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RESEARCH ARTICLE

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Surveillance of influenza B severe hospitalized cases during 10 seasons in Catalonia: Does the lineage make a difference?

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Abstract

Influenza B viruses circulate in two lineages (B/Victoria and B/Yamagata). Although classically affecting children, recently it has shown a high rate of infection and increased hospitalization in the elderly. To describe and analyze the clinical and epidemiological characteristics of severe hospitalized laboratory-confirmed influenza B virus (SHLCI-B) cases in Catalonia associated with mismatch from Influenza B virus strain included in the trivalent influenza vaccine (TIV). SHLCI-B was registered by the influenza sentinel surveillance system of Catalonia (PIDIRAC) during ten surveillance seasons from 2010 to 2020. Variables age, comorbidities, and vaccination status were recorded. Vaccine effectiveness was estimated as (1-OR) for intensive care unit (ICU) admission. Statistical significance was established at $p < 0.05$. A total of 1159 SHLCI-B were registered, of these 68.2% (791) corresponded to the 2017–2018 season; 21.8% (253) were admitted to ICU and 13.8% (160) were exitus; 62.5% (725) cases occurred in those aged >64 years; most frequent risk factor was cardiovascular disease (35.1%, 407) followed by chronic pulmonary obstructive disease-COPD (24.6%, 285) and diabetes (24.1%, 279). In four seasons, the predominant circulating lineage was B/Victoria, in two seasons the B/Yamagata lineage and four seasons had no IBV activity. Four seasons presented discordance with the strain included within the TIV. Vaccine effectiveness (VE) to prevent ICU admission was 31% (95% confidence interval [CI]: 4%–51%; $p = 0.03$); being 29% (95% CI: −3% to 51%) in discordant and 43% (95% CI:−43% to 77%) in concordant seasons. Significant differences were observed in the number of affected aged > 64 years (odds ratio [OR] = 2.5; 95% CI: 1.9–3.4; $p < 0.001$) and in patients with heart disease (OR = 2.40 95% CI: 1.7–3.4; $p < 0.001$), COPD (OR = 1.6 95% CI: 1.1–2.3; $p = 0.01$), and diabetes (OR = 1.5 95% CI: 1.1–2.1; $p = 0.04$) between discordant and concordant seasons. The increase in hospitalization rate in people> 64 years of age and those presenting comorbidities in seasons with circulating influenza B virus belonging to a lineage discordant with the strain included in the TIV and the decrease of VE to prevent ICU

admissions evidence the vital need to administer the quadrivalent influenza vaccine regardless of the findings of predominant circulation in the previous season.

KEYWORDS
Influenza B virus, lineage, surveillance, vaccine

1 | INTRODUCTION

Influenza B viruses (IBV), enveloped viruses with single-stranded, negative, and segmented RNA genome, cause significant morbidity and mortality through the influenza season.[1,2] Influenza B was first isolated in 1940, and has circulated in humans for almost a century, showing a particular epidemiological pattern, while in some influenza seasons IBV predominates globally, in others is less prevalent or missing.[3,4] IBV undergoes continuous evolution through genetic variations such as genetic drift from cumulative mutations, including insertions and deletions, that could alter antigenic features, and segment reassortment among co-circulating strains.[5,6] In contrast with influenza A viruses, IBV has a limited host range, almost exclusive to humans and therefore, apparently, lacking pandemic potential. Based on genetic divergence of the viral hemagglutinin (HA) gene, two antigenically distinct phylogenetic lineages represented by the prototype virus B/Victoria/2/87 (B/Victoria-lineage, B/VIC) and B/Yamagata/16/88 (B/Yamagata-lineage, B/YAM) have been co-circulating globally and often alternating in regional dominance.[7,8] Since 2015, during the pre-COVID-19 pandemic seasons, both lineages have shown unusually high levels of epidemic activity, the reasons for which are still unclear.[9,10]

The primary measure to prevent influenza-related disease is vaccination. Since late 1970s a trivalent vaccine composition containing one influenza A (H1)/A (H1) pdm09, one A (H3) antigens, and a single influenza B antigen has been used for seasonal influenza prevention and control. Data regarding the burden of severe influenza B are critical to understanding the rationale of the administration of quadrivalent Influenza vaccine (QIV) in the influenza immunization program.[11] Although the two IBV lineages have circulated since the mid 1980s showing antigenic differences between them and a low level of cross-protection with TIV vaccine with a single influenza B lineage component,[12–14] both Influenza B lineages have co-circulated since the mid 1980s showing little cross-protection between them and making available quadrivalent vaccines a current recommendation.[12] In parallel to the monitoring of influenza activity, antigenic and genetic characterization of influenza viruses based on antigen (HA and NA) properties of circulating strains should be further carried out to monitor IBV genetic diversity, update the composition of the influenza vaccine, to monitor the emergence of resistant viruses to antivirals and to detect changes in tissue tropism and virulence. IBV is an essential component of the annual influenza vaccine and the best method for preventing influenza. In addition to the two strains of different influenza A subtypes, only one strain of IBV is included in the trivalent vaccine based on the circulating strains at the time and two in the quadrivalent vaccine. The antigenic divergence between IBV lineages can be responsible for the lack of cross-reactivity.[12]

Regarding the B lineage, the no concordance between circulating viruses and vaccine strains might lower vaccine effectiveness in the prevention of severity, meaning higher hospitalization, intensive care unit admissions, and mortality. Since 2010, the Acute Respiratory Infection Surveillance Plan in Catalonia (PIDIRAC) included the surveillance of severe hospitalized laboratory-confirmed influenza cases to prospectively collect epidemiological and virological data on patients hospitalized with confirmed influenza virus infection. The system is based on a hospital sentinel network, coordinated by the Public Health Agency of Catalonia, which is made up of 14 tertiary level hospitals distributed along with the territory and covers approximately 62% of the total population.[15] The study described influenza B virus strain circulation in participant hospitals and examined factors associated with complicated hospitalization among patients admitted with laboratory-confirmed influenza B illness.

The aim of this retrospective surveillance study during 10 epidemic seasons (2010—2020) was to describe and analyze the clinical and epidemiological characteristics of severe hospitalized laboratory-confirmed influenza B virus (SHLCI-B) cases in Catalonia and to analyze the association of clinical characteristics and influenza B virus lineages.

2 | MATERIALS AND METHODS

A retrospective observational epidemiological study was carried out in patients hospitalized due to severe acute influenza virus infection caused by Influenza virus type B during 10 epidemic seasons (2010–2020). A severe hospitalized laboratory-confirmed influenza (SHLCI) case was defined as a case of laboratory-confirmed influenza virus infection that required hospitalization due to pneumonia, septic shock, multiorgan failure, or any other severe condition, including ICU admission or death.[16] The diagnosis was confirmed by polymerase chain reaction (PCR) and/or culture of nasopharyngeal swabs on admission. Subsequently, two specific one-step multiplex real-time PCR techniques using Stratagene Mx3000P QPCR Systems (Agilent Technologies) were carried out to type A/B influenza viruses.[17] Phylogenetic analysis of HA1 and NA sequences from SHLCI-related IBV were performed to determine the genetic clade classification as described previously,[18] together with reference sequences as guided by ECDC/GISRS.

2.1 | Statistical analysis

Variables studied were age, comorbidities, IBV lineage, and strain included in recommended TIV composition per season and vaccination status. Comparison of proportions was assessed by the z statistic and *t* Student for the comparison of means. We estimated crude and adjusted odds ratio (OR) and their corresponding 95% confidence intervals (CI) using logistic regression models. Vaccine effectiveness (1-OR) to prevent intensive care unit (ICU) admission was assessed. Significance was established at $p < 0.05$. Analysis was performed using the SPSS v.25 statistical package and R v3.5.0 statistical software (http://cran.r-project.or).

3 | RESULTS

The study included 1159 SHLCI cases caused by IBV infection at the sentinel hospitals. Of these, 68.2% (791) corresponded to the 2017–2018 seasons (Figure 1), 21.8% (253) were admitted to ICU, and 62.5% (725) cases occurred in those aged 64 years and older. The most affected age group among the pediatric population (0–14 years) was the 0–4 years group (63.4%; 64). The most frequent risk factor was cardiovascular disease (35.1%, 407) followed by chronic pulmonary obstructive disease COPD (24.6%, 285), and diabetes (24.1%, 279). Sixty-five percent (758) of cases presented pneumonia and 43% (325) of these with bacterial coinfection.

In four epidemic seasons (2010–2011, 2015–2016, 2016–2017, and 2019–2020) the B/Victoria lineage circulated, although the IBV circulation was only considerable in the 2015–2016 season (21.5% of the total SHLCI-B), in two of the six seasons (2011–2015 and 2017–2019) with circulation of B/Yamagata lineage, IBV was predominant (2012–2013 and 2017–2018 with 59.3% and 60.7%, respectively). Of the B/Victoria lineage circulating during the 2017–2018 influenza season, 66 (54%) belonged to a subgroup represented by B/Norway/2409/2017, which carries HA1 double amino acid deletion, Δ162–163 (deletion of amino acids K162 and N163 in the HA1 subunit), characteristic of a new antigenically distinct subgroup (Table 1).

Mean age of cases was 64.7 year (SD 24.4) and the median was 71 year (range 0–101). Differences in mean age of cases was observed, being 67.5 year (SD 21.6) for cases in B/Yamagata lineage predominant seasons versus 51.8 year (SD 31) for B/Victoria lineage being the difference statistically significant ($p < 0.001$). B/Victoria lineage affected a greater proportion of the 0–14 and 15–44 age groups (22.5% and 11.8% vs. 5.8% and 5.1%; $p < 0.001$) while B/Yamagata affected a greater proportion of the >64 age group (65.9 vs. 46.6; $p < 0.001$). Significant differences were observed between discordant and concordant seasons in the number of affected aged >64 years (66.9% vs. 44.3%; OR = 2.5 95% CI: 1.9–3.4; $p < 0.001$), in patients with cardiovascular disease (OR = 2.40 95% CI: 1.7–3.4; $p < 0.001$), COPD (OR = 1.6 95% CI: 1.1–2.3; $p = 0.01$) and diabetes (OR = 1.5 95% CI: 1.1–2.1; $p = 0.04$) as comorbidity risk factors for severe outcomes. Age and comorbidity distribution of SHLCI-B cases according to predominant lineage circulation are shown on Tables 2 and 3.

In four seasons (2013–2014, 2015–2016, and 2017–2019) (57%) discordance was observed with the strain of IBV included in the trivalent influenza vaccine (TIV). Table 1. Vaccine effectiveness (VE) of TIV to prevent ICU admission was 31% (4%–51%; $p = 0.03$) being 29% in discordant seasons and 43% in concordant seasons. In B/Yamagata lineage predominant seasons, VE was 32% (95% CI; 1, 53: $p = 0.04$) and adjusted VE (aVE) was 17% (95% CI; −24 to 44: $p = 0.36$) while in B/Victoria predominant seasons VE was 30% (95% CI; −54 to 69: $p = 0.37$) and aVE was 5% (95% CI; −131 to 61: $p = 0.91$) (Table 4).

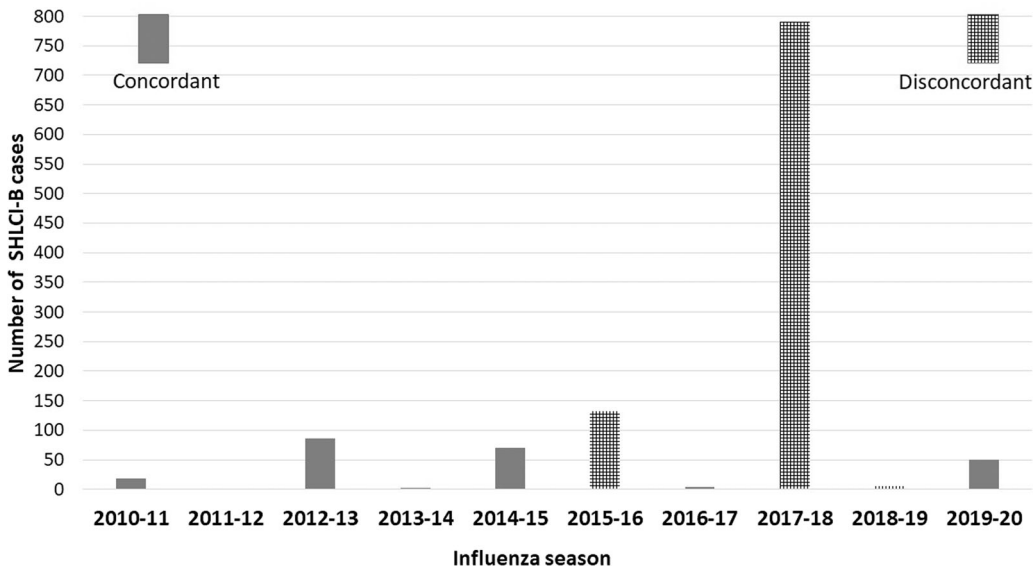

FIGURE 1 Distribution of severe hospitalized laboratory-confirmed influenza B cases hospitalized (SHLCI-B) by season and concordance or discordance with the trivalent vaccine strain of IBV. Catalonia 2010–2020.

TABLE 1 Strains included in trivalent influenza vaccine and main circulating strains during each season

Influenza season	Strains included in trivalent influenza vaccine	Main circulating Influenza B virus strains
2010/2011	B/Brisbane/60/2008 (B/Victoria)	B/Brisbane/60/2008 (B/Victoria)
2011/2012	B/Brisbane/60/2008 (B/Victoria)	No relevant circulation of IBV
2012/2013	B/Wisconsin/1/2010 (B/Yamagata)	B/Estonia//55669/2012 B/Yamagata) B/Wisconsin/1/2010 (B/Yamagata)
2013/2014	B/Massachusetts/2/2012 (B/Yamagata)	No relevant circulation of IBV
2014/2015	B/Massachusetts/2/2012 (B/Yamagata)	B/Phuket/3073/2013 (B/Yamagata)
2015/2016	B/Phuket/3073/2013 (B/Yamagata)	B/Brisbane/60/2008 (B/Victoria)
2016/2017	B/Brisbane/60/2008 (B/Victoria)	No relevant circulation of IBV
2017/2018	B/Brisbane/60/2008 (B/Victoria)	B/Phuket/3073/2013 (B/Yamagata) B/Norway/2409/2017 (B/Victoria)*
2018/2019	B/Colorado/06/2017 (B/Victoria) (B/Victoria/2/87 lineage)	No relevant circulation of IBV
2019/2020	B/Colorado/06/2017 (B/Victoria) (B/Victoria/2/87 lineage)	B/Washington/02/2019 (B/Victoria)

Note: Adapted from WHO (Global Influenza Programme (who.int)) and SVGE (Sistema de Vigilancia de la Gripe en España. Red Nacional de Vigilancia Epidemiológica (isciii.es)). B/Victoria lineage clade 1A viruses, 66 (54%) belonged to a subgroup represented by B/Norway/2409/2017, which carries HA1 double amino acid deletion, Δ162–163 (deletion of amino acids K162 and N163 in the HA1 subunit), characteristic of a new antigenically distinct subgroup of viruses that have been detected in several countries during the season.

*This group is antigenically different from the rest of the viruses included in the Victoria lineage. This is also discordant with the strain contained in the vaccine for 2017–2018.

TABLE 2 Distribution of severe hospitalized laboratory-confirmed influenza B cases (SHLCI-B) according to lineage and age group. Catalonia, 2010–2020

Age group (year)	B/Yamagata predominant IBV number of cases (%)	B/Victoria predominant IBV number of cases (%)	*p* value
0–14	55 (5.8)	46 (22.5)	<0.001
15–44	49 (5.1)	24 (11.8)	<0.001
45–64	222 (23.2)	39 (19.1)	0.205
65–84	424 (44.4)	67 (32.8)	0.004
>84	205 (21.5)	28 (143.7)	0.021

4 | DISCUSSION

The present study summarizes the activity and phylogenetic analysis of influenza B viruses circulating in Catalonia during 10 epidemic seasons. The activity and genetic diversity of influenza B viruses in Catalonia were similar to that previously reported in many other countries, particularly in Europe.[4,19,20] In Catalonia, B/Victoria and B/Yamagata strains alternated predominance in the 10 epidemic seasons studied, some of them concordant with trivalent vaccine administered and others discordant. This might present a problem for vaccine effectiveness in the prevention of severity, meaning higher hospitalization, intensive care unit admissions, and mortality.

IBV activity was variable during the study period, with sporadic detections at the beginning of annual epidemics or in the later part of the season, showing particular epidemiology previously reported.[21] Influenza B virus strains for inclusion in influenza vaccine composition in Northern Hemisphere are recommended in February or March based on prevalence of the different circulating antigenic groups and results from seroepidemiological studies in the community worldwide. During the 10 consecutive influenza seasons studied, both lineages have been co-circulating at varying levels in Catalonia, and circulating viruses are congruent with the expected circulation in the upcoming season according to the recommendations by WHO. However, the predominant lineage did not match to the lineage of recommended vaccine strain in 3 out of 10 influenza seasons studied. Since inaccurate prediction of the predominant influenza B lineage in recommended TIV composition might provide limited to no protection against circulating opposite-lineage strains, many vaccinated individuals could be with suboptimal protection against influenza B disease.[22,23] Our data from SHLCI-B cases support the inclusion of both lineages in the quadrivalent seasonal influenza vaccine to improve protection against influenza, resulting in a reduction in the burden of disease in both the community and the healthcare system, and individually, in the prevention of clinical complications, especially in those at high risk for severe disease, as previously suggested by other authors.[24,25]

The divergence of influenza B viruses into two lineages, with year-to-year fluctuations has low seasonal influenza vaccine

TABLE 3 Characteristics of severe hospitalized laboratory-confirmed influenza B cases (SHLCI-B) according to concordance or discordance with circulating lineages with respect to seasonal trivalent influenza vaccine

Age group (year)	Discordant with trivalent vaccine (*N* = 931)	Concordant with trivalent vaccine (*N* = 228)	OR (95%CI)	*p* value	aOR (95%CI)	*p* value
0–14	50 (5.4%)	51 (22.4%)	Ref.		Ref.	
15–44	51 (5.5%)	22 (9.6%)	2.36 (1.25–4.46)	0.01	2.36 (1.25–4.46)	0.01
45–64	207 (22.2%)	54 (23.7%)	3.91 (2.39–6.39)	<0.001	3.91 (2.39–6.39)	<0.001
65–84	415 (44.6%)	76 (33.3%)	5.57 (3.51–8.83)	<0.001	5.57 (3.51–8.83)	<0.001
>84	208 (22.3%)	25 (11.0%)	8.49 (4.80–15.00)	<0.001	8.49 (4.80–15.00)	<0.001
Asthma						
Yes	72 (7.7%)	14 (6.3%)	1.25 (0.69–2.26)	0.46	1.53 (0.83–2.82)	0.18
No	859 (92.3%)	209 (93.7%)	Ref.		Ref.	
COPD						
Yes	245 (26.3%)	40 (18.1%)	1.62 (1.11–2.34)	0.01	1.19 (0.81–1.76)	0.38
No	686 (73.7%)	181 (81.9%)	Ref.		Ref.	
Obesity (BMI > 30)						
Yes	62 (6.7%)	9 (4.1%)	1.68 (0.82–3.44)	0.16	1.55 (0.75–3.20)	0.23
No	869 (93.3%)	212 (95.9%)	Ref.		Ref.	
Diabetis						
Yes	237 (25.5%)	42 (18.9%)	1.46 (1.01–2.11)	0.04	1.04 (0.71–1.53)	0.83
No	694 (74.5%)	180 (81.1%)	Ref.		Ref.	
Renal impairement						
Yes	163 (17.5%)	33 (14.7%)	1.23 (0.82–1.85)	0.31	0.83 (0.54–1.27)	0.38
No	768 (82.5%)	192 (85.3%)	Ref.		Ref.	
Immunodeficiency						
Yes	142 (15.4%)	44 (20.0%)	0.73 (0.50–1.06)	0.10	0.70 (0.48–1.03)	0.07
No	779 (84.6%)	176 (80.0%)	Ref.		Ref.	
Cardiovascular disease						
Yes	361 (38.9%)	46 (20.9%)	2.40 (1.69–3.41)	<0.001	1.66 (1.14–2.41)	0.01
No	568 (61.1%)	174 (79.1%)	Ref.		Ref.	
Liver impairement						
Yes	58 (6.3%)	14 (6.5%)	0.97 (0.53–1.77)	0.91	0.91 (0.49–1.67)	0.76
No	866 (93.7%)	202 (93.5%)	Ref.		Ref.	
Other comorbidities						
Yes	118 (12.8%)	19 (9.2%)	1.45 (0.87–2.41)	0.16	1.46 (0.86–2.47)	0.16
No	803 (87.2%)	187 (90.8%)	Ref.		Ref.	

Note: Catalonia 2010–2020.

Abbreviation: CI, confidence interval; COPD, chronic pulmonary obstructive disease; OR, odds ratio.

effectiveness due to a failure in the prediction of the influenza B components for the trivalent influenza vaccine. In our study, lineage mismatch between vaccine and IBV circulating strains occurred in 57% of seasons, similar to what was observed elsewhere.[9,12] Influenza B cases followed year-to-year fluctuations, being the highest value in 2017–2018 season, which was characterized by a significant influenza B activity in Catalonia and in the European region, being much higher than during the previous seasons with IBV

TABLE 4 Vaccine effectiveness of trivalent Influenza vaccine to prevent intensive care unit admission according to circulating IBV strain concordance with the seasonal vaccine and to predominant lineage

Season with IBV circulation concordant with trivalent vaccine						
	Intensive care admission (*N* = 36)	**Nonintensive care admission (*N* = 125)**	**OR (95% CI)**	***p* value**	**aOR (95% CI)**	***p* value**
Vaccinated						
Yes	7 (19.4%)	37 (29.6%)	0.57 (0.23–1.43)	0.23	0.48 (0.18–1.28)	0.48
No	29 (80.6%)	88 (70.4%)	Ref.		Ref.	
Season with IBV circulation discordant with trivalent vaccine						
	Intensive care admission (*N* = 168)	**Nonintensive care admission (*N* = 659)**	**OR (95% CI)**	***p* value**	**aOR (95% CI)**	***p* value**
Vaccinated						
Yes	51 (30.4%)	250 (37.9%)	0.71 (0.49–1.03)	0.07	0.96 (0.65–1.42)	0.84
No	117 (69.6%)	409 (62.1%)	Ref.		Ref.	
Season with IBV predominant circulation of B/Victoria lineage						
	Intensive care admission (*N* = 44)	**Nonintensive care admission (*N* = 138)**	**OR (95% CI)**	***p* value**	**aOR (95%CI)**	***p* value**
Vaccinated						
Yes	10 (22.7%)	41 (29.7%)	0.70 (0.31–1.54)	0.37	0.95 (0.39–2.31)	0.91
No	34 (77.3%)	97 (70.3%)	Ref.		Ref.	
Season with IBV predominant circulation of B/Yamagata lineage						
	Intensive care admission (*N* = 162)	**Nonintensive care admission (*N* = 644)**	**OR (95% CI)**	***p* value**	**aOR (95%CI)**	***p* value**
Vaccinated						
Yes	48 (29.6%)	246 (38.2%)	0.68 (0.47–0.99)	0.04	0.83 (0.56–1.24)	0.36
No	114 (70.4%)	398 (61.8%)	Ref.		Ref.	

Note: Catalonia 2010–2020.

Abbreviations: CI, confidence interval; OR, odds ratio.

circulation. Overall, a high proportion of SHLCI cases reported in that season were due to influenza B infection. The marked increase in hospitalizations could be explained by the surge of a new antigenically distinct subgroup of viruses that has been detected in several countries during the season.[23,26] Aligned with what has been observed by other researchers,[27,28] our results showed that B/Victoria lineage is more frequent in younger populations in comparison with B/Yamagata lineage.

Our results are in accordance with works published by other researchers[29–31] that suggest a lower Influenza vaccine effectiveness against influenza B viruses among the elderly in seasons characterized by a mismatch between TIV vaccine and circulating strains. Moreover, we found that not only vaccine effectiveness (VE) of the TIV to prevent ICU admission was higher in concordant seasons but also when the predominant circulating lineage was B/Yamagata. Perhaps, the slower antigenic change of B/Yamagata viruses than B/Victoria viruses may not be hindering this immune protection acquired year after year, either by vaccination or by natural infection, contributing to a lower VE.[5]

As to risk factors for severe outcomes, we found significant differences between TIV concordant and discordant seasons, especially in patients with cardiovascular disease, COPD, and diabetes as comorbidity for severe outcomes. These findings have also been observed in other studies carried out during several seasons.[15,32,33]

Our study has several limitations, one is due to the selective phylogenetic study of samples because of only those samples with high viral load. This implies that circulating lineage is considered predominant according to the results rendered by the sample of studied isolates. Another limitation is the fact that only severe hospitalized cases has been taken into account, yet this does not affect the results on vaccine effectiveness to prevent ICU admission because this is a condition that is accountable only for hospitalized patients.

5 | CONCLUSIONS

Our study provides a description of influenza B disease in hospitalized patient and its relationship to the lineages detected. The alternation of Influenza B virus lineage increases the risk for mismatch with trivalent vaccine strain causing greater severity in the >64 years old, but also presenting greater number of hospitalizations in younger groups. These findings reinforce the implementation of the quadrivalent influenza vaccine regardless of predominant circulation in the previous season albeit close surveillance on

antigenic changes will still be needed to upgrade VE regardless of circulating IBV.

AUTHOR CONTRIBUTIONS

All the authors participated in the study design, implementation, and interpretation. Ángela Domínguez and Núria Torner designed the study and drafted the report. Núria Soldevila conducted the statistical analysis. Luca Basile, Ana Martínez, MMar Mosquera, M Ángeles Marcos, Andrés Antón, Cristina Andrés, Cristina Rius, and Tomàs Pumarola supervised the study, and reviewed the draft report. The authors of The PIDIRAC Working Group on Surveillance of Hospitalized Cases of Severe Influenza in Catalonia have participated in the detection of cases, gathering epidemiological information and taking clinical samples and sending samples to the laboratory. All authors reviewed and approved the final version of the article.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

All data used in the analysis were collected during routine public health surveillance activities, as part of the legislated mandate of the Health Department of Catalonia, the competent authority for the surveillance of communicable diseases, which is officially authorized to receive, treat and temporarily store personal data on cases of infectious disease. Therefore, data were exempt from institutional board review and did not require informed consent. All data were fully anonymized.

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