Hospitalization for Influenza A Versus B

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abstract

BACKGROUND: The extent to which influenza A and B infection differs remains uncertain.

METHODS: Using active surveillance data from the Canadian Immunization Monitoring Program Active at 12 pediatric hospitals, we compared clinical characteristics and outcomes of children ≤16 years admitted with laboratory-confirmed influenza B or seasonal influenza A. We also examined factors associated with ICU admission in children hospitalized with influenza B.

RESULTS: Over 8 nonpandemic influenza seasons (2004-2013), we identified 1510 influenza B and 2645 influenza A cases; median ages were 3.9 and 2.0 years, respectively ($P <$ .0001). Compared with influenza A patients, influenza B patients were more likely to have a vaccine-indicated condition (odds ratio [OR] = 1.30; 95% confidence interval [CI] = 1.14–1.47). Symptoms more often associated with influenza B were headache, abdominal pain, and myalgia ($P <$ .0001 for all symptoms after adjustment for age and health status). The proportion of deaths attributable to influenza was significantly greater for influenza B (1.1%) than influenza A (0.4%); adjusted for age and health status, OR was 2.65 (95% CI = 1.18–5.94). A similar adjusted OR was obtained for all-cause mortality (OR = 2.95; 95% CI = 1.34–6.49). Among healthy children with influenza B, age ≥10 years (relative to <6 months) was associated with the greatest odds of ICU admission (OR = 5.79; 95% CI = 1.91–17.57).

CONCLUSIONS: Mortality associated with pediatric influenza B infection was greater than that of influenza A. Among healthy children hosptialized with influenza B, those 10 years and older had a significant risk of ICU admission.

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WHAT'S KNOWN ON THIS SUBJECT: Although influenza B has often been perceived to be milder than influenza A, recent data suggest that influenza B can pose a significant disease burden globally. Data regarding differences in outcomes between influenza A and B, however, remain limited.

WHAT THIS STUDY ADDS: Influenza B resulted in greater mortality than influenza A among children who were hospitalized due to influenza. Healthy children 10 years and older were at increased risk of developing severe disease from influenza B infection.

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To date, influenza B has been less researched than influenza A, partly because influenza A is capable of causing pandemics, and partly because influenza B is considered less virulent. However, there is increasing recognition of the substantial impact of influenza B[1] and the need to characterize differences in outcomes between influenza A and B.[2] The literature comparing the outcomes of influenza A and B among hospitalized patients is limited (most studies involve small sample sizes or single-center experiences).[3–6]

Influenza B accounts for a variable proportion of influenza cases each year. Based on 2001–2011 surveillance data in the United States (excluding the 2009-2010 pandemic), the percentage of total clinical isolates attributed to influenza B ranged from <1% to 44%.[7] In 5 of these 10 years, the predominant circulating B lineage differed from the World Health Organization recommended B lineage for the Northern hemisphere trivalent inactivated influenza vaccine (TIV), accounting for 77% to 98% of all influenza virus isolates.[7] In Canada, influenza B accounted for 1.4% to 53.1% of laboratory-confirmed cases from 2001 to 2013, not including the 2009-2010 pandemic.[8] A substantial proportion of B virus isolates were of the B lineage not included in the TIV in 7 of these 11 seasons.[8]

A mismatch of the B lineage in the annual TIV can have a substantial impact on vaccine effectiveness and disease burden. During the 2007–2008 season in the United States, influenza B accounted for almost 30% of influenza viruses tested by the Centers for Disease Control and Prevention and 98% of them did not match the lineage contained in the TIV vaccine.[9] Given that 2 distinct B virus lineages continue to co-circulate and provide little cross protection, multiple vaccine manufacturers have developed seasonal quadrivalent influenza vaccines (QIVs), which are now recommended for children in Canada and the United States. In Canada, an inactivated QIV is preferentially recommended over TIV for children 6 to 23 months, and quadrivalent live attenuated influenza vaccine for healthy children aged 2 to 17 years.[10] In contrast, the Advisory Committee on Immunization Practices does not express a preference for use of any particular vaccine formulation,[11] and the American Academy of Pediatrics Committee on Infectious Diseases states that neither TIV nor QIV is preferred over the other.[12]

Data regarding the burden of influenza B compared with A are critical to understanding the impact of various strategies of incorporating QIV into an influenza immunization program. This study aimed to assess the burden of disease attributable to influenza B relative to seasonal influenza A among children admitted to pediatric hospitals across Canada, compare the severity of influenza B infection in children hospitalized during B vaccine-mismatched seasons to those admitted during B vaccine-matched seasons, and identify factors associated with severe influenza B infection.

METHODS

Patients

Patients were ascertained through active surveillance for laboratory-confirmed influenza admissions at the 12 pediatric referral centers of the Canadian Immunization Monitoring Program Active (IMPACT), a national surveillance initiative with centers in Newfoundland, Nova Scotia, Quebec, Ontario, Manitoba, Saskatchewan, Alberta, and British Columbia. These centers admit over 75 000 children annually, account for ~90% of pediatric tertiary care beds in the country, receive referrals from all provinces and territories, and serve a population of ~50% of Canada's children.[13] All centers routinely test children admitted with wintertime respiratory illnesses for influenza and have institutional ethics approval for surveillance. The influenza testing algorithm varies by center; and since 2010, all centers use polymerase chain reaction (PCR) alone or PCR to supplement immunofluorescence or viral culture when they yield negative results. Before the 2009-2010 pandemic, PCR was not used by all centers.

A trained nurse monitor at each center screens daily laboratory results for eligible cases. Case details are abstracted from medical charts by using electronic standardized data collection forms (Daciforms, Dacima Software, Inc, Montreal, Quebec, Canada). Data collected include demographics, preexisting medical conditions, influenza vaccination history, influenza type, clinical manifestations, treatment, complications, level of care required, duration of hospital stay, and outcome.

Eligible for inclusion in the study were children aged ≤16 years hospitalized because of influenza A or B confirmed by PCR, immunofluorescence, or viral culture from September 11, 2004, to June 30, 2013. Those admitted during the 2009-2010 pandemic (May 1, 2009, to June 30, 2010) were excluded. In addition, influenza A cases admitted in April 2009 were excluded to minimize the risk of case misclassification due to the potential circulation of influenza A (H1N1) pdm09 virus before the availability of A(H1N1)pdm09-specific PCR.

Variables of Interest and Definitions

We focused on demographics, health status, seasonal influenza vaccination status, presenting signs and symptoms, antiviral and antibiotic prescription, and measures of illness severity (mortality, influenza-related complications, ICU admission, mechanical ventilation,

TABLE 1 Distribution of Hospital Admissions by Influenza Type and Season

Influenza Type	Season[a]									
	2004–2005 (*n* = 392)	2005–2006 (*n* = 373)	2006–2007 (*n* = 368)	2007–2008 (*n* = 496)	2008–2009 (*n* = 378)	2010–2011 (*n* = 671)	2011–2012 (*n* = 588)	2012–2013 (*n* = 889)	2004–2013 (*n* = 4155)	Matched B Seasons[b] (*n* = 2320)	Mismatched B Seasons[c] (*n* = 1835)
Influenza A	272 (69.4)	231 (61.9)	311 (84.5)	313 (63.1)	197 (52.1)	451 (67.2)	245 (41.7)	625 (70.3)	2645 (63.7%)	1659 (71.5)	986 (53.7)
Influenza B	120 (30.6)	142 (38.1)	57 (15.5)	183 (36.9)	181 (47.9)	220 (32.8)	343 (58.3)	264 (29.7)	1510 (36.3%)	661 (28.5)	849 (46.3)

[a] Data are *n* (column %) unless otherwise indicated.
[b] 2004–2005, 2006–2007, 2010–2011, 2012–2013.
[c] 2005–2006, 2007–2008, 2008–2009, 2011–2012.

extracorporeal membrane oxygenation, and ICU and hospital length of stay). Some of the above parameters were not captured in all seasons: comparison between influenza B and seasonal influenza A was confined to the 2008–2009 to 2012–2013 seasons for ethnicity, and the 2006–2007 to 2012–2013 seasons for presenting signs and symptoms. Based on strain characterization data from Canada's National Microbiology Laboratory, B vaccine-mismatched seasons were defined as those in which the predominant circulating influenza B lineage was different from that contained in the vaccine.

Statistical Considerations

Differences in continuous variables were analyzed by using Student's *t* test or Mann–Whitney *U* test. Comparisons of categorical variables were made by using the χ^2 test, Fisher's exact test, or log linear analysis as appropriate. Logistic regression and multivariable logistic regression were used to determine crude and adjusted odds ratios (ORs). No inferential statistics were conducted for variables with significant missing data (ie, ethnicity and influenza vaccination status). To identify independent predictors of pneumonia and ICU admission for influenza B (such analyses for influenza A had been previously conducted),[14] we constructed univariate and multivariable logistic regression models including only variables without significant missing data. All variables with univariate $P < .1$ were considered for entry into the multivariable models. The contribution of age, health status, and an interaction term for age and health status as independent variables was examined in all multivariable logistic regression models. When the age × health status interaction term was significant, the relationship between age and the dependent variable of interest was analyzed separately for each health status category. All tests were 2-sided and a $P < .05$ was considered statistically significant. Data were analyzed by SPSS statistical software (version 22.0; SPSS, Inc, Chicago, IL).

RESULTS

Over 8 nonpandemic influenza seasons, from 2004 to 2013, 4155 children with influenza were admitted to IMPACT centers, with influenza B accounting for 15.5% to 58.3% of influenza-related admissions per season (median = 34.8%; interquartile range [IQR] = 29.9%–45.4%; Table 1). The proportion of hospitalizations due to influenza B was significantly higher in the 4 B vaccine-mismatched than the 4 B vaccine-matched seasons (46.3% vs 28.5%; $P < .0001$).

Patient Characteristics

The age distribution of influenza B cases differed from that of influenza A cases, with a shift toward older children among influenza B admissions (Table 2). Children admitted with influenza B, compared with influenza A, had higher odds of having a vaccine-indicated condition (OR = 1.30; 95% confidence interval [CI] = 1.14–1.47) and lower odds of having no underlying medical condition (OR = 0.80; 95% CI = 0.71–0.91). There was a significant interaction between age group and health status ($P < .0001$). The association between influenza type and age group was significant for all health status categories ($P \leq .001$ for the categories no underlying conditions and vaccine-indicated condition and $P = .001$ for other underlying conditions). However, the shift of the age distribution to older children in influenza B cases relative to influenza A was most pronounced among those without an underlying condition (Supplemental Fig 1). A significant amount of data was not available for ethnicity: 44%

TABLE 2 Characteristics of Hospitalized Patients by Influenza Type

Characteristics	Influenza Type[a]		
	Influenza A (n = 2645)	Influenza B (n = 1510)	Unadjusted OR/P
Boys	1554 (58.8)	875 (57.9)	0.97 (0.85–1.10)
Age, y			
Mean (SD)	3.4 (3.9)	5.0 (4.3)	<.0001
Median (IQR)	2.0 (0.6–4.8)	3.9 (1.4–7.2)	<.0001
Age group			<.0001
0–5 mo	586 (22.2)	170 (11.3)	—
6–23 mo	749 (28.3)	305 (20.2)	—
24–59 mo	681 (25.7)	423 (28.0)	—
5–9 y	406 (15.3)	401 (26.6)	—
≥10 y	223 (8.4)	211 (14.0)	—
Health status			.0004
No underlying condition	1342 (50.7)	684 (45.3)	—
Vaccine-indicated condition	976 (36.9)	651 (43.1)	—
Other underlying condition	327 (12.4)	175 (11.6)	—
Ethnic origin[b]			
White	532/845 (63.0)	337/591 (57.0)	—
Asian	92/845 (10.9)	60/591 (10.2)	—
Middle Eastern	51/845 (6.0)	45/591 (7.6)	—
Black	49/845 (5.8)	74/591 (12.5)	—
Latin American	17/845 (2.0)	11/591 (1.9)	—
Aboriginal	81/845 (9.6)	46/591 (7.8)	—
Other/mixed	23/845 (2.7)	18/591 (3.0)	—
Data not available	675	419	—
Influenza vaccination status[c]			
Received influenza vaccine	98/1504 (6.5)	59/855 (6.9)	—
Data not available	555	485	—

—, Inferential statistical analysis was not conducted.

[a] Data are n (column %) unless otherwise indicated; where fractions are shown, denominator is the number of cases with data available.

[b] Data available only for 2008–2009 season onward; n = 1520 (influenza A), n = 1010 (influenza B).

[c] Includes children ≥6 mo; n = 2059 (influenza A), n = 1340 (influenza B).

(influenza A) and 41% (influenza B). A very small proportion of hospitalized children had received influenza vaccination (6.5% and 6.9% for influenza A and B, respectively), although this data were only available for 73% of influenza A cases and 64% of influenza B cases.

Clinical Presentation, Treatment, and Illness Severity

Compared with influenza A cases, children admitted with influenza B had greater adjusted odds of presenting with headache, abdominal pain, and myalgia, ranging from 1.38 for abdominal pain to 3.19 for myalgia (Table 3). There were no significant differences in antiviral or antibiotic use between influenza A and B cases (Table 4).

Myositis was diagnosed more frequently in influenza B cases (Table 4). Mortality attributable to influenza, as well as all-cause mortality, also occurred more commonly in children hospitalized with influenza B. These differences in markers of illness severity remained statistically significant in adjusted analyses. These findings were also evident when only influenza A cases ascertained during H3N2-predominant seasons (2004–2007 and 2010–2013) served as the comparator, with the following ORs for influenza B relative to A, adjusted for age group and health status: OR = 5.68 (95% CI = 3.38–9.52) for myositis; OR = 2.36 (95% CI = 1.03–5.44) for influenza-attributable mortality; OR = 2.63 (95% CI = 1.16–5.95) for all-cause mortality. When influenza B admissions from B vaccine-mismatched seasons (n = 849) were compared with influenza B cases from B vaccine-matched seasons (n = 661), myositis was diagnosed less frequently during the B mismatched seasons (adjusted OR = 0.64; 95% CI = 0.41–0.98). During B mismatched seasons, influenza-attributable and all-cause deaths occurred in 1.3% and 1.4% of influenza B cases respectively; the corresponding figures for B vaccine-matched seasons were 0.8% and 0.9%, respectively. This translates to crude ORs of 1.72 for influenza-attributable and 1.57 for all-cause mortality. These differences, however, were not statistically significant. Other measures of illness severity did not differ significantly between B vaccine-mismatched and vaccine-matched seasons.

Predictors of Pneumonia and ICU Admission in Influenza B Infection

In multivariable modeling, ages 6 to 23 and 24 to 59 months (compared with <6 months), and presence of a vaccine-indicated condition were independently associated with

TABLE 3 Signs and Symptoms of Hospitalized Patients by Influenza Type

Sign or Symptom[a]	Influenza Type[b]			
	Seasonal A (*n* = 2142)	Influenza B (*n* = 1248)	Unadjusted OR	Adjusted OR[c]
Systemic				
Fever	1990 (92.9)	1167 (93.5)	1.10 (0.83–1.46)	—
Headache	78 (3.6)	123 (9.9)	2.89 (2.16–3.88)	1.85 (1.36–2.52)
Lethargy	741 (34.6)	465 (37.3)	1.12 (0.97–1.30)	—
Respiratory				
Coryza	1277 (59.6)	744 (59.6)	1.00 (0.87–1.15)	—
Cough	1835 (85.7)	1051 (84.2)	0.89 (0.73–1.08)	—
Wheezing	476 (22.2)	260 (20.8)	0.92 (0.78–1.09)	—
Respiratory distress	904 (42.2)	489 (39.2)	0.88 (0.76–1.02)	—
Apnea	65 (3.0)	37 (3.0)	0.98 (0.65–1.47)	—
Extrarespiratory				
Abdominal pain	119 (5.6)	126 (10.1)	1.91 (1.47–2.48)	1.38 (1.05–1.81)
Vomiting and/or diarrhea and/or dehydration	1003 (46.8)	569 (45.6)	0.95 (0.83–1.10)	—
Myalgia	38 (1.8)	102 (8.2)	4.93 (3.37–7.20)	3.19 (2.16–4.72)
Arthralgia	10 (0.5)	15 (1.2)	2.59 (1.16–5.79)	1.95 (0.86–4.40)
Seizure	238 (11.1)	116 (9.3)	0.82 (0.65–1.04)	—

—, adjusted OR was not calculated.

[a] Individuals had >1 sign or symptom and percentages do not add up to 100%.

[b] Data are *n* (column %) unless otherwise indicated; data available only for 2006–2007 season onward.

[c] Adjusted for age group and health status.

TABLE 4 Treatment and Illness Severity of Hospitalized Patients by Influenza Type

Treatment	Influenza Type[a]			
	Seasonal A (*n* = 2645)	Influenza B (*n* = 1510)	Unadjusted OR/*P*	Adjusted OR/*P*[b]
Antiviral				
Antibiotic	400/2643 (15.1)	202/1508 (13.4)	0.87 (0.72–1.04)	—
Measures of illness severity	1913/2640 (72.5)	1050/1508 (69.6)	0.87 (0.76–1.00)	—
Respiratory complications				
Croup	101 (3.8)	51 (3.4)	0.88 (0.62–1.24)	—
Pneumonia (radiologically confirmed)	595 (22.5)	364 (24.1)	1.09 (0.94–1.27)	—
Extrarespiratory complications				
Myositis	18 (0.7)	101 (6.7)	10.46 (6.31–17.35)	6.95 (4.15–11.64)
Myocarditis	6 (0.2)	6 (0.4)	1.75 (0.56–5.45)	—
Hepatitis	24 (0.9)	22 (1.5)	1.61 (0.90–2.89)	—
Meningitis	6 (0.2)	4 (0.3)	1.17 (0.33–4.15)	—
Encephalitis	42 (1.6)	36 (2.4)	1.51 (0.97–2.37)	—
Length of hospital stay, median (IQR), d	3.0 (2.0–5.0)	3.0 (2.0–5.0)	0.60	—
Mortality				
Attributable to influenza	10 (0.4)	16 (1.1)	2.82 (1.28–6.23)	2.65 (1.18–5.94)
All-cause	10 (0.4)	18 (1.2)	3.18 (1.46–6.90)	2.95 (1.34–6.49)
Admitted to ICU	337 (12.7)	190 (12.6)	0.99 (0.82–1.19)	—
Required mechanical ventilation[c]	212 (62.9)	124 (65.3)	1.11 (0.76–1.61)	—
Required extracorporeal membrane oxygenation[c]	7 (2.1)	6 (3.2)	1.54 (0.51–4.64)	—
Length of ICU stay, median (IQR), d[c]	3.0 (1.0–6.5)	3.0 (1.0–7.0)	0.62	—

—, adjusted OR or *P* was not calculated.

[a] Data are *n* (column %) unless otherwise indicated; where fractions are shown, denominator is the number of cases with data available.

[b] Adjusted for age group and health status.

[c] Denominator of the percentage is the number of ICU admitted cases.

influenza B-associated radiologically confirmed pneumonia (Table 5). Multivariable modeling of ICU admission identified age 6 to 23 months and ≥10 years (compared with <6 months), and presence of an underlying condition (both vaccine-indicated and other underlying conditions) as independent predictors of ICU admission. However, a significant age group × health status interaction effect was detected ($P = .045$). Separate analyses for each health category revealed that the effect of age group remained for healthy children (ie, children without an underlying condition) and children with vaccine-indicated conditions but not for those with other underlying conditions (Table 6). Among healthy children, those aged 6 to 23 months and ≥10 years had greater odds of being admitted to ICU than infants <6 months. Children

TABLE 5 Factors Associated With Radiologically Confirmed Pneumonia in Patients Hospitalized With Influenza B

	Radiologically Confirmed Pneumonia			
	Univariate Analysis (n = 1510)		Multivariable Analysis[a] (n = 1510)	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Boys	0.94 (0.74–1.20)	.63	—	—
Age, y	0.98 (0.95–1.01)	.13	—	—
Age group		<.0001		<.0001
0–5 mo	Reference		Reference	
6–23 mo	3.29 (1.94–5.57)	<.0001	2.88 (1.69–4.91)	<.0001
24–59 mo	3.33 (2.00–5.54)	<.0001	2.66 (1.58–4.47)	.0002
5–9 y	1.75 (1.03–2.98)	.04	1.40 (0.82–2.40)	.22
≥10 y	2.03 (1.15–3.60)	.01	1.48 (0.82–2.66)	.19
Health status		<.0001		<.0001
No underlying condition	Reference		Reference	
Vaccine-indicated condition	1.95 (1.51–2.52)	<.0001	1.93 (1.47–2.51)	<.0001
Other underlying condition	1.27 (0.85–1.90)	.25	1.25 (0.83–1.89)	.28

—, sex and age (in years) were not included in the multivariable model.

[a] Multivariable model included age group and health status as independent variables.

≥10 years also had greater odds of requiring ICU admission than their 5- to 9-year-old counterparts (OR = 3.41; 95% CI = 1.39–8.38).

DISCUSSION

Our study revealed that (1) influenza B accounted for at least one-third of influenza-associated hospitalizations in 4 of the 8 nonpandemic influenza seasons, with greater proportions during B vaccine-mismatched than during B vaccine-matched seasons; (2) children admitted with influenza B were older and more likely to present with headache, abdominal pain, and myalgia, and be diagnosed with myositis; (3) the odds of mortality (both influenza-attributable and all-cause) was significantly greater with influenza B than with A and was not entirely explained by underlying health conditions; and (4) among healthy children hospitalized with influenza B, age ≥10 years conferred the highest risk of ICU admission.

The proportion of influenza B relative to influenza A infections in this analysis was similar to those found in pediatric studies from the United States (0.1%–44.6%)[15,16] and Taiwan (6.4%–62.9%).[17,18] This contrasts with lower proportions (0%–16.4%) observed in studies from Europe,[19] Korea,[20] Southeast Asia,[21] South America,[22] Australia and New Zealand.[23] It is unclear whether these regional differences represent true incidence differences, coverage of different influenza seasons, study population characteristics, or varying ascertainment methods. We also found that the burden of influenza B relative to A varied considerably year to year, with the proportion of influenza B-associated hospitalizations being significantly higher during B vaccine-mismatched than vaccine-matched seasons. Although this may seem intuitive, previous studies have revealed either similar[24] or lower[25] relative proportions of influenza B infection in B vaccine-mismatched seasons. However, these studies included both ambulatory and hospitalized influenza cases in their analyses. It is unknown whether the limited cross-protection afforded by the vaccine during B vaccine-mismatched seasons exerts a differential impact on the incidence of severe versus nonsevere influenza B infection. In our study, patients with influenza B admitted during B vaccine-mismatched seasons, compared with those hospitalized during vaccine-matched seasons, had higher crude ORs of experiencing influenza-attributable (1.72) and all-cause mortality (1.57), but these were not statistically significant. Considering the rarity of these outcomes, our sample sizes were relatively modest and may have limited our ability to detect statistically significant differences. Notably, 1 study referred to above[25] demonstrated higher per-patient influenza-related direct and indirect costs (including inpatient costs and workplace absence costs) during B vaccine-mismatched seasons, suggesting that influenza severity during the vaccine-mismatched seasons differed from the vaccine-matched seasons.

Children with influenza B infection in our cohort tended to be almost 2 years older than those hospitalized with influenza A. This is consistent with previous analyses of ambulatory and hospitalized influenza-infected pediatric patients.[4,18,26,27] The slower accumulation of natural immunity to influenza B compared with A in children[28] is consistent with the increased incidence of influenza B illness relative to A among older children. This pattern of influenza acquisition was best illustrated by the age distributions of influenza A and B cases in children with no underlying condition. In a single-center study of hospitalized children in Australia, a significantly higher proportion of influenza B cases had

TABLE 6 Factors Associated With ICU Admission in Patients Hospitalized With Influenza B

	Univariate Analysis (n = 1510)		Univariate Analysis by Health Status[a]					
			No Underlying Condition (n = 684)		Vaccine-Indicated Condition[b] (n = 651)		Other Underlying Condition (n = 175)	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Boys	1.13 (0.83–1.54)	.44	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Age, y	1.03 (0.99–1.06)	.10	—[c]	—[c]	—[c]	—[c]	—[c]	—[c]
Age group		.05		.01		.13		.59
0–5 mo	Reference		Reference	—	Reference	—	Reference	—
6–23 mo	1.28 (0.70–2.35)	.42	3.46 (1.26–9.49)	.02	0.33 (0.11–0.96)	.04	0.43 (0.11–1.70)	.23
24–59 mo	1.46 (0.82–2.58)	.20	2.64 (0.95–7.35)	.06	0.47 (0.18–1.21)	.12	0.62 (0.17–2.26)	.47
5–9 y	0.97 (0.53–1.77)	.92	1.70 (0.57–5.01)	.34	0.29 (0.11–0.78)	.01	0.57 (0.16–2.08)	.40
≥10 y	1.91 (1.04–3.54)	.04	5.79 (1.91–17.57)	.002	0.41 (0.15–1.13)	.08	1.13 (0.29–4.44)	.86
Health status		.002						
No underlying condition	Reference		—[d]	—[d]	—[d]	—[d]	—[d]	—[d]
Vaccine-indicated condition	1.68 (1.20–2.35)	.003	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]
Other underlying condition	2.00 (1.25–3.21)	.004	—[d]	—[d]	—[d]	—[d]	—[d]	—[d]

[a] Conducted due to detection of an interaction between age group and health status (P = .045) on multivariable analysis.

[b] For the 0–5 mo age group, a vaccine-indicated condition refers to an underlying condition for which influenza vaccination is particularly recommended in individuals aged ≥6 mo, and does not indicate that influenza vaccination should be given to this age group.

[c] Sex and age (in years) were not included in the multivariable model.

[d] N/A.

an underlying illness.[3] Although this observation was replicated in our study in univariate analysis, we also demonstrated that age served as an effect modifier with a significantly higher proportion of children aged 5 to 9 years hospitalized with influenza B having no underlying condition.

Although some studies have revealed no difference in symptomatology by influenza type,[3,29] others have revealed myalgia, sore throat, hoarseness, and gastrointestinal symptoms (eg, vomiting, diarrhea, abdominal pain) to be more common in patients with influenza B.[4,27,30] This may be influenced by the ability of older children to localize symptoms, exemplified by a study that documented significant differences by age, with older patients more likely to report headache, sore throat, and myalgia.[29] In our study, children hospitalized with influenza B were more likely to have experienced myalgia and been diagnosed with myositis, even after adjusting for age.

There is limited published data comparing severity, particularly mortality, of influenza B to that of seasonal influenza A in children. For children and adults combined, estimates of influenza-associated hospitalization rates in the United States have been highest for seasonal influenza A(H3N2), followed by B and then seasonal A(H1N1).[31] In 1 pediatric study, influenza B was associated with increased odds of hospitalization after an emergency department visit compared with seasonal influenza A infection.[16] In another, the average lengths of stay for children hospitalized with influenza B and seasonal influenza A were not significantly different (mean of 4.0 and 4.8 days, respectively).[3] Similarly, lengths of stay for influenza B and A cases in our cohort were comparable (median of 3.0 days for both). However, we found the odds of influenza-attributable and

all-cause mortality to be significantly greater in children hospitalized with influenza B. Of course, depending on the magnitude of influenza B activity relative to A for a given season, the attributable risk of mortality for influenza B may be significantly lower than the greater ORs for influenza B would indicate. We were not able to identify other studies that revealed mortality stratified by influenza type for comparison. Based on statistical modeling of national mortality and viral surveillance data, the annual estimate of underlying pneumonia and influenza deaths associated with influenza B for all age groups in the United States falls between that for seasonal influenza A(H1N1) and A(H3N2), with that of A(H3N2) being the highest.[32] However, from the 1976–1977 through the 1998–1999 seasons, 48.6% of excess all-cause deaths in children under 5 were associated with influenza B, more than estimates of either influenza A(H1N1) or A(H3N2).[32] Of note, influenza B viruses have been revealed to exhibit lower sensitivity (higher 50% inhibitory concentration) to oseltamivir than influenza A viruses.[33] Oseltamivir has also been shown to be less effective in shortening duration of viral shedding and febrile illness in young children infected with influenza B compared with influenza A viruses.[34] Whether this lower clinical effectiveness of oseltamivir against influenza B relative to influenza A infection translates to differences in severe outcomes is unknown.

With numerous influenza vaccine formulations being made available to public health agencies at varying costs, determining the optimal vaccine formulation for each target population can be challenging. If prioritization of QIV in children is to reflect age group-specific burden of severe disease from influenza B, previous studies would indicate that young children should be targeted as QIV recipients.[35,36] A study in Colorado observed the highest influenza B hospitalization rates in children <6 months and 6 to 23 months,[35] whereas a cohort of Hong Kong children aged 2 to 4 years had the greatest hospitalization rates for influenza B.[36] Consistent with these findings, healthy children aged 6 to 23 months in our study were more likely to be admitted to ICU compared with healthy infants <6 months, and age groups 6 to 23 and 24 to 59 months were independently predictive of radiologically confirmed pneumonia. However, our study also demonstrated that among healthy children hospitalized with influenza B, risk of ICU admission was highest for those 10 and older. Importantly, unlike the younger age groups, current Canadian and US influenza immunization guidelines do not include healthy children 10 to 16 years among those at high risk of influenza-related complications for whom concerted influenza vaccination efforts is recommended.[10,12] As influenza immunization programs worldwide consider the adoption of QIV, our data will be useful to populate economic analyses assessing the cost-benefit of QIV relative to TIV.

This study has limitations. There was insufficient influenza A subtype information for subtype-specific comparisons with influenza B. However, increased odds of myositis, influenza-attributable mortality, and all-cause mortality remained significant even when analyses were restricted to influenza A cases ascertained during A(H3N2)-predominant seasons. The transition to inclusion of molecular methods in the detection of influenza after the 2009-2010 pandemic across all centers could have introduced systematic bias by enabling increased ascertainment of less severe cases in the later years. However, the proportions of cases attributable to influenza B were similar before and after the pandemic (34.0% vs 38.5%). Moreover, the slightly higher proportion of B cases identified during the period with more common use of PCR would have resulted in an underestimation of the mortality ORs for influenza B relative to A. Lack of ethnicity data before the 2008-2009 season and missing ethnicity data for 41% to 44% of cases prevented us from incorporating these variables in multivariable analyses. Infrequent influenza immunization in our study population, combined with the significant missing immunization data, could have hindered our ability to detect differences in illness severity between B vaccine-mismatched and matched seasons.

CONCLUSIONS

Among hospitalized children, influenza A and B infections resulted in similar morbidity while mortality was greater for influenza B disease. Among healthy children hospitalized with influenza B, those aged 10 to 16 years were most likely to require ICU admission. These children should be considered at high risk for complicated influenza B infection and be specifically targeted by immunization programs to receive influenza vaccination, and in particular, a QIV.

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ABBREVIATIONS

CI: confidence interval
IMPACT: Canadian Immunization Monitoring Program Active
IQR: interquartile range
OR: odds ratio
PCR: polymerase chain reaction
QIV: quadrivalent influenza vaccine
TIV: trivalent inactivated influenza vaccine

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