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Nirsevimab Immunisation Significantly Reduces Respiratory Syncytial Virus-Associated Bronchiolitis Hospitalisations and Alters Seasonal Patterns

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ABSTRACT

Aim: This work was performed to assess the impact of nirsevimab immunisation on acute bronchiolitis hospitalisations during nearly the entire 2023–2024 epidemic year.

Methods: An observational, multicentre, prospective study was conducted from 1 September 2021 to 15 June 2024 across 20 hospitals in two Spanish regions. Infants up to 12 months old admitted for acute bronchiolitis were included. Demographic, clinical and microbiological data were analysed across three epidemic years (2021–2022, 2022–2023 and 2023–2024). Statistical analyses were performed to evaluate the effectiveness of nirsevimab in preventing respiratory syncytial virus (RSV)-associated hospitalisations.

Results: In total, 2656 patients were included. Bronchiolitis hospitalisations significantly declined in the post-nirsevimab epidemic year compared with previous years. The 2023–2024 season displayed a bimodal distribution, with the first peak dominated by RSV cases and the second by rhinoviruses and metapneumovirus. The proportion of RSV-associated bronchiolitis hospitalisations decreased by 20%–30%, while rhinovirus- and metapneumovirus-associated bronchiolitis cases increased by 10%–20%. The effectiveness of nirsevimab in preventing RSV-associated admissions was estimated to be approximately 70%.

Conclusion: Nirsevimab immunisation significantly reduced RSV-associated bronchiolitis admissions, though an increase in rhinovirus- and metapneumovirus-associated cases was observed.

1 | Introduction

Acute bronchiolitis is one of the most significant conditions encountered by paediatricians in daily clinical practice. It remains a leading cause of respiratory infections in infants, contributing to considerable morbidity and healthcare costs [1]. Most patients only present with mild symptoms and can be managed at home with supportive care, but approximately 3% require hospitalisation, and around 10% of these patients need intensive care, primarily for respiratory support [2]. The most common cause is

Abbreviations: ICU, intensive care unit; RSV, respiratory syncytial virus.

Summary

- This study was the first to evaluate the impact of nirsevimab immunisation on all aetiology bronchiolitis hospitalisations in infants up to 12 months old during nearly the entire 2023–2024 epidemic year.
- A significant decline in total bronchiolitis hospitalisations was observed in 2023–2024 compared with previous epidemic years.
- While nirsevimab immunisation effectively reduced respiratory syncytial virus-associated bronchiolitis admissions, an increase in cases caused by rhinoviruses and metapneumovirus was observed.

respiratory syncytial virus (RSV), although other viruses such as rhinoviruses, influenza and parainfluenza can produce similar clinical presentations [3].

Nowadays, no effective treatment exists to shorten the duration of bronchiolitis, alleviate its symptoms or reduce its severity, making prevention especially crucial in minimising morbidity [4]. To address this, in late October 2022, the European Medicines Agency approved a new monoclonal antibody, nirsevimab, for the prevention of RSV-associated bronchiolitis in both preterm and full-term infants during their first RSV season [5–8]. In late September 2023, Spain incorporated nirsevimab immunisation into its national vaccination programme as a universal RSV prophylaxis for all infants born on or after 1 April 2023 [9].

Controlled clinical trials have demonstrated significant potential for this drug in reducing RSV-associated bronchiolitis admissions and the severity of hospitalised cases [5–8]. However, its clinical effectiveness under real-world conditions has only been preliminarily validated using datasets collected before the end of the 2023–2024 epidemic year [10]. Indeed, most studies conducted in Spain [11–17], as well as in other countries [18–22], only gathered data until the end of February 2024 or earlier. Moreover, these studies mainly focused on the impact of nirsevimab on RSV-associated hospitalisations, overlooking its effects on bronchiolitis caused by other pathogens. In addition, most were based on data from a limited number of hospitals with similar patient populations, often concentrated in a single region (such as, Catalonia [12, 13], Madrid [15, 16], Navarre [17], or Galicia [14]), providing a narrow, localised perspective. The main aim of this study was to assess the impact of nirsevimab immunisation over nearly the entire 2023–2024 epidemic year on the burden of bronchiolitis cases associated with RSV and other viruses, including those admitted to general paediatric wards and intensive care units (ICUs) across 20 hospitals in two different regions of Spain.

2 | Materials and Methods

2.1 | Study Design and Context

An observational, descriptive, multicentre, prospective study was conducted from 1 September 2021 to 15 June 2024 as part of a larger Spanish research initiative on acute bronchiolitis [23]. Data were collected over three consecutive epidemic years from 20 Spanish hospitals located in the regions of Castilla-La Mancha and Comunidad Valenciana. Together, these regions account for more than 20% of Spain's total land area and just over 15% of its population, representing both an inland, predominantly agricultural area and a coastal, industrial and highly touristic zone. The participating hospitals collectively serve approximately 3.6 million people, including more than 550 000 children aged 0–14 years (Table 1). Each year, these hospitals manage approximately 23 000 births and admit nearly 8000 infants under 12 months old. Routine clinical practices in these hospitals remained unchanged during the study period to ensure a realistic representation of how patients hospitalised with acute bronchiolitis were managed.

2.2 | Definitions and Inclusion Criteria

Some relevant definitions for this study were as follows. Bronchiolitis was defined as the first episode of a viral lower respiratory tract infection accompanied by respiratory distress [24, 25]. Eligible patients for immunisation included three groups [26]. The first group consisted of healthy term and late preterm newborns born between 1 October 2023 and 31 March 2024, who were offered immunisation in the maternity ward before discharge. The second group included healthy term and late preterm newborns born between 1 April 2023 and 30 September 2023, who were offered immunisation through primary care. The third group comprised infants up to 24 months of age at the beginning of the season with associated risk factors for severe bronchiolitis due to RSV.

The epidemic year was defined as the period from 1 September of 1 year to 31 August of the following year [27]. The start of the season referred to the week when admissions began to increase significantly and did not decline compared with previous weeks [27]. The end of the season was identified as the week when admissions decreased and remained consistently at or below the pre-epidemic season level [27]. The epidemic season encompassed the period between the start and the end of the season [27].

All infants up to 12 months of age who were admitted for bronchiolitis during the study period were considered. However, certain infants were excluded based on the following criteria. Those who had visited any healthcare provider (a primary care doctor or hospital physician) for symptoms of bronchiolitis, bronchitis or pneumonia more than 1 month before hospitalisation were not included [25]. Infants who had received a preventive treatment for severe bronchiolitis other than nirsevimab, such as palivizumab, were also excluded. It is important to note that a maternal immunisation programme against RSV had not yet been implemented in Spain at the time of this study. In addition, those whose parents did not provide written informed consent to participate in the study were not included.

2.3 | Collection and Assessment of Data

The total number of infants with bronchiolitis hospitalised in the participating hospitals, according to the specified inclusion and exclusion criteria, was quantified for each epidemic year: 2021–2022,

TABLE 1 | Information related to the participating hospitals and number of bronchiolitis cases included in the study for the three analysed epidemic years. Data are divided into RSV-positive, RSV-negative and non-tested cases.

			Epidemic year 2021–2022			Epidemic year 2022–2023			Epidemic year 2023–2024		
Hospital	**Catchment**[a]	**Births**[b]	**Pos. RSV**	**Neg. RSV**	**Non-tested**	**Pos. RSV**	**Neg. RSV**	**Non-tested**	**Pos. RSV**	**Neg. RSV**	**Non-tested**
CHUA	40 071	1339	76 (69.09%)	33 (30,00%)	1 (0.91%)	67 (72.04%)	26 (27.96%)	0 (0.00%)	15 (33.33%)	13 (28.89%)	17 (37.78%)
HVLi	18 265	936	18 (78.26%)	5 (21.74%)	0 (0.00%)	28 (80.00%)	7 (20.00%)	0 (0.00%)	3 (25.00%)	8 (66.67%)	1 (8.33%)
HGUA	41 587	1982	77 (64.17%)	43 (35.83%)	0 (0.00%)	103 (71.03%)	42 (28.97%	0 (0.00%)	25 (39.68%)	38 (60.32%)	0 (0.00%)
HULR	34 937	1291	19 (46.34%)	21 (51.22%)	1 (2.44%)	50 (59.52%)	32 (38.10%)	2 (2.38%)	12 (29.27%)	20 (48.78%)	9 (21.95%)
HGUC	33 051	1421	1 (50.00%)	1 (50.00%)	0 (0.00%)	65 (55.56%)	49 (41.88%)	3 (2.56%)	18 (47.37%)	20 (52.63%)	0 (0.00%)
HGUCR	35 981	1769	44 (66.67%)	22 (33.33%)	0 (0.00%)	71 (87.65%	10 (12.35%)	0 (0.00%)	12 (42.86%)	16 (57.14%)	0 (0.00%)
HVL	16 486	711	21 (61.76%)	13 (38.24%)	0 (0.00%)	23 (79.31%)	5 (17.24%)	1 (3.45%)	8 (50.00%)	8 (50.00%)	0 (0.00%)
HFB	27 031	1012	30 (66.67%)	12 (26.67%)	3 (6.67%)	12 (18.18%)	6 (9.09%)	48 (72.73%)	5 (21.74%)	14 (60.87%)	4 (17.39%)
HUG	33 929	1222	17 (53.13%)	15 (46.88%)	0 (0.00%)	39 (69.64%)	17 (30.36%)	0 (0.00%)	9 (39.13%)	7 (30.43%)	7 (30.43%)
HUPLF	90 484	4429	103 (55.38%)	71 (38.17%)	12 (6.45%)	155 (73.46%)	51 (24.17%)	5 (2.37%)	47 (51.65%)	44 (48.35%)	0 (0.00%)
HULP	28 452	1225	12 (46.15%)	14 (53.85%)	0 (0.00%)	40 (72.73%)	15 (27.27%)	0 (0.00%)	6 (21.43%)	22 (78.57%)	0 (0.00%)
HVA	5186	343	15 (83.33%)	3 (16.67%)	0 (0.00%)	17 (80.95%)	4 (19.05%)	0 (0.00%)	3 (100.00%)	0 (0.00%)	0 (0.00%)
HUDP	37 896	1132	21 (43.75%)	27 (56.25%)	0 (0.00%)	38 (74.51%)	13 (25.49%)	0 (0.00%)	6 (21.43%	22 (78.57%)	0 (0.00%)
HSB	7616	285	7 (43.75%)	9 (56.25%)	0 (0.00%)	21 (87.50%)	3 (12.50%)	0 (0.00%)	4 (57.14%)	3 (42.86%)	0 (0.00%)
HSAG	21 846	653	11 (47.83%)	11 (47.83%)	1 (4.35%)	28 (80.00%)	7 (20.00%)	0 (0.00%)	5 (55.56%)	4 (44.44%)	0 (0.00%)
HGT	8258	361	12 (42.86%)	16 (57.14%)	0 (0.00%)	13 (35.14%)	24 (64.86%)	0 (0.00%)	3 (20.00%)	12 80.00%	0 (0.00%)
HGV	7120	357	5 (41.67%)	7 (58.33%)	0 (0.00%)	16 (94.12%)	1 (5.88%)	0 (0.00%)	3 (60.00%)	2 (40.00%)	0 (0.00%)
HUV	23 898	1348	13 (59.09%)	9 (40.91%)	0 (0.00%)	31 (83.78%)	6 (16.22%)	0 (0.00%)	8 (57.14%)	3 (21.43%)	3 (21.43%)
HCV	13 073	478	10 (50.00%)	10 (50.00%)	0 (0.00%)	18 (75.00%)	6 (25.00%)	0 (0.00%)	5 (55.56%)	4 (44.44%)	0 (0.00%)
HLA	28 348	636	17 (70.83%)	7 (29.17%)	0 (0.00%)	26 (81.25%)	6 (18.75%)	0 (0.00%)	6 (54.55%)	5 (45.45%)	0 (0.00%)
Total	553 515	22 930	529 (59.04%)	349 (38.95%)	18 (2.01%)	861 (68.88%)	330 (26.40%)	59 (4.72%)	203 (39.88%)	265 (52.06%)	41 (8.06%)

Abbreviations: CHUA, Complejo Hospitalario de Albacete (Castilla-La Mancha); HCV, Hospital Comarcal de Vinarós (Comunidad Valenciana); HFB, Hospital Francesc de Borja, Gandía (Comunidad Valenciana); HGT, Hospital General de Tomelloso (Castilla-La Mancha); HGUA, Hospital General Universitario de Alicante (Comunidad Valenciana); HGUC, Hospital General Universitario de Castellón (Comunidad Valenciana); HGUCR, Hospital General Universitario de Ciudad Real (Castilla-La Mancha); HGV, Hospital General de Villarrobledo (Castilla-La Mancha); HLA, Hospital Lluís Alcanyís, Xátiva (Comunidad Valenciana); HSAG, Hospital de Sagunto (Comunidad Valenciana); HSB, Hospital Santa Bárbara de Puertollano (Castilla-La Mancha); HUDP, Hospital Universitario Dr. Peset, Valencia (Comunidad Valenciana); HUG, Hospital Universitario de Guadalajara (Castilla-La Mancha); HULP, Hospital Universitario de La Plana, Villareal (Comunidad Valenciana); HULR, Hospital Universitario de La Ribera, Alzira (Comunidad Valenciana); HUPLF, Hospital Universitario y Politécnico La Fe, Valencia (Comunidad Valenciana); HUV, Hospital Universitario del Vinalopó (Comunidad Valenciana); HVA, Hospital Virgen de Altagracia, Manzanares (Castilla-La Mancha); HVL, Hospital Virgen de la Luz, Cuenca (Castilla-La Mancha); HVLi, Hospital Virgen de los Lirios, Alcoy (Comunidad Valenciana); RSV—respiratory syncytial virus.

[a]Paediatric population under 14years attended each hospital, according to data for the year 2022.

[b]Births in the year 2022 for each hospital.

2022–2023 and 2023–2024. The three corresponding epidemic seasons were then characterised by determining their start and end weeks, as previously defined, along with the week when the peak number of cases was recorded. In addition, demographic, clinical and microbiological data from the patients were collected. These included sex, age, ethnicity and comorbidities, such as prematurity (≤ 36 weeks of gestation), haemodynamically significant heart disease, chronic pulmonary disease of prematurity, hypotonia, severe immunosuppression, inborn errors of metabolism, severe pulmonary malformations, genetic syndromes with significant respiratory problems and cystic fibrosis [26]. Data on bacterial infections and bronchiolitis aetiology were also gathered.

According to international clinical guidelines [3], diagnostic tests were performed only when gastroenteritis, urinary tract infection, pneumonia, otitis, sepsis or pertussis were suspected. Each participating hospital followed its routine diagnostic practices. The confirmation of at least one of these conditions was sufficient to establish the coexistence of a bacterial infection. Bronchiolitis aetiology was determined for most patients using nasopharyngeal aspirate samples analysed with a multiplex polymerase chain reaction assay for multiple pathogen detection. However, some infants were not tested, following the routine clinical practices of each hospital. Regarding treatment, the length of stay in the general paediatric ward and, when necessary, in the ICU was recorded. The need for oxygen therapy was also documented, including the use of low-flow nasal cannula, high-flow nasal cannula, non-invasive ventilation and mechanical ventilation. In addition, the use of antibiotic treatment and maintenance intravenous fluid therapy was registered.

These variables were compared between the pre-nirsevimab (2021–2022 and 2022–2023) and post-nirsevimab (2023–2024) epidemic years. A global statistical analysis was conducted across all 3 years, while a separate comparison was made between 2022–2023 and 2023–2024. This latter comparison was relevant because the 2022–2023 epidemic year exhibited seasonal patterns and case numbers for both all-cause and RSV-associated bronchiolitis similar to those observed in years before the COVID-19 pandemic. By contrast, the 2021–2022 epidemic year was still significantly influenced by non-pharmacologic measures implemented to curb the spread of the coronavirus, leading to a much lower number of admissions and an earlier peak [28]. A similar statistical comparison was performed between immunised and non-immunised patients during the post-nirsevimab year (2023–2024), as well as between immunised and non-immunised infants with RSV-associated bronchiolitis. Finally, the effectiveness of nirsevimab in preventing hospitalisation due to RSV-associated cases was analysed for all eligible patients and specific subpopulations.

2.4 | Statistical Analysis

Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. All continuous variables followed a non-normal distribution, as determined by the Kolmogorov–Smirnov test, and were described using the median and interquartile range. Comparisons between two groups were conducted using the Mann–Whitney U test, while comparisons among three groups were performed using the Kruskal–Wallis test. The effectiveness of nirsevimab in preventing RSV-associated bronchiolitis hospitalisations was estimated using a test-negative case–control study. Case patients were infants who tested positive for RSV by polymerase chain reaction, while control patients were those who tested negative. Immunisation effectiveness was calculated using the formula: immunisation effectiveness = (1−OR) × 100%, where OR represented the odds ratio comparing the likelihood of nirsevimab administration among cases versus controls. This odds ratio was derived from a multivariable logistic regression model, adjusted for sex, age categorised as < 3 and > 3 months [19], presence of at least one comorbidity, epidemiological week of admission and the region where the hospital was located. These potential confounders were identified using the disjunctive causal criterion, considering factors influencing both nirsevimab exposure and bronchiolitis-associated hospitalisation [29], aligning with previous studies [12, 19, 20, 22]. The significance level was set at 0.05 for all analyses, which were conducted using Matlab Release 2024a (MathWorks Inc., Massachusetts, USA).

2.5 | Ethics

This study was approved by the ethics committee of the coordinating hospital (Approval No. PI01122019). All procedures related to data collection, transfer and analysis, as well as interactions with patients' families, were carried out in accordance with the Declaration of Helsinki and Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights. Informed consent was obtained from the parents or legal guardians of the infants for both participation in the study and access to their health records.

3 | Results

Less than 1% of infants with bronchiolitis admitted to the participating hospitals were excluded each epidemic year based on the previously described criteria. We finally enrolled 2656 patients (61.26% males) in the study at a median age of 2.6 months (interquartile range, 1.5–5.0 months). Of these, 13.37% had comorbidities, with prematurity being the most common (10.17%). ICU admission was required for 14.00% of infants, with a median age of 1.8 months (interquartile range, 1.1–3.3 months). Among these patients, 60.48% were male and 20.97% had comorbidities, with prematurity being the most frequent (16.40%).

3.1 | Epidemiological Impact of Nirsevimab

As shown in Table 1, the number of patients enrolled at each participating hospital varied, reflecting differences in hospital size, care complexity and routine clinical practices for managing bronchiolitis cases. Virological tests were conducted in nearly 98%, 95% and 92% of hospitalised infants during the 2021–2022, 2022–2023 and 2023–2024 epidemic years, respectively.

Across the entire sample, the post-nirsevimab season (2023–2024) had a lower number of cases than the two previous seasons and showed a delayed onset and peak (Figure 1). In addition, the total number of admissions during the start, peak and end

weeks differed significantly from the prior seasons, with a clear trend towards lower hospitalisation rates (Table 2). Notably, the 2023–2024 season exhibited a distinct pattern, characterised by two clearly differentiated waves. The first wave was primarily composed of RSV-associated admissions, while the second consisted of bronchiolitis cases caused by other viruses, mainly rhinoviruses and metapneumovirus. This is described in detail in the following section.

3.2 | Comparison of Periods Before and After Nirsevimab

As shown in Figure 1, bronchiolitis-associated hospitalisations in the post-nirsevimab year (2023–2024) decreased by approximately 43% (509 vs. 896) compared with 2021–2022 and 59% (509 vs. 1250) compared with 2022–2023 (Table 3). Among the infants tested for bronchiolitis aetiology, the percentage of RSV-associated admissions declined by 20%–30% in 2023–2024. By contrast, hospitalisations caused by other viruses, such as rhinoviruses and metapneumovirus, increased by 10%–20%. In addition, the proportion of infants with coinfections excluding RSV grew significantly, rising by approximately 8% in the last epidemic year. Patients hospitalised in the post-nirsevimab year were generally older, had a higher frequency of comorbidities and were more likely to present with concomitant bacterial infections compared with previous years. Furthermore, the number of infants requiring ICU admission and oxygen support, including the use of high-flow nasal cannula, non-invasive ventilation and mechanical ventilation, was significantly lower in 2023–2024 than in the two preceding years.

3.3 | Analysis of Eligible and Non-Eligible Infants for Nirsevimab Immunisation

In line with most Spanish regions, the two regions where the 20 participating hospitals are located achieved an

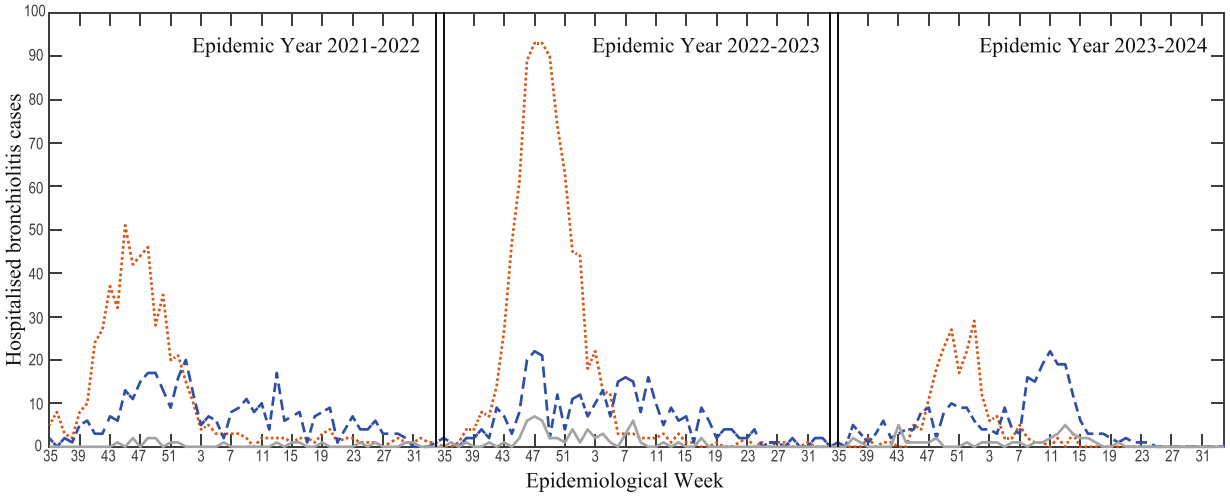

FIGURE 1 | Distribution of infants hospitalised for each epidemic year, divided into RSV-positive (orange dotted line), RSV-negative (blue dashed line) and non-tested (grey solid line) bronchiolitis cases.

TABLE 2 | Information associated with the weeks of start, peak and end of each analysed epidemic year.

	Epidemic season 2021–2022	Epidemic season 2022–2023	Epidemic season 2023–2024
Epidemiological week of season start	39	42	45
Epidemiological week of season peak	48	47	50
Epidemiological week of season end	20	9	15
Total duration of the season (weeks)	33	19	22
Admissions in the week of season start	13	23	10
Admissions in the week of season peak	65	122	37
Admissions in the week of season end	13	11	8
Admissions in the entire season	814	1090	447
Admissions tested for RSV in the season	800 (98.28%)	1038 (95.23%)	419 (93.74%)
Admissions with RSV in the season	494 (60.69%)	816 (74.86%)	199 (44.52%)

Abbreviation: RSV, respiratory syncytial virus.

TABLE 3 | Comparison of demographic, clinical and microbiological data for bronchiolitis cases hospitalised in the three analysed epidemic years.

	Year 2021–2022, *N* = 896	Year 2022–2023, *N* = 1250	Year 2023–2024, *N* = 509	Comparison of 3 years, *p*	Comparison of years 2022–2023 and 2023–2024, *p*
Gender (male), *N* (%)	537 (59.93%)	763 (61.14%)	327 (64.24%)	0.266	0.224
Age (months), *MD* (IQR)	2.43 (1.43–4.77)	2.52 (1.47–4.70)	3.40 (1.77–6.56)	< 0.001	< 0.001
Ethnicity, *N* (%)					
White/Caucasian	787 (88.43%)	1072 (86.45%)	432 (86.75%)	0.424	0.870
Hispanic/Latino	27 (3.03%)	37 (2.98%)	25 (5.02%)	0.081	0.039
Black/African	70 (7.87%)	107 (8.63%)	34 (6.83%)	0.446	0.214
Asian	6 (0.67%)	24 (1.94%)	7 (1.41%)	0.051	0.451
Comorbidities, *N* (%)					
None	799 (89.17%)	1074 (85.92%)	427 (83.89%)	0.015	0.275
Prematurity	81 (9.04%)	137 (10.96%)	52 (10.22%)	0.344	0.648
Cardiopathy	13 (1.45%)	32 (2.56%)	14 (2.75%)	0.151	0.820
Pneumopathy	10 (1.12%)	15 (1.20%)	9 (1.77%)	0.544	0.352
Hypotonia	9 (1.00%)	16 (1.28%)	10 (1.96%)	0.311	0.281
Other[a]	1 (0.11%)	3 (0.24%)	17 (3.34%)	< 0.001	< 0.001
Two or more	14 (1.56%)	22 (1.76%)	26 (5.11%)	< 0.001	< 0.001
Bacterial infection, *N* (%)	129 (14.40%)	187 (14.96%)	97 (19.06%)	0.049	0.034
Viral aetiology, *N* (%)[b]					
RSV	529 (60.25%)	861 (72.29%)	203 (43.38%)	< 0.001	< 0.001
Rhinoviruses/ Enteroviruses	82 (9.34%)	75 (6.30%)	108 (23.08%)	< 0.001	< 0.001
Coronavirus	8 (0.91%)	14 (1.18%)	11 (2.35%)	0.074	0.077
Influenza	5 (0.57%)	21 (1.76%)	7 (1.50%)	0.055	0.704
Metapneumovirus	60 (6.83%)	35 (2.94%)	77 (16.45%)	< 0.001	< 0.001
Parainfluenza	36 (4.10%)	29 (2.43%)	22 (4.70%)	0.030	0.016
SARS COV-2	12 (1.37%)	15 (1.26%)	16 (3.42%)	0.006	0.004
Adenovirus	9 (1.03%)	15 (1.26%)	13 (2.78%)	0.0280	0.031
Bocavirus	0 (0.00%)	1 (0.08%)	2 (0.43%)	0.0843	0.139
Unknown virus	180 (20.50%)	177 (14.86%)	61 (13.03%)	< 0.001	0.339
Viral coinfection with RSV	94 (10.71%)	76 (6.38%)	34 (7.26%)	0.001	0.515
Viral coinfection without RSV	39 (4.44%)	49 (4.11%)	56 (11.97%)	< 0.001	< 0.001
Length of stay in hospital (days), MD (IQR)	4 (2–5)	4 (3–6)	4 (2–6)	< 0.001	0.016
Admission at ICU, *N* (%)	102 (11.38%)	215 (17.20%)	55 (10.81%)	< 0.001	< 0.001
Length of stay in ICU (days), MD (IQR)[c]	5 (3–8)	5 (3–7.5)	5 (3–7)	0.364	0.222

(Continues)

TABLE 3 | (Continued)

	Year 2021–2022, $N=896$	Year 2022–2023, $N=1250$	Year 2023–2024, $N=509$	Comparison of 3 years, p	Comparison of years 2022–2023 and 2023–2024, p
Respiratory Support, *N* (%)					
Low-flow nasal cannula	552 (61.61%)	845 (67.60%)	329 (64.64%)	0.015	0.232
High-flow nasal cannula	162 (18.10%)	346 (27.68%)	106 (20.83%)	<0.001	0.003
Non-invasive ventilation	79 (8.82%)	128 (10.24%)	9 (1.77%)	<0.001	0.001
Mechanical ventilation	14 (1.56%)	26 (2.08%)	2 (0.39%)	0.037	0.010
Antibiotic prescription, *N* (%)	140 (15.63%)	197 (15.76%)	96 (18.86%)	0.220	0.114
Intravenous fluid therapy, *N* (%)	389 (43.42%)	553 (44.24%)	227 (44.60%)	0.883	0.891

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MD, median; RSV, respiratory syncytial virus.
[a]This row includes severe immunosuppression, inborn errors of metabolism, severe pulmonary malformations, genetic syndromes with significant respiratory problems and cystic fibrosis.
[b]This analysis was only conducted on those patients tested for RSV, $N=2537$ (878 in the year 2021–2022, 1191 in the year 2022–2023 and 468 in the year 2023–2024).
[c]This analysis was only conducted on those patients admitted to the ICU and with available information, $N=366$ (101 in the year 2021–2022, 212 in the year 2022–2023 and 52 in the year 2023–2024).

overall nirsevimab coverage of approximately 90% for infants immunised in maternity wards and 85% for those immunised through primary care during the 2023–2024 epidemic year [30]. Among infants hospitalised for bronchiolitis, 77 (15.31%) were not eligible for immunisation, 329 (65.41%) received a dose of nirsevimab and 97 (19.28%) were eligible but not immunised. Six healthy infants were excluded from this analysis because they did not meet Spain's official criteria for nirsevimab distribution, having been born before 1 April 2023 and receiving immunisation. Non-eligible infants were significantly older than those eligible but not immunised, who in turn were significantly older than those eligible and immunised (Table 4). However, no significant differences were observed in the presence of comorbidities among the three groups.

Among infants tested for bronchiolitis aetiology, RSV detection was approximately 30% lower in those immunised with nirsevimab than in those eligible but not immunised, and 50% lower than in non-eligible infants (Table 4). By contrast, the proportion of cases associated with rhinoviruses and metapneumovirus increased significantly, by 5%–20%, among both eligible but not immunised and immunised infants compared with non-eligible ones. Similarly, the percentage of viral coinfections without RSV was 8%–12% higher in eligible infants, both immunised and not immunised, than in non-eligible infants. On the other hand, no statistically significant differences were observed in most treatment-related aspects among the three groups, including ICU admissions, length of hospital and ICU stay, antibiotic use and oxygen therapy requirements. The only notable difference was a significant 20% reduction in the use of low-flow nasal cannula among eligible infants compared with non-eligible ones.

When considering only eligible patients with RSV, non-immunised infants were significantly older than immunised ones (Table 5). A slightly higher proportion of immunised patients had comorbidities, presented viral coinfection with RSV and required ICU admission, although these differences were not statistically significant compared with non-immunised infants. Similarly, no significant differences were observed between the two groups in terms of length of stay in the paediatric ward or ICU, need for respiratory support, antibiotic use and intravenous fluid therapy.

3.4 | Nirsevimab Immunisation Effectiveness

A first analysis of nirsevimab immunisation effectiveness in preventing RSV-associated bronchiolitis hospitalisations was conducted on all eligible patients, yielding a value of approximately 70% ($p<0.001$) (Table 6). When analysing different age groups, effectiveness was not statistically significant for infants up to 3 months old. However, a notably higher effectiveness of approximately 80% ($p<0.001$) was observed in infants aged 4–6 months. Similarly, a meaningful effectiveness of approximately 70% ($p<0.001$) was found when analysing healthy patients. By contrast, effectiveness was not statistically significant for infants with the most prevalent comorbidity, which was prematurity. Finally, no significant effectiveness was observed for infants with viral coinfection that included RSV, whereas for those infected only with RSV, effectiveness exceeded 72% ($p<0.001$).

4 | Discussion

4.1 | Main Findings

To the best of our knowledge, this is the first study to analyse the impact of nirsevimab immunisation over nearly the entire 2023–2024 epidemic year in two Spanish regions while also considering viruses other than RSV as causes of bronchiolitis. As mentioned in the Introduction section, all previous studies assessing the effectiveness of nirsevimab under real-world conditions, both in Spain [11–17] and in other countries [18–22], began data collection late and ended prematurely, between

TABLE 4 | Comparison of demographic, clinical and microbiological data for eligible and non-eligible infants for nirsevimab immunisation. Within the eligible patient group, immunised and non-immunised infants were compared.

		Eligible patients			
	Non-eligible pat. $N=77$	Non-immunised $N=97$	Immunised $N=329$	Comparison of three groups, p	Comparison of immunised and non-immunised groups, p
Gender (male), N (%)	44 (57.14%)	68 (70.10%)	210 (63.83%)	0.208	0.254
Age (months), MD (IQR)	10.3 (9.44–11.10)	3.53 (1.76–5.83)	2.6 (1.57–4.18)	<0.001	0.011
Ethnicity, N (%)					
White/Caucasian	66 (88.00%)	77 (81.05%)	284 (88.20%)	0.185	0.073
Hispanic/Latino	3 (4.00%)	8 (8.42%)	14 (4.35%)	0.254	0.119
Black/African	4 (5.33%)	9 (9.47%)	20 (6.21%)	0.470	0.272
Asian	2 (2.67%)	1 (1.05%)	4 (1.24%)	0.608	0.881
Comorbidities, N (%)					
None	69 (89.61%)	88 (90.72%)	267 (81.16%)	0.028	0.026
Prematurity	3 (3.90%)	6 (6.19%)	41 (12.46%)	0.030	0.083
Cardiopathy	2 (2.60%)	3 (3.09%)	9 (2.74%)	0.977	0.852
Pneumopathy	0 (0.00%)	2 (2.06%)	6 (1.82%)	0.473	0.879
Hypotonia	2 (2.60%)	2 (2.06%)	5 (1.52%)	0.793	0.712
Other[a]	3 (3.90%)	3 (3.09%)	11 (3.34%)	0.957	0.903
Two or more	4 (5.19%)	5 (5.15%)	15 (4.56%)	0.954	0.808
Bacterial infection, N (%)	17 (22.08%)	18 (18.56%)	62 (18.84%)	0.795	0.949
Viral aetiology, N (%)[b]					
RSV	60 (82.19%)	52 (61.90%)	91 (29.64%)	<0.001	<0.001
Rhinoviruses/Enteroviruses	5 (6.85%)	15 (17.86%)	87 (28.34%)	<0.001	0.053
Coronavirus	1 (1.37%)	1 (1.19%)	9 (2.93%)	0.538	0.370
Influenza	1 (1.37%)	0 (0.00%)	6 (1.95%)	0.426	0.197
Metapneumovirus	2 (2.74%)	7 (8.33%)	68 (22.15%)	<0.001	0.004
Parainfluenza	2 (2.74%)	3 (3.57%)	17 (5.54%)	0.514	0.469
SARS COV-2	0 (0.00%)	2 (2.38%)	14 (4.56%)	0.133	0.372

(Continues)

TABLE 4 | (Continued)

	Non-eligible pat. $N=77$	Eligible patients		Comparison of three groups, p	Comparison of immunised and non-immunised groups, p
		Non-immunised $N=97$	Immunised $N=329$		
Adenovirus	1 (1.37%)	3 (3.57%)	8 (2.61%)	0.686	0.635
Bocavirus	0 (0.00%)	1 (1.19%)	0 (0.00%)	0.104	0.056
Unknown virus	2 (2.74%)	8 (9.52%)	49 (15.96%)	0.006	0.139
Viral coinfection with RSV	9 (12.33%)	8 (9.52%)	17 (5.54%)	0.094	0.186
Viral coinfection without RSV	2 (2.74%)	8 (9.52%)	45 (14.66%)	0.014	0.223
Length of stay in hospital (days), MD (IQR)	4 (2–6)	4 (2–6)	4 (2–6)	0.966	0.920
Admission at ICU, *N* (%)	6 (7.79%)	8 (8.25%)	39 (11.85%)	0.415	0.319
Length of stay in ICU (days), MD (IQR)[c]	5 (4–7)	5.5 (2–6)	5 (3–7)	0.977	0.837
Respiratory Support, *N* (%):					
Low-flow nasal cannula	65 (84.42%)	59 (60.82%)	199 (60.49%)	<0.001	0.952
High-flow nasal cannula	14 (18.18%)	19 (19.59%)	71 (21.58%)	0.769	0.673
Non-invasive ventilation	0 (0.00%)	3 (3.09%)	5 (1.52%)	0.265	0.316
Mechanical ventilation	0 (0.00%)	1 (1.03%)	1 (0.30%)	0.506	0.357
Antibiotic prescription, *N* (%)	17 (22.08%)	19 (19.59%)	60 (18.24%)	0.735	0.764
Intravenous fluid therapy, *N* (%)	39 (50.65%)	40 (41.24%)	146 (44.38%)	0.452	0.584

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MD, median; RSV, respiratory syncytial virus.
[a]This row includes severe immunosuppression, inborn errors of metabolism, severe pulmonary malformations, genetic syndromes with significant respiratory problems, and cystic fibrosis.
[b]This analysis was only conducted on those patients tested for RSV, $N=464$ (73 non-eligible patients, 84 eligible but non-immunised infants and 307 eligible and immunised infants).
[c]This analysis was only conducted on those patients admitted to the ICU and with available information, $N=50$ (6 non-eligible patients, 6 eligible but non-immunised infants and 38 eligible and immunised infants).

TABLE 5 | Comparison of demographic, clinical and microbiological data between immunised and non-immunised infants with RSV-associated bronchiolitis who were eligible for receiving a dose of nirsevimab.

	Eligible infants		
	Non-immunised	Immunised	
	N = 52	*N* = 91	*p*
Gender (male), *N* (%)	39 (75.00%)	63 (69.23%)	0.463
Age (months), MD (IQR)	3.60 (1.97–6.32)	2.23 (1.51–3.91)	0.001
Ethnicity, *N* (%)			
White/Caucasian	39 (76.47%)	81 (89.01%)	0.048
Hispanic/Latino	4 (7.84%)	3 (3.30%)	0.230
Black/African	7 (13.73%)	6 (6.59%)	0.157
Asian	1 (1.96%)	1 (1.10%)	0.676
Comorbidities, *N* (%)			
None	47 (90.38%)	80 (87.91%)	0.652
Prematurity	3 (5.77%)	6 (6.59%)	0.845
Cardiopathy	2 (3.85%)	2 (2.20%)	0.565
Pneumopathy	1 (1.92%)	0 (0.00%)	0.184
Hypotonia	1 (1.92%)	3 (3.30%)	0.632
Other[a]	1 (1.92%)	2 (2.20%)	0.912
Two or more	3 (5.77%)	2 (2.20%)	0.263
Bacterial infection, *N* (%)	13 (25.00%)	15 (16.48%)	0.217
Viral coinfection, *N* (%)	8 (15.38%)	17 (18.68%)	0.618
Length of stay in hospital (days), MD (IQR)	4 (3–7)	4 (3–5.75)	0.197
Admission at ICU, *N* (%)	5 (9.62%)	13 (14.29%)	0.418
Length of stay in ICU (days), MD (IQR)[b]	2 (1.25–5)	5 (3–6)	0.396
Respiratory Support, *N* (%)			
Low-flow nasal cannula	33 (63.46%)	58 (63.74%)	0.974
High-flow nasal cannula	10 (19.23%)	21 (23.08%)	0.591
Non-invasive ventilation	2 (3.85%)	1 (1.10%)	0.270
Mechanical ventilation	1 (1.92%)	0 (0.00%)	0.184
Antibiotic prescription, *N* (%)	13 (25.00%)	16 (17.58%)	0.289
Intravenous fluid therapy, *N* (%)	25 (48.08%)	57 (62.64%)	0.090

Abbreviations: ICU, intensive care unit; IQR, interquartile range; MD, median.
[a]This row includes severe immunosuppression, inborn errors of metabolism, severe pulmonary malformations, genetic syndromes with significant respiratory problems and cystic fibrosis.
[b]This analysis was only conducted on those patients admitted to the ICU and with available information, *N* = 16 (3 non-immunised and 13 immunised infants).

October 2023 and February 2024 or earlier. As a result, a significant portion of the epidemic year was not accounted for. By contrast, the extended data collection period in this study, from 1 September 2023 to 15 June 2024, provides a broader and more comprehensive assessment of nirsevimab's impact over a longer period following infant immunisation. This is particularly relevant given that recent studies suggest nirsevimab's effectiveness declines over time [16], with passive immunity lasting approximately 150 days [5] and a half-life of approximately 68 days in vivo [6]. Consequently, previous studies that ended data collection early only captured the theoretical window of maximum protection, overlooking what happens when antibody levels decrease significantly. Had this study only considered the period from 1 October to 31 January, 27.90% of cases in 2021–2022, 17.84% in 2022–2023 and 41.85% in 2023–2024 would have been excluded. For RSV-confirmed cases, the proportion of unaccounted cases outside this time frame would have been 13.99%, 5.57% and 9.36%, respectively.

TABLE 6 | Immunisation effectiveness of nirsevimab in preventing RSV-associated bronchiolitis hospitalisations for different subpopulations of eligible patients.

Population	Control patients non-immunised	Control patients immunised	Case patients non-immunised	Case patients immunised	Immunisation effectiveness (%)	95% CI	*p*
All eligible infants	32	216	52	91	70.53	49.58%–82.77%	<0.001
Eligible infants up to 3 months of age	18	116	21	56	43.59	0%–73.65%	0.140
Eligible infants between 4 and 6 months old	10	73	17	27	81.58	50.00%–93.21%	<0.001
Eligible infants without comorbidities	28	168	47	80	69.38	45.50%–82.80%	<0.001
Eligible preterm infants	3	32	3	6	81.79	0%–97.52%	0.094
Eligible infants infected only with RSV	32	216	44	74	72.58	51.60%–84.47%	<0.001
Eligible infants coinfected with RSV and other viruses	32	216	8	17	51.50	0%–82.02%	0.153

Abbreviations: CI, confidence interval; RSV, respiratory syncytial virus.

The data collected for nearly the entire 2023–2024 epidemic year, along with the aetiology analysis for most infants, revealed a notably different distribution of bronchiolitis cases compared with previous years. As shown in Figure 1, the 2023–2024 season was highly atypical, not only due to a reduction in total hospitalisations but also because of delays in both the season onset, Week 45, and the peak admission, Week 50 (Table 2). In addition, unlike previous years, the 2023–2024 epidemic wave exhibited a bimodal pattern with two nearly equal peaks. The first was associated with RSV-confirmed cases, while the second was driven by other viruses, mainly rhinoviruses and metapneumovirus. Although a recent study suggested an increase in infants with rhinovirus-associated bronchiolitis requiring ICU admission [13], its early conclusion in February 2024 may have prevented it from capturing the full impact of the second wave, which in this study extended from late February to mid-April. Other previous studies were also unable to identify this pattern. Most focused exclusively on RSV-associated admissions [15–17], while the few that considered all bronchiolitis cases did not conduct separate analyses for different viruses [14].

The factors contributing to this bimodal distribution of bronchiolitis cases are likely multiple, varied and complex, but nirsevimab may have played a role. According to 2023–2024 data (Table 4), the proportion of rhinovirus- and metapneumovirus-associated cases increased significantly among immunised infants, while similar or only slightly higher proportions were observed among non-immunised and non-eligible infants compared with the pre-nirsevimab years. In addition, the rate of viral coinfections without RSV was significantly higher among immunised patients than among non-immunised and non-eligible infants. However, data from a single post-nirsevimab epidemic year are insufficient to draw definitive conclusions. Further studies in the coming years are necessary to determine whether this bimodal pattern recurs cyclically and whether the ecological niche left by RSV may be at least partially filled by other viruses. It is also important to note that this study focused exclusively on bronchiolitis, defined as the first episode of lower respiratory tract infection, in line with many previous studies [24, 25] and standard practice in Spain [12, 13]. Therefore, no conclusions can be drawn about the impact of nirsevimab immunisation on hospitalisations related to other lower respiratory tract infections.

In line with the overall reduction in bronchiolitis admissions during the 2023–2024 epidemic year, the first wave shown in Figure 1 also exhibited a substantial decrease in RSV-confirmed cases, both in absolute and relative terms, compared with previous years. Because this wave occurred primarily between early November and mid-February, that finding aligns with previous real-world studies that have reported significant reductions in RSV-associated cases across different levels of care, including ambulatory care [31, 32], hospital emergency departments [33, 34] and hospital admissions [14, 18]. As before, nirsevimab appears to have contributed to this decline in RSV-associated hospitalisations. The data for 2023–2024 (Table 4) show that the

proportion of RSV-confirmed cases among non-eligible infants and those eligible but not immunised remained similar to that of the overall population in 2021–2022 and 2022–2023, approximately 60% or more. By contrast, among immunised infants, the proportion of RSV-confirmed cases was significantly reduced by half, to approximately 30%.

Consistent with these findings, most estimates of nirsevimab immunisation effectiveness in preventing RSV-associated hospitalisations during the 2023–2024 epidemic year were statistically significant and exceeded 70% (Table 6). These values were slightly lower than those reported in most previous real-world studies and controlled trials, which reported notable variability, ranging from 80% to 95% [8, 11, 12, 16, 19, 32]. While differences in study design, outcome measures and sample size may explain some of this variability, the lower effectiveness observed in this study could also be attributed to the longer analysis period. Unlike previous works, which primarily relied on data collected before February 2024, this study analysed nearly the entire epidemic year. As already discussed, antibody levels from passive immunisation decline over time, meaning that the longer the period since immunisation, the higher the expected risk of RSV infection [20, 22].

In line with previous real-world studies [13, 32], higher immunisation effectiveness was observed in infants aged 4–6 months, exceeding 81%, compared with other age groups. This explains why immunised infants hospitalised for both all-cause bronchiolitis (Table 4) and RSV-associated bronchiolitis (Table 5) were younger than eligible but non-immunised patients. In addition, this finding, along with the older age at admission among non-eligible infants, helps explain why the median age of hospitalised infants in 2023–2024 was higher than in the two previous years. This outcome aligns with Spain's nirsevimab implementation strategy [9, 26]. Precisely, RSV-confirmed bronchiolitis cases significantly decreased in infants under 6 months old, who were mostly eligible and immunised, while remaining relatively unchanged in older infants, who were predominantly non-eligible for immunisation (Table S1). This shift in the median age of hospitalisation due to widespread nirsevimab immunisation was also observed in previous studies [13, 33]. These findings contribute to the ongoing discussion about whether extending immunisation to infants older than 6 months would be beneficial.

Regarding the severity of hospitalised patients, it is important to note that definitions of severe bronchiolitis vary in the literature [6, 8, 13]. While some studies used severity scores at admission [13, 33], others defined severe cases as those requiring ICU admission [14] or non-invasive and mechanical ventilation [12, 15]. In this study, no severity score was used to maintain routine clinical practices across participating hospitals. However, significant reductions in ICU admissions and the need for respiratory support, including the use of high-flow nasal cannula, non-invasive ventilation and mechanical ventilation, were observed in the post-nirsevimab epidemic year compared with previous years (Table 3). Similar decreasing trends were reported in previous studies. However, some noted higher absolute numbers of patients requiring high-flow nasal cannula, non-invasive ventilation and mechanical ventilation [12]. This discrepancy may be influenced by the fact that many participating hospitals lacked their own ICUs and were reluctant to transfer patients to other centres. However, no available data confirm this hypothesis.

While it is reasonable to assume that the reduction in RSV-confirmed hospitalisations due to nirsevimab may also contribute to a decline in severe cases, accurately assessing the drug's true impact remains challenging. In the 2023–2024 epidemic year, no significant differences were found in ICU admissions or oxygen support requirements among non-eligible, non-immunised and immunised infants (Table 4). Similarly, among eligible patients with RSV, no significant differences were observed between immunised and non-immunised infants (Table 5). The small sample size in these analyses may have masked statistical differences between groups. However, similar findings were reported in previous studies [8, 12, 13]. Therefore, further research is needed to gain a better understanding of nirsevimab's role in preventing severe bronchiolitis, particularly within the immunised population.

4.2 | Strengths and Limitations

One of the key strengths of this study is its analysis of a broad and geographically representative database spanning two distinct regions of Spain. While more than 500 patients were analysed for the 2023–2024 epidemic year, most previous studies examined fewer than 200 cases [11–13, 15]. In addition, unlike previous studies that gathered data from a limited number of hospitals concentrated in a single region, such as Catalonia [12, 13], Madrid [15, 16], Navarre [17], or Galicia [14], this study collected data from 20 hospitals of varying sizes, complexity levels and routine clinical practices (Table 1). These hospitals are located in two regions that differ significantly in population density, climate, economic activities and mobility patterns of residents and visitors, all of which can influence infection rates and viral transmission. As a result, the dataset collected in this study ensures strong representativeness and generalisability of the findings at the population level.

Several limitations should also be acknowledged. First, this was an observational study, and the routine clinical practices of the participating hospitals were not altered. As a result, some infants were not tested for bronchiolitis aetiology. This approach aligns with international guidelines, which do not recommend routine testing for all infants because the results do not alter clinical management [3]. However, it is important to note that more than 92% of hospitalised infants were tested in each of the three analysed epidemic years (Table 1). Second, this study focused only on hospitalisations due to bronchiolitis, while the condition also leads to increased primary care visits and emergency department consultations, which were not analysed here. Third, in contrast to other European countries, where RSV circulation was slightly higher in 2022–2023 than in pre-COVID years [35], Spain recorded a similar or even slightly lower number of RSV-associated and all-cause bronchiolitis cases [28]. This suggests that the impact observed in the post-nirsevimab epidemic year may be slightly underestimated. Finally, while this study analysed a larger dataset than most previous studies, some subpopulations, such as preterm infants and patients with coinfections, remained too small for definitive conclusions. In addition, while data were collected for the entire 2021–2022 and

2022–2023 epidemic years, only most of the 2023–2024 year was covered. No data were available from 15 June to 31 August 2024. However, in previous years, fewer than 2% of total cases were recorded during that period [28], so the findings presented here remain largely representative. Long-term studies across different clinical settings and larger populations will be necessary in future complete epidemic years to validate the effectiveness of nirsevimab, better understand its role in RSV prevention and develop strategies to reduce the burden of acute bronchiolitis on healthcare systems.

5 | Conclusion

This study was among the first to analyse nearly the entire 2023–2024 epidemic year following the implementation of nirsevimab immunisation in Spain. The findings demonstrate a significant reduction in total and RSV-associated bronchiolitis hospitalisations during the post-nirsevimab epidemic year compared with the two previous years. The effectiveness of nirsevimab in preventing RSV-associated hospitalisations was estimated at approximately 70% for all eligible infants and other subpopulations. However, an increase in bronchiolitis cases caused by rhinoviruses and metapneumovirus was also observed, leading to a bimodal distribution of hospitalisations in the post-nirsevimab epidemic year. Additionally, a slight reduction was noted in the number of infants requiring intensive care and advanced respiratory support in 2023–2024. These findings highlight the need for continued monitoring and further research to validate these results and assess the long-term impact of nirsevimab on acute bronchiolitis and other respiratory infections in the coming years.

Author Contributions

Juan Manuel Rius-Peris: conceptualization, data curation, formal analysis, visualization, writing – original draft, methodology, investigation, supervision, writing – review and editing, validation, project administration. **Enrique Palomo-Atance:** data curation, investigation, writing – review and editing, validation, resources, conceptualization. **Eva Muro-Díaz:** conceptualization, data curation, writing – review and editing, resources, investigation. **Cristina Llorente-Ruiz:** conceptualization, data curation, investigation, writing – review and editing, resources. **Laura Murcia-Clemente:** conceptualization, data curation, investigation, validation, resources, writing – review and editing. **Raúl Alcaraz:** formal analysis, visualization, writing – original draft, methodology, supervision, project administration, writing – review and editing, software, validation, funding acquisition, resources.

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Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.