.7)	11 (0.9)	< 0.001	13.1 (4.7-37.0)
Chromosomal abnormality	4 (7.1)	11 (0.9)	< 0.001	8.4,(2.6-27.4)
Congenital malformation (exclude cardiac)	7 (12.5)	37 (3.0)	< 0.001	4.5 (1.9-10.7)
Global developmental delay	11 (19.6)	25 (2.1)	< 0.001	11.6 (5.4-25.1)
Any developmental delay	17 (30.4)	45 (3.7)	< 0.001	11.3 (6.0-21.6)

Table 3 Multivariate analysis of risk factors for cases admitted to ICU/ High dependency unit vs controls admitted to general wards

Characteristic	P value	Odds ratio	95% CI
Age > 5 yrs	0.021	2.0	1.1-3.6
Nosocomial	< 0.001	8.6	3.3-22.7
Neurologic disease	<0.001	3.9	1.8-8.2
Seizures on presentation	0.012	2.4	1.2-4.7
Any developmental delay	<0.001	4.0	1.9-8.6

It is likely that age > 5 yrs old as a risk factor for ICU/HD admission was due to its association with comorbidity (p< 0.001, OR 2.0 , 95% CI 1.7-2.3). But comorbidity alone was not significant in the multivariate analysis. Other risk factors e.g. diabetes mellitus (n=1), malignancy (n=10), long-term aspirin (n=2),immunosuppression (n=6), obesity (n=47) were not significant, likely due to small numbers. Asthma and chronic lung disease (n=111) was also not a risk factor associated with ICU/ HD admission.

Conclusions

All children > 5 year old, children with neurologic disease or developmental delay or who present with seizures or have frequent admissions to hospital have a high risk of ICU/ HD admission due to influenza infection. Nosocomial acquisition is a risk factor for more severe disease especially those with prolonged admissions. The current national recommendations for annual influenza vaccinations are only for children from 6 months- 5 years or with underlying risk factors; this will need to be modified to include well patients> 5 yrs old and those with developmental delay or had a seizure history.

Selected References

1. Doraisingham S, Goh KT, Ling AE, Yu M. Influenza surveillance in Singapore 1972-86. Bull World Health Organ 1988; 66: 57-63.
2. CY Chong, NWH Tan, Menon A, KC Thoon, NWS Tee, S Fu. Risk factors for complicated influenza A (H1N1) 2009 disease in children. Annals Acad Med 2013; 42: 232-236.

PATIENTS. AT THE HEART OF ALL WE DO.