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Influenza A/H3N2 and Its Co-infection with Other Respiratory Pathogens: Higher Pneumonia Rates and Prolonged Hospital Stays in Pediatric Patients

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Abstract

Background: In pediatric populations, influenza viruses such as influenza B, influenza A/H1N1, and influenza A/H3N2 present unique clinical challenges due to their distinct characteristics. Co-infections with other respiratory pathogens can lead to more severe disease progression in children, although the specific impacts of these co-infections are not yet fully understood.

Objectives: To explore the differences in clinical characteristics among children with single infections of influenza B, influenza A/H1N1, and influenza A/H3N2, and to assess the impact of co-infections with other respiratory pathogens on the severity of disease in children.

Methods: This retrospective study evaluated the severity of pediatric influenza hospitalizations during 2022 - 2023 by correlating virus types/subtypes with clinical outcomes, including pneumonia incidence, mechanical ventilation requirements, PICU admissions, and duration of hospital stay.

Results: The study included 1,380 pediatric patients with influenza: 343 with influenza A/H1N1, 678 with A/H3N2, and 359 with influenza B. In children aged six and older, influenza A/H3N2 infection resulted in higher pneumonia rates and longer hospital stays compared to influenza A/H1N1 and influenza B ($P < 0.05$). Laboratory result differences were also observed between single infections of influenza A and B in this age group. The co-infection rate for influenza A/H1N1 was 3.5%, significantly lower than that for H3N2 (11.9%) and influenza B (10.6%) ($P < 0.05$). Clinical differences were noted between single and co-infections of influenza A/H3N2 and B, with co-infections showing higher pneumonia rates and longer hospital stays compared to single infections ($P < 0.05$).

Conclusions: In children aged six and older, influenza A/H3N2 is associated with higher rates of pneumonia and longer hospital stays. Co-infections involving Influenza B or A/H3N2 with additional respiratory pathogens further increase the risk of pneumonia and extend the duration of hospitalization.

Keywords: Influenza A/H1N1, Influenza A/H3N2, Influenza B, Co-infection

1. Background

Children are significantly impacted by annual influenza epidemics, experiencing the highest attack rates among all age groups. Infants and young children are frequently hospitalized due to influenza-related illnesses, classifying them as a high-risk group (1, 2). Influenza viruses belong to the *Orthomyxoviridae* family and are enveloped viruses. Based on the antigenic differences of the nucleocapsid protein (NP) and matrix protein (MP) within the virus, they are classified into four types (3). Currently, the viruses causing seasonal influenza epidemics are the H1N1 and H3N2 subtypes of type A, and the Victoria and Yamagata lineages of type B. Although both influenza A and B viruses can lead to hospitalization and various complications in children, there are differences in disease severity and the age of the infected children. Children infected with influenza A are generally younger than those infected with influenza B (4). Additionally, the morbidity and mortality rates of influenza A are higher compared to influenza B (4).

Specifically, the clinical characteristics of influenza B infection in children and its comparisons with the influenza A subtypes H1N1 and H3N2 are topics of ongoing research. These influenza strains are associated with a variety of clinical presentations, and understanding these differences could potentially influence treatment strategies. However, the extent and nature of these differences, particularly in pediatric patients, remain largely unexplored. There have been reports suggesting that influenza virus co-infections with other respiratory pathogens (3, 5, 6) may add another layer of complexity. When considering the implications of co-infections in pediatric patients involving influenza B, influenza A/H1N1, and A/H3N2, these co-infections could potentially lead to more severe disease progression (6, 7). However, the specific dynamics of these co-infections and their impact on disease severity are not well-researched.

2. Objectives

This study aims to compare the clinical presentations in pediatric patients infected with influenza B versus influenza A subtypes H1N1 or H3N2 and to investigate whether co-infections with these strains and other respiratory pathogens worsen disease severity. By achieving these objectives, we hope to provide a more comprehensive understanding of these infections, potentially paving the way for improved treatment strategies.

3. Methods

3.1. Patient Selection

In a retrospective study conducted from 2022 to 2023, children aged 1 to 14 who were hospitalized with acute respiratory infections at the Maternal and Child Health Hospital of Hubei province were assessed. Disease severity across infection groups was evaluated based on predefined criteria such as pneumonia incidence, mechanical ventilation use, pediatric intensive care unit (PICU) admission rate, and duration of hospital stay. The analysis included demographic, epidemiological, diagnostic, and laboratory data.

3.2. Respiratory Pathogen Detection

All pathogen detection data were sourced from electronic medical records. Respiratory virus detection was performed using PCR, targeting influenza A/H1N1, H3N2, influenza B, human rhinovirus (HRV), respiratory syncytial virus (RSV), human parainfluenza virus (HPIV), human coronaviruses (HCoV), human adenovirus (HAdV), human metapneumovirus (hMPV), human bocavirus (HBoV), *Mycoplasma pneumoniae*, and *Chlamydia*. Microbial culture and identification were conducted within 24 hours of admission, following the hospital's standard diagnostic procedures.

3.3. Exclusion Criteria

The exclusion criteria for participants in the study were: (1) chronic pulmonary disease, aspiration pneumonia, or interstitial lung disease; (2) compromised immunity or the use of immunosuppressive drugs; (3) suspected hospital-acquired or fungal infections; (4) insufficient clinical information; and (5) confirmed cases of COVID-19 infection in children.

3.4. Statistical Analysis

Statistical analyses were performed using SPSS version 21.0. Frequency comparisons between groups were conducted using the chi-square or Fisher's exact test, while comparisons of mean values were performed using the independent sample *t*-test. A P-value of < 0.05 was considered statistically significant.

4. Results

4.1. Demographic Distribution by Influenza Virus Type and Subtype

A total of 1,380 pediatric patients with influenza virus infection were included in the study, consisting of 343 cases of Influenza A/H1N1, 678 cases of Influenza A/H3N2, and 359 cases of Influenza B. Among cases of single infections, the majority of children infected with Influenza A (H1N1 and H3N2) were aged 3 - 5 years, accounting for 49.5% and 48.5%, respectively. In contrast, Influenza B predominantly affected children aged 6 years and older, with a proportion of 43.9%. There were no significant differences in gender ratios across the groups (Table 1).

4.2. Comparative Clinical Characteristics of Single Infections: Influenza B vs. Influenza A/H1N1 and A /H3N2

In cases of mono-infection among children aged six and older, the incidence of pneumonia was significantly higher in those infected with Influenza A/H3N2 compared to Influenza A/H1N1 ($P = 0.007$) and Influenza B ($P = 0.013$). Additionally, the duration of hospitalization for A/H3N2 patients was longer than for those with the other two strains (H1N1: $P = 0.046$; B: $P =$

Table 1. Demographic Distribution by Influenza Virus Type and Subtype [a]

Demographics	Mono-infection				Co-infection			
	Influenza B (n = 321)	A/H1N1 (n = 331)	A/H3N2 (n = 597)	P-Value	Influenza B (n = 38)	A/H1N1 (n = 12)	A/H3N2 (n = 81)	P-Value
Age (y)				< 0.001				0.039
1 - 2	76 (23.7)	60 (18.1)	163 (27.3)		17 (44.7)	3 (25.0)	15 (18.5)	
3 - 5	104 (32.4)	164 (49.5)	290 (48.5)		8 (21.1)	5 (41.7)	33 (40.7)	
≥ 6	141 (43.9)	107 (32.3)	144 (24.1)		13 (34.2)	4 (33.3)	33 (40.7)	
Gender				0.340				0.371
Male	183 (57.0)	193 (58.3)	368 (61.6)		23 (60.5)	5 (41.7)	51 (63.0)	
Female	138 (43.0)	138 (41.7)	229 (38.4)		15 (39.5)	7 (58.3)	30 (37.0)	

[a] Values are expressed as No. (%).

0.044), as detailed in Table 2. Within the same age group, differences in laboratory results were observed between children with single infections of influenza A and B (Table 2). Children with influenza A/H1N1 exhibited a significantly higher proportion of lymphocytes compared to those with influenza A/H3N2 or influenza B, regardless of age ($P < 0.001$). Additionally, for children aged three and older, platelet counts were significantly higher in those with influenza A/H1N1 compared to those with influenza B ($P < 0.001$). The rate of antiviral drug usage among children infected with influenza A was significantly higher than that among children infected with influenza B across all age groups ($P < 0.001$).

4.3. Co-pathogens Detected in Influenza Virus Infections

The co-infection rate of Influenza A/H1N1 is 3.5%, which is significantly lower than the 11.9% for influenza A/H3N2 ($P < 0.001$) and 10.6% for influenza B ($P < 0.001$). In the 12 cases of co-infection with influenza A/H1N1, all co-infecting pathogens were viruses. In the 81 cases of Influenza A/H3N2 co-infections, 52 (64.2%) were co-infected with viruses, 4 (4.9%) with bacteria, 20 (24.7%) with *M. pneumoniae*, and 5 (6.2%) involved multiple co-infections (with three or more pathogens). Among the 38 cases of Influenza B co-infections, 29 (76.3%) were co-infected with viruses, 3 (7.9%) with bacteria, 3 (7.9%) with *M. pneumoniae*, and 3 (7.9%) involved multiple co-infections. Details of the co-infecting pathogens are provided in Table 3. The respiratory viruses that primarily co-infected with influenza include HRV, RSV, HPIV, HAdV, hMPV, HCoV, and HBoV. The co-infected bacteria were mainly *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*, with *S. pneumoniae* being the most common.

4.4. Comparative Clinical Characteristics: Single vs. Co-infections in Pediatric Patients with Influenza B, A/H1N1, and A/H3N2

There were significant differences in the clinical manifestations between the mono-infection and co-infection groups of influenza B and influenza A/H3N2. Patients with co-infections had a significantly higher incidence of pneumonia (B: $P = 0.003$; H3N2: $P < 0.001$) and longer hospital stays (B: $P = 0.005$; H3N2: $P = 0.023$) compared to those with mono-infections, as shown in Table 4. Additionally, individuals with co-infections of influenza A/H3N2 had a higher likelihood of being admitted to the PICU than those with mono-infections ($P = 0.024$).

5. Discussion

Existing literature presents differing opinions on the clinical characteristics and severity of influenza A and B, with some experts suggesting similarities, while others argue that certain strains may cause more severe illness with unique features (8-12). Our study revealed that children aged 6 and older infected with influenza A/H3N2 had a pneumonia rate of 41.7%, significantly higher than the rates for influenza A/H1N1 (25.2%) and influenza B (27.7%). Additionally, the average hospital stay for these children was 4.62 days, longer than the average stays for influenza A/H1N1 (4.27 days) and influenza B (4.23 days). For children aged one to five years, the differences in pneumonia incidence or hospital stay duration were insignificant among the three viruses, despite minor clinical and lab variations. The frequent antigenic drift in the Influenza A/H3N2 virus may account for its increased virulence compared to H1N1 and influenza B (13). Moreover, age is a critical factor when assessing influenza in children, as immune

Table 2. Comparative Clinical Characteristics of Single Infections: Influenza B vs. Influenza A/H1N1 and A /H3N2 [a]

Clinical Information	Influenza B (n = 76)	A/H1N1 (n = 60)	A/H3N2 (n = 163)	Influenza B (n = 104)	A/H1N1 (n = 164)	A/H3N2 (n = 290)	Influenza B (n = 141)	A/H1N1 (n = 107)	A/H3N2 (n = 144)
Age (y)	1 - 2			3 - 5			≥ 6		
Gender (male)	48 (63.2)	37 (61.7)	106 (65)	60 (57.7)	96 (58.5)	170 (58.6)	75 (53.2)	60 (56.1)	92 (63.9)
Fever	71 (93.4)	57 (95)	154 (94.5)	101 (97.1)	158 (96.3)	270 (93.1)	132 (93.6)	101 (94.4)	135 (93.8)
Cough	46 (60.5)	35 (58.3)	79 (48.5)	61 (58.7)	112 (68.3)	201 (69.3) [b]	96 (68.1)	69 (64.5)	102 (70.8)
Wheezing	3 (3.9)	2 (3.3)	3 (1.8)	4 (3.8)	1 (0.6)	12 (4.1)	0 (0)	0 (0)	1 (0.7)
Rales	17 (22.4)	14 (23.3)	42 (25.8)	19 (18.3)	26 (15.9)	57 (19.7)	13 (9.2)	9 (8.4)	27 (18.8) [b,c]
Pneumonia	29 (38.2)	24 (40.0)	55 (33.7)	39 (37.5)	73 (44.5)	121 (41.7)	39 (27.7)	27 (25.2)	60 (41.7) [b,c]
Bronchitis	16 (21.1)	11 (18.3)	34 (20.9)	26 (25.0)	48 (29.3)	72 (24.8)	59 (41.8)	35 (32.7)	45 (31.3)
Upper respiratory infection	31 (40.8)	25 (41.7)	74 (45.4)	39 (37.5)	43 (26.2)	97 (33.4)	43 (30.5)	45 (42.1)	39 (27.1)
Oxygen support	1 (1.3)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	0 (0)	0 (0)
Mechanical ventilation	0 (0)	0 (0)	0 (0)	1 (1.0)	1 (0.6)	0 (0)	1 (0.7)	0 (0)	0 (0)
PICU admission	1 (1.3)	1 (1.7)	1 (0.6)	0 (0)	2 (1.2)	2 (0.7)	1 (0.7)	0 (0)	0 (0)
Hospitalization length of stay (d)	4.79 ± 1.75	4.88 ± 1.94	4.46 ± 1.67	4.43 ± 1.42	4.86 ± 2.48	4.65 ± 1.50	4.23 ± 1.43	4.27 ± 1.23	4.62 ± 1.44 [b,c]
WBC, × 10 ^{9}/L	6.44 ± 3.40	5.66 ± 2.47	6.65 ± 2.88	6.00 ± 3.51	5.22 ± 2.20 [b]	6.73 ± 3.61	5.50 ± 3.03	5.18 ± 3.17	5.78 ± 2.75
Lymphocytes (%)	45.42 ± 21.40	59.19 ± 23.82 [b]	36.19 ± 21.03 [b,c]	36.21 ± 18.54	53.52 ± 20.41 [b]	35.42 ± 21.11 [c]	32.43 ± 17.03	44.97 ± 20.65 [b]	33.59 ± 20.94 [c]
PLT, × 10 ^{9}/L	210.24 ± 80.99	237.65 ± 102.92	242.39 ± 85.51 [b]	209.82 ± 68.64	252.18 ± 93.02 [b]	249.49 ± 97.69 [b]	201.72 ± 67.96	241.65 ± 79.32 [b]	228.52 ± 63.27 [b]
ALT, U/L	19.00 ± 11.05	20.09 ± 18.89	17.44 ± 8.46	16.63 ± 13.66	16.86 ± 20.68	13.86 ± 6.06 [b]	16.97 ± 17.50	22.21 ± 45.47	14.44 ± 67.6
AST, U/L	52.99 ± 21.72	48.24 ± 29.09	44.47 ± 12.86 [b]	46.11 ± 26.64	43.25 ± 22.28	38.21 ± 15.91 [b]	41.85 ± 31.69	41.29 ± 32.95	36.26 ± 19.34
CK-MB, U/L	34.07 ± 16.10	33.35 ± 28.17	32.06 ± 17.39	29.95 ± 17.47	31.03 ± 28.13	29.67 ± 20.51	26.27 ± 16.38	24.51 ± 20.29	24.33 ± 15.56
LDH, U/L	361.08 ± 73.03	327.60 ± 120.07	337.17 ± 83.99 [b]	310.35 ± 72.71	307.48 ± 117.70	307.76 ± 81.97	287.85 ± 79.95	270.62 ± 64.10	267.92 ± 58.02 [b]
Use of antiviral drugs	26 (34.2)	42 (70.0) [b]	106 (65.0) [b]	32 (30.8)	112 (68.3) [b]	165 (56.9) [b,c]	46 (32.6)	67 (62.6) [b]	92 (63.9) [b]

Abbreviation: PICU, pediatric intensive care unit.

[a] Values are expressed as No. (%) or mean ± SD.

[b] $P < 0.05$, compared with influenza B.

[c] $P < 0.05$, compared with influenza A/H1N1.

responses and their intensity can vary significantly with age.

A comprehensive examination of laboratory outcomes for children infected with influenza A and B revealed notable differences in lymphocyte and platelet counts across all age groups. Children with influenza A/H1N1 had significantly higher lymphocyte levels than those with influenza A/H3N2 or B. Additionally, in children aged 3 and older, those with influenza A/H1N1 exhibited higher platelet counts than those with influenza B. Similar findings have been reported in other studies (8). This observation underscores that infections caused by influenza A and B exhibit discernible differences across various facets, including pathogenic mechanisms, the magnitude of the host's immune response, and the degree of organ damage inflicted (14, 15). While co-infections involving influenza viruses and other respiratory pathogens are frequently reported, detailed analyses comparing co-infection rates across various influenza virus types and subtypes remain uncommon.

Influenza A/H1N1 has a co-infection rate of 3.5%, significantly lower than the 11.9% for influenza A/H3N2 and 10.6% for influenza B, highlighting notable differences in co-infection rates among these influenza types. Studies have shown that infections and immune responses caused by influenza viruses can alter the composition and function of respiratory microbiota. These changes, in turn, may modify the immune response to subsequent secondary pathogen infections or alter the dynamics of microbial interactions, thereby enhancing or inhibiting the proliferation of other

Table 3. Co-pathogens Detected in Influenza Virus Infections

Influenza B (n = 38)				A/H1N1 (n = 12)	A/H3N2 (n = 81)			
With Virus (n = 29)	With Bacteria (n = 3)	With *M. pneumoniae* (n = 3)	With More Than Two Pathogens (n = 3)	With Virus (n = 12)	With Virus (n = 52)	With Bacteria (n = 4)	With *M. pneumoniae* (n = 20)	With More Than Two Pathogens (n = 5)
HRV	*S. pneumoniae*		RSV + HAdV	HRV	HRV	*S. pneumoniae*		HAdV + *M. pneumoniae*
RSV	*P. aeruginosa*		RSV + HRV	RSV	RSV	*H. influenzae*		HPIV + *M. pneumoniae*
HAdV			*M. Pneumoniae* + HAdV	HAdV	HAdV			HPIV+HRV
HPIV				HPIV	HPIV			*M. Pneumoniae* + *S. pneumoniae*
hMPV					hMPV			
HCoV					HBoV			

Abbreviations: HRV, human rhinovirus; RSV, respiratory syncytial virus; HPIV, human parainfluenza virus; HCoV, human coronaviruses; HAdV, human adenovirus; hMPV, human metapneumovirus; HBoV, human bocavirus; *M. pneumonia*, *Mycoplasma pneumonia*; *S. pneumoniae*, *Streptococcus pneumoniae*; *H. influenzae*, *Haemophilus influenzae*; *P. aeruginosa*, *Pseudomonas aeruginosa*.

Table 4. Comparative Clinical Characteristics: Single vs. Co-infections in Pediatric Patients with Influenza B, A/H1N1, and A/H3N2 [a]

Clinical Information	Influenza B; Mono-infection (n = 321	Co-infection (n = 38	A/H1N1; Mono-infection (n = 331	Co-infection (n = 12	A/H3N2; Mono-infection (n = 597)	Co-infection (n = 81)
Clinical presentation						
Fever	304 (94.7)	36 (94.7)	316 (95.5)	12 (100)	559 (93.6)	78 (96.3)
Cough	203 (63.2)	31 (81.6) [b]	216 (65.3)	6 (50.0)	382 (64.0)	63 (77.8) [b]
Wheezing	7 (2.2)	3 (7.9)	3 (0.9)	0 (0)	16 (2.7)	4 (4.9)
Rales	49 (15.3)	11 (28.9) [b]	49 (14.8)	1 (8.3)	126 (21.1)	25 (30.9) [b]
Diagnosis						
Pneumonia	107 (33.3)	22 (57.9) [b]	124 (37.5)	4 (33.3)	236 (39.5)	54 (66.7) [b]
Bronchitis	101 (31.5)	7 (18.4)	94 (28.4)	2 (16.7)	151 (25.3)	15 (18.5)
Upper respiratory infection	113 (35.2)	9 (23.7)	113 (34.1)	6 (50.0)	210 (35.2)	12 (14.8) [b]
Treatment						
Oxygen support	1 (0.3)	0 (0)	0 (0)	0 (0)	2 (0.3)	2 (2.5)
Mechanical ventilation	2 (0.6)	0 (0)	1 (0.3)	0 (0)	0 (0)	1 (1.2)
PICU admission	2 (0.6)	1 (2.6)	3 (0.9)	0 (0)	3 (0.5)	3 (3.7) [b]
Hospitalization length of stay (d)	4.43 ± 1.52	5.16 ± 1.37 [b]	4.67 ± 2.06	4.75 ± 1.60	4.59 ± 1.53	5.14 ± 2.05 [b]
Use of antiviral drugs	104 (32.4)	14 (36.8)	221 (66.8)	11 (91.7)	363 (60.8)	52 (64.2)

Abbreviation: PICU, pediatric intensive care unit.

[a] Values are expressed as No. (%) or mean ± SD.

[b] $P < 0.05$.

potential pathogenic microorganisms (5, 16). This may explain the variation in co-infection rates among different types of influenza viruses. Other respiratory viruses remain the most common co-pathogens with all three influenza viruses. Among the co-pathogens of influenza A/H1N1, A/H3N2, and influenza B, the proportions of viral co-infections are 100%, 64.2%, and 76.3%, respectively. This observation aligns with previous studies that have documented the co-circulation and co-infection dynamics of influenza viruses with other respiratory viruses (17, 18). Additionally, the risk of co-infection increases when the epidemic periods of different pathogens overlap. In our study, the simultaneous outbreaks of Influenza A/H3N2 and *M. pneumoniae* may explain the elevated co-infection rate of 24.7%.

The impact of co-infection on illness severity or outcomes is still being debated (7, 19). We found that children infected with influenza B or influenza A/H3N2 who were co-infected with other respiratory pathogens

exhibited differences in clinical manifestations, pneumonia incidence, and hospital stay duration compared to those with single infections. Importantly, the findings reveal that *M. pneumoniae* is a common co-pathogen in influenza A/H3N2 cases, occurring in 24.7% of instances. This supports previous reports suggesting that *M. pneumoniae* may contribute to greater disease severity and poorer clinical outcomes in cases of influenza pneumonia (20). Consequently, we speculate that co-infection with other respiratory pathogens may exacerbate the condition in children infected with these two viruses. In contrast, no such differences were observed in the case of single and co-infections with influenza A/H1N1, consistent with previous reports (14).

The findings of this retrospective analysis should be interpreted with caution due to several limitations. Firstly, this study is based on data from a single center, which may limit the generalizability of the results to a broader population. Additionally, the relatively small number of co-infection cases involving influenza A/H1N1 could introduce bias in the statistical outcomes, so the conclusions drawn from these findings should be approached with careful consideration. Moreover, the significant prevalence of antibiotic use prior to admission in more than half of the children is a factor that could potentially affect the rates of co-infections, particularly bacterial co-infections. Further research involving larger, more diverse cohorts would be beneficial to provide deeper insights and enhance understanding of these complex interactions.

5.1. Conclusions

Our study highlights the influence of different influenza virus types/subtypes on the clinical manifestations, pneumonia incidence, and hospitalization duration in pediatric infections. In children aged six and older, influenza A/H3N2 infections are associated with a higher rate of pneumonia and longer hospital stays. Co-infections with other respiratory pathogens worsen the condition of patients with influenza B or A/H3N2.

Footnotes

Authors' Contribution: R. Y. S. and H. B. H.: Conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; Y. C.: Performed the study and analyzed the data.

Conflict of Interests Statement: The authors declared no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after its publication. The data are not publicly available due to privacy and confidentiality concerns.

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