Original Article

Clinical features and outcomes of influenza by virus type/subtype/lineage in pediatric patients

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Background: Recently, four influenza viruses are circulating worldwide: A(H1N1)pdm09, A(H3N2), B/Victoria, and B/Yamagata. However, information on the clinical differences among pediatric patients infected with four recently circulating influenza viruses is sparse.

Methods: Medical records of pediatric patients (<20 years of age) diagnosed with influenza between the 2014–2015 and 2018–2019 influenza seasons were retrospectively reviewed. Clinical features were compared between (I) patients infected with influenza A (FluA) and influenza B (FluB) viruses, (II) patients infected with FluA when A(H1N1)pdm09 and A(H3N2) circulated dominantly, and (III) patients infected with FluB when B/Victoria and B/Yamagata circulated dominantly.

Results: A total of 1,588 patients infected with FluA and 964 patients infected with FluB were included in this study. Patients infected with FluB were older (P<0.001) and more likely to report sore throat (P=0.002) than those infected with FluA. Otherwise, there were no significant differences in the clinical symptoms, diagnoses, and outcomes between patients infected with FluA and FluB. Overall, clinical features of influenza patients were similar regardless of the dominantly circulated subtype and lineage of the virus. In children aged ≤2 years, patients infected with FluB were more like to experience lower respiratory tract infection (P=0.034) and hospitalization (P=0.001) than those infected with FluA.

Conclusions: There were no significant clinical differences among pediatric patients infected with four recently circulating influenza viruses, except that FluB infection tended to be more severe than FluA infection in children aged ≤2 years.

Keywords: Influenza; influenza A virus; influenza B virus; children

Submitted Jul 16, 2020. Accepted for publication Nov 30, 2020.
doi: 10.21037/tp-20-196
View this article at: http://dx.doi.org/10.21037/tp-20-196

Introduction

Among influenza A, B, C, and D viruses, influenza A and B viruses cause seasonal influenza in humans (1). The differences in epidemiological and clinical features and outcomes by influenza virus type, subtype, and lineage can influence strategies for influenza vaccination and treatment. Children, especially those younger than 5 years of age, have higher rates of hospitalization and mortality than adults (2,3), and school-age children are reported to drive the spread of influenza in the community during influenza epidemics (4). Therefore, information on clinical and epidemiological characteristics of pediatric patients with influenza should be investigated for the appropriate control and prevention of influenza in the general population as well as in school settings. Previous studies have shown similar symptoms, signs, and severity between patients infected

with influenza A and B viruses; however, inconsistent results were found according to the type and subtype of circulating influenza viruses, characteristics of the included patients (e.g., age, hospitalized state, the presence of chronic underlying diseases), diagnostic methods for influenza, and antiviral therapy (5). Following the 2009 pandemic caused by influenza A(H1N1)pdm09 virus, A(H1N1)pdm09 and A(H3N2) have been the dominant influenza A virus circulating worldwide (1). The epidemiological and clinical features of influenza A virus infection have likely changed in the several years since A(H1N1)pdm09 became a seasonal influenza strain. For influenza B viruses, two lineages (Victoria and Yamagata lineages) have been circulating worldwide since the 1980s (6). Although B/Yamagata and B/Victoria lineages have caused seasonal epidemics alternately or concurrently since the 2000s (6), there are only a few reports on the clinical differences between pediatric patients infected with B/Yamagata and B/Victoria (7,8). In one study, children infected with B/Victoria were significantly older than those infected with B/Yamagata (7). Children infected with B/Yamagata experienced more frequent lower respiratory tract infection (LRI) than those infected with B/Victoria, whereas, the duration of hospitalization was significantly longer in children infected with B/Victoria than in those infected with B/Yamagata (7). However, the enrolled children of the previous study were not vaccinated against influenza at all, and the study was performed in the early 2000s. Considering that trivalent influenza vaccines, which have been administered for several decades, include antigens from both A(H1N1)pdm09 and A(H3N2), but only one of B/Yamagata and B/Victoria, the difference in vaccine-acquired immunity against influenza A and B viruses may cause some differences in epidemiological and clinical features between influenza A and B virus infections and between B/Yamagata and B/Victoria infections.

In this study, clinical features and outcomes of pediatric patients diagnosed with influenza between the 2014–2015 and 2018–2019 influenza seasons were investigated, and were compared according to influenza virus type, subtype, and lineage. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/tp-20-196).

Methods

Subject and data collection

Pediatric patients (<20 years of age) in whom influenza was diagnosed at the Daejeon St. Mary's Hospital (Daejeon, Korea) during the 2014–2015 and 2018–2019 influenza seasons were included in this study, and their medical records were retrospectively reviewed. Influenza was diagnosed using a commercial rapid influenza detection test (RIDT) kit (Alere BinaxNOW® Influenza A & B Card, Abbott, IL, USA). Patients who were positive for both influenza A and B viruses were excluded. Patients in whom a follow-up RIDT was repeated within 2 weeks after the diagnosis of influenza were also excluded. Patients who developed influenza-like illness symptoms ≥48 hours after admission or <48 hours after a previous discharge from the hospital were excluded because of the possibility of hospital-acquired infection. For the included patients, demographic data including sex and age, and clinical data including clinical diagnosis, presenting symptoms, chronic underlying diseases, antiviral therapy, and outcomes were collected. Because there were no deaths attributable to influenza during the study period, outcomes were evaluated based on the rates of hospitalization, oxygen supplementation, and mechanical ventilator care. In addition, the development of acute otitis media (AOM) and sinusitis was investigated based on the medical records up to 4 weeks after the diagnosis of influenza. The diagnosis of AOM and sinusitis was made by the clinician's decision based on physical examination and patient's symptoms. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Review Board of the Daejeon St. Mary's Hospital with a waiver of acquiring informed consent (approval number: DC19RISI0102).

Definition

The influenza season was defined from October through May. The included patients were divided into influenza A and B groups based on their RIDT results. The dominantly circulated subtype of influenza A virus and lineage of influenza B virus were defined based on the results of the annual influenza surveillance of the Korea Disease Control and Prevention Agency (KDCA, Table S1). For influenza A virus, the 2014–2015, 2016–2017, and 2017–2018 seasons were categorized as the A(H3N2) season and the 2015–2016 season was categorized as the A(H1N1)pdm09 season; the 2018–2019 season when the dominantly circulated type comprised less than 80% of influenza A virus infection cases was not categorized. For influenza B virus, the 2014–2015 and 2017–2018 seasons were categorized as the B/Yamagata season and the 2015–2016 and 2018–2019

seasons were categorized as the B/Victoria season; the 2016–2017 season when the exact occupying ratios of B/Yamagata and B/Victoria lineages were not reported was not categorized. Patients who were hospitalized due to influenza-related problems on or within 1 week after the diagnosis of influenza were categorized as the hospitalized group, and the remaining patients were categorized as the non-hospitalized patients. Age groups were divided into 0–2 years (half-dose of trivalent influenza vaccine), 3–6 years (pre-school children), 7–12 years (pre-puberty), and ≥13 years (puberty) with consideration of vaccination effects and biological and social factors. Clinical diagnoses consisted with upper respiratory tract infection (URI), LRI, fever without a focus, and acute gastroenteritis (AGE). URI included rhinitis, pharyngitis, tonsillitis, and croup, and LRI included bronchiolitis, bronchitis, and pneumonia. Among the LRI, suspicious bacterial pneumonia was defined when abnormal breath sounds were heard on auscultation and lobar or segmental consolidations were shown on the chest X-ray. Fever without a focus was defined when there was no abnormality on physical examination in febrile patients without localized symptoms. AGE was defined when gastrointestinal symptoms developed without any respiratory symptoms. If gastrointestinal and respiratory manifestations occurred concurrently, clinical diagnosis was decided based on the respiratory manifestations. Antiviral therapy was defined when 10 or more body weight-adjusted doses of oral oseltamivir or one or more body weight-adjusted doses of intravenous peramivir were administered.

Statistical analysis

The collected demographic and clinical data were compared between the influenza A and B groups and between the hospitalized and non-hospitalized groups. The collected data were also compared between the A(H3N2) and A(H1N1)pdm09 seasons of the influenza A group and between the B/Victoria and B/Yamagata seasons of the influenza B group. In each age group, the collected data were also compared between the influenza A and B groups, between the A(H3N2) and A(H1N1)pdm09 seasons of the influenza A group, and between the B/Yamagata and B/Victoria seasons of the influenza B group. SPSS 21 (IBM Corp., Armonk, NY, USA) was used for statistical analyses. For each comparison between patient groups, continuous and categorical data were compared using Mann-Whitney and Fisher's exact tests, respectively. Statistical significance was defined as a two-sided $P<0.05$.

Results

During the study period, RIDTs were performed in 7,807 pediatric patients, and 110 (1.4%) of them were consistent with the exclusion criteria (*Figure 1*). Of the remaining 7,697 patients, 2,634 (34.2%) were positive for influenza viruses. Excluding 79 (3.0%) patients who were positive for both of influenza A and B viruses and three (0.1%) patients whose medical records were incomplete, 2,552 (96.9%) patients were eventually included in this study (*Figure 1*).

Comparison of clinical features and outcomes by influenza virus type, subtype, and lineage

Of the included 2,552 patients, 1,588 (62.2%) and 964 (37.8%) were included in the influenza A and B groups, respectively (*Table 1*). Patients in the influenza B group were older ($P<0.001$) and complained of sore throat more frequently ($P=0.002$) than those in the influenza A group. Antiviral therapy was performed in 79.5% (n=2,028) of the whole study population, and LRI and suspicious bacterial pneumonia were diagnosed in 11.6% (n=295) and 0.3% (n=7) of them, respectively. Clinical diagnoses and outcomes were comparable between the patients in the influenza A and B groups (*Table 1*).

For the influenza A group excluding 298 patients of the 2018–2019 season, patients in the A(H1N1)pdm09 season were younger ($P=0.003$) and diagnosed with LRI more frequently ($P=0.020$) than those in the A(H3N2) season (*Table 1*). Patients in the A(H3N2) season were more likely to experience myalgia ($P=0.006$) and seizures ($P=0.035$) than those in the A(H1N1)pdm09 season; however, the differences were only 4.1% and 2.6%, respectively. Between the two influenza A seasons, there were no differences in clinical outcomes (*Table 1*).

For the influenza B group excluding 46 patients of the 2016–2017 season, patients in the B/Victoria season tended to be younger than those in the B/Yamagata season but without statistical significance (*Table 1*). There were no differences in clinical features and outcomes between the two seasons except that more patients in the B/Yamagata season complained of myalgia ($P=0.017$) than those in the B/Victoria season (*Table 1*).

Comparison between the non-hospitalized and hospitalized groups

A total of 571 (22.4%) patients were included in the hospitalized group: 492 (19.3%) patients were hospitalized

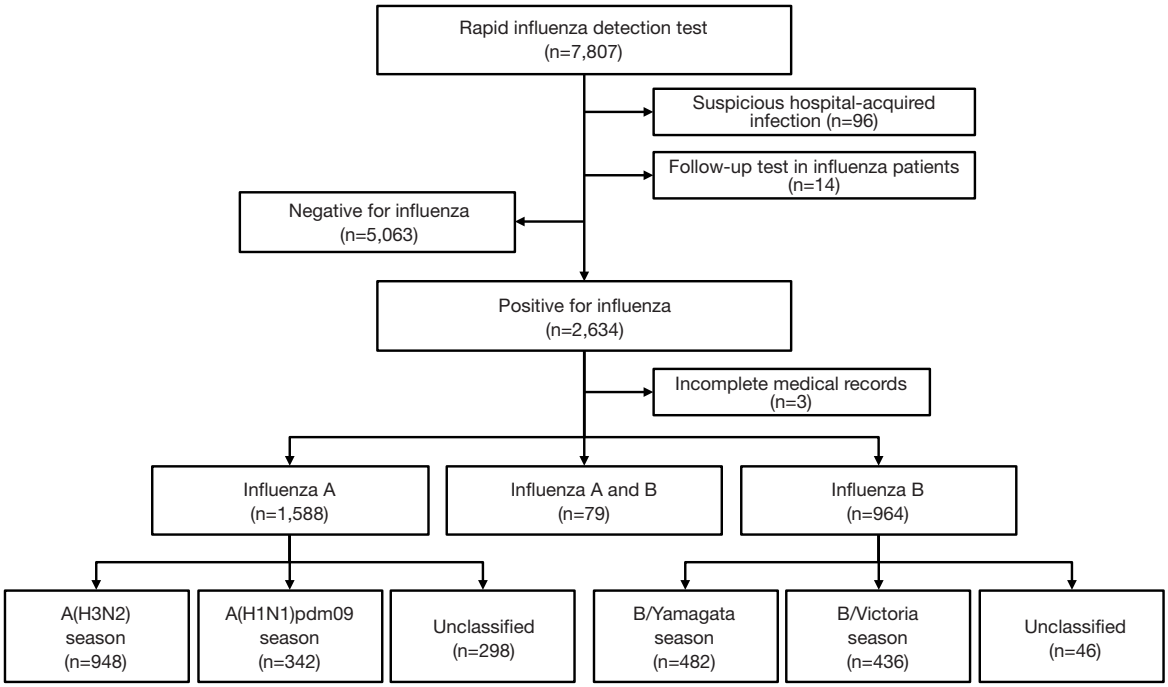

Figure 1 The flowchart for the inclusion and classification of the subjects.

on the day of influenza diagnosis, and 79 (3.1%) patients were hospitalized during follow-up visits after influenza diagnosis. Hospitalized patients were younger (P<0.001) and diagnosed with LRI more frequently (P<0.001) than non-hospitalized patients (*Table 2*). All of the investigated respiratory symptoms except for sore throat occurred more frequently in hospitalized patients than in non-hospitalized patients (*Table 2*).

For the hospitalized patients, the age distribution between the influenza A and B groups was similar (*Table 2*). Sputum (P=0.004) and abdominal pain (P=0.034) were reported more frequently in the influenza B group than in the influenza A group; however, clinical diagnoses and outcomes were comparable between the influenza A and B groups of the hospitalized patients (*Table 2*).

For the non-hospitalized patients, patients in the influenza B group were older (P<0.001) and reported sore throat more frequently (P=0.004) than those in the influenza A group: identical to the results for all included patients (*Table 2*).

Comparisons of clinical features and outcomes in each age group

The clinical features and outcomes by the type/subtype/lineage of influenza virus were compared in each age group because the age distribution was significantly different between the influenza A and B groups (*Table 3*). In patients aged 0–2 years, the frequencies of rhinorrhea (P=0.042), sputum (P=0.011), LRI (P=0.034), and hospitalization (P=0.001) were higher in the influenza B group than in the influenza A group (*Table 3*). In patients aged 3–6 years, there were no significant differences in clinical diagnoses and outcomes between the influenza A and B groups although sore throat was reported more frequently in the influenza B group than in the influenza A group (P=0.003). Although no significant differences in demographic and clinical features were identified between the influenza A and B groups in patients aged 7–12 years, LRI was diagnosed more frequently in the influenza B group than in the influenza A group in patients aged 13–19 years (P=0.009) without significant differences in clinical symptoms and outcomes. There were marginal differences in clinical features between the A(H3N2) and A(H1N1)pdm09 seasons and between the B/Yamagata and B/Victoria seasons in each age group (Tables S2-S5).

Discussion

In this study, clinical features of pediatric patients diagnosed with influenza during the five influenza seasons were investigated. Clinical features and outcomes showed no

Table 1 Comparison of clinical features and outcomes by influenza virus type/subtype/lineage

Factor	Influenza A group (n=1,588), n (%)				Influenza B group (n=964), n (%)				P†
	Total	A(H3N2) season (n=948)	A(H1N1)pdm09 season (n=342)	P‡	Total	B/Yamagata season (n=482)	B/Victoria season (n=436)	P§	
Male sex	856 (53.9)	506 (53.4)	182 (53.2)	1.000	518 (53.7)	266 (55.2)	225 (51.6)	0.289	0.935
Age group				0.018				0.284	<0.001
0–2 years	430 (27.1)	250 (26.4)	113 (33.0)		186 (19.3)	84 (17.4)	86 (19.7)		
3–6 years	549 (34.6)	332 (35.0)	128 (37.4)		385 (39.9)	190 (39.4)	185 (42.4)		
7–12 years	413 (26.0)	248 (26.2)	69 (20.2)		288 (29.9)	149 (30.9)	126 (28.9)		
≥13 years	196 (12.3)	118 (12.4)	32 (9.4)		105 (10.9)	59 (12.2)	39 (8.9)		
Underlying disease	39 (2.5)	22 (2.3)	7 (2.0)	1.000	19 (2.0)	7 (1.5)	12 (2.8)	0.245	0.494
Clinical diagnoses				0.020				0.115	0.107
Upper respiratory tract infection	1,396 (87.9)	848 (89.5)	291 (85.1)		825 (85.6)	418 (86.7)	378 (86.7)		
Lower respiratory tract infection	167 (10.5)	83 (8.8)	48 (14.0)		128 (13.3)	55 (11.4)	56 (12.8)		
Fever without a focus	16 (1.0)	12 (1.3)	1 (0.3)		5 (0.5)	3 (0.6)	2 (0.5)		
Acute gastroenteritis	9 (0.6)	5 (0.5)	2 (0.6)		6 (0.6)	6 (1.2)	0 (0.0)		
Clinical symptoms									
Fever	1,582 (99.6)	946 (99.8)	342 (100.0)	1.000	959 (99.5)	479 (99.4)	435 (99.8)	0.626	0.757
Respiratory symptoms, any	1,472 (92.7)	872 (92.0)	322 (94.2)	0.229	911 (94.5)	453 (94.0)	414 (95.0)	0.566	0.084
Cough	1,322 (83.2)	779 (82.2)	290 (84.8)	0.315	816 (84.6)	407 (84.4)	370 (84.9)	0.927	0.376
Rhinorrhea	1,043 (65.7)	627 (66.1)	211 (61.7)	0.146	653 (67.7)	331 (68.7)	293 (67.2)	0.671	0.299
Sputum	686 (43.2)	398 (42.0)	154 (45.0)	0.339	419 (43.5)	212 (44.0)	182 (41.7)	0.505	0.902
Sore throat	270 (17.0)	156 (16.5)	49 (14.3)	0.389	212 (22.0)	115 (23.9)	91 (20.9)	0.303	0.002
Dyspnea	21 (1.3)	11 (1.2)	4 (1.2)	1.000	5 (0.5)	3 (0.6)	2 (0.5)	1.000	0.066
Gastrointestinal symptoms, any	301 (19.0)	171 (18.0)	69 (20.2)	0.418	179 (18.6)	90 (18.7)	83 (19.0)	0.933	0.835
Vomiting	191 (12.0)	108 (11.4)	47 (13.7)	0.246	97 (10.1)	52 (10.8)	41 (9.4)	0.512	0.138
Abdominal pain	121 (7.6)	63 (6.6)	28 (8.2)	0.327	90 (9.3)	46 (9.5)	41 (9.4)	1.000	0.138
Diarrhea	59 (3.7)	30 (3.2)	13 (3.8)	0.599	38 (3.9)	21 (4.4)	16 (3.7)	0.619	0.831
Headache	171 (10.8)	99 (10.4)	30 (8.8)	0.402	111 (11.5)	64 (13.3)	45 (10.3)	0.184	0.559
Myalgia	107 (6.7)	69 (7.3)	11 (3.2)	0.006	70 (7.3)	46 (9.5)	23 (5.3)	0.017	0.630
Seizure activity	63 (4.0)	44 (4.6)	7 (2.0)	0.035	24 (2.5)	12 (2.5)	11 (2.5)	1.000	0.055
Antiviral therapy	1,251 (78.8)	722 (76.2)	297 (86.8)	<0.001	777 (80.6)	393 (81.5)	347 (79.6)	0.504	0.289
Outcomes									
Hospitalization	349 (22.0)	219 (23.1)	71 (20.8)	0.406	222 (23.0)	99 (20.5)	103 (23.6)	0.265	0.557
Oxygen therapy	5 (0.3)	2 (0.2)	2 (0.6)	0.287	0 (0.0)	0 (0.0)	0 (0.0)	NA	0.164
Mechanical ventilation	1 (0.1)	0 (0.0)	1 (0.3)	0.265	0 (0.0)	0 (0.0)	0 (0.0)	NA	1.000
Acute otitis media	25 (1.6)	12 (1.3)	8 (2.3)	0.200	15 (1.6)	7 (1.5)	7 (1.6)	1.000	1.000
Sinusitis	8 (0.5)	5 (0.5)	2 (0.6)	1.000	6 (0.6)	3 (0.6)	2 (0.5)	1.000	0.784

†, comparison between the influenza A and B groups; ‡, comparison between the A(H3N2) and A(H1N1)pdm09 seasons; §, comparison between the B/Yamagata and B/Victoria seasons; NA, not applicable.

Table 2 Comparison of clinical features and outcomes between the non-hospitalized and hospitalized groups

Factor	Non-hospitalized group (n=1,981), n (%)				Hospitalized group (n=571), n (%)				P†
	Total	Influenza A group (n=1,239)	Influenza B group (n=742)	P‡	Total	Influenza A group (n=349)	Influenza B group (n=222)	P‡	
Male sex	1,053 (53.2)	663 (53.5)	390 (52.6)	0.71	321 (56.2)	193 (55.3)	128 (57.7)	0.604	0.199
Age group				<0.001				0.999	<0.001
0–2 years	412 (20.8)	305 (24.6)	107 (14.4)		204 (35.7)	125 (35.8)	79 (35.6)		
3–6 years	743 (37.5)	432 (34.9)	311 (41.9)		191 (33.5)	117 (33.5)	74 (33.3)		
7–12 years	565 (28.5)	330 (26.6)	235 (31.7)		136 (23.8)	83 (23.8)	53 (23.9)		
≥13 years	261 (13.2)	172 (13.9)	89 (12.0)		40 (7.0)	24 (6.9)	16 (7.2)		
Underlying disease	39 (2.0)	27 (2.2)	12 (1.6)	0.41	19 (3.3)	12 (3.4)	7 (3.2)	1.000	0.078
Clinical diagnoses				0.227				0.529	<0.001
Upper respiratory tract infection	1,794 (90.6)	1,131 (91.3)	663 (89.4)		427 (74.8)	265 (75.9)	162 (73.0)		
Lower respiratory tract infection	156 (7.9)	87 (7.0)	69 (9.3)		139 (24.3)	80 (22.9)	59 (26.6)		
Fever without a focus	19 (1.0)	14 (1.1)	5 (0.7)		2 (0.4)	2 (0.6)	0 (0.0)		
Acute gastroenteritis	12 (0.6)	7 (0.6)	5 (0.7)		3 (0.5)	2 (0.6)	1 (0.5)		
Clinical symptoms									
Fever	1,973 (99.6)	1,234 (99.6)	739 (99.6)	1.000	568 (99.5)	348 (99.7)	220 (99.1)	0.563	0.718
Respiratory symptoms, any	1,837 (92.7)	1,140 (92.0)	697 (93.9)	0.128	546 (95.6)	332 (95.1)	214 (96.4)	0.535	0.013
Cough	1,624 (82.0)	1,012 (81.7)	612 (82.5)	0.673	514 (90.0)	310 (88.8)	204 (91.9)	0.255	<0.001
Rhinorrhea	1,232 (62.2)	766 (61.8)	466 (62.8)	0.667	464 (81.3)	277 (79.4)	187 (84.2)	0.154	<0.001
Sputum	725 (36.6)	470 (37.9)	255 (34.4)	0.112	380 (66.5)	216 (61.9)	164 (73.9)	0.004	<0.001
Sore throat	416 (21.0)	235 (19.0)	181 (24.4)	0.004	66 (11.6)	35 (10.0)	31 (14.0)	0.179	<0.001
Dyspnea	14 (0.7)	12 (1.0)	2 (0.3)	0.096	12 (2.1)	9 (2.6)	3 (1.4)	0.384	0.007
Gastrointestinal symptoms, any	333 (16.8)	212 (17.1)	121 (16.3)	0.664	147 (25.7)	89 (25.5)	58 (26.1)	0.922	<0.001
Vomiting	201 (10.1)	132 (10.7)	69 (9.3)	0.357	87 (15.2)	59 (16.9)	28 (12.6)	0.189	0.001
Abdominal pain	152 (7.7)	93 (7.5)	59 (8.0)	0.728	59 (10.3)	28 (8.0)	31 (14.0)	0.034	0.047
Diarrhea	52 (2.6)	31 (2.5)	21 (2.8)	0.665	45 (7.9)	28 (8.0)	17 (7.7)	1.000	<0.001
Headache	228 (11.5)	140 (11.3)	88 (11.9)	0.716	54 (9.5)	31 (8.9)	23 (10.4)	0.561	0.174
Myalgia	138 (7.0)	87 (7.0)	51 (6.9)	0.928	39 (6.8)	20 (5.7)	19 (8.6)	0.233	1.000
Seizure activity	49 (2.5)	37 (3.0)	12 (1.6)	0.072	38 (6.7)	26 (7.4)	12 (5.4)	0.392	<0.001
Antiviral therapy	1,565 (79.0)	977 (78.9)	588 (79.2)	0.864	463 (81.1)	274 (78.5)	189 (85.1)	0.049	0.29
Outcomes									
Oxygen therapy	0 (0.0)	0 (0.0)	0 (0.0)	NA	5 (0.9)	5 (1.4)	0 (0.0)	0.162	0.001
Mechanical ventilation	0 (0.0)	0 (0.0)	0 (0.0)	NA	1 (0.2)	1 (0.3)	0 (0.0)	1.000	0.224
Acute otitis media	22 (1.1)	15 (1.2)	7 (0.9)	0.663	18 (3.2)	10 (2.9)	8 (3.6)	0.631	0.002
Sinusitis	9 (0.5)	5 (0.4)	4 (0.5)	0.735	5 (0.9)	3 (0.9)	2 (0.9)	1.000	0.214

†, comparison between the hospitalized and non-hospitalized groups; ‡, comparison between the influenza A and B groups. NA, not applicable.

Table 3 Comparison of clinical features and outcomes between the influenza A and B groups in each age group

Factor	0–2 years			3–6 years			7–12 years			13–19 years		
	Influenza A group (n=430)	Influenza B group (n=186)	P	Influenza A group (n=549)	Influenza B group (n=385)	P	Influenza A group (n=413)	Influenza B group (n=288)	P	Influenza A group (n=196)	Influenza B group (n=105)	P
Male sex	235 (54.7)	111 (59.7)	0.252	309 (56.3)	214 (55.6)	0.841	223 (54.0)	147 (51.0)	0.443	89 (45.4)	46 (43.8)	0.809
Underlying disease	5 (1.2)	1 (0.5)	0.674	13 (2.4)	6 (1.6)	0.484	10 (2.4)	8 (2.8)	0.811	11 (5.6)	4 (3.8)	0.588
Clinical diagnoses			0.034			0.620			0.654			0.009
Upper respiratory tract infection	345 (80.2)	136 (73.1)		478 (87.1)	334 (86.8)		381 (92.3)	260 (90.3)		192 (98.0)	95 (90.5)	
Lower respiratory tract infection	77 (17.9)	48 (25.8)		61 (11.1)	47 (12.2)		26 (6.3)	25 (8.7)		3 (1.5)	8 (7.6)	
Fever without a focus	8 (1.9)	1 (0.5)		5 (0.9)	3 (0.8)		2 (0.5)	1 (0.3)		1 (0.5)	0 (0.0)	
Acute gastroenteritis	0 (0.0)	1 (0.5)		5 (0.9)	1 (0.3)		4 (1.0)	2 (0.7)		0 (0.0)	2 (1.9)	
Clinical symptoms												
Fever	429 (99.8)	185 (99.5)	0.513	549 (100.0)	384 (99.7)	0.412	412 (99.8)	287 (99.7)	1.000	192 (98.0)	103 (98.1)	1.000
Respiratory symptoms, any	392 (91.2)	176 (94.6)	0.189	500 (91.1)	363 (94.3)	0.079	391 (94.7)	271 (94.1)	0.741	189 (96.4)	101 (96.2)	1.000
Cough	351 (81.6)	155 (83.3)	0.648	457 (83.2)	330 (85.7)	0.317	349 (84.5)	243 (84.4)	1.000	165 (84.2)	88 (83.8)	1.000
Rhinorrhea	329 (76.5)	156 (83.9)	0.042	365 (66.5)	258 (67.0)	0.888	242 (58.6)	171 (59.4)	0.876	107 (54.6)	68 (64.8)	0.111
Sputum	184 (42.8)	101 (54.3)	0.011	253 (46.1)	156 (40.5)	0.094	162 (39.2)	112 (38.9)	0.937	87 (44.4)	50 (47.6)	0.628
Sore throat	14(3.3)	5 (2.7)	0.805	55 (10.0)	65 (16.9)	0.003	114 (27.6)	88 (30.6)	0.398	87 (44.4)	54 (51.4)	0.276
Dyspnea	11 (2.6)	1 (0.5)	0.119	3 (0.5)	3 (0.8)	0.695	3 (0.7)	1 (0.3)	0.648	4 (2.0)	0 (0.0)	0.302
Gastrointestinal symptoms, any	77 (17.9)	32 (17.2)	0.909	120 (21.9)	79 (20.5)	0.685	74 (17.9)	49 (17.0)	0.840	30 (15.3)	19 (18.1)	0.623
Vomiting	51 (11.9)	17 (9.1)	0.401	72 (13.1)	41 (10.6)	0.264	50 (12.1)	30 (10.4)	0.547	18 (9.2)	9 (8.6)	1.000
Abdominal pain	11 (2.6)	6 (3.2)	0.603	64 (11.7)	52 (13.5)	0.421	34 (8.2)	22 (7.6)	0.888	12 (6.1)	10 (9.5)	0.353
Diarrhea	27 (6.3)	13 (7.0)	0.725	19 (3.5)	11 (2.9)	0.708	7 (1.7)	9 (3.1)	0.304	6 (3.1)	5 (4.8)	0.524
Headache	5 (1.2)	1 (0.5)	0.674	29 (5.3)	23 (6.0)	0.666	82 (19.9)	54 (18.8)	0.771	55 (28.1)	33 (31.4)	0.595
Myalgia	0 (0.0)	1 (0.5)	0.302	24 (4.4)	14 (3.6)	0.618	28 (6.8)	26 (9.0)	0.314	55 (28.1)	29 (27.6)	1.000
Seizure activity	29 (6.7)	12 (6.5)	1.000	27 (4.9)	9 (2.3)	0.056	7 (1.7)	2 (0.7)	0.321	0 (0.0)	1 (1.0)	0.349
Antiviral therapy	344 (80.0)	153 (82.3)	0.579	447 (81.4)	317 (82.3)	0.731	308 (74.6)	226 (78.5)	0.243	152 (77.6)	81 (77.1)	1.000
Outcomes												
Hospitalization	125 (29.1)	79 (42.5)	0.001	117 (21.3)	74 (19.2)	0.459	83 (20.1)	53 (18.4)	0.628	24 (12.2)	16 (15.2)	0.480
Oxygen therapy	1 (0.2)	0 (0.0)	1.000	1 (0.2)	0 (0.0)	1.000	1 (0.2)	0 (0.0)	1.000	2 (1.0)	0 (0.0)	0.544
Mechanical ventilation	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	1 (0.5)	0 (0.0)	1.000
Acute otitis media	18 (4.2)	8 (4.3)	1.000	7 (1.3)	6 (1.6)	0.780	0 (0.0)	1 (0.3)	0.411	0 (0.0)	0 (0.0)	NA
Sinusitis	2 (0.5)	1 (0.5)	1.000	2 (0.4)	2 (0.5)	1.000	2 (0.5)	0 (0.0)	0.515	2 (1.0)	3 (2.9)	0.347

NA, not applicable.

clinically significant differences according to influenza virus type, subtype, and lineage. However, influenza B virus infection seemed to be more severe than influenza A virus infection in children aged ≤2 years.

The hospitalization rate in this study was 22.4%, which was higher than some previously reported rates of 0.5–3.7% (9-12), but lower than those of other reported rates of 33–57% (12,13). Considering no deaths due to influenza, lower rates of secondary bacterial infections, such as AOM (1.6% *vs.* 5.6–22.3%), sinusitis (0.5% *vs.* 2.4–5.9%), and suspicious bacterial pneumonia (0.3% *vs.* 0.4–6.3%), and the lower oxygen supplementation rate (0.2% *vs.* 0.8%) in this study than previously reported rates (10-17), the high hospitalization rate was likely not caused by a truly high severity of influenza in our hospital but by a low medical cost and high access to health care in Korea that was arisen from the National Health Insurance system. The hospitalized patients in this study were younger than the non-hospitalized patients, which was consistent with the increased hospitalization rate due to influenza in children aged <5 years (2). Resultantly, the age distribution between the influenza A and B groups of the hospitalized patients was similar, although the age of the influenza A group was younger than that of the influenza B group in the whole study population. Furthermore, respiratory and gastrointestinal symptoms and LRI were more common in the hospitalized patients than in the non-hospitalized patients. Therefore, hospitalized patient-oriented research for the clinical features of influenza may overestimate the symptoms and severity of influenza, although clinical diagnoses and outcomes were similar in the influenza A and B groups of the hospitalized patients in this study.

Previous studies reported inconsistent but comparable clinical features and outcomes between patients infected with influenza A and B viruses, except for the age distribution (5,10-16,18). The age difference between patients infected with influenza A and B viruses was not same in adults and children. Adult patients infected with influenza A virus were older than those infected with influenza B virus, while, similar to our results, pediatric patients infected with influenza A were younger than those infected with influenza B virus (12,16,18,19). Because there were no clinically significant differences except for age by the type/subtype/lineage of influenza virus in this study, clinical features and outcomes by the type/subtype/lineage of influenza virus were compared in each age group, showing a few differences in clinical features by the type/subtype/lineage of influenza virus. In children aged ≤2 years, the influenza B group exhibited higher rates of LRI and hospitalization than the influenza A group. The severity of influenza was higher in patients infected with A(H3N2) than in those infected with seasonal influenza A(H1N1) and B viruses in a study performed before the 2009 pandemic (2), which might represent insufficiently accumulated herd immunity against A(H3N2) in the three decades after the introduction of A(H3N2) in 1968 (20). Recent studies performed after the 2009 pandemic showed no significant differences in severity between A(H1N1)pdm09 and other type/subtype/lineage of influenza viruses (5,8,10,11,21,22). Similarly, in this study, we did not identify a higher severity of A(H1N1)pdm09 infection than other influenza virus infections, although only about 10 years have passed since the 2009 pandemic. The relatively high vaccination rate against influenza in Korean children (about 50%), especially in those aged <5 years (about 80%), through the 2010s may contribute to maintaining sufficient herd immunity against A(H1N1)pdm09 and reducing the severity of A(H1N1)pdm09 infection (23). The combination of a high vaccination rate and high rate (79.5%) of antiviral therapy in this study might further decrease the severity of influenza A virus infection. Because quadrivalent influenza vaccines for children aged ≤2 years were approved in Korea in 2018, almost none of the patients aged ≤2 years included in this study have been exposed to both of the lineages of influenza B virus by vaccination and natural infection. Lower levels of protective immunity against influenza B virus compared with influenza A virus might cause the different frequencies of LRI and hospitalization between influenza A and B groups in children aged ≤2 years of age. Expanded use of quadrivalent influenza vaccines in infants and young children could affect the clinical features and severity of influenza B virus infection in the future. LRI was also diagnosed more frequently in the influenza B group than in the influenza A group in patients aged 13–19 years. However, clinical outcomes including hospitalization rate were not significantly different between the influenza A and B groups, and the frequency of LRI in this age group was lower than that in other age groups. There has been no report that compared clinical features of influenza A and B virus infection exclusively in adolescents. This should be further explored. Although A(H3N2) did not cause more severe infection than A(H1N1)pdm09, recently, A(H3N2) has circulated dominantly during more influenza seasons than A(H1N1)pdm09. Efforts for improving the immunogenicity against A(H3N2) in influenza vaccines should be conducted along with the use of quadrivalent

influenza vaccines.

This study had some limitations. The retrospective nature of this study made it impossible to determine the exact time of symptom onset and termination and influenza vaccination rates for the included patients, and to avoid selection bias. The low rates of AOM and sinusitis might be due to the lack of unified diagnostic criteria for AOM and sinusitis applied in this study, and therefore, some cases with AOM and sinusitis might be missed. However, the low rates could represent truly low rates of secondary bacterial complications in patients receiving antiviral therapy at a high rate. Because the subtype and lineage of the influenza viruses were determined based on the surveillance data of the KDCA rather than individualized tests in each patient, clinical features of each influenza season might be complicated by the other type or lineage of virus. To overcome this limitation, only the influenza seasons when the dominantly circulated subtype or lineage occupied ≥80% of the identified influenza type were included in the analysis. However, regional differences in the distribution of subtype and lineage of circulated influenza virus might be present even in the same country. Therefore, each hospital should collect its own data on epidemiological and clinical characteristics of influenza patients based on the regional and national epidemiological changes in influenza virus infection. The application of a polymerase chain reaction (PCR) test with a higher sensitivity compared to an RIDT may affect clinical features or outcomes of influenza. However, the PCR test tends to detect a lower viral load compared with RIDT, and therefore, influenza patients with milder symptoms can be more easily identified with the use of a PCR test. Although other co-infected respiratory pathogens might modify clinical features and outcomes of influenza, a multiplex PCR test identifying multiple respiratory pathogens simultaneously was not applied in most of the included patients. A prospective study adjusted for above-mentioned limitations should be adequate for determining clinical features and outcomes of influenza caused by recently circulating viruses.

Conclusions

There were no clinically significant differences by the type/subtype/lineage among patients infected with four recently circulating influenza viruses. In children aged ≤2 years, influenza B virus infection seemed to be more severe than influenza A virus infection. Considering the recent approval of quadrivalent influenza vaccines for children aged between 6 and 36 months and their expected expanded use in infants and young children, repeat studies on the clinical differences of influenza by the virus type/subtype/lineage in each age group should be planned.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at http://dx.doi.org/10.21037/tp-20-196

Data Sharing Statement: Available at http://dx.doi.org/10.21037/tp-20-196

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tp-20-196). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and the Harmonized Tripartite Guideline for Good Clinical Practice from the International Conference on Harmonization. This study was reviewed and approved by the Institutional Review Board of the Daejeon St. Mary's Hospital with a waiver of acquiring informed consent (approval number: DC19RISI0102).

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Cite this article as: Han SB, Rhim JW, Kang JH, Lee KY. Clinical features and outcomes of influenza by virus type/subtype/lineage in pediatric patients. Transl Pediatr 2021;10(1):54-63. doi: 10.21037/tp-20-196