Original Article

Clinical Characteristics and Outcomes of Influenza in Hospitalized Pediatric Patients in King Chulalongkorn Memorial Hospital

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Objective: To describe clinical characteristics and outcomes of laboratory-confirmed influenza in hospitalized children in a tertiary care center and to identify factors associated with the severity.

Materials and Methods: The present study was a retrospective medical chart review study conducted at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Data were extracted from children aged under 15 years old hospitalized between January 2014 and December 2018. Patients who had laboratory-confirmed influenza by rapid antigen detection or molecular testing were included. Severe influenza was defined as patients who developed influenza complications or duration of hospitalization for more than three days. Multivariate logistic regression was used to identify the associated factors with the severity of the disease.

Results: Three hundred fifty-seven influenza patients were included with median age of 43 months (IQR 19 to 81), of which 63.3% were aged under 60 months. There were 174 patients (48.7%) with comorbidities, most common were immunosuppression (18.2%), chronic pulmonary disease (12.2%), and congenital heart disease (11.5%). Fifty-seven out of 183 patients (31.1%) had history of influenza vaccination in the medical records. One hundred sixty-one patients (45.1%) had 212 influenza complications including influenza-related pneumonia (89, 24.9%), secondary bacterial infection (53, 14.8%), and neurologic complications (47, 13.2%), in which 27 cases (7.6%) were transferred to intensive care unit (ICU). Four cases (1.1%) died but not directly related to influenza. Associated factors with complicated influenza were aged less than 24 months [aOR 2.67 (95% CI 1.68 to 4.26)] and presence of chronic lung disease [aOR 4.34 [95% CI 2.01 to 9.35)].

Conclusion: Two-third of the children hospitalized with influenza were younger than 60 months. Nearly half developed complications most associated with the age of less than two years old and patients with chronic lung disease. Low rates of vaccination were demonstrated.

Keywords: Influenza, Pediatrics, Complications, Pneumonia, Hospitalization

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Influenza is a contagious respiratory infection. The virus spreads easily by person-to-person transmission, regardless of age and genders. Moreover, the outbreak is seasonal, frequently occurred in rainy season and winter. It can cause mild to severe illness, and at times can lead to death. In children, influenza is more dangerous than the common cold. Each year, millions of children are afflicted with seasonal influenza where thousands of children are hospitalized, and some children died. Children with influenza, especially those under five years old, often need medical care[(1)].

According to the Centers for Disease Control and Prevention (CDC)[(1)], influenza-related hospitalization among children younger than five years old has ranged from 7,000 to 26,000 admissions in the United States since 2010. Influenza deaths in children are also high.

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In the past three years (2016 to 2019)[2], influenza-associated pediatric deaths have been about 140 deaths annually in the United States.

In Thailand, the Bureau of Epidemiology[3], Department of Disease Control reported that between 2013 and 2017, children under 15 years old diagnosed with influenza has gradually increased from 45,000 to over 200,000 cases per year, while the average has been 113,000 cases per year. Every year, about 50 children died from influenza complications.

There were two studies in Thailand conducted by the Queen Sirikit National Institute of Child Health (QSNICH). The first study in 2007, demonstrated that 9% of children aged 0 to 5 years old hospitalized with lower respiratory tract infections were caused by an influenza virus[4]. Another study in 2010 described that most of the children hospitalized with influenza had an uncomplicated clinical course. However, younger children and those with predisposing comorbidities were at increased risk for extended hospitalization and higher treatment costs[5]. Additionally, a study at the King Chulalongkorn Memorial Hospital (KCMH)[6], Bangkok in 2008, reported that influenza pneumonia was a life-threatening disease and had led to an overall mortality of 3.1%.

Oseltamivir was first approved for medical use in the United States in 1999. On August 3, 2016, the U.S. Food and Drug Administration (FDA) approved the first generic version of Tamiflu (oseltamivir phosphate), a widely use medication for the treatment of influenza in patients from the age two weeks old and older who have had flu symptoms for no more than 48 hours[7].

Even though oseltamivir was widely used in 2016, the authors were unable to acquire enough information on the treatment and outcomes of influenza patients at KCMH. The lack of data and limited population from previous studies generated the interest to further study influenza at KCMH.

The objectives of the present study were to describe clinical characteristics and outcomes of laboratory-confirmed influenza in hospitalized children in a tertiary care center and to identify factors associated with the severity of the disease.

Materials and Methods

A retrospective chart review study was conducted at KCMH, Bangkok, Thailand. The study was approved by the Institutional Review Board, Faculty of Medicine, Chulalongkorn University (IRB no. 318/61).

The inclusion criteria were patients aged less than 15 years who had a laboratory-confirmed influenza virus infection and were hospitalized at KCMH between January 1, 2014 and December 31, 2018. The exclusion criteria were cases with unavailable data and without laboratory-confirmed influenza virus infection. The cases were identified from medical database with ICD-10 code J10, influenza due to other identified influenza viruses and J11, influenza due to an unidentified influenza virus. The patients' data were reviewed for their demographic data, history of influenza immunization, clinical characteristics, complications, treatment, and outcomes.

Laboratory analysis

Laboratory-confirmed influenza virus infection included influenza A, B antigen (immunochromatography test) (QuickNavi Flu®, Denka Seiken), which had been used in KCMH between 2008 and 2017, and the same test with an additional detection of the respiratory syncytial virus antigen (QuickNavi Flu® + RSV, Denka Seiken) had replaced the single influenza virus rapid test in our setting since 2017. Occasionally, clinicians requested a molecular test, therefore, patients who had laboratory-confirmed influenza by microarray or reverse transcription polymerase chain reaction (RT-PCR) methods were also included.

Clinical definitions and evaluation of the outcomes

According to the Infectious Disease Society of America (IDSA)[8], persons at high risk for influenza infections were children aged less than two years old, children who had comorbidities including chronic pulmonary disease such as asthma, congenital heart disease, renal disease, hepatic disease, hematologic disease especially thalassemia, neurologic and neurodevelopmental conditions including disorders of the brain such as, cerebral palsy, epilepsy, stroke, intellectual disability, moderate to severe developmental delay, muscular dystrophy, or spinal cord injury, and immunosuppressive status caused by medications or by HIV infection.

Influenza complications were defined as any clinical syndrome that occurred after the influenza infection. Influenza pneumonia was defined as influenza with lower respiratory tract infections diagnosed by attending physician or chest X-ray findings[9]. Patients should have a fever, productive cough, tachypnea, abnormal lung sounds in the physical examination, and no evidence of superimposed bacterial infection. Patients who were diagnosed with influenza pneumonia and developed clinical signs and symptoms of respiratory distress

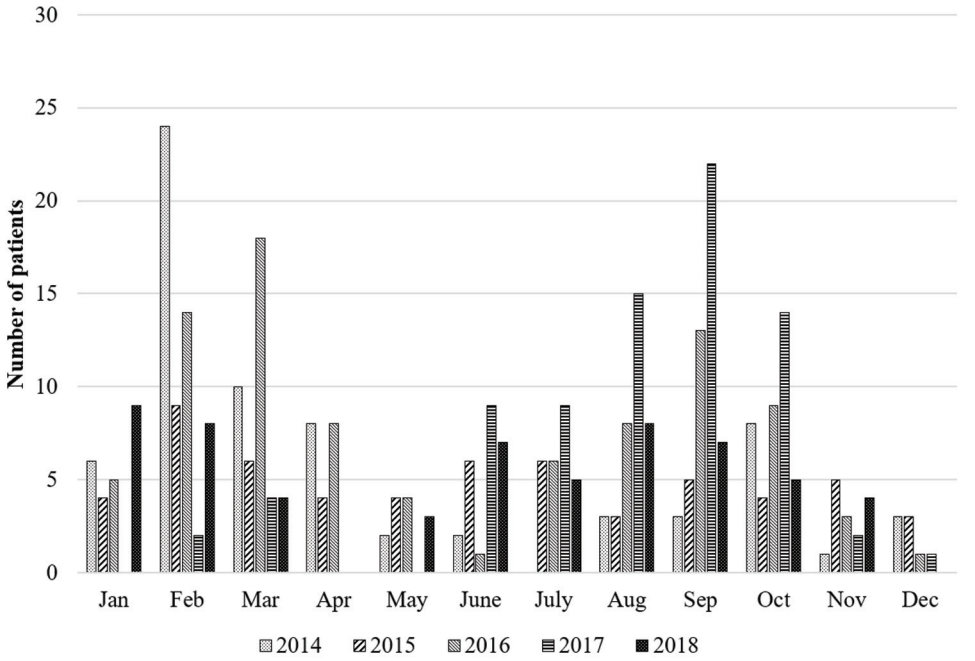

Figure 1. Monthly distribution of 357 hospitalized children with laboratory-confirmed influenza at King Chulalongkorn Memorial Hospital between 2014 and 2018.

and the need for intubation and respiratory support were defined that they had influenza pneumonia with acute respiratory failure. Febrile seizure was defined as a seizure found with a high-graded fever and no alteration of consciousness[10], given that the seizure was not caused by infection of the central nervous system. Encephalitis or encephalopathy were defined as patients diagnosed with influenza who developed alteration of consciousness[11]. Secondary bacterial infection was defined as an influenza infection followed by a clinical course of bacterial infection[12], which was taken into consideration from either the medical record of the clinical diagnosis of a bacterial infection or microbiological evidence for a bacterial infection.

Severe influenza was considered from the presence of the complications or duration of hospitalization for more than three days[5]. Treatment outcomes were assessed upon the discharge status.

Statistical analysis

Categorical data were presented using frequencies and percentages. Continuous data were expressed as a median value (range) or mean (standard deviation [SD]). Continuous variables were compared using a student's t-test or Mann-Whitney test, as appropriate, between the patient groups. The chi-square or Fisher's exact test was used for the comparison of the categorical variables between the groups. To identify the factors associated with the severity of the disease, multiple logistic regression was performed. Factors with p-value less than 0.05 from univariate analysis were included in the multivariate analysis. Statistical analysis was performed using IBM SPSS Statistics, version 22 (IBM Corp., Armonk, NY, USA), and a p-value of less than 0.05 was considered statistically significant.

Results

Three hundred seventy-seven influenza cases were identified from the KCMH's database between January 2014 and December 2018. Among these, 20 cases were excluded due to non-laboratory-confirmed influenza diagnosis, therefore, 357 cases were included in the present study. The highest number of patients was in 2016, which comprised of 90 patients.

Demographic data

The highest number of cases were identified during two periods of each year, the first period was between January and March (n=123), and the second period was between September and October (n=127). The monthly distribution of hospitalized children with laboratory-confirmed influenza is shown in Figure 1.

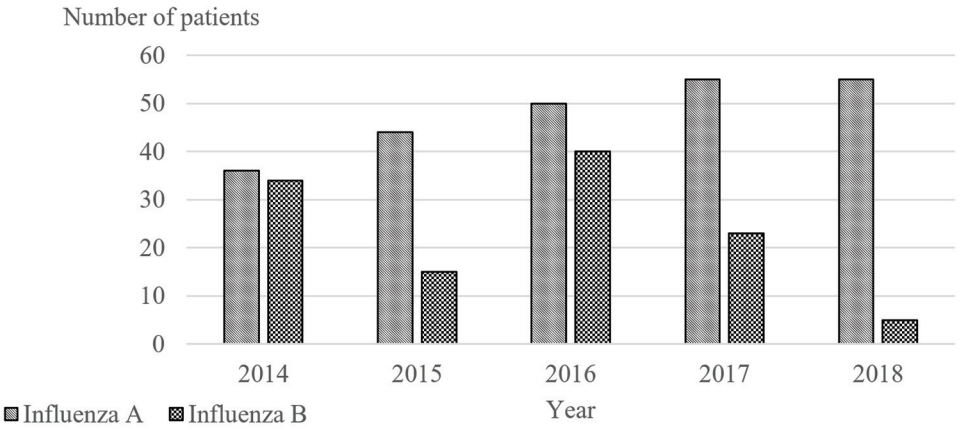

Figure 2. Yearly distribution of 357 hospitalized children with laboratory-confirmed influenza, divided by type of influenza, at King Chulalongkorn Memorial Hospital between 2014 and 2018.

Among the 357 hospitalized patients with laboratory-confirmed influenza, there were 240 cases (67.2%) with influenza A infection, and 117 cases (32.8%) with influenza B infection. The yearly distribution of patients categorized by each type of influenza is shown in Figure 2. With regards to the confirmatory methods, 321 cases (89.9%) were tested with an immunochromatography test, 25 cases (7%) were tested with the microarray method, and 11 cases (3.1%) were tested with the RT-PCR method.

Among the 357 hospitalized patients with influenza, 210 patients (58.8%) were male. The median age was 43 months (interquartile range [IQR] 18.5 to 81 months). Patients aged under 60 months accounted for 63.3% of all cases. Twenty-one (5.9%) patients were infants aged less than six months. Predisposing comorbidities were also present in 174 patients (48.7%), 65 patients had an immunosuppressive status (18.2%), 43 patients had chronic pulmonary disease (12%), and 41 patients had cardiovascular disease (11.5%). Patients who had an immunosuppressive status were divided into 40 patients treated with chemotherapy (11.2%), 20 patients taking immunosuppressive drugs (5.6%), four primary immunodeficiency (1.1%), and one HIV patient (0.3%). Nosocomial influenza accounted for 9.2%. For the history of immunization, 183 patients (51.3%) had information on influenza vaccination in the past year. Of them, 57 patients (31.1%) had received an influenza vaccination. The demographic data are shown in Table 1.

Table 1. Demographic data of 357 hospitalized children with laboratory-confirmed influenza at King Chulalongkorn Memorial Hospital between 2014 and 2018

Characteristics	n (%)
Sex: male	210 (58.8)
Age (months); median (IQR)	43 (18.5 to 81)
Age group	
≤6 months	21 (5.9)
7 to 24 months	91 (25.5)
25 to 60 months	114 (31.9)
61 to 120 months	85 (23.8)
≥121 months	46 (12.9)
Age ≤24 months	112 (31.4)
Predisposing comorbidities	174 (48.7)
Immunosuppression	65 (18.2)
Chronic pulmonary disease	43 (12.0)
Cardiovascular disease	41 (11.5)
Neurological disease	35 (9.8)
Chronic renal disease	11 (3.0)
Hepatic disease	9 (2.5)
Thalassemia	7 (1.9)
Previously received influenza vaccine in 1 year (n=183)	57 (31.1)

IQR=interquartile range

Clinical characteristics and complications

Fever was the most common sign and symptom comprising 343 cases (96%), while upper respiratory tract symptoms were present in 222 cases (62.2%), followed by acute diarrhea or vomiting in 119 cases (33.3%). Only 31 patients (8.6%) had myalgia. The mean body temperature was 39°C (SD 1.8) with the highest at 41.3°C. The most common provisional clinical diagnosis was an upper respiratory tract infection or common cold (140, 39.2%), followed

by acute febrile illness (97, 27.2%), lower respiratory tract infections (85, 23.8%), and acute gastroenteritis (30, 8.4%). There were 161 cases (45.1%) of influenza with 212 influenza complications. Influenza pneumonia was the most frequent complication consisting of 89 patients (24.9%) and 15 (4.2%) of these developed acute respiratory failures. Secondary bacterial infection occurred in 53 patients (14.8%), of these, 34 patients (9.5%) were diagnosed with bacterial pneumonia and 19 patients were another clinical diagnosis of secondary bacterial infection. Febrile seizure was diagnosed in 40 patients (11.2%) and seven cases of influenza encephalitis or encephalopathy (2.0%) were identified. Patients who were diagnosed with febrile seizures had a variety of clinical diagnosis, 19 first episode of febrile seizures (5.3%), 12 fever provoked seizures (3.4%), and nine complex febrile seizures (2.5%). Other complications included seven patients with culture-negative sepsis (2.0%), and seven patients with thrombocytopenia (platelet counts <150,000/uL) (2.0%). The clinical characteristics and complications are shown in Table 2.

Treatment and outcomes

With regards to treatment, 327 cases (91.6%) were prescribed oseltamivir, and 114 cases (31.9%) were prescribed antibiotics. Only 10 cases were documented with the reason for not being administered oseltamivir. Six patients did not indicate oseltamivir administration because they were more than two years old and had no predisposing comorbidities and four patients displayed clinical improvement when the laboratory result was reported. For the outcomes of the treatment, the median (IQR) of the hospital stay was three days (2 to 5). Twenty-seven cases (7.6%) were admitted to the intensive care unit (ICU). Nine cases (2.5%) developed morbidity associated with influenza after discharge such as the need to use home oxygen therapy, in which all of them have had predisposing comorbidities. Four patients (1.1%) died in the present study. One patient was diagnosed cerebral edema from multiple causes (inborn error metabolic disease and necrotizing encephalopathy from influenza). One patient who had underlying disease of chronic lung disease and died after being diagnosed influenza, 445 days later because of multiple hospital-acquired infections not directly related to influenza. Two patients died from their predisposing comorbidities, end-stage renal disease, and decompensated liver cirrhosis. The treatment and outcomes are shown in Table 2.

Table 2. Clinical presentations, treatment and outcomes of 357 hospitalized children with laboratory-confirmed influenza at King Chulalongkorn Memorial Hospital between 2014 and 2018

	n (%)
Signs and symptoms	
Fever	343 (96.0)
URI symptoms	222 (62.2)
Acute diarrhea/nausea and vomiting	119 (33.3)
LRTI symptoms	79 (22.1)
Myalgia	31 (8.6)
Clinical syndrome	
URI/common cold	140 (39.2)
Acute febrile illness	97 (27.2)
LRTI/croup/pneumonia	85 (23.8)
Acute gastroenteritis	30 (8.4)
Others	5 (1.4)
Complications	161 (45.1)
Respiratory system	
• Influenza pneumonia	89 (24.9)
• Influenza pneumonia with acute respiratory failure	15 (4.2)
• Others respiratory complications	4 (1.1)
Neurological system	
• Febrile seizure	40 (11.2)
• Influenza encephalitis/encephalopathy	7 (2.0)
Secondary bacterial infection	53 (14.8)
Other complications	19 (5.4)
• Culture-negative sepsis	7 (2.0)
• Thrombocytopenia (platelet counts <150,000/uL)	7 (2.0)
• Others*	5 (1.4)
Oseltamivir treatment	327 (91.6)
Antibiotics treatment	114 (31.9)
Admitted to intensive care unit	27 (7.6)
Hospital stay (days); median (IQR)	3 (2 to 5)
Morbidity	9 (2.5)
Death	4 (1.1)

URI=upper respiratory tract infection; LRTI=lower respiratory tract infection; IQR=interquartile range

* Other complications include two patients with supraventricular tachycardia, one patient with viral myositis, one patient with acute hemolysis with HbH CS thalassemia, and one patient with hypoxic spell

Comparison between the influenza A and influenza B virus infections

Comparing the severity of the disease between the influenza A and B viruses, patients with an influenza A infection were significantly younger than

Table 3. Comparison between influenza A and influenza B patients

	Influenza A (n=240) n (%)	Influenza B (n=117) n (%)	p-value*
Age (months); median (IQR)	39.5 (17.3 to 72.8)	50 (21 to 94)	0.028
Sex: male	145 (60.4)	65 (55.6)	0.381
Previously received influenza vaccine in 1 year	38 (15.8)	19 (16.2)	0.435
Signs and symptoms			
Body temperature (°C); mean±SD	39.2±0.8	38.9±0.8	0.026
Fever (n=343)	232 (96.7)	111 (94.9)	0.400
URI symptoms (n=222)	156 (65.0)	66 (56.4)	0.542
LRTI symptoms (n=79)	50 (20.8)	29 (24.8)	0.690
Myalgia (n=31)	22 (9.2)	9 (7.7)	0.351
Acute diarrhea/nausea and vomiting (n=119)	82 (34.2)	37 (31.6)	0.509
Complication			
Respiratory system (n=93)	63 (26.3)	30 (25.6)	0.902
Neurological system (n=47)	35 (14.6)	12 (10.3)	0.256
Secondary bacterial infection (n=53)	31 (12.9)	22 (18.8)	0.142
Other complications (n=19)	13 (5.4)	6 (5.1)	0.909
Admitted to intensive care unit	17 (7.1)	10 (8.5)	0.623
Oseltamivir treatment	229 (95.4)	98 (83.8)	<0.001
Antibiotics treatment	68 (28.3)	46 (39.3)	0.037
Hospital stay (days), median (IQR)	3 (2 to 5)	4 (2 to 6)	0.037
Morbidity	6 (2.5)	3 (2.6)	0.971
Death	3 (1.3)	1 (0.9)	1.000

URI=upper respiratory tract infection, LRTI=lower respiratory tract infection; IQR=interquartile range; SD=standard deviation

* Data were analyzed with chi-square test or Fisher's exact test for categorical data, independent t-test or Mann-Whitney U test for continuous data; statistically significant difference level of the 0.05

those with an influenza B infection with a median age of 39.5 versus 50 months, respectively (p=0.028). Patients with influenza A infection had significantly higher fever than those with influenza B infection with a mean body temperature of 39.2°C (SD 0.8) versus 38.9°C (SD 0.8), respectively (p=0.026). Influenza B infection tended to have a higher rate of secondary bacterial infection, but it was not statistically significant at 18.8% versus 12.9%, (p=0.142). Antibiotics were prescribed for patients with influenza B infection at a higher rate than those with influenza A virus infection at 39.3% versus 28.3%, (p=0.037). The comparison between the influenza A and influenza B infections is shown in Table 3.

Comparison between vaccinated and unvaccinated influenza patients in the previous one-year period

Among 183 patients who had information on influenza vaccination in the past year, 57 (31.1%) had received influenza vaccination. Sixteen patients (28.1%) aged less than 24 months had received influenza vaccine compared to 50 patients (39.7%) older than 24 months, but this was not statistically significant (p=0.131). In patients with predisposing comorbidities, 34 patients (59.6%) received influenza vaccine, which was significantly higher than patients without comorbidities (41, 32.5%), (p=0.001). There was no statistical significance in signs and symptoms, influenza complications, and hospital stay between vaccinated and unvaccinated influenza patients in the previous year.

Prediction factors of severe influenza

Patients aged under 24 months and patients with chronic lung disease were significantly associated with the presence of complications from influenza [adjusted odds ratio 2.67 (95% CI 1.68, 4.26) and 4.34 (95% CI 2.01, 9.35), respectively]. Patients aged under 24 months and patients with comorbidities were significantly associated with prolonged

Table 4. Factors associated with the presence of complications from influenza (n=161)

Risk factors	Univariate				Multivariate		
	n (%)	OR	95% CI	p-value	OR	95% CI	p-value*
Age ≤24 months	68 (42.2)	2.52	1.58 to 4.00	<0.001	2.67	1.68 to 4.26	<0.001
Presence of comorbidities	85 (52.8)	1.35	0.89 to 2.04	0.165			
Patients with immunosuppression	19 (11.8)	0.43	0.25 to 0.79	0.005	0.44	0.24 to 0.78	0.006
Patients with chronic lung disease	32 (19.9)	4.17	2.03 to 8.58	<0.001	4.34	2.01 to 9.35	<0.001
Patients with cardiovascular disease	22 (13.7)	1.47	0.77 to 2.83	0.244			
Patients with neurological disease	21 (13.0)	1.95	0.96 to 3.97	0.066			
Previously received influenza vaccine in 1 year	29 (18.0)	1.07	0.58 to 1.99	0.834			
Received oseltamivir for treatment	147 (91.3)	0.93	0.44 to 1.98	0.857			

OR=odds ratio; CI=confidence interval

* Data were analyzed with multiple logistic regression analysis; statistically significant difference level of the 0.05

Table 5. Factors associated with hospitalization 3 days or more (n=174)

Risk factors	Univariate				Multivariate		
	n (%)	OR	95% CI	p-value	OR	95% CI	p-value*
Age ≤24 months	63 (36.2)	1.64	1.04 to 2.56	0.035	1.86	1.15 to 3.00	0.011
Presence of comorbidities	109 (62.6)	3.04	1.98 to 4.69	<0.001	3.31	2.12 to 5.15	<0.001
Patients with immunosuppression	44 (25.3)	2.62	1.48 to 4.64	0.001	2.61	1.48 to 4.61	<0.001
Patients with chronic lung disease	27 (15.5)	2.00	0.99 to 3.70	0.041	1.92	0.99 to 3.70	0.052
Patients with cardiovascular disease	27 (15.5)	2.09	1.05 to 4.19	0.035	2.22	1.12 to 4.34	0.022
Patients with neurological disease	19 (10.9)	1.28	0.64 to 2.58	0.490			
Previously received influenza vaccine in 1 year	29 (16.7)	1.43	0.76 to 2.67	0.268			
Received oseltamivir for treatment	160 (92.0)	1.09	0.52 to 2.32	0.812			

OR=odds ratio; CI=confidence interval

* Data were analyzed with multiple logistic regression analysis; statistically significant difference level of the 0.05

hospitalization for more than three days [adjusted odds ratio 1.86 (95% CI 1.15, 3.00) and 3.31 (95% CI 2.12, 5.15), respectively]. The multivariate analysis of factors associated with severe influenza is shown in Table 4 and 5.

Discussion

Influenza has affected many children, especially those under five years old. Similar to the published data[13], the present study found that more than half of the hospitalized patients were under 60 months old. For the predisposing comorbidities, patients with immunosuppression were the highest populations, followed by patients with chronic lung disease. Previous studies from Taiwan found that chronic lung disease, especially bronchial asthma, was the most common risk factor in influenza patients[14]. The difference between the common predisposing comorbidities may be explained by the difference in hospital settings in each study. The current study was conducted at a tertiary care hospital where patients were referred for specific treatment for their underlying disease, especially hematologic malignancy and oncologic patients. The study demonstrated that only 31.1% of the hospitalized influenza patients had complete influenza immunization even though there was free coverage for influenza immunization programs in Thailand among children aged six months to three years old. The percentage of influenza vaccinated children was low, like the previous studies from Thailand[15]. However, there was a limitation on the percentage of vaccinated influenza patients because of the lack of data in the medical records. About 48.7% of the patients had not recorded their history of receiving an influenza vaccination in one year. Incomplete data is similar to a previous study from the United States[16]. Therefore, it was difficult to determine the

impact of the expanded vaccination recommendation on the burden of the influenza disease. This included the fact that influenza vaccination could decrease the severity and complications in hospitalized patients. In addition, the present study reported that 5.9% of infants aged less than six months received maternal influenza immunization during pregnancy to protect them from influenza in the first six months of life. This reason was supported by a previous study[17], which reported that influenza vaccination of pregnant women might reduce the risk of influenza-attributable hospitalization among infants in the first six months of life.

Clinical presentations were similar to the previous study[4,6,18]. Fever was the most common presentation in hospitalized patients, followed by upper respiratory tract symptoms, acute diarrhea or nausea, vomiting, and lower respiratory tract symptoms. Approximately one-third of the patients were initially diagnosed with an acute febrile illness. Like a previous study from Cambodia[19], about 26% of the patients who were diagnosed with acute febrile illness had influenza. In a prior study from Indonesia[20], detectable influenza viral RNA and viable influenza virus from a stool exam suggested that the influenza virus could be localized in the gastrointestinal tract in children. Therefore, digestive tract symptoms could be found in patients with influenza. In the present study, nearly 10% of the patients were diagnosed with acute gastroenteritis. A previous study from South Korea found that diarrhea or vomiting were commonly presented in children, more than in adults[21]. About 45% of the hospitalized patients developed a complication. This percentage was lower than a previous study from the United States[22]. Influenza pneumonia was the most common complication, followed by secondary bacterial infection and febrile seizure. A study by Rojo et al[23] showed that about 21% of the patients with community-acquired influenza developed pneumonia, which is similar to the current study. In that study, febrile seizure was the most frequent neurological complication in patients with influenza, followed by acute encephalitis and encephalopathy. This correlates with the finding in the study done by Newland in 2007[24]. There were no long-term morbidity or mortality in patients who were diagnosed with acute encephalitis or encephalopathy in the current study.

For the treatment and outcomes, almost all the patients in the present study were prescribed oseltamivir. Approximately 10% did not receive oseltamivir because they did not have predisposing comorbidities. However, according to the 2018 Guidelines by the IDSA[8], clinicians should start antiviral treatment in patients hospitalized with influenza. About 30% of the patients were prescribed antibiotics for treatment. This percentage was lower than the previous research from Poland[25], where 93% of the hospitalized patients in that study were treated with antibiotics. In the current study, there was a lower number of patients diagnosed with secondary bacterial infection than those who were prescribed antibiotics. This result implied that there was an overuse of antibiotics for the treatment of influenza. A small group of patients needed admission to the ICU, which is similar to a previous study from the United States[26], where the most common cause of ICU admission was acute respiratory failure and requirement for ventilatory support. The outcomes of hospitalized influenza patients were good with low morbidity and mortality rates. The mortality rate in the current study was the same as a previous study from Europe[27], where about 1% of the mortality rate was identified.

From the comparison between influenza A and B, influenza A patients were significantly younger than the influenza B patients. This result was similar to the published data from Australia[28]. There was a statistical difference in the mean highest recorded body temperature, but there was no difference in the presented signs and symptoms between the influenza A and B virus infections. These results were similar to previous studies[28,29]. Therefore, it was not possible to differentiate between influenza A or B virus infections from the presented clinical signs and symptoms. In general, except for a longer duration of hospital stay among influenza A patients, no significant differences were noted regarding the severity of the disease in morbidity and mortality between influenza A and B. These results were similar to the study from South Korea[30].

According to a previous study[15], patients aged less than 24 months had a low rate of influenza vaccination. Patients with predisposing comorbidities, especially patients with chronic lung disease, received influenza vaccination at a higher rate than patients aged less than 24 months. Nevertheless, both groups had a low rate of influenza vaccination. Doctors should provide more coverage in the influenza vaccine in the high-risk groups, according to IDSA[8].

Patients under 24 months were more prone to develop complications and extend their hospital stay. The results of the prediction of the severity of the disease were the same as in a previous study[31].

They reported that young children with or without pre-existing health conditions had a chance of developing severe illness from influenza compared to those who had no comorbidities. These results let the authors pay higher attention to young children, as they could develop further complications. Similar to a previous study[5], the present study detected that patients aged less than 24 months and patients with predisposing comorbidities might have hospital stays for more than three days.

The present study was performed after the improvement in laboratory investigations in the authors' hospital. The authors included patients who had laboratory-confirmed influenza by the RT-PCR and microarray methods. Consequently, the authors could integrate more patients who had influenza. The current study had a few limitations. First, outpatients who had an influenza infection were not included, so the authors could not identify the rate of hospitalization. Second, the authors did not collect the data on the duration of disease onset to oseltamivir treatment, which might affect treatment outcome. Last, there was a limitation on the influenza vaccination data because some patients had no records about their vaccination status, so the authors did not have accurate data for the prediction of the severity after influenza vaccination.

Conclusion

Approximately two-third of children hospitalized with influenza were younger than 60 months old. Influenza complications were found in half of the patients with influenza, especially patients aged younger than 24 months. Longer hospitalizations were associated with aged less than 24 months and patients with predisposing comorbidities. Low rates of vaccination were demonstrated, however, further study may be needed as the data was incomplete.

What is already known on this topic?

Influenza is common in young children aged less than five years. The common presentation of influenza is fever, cough, rhinorrhea, or dyspnea. Children aged less than 24 months and having predisposing comorbidities are at high-risk for developed influenza complications.

What this study adds?

This study described the clinical characteristics and treatment outcomes of hospitalized influenza in pediatric patients in Thailand. This study review is carried out in an era of improved diagnostic tools along with widely use of oseltamivir for treatment.

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Conflicts of interest

The authors declare no conflict of interest.

References

1. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). Children and Influenza (Flu) [Internet]. October 23, 2019 [cited 2020 Jan 3]. Available from: https://www.cdc.gov/flu/highrisk/children.htm.
2. Centers for Disease Control and Prevention. Weekly U.S. influenza surveillance report (FluView) [Internet]. January 24, 2020 [cited 2020 Jan 25]. Available from: https://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html.
3. The Bureau of Epidemiology, Department of Disease Control, Ministry of Public Health, Thailand. Influenza surveillance [Internet]. March 7, 2020 [cited 2020 Mar 7]. Available from: http://www.boe.moph.go.th/boedb/surdata/disease.php?dcontent=old&ds=15.
4. Suntarattiwong P, Sian-nork C, Thongtipa P, Thawatsupha P, Kitphati R, Chotpitayasunondh T. Influenza-associated hospitalization in urban Thai children. Influenza Other Respir Viruses 2007;1:177-82.
5. Punpanich W, Chirapanyanon P, Srisarang S. Clinical characteristics and hospital charges among Thai children hospitalized with influenza. Southeast Asian J Trop Med Public Health 2014;45:75-84.
6. Samransamruajkit R, Hiranrat T, Chieochansin T, Sritippayawan S, Deerojanawong J, Prapphal N, et al. Prevalence, clinical presentations and complications among hospitalized children with influenza pneumonia. Jpn J Infect Dis 2008;61:446-9.
7. The U.S. Food and Drug Administration. The FDA approves first generic version of widely used influenza drug, Tamiflu [Internet]. 2016 [cited 2020 Feb 29]. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fda-approves-first-generic-version-widely-used-influenza-drug-tamiflu.
8. Uyeki TM, Bernstein HH, Bradley JS, Englund JA, File TM, Fry AM, et al. Clinical Practice Guidelines by the Infectious Diseases Society of America: 2018 Update on Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management of Seasonal Influenzaa. Clin Infect Dis 2019;68:e1-47.
9. Gereige RS, Laufer PM. Pneumonia. Pediatr Rev

2013;34:438-56.
10. Subcommittee on Febrile S, American Academy of Pediatrics. Neurodiagnostic evaluation of the child with a simple febrile seizure. Pediatrics 2011;127:389-94.
11. Lewis P, Glaser CA. Encephalitis. Pediatr Rev 2005;26:353-63.
12. Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. Front Microbiol 2017;8:1041.
13. Hernández-Bou S, Novell CB, Alins JG, García-García JJ. Hospitalized children with influenza A H1N1 (2009) infection. Pediatr Emerg Care 2009;29:49-52.
14. Leung CH, Tseng HK, Wang WS, Chiang HT, Wu AY, Liu CP. Clinical characteristics of children and adults hospitalized for influenza virus infection. J Microbiol Immunol Infect 2014;47:518-25.
15. Owusu JT, Prapasiri P, Ditsungnoen D, Leetongin G, Yoocharoen P, Rattanayot J, et al. Seasonal influenza vaccine coverage among high-risk populations in Thailand, 2010-2012. Vaccine 2015;33:742-7.
16. Poehling KA, Edwards KM, Griffin MR, Szilagyi PG, Staat MA, Iwane MK, et al. The burden of influenza in young children, 2004-2009. Pediatrics 2013;131:207-16.
17. Poehling KA, Szilagyi PG, Staat MA, Snively BM, Payne DC, Bridges CB, et al. Impact of maternal immunization on influenza hospitalizations in infants. Am J Obstet Gynecol 2011;204(6 Suppl 1):S141-8.
18. Peltola V, Ziegler T, Ruuskanen O. Influenza A and B virus infections in children. Clin Infect Dis 2003;36:299-305.
19. Kasper MR, Wierzba TF, Sovann L, Blair PJ, Putnam SD. Evaluation of an influenza-like illness case definition in the diagnosis of influenza among patients with acute febrile illness in Cambodia. BMC Infect Dis 2010;10:320.
20. Dilantika C, Sedyaningsih ER, Kasper MR, Agtini M, Listiyaningsih E, Uyeki TM, et al. Influenza virus infection among pediatric patients reporting diarrhea and influenza-like illness. BMC Infect Dis 2010;10:1-5.
21. Hong KW, Cheong HJ, Song JY, Noh JY, Yang TU, Kim WJ. Clinical manifestations of influenza A and B in children and adults at a tertiary hospital in Korea during the 2011-2012 season. Jpn J Infect Dis 2015;68:20-6.
22. Dawood FS, Chaves SS, Perez A, Reingold A, Meek J, Farley MM, et al. Complications and associated bacterial coinfections among children hospitalized with seasonal or pandemic influenza, United States, 2003-2010. J Infect Dis 2014;209:686-94.
23. Rojo JC, Ruiz-Contreras J, Fernandez MB, Marin MA, Folgueira L. Influenza-related hospitalizations in children younger than three years of age. Pediatr Infect Dis J 2006;25:596-601.
24. Newland JG, Laurich VM, Rosenquist AW, Heydon K, Licht DJ, Keren R, et al. Neurologic complications in children hospitalized with influenza: characteristics, incidence, and risk factors. J Pediatr 2007;150:306-10.
25. Nitsch-Osuch A, Gyrczuk E, Wardyn A, Zycinska K, Brydak L. Antibiotic prescription practices among children with influenza. Adv Exp Med Biol 2016;905:25-31.
26. Randolph AG, Vaughn F, Sullivan R, Rubinson L, Thompson BT, Yoon G, et al. Critically ill children during the 2009-2010 influenza pandemic in the United States. Pediatrics 2011;128:e1450-8.
27. Jané M, Vidal MJ, Soldevila N, Romero A, Martínez A, Torner N, et al. Epidemiological and clinical characteristics of children hospitalized due to influenza A and B in the south of Europe, 2010-2016. Sci Rep 2019;9:12853.
28. Daley AJ, Nallusamy R, Isaacs D. Comparison of influenza A and influenza B virus infection in hospitalized children. J Paediatr Child Health 2000;36:332-5.
29. Mosnier A, Caini S, Daviaud I, Nauleau E, Bui TT, Debost E, et al. Clinical characteristics are similar across type A and B influenza virus infections. PLoS One 2015;10:e0136186.
30. Oh YN, Kim S, Choi YB, Woo SI, Hahn YS, Lee JK. Clinical similarities between influenza A and B in children: a single-center study, 2017/18 season, Korea. BMC Pediatr. 2019;19:472.
31. Garcia MN, Philpott DC, Murray KO, Ontiveros A, Revell PA, Chandramohan L, et al. Clinical predictors of disease severity during the 2009-2010 A(HIN1) influenza virus pandemic in a paediatric population. Epidemiol Infect 2015;143:2939-49.