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Original Article

Influenza-associated hospitalization in urban Thai children

Piyarat Suntarattiwong[a], Chotip Sian-nork[a], Parada Thongtipa[a], Pranee Thawatsupha[b], Rungreung Kitphati[b], Tawee Chotpitayasunondh[a]

[a]Department of Pediatrics, Queen Sirikit National Institute of Child Health, Ministry of Public Health, Thailand. [b]National Institute of Health, Department of Medical Science, Ministry of Public Health, Thailand.
Correspondence: Piyarat Suntarattiwong, MD, Queen Sirikit National Institute of Child Health, 420/8 Ratchawithi Road, Bangkok 10400, Thailand. Email: drjunes@childrenhospital.go.th; drjunesunta@yahoo.com

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Background Studies in North America and Europe have shown that young children are at increased risk of serious complications and hospitalization from influenza infection. In Thailand, however, influenza is commonly considered a mild infection that rarely requires hospitalization. An improved understanding of the burden of serious complications from influenza infection in young children is needed to inform clinical treatment and vaccination guidelines.

Methods We conducted a prospective study of children 0–5 years of age with lower respiratory tract infection or influenza-like illness admitted to a pediatric tertiary-care hospital in Bangkok, Thailand during July 2004 to July 2005. All respiratory specimens were tested for influenza using a rapid antigen test and tissue cell culture.

Results Thirty-nine of 456 (8.6%) hospitalized children had culture-positive influenza. Eighty percent of hospitalized influenza patients had no underlying chronic illnesses. Nineteen (49%) influenza patients required hospital stays of 5 days or more and two patients required mechanical ventilation. Influenza activity demonstrated bimodal seasonal variation with peak activity from August to October and January to April. Cough was present in 38 (97%) cases and fever >38.5°C was significantly associated with influenza.

Conclusion Influenza is an important cause of hospitalization in children <5 years of age in Thailand. Children <5 years should be considered as a target group when establishing clinical guidelines for antiviral treatment and influenza vaccination.

Key words Influenza, young children, hospitalization, Thailand.

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Introduction

Studies from the United States, Europe and Hong Kong indicate that young children are at risk for serious illness and hospitalization from influenza virus infection.[1–5] In the United States, 80% of influenza-associated hospitalization in children occurs in those <5 years of age and more than half of influenza mortality among children occurs in this age group.[6,7] Between 1996 and 2005, the Thailand Ministry of Public Health passive surveillance system reported between 21 176 and 55 559 cases of clinically diagnosed influenza (inpatient and outpatient) annually for an incidence of between 34 and 87 cases per 100 000 population.[8] Between 1999 and 2002, the national influenza surveillance system reported an average annual age-specific incidence rate in children aged 0–4 years were only 42 per 100 000 population.[9] This figure may underestimate the true burden since influenza often presents with non-specific respiratory tract symptoms in young children and laboratory confirmation of influenza is not routinely performed in Thailand. In 2001, virological influenza surveillance conducted in outpatient clinics in Thailand identified influenza virus in cell culture in 341 (48%) of 711 respiratory specimens tested. Sixty percent of these specimens were from children.[10] In 2004, a large study in rural eastern Thailand found that 11% of hospitalized pneumonia and 23% of influenza-like illness (ILI) managed in the outpatient department was the result of influenza virus infection. This population-based study included comprehensive laboratory confirmation and reported that young children and the elderly were most affected by influenza. The researchers estimated an incidence of 1420 influenza infections per

100 000 outpatients, a burden 43 times greater than that recorded by the national passive surveillance system during the same period.[11] And when compared to the age distribution of the population, the proportion of patients with laboratory confirmed influenza pneumonia who were <1 year of age was 6.2 times higher than expected.[12]

Influenza infection is characterized by non-specific symptoms that can make it difficult to distinguish from febrile respiratory illness caused by other pathogens.[13,14] In Thailand, the use of rapid diagnostic tests for influenza are increasing and have been shown to be useful for surveillance and to guide clinical decision making.[15,16] Studies from the United States have demonstrated a high burden of serious complications of influenza in otherwise healthy children which lead to a 2004 US Advisory Committee on Immunization Practices (ACIP) recommendation that healthy children aged 6–23 months receive influenza vaccine annually.[17] In 2006, the ACIP extended the recommendation for annual influenza vaccination to all children aged 6–59 months.[18] A limited but growing body of evidence suggests that influenza is also an important cause of illness in tropical countries, but more data are needed especially in toddlers and infants.[11] We studied influenza-associated pediatric hospital admissions, the clinical manifestations of influenza, and the performance of rapid diagnostic tests for influenza A in children <5 years of age at Queen Sirikit National Institute of Child Health, a tertiary-care, hospital for children in Bangkok, Thailand.

Materials and methods

We conducted a prospective study of hospitalized children aged 0–5 years at Queen Sirikit National Institute of Child Health during July 5, 2004 to July 3, 2005. All enrolled patients resided in Bangkok metropolitan area. Patients with a diagnosis of lower respiratory tract infections including; viral croup, bronchitis, bronchiolitis and pneumonia were enrolled. In addition, patients with ILI per the WHO case definition with fever >38°C and cough or sore throat in the absence of other known causes (e.g., urinary tract infections, dengue fever etc). Patients reporting an onset of symptoms more than 5 days before admission were excluded. The study was explained to care-givers and written informed consent was obtained. We then obtained a medical history, conducted a physical examination and collected respiratory swab specimens. All patients were tested using one of two rapid influenza diagnostic tests and also influenza viral culture upon admission. Other medical investigations and treatments were provided by attending physicians according to the routine standard of care.

We evaluated the Directigen FLU A® and Now FLU A® antigen detection tests. These tests detect influenza type A and yield results in 15–30 min, but are not able to detect influenza type B. Nasal swabs were collected with plain cotton swab for both rapid tests. Nasopharyngeal swabs for influenza virus isolation were collected with Dacron swab and placed in viral transport media composed of NaCl 1 gm, K_2HPO_4 1 gm, Beef extract 1 gm, peptone 3 gm, add DW_2 up to 200 ml, add antibiotics to make final concentration as follow; Penicillin 1000 unit/ml, Streptomycin 1000 μg/ml, Fungizone 5 μg/ml and pH was adjusted to 7.0 ± 0.2 with 1 N NaOH, VTM then transported chill to the Thai National Influenza Center, National Institute of Health, Ministry of Public Health for influenza virus isolation. The specimens were cultured using Madin Darby Canine Kidney (MDCK) cells and observed for cytopathic effect. Isolated viruses were confirmed as influenza and typed by reference antisera for influenza A or B with immunofluorescent staining technique. Patients with a positive rapid test were treated with oseltamivir (Tamiflu™) according to the recommended doses per kilogram. The patients were followed until improvement or discharge. Because tissue cell culture is considered the gold standard diagnostic method, only children with a positive viral culture were included in this analysis. Clinical findings of influenza and non-influenza patients were compared using chi-square test and considered significant at $P < 0.05$. Statistical analyses were performed using SPSS software version 12.0 (SPSS Inc., Chicago, IL, USA).

Results

Four hundred and fifty six patients were enrolled. The male to female ratio was 1.5:1. Eighty percent of patients were younger than 2-years old. Sixty-three percent of patients were enrolled on day 4 or 5 after the onset of the illness (Table 1).

Influenza viruses were isolated in 39 patients (8.6%). Thirty-four of them were influenza A (87.2%) and five of them were influenza B (12.8%). Most of the influenza B viruses were isolated during December 2004 to February 2005 (Fig. 1). Influenza was isolated throughout the year except in November and May. Influenza activity demonstrated seasonal variation with two peaks during August to October and January to April. The highest monthly proportion of influenza positive patients was in February (16.7%) (Fig. 1).

Among 39 cases of culture-confirmed influenza, the mean age of influenza positive patients in this study was 20 months (3–53 months). Thirty-one patients (79.5%) were previously healthy while others had underlying diseases, including asthma or hyperactive airway diseases 4 (10.3%), cerebral palsy 1 (2.6%), ventricular septal defect 1 (2.6%), adrenogenital syndrome 1 (2.6%) and Sotos syndrome 1 (2.6%). The clinical features of influenza were high fever ($T > 38.5$°C), cough, constitutional symptoms

Table 1. Characteristics of the enrolled patients

	Number of patients (%)
Age (month)	
0–12	231 (50.7)
13–24	134 (29.4)
25–36	48 (10.5)
36–48	28 (6.1)
>48	15 (3.3)
Gender	
Male	274 (60.1)
Female	182 (39.9)
Chronic underlying condition	
None	354 (77.6)
Pulmonary	53 (11.6)
Cardiac	19 (4.2)
Neurologic	13 (2.9)
Others	17 (3.7)
Enrollment day since onset of illness	
1	3 (0.7)
2	53 (11.6)
3	111 (24.3)
4	125 (27.4)
5	164 (36.0)

Table 2. Clinical features of influenza and non-influenza children

Symptom	Number of patients (%)		*P*-value
	Influenza (*n* = 39)	Non-influenza (*n* = 417)	
Temperature			
36.5–37.5°C	7 (17.9)	98 (23.5)	0.431
37.6–38.5°C	9 (23.1)	159 (38.1)	0.062
38.6–41°C	23 (59.0)	160 (38.4)	0.012*
Cough	38 (97.4)	408 (97.8)	0.595
Constitutional symptoms	38 (97.4)	392 (94.0)	0.715
Rhinorrhea	38 (97.4)	402 (96.4)	1.000
Myalgia	5[a] (71.4)	14[b] (43.8)	0.235
Vomiting	26 (66.7)	297 (71.2)	0.589
Respiratory distress	22 (56.4)	305 (73.1)	0.027*
Abnormal breath sounds			
Wheezing, rhonchi	22 (56.4)	265 (63.5)	0.377
Rale	11 (28.2)	219 (52.5)	0.004*
Inspiratory stridor	8 (20.5)	13 (3.1)	0.000*
Injected pharynx	18 (46.2)	154 (36.9)	0.256
Diarrhea	13 (33.3)	95 (22.8)	0.167
Conjunctival injection	4 (10.3)	9 (2.2)	0.019*
Seizure	4 (10.3)	31 (7.4)	0.526

[a]*n* = 7; [b]*n* = 32 (only in evaluable older children); *$P < 0.05$.

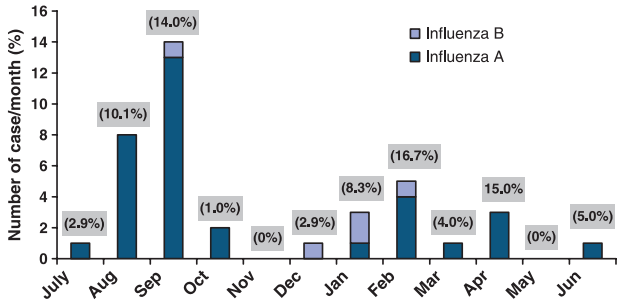

Figure 1. Influenza infection by months.

(anorexia, irritability, and lethargy), rhinorrhea, myalgia, vomiting, respiratory distress, abnormal chest auscultations (wheezing, rale, and stridor), injected pharynx, diarrhea, conjunctival injection, and seizure. Temperature >38.6°C, conjunctival injection and stridor were significantly higher in influenza patients ($P < 0.05$) while respiratory distress and rale were significantly higher in non-influenza patients ($P < 0.05$). Seizures were presented in 10.3% of influenza patients and 7.4% of non-influenza patients (Table 2).

There were seven children with influenza were positive by rapid test but not the viral culture. The mean age of these patients was 14 months compared to 20 months in culture-confirmed patients. Among the seven patients, clinical features were high fever ($T > 38.5$°C) (100%), cough (100%), constitutional symptoms (anorexia, irritability, and lethargy) (100%), rhinorrhea (86%), vomiting (71%), respiratory distress (43%), and seizure (14%). The features were similar to culture-confirmed patients except the fever; all seven patients had high fever ($T > 38.5$°C) while in culture-confirmed influenza the majority (59%) had high fever and the rest had low-grade or no fever (Table 2).

The clinical diagnosis on admission for these children with culture-confirmed influenza included lower respiratory tract infection (pneumonia, bronchitis, bronchiolitis, and viral croup), upper respiratory tract infection (rhinopharyngitis and pharyngitis), influenza, viral myositis, and gastroenteritis (Table 3).

Among 39 influenza patients, 20 (51%) required oxygen therapy. Two patients needed mechanical ventilation; one case was previously healthy and the other had underlying Sotos syndrome with recurrent pneumonia. No patient died. The length of the hospital stay was 1–24 days, the highest percentage was between 6–10 days (23.1%) and 48.8% required hospital stays of 5 days or longer (Table 4).

Performance of the rapid diagnostic test for influenza A

Rapid tests for influenza A was evaluated compared to viral tissue cell culture. Directigen FLU A® was tested in 394 patients and Now FLU A® was tested in 62 patients

Table 3. Clinical diagnosis on admission

Diseases	Number of patients (%)
Lower respiratory tract infection	27 (68.9)
Pneumonia	14 (35.6)
Bronchiolitis	2 (5.1)
Bronchitis	3 (7.7)
Croup	8 (20.5)
Upper respiratory tract infection	7 (18.0)
Rhinopharyngitis	6 (15.4)
Pharyngitis	1 (2.6)
Others	5 (12.9)
Influenza	3 (7.7)
Viral myositis	1 (2.6)
Gastroenteritis	1 (2.6)
Total	39 (100)

Table 4. Length of hospital stay

Length of stay (day)	Number of patients (%)
1	2 (5.1)
2	5 (12.8)
3	7 (17.9)
4	6 (15.4)
5	4 (10.3)
6–10	9 (23.1)
>10	6 (15.4)
Total	39 (100)

(according to changes in the test supplied by the Department of Communicable Diseases Control). The sensitivity of Directigen FLU A® was 50% and specificity was 98% while Now FLU A® had sensitivity 33% and specificity 98% (Tables 5 and 6).

Table 5. Sensitivity and specificity of Directigen FLU A®

	Rapid test ⊕ Influenza A	Rapid test ⊖ influenza A	Total
Disease (viral culture*)			
Influenza A	14	14	28
Not influenza A	6	360	366
Total	20	374	394

Table 6. Sensitivity and specificity of Now FLU A®

	Rapid test ⊕ Influenza A	Rapid test ⊖ influenza A	Total
Disease (viral culture*)			
Influenza A	2	4	6
Not influenza A	1	55	56
Total	3	59	62

*Positive viral cultures for influenza A but not influenza B (34 from 39 totals) were used to evaluate sensitivity and specificity of the rapid tests, since the tests specified for influenza A diagnosis.

Discussion

During 2004–2005, 9% of children ≤5-years old that were hospitalized with lower respiratory tract infection or ILI were culture-positive for influenza virus infection. Because our study did not use the more sensitive RT-PCR or serological laboratory diagnostic methods, it is likely that the true proportion of influenza-associated hospital admissions was even greater. Influenza was isolated throughout the year round and peak activities occurred during June to October and January to March, a finding that was consistent with published reports.[10,11,19] Of interest, peak influenza activity in Thailand usually follows the beginning of school year in the middle of May each year. School aged children are believed to play a major role in the propagation of seasonal influenza epidemics.[18,20,21]

The clinical manifestations of influenza infection in our study are similar to those previously described.[22] Fever, cough, rhinorrhea, and constitutional symptoms are the most common presenting symptoms. Respiratory distress and abnormal breath sounds were common physical findings. Influenza in young children was significantly associated with high-grade fever (temperature >38.6°C). And we found unusual diagnoses included viral myositis and gastroenteritis which shows that in young children influenza virus infection may not present with respiratory tract infection. In our study, seizures were presented in four (10.3%) of influenza patients probably due to high-grade fevers. Neurological manifestations of influenza virus infection, including febrile seizures, encephalitis, and meningitis have been reported and warrant further study in Thai children.[23,24]

While the rapid test is proved very useful to identify influenza patients to conduct research and guide treatment decisions, the sensitivity of the tests was less than that reported elsewhere.[25,26] The sensitivity of Now Flu A® test and Directigen Flu A® were only 33% and 50%, respectively. These markedly low figures were probably due to

two reasons; first, most of the patients in our study were enrolled at the 4th or 5th day of illness, a time when influenza viral antigen may no longer be present in the nasopharynx in sufficient quantities to yield a positive rapid test. Second, we used of a nasal swab specimen rather than a nasal wash, a nasopharyngeal aspirate or a nasopharyngeal swab specimen that is recommended by the manufacturers. This finding underscores the importance of proper training and supervision of clinical staff who use rapid influenza diagnostic tests.[27]

In conclusion, our study demonstrates that influenza virus infection is an important cause of hospitalization in healthy Thai children <5 years of age. Clinical characteristics of influenza in young children are high-grade fever, cough, constitutional symptoms, rhinorhea, and abnormal breath sounds. Especially during the months of July to October and January to March when influenza activity appears to be highest, influenza infection should be considered in the differential diagnosis when caring for patients with acute upper or lower febrile respiratory infection. Rapid tests for influenza A had a moderate sensitivity and high specificity that can help guide clinical treatment and the wider application of these tests in Thailand should be considered. Further research on influenza infection in Thai children using RT-PCR, serology, and tissue cell culture laboratory diagnostic method is needed to improve clinical care, inform vaccine introduction decisions, and to develop improved practices for non-pharmaceutical interventions to control seasonal epidemics.

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