Comparative Severity of Influenza A and B Infections in Hospitalized Children

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Background: Influenza A viruses are conventionally thought to cause more severe illnesses than B viruses, but few studies with long observation periods have compared the clinical severity of A and B infections in hospitalized children.

Methods: We analyzed the clinical presentation, outcomes and management of all children <16 years of age admitted to Turku University Hospital, Finland, with virologically confirmed influenza A or B infection during the 14-year period of 1 July 2004 to 30 June 2018. All comparisons between influenza A and B were performed both within predefined age groups (0–2, 3–9 and 10–15 years) and in all age groups combined.

Results: Among 391 children hospitalized with influenza A or B infection, influenza A was diagnosed in 279 (71.4%) and influenza B in 112 (28.6%) children. Overall, there were no significant differences in any clinical features or outcomes, management, treatment at intensive care unit or length of stay between children with influenza A and B, whether analyzed by age group or among all children. As indicators of the most severe clinical presentations, blood cultures were obtained from 101 (36.2%) children with influenza A and 39 (34.8%) with influenza B ($P = 0.80$), and lumbar puncture was performed to 16 (5.7%) children with influenza A and 11 (9.8%) children with influenza B ($P = 0.15$).

Conclusions: The clinical severity of influenza A and B infections is similar in children. For optimal protection against severe influenza illnesses, the use of quadrivalent vaccines containing both lineages of B viruses seems warranted in children.

Key words: influenza A, influenza B, clinical severity, hospitalization, influenza vaccines

Influenza viruses are known to place a great burden of illness on children.[1–5] The annual rates of influenza are consistently highest in the youngest children who are also frequently hospitalized for influenza-associated illnesses.[6–8] The population-based rates of hospitalization are highest among infants less than 6 months of age, in which age group influenza often presents as a sepsis-like illness that usually results in empirical antibiotic treatment.[8,9]

Although both influenza A and B viruses predispose children to hospitalization and a wide range of complications, type A viruses are conventionally thought to cause more severe illnesses than B viruses. This may be partly because of the higher incidence of influenza A infections during annual outbreaks and the capability of A viruses to cause pandemics. However, when comparing the severity of influenza A and B infections in children, all outcomes should be adjusted for age because children with influenza A are generally younger than those with influenza B, and the clinical presentation of the illness varies between different age groups.[10]

The recent availability of quadrivalent influenza vaccines that contain both circulating lineages of influenza B viruses has increased interest in the clinical importance of type B viruses.[11–14] Previous studies comparing the clinical features of influenza A and B infections in both outpatient and hospitalized children have indicated that the clinical manifestations are largely similar across the types of influenza viruses.[15–22] However, many of those studies have included only 1 influenza season or relatively small sample sizes. To inform the optimal use of different types of influenza vaccines in children, more comparative data on the clinical severity of influenza A and B infections are needed. As hospitalized children represent the most severe forms of influenza, studies with long observation periods among hospitalized children represent the most adequate setting for determination of the relative severity of influenza A and B viruses. We sought to compare the clinical presentation, outcomes and management of children hospitalized with virologically confirmed influenza A and B infections during a period of 14 consecutive years.

MATERIALS AND METHODS

Study Design and Subjects

This retrospective study was conducted at the Department of Pediatrics, Turku University Hospital, Finland. Turku University Hospital is the only tertiary-care hospital in Southwestern Finland and the sole provider of acute pediatric hospital care for children. The study population consisted of all children <16 years of age who were admitted to the hospital with virologically confirmed influenza A or B infection during the 14-year period of 1 July 2004 to 30 June 2018. Viral sampling for the identification of respiratory viruses was routine for children hospitalized with respiratory symptoms during the study.

Sources of Data

To identify all children who were hospitalized with virologically confirmed influenza, we searched for data from 4 different sources: 1) the database at the Department of Virology, University of Turku, 2) the central database of Turku University Hospital, 3) the files of the pediatric infectious diseases ward and 4) the database at the pediatric intensive care unit. The medical records of all children with an International Classification of Diseases (ICD) code related to influenza (ICD, 10th revision: J10-J11) who were not found from the virologic databases were carefully examined to confirm or rule out the viral diagnosis of influenza.

Of 404 children who were hospitalized with confirmed influenza during the study period, we excluded 5 children in whom influenza A and B viruses were detected simultaneously, 1 with an unclear influenza type and 7 with nosocomial influenza infection. All data on the clinical presentation, outcomes, management

and duration of hospitalization were retrieved by systematic hand search of the medical records of the children.

Viral Diagnosis

During the 14-year study period, several diagnostic methods were used for the detection of influenza viruses in nasopharyngeal specimens from the children. Overall, 48% of all influenza-positive findings came from the Department of Virology where identification of viruses was based either on detection of antigens by time-resolved fluoroimmunoassay or detection of nucleic acids by reverse-transcriptase polymerase chain reaction. Another 48% of the findings were made by rapid influenza testing performed at the hospital emergency department or on the pediatric infectious diseases ward. Directigen A+B (Becton Dickinson Diagnostic Systems, Sparks, MD) was mostly used up to year 2011, and mariPOC respi test (ArcDia International Ltd, Turku, Finland) since year 2012 onwards. In 4% of cases, the exact method of viral diagnosis remained undetermined. Children positive for influenza A or B by any of these tests were considered as having influenza.

Definitions

The length of hospital stay was recorded as the number of nights spent on the ward. In case a child was admitted in the morning and discharged in the evening of the same day, the length of hospital stay was recorded as 1 day. The length of stay in the pediatric intensive care unit was recorded similarly, and it is reported as a subset of the total length of stay. Seven children had been admitted to another hospital before being transferred to Turku University Hospital. In those cases, the length of hospital stay was calculated by adding up the durations of the hospitalizations.

To adjust for age when comparing influenza A and B infections, the children were divided into 3 age groups (0–2, 3–9 and 10–15 years) on basis of their age on the day of admission. Eight children each were hospitalized twice with influenza during the study period. For the purposes of this study, these children were considered separate children, and they were analyzed in the age group that they belonged to at the time of the illness.

The diagnosis of pneumonia was based on radiologic confirmation of the condition. Convulsions with fever were classified as febrile convulsions except in children who already had a diagnosis of epilepsy. The use of antibiotics was considered justified if the child was diagnosed with any bacterial infection during the hospital stay. Underlying medical conditions included pulmonary, cardiac, endocrine, liver, kidney and major neurologic disorders plus malignancies and other immunosuppressive states.

Statistical Methods

For continuous data, the groups were compared by the *t* test or the Mann-Whitney *U* test. Comparison of proportions between the groups was performed by the χ^2 test or Fisher exact test. All tests were 2-sided, and *P* values <0.05 were considered to indicate statistical significance. The analyses were performed with StatsDirect software (version 2.8.0; StatsDirect Ltd, Cambridge, United Kingdom).

RESULTS

Patient Characteristics

A total of 391 children were hospitalized with virologically confirmed influenza A or B (Table 1). Influenza A was diagnosed in 279 (71.4%) and influenza B in 112 (28.6%) children. Children hospitalized with influenza A were significantly younger than those with B (mean, 4.2 vs 6.4 years; median, 2.6 vs 6.4 years; *P* < 0.0001

TABLE 1. Demographic and Clinical Characteristics of 391 Children Hospitalized With Influenza

Variable	Influenza A (n = 279)	Influenza B (n = 112)	Total (n = 391)
Age, yr			
Mean (SD)	4.2 (4.3)	6.4 (4.9)	4.9 (4.6)
Age group, n (%)			
0–2 yr	152 (54.5)	39 (34.8)	191 (48.8)
<3 mo	35 (12.5)	8 (7.1)	43 (11.0)
3–35 mo	117 (41.9)	31 (27.7)	148 (37.9)
3–9 yr	86 (30.8)	44 (39.3)	130 (33.2)
10–15 yr	41 (14.7)	29 (25.9)	70 (17.9)
Sex, n (%)			
Male	163 (58.4)	58 (51.8)	221 (56.5)
Female	116 (41.6)	54 (48.2)	170 (43.5)
Underlying condition, n (%)	80 (28.7)	38 (33.9)	118 (30.2)

for both). Influenza B accounted for 20.4% of hospitalizations in children 0–2 years of age, 33.8% in the age group 3–9 years and 41.4% in children 10–15 years of age (*P* = 0.001).

Influenza A and B Hospitalizations During Different Seasons

The relative proportions of influenza A and B hospitalizations ranged widely during the study years (Fig. 1). Excluding the pandemic A season of 2009–2010, the proportion of influenza A ranged from 45% to 93% and that of influenza B from 7% to 55% of hospitalizations during different seasons.

Clinical Presentation and Outcomes

The signs and symptoms, laboratory findings and complications in children hospitalized with influenza A and B were compared within the 3 age groups and in all age groups combined (Table 2). None of the differences between A and B viruses in any of these groups were statistically significant. In the group of all children, febrile convulsion occurred in 12 (10.7%) children with influenza B and in 15 (5.4%) with influenza A (*P* = 0.06). Myositis was diagnosed in 5 (4.5%) children with influenza B and in 3 (1.1%) with influenza A (*P* = 0.09). Two children in the youngest age group died; 1 with influenza A and another with B.

Treatment and Length of Stay

Because of clinical suspicion of sepsis, blood cultures were obtained from 101 (36.2%) children with influenza A and 39 (34.8%) with influenza B (*P* = 0.80) (Table 3). In 3 children (all with influenza A), the blood cultures yielded a bacterial pathogen (1 each of *Streptococcus pneumoniae, S. pyogenes* and *Staphylococcus aureus*). Cerebrospinal fluid specimens for suspected meningitis were obtained from 16 (5.7%) children with influenza A and 11 (9.8%) children with influenza B (*P* = 0.15); no bacteria were detected in any of these specimens.

A total of 144 (51.6%) children with influenza A and 54 (48.2%) with influenza B received antibiotic treatment (*P* = 0.54). Overall, 53 of 198 (26.8%) children treated with antibiotics did not have any bacterial infection diagnosed. Antiviral treatment with oseltamivir was given to 168 (60.2%) children with influenza A and 63 (56.3%) with influenza B (*P* = 0.47).

The mean duration of hospital stay was 2.3 days in children with influenza A and 2.7 days in those with influenza B (*P* = 0.34). Thirty-six (12.9%) children with influenza A and 17 (15.2%) with influenza B required treatment at the intensive care unit (*P* = 0.55). Eight (2.9%) children with influenza A and 6 (5.4%) with B were mechanically ventilated (*P* = 0.37).
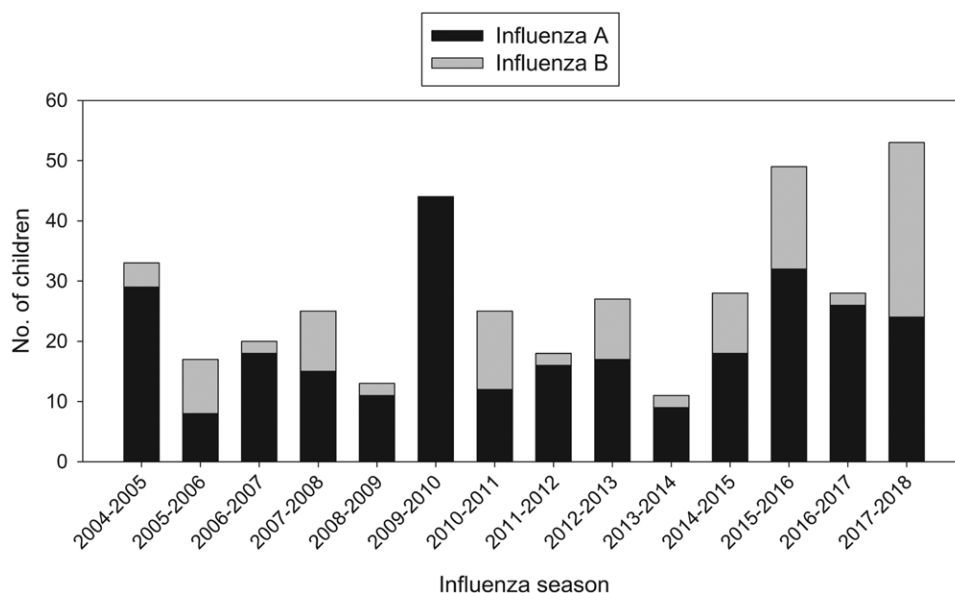
FIGURE 1. Numbers of children hospitalized with influenza A and B during each season of the study.

TABLE 2. Clinical Features and Laboratory Findings of Hospitalized Children by Age Group and Influenza Type*

Variables	Age 0–2 yr		Age 3–9 yr		Age 10–15 yr		All Age Groups		Total
	A (n = 152)	B (n = 39)	A (n = 86)	B (n = 44)	A (n = 41)	B (n = 29)	A (n = 279)	B (n = 112)	A or B (n = 391)
Length of symptoms before admission, mean (SD), d	2.5 (2.1)	3.0 (4.1)	2.9 (2.5)	3.3 (2.0)	3.4 (2.5)	3.9 (2.9)	2.8 (2.3)	3.4 (3.1)	2.9 (2.6)
Length of fever before admission, mean (SD), d	1.9 (1.9)	1.9 (1.9)	2.3 (2.4)	2.9 (2.0)	3.0 (2.5)	3.3 (2.7)	2.2 (2.2)	2.7 (2.3)	2.3 (2.2)
Highest fever before admission, mean, °C	38.9	39.1	39.4	39.4	39.2	39.2	39.1	39.2	39.1
Fever at admission, mean, °C	38.5	38.5	38.3	38.2	38.1	37.6	38.4	38.2	38.3
WBC count at admission, mean, $\times 10^9$ cells/L	9.2	9.2	6.7	6.2	6.5	7.3	8.0	7.5	7.8
CRP level at admission, mean, mg/L	25.4	27.4	29.4	35.2	49.4	49.5	30.5	36.4	32.2
Wheezing	17 (11.2)	7 (17.9)	8 (9.3)	2 (4.5)	3 (7.3)	1 (3.4)	28 (10.0)	10 (8.9)	38 (9.7)
Laryngitis	27 (17.8)	7 (17.9)	9 (10.5)	2 (4.5)	1 (2.4)	3 (10.3)	37 (13.3)	12 (10.7)	49 (12.5)
Febrile convulsion	10 (6.6)	7 (17.9)	4 (4.7)	5 (11.4)	1 (2.4)	0	15 (5.4)	12 (10.7)	27 (6.9)
Nonfebrile convulsion	1 (0.7)	0	3 (3.5)	1 (2.3)	1 (2.4)	3 (10.3)	5 (1.8)	4 (3.6)	9 (2.3)
Myalgia	1 (0.7)	0	5 (5.8)	4 (9.1)	7 (17.1)	4 (13.8)	13 (4.7)	8 (7.1)	21 (5.4)
Abdominal pain	3 (2.0)	0	13 (15.1)	9 (20.5)	7 (17.1)	3 (10.3)	23 (8.2)	12 (10.7)	35 (9.0)
Vomiting	30 (19.7)	7 (17.9)	34 (39.5)	13 (29.5)	12 (29.3)	7 (24.1)	76 (27.2)	27 (24.1)	103 (26.3)
Dehydration	50 (32.9)	14 (35.9)	34 (39.5)	18 (40.9)	18 (43.9)	15 (51.7)	102 (36.6)	47 (42.0)	149 (38.1)
Acute otitis media	47 (30.9)	9 (23.1)	12 (14.0)	6 (13.6)	2 (4.9)	2 (6.9)	61 (21.9)	17 (15.2)	78 (19.9)
Pneumonia	21 (13.8)	5 (12.8)	14 (16.3)	6 (13.6)	9 (22.0)	8 (27.6)	44 (15.8)	19 (17.0)	63 (16.1)
Myositis	0	0	2 (2.3)	2 (4.5)	1 (2.4)	3 (10.3)	3 (1.1)	5 (4.5)	8 (2.0)
Perimyocarditis	0	0	0	0	1 (2.4)	1 (3.4)	1 (0.4)	1 (0.9)	2 (0.5)
Encephalitis	0	0	3 (3.5)	1 (2.3)	0	1 (3.4)	3 (1.1)	2 (1.8)	5 (1.3)
Death	1 (0.7)	1 (2.6)	0	0	0	0	1 (0.4)	1 (0.9)	2 (0.5)

*Data are n (column %) unless otherwise indicated.

CRP indicates C-reactive protein.

DISCUSSION

Our findings provide strong evidence against the conventional concept that influenza A viruses cause more severe illnesses than B viruses in children. In an extensive analysis of influenza-associated hospitalizations during 14 consecutive seasons, we could not find any significant differences in the clinical presentation, outcomes or treatment between children with influenza A and B. The long observation period with varying circulation of A and B viruses during different seasons balances any potential year-to-year variation in the findings. There is no doubt that children who are hospitalized because of influenza represent the most severe forms of the illness. If infections caused by 1 type of influenza virus were clinically more severe than those caused by the other type, the differences should be seen especially among hospitalized children. However, another important factor to be considered in assessing the overall severity of A and B viruses is the relative risk of hospitalization during A or B infection at the population level. According to the National Infectious Diseases Register in Finland,[23] the average annual proportion of influenza A viruses among all influenza viruses detected in children <15 years of age in our catchment area during the 14-year period of our study was 72.3% and that of influenza B viruses 27.7%. These frequencies are similar

TABLE 3. Clinical Management of Hospitalized Children by Age Group and Influenza Type*

Variables	Age 0–2 yr A (n = 152)	Age 0–2 yr B (n = 39)	Age 3–9 yr A (n = 86)	Age 3–9 yr B (n = 44)	Age 10–15 yr A (n = 41)	Age 10–15 yr B (n = 29)	All Age Groups A (n = 279)	All Age Groups B (n = 112)	Total A or B (n = 391)
Blood culture	52 (34.2)	14 (35.9)	30 (34.9)	13 (29.5)	19 (46.3)	12 (41.4)	101 (36.2)	39 (34.8)	140 (35.8)
Cerebrospinal fluid	7 (4.6)	4 (10.3)	7 (8.1)	4 (9.1)	2 (4.9)	3 (10.3)	16 (5.7)	11 (9.8)	27 (6.9)
Antibiotic treatment	84 (55.3)	22 (56.4)	42 (48.8)	18 (40.9)	18 (43.9)	14 (48.3)	144 (51.6)	54 (48.2)	198 (50.6)
Antibiotic treatment unnecessary	19 (12.5)	9 (23.1)	14 (16.3)	5 (11.4)	4 (9.8)	2 (6.9)	37 (13.3)	16 (14.3)	53 (13.6)
Antiviral treatment	88 (57.9)	25 (64.1)	51 (59.3)	23 (52.3)	29 (70.7)	15 (51.7)	168 (60.2)	63 (56.3)	231 (59.1)
Length of hospital stay, mean (SD), d	2.3 (2.5)	2.2 (1.7)	2.6 (3.8)	2.1 (2.6)	2.2 (2.7)	4.4 (7.0)	2.3 (3.0)	2.7 (4.1)	2.5 (3.4)
Treatment at PICU	19 (12.5)	8 (20.5)	13 (15.1)	3 (6.8)	4 (9.8)	6 (20.7)	36 (12.9)	17 (15.2)	53 (13.6)
Mechanical ventilation	5 (3.3)	2 (5.1)	2 (2.3)	0	1 (2.4)	4 (13.8)	8 (2.9)	6 (5.4)	14 (3.6)
Length of PICU stay, mean (SD), d	1.9 (2.2)	1.9 (1.7)	3.5 (4.8)	3.3 (4.0)	3.8 (4.2)	7.7 (11.1)	2.7 (3.5)	4.2 (7.0)	3.2 (4.9)

*Data are n (column %) unless otherwise indicated.
PICU indicates pediatric intensive care unit.

to our observed percentages of children hospitalized with A and B infections (71.4% and 28.6%), and the proportions of children hospitalized with A and B viruses during each individual season were very well in agreement with the proportions of A and B viruses detected in the child population. These data indicate that the risk of hospitalization was similar between children with influenza A and B infections.

In a substantial proportion of young children hospitalized with influenza, the primary reason for admission is a sepsis-like illness that often results in invasive examinations and empirical antibiotic treatment.[9] In our study, there were no significant differences between influenza A and B infections with respect to the frequencies of any type of management of the children, whether analyzed by age group or among all children. The overall clinical severity of influenza virus infection is well depicted by the findings that because of clinical suspicion of a septic illness, blood cultures were obtained from 36% of the children, and lumbar puncture was performed in 7% of the cases. Furthermore, 14% of the children were treated at the intensive care unit, and about one-fourth of those children required mechanical ventilation. Our observed rates of intensive care unit treatment are comparable to a study from Canada that also found no differences in admission to intensive care between children with influenza A and B.[20]

Some previous studies have compared the clinical features of influenza A and B infections in both outpatient and hospitalized children.[15–22] Although some of the reports have covered only a single influenza season, the common message is that the clinical manifestations of influenza A and B are largely similar in children. In a recent surveillance study comparing influenza A and B in hospitalized children during 8 nonpandemic influenza seasons in Canada,[20] the investigators did not find any indication of A viruses causing more severe illnesses. By contrast, even after adjustment for age and health status, children with influenza B had significantly more headache, abdominal pain, myalgia and myositis, and a greater mortality than those with influenza A. Myalgia or myositis have been more commonly associated with influenza B also in some other studies.[9,16,19,24] In the present study, despite similar trends, the differences were not statistically significant.

Approximately half of all children hospitalized with influenza were treated with antibiotics, with no difference between influenza A and B. While in the majority of these children the use of antibiotics was considered appropriate because of influenza-associated or other concomitant bacterial infections, 27% of children receiving antibiotics did not have any apparent bacterial infection. In previous reports from the United States and Australia,[25,26] the proportions of children receiving antibiotics without a proper indication ranged from 36% to 57%. These findings are of great clinical importance because unnecessary use of antibiotics in hospitalized children is likely to increase costs, adverse effects and antimicrobial resistance. One way to combat unnecessary antibiotic treatment is to increase the use of point-of-care influenza testing that has been shown to reduce the use of antibiotics in several studies.[27–31]

Because the relative proportion of B viruses among all circulating influenza viruses varies greatly during different seasons, long observation periods are needed for a meaningful estimation of the role of B viruses. In our study that included the pandemic influenza A season of 2009–2010, influenza B accounted for 29% of all influenza-associated hospitalizations. In previous studies covering 8–20 years of follow-up, the corresponding proportion has ranged from 18% to 36%.[8,12,16,20] It appears safe to conclude that in the long term, influenza B viruses account for approximately 25% of all influenza-associated hospitalizations in children.

As sampling for respiratory viruses was a routine practice for children hospitalized with respiratory infections during the study period, it is unlikely that a substantial number of influenza-positive cases would have been left undiagnosed. Obviously, it is possible that some children with influenza were not sampled, and some of the tests may have yielded false-negative results, but there is little reason to believe that those factors would have had an impact on the comparison between A and B viruses. Our study has also some limitations. Although the study period included 14 years, the numbers of children especially for some subgroup analyses were relatively small, which resulted in reduced power to show statistically significant differences. However, it is important to notice that even though children with influenza A were substantially younger and thereby had a higher risk of a severe clinical presentation than those with influenza B, no significant differences could be demonstrated in any variables between all children with influenza A and B. Our study was conducted at a single hospital, which restricted the size of the study population. On the other hand, this could be seen as a strength because it effectively reduced the variation in clinical practices in different centers and therefore allowed for a more precise comparison of the management of influenza A and B illnesses. A further limitation of the study is that the lengths of stay in the hospital and in the pediatric intensive care unit were available only in days instead of hours that might have provided more precise estimates of these durations.

The implications of our study for the development of influenza immunization programs for children are evident. Although the ultimate goal of vaccination is to prevent all influenza illnesses, prevention of the most severe forms of the disease is the highest priority that also provides the greatest health and economic benefits to children and the society as whole.[13,32,33] As influenza B accounts for a substantial proportion of all influenza illnesses and because

the clinical severity of B infections is similar to influenza A, the use of quadrivalent influenza vaccines that contain both circulating lineages of B viruses seems warranted in children. This conclusion is also supported by several recent modeling studies carried out in different countries that have specifically assessed the cost-effectiveness of switching from trivalent to quadrivalent influenza vaccines.[34–36]

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