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Comparative epidemiology of influenza B by lineage in intensive care unit-admitted patients with complications: A nationwide study in Taiwan, 2013–2017

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ABSTRACT

Background: We describe the relative proportions and epidemiological features of influenza B/Victoria and B/Yamagata, using data from nationwide surveillance systems.
Methods: We collected respiratory samples from outpatients with influenza-like illness (ILI) and intensive care unit (ICU)-admitted patients with complications (pulmonary or neurological complications, myocarditis/pericarditis or invasive bacterial infection) for virus isolation and lineage typing. Demographics, epidemiological features, and vaccination history from ICU-admitted patients with complications were analyzed.
Results: From July 2013–June 2017, 21% of 11517 influenza isolates were influenza B. B/Victoria was the predominant circulating strain in 2013–2014, accounted for 56% of all influenza B positive samples and B/Yamagata was predominant in 2014–2017 (82%, 69%, and 85%, respectively). Among all typed viruses, the proportion of B/Yamagata was higher among specimens from ICU-admitted patients with complications (77%, 154/199) than from ILI outpatients (66%, 276/418, $p < 0.005$). Compared to B/Victoria, B/Yamagata infected ICU-admitted patients with complications were older, median age (71 vs. 59 years, $p < 0.05$), had longer durations of hospitalization (15 vs. 7.5 days, $p < 0.05$) and ICU stays (8.5 vs. 5.5 days, $p < 0.05$).
Conclusions: Two lineages of influenza B viruses co-circulate annually in Taiwan. Among ICU-admitted patients with complications, B/Yamagata causes more severe illness than B/Victoria.

Introduction

Influenza B viruses can be divided into two antigenically and genetically distinct lineages, represented by B/Victoria/2/87 and B/Yamagata/16/88 viruses (Rota et al., 1990). These lineages have co-circulated since 2001 in variable, unpredictable proportions (Ray et al., 2017). In Taiwan, the two lineages of influenza B viruses evolved contemporaneously and independently (Yang et al., 2012; Kuo et al., 2016). Influenza B viruses are generally thought to affect a younger population and cause less severe illness than influenza A viruses (Chi et al., 2008; Caini et al., 2015; Jennings et al., 2018). Previous studies have compared the epidemiological features of patients infected by the two influenza B virus lineages and had conflicting results. Studies in Italy and Canada showed the median age of influenza B/Victoria cases was lower than B/Yamagata cases (Orsi et al., 2017 and Skowronski et al., 2017). On the contrary, a study in Thailand showed the median age did not differ between patients infected with different lineages, but B/Victoria cases had longer hospital stays and higher proportion of secondary bacterial infection (Horthongkham et al., 2016).

Since 1998, Taiwan's government-funded seasonal influenza vaccination campaign has provided a trivalent seasonal influenza vaccine (TIV), which only contains one of the two influenza B lineages. Free vaccines are offered to a list of prioritized groups including pre- and school age children, pregnant women, adults over 50 years of age, people living with chronic illness, healthcare workers, etc. (Su et al., 2019). From 2002 to 2012, a lineage-mismatch occurred between the vaccine and circulating influenza B virus strains in five of the 10 influenza seasons (Lo et al., 2013).

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Although it is accepted that matched strains provide the best protection, recent studies provide us more evidence on the protective efficacy of mismatched strains (Beyer et al., 2017). A systemic review of randomized clinical trials showed that TIV afforded significant protection against mismatched influenza B among adults (Tricco et al., 2013), and the impact of influenza B lineage mismatch on vaccine effectiveness (VE) was largest in population with low pre-seasonal immunity, namely infants and young children (Beyer et al., 2017). Field studies in recent seasons also showed that VE against influenza B exceeded 50% regardless of lineage match to circulating viruses (Skowronski et al., 2019; Castilla et al., 2018). However, when TIV-vaccinated patients later were infected by influenza B of the other lineage, little is known about the impact of the lineage-mismatched vaccination on the patients' epidemiological and clinical features.

In Taiwan, the most recent community outbreak caused by influenza B occurred in the 2011–2012 season, resulting in 154 deaths and 1704 cases of influenza with complications (pulmonary or neurological complications, myocarditis/pericarditis, or invasive bacterial infection). In that season, influenza B accounted for 72% of all influenza isolates, and among influenza B specimens subject to genetic characterization, 87.2% were of the B/Yamagata lineage, which was not contained in TIV that season (Lo et al., 2013). Since then, the impact of lineage-mismatch on the epidemiology of influenza B has garnered great interest. In this study, we summarize the epidemiology of influenza B following that outbreak, from July 2013 to June 2017, with special emphasis on comparing the occurrence of complications among influenza B patients infected with different lineages and evaluating the impact of lineage-mismatched vaccination.

Methods

Virological surveillance

Taiwan Centers for Disease Control (TCDC) operates a national influenza laboratory surveillance network that collects respiratory specimens from different sources to monitor changes in the circulating influenza strains. We analyzed all available data retrieved from two surveillance systems from July 1, 2013 to June 30, 2017. The influenza seasons were defined as starting on July 1 and ending on June 30 of the next year.

1. Surveillance for influenza-like illness (ILI) outpatients

Convenience respiratory samples (throat or nasal swabs) from outpatients with ILI were collected by general practitioners in local clinics or doctors in medical centers, from 21 of the 22 counties/cities in Taiwan (Lo et al., 2013). ILI is defined as fever $\geq$38.0 °C plus respiratory symptoms and at least one of the following: myalgia, headache, or general malaise.

1. Surveillance for intensive care unit (ICU)-admitted influenza patients with complications

In Taiwan, severe complicated influenza is a nationally notifiable disease. During the 2013–2014 influenza season, a suspected case was defined as a patient who was hospitalized or died within four weeks of the onset of ILI associated with at least one specific complication (pulmonary or neurological complications, myocarditis/pericarditis, or invasive bacterial infection). A confirmed case was a suspected case with a positive influenza reverse transcription-polymerase chain reaction (RT-PCR) and/or virus isolation (Lo et al., 2013). During the subsequent seasons from 2014–2017, the definition of a confirmed case was restricted to patients admitted to ICU within two weeks of ILI onset with at least one specific complication and virological evidence of influenza infection (Taiwan Centers for Disease Control, 2014). In the 2013–2014 season, only ICU-admitted cases were included in the current study to ensure data consistency.

1. Specimens processing, virus culture, and antigenic analysis

Respiratory specimens collected from the above systems were sent to one of the eight contract laboratories for influenza viral culture and/or RT-PCR. Influenza viruses isolated using Madin-Darby canine kidney (MDCK) cells were sent to the TCDC central laboratory. For genetic characterization, we randomly selected 2–3 isolates of each type/subtype influenza viruses per week and per contract laboratory. Because the hemagglutination inhibition titer of isolates needs to be $\geq$8 for successful characterization, we chose isolates with high titer for further antigenic characterization. Detailed methods have been described previously (Yang et al., 2012).

We calculated the proportion of influenza B among all influenza isolates and the relative proportions of the two influenza B lineages among all genetically characterized isolates for each season. The lineage that accounted for more than 50% of all influenza B characterized was designated as the predominant circulating lineage of the season. Vaccine strains of influenza B virus contained in the northern hemisphere TIV in each season were retrieved from World Health Organization recommendations (WHO website, 2019). Mismatch status was defined as the predominant circulating influenza B lineage is different from what is contained in the TIV of the corresponding season.

Collection of epidemiological information

For ILI outpatients, reporting of epidemiological information is not mandatory, therefore the information completeness is suboptimal and not used for further analysis. For ICU-admitted influenza patients with complications, epidemiological information was mandatorily collected through National Notifiable Disease Surveillance System (NNDSS) to TCDC data warehouse. Medical institutions are required to report suspected cases to corresponding local health department $\leq$7 days of case identification. Local public health professionals verified case characteristics including presenting symptoms, dates of illness onset and hospitalizations, types of complications, vaccination status and underlying medical conditions based on physician's reports and hospital records (Lo et al., 2013). Valid influenza vaccination was defined as completion of influenza vaccination of the corresponding season more than 14 days prior to the onset of illness. We compared the demographics, underlying diseases, clinical manifestations, vaccination history, and treatment courses between ICU-admitted patients infected with different influenza B lineages.

Statistical analysis

Variables were analyzed using SAS® 9.4 software (SAS Institute Inc., Cary, North Carolina, USA). Nominal variables were compared using the chi-square test or Fisher's exact test, and continuous variables were compared using the Wilcoxon rank-sum test. Statistical significance was set at $p < 0.05$.

Ethics statement

Data analyzed in this study were obtained for surveillance purposes. TCDC determined this research a public health response and exempt from Institutional Review Board review.

Results

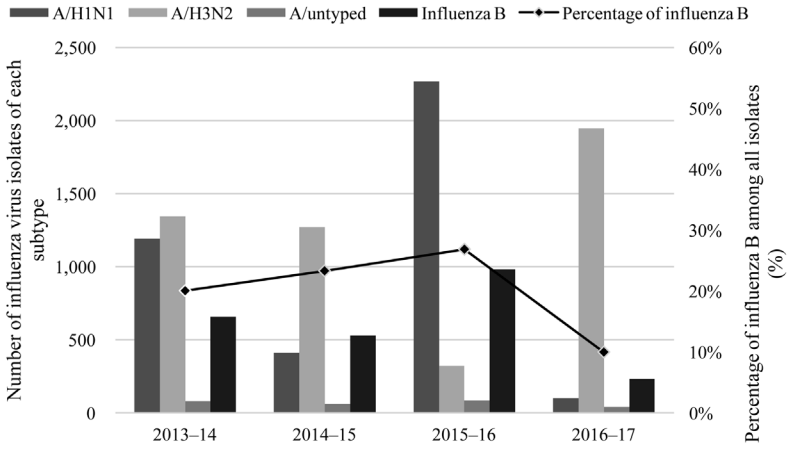
Overview of circulating influenza strains in the seasons of 2013–2017

During the four influenza seasons of surveillance included in this study, 11517 influenza virus isolates were collected from ILI outpatients and ICU-admitted influenza patients with complications. Influenza B viruses accounted for 20% (657/3271), 23% (528/2270), 27% (981/3656), and 10% (231/2320) of all influenza virus isolates from the 2013–2017 influenza seasons, respectively (Figure 1). Among ILI cases in the four seasons, 30.7% (429/1395) in 2013–2014, 27.3% (405/1481) in 2014–2015, 43.9% (720/1639) in 2015–2016, and 11.6% (163/1401) in 2016–2017 were caused by influenza B, respectively. Among ICU-admitted influenza patients with complications in the four seasons, 12.1% (228/1876), 15.6% (123/789), 12.9% (261/2017), and 7.4% (68/919) were caused by influenza B, respectively. The proportion of influenza B infections were higher among ILI outpatients than among ICU-admitted influenza patients with complications, and this difference was consistent across all seasons ($p < 0.01$).

In the study period, a random sample of 617 of the overall 2397 (25.7%) influenza B isolates from ILI outpatients or ICU-admitted influenza patients with complications underwent further genetic and antigenic characterization. Influenza B/Victoria was the predominant circulating lineage in the 2013–2014 season, accounting for 56% among all influenza B isolates characterized. Influenza B/Yamagata was the predominant circulating lineage in the following three seasons, accounting for 82%, 69%, and 85% of all influenza B isolates characterized in 2014–2015, 2015–2016, and 2016–2017, respectively (Figure 1). Compared to specimens collected from ILI outpatients, the proportion of influenza B/Yamagata among all influenza B isolates characterized was higher among specimens collected from ICU-admitted influenza patients with complications (Figure 2).

Epidemiological features of ICU-admitted influenza B patients with complications

From July 1, 2013 to June 30, 2017, 6525 cases of influenza with complications were reported to NNDSS and confirmed. To ensure data consistency, we excluded non-ICU admission (n = 219), duplicate records (n = 102), and cases with no confirmed vaccination status for the corresponding season (n = 5), which left 490 patients for further analysis (Table 1). The median age of patients was significantly lower in the 2013–2014 season (53 vs. 60–67 years, $p < 0.05$), which was the only season predominated by B/Victoria. Seventy-six percent (375/490) of all patients had at least one underlying condition and the distribution of diseases slightly differed between seasons. The overall mortality was 20%



Vaccine lineage[a]	Yamagata	Yamagata	Yamagata	Victoria
Vaccine strain	B/Massachusetts/2-2012-like	B/Massachusetts/2-2012-like	B/Phuket/3073/2013-like	B/Brisbane/60/2008-like
Predominant circulating lineage (%[b])	Victoria (56)	Yamagata(82)	Yamagata(69)	Yamagata(85)
Match status[c]	Mismatch	Match	Match	Mismatch

a. The lineage of influenza B virus contained in the northern hemisphere trivalent influenza vaccine for the corresponding season.

b. Proportion of the specific lineage obtained from randomly selected influenza B isolates from patients with influenza-like illness and intensive care unit-admitted patients with complications in the corresponding year.

c. Mismatch indicates that the vaccine strain and predominant circulating strain are of different lineages.

Figure 1. Number and percentage of influenza infections and their relation to the vaccine strain, Taiwan, 2013–2017 (n = 11517).

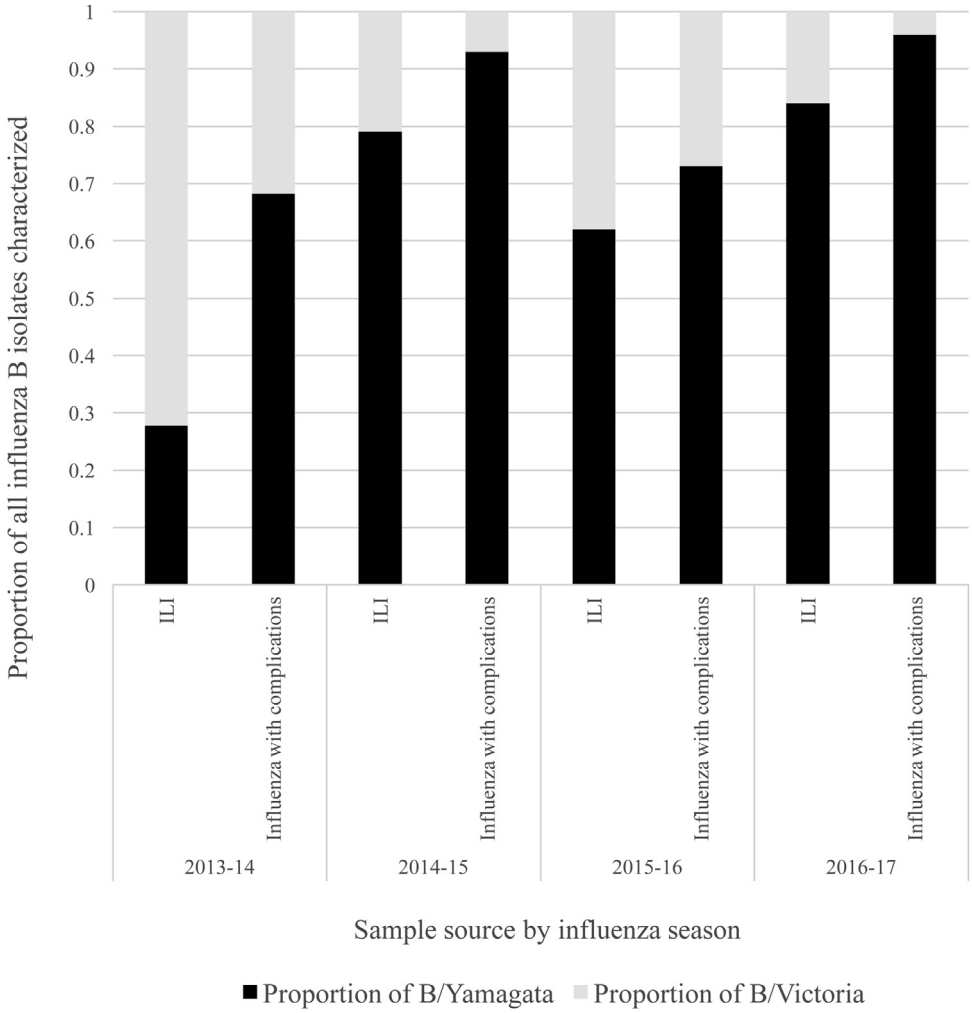


Figure 2. The annual proportion of B/Yamagata and B/Victoria among the subset of influenza B isolates characterized from outpatients with influenza-like illness (ILI) and intensive care unit-admitted influenza patients with complications, 2013–2017.

(98/490). Only 12.2% of all cases had received valid seasonal influenza vaccine for the corresponding season.

Comparative epidemiology of ICU-admitted influenza B patients with complications by lineage

Among the 490 ICU-admitted influenza B patients with complications, genetic characterization of virus isolate was conducted for 136; 111 of these patients were infected with B/Yamagata and 25 were infected with B/Victoria. The characteristics of the patients infected by each lineage are compared in Table 2. The median age of B/Victoria infected patients was lower (59 vs. 71 years, $p < 0.05$). While 24% of B/Victoria cases were $\leq$18 years old, only 8% of B/Yamagata cases were $\leq$18 years old.

Sixty-eight percent of all patients had at least one underlying disease, with metabolic diseases the most prevalent (32% of all patients). In general, the prevalence of underlying diseases did not differ between patients infected with the different lineages; the exception was cardiovascular diseases, which were more common in B/Yamagata infected patients (35% vs. 8%, $p < 0.05$). More than 80% of patients had pulmonary complications, and 96% of all patients were treated with neuraminidase inhibitors, with more than half treated within 48 h of illness onset. Both the duration of hospitalization and ICU stay were longer in B/Yamagata infected patients (15 vs. 7.5 days, $p < 0.05$ and 8.5 vs. 5.5 days, $p < 0.05$, respectively).

Age-stratified analysis was performed to clarify the effect of age on duration of hospitalization and ICU stay. Among patients younger than 65 years of age with duration of hospitalization available, the hospitalization duration of B/Yamagata infected patients ($n = 29$) was longer than those infected with B/Victoria ($n = 10$; 13 vs. 6.5 days, $p < 0.05$). The duration of ICU stay was also longer among B/Yamagata infected patients ($n = 32$ vs. 9; 8.5 vs. 3 days, $p < 0.05$). With further stratification, a similar but statistically insignificant trend in duration of hospitalization was observed for patients $\leq$18 years-old ($n = 5$ vs. 5; 19 vs. 6 days, $p = 0.4$) but not in the 19 to 64 year-old group ($n = 24$ vs. 5; 13 vs. 11 days, $p = 0.13$). Among patients older than 65 years of age, the duration of hospitalization did not differ between patients infected with different lineages (13 days for B/Victoria, $n = 8$ vs. 15 days for B/Yamagata, $n = 50$, $p = 0.79$). The duration of ICU stay showed similar results in this age group (9 days for B/Victoria, $n = 9$ vs. 8.5 days for B/Yamagata, $n = 48$, $p = 0.65$).

Comparative epidemiology of ICU-admitted influenza B patients with complications infected with lineage-level match and mismatch strains

Sixty ICU-admitted influenza B patients with complication had received valid seasonal influenza vaccine. Their median age was 71.5 years old and 50% were 65 years or above. Isolates from 24 of the 60 patients underwent genetic characterization. Compared with vaccine strains for the corresponding season, 13 patients were

Table 1
Epidemiological features of intensive-care unit (ICU)-admitted influenza B patients with complications, Taiwan, 2013–2017 (n = 490).[a]

Influenza season	2013–14 (n = 62)	2014–15 (n = 108)	2015–16 (n = 254)	2016–17 (n = 66)	*p* Value
Age [years; median (range)]	53 (0–95)	60 (1–94)	67.5 (1–100)	66 (4–96)	<0.05
Age group [n(% by column)]					
0–6 years old	8 (13)	4 (4)	11 (4)	2 (3)	
7–18 years old	8 (13)	7 (6)	17 (7)	7 (11)	
19–49 years old	11 (18)	18 (17)	32 (13)	6 (9)	
50–64 years old	14 (23)	32 (30)	54 (21)	17 (26)	
65 years and above	21 (34)	47 (44)	140 (55)	34 (52)	
Sex [males (%)]	44 (71)	67 (62)	156 (61)	45 (68)	0.44
Underlying diseases					
Cardiovascular diseases	15 (24)	32 (30)	53 (21)	23 (35)	0.07
Metabolic diseases	11 (18)	33 (31)	65 (26)	0 (0)	<0.05
Pulmonary diseases	9 (15)	20 (19)	41 (16)	1 (2)	<0.05
Renal disease	5 (8)	18 (17)	31 (12)	14 (21)	0.12
Liver diseases	4 (6)	7 (6)	19 (7)	7 (11)	0.75
Neuromuscular diseases	2 (3)	7 (6)	7 (3)	4 (6)	0.29
Malignancy	0	2 (2)	11 (4)	6 (9)	0.04
At least one of the above	41 (66)	90 (83)	183 (72)	61 (92)	<0.05
Clinical manifestations					
Pulmonary complications	52 (84)	100 (93)	229 (90)	60 (91)	0.35
Neurological complications	5 (8)	5 (5)	15 (6)	5 (8)	0.73
Pericarditis or myocarditis	3 (5)	6 (6)	9 (4)	2 (3)	0.77
Invasive bacterial infections	2 (3)	5 (5)	4 (2)	2 (3)	0.30
Treatment courses					
Treatment with neuraminidase inhibitors	61 (98)	108 (100)	246 (97)	65 (98)	0.25
Treatment with neuraminidase inhibitors with 48 h of illness onset[b]	45 (74) (n = 61)	83 (77) (n = 108)	182 (72) (n = 254)	48 (74) (n = 65)	0.86
Duration of hospitalization[b] [days; median (range)]	15 (1–106) (n = 56)	15 (0–57) (n = 87)	15 (0–129) (n = 183)	12 (0–110) (n = 56)	0.67
Length of ICU stay[b] [days; median (range)]	7 (0–43) (n = 53)	7 (0–53) (n = 82)	9 (0–57) (n = 185)	7 (0–66) (n = 51)	0.38
Death	12 (19)	17 (16)	53 (21)	16 (24)	0.55
Valid seasonal influenza vaccine (%)[c]	7 (11)	11 (10)	30 (12)	12 (18)	0.44

[a] Values are number (percentage) unless otherwise indicated.
[b] Only valid values were included in the analyses.
[c] A valid vaccination was defined as completion of influenza vaccination of the corresponding season >14 days before symptom onset.

infected with the matching strain and 11 were infected with the mismatching strain. The patient demographics, underlying diseases, clinical manifestations, and treatment courses did not differ based on whether their infection lineage was contained in the vaccine (Table 3). Among the 24 cases, 18 were infected by B/Yamagata and six by B/Victoria. While none of the six vaccinated patients infected by B/Victoria virus had received a matched strain vaccine, 72% (13/18) vaccinated patients infected by B/Yamagata had been vaccinated against the same lineage.

Discussion

In this nationwide study of influenza B epidemiology over four consecutive seasons, we found that after a major epidemic in 2011–2012, the influenza B virus continuously circulated in Taiwan and accounted for 10%–27% of all influenza isolates in the following years. The Global Influenza B Study (GIBS) collected virological and epidemiological data from 26 countries during the period of 2000–2013; it showed that the median proportion of influenza B among influenza cases was 22.6%, varying between countries from 7% to 38% (Caini et al., 2015). Our results are in accordance with global epidemiological data and show that although the proportion of ICU-admitted influenza patients with complications caused by influenza B was lower than influenza A, influenza B still poses a non-negligible threat to the community in most seasons.

Influenza B/Yamagata and B/Victoria tend to co-circulate in Taiwan. A previous study performed by our group showed that in 2004–2012, the two lineages of influenza B tended to co-circulate for two to three seasons, and an abrupt switch in lineage predominance may take place in the following year (Yang et al., 2012). Data from other related studies also showed similar results (Caini et al., 2015; Chan et al., 2013). In Taiwan, B/Yamagata was the predominant lineage from 2014 to 2017. Lineage switch, as well as the emergence of a different B/Yamagata virus clade, may lead to the next epidemic (Yang et al., 2012; Cowling et al., 2017). The importance of cautiously monitoring changes in influenza B epidemiology cannot be over-emphasized. TCDC has multiple surveillance systems to monitor influenza epidemiology (Jian et al., 2017). ILI syndromic surveillance and pneumonia & influenza mortality surveillance provides information on real-time epidemic trend and the disease burden, but no case-based information or virological sample is available. Surveillance for ILI patients and ICU-admitted influenza patients with complications provide virological specimens for testing and further genetic analysis. Together with the epidemiological information of ICU-admitted influenza patients with complications collected from NNDSS, we are able to describe the epidemiology of these patients in more detail. Case-based surveillance for patients with all levels of severity (from ILI to death) provides the most abundant information on the changing epidemiology but is not possible in nationwide surveillance systems. Our current surveillance system targeting ICU-admitted influenza patients with complications allows us to monitor change in virology that poses the most severe threat to human health.

Age differences in patients infected with B/Yamagata and B/Victoria have been reported. A community-based study in Canada across 16 influenza seasons showed that in outpatients with ILI, the median age of B/Victoria infected patients was 20

Table 2
Characteristics of intensive care unit (ICU)-admitted influenza B patients with complications by lineage, Taiwan, 2013–2017[a] (n = 136).

Characteristics	Victoria-lineage (n = 25)	Yamagata-lineage (n = 111)	*p* Value
Age [years; median (range)]	59 (3–100)	71 (4–95)	<0.05
Age groups [n (% by column)]			
0–6 years old	2 (8)	3 (3)	
7–18 years old	4 (16)	5 (5)	
19–49 years old	5 (20)	9 (8)	
50–64 years old	2 (8)	28 (25)	
65 years old and above	12 (48)	66 (59)	
Sex [males (%)]	15 (60)	69 (62)	0.82
Underlying diseases			
Metabolic diseases	7 (28)	36 (32)	0.81
Pulmonary diseases	4 (16)	18 (16)	1.00
Renal disease	4 (16)	16 (14)	0.76
Liver diseases	3 (12)	8 (7)	0.42
Cardiovascular diseases	2 (8)	39 (35)	<0.05
Neuromuscular diseases	2 (8)	5 (5)	0.61
Malignancy	0	3 (3)	1.00
At least one of the above	14 (56)	78 (70)	0.24
Clinical manifestations			
Pulmonary complications	22 (88)	101 (91)	0.71
Neurological complications	3 (12)	3 (3)	0.08
Pericarditis or myocarditis	1 (4)	2 (2)	0.46
Invasive bacterial infections	0	1 (1)	1.00
Treatment courses			
Treatment with neuraminidase inhibitors	24 (96)	107 (96)	1.00
Treatment with neuraminidase inhibitors within 48 h of illness onset[b]	18 (75) (n = 24)	85 (79) (n = 107)	0.63
Duration of hospitalization[b] [days; median (range)]	7.5 (0–57) (n = 18)	15 (0–73) (n = 79)	<0.05
Length of ICU stay[b] [days; median (range)]	5.5 (0–17) (n = 18)	8.5 (0–53) (n = 80)	<0.05
Death	4 (16)	26 (23)	0.59
Vaccination[c]	6 (24)	18 (16)	0.39
Days from vaccination to illness onset [days; median (range)]	145 (108–187)	161 (81–303)	0.55

[a] Values indicate number (percentage) of patients unless otherwise indicated.
[b] Only valid values were included in the analyses.
[c] A valid vaccination was defined as >14 days between completion of season influenza vaccination and symptom onset.

years younger than B/Yamagata infected patients (20 vs. 40 years) (Skowronski et al., 2017). A 13-year study conducted in Australia and New Zealand showed that the mean age of B/Victoria infected patients was 10 years younger (16.8 vs. 26.6 years) (Vijaykrishna et al., 2015). Both studies showed that B/Yamagata cases had a bimodal age distribution, preferentially affecting those younger than 20 and 25–64 years of age (Skowronski et al., 2017; Vijaykrishna et al., 2015). Possible pathophysiological explanations of the age differences among patients infected with B/Yamagata and B/Victoria are summarized as follows. First, subtle differences in the prevalence of alpha-2,3- and alpha-2,6-linked glycans on the cells of the respiratory tract of young children and a higher effective transmission coefficient could both account for the observed differential age distribution of the two influenza B lineages (Vijaykrishna et al., 2015). Second, B/Victoria viruses may induce a broader immune response and confer better protection in older age groups (Vijaykrishna et al., 2015). Third, historical influenza B exposures may later modify the risk of contemporary influenza B infection by age, causing birth (immunological) cohort effect (Skowronski et al., 2017). We collected data from ICU-admitted influenza patients with complications and a median age around 60, which is different from the population of previous studies, and likewise found that patients infected with B/Yamagata were significantly older (71 vs. 59 years of age).

There have been several reports with conflicting results regarding differences in the clinical presentation and severity of cases involving influenza B/Yamagata and B/Victoria infection. A study of children in Hong Kong revealed that influenza B/Victoria infection was associated with greater hospitalization burden compared with B/Yamagata (Cowling et al., 2017). In contrast, a study in southern Taiwan showed B/Yamagata was associated with more invasive infections in children (Chi et al., 2008). Minor differences in the distribution of signs and symptoms across B/Yamagata and B/Victoria have also been reported (Mosnier et al., 2015). Our study presents several findings suggesting that B/Yamagata causes more severe illness. First, influenza B/Yamagata was the major lineage causing ICU-admitted influenza B with complications. Second, among the patients younger than 65 years of age, the hospitalization duration and length of ICU stay were longer in B/Yamagata infected ICU-admitted patients with complications than those infected with B/Victoria. Our surveillance system collects ICU-admitted patients with high median age and high prevalence of underlying medical conditions. Since patient age is a potential confounder that may bias the association between virus subtype and disease severity, we performed age-stratified analysis and found hospitalization duration and length of ICU stay were longer in B/Yamagata infected ICU-admitted patients younger than 65 years old but similar in those older than 65 years old. Although we were unable to demonstrate a difference in mortality among our group of ICU-admitted patients, the difference in hospitalization and ICU stay length may serve as a proxy for illness severity. Differences in the length of hospital stay of patients infected by various influenza viruses has been thoroughly reviewed in recent articles (Álvarez-Lerma et al., 2017; Puig-Barberà et al., 2016) but comparisons between B/Victoria and B/Yamagata are lacking. To our knowledge, our study is the first report showing that B/Yamagata infected ICU-admitted patients

Table 3
Comparative epidemiology of intensive care unit (ICU)-admitted influenza B patients with complications infected with lineage-level match and mismatch strains compared with vaccine strains, Taiwan, 2013–2017[a] (n = 24).

Characteristics	Lineage-match (n = 13)	Lineage- mismatch (n = 11)	*p* Value
Age [years; median (range)]	84 (7–91)	73 (8–89)	0.20
Age groups [n (% by column)]			
0–6 years old	0	0	
7–18 years old	3 (23)	3 (27)	
19–49 years old	0	1 (9)	
50–64 years old	1 (8)	1 (9)	
65 years old and above	9 (69)	6 (55)	
Male	6 (46)	8 (73)	0.24
Underlying diseases			
Cardiovascular diseases	3 (23)	3 (27)	1.00
Metabolic diseases	2 (15)	2 (18)	1.00
Pulmonary diseases	2 (15)	2 (18)	1.00
Renal disease	2 (15)	1 (9)	1.00
Neuromuscular diseases	2 (15)	0	0.48
At least one of the above	9 (69)	6 (55)	0.68
Clinical manifestations			
Pulmonary complications	11 (85)	9 (82)	1.00
Neurological complications	0	1 (9)	0.46
Pericarditis or myocarditis	0	1 (9)	0.46
Treatment courses			
Treatment with neuraminidase inhibitors	12 (92)	10 (91)	1.00
Treatment with neuraminidase inhibitors within 48 h of illness onset[b]	8 (67) (n = 12)	9 (90) (n = 10)	0.44
Duration of hospitalization[b] [days; median (range)]	19 (0–47) (n = 11)	8 (1–22) (n = 9)	0.07
Length of ICU stay[b] [days; median (range)]	10 (0–25) (n = 11)	7 (1–17) (n = 7)	0.53
Death	4 (31)	1 (9)	0.32

[a] Values indicate number (percentage) of patients unless otherwise indicated.
[b] Only valid values were included in the analyses.

with complications have longer hospitalizations and ICU stays, indicating that B/Yamagata causes more severe illness.

Taiwan has annual seasonal influenza mass vaccination campaigns. TIV have been used since the campaign started in 1998. The vaccine coverage among the Taiwanese population has gradually increased from less than 10% in 2001 to 26% in the 2016–2017 season (Meyer et al., 2018). In the 2017–18 season, the TIV coverage for elderly ≥65 years old, school-aged children/adolescent 7–18 years old and children 0.5–6 years old are 49%, 76% and 58%, respectively (Su et al., 2019). After the vaccine-mismatched influenza B outbreak in 2011–2012, there has been debate about whether quadrivalent vaccine should be used to offer better protection for the population. In years when both lineages co-circulate, the protection offered by TIV may be limited even when the predominant lineage matches the one contained in the vaccine. We analyzed patients infected with lineage matched and mismatched influenza B strains and assumed that patients infected with lineage matched influenza B strains will have less severe illness because vaccine-induced antibody may modify illness course and provide some protection. However, in our case series of ICU-admitted influenza patients with complications, their clinical and demographic characteristics did not differ. The small case number and lack of statistical power impede us from drawing any conclusion on this issue and more study is needed.

In Taiwan, influenza B/Yamagata viruses had multiple interlaced clades that evolved independently over time, whereas influenza B/Victoria viruses evolved from a single cluster resulting in ladder-like branches (Yang et al., 2012; Kuo et al., 2016). Our previous study, conducted in 2011–2012, revealed that when multiple clades of B/Yamagata co-circulate in the community, the hemagglutinin inhibition titer would decrease, indicating that the viruses have diversified antigenically and may lead to lower vaccine-induced protection (Yang et al., 2012; Kuo et al., 2016). Seasonal change in virus antigenicity, difference in antibody response induced by vaccination containing different virus strains, and host factors may all contribute to infection in vaccinated patients. Given small numbers and without a control group, we could not evaluate lineage-specific VE. Study of the genetics and antigenicity of influenza B viruses from 2013–2017 in Taiwan is underway and will hopefully provide more information on the effects of antigenic change on the level of vaccine protection.

There are several limitations of this study. First, genetic analysis was only performed on 27.8% (136/490) of all influenza B isolates from ICU-admitted influenza patients with complications. Although the isolates were randomly selected for genetic analysis as previously described, there is a possibility that those with higher viral loads were selected more frequently. Second, samples from ILI patients were collected by sentinel doctors by convenience rather than using a systemic random sampling method. Third, age and demographic information for the ILI patients collected through sentinel surveillance is lacking. Therefore, comparison between ILI and ICU-admitted influenza patients with complications was not possible. Fourth, the number of cases with genetic analysis is not enough for us to perform multivariate analysis to elucidate the effect of underlying diseases, treatment courses and other factors that may affect the severity and outcome of influenza infection. Finally, because no control group was available, the VE and level of cross-protection between mismatch strains could not be evaluated. However, as these findings have been obtained from a nationwide surveillance system with more than 10,000 samples, we believe that the results of our study still shed light on lineage-specific epidemiology of influenza B.

In conclusion, we found that the two lineages of influenza B tend to co-circulate and affect different age groups in Taiwan. B/Yamagata causes more severe illness in an older age group. Further research is needed to calculate VE and level of

cross-protection of vaccines for the two lineages of influenza B in Taiwan.

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Conflicts of interest

The authors declare no conflict of interest.

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