

# CLINICAL SYMPTOMS AND RESPIRATORY COMPLICATIONS AMONG CHILDREN WITH SEASONAL INFLUENZA AT NATIONAL CHILDREN'S HOSPITAL, VIETNAM, 2020-2021

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**Abstract.** Seasonal influenza is a public health problem among children. In this study we aimed to determine the clinical manifestations and complications among children in Vietnam with seasonal influenza in order to inform influenza complication prevention programs. Study subjects were children aged <16 years diagnosed with and hospitalized for influenza at the Center for Tropical Diseases, National Children's Hospital, Vietnam, during June 2020-July 2021. The study was conducted retrospectively. In each subject, a nasopharyngeal or tracheal aspirate for real-time polymerase chain reaction test was performed to determine the presence, group and subtype of influenza. A total of 200 subjects were included in the study (187 influenza A, 13 influenza B), 55% male. The mean age of our study subjects was 27.1 months. About one quarter (26.5%) of subjects had received an influenza vaccine within the previous 12 months and 73.5% had either received an influenza vaccine greater than 12 months previously or had never received an influenza vaccine. Eighty-four percent of subjects had the H3N2 subtype of influenza and 9.5% had the H1N1 subtype of influenza. The most common symptoms among study subjects were: fever (100.0%), cough (85.5%), runny nose (62.5%) and sore throat (58.5%). The most common complications among study subjects were febrile convulsion (45%), bronchopneumonia (41%) and respiratory failure (25.5%). Risk factors significantly associated with bronchopneumonia were: preterm birth (crude odds ratio) cOR= 2.4, 95% confidence interval (CI): 0.9-6.7,  $p = 0.038$ ), subject age <24 months (cOR=5.5, 95% CI: 2.8-11.2,  $p < 0.00001$ ), having an underlying comorbid condition (cOR=5.5, 95% CI: 2.2-8.3,  $p = 0.00001$ ) and having a co-infection (cOR=32.4, 95% CI: 9.5-172.9,  $p < 0.00001$ ). The most common co-infections among study subjects were: *Streptococcus pneumoniae* (6%) and *Haemophilus influenzae* (5%). Study subjects who received oseltamivir within 48 hours of symptom onset had resolution of fever ( $3.5 \pm$  standard deviation (SD) 2.2 days) significantly ( $p < 0.05$ ) earlier than those who received oseltamivir after 48 hours of symptoms ( $5.1 \pm 3.1$  days). No deaths occurred in the study among study subjects. In summary, the most common clinical symptoms among our

study subjects were fever, cough, runny nose and sore throat. Complications were common and consisted of febrile convulsions, bronchopneumonia and respiratory failure and these were more common among younger subjects or subjects with an underlying condition or a secondary bacterial or viral infection. We conclude the complication rates in our study population were high and underline the importance of education about influenza vaccinations and good hygiene in this study population.

**Keywords:** seasonal influenza, complications, children, Vietnam

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## INTRODUCTION

Influenza is a contagious public health problem affecting not only finances but interfering with education through absenteeism of the children who contract it. A meta-analysis from worldwide data reported there are an estimated 32 million influenza-associated lower respiratory tract infections (LRI) with 5.6 million hospitalizations due to LRI yearly among adults (Lafond *et al*, 2021). Another study based on a review of world-wide data estimated there are 291,000-645,000 deaths yearly due to seasonal influenza (Iuliano *et al*, 2018). Another study using world-wide data estimated among children aged <5 years there are 109,500,000 cases of influenza per year of whom 870,000 develop acute LRI and 34,000 die (Wang *et al*, 2020).

In Vietnam, national surveillance has estimated the influenza-associated

hospitalization rate to be 218 per 100,000 population and among children aged <5 years the estimated number of hospitalizations due to influenza-associated severe acute respiratory infection is 1123 cases per 100,000 population (Nguyen *et al*, 2021). Based on internal data at the Center for Tropical Diseases, National Children's Hospital, by the end 2019, there were approximately 100 influenza cases diagnosed among children each week, several of which were hospitalized each week.

In this study we aimed to determine the clinical manifestations and complications among children in Vietnam with seasonal influenza in order to inform influenza complication prevention programs.

## MATERIALS AND METHODS

All patients aged <16 years diagnosed with influenza and admitted

to the Center for Tropical Diseases, Vietnam National Children's Hospital, Hanoi, Vietnam during June 2020-July 2021 were included in the study. This study was conducted retrospectively.

In each subject the following data were determined: age, gender, signs and symptoms, other clinical information. In each subject a nasopharyngeal or tracheal aspirate for real-time polymerase chain reaction test was performed to determine the presence, group and subtype of influenza. All patients were treated with oseltamivir following the guidelines of the National Children's Hospital. Influenza virus type A (H1N1, H3N2) and type B were examined to subtype level by real-time reverse transcriptase polymerase chain reaction (RT-PCR) using nasopharyngeal or tracheal aspirate. The assays were conducted at the National Institute of Hygiene and Epidemiology, Vietnam.

We used univariate analysis to assess individual risk factors for their association with bronchopneumonia and to evaluate the efficacy of oseltamivir based on the numbers of complications. We used the t-test to compare days of fever between those who initiated oseltamivir within  $\leq 48$  hours of fever onset with those who initiated it  $> 48$  hours after symptom onset. We used the Fisher's exact test to calculate p-values and crude odds ratios of each risk factor and to assess the efficacy of oseltamivir. The data were entered into the Statistical Package for the Social Sciences (SPSS), version 22.0 (SPSS

Statistics for Windows, IBM, Chicago, IL).

This study was approved by the Vietnam National Children's Hospital Ethics Committee (No. 1836/BVNTW-VNCSKTE).

## RESULTS

A total of 200 subjects were included in the study (187 influenza A, 13 influenza B), 55% male. The mean age of our study subjects was 27.1 months. About one quarter (26.5%) of subjects had received an influenza vaccine within the previous 12 months; the remaining 73.5% had either received the vaccine greater than 12 months previously, had never received the vaccine or the parents did not remember when the previous vaccine was given. Eighty-four percent of subjects had the H3N2 subtype of influenza and 9.5% had the H1N1 subtype of influenza (Table 1).

The most common symptoms among study subjects were: fever (100.0%) (53.5% of subjects had a temperature  $> 39^{\circ}\text{C}$ ), cough (85.5%), runny nose (62.5%), sore throat (58.5%) and diarrhea (35.0%) (Table 2). The most common complications among study subjects were febrile convulsions (45%), bronchopneumonia (41%) and respiratory failure (25.5%). Only 6.5% of the total subjects ( $n = 13$ ) had a central nervous system symptom (CNS) complication, consisting of cognitive changing (13/13), spasticity (6/13) and convulsions (4/13). The CNS symptoms had their onset 3-5 days after fever onset.

Table 1  
Selected characteristics by influenza subtype among study subjects

Characteristics	Total (N=200)	Influenza A (N=187)		Influenza B (N= 13)
		Subtype H3N2 (N=168)	Subtype H1N1 (N=19)	
Gender, <i>n</i> (%)				
Male	111 (55.5)	95 (47.5)	10 (5.0)	6 (3.0)
Female	89 (45.5)	73 (36.5)	9 (4.5)	7 (3.5)
Mean age in months	27	26	26	42
Influenza exposure, <i>n</i> (%)				
Family	25 (12.5)	17 (8.5)	6 (3.0)	2 (1.0)
Community	60 (30.0)	55 (27.5)	3 (1.5)	2 (1.0)
Unknown	115 (57.5)	96 (48.0)	10 (5.0)	9 (4.5)
Previous influenza vaccination, <i>n</i> (%)				
>1 year or never	147 (73.5)	125 (62.5)	15 (7.5)	7 (3.5)
<1 year	53 (26.5)	43 (21.5)	5 (2.0)	6 (3.0)
Comorbid health conditions, <i>n</i> (%)				
Yes	71 (35.5)	58 (29.0)	8 (4.0)	5 (2.5)
No	129 (64.5)	110 (55.0)	11 (5.5)	8 (4.0)

Table 1 (cont)

Characteristics	Total (N=200)	Influenza A (N=187)		Influenza B (N=13)
		Subtype H3N2 (N=168)	Subtype H1N1 (N=19)	
Complications, <i>n</i> (%)				
Febrile convulsion	90 (45.0)	87 (43.5)	1 (0.5)	2 (1.0)
Bronchopneumonia	82 (41.0)	70 (35.0)	11 (5.5)	1 (0.5)
Respiratory failure	51 (25.5)	42 (21.0)	8 (4.0)	1 (0.5)
Otitis media	23 (11.5)	19 (9.5)	4 (2.0)	0 (0)
Bronchitis	15 (7.5)	13 (6.5)	0 (0)	2 (1.0)
Laryngitis	11 (5.5)	9 (4.5)	1 (0.5)	1 (0.5)
Pleural effusion	1 (0.5)	1 (0.5)	0 (0)	0 (0)
Central nervous system	13 (6.5)	13 (6.5)	0 (0)	0 (0)

Table 2

Study subject symptoms by influenza subtype (N = 200)

Symptoms	Influenza A		Influenza B (N =13)
	Of 168 H3N2 <i>n</i> (%)	Of 19 H1N1 <i>n</i> (%)	
Fever	168 (100.0)	19 (100.0)	13 (100.0)
Cough	149 (88.7)	15 (78.9)	7 (53.8)
Runny nose	102 (60.7)	13 (68.4)	10 (76.9)
Sore throat	100 (59.5)	11 (57.9)	6 (46.2)
Painful swallowing	34 (20.2)	1 (5.3)	2 (15.4)
Diarrhea	59 (35.1)	10 (52.6)	1 (7.7)
Vomiting	31 (18.5)	1 (5.3)	0 (0.0)
Myalgia	15 (8.9)	1 (5.3)	3 (2.3)
Headache	16 (9.5)	1 (5.3)	3 (2.3)

Risk factors significantly associated with bronchopneumonia were: preterm birth (crude odds ratio) cOR =3.1; 95% confidence interval (CI): 0.9-6.7;  $p = 0.038$ ), subject age <24 months (cOR =5.5; 95% CI: 2.8-11.2;  $p < 0.00001$ ), having an underlying comorbid condition (cOR = 5.5; 95% CI: 2.2-8.3;  $p < 0.00001$ ) and having a co-infection with both a virus and a bacteria (cOR =32.4; 95% CI: 9.5-172.9;  $p < 0.00001$ ) (Table 3).

About one-fifth (20.5%) of subjects had a co-infection in addition to influenza, 13% had a co-infection with bacteria, 4.5% had a co-infection with another virus and 3% had a co-infection with bacteria and another virus. Co-infectious agents identified in our

study were: *Streptococcus pneumoniae* (6%), *Haemophilus influenzae* (5%), *Mycoplasma pneumoniae* (2%), respiratory syncytial virus (2.5%), adenovirus (1%) and rhinovirus (1%) (Table 4).

Study subjects who received oseltamivir within 48 hours of symptom onset had resolution of fever ( $3.5 \pm$  standard deviation (SD) 2.2 days) significantly ( $p < 0.05$ ) earlier than those who received oseltamivir after 48 hours of symptoms ( $5.1 \pm 3.1$  days). Onset of oseltamivir > 48 hours of symptom onset was associated with a significantly greater number of cases with CNS complications (cOR = 5.9; 95% CI: 1.4-34.6;  $p = 0.004$ ) (Table 5). There were

Table 3

Assessment of factors among study subjects with influenza significantly ( $p < 0.05$ ) associated with bronchopneumonia

Factors	Bronchopneumonia <i>n</i> (%)	OR (95% confidence interval)
Preterm birth (N = 23)	14 (60.9)	2.4 (0.9-6.7)
Not preterm (N = 177)	69 (38.9)	
Age <24 months (N = 110)	64 (58.2)	5.5 (2.8-11.2)
Age ≥24 months (N = 90)	18 (2.5)	
Comorbidity (N = 71)	45 (63.4)	5.5 (2.2-8.3)
No comorbidity (N = 129)	37 (28.7)	
Co-infection (N= 41)	38 (92.7)	32.4 (9.5-172.9)
Not co-infection (N = 159)	44 (22.7)	

Table 4

Co-infection pathogens among study subjects with influenza (N=41)

Co-infection pathogens	Influenza A <i>n</i> (%)	Influenza B <i>n</i> (%)
Viruses		
Respiratory Syncytial Virus	5 (2.5)	0 (0.0)
Adenovirus	2 (1.0)	0 (0.0)
Rhinovirus	2 (1.0)	0 (0.0)
Bacteria		
<i>Streptococcus pneumoniae</i>	12 (6.0)	0 (0.0)
<i>Haemophilus influenzae</i>	10 (5.0)	0 (0.0)
<i>Mycoplasma pneumoniae</i>	4 (2.0)	0 (0.0)
More than one type co-infection pathogen	6 (3.0)	0 (0.0)

Table 5  
Influenza complications among study subjects by time of onset of oseltamivir treatment (N = 200)

Type of complication	Number of cases with complication n (%)	Oseltamivir >48h (N=77) n (%)	Oseltamivir ≤48h (N=123) n (%)	cOR (95% CI)	p-value
Febrile convulsions	90 (45.0)	33 (16.5)	57 (28.5)	0.9 (0.5-1.6)	0.37
Bronchopneumonia	82 (41.0)	35 (17.5)	47 (23.5)	1.3 (0.7-2.5)	0.19
Respiratory failure	51 (25.5)	25 (12.5)	26 (13.0)	1.8 (0.9-3.6)	0.053
Otitis media	23 (11.5)	9 (4.5)	14 (7.0)	1.0 (0.4-2.7)	0.56
Bronchitis	15 (7.5)	4 (2.0)	11 (5.5)	0.6 (0.2-1.8)	0.24
Laryngitis	11 (5.5)	7 (3.5)	4 (2.0)	2.9 (0.7-14.2)	0.07
Pleural effusion	1 (0.5)	1 (0.5)	0 (0.0)	undefined	0.38
Central nervous system	13 (6.5)	10 (5.0)	3 (1.5)	5.9 (1.4-34.6)	0.004

CI: confidence interval; cOR: crude odds ratio

no other factors significantly associated with time to onset of oseltamivir

No deaths occurred in the study among study subjects.

## DISCUSSION

The majority of our subjects had H3N2 influenza followed by H1N1 influenza and influenza B; the etiological organisms in our study were similar to the findings from the World Health Organization Regional Office for the Western Pacific (WHO WPRO, 2021) but the WHO reported influenza B to be the most common influenza group but in our study influenza A was the most common influenza group. The reason for this difference needs further study.

In our study, the proportions of subjects by symptom were similar to those of other studies (Mancinelli *et al*, 2016; Danier *et al*, 2019). More than a third of our subjects had diarrhea. Diarrhea is a sign of serious complications in children infected with influenza (Minodier *et al*, 2015).

Thirteen of our subjects had CNS complications, but there is not enough data regarding these cases to determine if they had encephalitis. There are reports of influenza among adults and children causing encephalitis (Meijer *et al*, 2016; Britton *et al*, 2017). A previous study from Vietnam reported the case of a child with encephalitis in whom influenza virus A was detected in the cerebrospinal fluid (Le *et al*, 2010).

In summary, the most common clinical symptoms among study subjects were fever, cough, runny nose and sore throat. Complications were common and consisted of febrile convulsions, bronchopneumonia and respiratory failure and these were more common among younger subjects or subjects with an underlying condition or a secondary bacterial or viral infection. We conclude the complication rates in our study population were high and underline the importance of education about influenza vaccinations and good hygiene in this study population

## ACKNOWLEDGEMENTS

The authors would like to thank the study subjects and their families for their contribution in this study.

## CONFLICT OF INTEREST DISCLOSURE

The authors declare no conflict of interest.

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