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Epidemiological, clinical characteristics and the association between influenza vaccination, oseltamivir treatment, and complications in children with seasonal influenza

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Abstract:

Influenza, a historical and contemporary public health challenge, is an acute respiratory infection caused mainly by influenza A or B viruses. This descriptive case series describes 194 children treated for seasonal influenza at the Department of Pediatrics, 103 Military Hospital, Vietnam Military Medical University, from May 2022 to May 2023. Influenza primarily occurred during winter and early spring, peaking in December and January, 57.2% were aged 12-60 months, boys. Vaccination coverage was limited (36.3%), especially post-COVID-19. Complications were seen in 75.3% of the cases, including febrile seizures (42.3%), bronchopneumonia (40.2%), respiratory failure (8.2%), acute myocarditis, influenza-associated encephalopathy, and septic shock. The study reveals bacterial coinfections, affected 20% of the cases, mainly by *Streptococcus pneumoniae* and *S. aureus*, and atypical bacteria *Mycoplasma pneumoniae*. Non-vaccinated children faced significantly higher risks of complications, oseltamivir within 48 hours reducing the risks of complications. Influenza predominantly affects 12-60 month-olds, males, and peaks annually in winter. Severe conditions stem from bacterial coinfections, emphasizing the importance of vaccination and prompt antiviral treatment to mitigate complications. The study highlights a critical need for increased vaccination, especially in the post-COVID-19 era, to manage influenza in children effectively.

Keywords: **children, complications, influenza, vaccination.**

Classification number: **3.2**

1. Introduction

Influenza, a perennial public health challenge, has historically wielded substantial socio-economic repercussions, leaving an indelible mark on global mortality and morbidity rates. This viral infection, caused predominantly by influenza viruses type A or B (occasionally type C), contributes significantly to the landscape of acute infectious respiratory diseases, which collectively impose a noteworthy burden on public health worldwide [1]. The transmission of the influenza virus occurs via aerosol droplets during coughing, sneezing, or close contact with an infected individual, potentially leading to upper or lower respiratory tract infections and complications affecting various extra-pulmonary organs, such as acute encephalopathy, and myocarditis [2, 3].

Yearly global outbreaks, typically prevalent during the winter season in temperate climate regions, affect an estimated 32 million people, resulting in approximately 5 million hospitalizations due to influenza-induced acute respiratory tract infections (ARI) in adults [1]. Alarmingly, children under 5 years old bear a significant brunt, with approximately 110 million reported cases of influenza virus infection in 2018. In developing countries, where vaccination rates are constrained, these young children frequently experience acute respiratory tract inflammation, leading to elevated rates of hospital admissions and mortality [4]. In Vietnam, the under-5 age group exhibits the highest incidence rate of seasonal influenza, with a mortality rate of 0.3% associated with ARI or severe acute respiratory infections (SARI) [5].

The burgeoning incidence of ARI hospitalizations poses an escalating burden on both the healthcare system and economic society. Recognizing influenza vaccination as a crucial strategy for safeguarding children and the broader community, particularly in the wake of co-circulating pathogens like severe acute respiratory syndrome-

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coronavirus 2 (SARS-CoV-2), the American Academy of Pediatrics (AAP) and World Health Organization (WHO) recommend annual influenza vaccine injections for all children without medical contraindications, starting at 6 months of age. This targeted vaccination not only bolsters individual immunity but also collectively alleviates the overall burden of respiratory illnesses [1, 6, 7].

However, the emergence of the COVID-19 pandemic has ushered in a new era, marked by social distancing measures, reduced children's exposure to infections, and a notable decline in vaccination rates. This unprecedented shift has not only impacted the trajectory of respiratory virus spread but has also set the stage for a potential resurgence of seasonal influenza [8, 9]. Acknowledging the intricate interplay of these factors, we embarked on a comprehensive study titled "Epidemiological, clinical characteristics and the association between influenza vaccination, oseltamivir treatment and complications in children with seasonal influenza". This study aims to unravel the multifaceted implications of influenza in the post-COVID-19 landscape, offering critical insights for informed public health interventions and preparedness strategies.

2. Objects and method

2.1. Objects

Inclusion criteria: A total of 194 patients aged 1 month to 16 years exhibiting suspected seasonal influenza symptoms, such as high fever, cough, runny nose, sore throat, post-orbital pain, and muscle aches, were included. Patients tested positive for influenza antigen via rapid test or real-time RT-PCR from throat swab specimens, adhering to Ministry of Health guidelines, Vietnam. The study was conducted between December 2022 to May 2023 and took place at the Department of Pediatrics, 103 Military Hospital, Vietnam Military Medical University. Data collection encompassed epidemiological factors, clinical symptoms, selected indicators, chest X-rays, and treatment outcomes.

Exclusion criteria: Patients with underlying conditions (congenital heart disease, immunodeficiency, lung disorders, chromosomal abnormalities) or those with family members declining participation were excluded.

2.2. Methods

A descriptive case series study utilized a convenience sampling method.

2.3. Data processing

Statistical software: SPSS 26 and Microsoft Excel in a Medical Context facilitated data analysis. Results were presented as percentages, with continuous variables expressed as mean and standard deviation. P-values <0.05 were considered statistically significant. Univariate and multivariate regression models analyzed the relationship between complications, influenza vaccination, and oseltamivir treatment.

2.4. Research ethics

Researcher presentations ensured understanding of study content and objectives among children's families, emphasizing voluntary participation and the right to withdraw. Confidentiality of information was guaranteed for research purposes only, ensuring no negative impact on participating patients.

3. Results

3.1. Epidemiological characteristics

The prevalence of influenza was higher in male children than female children, accounting for 56.2%. The average age was 36.73±3.13 months, with the age group from 12 to 60 months representing 57.2%. Influenza A and B detection rates using rapid antigen testing and real-time RT-PCR with nasopharyngeal samples were 85.6 and 9.8%, respectively (Table 1).

Table 1. Epidemiological characteristics of the objects.

Epidemiological characteristics		Number of pediatric patients (n=194)	Percentage (%)
Sex	Male	109	56.2
	Female	85	43.8
Age	<12 months old	26	13.4
	Between 12-60 months old	111	57.2
	>5 years old	57	29.4
	X±SD	36.73±3.13	
	Min	1-month-old	
	Max	15 years old	
Classification	Influenza A	166	85.6
	Influenza B	19	9.8
	Influenza A and B	9	4.6

Influenza usually occurrs between winter and early spring. From April to October, the percentage of people suffering from influenza remains low, approximately under 5% (Fig. 1). The infection increased dramatically to 18.5% in November and reached its peak of 27% in December and January.

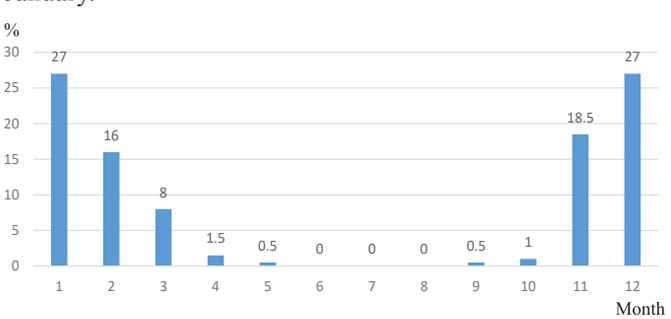

Fig. 1. Monthwise distribution of influenza.

The percentage of vaccinated children accounted for 36%, which is just a little more than half when compared to 64% of children who are either unvaccinated or have an unknown status (Fig. 2).

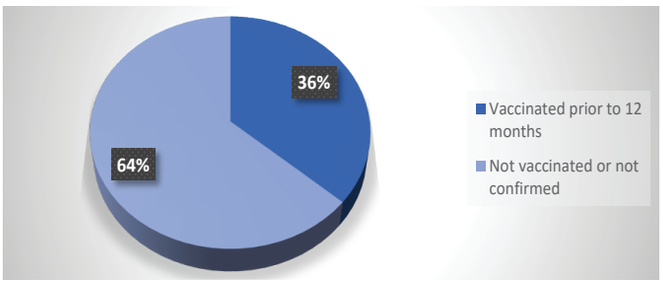

Fig. 2. The proportion of children received the influenza vaccination.

3.2. Clinical and laboratory manifestations

The average hospitalization duration was 3.78±2.13 days. All research patients presented with fever, with an average temperature of 38.79±0.67°C upon admission (Table 2). The average duration of fever was 4±1.43 days, with the longest recorded case lasting 9 days. The prevalence of sore throat, runny nose, and cough symptoms was 72.7 and 96.9%, respectively, while shortness of breath accounted for 4.1%. Muscle pain was reported in 37.6% of children, generalised rash in 6.2%, swollen and painful lymph nodes in the neck region in 4.1%, and gastrointestinal symptoms in 10.3%.

Table 2. Clinical characteristics of the objects.

Clinical symptoms		Number of pediatric patients (n=194)	Percentage (%)
Hospitalization duration (days)	x̄±SD	3.78±2.13	
	Min	1	
	Max	11	
Fever duration (days)	x̄±SD	4±1.43	
	Min	1	
	Max	9	
Temperature upon admission (°C)	x̄±SD	38.79±0.67	
	Min	38	
	Max	41	
Fever		194	100
Cough		188	96.9
Sore throat		141	72.7
Runny nose		141	72.7
Muscle pain		73	37.6
Shortness of breath		8	4.1
Swollen and painful lymph nodes in the neck region		8	4.1
Generalised rash		12	6.2
Gastrointestinal symptoms		20	10.3

The average number of WBC was 7.59±2.22 ($x10^3/mm^3$), with the highest recorded value being 16.6 ($x10^3/mm^3$) (Table 3). The average Hb and HCT levels were 118.83±14.14 g/l and 38.88±3.29%, respectively. The average PLT count was 218±111 ($x10^3/mm^3$), and the CRP level was 8.25±3.22 mg/l, with one case showing an elevated CRP level of 50 mg/l.

Table 3. Laboratory findings of the study population.

Indicator	x̄±SD	Min	Max
WBC ($x10^3/mm^3$)	7.59±2.22	3.14	16.6
Hb (g/l)	118.83±14.14	89	156
HCT (l/l)	38.88±3.29	30.9	46
PLT ($x10^3/mm^3$)	218±111	100	551
CRP (mg/l)	8.25±3.22	0.12	50

WBC: white blood cell count; PTL: platelet count; Hb: hemoglobin; HCT: hematocrit, CRP: C-reactive protein.

Bronchial wall thickening, consolidation, and interstitial infiltration frequently feature in children diagnosed with influenza. Among them, bronchial wall thickening was the most common occurrence, observed in approximately 32.98% of patients (Fig. 3). In contrast, the pleural effusion was rarely seen, with a percentage of around 2.06%.

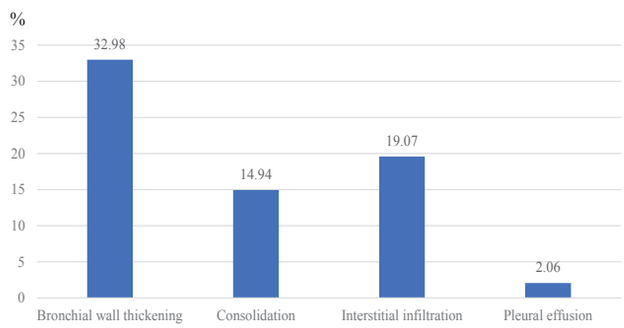

Fig. 3. Chest radiography findings in pediatric patients diagnosed with influenza viruses type A and B infection.

Gram-positive bacteria *S. pneumoniae* and *S. aureus* are observed in 30% of patients (58/194) and 23.71% (46/194), respectively (Fig. 4). While the rate of coinfection with atypical bacteria *Mycoplasma pneumoniae* was 19.07% (37/194).

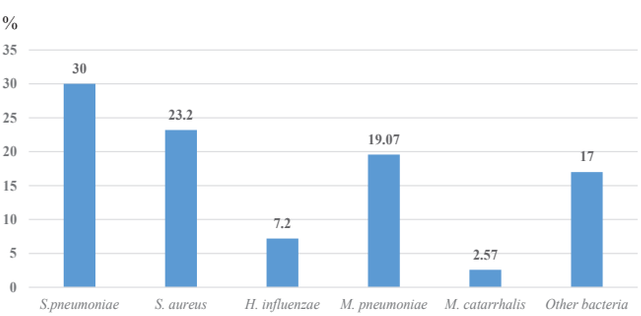

Fig. 4. Incidence of influenza and bacterial coinfections.

3.3. Association between influenza vaccination and Oseltamivir treatment with selected complications in patients with influenza

The number of cases with complications accounted for 146/194 (75.3%), with 82/194 (42.3%) patients experiencing febrile seizures, 78/194 (40.2%) cases of bronchopneumonia, 16/194 (8.2%) cases of respiratory failure, and 7/194 (3.6%) cases of acute otitis media (Table 4). In some cases, influenza-associated with acute myocarditis and encephalopathy 1/194 (0.52%) and septic shock 3/194 (1.55%). The incidence of acute diarrhea was 6/194 (3.1%), with no cases of influenza-associated neurological complications.

Table 4. Selected complications of the study population.

Influenza-related complications	Number of pediatric patients (n=194)	Percentage (%)
Febrile seizures	82	42.3
Bronchopneumonia	78	40.2
Acute otitis media	7	3.6
Diarrhea	6	3.1
Respiratory failure	16	8.2
Acute myocarditis	1	0.52
Septic shock	3	1.55
Influenza-associated encephalopathy	1	0.52
Presence of complications	146	75.3

The risk of experiencing febrile seizures, and bronchopneumonia, in the non-vaccinated group was significantly higher, with an odds ratio of 4.44 (95% CI: 2.4-8.18), 2.81 (95% CI: 1.55-5.1), respectively, compared to the group that received influenza vaccination (Table 5).

Table 5. Association between influenza vaccination and complications.

Complications	Vaccinated n (%)	Not vaccinated n (%)	p-value OR (95%CI)
Febrile seizures	25(30.5%)	57(69.5%)	<0.05 4.44 (2.4-8.18)
Bronchopneumonia	28(35.9%)	50(64.1%)	<0.05 2.81 (1.55-5.1)
Acute otitis media	4(57.1%)	3(49.2%)	>0.05
Diarrhea	2(33.3%)	4(66.7%)	>0.05

P value less than 0.05 indicates a statistical difference; OR: odds ratio CI: confidence interval.

The group without complications initiated Oseltamivir treatment was at an average of 1.22±0.56 days from admission (Table 6).

Table 6. Association between influenza complications and Oseltamivir treatment.

Use Oseltamivir	Complications		Without complications		p-value
	n	%	*n*	%	
Before 48 hours	108	71.5%	43	28.5%	<0.05
After 48 hours or untreated	38	88.4%	5	11.6%	
The number of days to starting Oseltamivir after disease onset	2.45±0.34		1.22±0.56		<0.05

4. Discussion

4.1. Epidemiological characteristics of the study population

Our study population had a mean age of 36.73±3.13 months, with ages ranging from 12 to 60 months accounting for 57.2% and males being more affected than females (56.2 and 43.8%, respectively). Most patients were infected with influenza virus type A (166/194, 85.6%). The vaccination rate for influenza immunisation within the past 12 months was 36.3%, while 63.4% of patients were either not vaccinated or had unclear vaccination status. Our study also yielded similar results to the study conducted by S.E. Coffin, et al. (2007) [10], on 745 pediatric patients over a 4-year period, which found a higher proportion of male cases (59% versus 41%), with the age group of 6 months to 5 years accounting for 52% of the cases. Furthermore, the prevalence of influenza virus type A was higher than that of type B (79% versus 21%). Similar findings were reported in the study by Y. Shi, et al. (2021) [11], which included a sample size of 36,047 children, where males accounted for 55% of the cases, and the mean age was 36±4.14 months. According to the study conducted by H.V. Pham, et al. (2021) [12] on 200 children, males accounted for 55.5% of the cases, with a mean age of 27 months. The prevalence of influenza type A was 93.5%, and the vaccination rate for influenza was 26.5% within the 12 months before illness. The number of flu patients tends to peak during the winter and spring, with the highest incidence in December and January. This phenomenon can be attributed to the lipoprotein structure of the flu virus, rendering the immune system weaker and more susceptible to infection in the absence of sunlight radiation. Consequently, the prevalence of flu is lower in warmer temperatures [13]. The vaccination rate for seasonal flu in the study population is 36.3%, significantly lower than the vaccination rates in the Regions of the Americas and Europe, which stand at 89%. This difference may be explained by variations in vaccination policies, economic capabilities, and vaccine distribution among high and upper-middle-income countries, and several low and middle-income countries (LMICs) [7]. Three regions Africa, the Middle East, and Southeast Asia-comprise 50% of the global population but receive only 6% of distributed seasonal influenza vaccine doses, leading to limited vaccine accessibility and hindering efforts to improve flu vaccination rates [14].

4.2. Clinical and laboratory characteristics of the objects

The average hospital stay for the patients was 3.78±2.13 days. The typical symptoms of influenza observed were fever (100%), with an average duration of 4±1.43 days, and an average temperature of 38.79±0.67 degrees Celsius upon admission. Other common symptoms included cough (96.9%), sore throat and runny nose (72.7%), dyspnea (4.1%), myalgia (37.6%), swollen lymph nodes under the jaw (4.1%), generalized rash (6.2%), and gastrointestinal symptoms (10.3%). These findings are consistent with the study conducted by H.V. Pham, et al.

(2021) [12], which reported fever in 100% of cases, cough in 85.5%, runny nose in 62.5%, and sore throat in 58.5%. Additionally, H. Silvennoinen, et al. (2009) [15] conducted a study involving 353 patients over 2 years and found that fever was present in 95% of cases, cough in 77%, runny nose in 78%, muscle aches in 7%, and gastrointestinal symptoms in 9%. These results are also consistent with our study.

The clinical laboratory values showed that the average white blood cell and platelet counts were 7.59±2.22 ($x10^3/mm^3$) and 218±111 ($x10^3/mm^3$), respectively. The highest recorded white blood cell count was 16.6 ($x10^3/mm^3$), while the lowest platelet count was 100 ($x10^3/mm^3$). Hemoglobin levels exhibited a downward trend, with an average of 118.83±14.14 g/l; the lowest recorded level was 89 g/l. The C-reactive protein level was also measured to be 8.25±3.22 mg/l, with the highest recorded level reaching 50 mg/l. Our results are consistent with Y. Shi, et al.'s (2021) [11] study on 36,047 children. The authors of that study found no significant differences in the levels of platelets and white blood cells. However, they observed decreased haemoglobin levels and increased C-reactive protein levels among children with severe influenza infection.

The study recorded the kind of damage to the lung on chest X-rays, such as bronchial wall thickening, consolidation, interstitial infiltration, and pleural effusion. The bronchial wall thickening is the most found, accounting for around 32.98% (64/194). However, pleural effusion is rare, with 3.1% (6/194). P. Rohani, et al. (2016) [16] conducted chest x-rays on patients diagnosed with influenza et al pneumonia and admitted to the ICU in the first 24 hours. The significant radiographic findings were ground-glass opacities (89%), consolidation (89%), reticular opacities (33%), peri broncho vascular in 61% patients, and multifocal patchy airspace opacities (56%). Chest radiographic changes in influenza pneumonia range from mild interstitial infiltration to poorly defined, patchy areas of consolidation, to extensive airspace disease due to hemorrhagic pulmonary edema. Pleural effusion is rare and usually represents bacterial coinfections.

In our study, gram-positive bacteria *S. pneumoniae* and *S. aureus* were observed in 30% of patients (58/194) and 23.71% (46/194), respectively. The rate of coinfection with atypical bacteria *Mycoplasma pneumoniae* was 19% (37/194), gram-negative bacteria *Haemophilus influenzae* and *Moraxella catarrhalis* were observed in 7.2% (14/194) and 2.5% (12/194), respectively. M. Qiao, et al. (2023) [17] conducted a systematic review of 39,762 influenza cases, 5578 of which had bacterial co-infection. The prevalence of influenza bacterial co-infection was 20.3%. Compared with influenza single-infection, bacterial co-infection increased the risk of death by 2.55-fold intensive care unit admission by 1.87-fold, and requirement for mechanical ventilation by 1.78-fold, approximately 23.8% of influenza deaths were attributable to bacterial co-infection. A systematic review and meta-analysis performed by E.Y Klein, et al. (2016) [18], including 3215 participants, indicated that coinfecting bacteria were *S. pneumoniae* and *S. aureus*, accounting for 35% and 28% of infections, respectively. Q.Y. Wang, et al. (2023) [19] retrospectively analyzed data for 64 pediatric patients with severe influenza virus-associated pneumonia, susceptible to bacterial infection, with gram-negative bacteria, especially *Haemophilus influenzae* and *Moraxella catarrhalis*, being the most common pathogens. In a systematic review and meta-analysis J.A. Herrero, et al. (2023) [20] studied 48,259 patients hospitalized with influenza of any age. Coinfecting bacteria were diagnosed in 11.2%. *S. pneumoniae* (30.7%) and *S. aureus* (30.4%) were the most frequent microorganisms, followed by *Haemophilus influenzae* (7.1%) and *Pseudomonas aeruginosa* (5.9%). Coinfecting bacteria increased death risk by 3.36-fold (95% CI: 2.56-4.41) compared with Influenza virus infection alone. The mechanisms by which bacteria act synergistically with influenza viruses include increased binding and invasion of bacteria, increased viral replication, and modification of the host inflammatory response. As the viral neuraminidase cleaves sialic acid to release new viral particles from host cells, damage to the epithelial layer of the airways occurs, exposing binding sites necessary for adherence to *S. pneumoniae* [21].

4.3. Relationship between influenza vaccination, Oseltamivir treatment, and certain complications in patients with influenza

The number of children with complications accounted for 146 out of 194 (75.3%) in our study. Among them, the most common complications were febrile seizures (42.3%) and bronchopneumonia (40.2%). Other less common complications included acute otitis media (3.6%), respiratory failure (4.1%), and acute diarrhoea (3.1%). Additionally, cases of acute myocarditis, influenza-associated encephalopathy, and septic shock were found, comprising 0.51% and 1.54%, respectively. A study by H.V. Pham, et al. (2021) [12] on 200 patients from 2020 to 2021 observed that febrile seizures and bronchopneumonia accounted for the highest proportions at 45% and 41%, respectively. However, respiratory failure and acute otitis media cases were higher, accounting for 25.5% and 11.5%, respectively. The complications in our patient group were lower compared to Y. Shi, et al.'s (2021) [11] study on 36,047 patients over 5 years from 2014 to 2019, which reported 118 severe influenza cases. The rates of complications such as bronchopneumonia, respiratory failure, and heart failure were 83.1, 84.7, and 12.7% of children experienced influenza-associated encephalopathy, 6.8% developed septic shock, and 15.3% experienced acute kidney injury. The differences observed may be attributed to our study's smaller sample size, geographical variations, and differences in immunization programs between countries. Influenza vaccination is an important strategy for protecting children and the broader community, as well as reducing the overall burden of respiratory illnesses when other viruses are cocirculating. The AAP recommends annual influenza vaccination of all children without medical contraindications starting at 6 months of age, children are at risk for hospitalization and death from influenza [22].

In our study, febrile seizures, bronchopneumonia, and respiratory failure were more prevalent in the group of children who were not vaccinated, with corresponding odds ratios of 4.44 (2.81 and 2.25), respectively. However, the two groups had no significant difference regarding complications such as diarrhea, acute otitis media, acute myocarditis, influenza-associated encephalopathy, and septic shock. A study by B. Flannery, et al. (2017) [23] conducted over 4 years from 2010 to 2014 on 358 deceased children aged 6 months to 17 years associated with seasonal influenza found that only 26% of children received influenza vaccination, which reduced the risk of death in the high-risk group of children with influenza. A study by J.M. Ferdinands, et al. (2014) [24] conducted in 21 pediatric intensive care units (PICUs) over 2 years from 2010 to 2012 found that full influenza vaccination reduced the risk of severe influenza complications by 75%. Oseltamivir has been shown to benefit adults with influenza, but its safety and efficacy are not as well demonstrated in children. Oseltamivir is an antiviral neuraminidase inhibitor with potent and selective competitive inhibition of the influenza virus neuraminidase, an enzyme necessary for viral replication. Oseltamivir interferes with the release of progeny influenza virus from infected host cells and thus halts the spread of infection to new host cells. Oral oseltamivir treatment reduces the duration by about 0.5 to 3 days and the severity of acute influenza and may decrease the incidence of secondary complications. In 2012, the United States Food and Drug Administration (FDA) approved oseltamivir for the treatment of influenza within 2 days of illness onset in children aged ≥14 days [25-27]. In our study, the group without complications initiated oseltamivir treatment at an average of 1.22±0.56 days from admission hospital. The group treated with Oseltamivir within 48 hours had a reduced risk of complications, compared to the group treated with Oseltamivir after 48 hours or left untreated. A study by R.J. Whitley, et al. (2001) [28] on 2 groups of patients treated with oseltamivir and a placebo group, randomized, double-blind, placebo-controlled study, it was found that the oseltamivir treatment group reduced fever duration by 36 hours (26%, $p<0.01$), symptoms of cough 32 hours (45%, $p<0.01$), the rate of complications and severity in the oseltamivir treatment group decreased by 40% and 29% compared with no treatment group. J. Qin, et al. (2022) [29] conducted an observational real-world study at Shanghai Children's Medical Center in 2018 showing that Oseltamivir treatment does not significantly shorten the duration of fever, nor does it significantly relieve influenza-like symptoms in children with infection of influenza. R.E. Malosh, et al. (2017) [27] conducted a systematic review to identify RCTs of oseltamivir therapy in children and showed that treatment with oseltamivir significantly reduced the duration of illness in those with influenza and lowered the risk of developing otitis media. However, children treated with oseltamivir had a higher frequency of emesis compared with those receiving placebo. P.S. Walsh, et al. (2022) [30] conducted a cohort study, a multicenter propensity score-weighted retrospective analysis of data for 55 799 children hospitalized with influenza between 2007 and 2020 revealed that early (hospital day 0 or 1) oseltamivir use was associated with shorter hospital stay and lower odds of 7-day readmission, transfer to the PICU, and in-hospital mortality or use of ECMO (extracorporeal membrane oxygenation). The AAP recommends antiviral treatment should be initiated as soon as possible and children with suspected or confirmed influenza who are hospitalized, have severe or progressive disease, or have underlying conditions that increase their risk of complications of influenza should be used, regardless of the duration of illness [22].

5. Conclusions

Influenza is predominantly observed in children aged 12 to 60 months, it happens more frequently in boys than in girls. The seasonal influenza vaccination rate was low, and the influenza patients easily cooperated with other bacteria like Gram-positive and atypical bacteria. Patients with influenza commonly present with fever, respiratory tract inflammation, gastrointestinal symptoms, varying degrees of mucocutaneous manifestations, and mostly normal laboratory parameters. Common complications included seizures, bronchiolitis, respiratory failure, and diarrhea. In contrast, the ratio of acute myocarditis and cases associated with nervous system problems dramatically decreased. Administration of seasonal influenza vaccine within 12 months and treatment with Oseltamivir within 48 hours of symptom onset in vaccinated children would likely reduce the duration of symptoms and the incidence of complications.

CRediT author statement

Manh Cuong Nguyen: Methodology, Formal analysis, Original draft preparation, Visualisation; Thi Thuy Hang Le: Supervision, Validation, Writing - Reviewing and Editing; Thanh Nam Do: Conceptualisation, Data curation, Investigation; Thai Son Pham: Supervision, Validation, Writing - Reviewing and Editing; Hoang Long Trinh: Investigation, Visualisation, Formal analysis; Thi Bich Thuy Phung: Supervision, Validation, Writing - Reviewing and Editing; Yen Thi Hoang: Investigation, Visualisation, Formal analysis; Quang Khai Tran: Methodology, Formal analysis, Original draft preparation, Visualisation.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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