CLINICAL CHARACTERISTICS AND HOSPITAL CHARGES AMONG THAI CHILDREN HOSPITALIZED WITH INFLUENZA

Warunee Punpanich[1,2], Pawinee Chirapanyanon[1] and Suchada Srisarang[3]

[1]Department of Pediatrics, [3]Clinical Research Unit, Queen Sirikit National Institute of Child Health, Bangkok; [2]College of Medicine, Rangsit University, Pathum Thani, Thailand

Abstract. Infants and young children are at high risk for influenza-associated morbidity, mortality, and the need for hospitalization. Only limited information is available regarding the clinical findings, outcomes, and financial burden incurred by Thai children hospitalized with severe influenza, therefore, we examined these areas in this retrospective study. The children were diagnosed with having influenza by either a real-time reverse transcriptase-polymerase chain reaction or rapid testing. Two hundred eighty-nine influenza cases hospitalized at the Queen Sirikit National Institute of Child Health, Bangkok, Thailand were reviewed. Influenza A, B, and mixed A/B infections were identified in 204 (70.6%), 79 (27.3%), and 6 cases (2.1%), respectively. Children aged younger than 5 years comprised the greatest proportion of cases (60.9%). Fever was the most common symptom (100%), followed by cough (90.3%) and rhinorrhea (70.6%). Diarrhea and thrombocytopenia were found in 22% and 10.4%, respectively. Most cases recovered uneventfully but 2 patients died (fatality rate =0.7%). The median (IQR) duration of hospitalization were 3 (3) days. The median hospital charge was USD169.4 (177.6). Being younger than 2 years old, having predisposing co-morbidities, and/or receiving oseltamivir treatment were significantly associated with longer hospitalization; the latter two were associated with higher hospital charges. On logistic regression analyses, being younger than 2 years old was an independent risk factor for disease severity. Most children hospitalized with pediatric influenza had an uncomplicated clinical course. Young children and those with predisposing co-morbidities are at increased risk for extended hospitalization and higher treatment costs.

Keywords: pediatric influenza, risk factors, hospital charges, treatment cost, Thailand

Correspondence: Warunee Punpanich, Department of Pediatrics, Queen Sirikit National Institute of Child Health, 420/8 Ratchawithi Road, Ratchathewi, Bangkok, 10400, Thailand.
Tel: +66 (0) 85 515 8299
E-mail: waruneep@gmail.com; warunee@vandepitte.eu

INTRODUCTION

Pandemic and seasonal influenza are major public health problems causing a financial burden worldwide (Peasah *et al*, 2013). Although uncomplicated upper respiratory tract infections are typical in influenza, lower respiratory tract in-

fections are common, especially among young children and those with underlying co-morbidities (Punpanich and Chotpitayasunondh, 2012). Although a minority of cases with influenza are hospitalized, the cost of hospitalization can be an economic burden. Infants and young children are at higher risk for influenza-associated hospitalizations and mortality (Fiore *et al*, 2010). Although influenza vaccines were made available free of charge for high-risk populations in Thailand since 2004, including for children aged 6 months to 2 years, the overall rates of vaccine uptake (using overall sale as a proxy measure) were rather low (Gupta *et al*, 2012). To better understand the clinical characteristics, and financial burdens of children hospitalized with influenza, we conducted a retrospective review of patients' medical records at the Queen Sirikit National Institute of Child Health (QSNICH), Bangkok, Thailand.

The study was reviewed and approved by the QSNICH Ethics Committee (IRB approval number: 54-051).

MATERIALS AND METHODS

We retrospectively reviewed the charts of children aged one month to 18 years hospitalized with influenza at the QSNICH between January 1 to December 31, 2010. Paitents were diagnosed by either a positive rapid influenza test or real-time reverse transcriptase-polymerase chain reaction (rRT-PCR). QSNICH is a tertiary care children's hospital in Bangkok, Thailand with a 426-bed inpatient capacity. The hospital has approximately 350,000 outpatients and 15,000 inpatients per year.

Potential subjects were identified as those having an ICD10 code of J10.0-J11.10. After reviewing the charts of potential cases, only those with positive rapid test and/or a positive rRT-PCR test for influenza were included in this study. The rRT-PCR tests were conducted at the Influenza Division, National Institute of Health, Ministry of Public Health, Thailand. The protocol for the rRT-PCR influenza test followed that of the United States Centers for Disease Control and Prevention (US CDC) [CDC Real-time RT-PCR Protocol for Detection and Characterization of Influenza, version 2007; CDC protocol for real-time RT-PCR for influenza A(H1N1), revision 2, 2009]. The rapid test used was the QuickVue® rapid tests. The sensitivities for detecting influenza A and B were >94% and >70%, respectively, and the specificities of influenza A and B were >90% and >97%, respectively (Quidel corporation, undated). Any discrepancies between the rRT-PCR and the rapid tests were decided by taking the rRT-PCR results. The clinical manifestation, complications, and outcomes were obtained from medical records. The hospital charges were obtained from the hospital financial database.

Statistical analysis

The data were descriptively analyzed. Differences in normally distributed continuous variables were analyzed using Student's *t*-test. Comparisons between skewed data (age, duration of hospitalization, hospital charges) were analyzed using the non-parametric Mann-Whitney method. The chi-square or Fisher's exact test was used for comparison of categorical variables between groups. To identify independent markers for disease severity, we performed logistic regression, adjusting for potential confounding effects. All statistical analyses were performed using SPSS, version 16 (SPSS, Armonk, NY).

RESULTS

Between January and December 2010, a total of 296 influenza cases were identified from the hospital database. Only 290 medical records were available for review. All 290 patients had rapid tests for influenza; 16 cases were tested with both the rapid test and rRT-PCR. One case with positive rapid test but negative with the rRT-PCR test on the same date was excluded. Therefore, a total of 289 cases were included in the study. The male to female ratio was 1.5:1. The greatest number of cases were identified during 2 periods: 1) January to March (late winter) and 2) August to October (rainy season). The median age [interquartile range (IQR)] of cases was 44.0 (62.5) months. Children aged <5 years comprised 60.9% of cases, children <2 years comprised 31.5% of cases, children aged 2-5 years comprised 29.4% of cases, children aged 5 years or older comprised 39.1% of cases and children <6 months comprised 4.5% of cases. Underlying predisposing conditions for severe influenza according to the Advisory Committee of Immunization Practice (ACIP) (Fiore *et al*, 2010) were identified in 41 cases (14.2%), with asthma being the most common (4.5%), followed by congenital heart disease (3.8%), hematologic malignancies (2.1%), neuromuscular disorders (2.1%), chronic lung disease (1.4%), HIV infection (1.4%), metabolic disease, (1%), renal disease (0.7%), and premature birth (0.3%). Rates of influenza immunization among those with and without an underlying predisposing co-morbidity were 4.9% and 0.4%, respectively.

Fever was the most common clinical manifestation (100%), followed by cough (90.3%) and rhinorrhea (70.6%). Other manifestations included diarrhea (22%), dyspnea (15.6%), sore throat (12.5%), headache (8.7%), seizures (7.6%), abdominal pain (4.8%) and conjunctivitis (1%). The median (IQR) duration between onset of fever and admission was 3 (3) days. The mean [standard deviation (SD)] peak axillary temperature was 39.1ºC (0.9ºC). Lower respiratory tract involvement, the most frequent complication, occurred in 89 cases (30.7%), which was diagnosed clinically as pneumonia in 13 cases (4.5%), radiographically confirmed pneumonia in 71 cases (24.5%), and bronchitis in 5 cases (1.7%). Other complications included febrile convulsions in 16 cases (5.5%), gastroenteritis in 8 cases (2.8%), and myositis in 5 cases (1.7%). Four cases (1.4%) required admission to the intensive care unit and 7 (2.4%) required mechanical ventilation.

Complete blood counts were performed in 285 cases. The median (IQR) white blood cell (WBC) count was 7,860 (5,570) cells/mm^3. The median (IQR) of percents of neutrophils and lymphocytes were 63%(32) and 30%(32), respectively. The median platelet count (IQR) was 251,000 (134,000) cells/mm^3. Leukopenia (WBC <5,000 leukocytes/mm^3) and thrombocytopenia (<150,000 platelets) were documented in 54 cases (18.7%) and 30 cases (10.4%), respectively.

Ninety-five percent of cases (*n*=273) received oseltamivir treatment. Antibiotics were prescribed in 121 cases (41.9%), and oxygen supplement was required in 30 cases (10.4%). Most patients had an uncomplicated course of illness, but there were 2 fatalities (0.7% case fatality rate). Both fatalities had underlying cardiovascular disease. One hundred eighty-five patients (65.1%) returned for follow-up. All had recovered uneventfully without complications.

Laboratory findings confirmed 204

Table 1
Demographic and clinical characteristics and outcomes of influenza A and influenza B patients.

Characteristics	Influenza A (*N*=204); *n* (%)	Influenza B (*N*=79); *n* (%)	*p*-value
Male gender	132 (64.7)	44 (55.7)	0.161
Median age in months (IQR)	37.5 (56)	68 (62)	0.001
Age group in years			0.002
<2	72 (35.5)	16 (20.3)	
2 to <5	65 (31.9)	19 (24.1)	
≥5	67 (32.8)	44 (55.7)	
Previously received an influenza vaccine	2 (1.0)	1 (1.3)	0.833
Presence of any predisposing co-morbidities	33 (16.2)	8 (10.1)	0.195
Asthma	13 (6.4)	0 (0.0)	0.023
Chronic lung disease	3 (1.5)	1 (1.3)	0.896
Congenital heart disease	8 (3.9)	3 (3.8)	0.961
Hematologic malignancy	5 (2.5)	1 (1.3)	0.535
Metabolic disease	3 (1.5)	0 (0.0)	0.279
Neuromuscular disease	5 (2.5)	1 (1.3)	0.535
Prematurity	1 (0.5)	0 (0.0)	0.533
Immunosuppression	3 (1.5)	1 (1.3)	0.896
Complications/outcomes	58 (28.4)	19 (24.1)	0.458
Febrile convulsions	11 (5.4)	5 (6.3)	0.759
Myositis	2 (1.0)	3 (3.8)	0.107
Gastroenteritis	5 (2.5)	3 (3.8)	0.540
Pneumonia	64 (31.4)	18 (22.8)	0.153
Admitted to the intensive care unit	4 (2.0)	0 (0.0)	0.209
Required mechanical ventilation	7 (3.4)	0 (0.0)	0.095
Required supplemental oxygen	25 (12.3)	3 (3.8)	0.033
Median length of stay in days (IQR)	3 (IQR 3)	3 (IQR 3)	0.375
Death	2 (1.0)	0 (0.0)	0.377
Median hospital charge in Thai Baht (IQR)	5,391.5 (5,787.5)	4,727 (3,231)	0.058
Received antiviral therapy	200 (98.0)	67 (84.8)	<0.001
Received antibiotics	95 (46.6)	23 (29.1)	0.008

IQR, interquartile ranges; 6 cases were positive for both influenza A and B and not included in this table; the exchange rate was approximately USD 1= THB 30.

patients (70.6%) had influenza A, 79 patients (27.3%) had influenza B, and 6 patients (2.1%) had mixed influenza A and B infection. A comparison between patients with influenza A and B is found in Tables 1 and 2.

Children with influenza A were significantly younger than those with influenza B, with median ages of 56 months and 62 months, respectively. Sixty-seven percent of influenza A patients were younger than 5 years, but more than half of influenza B patients were older than 5 years. Although not reaching statistical significance (except for asthma), the proportion of children with any underlying

Table 2
Clinical manifestations and laboratory findings among influenza A and influenza B patients.

Characteristics	Influenza A (*N*=204); *n* (%)	Influenza B (*N*=79); *n* (%)	*p*-value
Mean peak temperature (SD)	39.2 (1.2)	39.1 (1.4)	0.164
Cough	186 (91.2)	70 (88.6)	0.509
Rhinorrhea	147 (72.1)	53 (67.1)	0.410
Abdominal pain	9 (4.4)	5 (6.3)	0.505
Vomiting	98 (48.0)	54 (68.4)	0.002
Diarrhea	49 (24.0)	15 (19.0)	0.364
Dyspnea	37 (18.1)	7 (8.9)	0.053
Seizure	17 (8.3)	5 (6.3)	0.572
Conjunctivitis	1 (0.5)	2 (2.5)	0.133
Rash	2 (1.0)	2 (2.5)	0.321
Median total white blood cell count (IQR)	8,585 (5,453)	5,970 (3,570)	<0.001
Median percent neutrophils (IQR)	64 (31)	60 (30)	0.713
Median percent lymphocytes (IQR)	29 (32)	32 (29)	0.534
Leukopenia (WBC <5,000/mm^3)	27 (13.5)	26 (32.9)	<0.001
Lymphopenia (lymphocytes <800/mm^3 or <15% of total WBC)	47 (23.5)	15 (19.0)	0.414
Thrombocytopenia (total platelets <150,000/mm^3)	18 (9.0)	12 (15.2)	0.133

WBC, white blood cells; SD, standard deviation.

co-morbidity was slightly greater among influenza A patients, possibly resulting in the significantly higher rate of oseltamivir and antibiotic use among influenza A cases than among influenza B cases.

Hospitalization varied in duration from 1 to 73 days, with a median (IQR) of 3 (3) days. Major contributors to hospital charges were diagnostics, therapeutics, accommodations, supplies and health care services. The median (IQR) hospital charge was 5,083 (5,329) Thai Baht (THB) [approximately USD 169.4 (177.6)]. The total hospital charges for all patients in this study was THB 3,437,403 (USD 114,580.10) (exchange rate USD 1 = THB 30). The hospital charges for 83.4% of cases were covered by the government. Hospital charges were comparable between influenza A and B cases (Table 1) and payment sources. The median (IQR) hospital charges for out-of-pocket payments, government subsidized schemes, and universal health coverage were USD 151.4 (110.8), 160.7 (110.2), and 181.38 (208.8), respectively (p=0.064).

Based on univariate analysis (Table 3), factors associated with extended hospital stay included age <2 years, the presence of underlying predisposing co-morbidity, and oseltamivir treatment; the latter two factors were associated with significantly higher hospital charges. We were unable to use multivariate linear regression to identify significant predictors for extended duration of hospitalization and

Table 3
Markers for disease severity among study subjects.

Variable	Median (IQR) duration of hospitalization	*p*-value	Median (IQR) hospital charge	*p*-value	Presence of complications	*p*-value
Age <6 months	6 (10)	0.006	8,545 (16,549)	0.026	7 (53.8)	0.026
Age ≥6 months	3 (3)		5,048 (5,251)		71 (25.7)	
Age <24 months	4 (4)	<0.001	6,103 (7,872)	0.064	32 (35.2)	0.034
Age ≥24 months	3 (2)		4,888 (4,307)		46 (23.2)	
Presence of underlying disease	4 (6)	0.003	7,875 (16,819)	0.001	15 (36.6)	0.135
No underlying disease	3 (3)		4,863.5 (4,662)		63 (25.4)	
Influenza A infection	3 (3)	0.375	5,391.5 (5,764.5)	0.058	58 (28.4)	0.458
Influenza B infection	3 (3)		4,727 (3,231)		19 (24.1)	
Oseltamivir given	3 (3)	0.003	5,378 (5,185)	0.002	76 (27.8)	0.179
Oseltamivir not given	2 (1)		2,879.5 (2,919)		2 (12.5)	
Leukopenia	3 (3)	0.726	5,407.5 (5,610)	0.445	18 (33.3)	0.246
No leukopenia	3 (3)		4,989 (5,340)		59 (25.5)	
Thrombocytopenia	4 (4)	0.611	6,314.5 (9,219)	0.180	10 (33.3)	0.410
No thrombocytopenia	3 (3)		5,054 (5,246)		67 (26.3)	

Complications included pneumonia or other systemic involvement (*eg*, gastroenteritis, myositis, febrile convulsion), ICU admission, mechanical ventilation, death.

hospital charges without violation of key assumptions of this analytic strategy, mainly due to the lack of a linear relationship between predictors and outcome variables.

Given the low fatality rate and number of ICU admissions, we used a composite outcome as an indicator of disease severity in the logistic regression model to identify independent risk factors for disease severity. This composite outcome included the presence of complications, such as pneumonia, other systemic involvement, such as gastroenteritis, myositis, febrile convulsions, ICU admissions, the use of mechanical ventilation, and death. A backward stepwise approach to control for known and potentially confounding factors identified on univariate analysis with a *p*-value <0.2 was used to construct the final model. Our results showed that age < 2 years was the only independent marker of disease severity, with an adjusted odds ratio (aOR) of 2.40 [95% confidence interval (CI): 1.04- 5.53]. This analytic strategy also found that children age< 6 months were at an even higher risk for complications, with an aOR of 3.33 (95% CI: 1.08-10.25).

DISCUSSION

Our findings showed that influenza-associated hospitalizations had two peaks, one during the winter and the other during the rainy season, similar to studies from other tropical regions

(Azziz Baumgartner *et al*, 2012; Kanchana *et al*, 2012). Thirteen cases (4.5%) were younger than 6 months, which could potentially have been prevented by maternal influenza vaccination; not commonly prescribed in Thailand (Dawood *et al*, 2011). Young children were more likely to develop respiratory failure (14% of those younger than 6 months and 42.8% of those younger than two years required mechanical ventilation). These findings emphasize the importance of influenza vaccination during pregnancy.

Similar to other studies reviewed by Punpanich and Chotpitayasunondh (2012), clinical manifestations and outcomes of the patients in our study were generally mild, with a low risk for mortality. Rates of ICU admission, mechanical ventilation, and mortality are comparable with previous studies from Thailand and other parts of the world (Kwong *et al*, 2009; Lochindarat and Bunnag, 2011; Suntarattiwong *et al*, 2011). Similar to previous reports from Thailand, fever and cough were among the most common clinical findings identified in more than 90% of patients (Lochindarat and Bunnag, 2011; Udompornwattana *et al*, 2012), whereas rash and conjunctivitis were only found in approximately 1% of patients. Diarrhea was common, and was seen in about one-fifth of cases, higher than a previous report of 13% among those infected with the 2009 pandemic influenza A (H1N1) virus (Khandaker *et al*, 2011).

Similar to a previous report from Thailand (Simmerman *et al*, 2009), the clinical manifestations were comparable between influenza type A and type B. We did see influenza A in a significantly younger age, a higher proportion with asthma, lower rates of vomiting and leukopenia, and higher rates of needing oxygen supplementation, antiviral and antibiotic therapy. Three point four percent of influenza A patients had respiratory failure requiring mechanical ventilation, but none with influenza B had respiratory failure but the numbers were too small to reach significance. Our findings support some studies on influenza A which found that it had a greater association with underlying co-morbidities and poorer outcomes than influenza B subtype infection (Simonsen *et al*, 1997; Thompson *et al*, 2009; Wie *et al*, 2013). This could be due to the higher mutation rate of influenza A virus than influenza B virus (Yamashita *et al*, 1988; Matsuzaki *et al*, 2004; Chen and Holmes, 2008). Influenza A is more likely to elude early immune recognition than influenza B, causing more severe disease and poorer outcomes. Early host recognition of influenza B may contribute to a better control through prevention of viral replication and pathogenicity than influenza A (Osterlund *et al*, 2012).

The prevalence of ACIP-designated high-risk conditions in this study was 14.2%, which is at the low end compared to previous studies of 14.2-84% (Punpanich and Chotpitayasunondh, 2012) and low compared to previous reports of children hospitalized with influenza (Udompornwattana *et al*, 2012). We had a relatively large proportion (about 1/3) of very young children (< 2 years of age) in our study. Rates of influenza immunization among those with ACIP-designated underlying medical conditions for influenza vaccine were disappointingly low in our study, despite public education efforts during the influenza A(H1N1) pandemic beginning in 2009. The two fatalities in our study among children with underlying cardiovascular disease highlight the importance of influenza immunization in high risk populations.

Leukopenia was found in 18.7% of

patients, making it difficult to distinguish these cases from dengue infections, which are endemic in Thailand and have a similar seasonal pattern. Thrombocytopenia occurred in 10.4% of patients. Eleven patients (3.8 %) had a platelet counts <100,000 cells/mm^3. Lymphopenia (total lymphocytes <800/mm^3 or lymphocytes <15% of total white blood cells), is common in influenza infection (Liem *et al*, 2009; Lupovitch, 2005; Cunha, 2010), and was seen in 22.1% of cases in our study.

The cost of influenza can be substantial (Keren *et al*, 2006). A study conducted in China (Zhang *et al*, 2012) found the mean cost for treating a child hospitalized with influenza was USD 624 (THB 18,720) substantially higher than our mean [mean hospital charge was USD 396.47 (THB 11,894)]. The costs of hospitalization were obtained from the hospital billing data system which contains detailed line-item charges for all diagnostic tests, therapeutics, supplies and room fees. The higher cost in the study from China could be due to the longer duration of hospitalization (median of 7 days in China compared to 3 days in our study).

We were unable to detect significant differences between influenza subtypes in terms of duration of hospitalization, need for ICU admission, requirements for mechanical ventilation, fatalities or hospital charges. Our findings agree with earlier reports from Thailand where the influenza subtype did not appear to be associated with disease severity (Simmerman *et al*, 2009).

There were several limitations in this study: it was retrospectively conducted at a single center and was hospital-based. The small numbers of patients requiring ICU admission and mechanical ventilation and the low fatality rate prevent us from identifying independent prognostic factors. Certain markers of disease severity, such as ICU admissions, duration of hospitalizations, and hospital charges, may be influenced by non-medical factors, such as bed availability or level of parental concern, particularly during a period of high influenza activity. The use of oxygen supplement was at physician's discretion and in many cases the oxygen saturation prior to oxygen therapy was not recorded in the charts. We were not able to include a large proportion of cases for two reasons: 1) rRT-PCR and rapid influenza testing were done at the discretion of attending physician without a specific case definition criteria and 2) rapid influenza testing has a large percentage of false-negative results. One study found a much lower sensitivity with the rapid influenza test than that reported by the manufacturer (Uyeki *et al*, 2009). However, some studies report a fairly high specificity and positive predictive value with this test (Uyeki, 2003; Agoritsas *et al*, 2006; Grijalva *et al*, 2007; Mehlmann *et al*, 2007, Rashid *et al*, 2007; Hurt *et al*, 2009; Uyeki *et al*, 2009). It is likely that our sample had only a small proportion of false-positive cases due to the high specificity of the test. Physicians should bear in mind the limitations of this test when interpreting the results.

In conclusion, most patients in our study had an uncomplicated clinical course and good outcome. The median hospital stay was 3 days and the average hospital charge of USD 169.4 (THB 5,083). Young children and those with predisposing co morbidities were at increased risk of extended hospitalization and higher hospital charges. Being younger than age 2 years, and especially younger than 6 months was independently associated with disease severity. Very young children and those with underlying co-morbidities

should receive influenza immunization and timely antiviral treatment to prevent serious complications.

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