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Nirsevimab immunization's real-world effectiveness in preventing severe bronchiolitis: A test-negative case–control study

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Abstract

Background: Several clinical trials have shown that nirsevimab, an antibody targeting the respiratory syncytial virus (RSV), reduces RSV bronchiolitis requiring admission. In 2023–2024, Catalonia and Andorra adopted immunization strategies for children <6 months and those born during the epidemic season. This study evaluates the effectiveness of nirsevimab in preventing hospitalizations from RSV bronchiolitis.

Methods: In the epidemic season of 2023–2024, a test-negative case–control study was conducted in three hospitals from Catalonia and Andorra. Patients <12 months old admitted with bronchiolitis and tested for RSV using molecular microbiology tests were included.

The effectiveness in preventing RSV bronchiolitis hospitalization and severe disease was estimated using multivariate models. Comparisons between immunized,

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non-immunized, and non-eligible patients were made in prospectively collected epidemiological, clinical, and microbiological variables.

Results: Two hundred thirty-four patients were included. RSV was detected in 141/234 (60.2%), being less common in the immunized group (37% vs 75%, $p < .001$). The rate of immunized patients among those eligible was 59.7%. The estimated effectiveness for RSV-associated lower respiratory tract infection was 81.0% (95% confidence interval: 60.9–90.7), and for preventing severe disease (the need for NIV/CMV), 85.6% (41.7–96.4%). No significant differences by immunization status were observed in patients with RSV concerning viral coinfections, the need for NIV/CMV or length of hospital stay.

Conclusions: This study provides real-world evidence of the effectiveness of nirsevimab in preventing RSV-lower respiratory tract infection hospitalization and severe disease in infants during their first RSV season following a systematic immunization program. Immunized patients did not exhibit a higher rate of viral coinfections nor differences in clinical severity once admitted.

KEYWORDS
bronchiolitis, effectiveness, immunization, nirsevimab, pediatrics, severity

1 | INTRODUCTION

Respiratory syncytial virus (RSV) is the primary cause of acute lower respiratory tract infection (LRTI) in infants under 1 year old.[1] It is associated with significant morbidity and mortality worldwide in children.[1,2] RSV infection is a leading reason for hospitalization in infants up to 2 years old.[3,4] A recent study estimated a hospitalization rate for infants under 1 year at over 3.800 cases per 100.000 healthy infants in Spain.[5]

Preventing RSV infections has been a challenge for clinicians and healthcare systems. Until now, the only available RSV prophylaxis was palivizumab, a monoclonal antibody administered monthly to selected high-risk patients.[6,7] Therefore, healthy term-born infants, who constitute the main burden of hospitalizations, were not included.[5,8]

Nirsevimab, a new monoclonal antibody, has been approved for the prevention of RSV-associated LRTI in both preterm and full-term infants during their first RSV season.[9–12] It has shown greater potency in reducing RSV infection and a more extended half-life than palivizumab.[13] Clinical trials revealed a decrease in the incidence of RSV-LRTI and hospitalization after a single intramuscular dose of nirsevimab, exhibiting a favorable safety profile.[14–16] In addition, the HARMONIE study, conducted in a real-world clinical trial setting, showcased an 83% reduction in RSV-associated admissions and a 76% effectiveness in diminishing the severity of hospitalized RSV cases.[17] This impact was reported for infants under 1 year of age, but significant results were only achieved for the 0–3 months old age range.

In July 2023, Spain's Public Health Commission recommended systematic immunization for infants up to 6 months during their first RSV season (born in April).[18] In October, Catalonia implemented universal RSV prophylaxis for newborns, with a catch-up strategy for older infants.[19] Meanwhile, Andorra began nirsevimab immunization for high-risk children, later approving it for all newborns in 2024. The RSVpreF vaccine[20] was not introduced in Spain until January 2024, making it unavailable this season.

Despite promising results from clinical trials and early post-immunization analyses,[21,22] which confirm the trial data, the impact of nirsevimab on severe outcomes, coinfections, and its effectiveness in certain subpopulations remains unknown.

The main aim of the study was to evaluate the effectiveness of nirsevimab in preventing hospitalization due to RSV-LRTI in patients eligible for immunization after implementing a systematic program. This study also analyses differences in epidemiological, clinical, and microbiological characteristics between immunized and non-immunized patients despite eligibility.

Key message

In a real-world setting, immunization with nirsevimab has shown an estimated effectiveness of over 80% in preventing hospitalizations caused by RSV bronchiolitis in infants under 6 months. This also includes cases that require non-invasive or invasive ventilation. The effectiveness of this immunization was clear in both preterm and previously healthy babies across all age ranges, including infants aged 3–6 months, without observing an immediate replacement by other viral etiologies.

2 | MATERIALS AND METHODS

2.1 | Study design

A prospective multicentric observational study was performed from November 2023 through February 2024. Three centers participated: Hospital Sant Joan de Déu Barcelona (HSJD), Hospital Universitari General de Catalunya (HUGC) (Sant Cugat del Vallès, Barcelona), and Hospital Nostra Senyora Meritxell (HNSM) (Andorra).

HSJD, a university center and one of Europe's largest pediatric hospitals, provides services to 350,000 children. This represents 20% of pediatric admissions in Catalonia. Meanwhile, HUGC, a private university hospital, caters to 80,000 insured children, making up 4% of Catalonia's pediatric admissions. Lastly, HNSM, the only hospital in Andorra, serves an area that includes 9000 children.

2.2 | Inclusion criteria and definitions

Patients aged up to 12 months, admitted for at least 24 hours in any participant centers, and tested for RSV in nasopharyngeal aspirate using polymerase chain reaction (PCR)-based tests (Qiagen Multiplex PCR or Filmarray Respiratory Panel) were consecutively included. The study period covers the entire epidemic season in the regions. The beginning and conclusion of the epidemic is determined as follows: The start is marked by the first of two successive weeks where the percentage of RSV-positive PCR tests exceeds 3%. Conversely, the end is identified as the first of two consecutive weeks when this percentage falls below 3%. This is based on data from the Catalan Surveillance System for Respiratory Infections.[23]

The exclusion criteria included patients who only underwent an antigen-detection-based test, as well as those with a previous episode of bronchiolitis or LRTI (bronchitis, bronchopneumonia, or pneumonia).

Definitions:

- Bronchiolitis: The first episode in a patient's clinical history that presents signs of LRTI.[24]
- Severe bronchiolitis: Bronchiolitis requiring NIV such as continuous positive airway pressure, bi-level positive airway pressure, or CMV.

2.3 | Data collection and outcomes

Epidemiological, clinical, and microbiological data were collected prospectively. The primary outcome was the effectiveness of nirsevimab in preventing hospitalization due to RSV-associated bronchiolitis and severe RSV disease. Secondary outcomes included the bronchiolitis Score of Sant Joan de Déu (BROSJOD) at admission,[25] the need for oxygen support, and the length of hospital stay (LOS).

2.4 | Statistical analyses

Descriptive statistics were reported as frequencies and percentages. Categorical data comparisons were done using Pearson chi-square or Fisher exact test. Continuous non-normal variables were described as median and interquartile ranges (IQR) and compared using the Mann–Whitney U test and Kruskal–Wallis analysis.

A multivariate analysis was conducted to estimate the odds ratio of various potential risk factors for developing severe disease. This analysis utilized a logistic regression model, incorporating all variables with a p-value less than 0.1, with "severe disease" as the response variable. The Hosmer–Lemeshow test was used as a measure of model fit, with the model considered appropriate if $p > .05$. Statistical analysis was performed with SPSS v24.0 software (Armonk, NY: IBM Corp).

Immunization effectiveness (IE) was calculated as 100% × (1 − adjusted odds ratio [aOR]), where the aOR is the odds ratio of immunization among RSV-positive cases compared with RSV-negative control patients, adjusted for potential confounders. When using mixed-effects logistic regression, estimates were adjusted for age, weight, and the presence of at least one preexisting condition as fixed effects; the month of admission and hospital were treated as random effects. Separate analyses were conducted to estimate IE by different age ranges and for previously healthy infants or those with comorbidities. When determining IE for previously healthy infants or those with comorbidities, the presence of at least one preexisting condition was not considered a covariate. All analyses were performed using R software (version 4.3.2; R Foundation) and the lme4 library v1.1-14. Statistical significance was assigned to p-values $< .05$.

2.5 | Ethics

This study was approved by the Ethics Committee and Institutional Review Board of the Sant Joan de Déu Hospital (EOM-21-23). Informed consent was obtained from all patients' legal tutors.

3 | RESULTS

Two hundred fifty-five patients were admitted to the three hospitals with bronchiolitis (HSJD, 182; HUGC, 43; HNSM, 30). Twenty-one patients were excluded as they had only antigen-based tests. Therefore, a total of 234 were included in the study. The median age was 3.6 months, with an interquartile range (IQR) of 1.5–8.1. The majority were previously healthy (170/234, 72.6%). RSV was detected in 141/234 (60.2%) of patients. Rhinovirus (RV) was the second most frequently detected virus, followed by metapneumovirus. Among the cases where typing was possible, RSV-A was more prevalent than RSV-B (59 of 81 (73%) versus 25/81 (31%), respectively). There were three cases in which both RSV-A and RSV-B were detected. RSV was also detected alongside other viruses in 48 out of the 130 patients (37%) who underwent a multiplex panel, primarily with RV as the main codetection (33/48, 69%). Overall, 88% required

at least supplementary oxygen with a low-flow nasal cannula (LFNC), whereas 67 patients (29%) required either NIV or CMV. Detailed information on the epidemiology, clinical, and microbiological characteristics of the patients included can be found in Table 1.

Regarding immunization coverage, 46.6% (109 patients) had received nirsevimab, and 30.8% (72 patients) were eligible for immunization but were not immunized. Fifty-three patients were not eligible for immunization according to local recommendations.

TABLE 1 Demographic, clinical, and microbiological characteristics of patients admitted with bronchiolitis. Comparisons based on their immunization status and whether or not they were eligible for immunization.

		Eligible patients for immunization ($n=181$)				
	Total ($n=234$)	Not immunized ($n=72$)	Immunized ($n=109$)	p-value*	Non-eligible patients for immunization ($n=53$)	p-value**
Gender (male)	139 (59%)	41 (57%)	72 (66%)	0.215	26 (49%)	0.081
Age (months)[a]	3.6 (1.5–8.1)	2.9 (1.4–5.5)	1.7 (1.2–4.1)	0.037	10 (9.2–10.7)	<0.001
0–89 days (n)	105 (50%)	36 (50.0)	69 (63%)	0.196	0 (0.0)	<0.001
90–179 days (n)	45 (19%)	23 (31%)	23 (21%)		0 (0.0)	
180–364 days (n)	84 (36%)	14 (19%)	17 (16%)		53 (100)	
Weight (kg)[a]	5.6 (4.3–8.0)	5.4 (4.4–7.3)	4.7 (4.0–6.1)	0.003	8.5 (7.8–9.9)	<0.001
Comorbidities (n)						
None	170 (73%)	55 (76%)	65 (60%)	0.020	50 (94%)	<0.001
Prematurity < 36 wga	39 (17%)	8 (11%)	31 (28%)	0.006	0	<0.001
Congenital heart disease	10 (4%)	4 (6%)	6 (5%)	1.000	0	0.122
Chronic lung disease	4 (2%)	0	4 (4%)	0.152	0	0.577
Neurological disorders	3 (1%)	1 (1%)	2 (3%)	1.000	0	1
Other	8 (3%)	4 (6%)	1 (1%)	0.326	3 (6%)	0.145
Viral detections (n)						
RSV	141 (60%)	54 (75%)	40 (37%)	<0.001	47 (89%)	<0.001
RSV-A	59/81 (73%)	14/23 (61%)	24/32 (75%)	0.263	21/26 (81%)	0.277
RSV-B	25/81 (31%)	9/23 (39%)	9/32 (28%)	0.391	7/26 (27%)	0.595
RV	77/215 (36%)	16/66 (24%)	37/103 (36%)	0.110	24/46 (52%)	0.010
Metapneumovirus	14/215 (6%)	4/66 (6%)	10/103 (10%)	0.401	0/46 (0%)	0.084
Influenza	10 (4%)	1 (1%)	8 (7%)	0.089	1 (2%)	0.095
Adenovirus	9/215 (4%)	2/66 (3%)	4/103 (4%)	1.000	3/46 (6%)	0.648
Coronavirus pre-pandemic	10/215 (5%)	3/66 (4%)	4/103 (4%)	1.000	3/46 (6%)	0.699
Bocavirus	9/215 (4%)	1/66 (1%)	4/103 (4%)	0.649	4/46 (7%)	0.171
RSV codetected with other viruses	48/130 (37%)	15/51 (29%)	8/39 (20%)	0.337	25/40 (62%)	<0.001
BROSJOD upon hospital admission[a]	8 (6–9)	8 (6–8)	7 (6–9)	0.971	8 (7–9)	0.663
Respiratory support (n)						
LFNC	206 (88%)	63 (87%)	93 (88%)	0.678	50 (94%)	0.249
HFNC	151 (64%)	51 (71%)	72 (66%)	0.500	28 (53%)	0.043
Non-invasive ventilation	67 (29%)	20 (28%)	40 (37%)	0.213	7 (13%)	0.008
Mechanical ventilation	12 (5%)	5 (7%)	7 (6%)	1.00	0 (0%)	0.073
Antibiotic prescription (n)	44 (1%)	12 (17%)	18 (16%)	0.978	14 (26%)	0.107
Hospital LOS (days)[a]	5 (4–8)	5 (3–8)	6 (4–9)	0.077	5 (3–6)	0.043
CRP on admission (mg/L)[a]	15.1 (4.9–37.7)	15.8 (5.2–38.4)	9.1 (2.3–28.3)	0.141	25.0 (13.0–75.6)	0.008
PCT on admission (ng/mL)[a]	0.13 (0.07–0.32)	0.11 (0.06–0.39)	0.09 (0.06–0.18)	0.390	0.51 (0.17–2.02)	<0.001

Abbreviations: BROSJOD, Bronchiolitis Score of Sant Joan de Déu; CRP, C-reactive protein; HFNC, high-flow nasal cannula; LFNC, low-flow nasal cannula; LOS, length of stay; PCT, Procalcitonin; RSV, respiratory syncytial virus; RV, rhinovirus; Wga, weeks gestational age.

[a]Median (interquartile range).

*Comparisons between patients who were immunized and those who were not among the eligible individuals. **Comparisons between the three groups.

Therefore, the rate of immunized patients among those eligible was 109/181 (60.2%). Selecting only Catalan children, a significantly higher proportion of immunization with nirsevimab was observed in newborns, 81% (40/49), compared to infants who could have received the monoclonal on an outpatient basis (catch-up), 63% (69/110) ($p = .029$). In patients who were not eligible for immunization, RSV was detected in 89%, a rate significantly higher than in the immunized group, 37% ($p < .001$). Ineligible patients, who were older, had fewer risk comorbidities, a lower rate of NIV, and a shorter LOS and also exhibited higher levels of inflammatory markers such as C-reactive protein and procalcitonin; Table 1.

3.1 | Immunization effectiveness

When considering only patients eligible for nirsevimab, the estimated IE for RSV-associated LRTI was 81.0% (95% confidence interval (CI): 60.9–90.7, $p < .001$) (Figure 1). For patients under 3 months old, effectiveness was 78.2% (42.8–91.7, $p = .002$); for those aged 3 to 6 months, it was 85.3% (22.5–97.2, $p = .024$). When only healthy patients were analyzed, the effectiveness of the immunization was 82.4% (59.5–92.4, $p < .001$). Meanwhile, in ex-preterm with less than 36 weeks of gestational age, its effectiveness was 98.9% (33–100; $p < .001$). The IE did not significantly change when considering only pure RSV infections or RSV with other detections. Finally, for preventing severe disease (the need for NIV/CMV), the immunization effectiveness was 85.6% (41.7–96.4%, $p = .007$).

3.2 | Differences in epidemiological, clinical, and microbiological characteristics between immunized and non-immunized

Table 2 describes the main differences between patients who required either LFNC and/or NIV/CMV and those who did not, among those eligible for immunization. In the multivariate analysis, weight was the only variable associated with NIV/CMV, regardless of whether they had received nirsevimab.

The same analysis was conducted on the subgroup of eligible patients where RSV was detected, Table 3. The only variable associated with a reduced need for LFNC was immunization. Meanwhile, weight and age were the only variables correlated with the need for NIV/IMV.

Eligible patients in whom RSV was detected were subsequently compared based on having received nirsevimab or not (Table 4). Among the RSV-positive eligible individuals, those who had been immunized had significantly lower weight and a history of prematurity less than 36 weeks gestational age compared to those who were not immunized. Among immunized patients, RSV was detected in 40 patients (36.7%). Of these, 24 were RSV-A, 9 were RSV-B, and 7 were not typed. Although there was a slightly higher detection rate of RSV-A in immunized patients compared to non-immunized ones, this difference was not statistically significant. Additionally, 20.5% (eight patients) exhibited coinfection with other viruses: three with RV, two with adenovirus, one with parainfluenza, one with pre-pandemic coronavirus, and one with influenza A. Viral coinfection was not more common in immunized patients. Despite the use of oxygen with LFNC was higher in the non-immunized group, no significant differences were observed in the severity score (BROSJOD) upon hospital admission, NIV/CMV support, or LOS. As significant differences in weight and comorbidities between immunized and non-immunized were observed, a subgroup analysis was performed only on healthy patients to avoid biases and the outcomes for the previously stated variables remained consistent.

4 | DISCUSSION

This study provides early real-world evidence that nirsevimab immunization can prevent RSV-LRTI hospitalization and severe disease

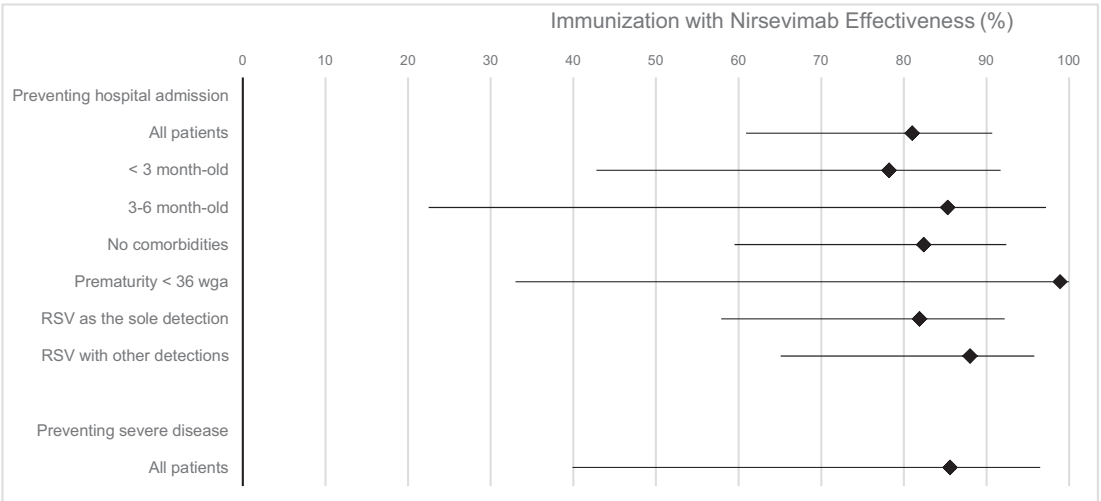

FIGURE 1 Effectiveness of nirsevimab in preventing hospital admissions and severe disease. General and subgroup analysis.

TABLE 2 Variables associated with severity among those eligible for immunization.

	No oxygen needed (*n* = 25)	Oxygen needed (*n* = 156)	Univariate	Multivariable analysis*		No NIV/CMV (*n* = 120)	NIV/CMV (*n* = 61)	Univariate	Multivariable analysis*	
			p-value	Odds ratio (95% CI)	*p*-value			*p*-value	Odds ratio (95% CI)	*p*-value
Age (months)**	1.5 (0.9–3.7)	2.5 (1.3–4.9)	0.083	1.14 (0.94–1.38)	0.833	3.0 (1.4–5.3)	1.5 (1.0–2.5)	**<0.001**	0.98 (0.81–1.19)	0.833
Weight (kg)**	4.7 (4.2–5.3)	5.1 (4.1–7.0)	0.482	-	-	5.4 (4.3–7.4)	4.3 (3.8–5.2)	**<0.001**	0.70 (0.53–0.94)	**0.017**
Sex (male)	9 (36%)	104 (67%)	**0.003**	3.2 (1.3–8.1)	**0.013**	73 (61%)	40 (66%)	0.534	-	-
Comorbidity (*n*)	8 (32%)	53 (34%)	0.846	-	-	40 (33%)	21 (34%)	0.883	-	-
Prematurity < 36 wga	2 (8%)	37 (24%)	0.076	0.3 (0.1–1.4)	0.116	22 (18%)	17 (28%)	0.140	-	-
Congenital heart disease	4 (16%)	6 (4%)	**0.034**	3.4 (0.7–16.4)	0.130	7 (6%)	3 (5%)	1	-	-
Chronic lung disease	1 (4%)	3 (2%)	0.451	-	-	3 (1%)	1 (1%)	1	-	-
Neurological disorders	0	3 (2%)	1	-	-	0	3 (5%)	**0.037**	0 (0–0)	0.999
Immunized (*n*)	16 (64%)	93 (60%)	0.678	0.92 (0.46–1.85)	0.826	69 (57%)	40 (66%)	**0.016**	0.92 (0.46–1.85)	0.826
Lag time between nirsevimab administration and admission	42 (23–71)	37 (24–62)	0.709	-	-	40 (23–65)	32 (22–32)	0.346	-	-
Viral detection										
RSV (*n*)	9 (36%)	85 (54%)	0.086	0.5 (0.2–1.3)	0.135	58 (48%)	36 (59%)	0.174	-	-
RSV-A	5/7 (71%)	33/48 (69%)	0.886			20/29 (69%)	18/26 (69%)	0.983		
RSV-B	2/7 (29%)	16/48 (33%)	1			9/29 (31%)	9/26 (25%)	0.778		
Rhinovirus (*n*)	5/18 (28%)	48/151 (32%)	0.729	-	-	32/108 (29%)	21/61 (34%)	0.519	-	-
Other viral detections (*n*)	7/18 (39%)	45/151 (30%)	0.430	-	-	36/108 (33%)	16/61 (26%)	0.337	-	-
RSV codetected with other viruses (*n*)	0/8 (0%)	23/82 (30%)	0.108	-	-	12/54 (22%)	11/36 (30%)	0.375	-	-
CRP on admission (mg/L)**	23 (6–39)	10 (3–29)	0.478	-	-	9 (5–35)	11 (2–29)	0.740	-	-
PCT on admission (ng/mL)**	0.09 (0.06–0.10)	0.11 (0.06–0.23)	0.562	-	-	0.10 (0.07–0.24)	0.11 (0.06–0.23)	0.508	-	-

Abbreviations: CMV, conventional mechanical ventilation; CRP, C-reactive protein; NIV, non-invasive ventilation; PCT, Procalcitonin; RSV, respiratory syncytial virus; Wga, weeks gestational age.

*Hosmer–Lemeshow $p = .922$. **Median (interquartile range).

Values that are statistically significant are marked in bold

TABLE 3 Variables associated with severity among those in whom RSV was detected and eligible for immunization.

	No oxygen needed ($n=9$)	Oxygen needed ($n=85$)	p-value	No NIV/CMV ($n=58$)	NIV/CMV ($n=36$)	p-value
Age (months)**	1.6 (1.1–3.7)	2.1 (1.4–4.4)	0.332	3.0 (1.5–4.9)	1.6 (1.1–2.6)	**0.009***
Weight (kg)**	4.8 (4.4–5.3)	5.2 (4.1–7.0)	0.585	5.4 (4.4–7.1)	4.6 (4.0–5.9)	**0.008***
Sex (male)	4 (44%)	54 (63%)	0.296	33 (57%)	11 (20%)	0.224
Comorbidity (*n*)	2 (22%)	25 (29%)	1	15 (26%)	12 (22%)	0.436
Prematurity < 36 wga	1 (11%)	18 (21%)	0.681	9 (15%)	10 (18%)	0.150
Congenital heart disease	0	1 (1%)	1	1 (2%)	0	1
Immunized (*n*)	7 (77%)	33 (38%)	**0.034**	22 (38%)	18 (50%)	0.250
Lag time between nirsevimab administration and admission	44 (26–78)	38 (25/61)	0.601	43 (26–70)	36 (26–59)	0.510
Viral codetection:						
Rhinovirus (*n*)	0/8	13/82 (16%)	0.597	6/54 (11%)	7/36 (19%)	0.271
Other viral detections (*n*)	1/8 (12%)	12/82 (15%)	1	9/54 (17%)	4/36 (11%)	0.463
RSV codetected with other viruses (*n*)	0	23/82 (28%)	0.108	12/54 (22%)	11/36 (30%)	0.375
CRP on admission (mg/L)**	-	9.5 (3.6–29)	-	9 (5–25)	11 (2–32)	0.696
PCT on admission (ng/mL)**	-	0.09 (0.06–0.22)	-	0.09 (0.06–0.24)	0.09 (0.06–0.23)	0.649

Abbreviations: CMV, conventional mechanical ventilation; CRP, C-reactive protein; NIV, non-invasive ventilation; PCT, Procalcitonin; RSV, respiratory syncytial virus; Wga, weeks gestational age.

*A multivariable analysis was conducted, but the results are not displayed because the Hosmer–Lemeshow test returned a p-value of less than 0.05.

**Median (interquartile range).

Values that are statistically significant are marked in bold

in infants following a universal systematic immunization program. Recent early real-world data from Luxembourg, Spain, and the United States have shown varying rates of reduction in hospitalizations, ranging from 69% to 90%.[21,22,26] Various factors could account for these differences between studies. Some of these factors include the small number of patients included in some studies,[21,26] differing implementation strategies, and the use of antigen-based tests, which could result in false-negative RSV results. The estimated global effectiveness of nirsevimab in our population for preventing RSV-LRTI hospitalization was 82.1%, in the high range of results reported in clinical trials[14,15] and very similar to the HARMONIE study, which was conducted under conditions closest to the real-world.[17] Notably, our study illustrates the effectiveness of immunization in children aged 3 to 6 months, an aspect that could not be demonstrated with real-world data before. For reference, recent data from the Surveillance System of Acute Respiratory Infections in Spain (SiVIRA) reports 13,120 and 3357 hospitalizations of children under 1 year old with RSV in the 2022–23 and 2023–24 seasons, respectively.[27] This data offers a different viewpoint on the impact, despite the inherent limitations of cross-seasonal data comparison, and the inclusion of patients ineligible for nirsevimab.

Our study estimated an effectiveness of 85.6% in preventing severe RSV disease, defined as the need for NIV or CMV. These therapies are typically applied in the PICU setting in most hospitals. In clinical trials, "very severe RSV-associated LRTI" was often defined as low oxygen saturation at any time during hospitalization or the need for supplementary oxygen.[17] We suggest that using our definition, the implications change significantly. The need for a PICU becomes the most concerning aspect due to resource scarcity during seasonal bronchiolitis epidemics.

On the other hand, a significant reduction in hospitalizations led to fewer PICU admissions. It is worth noting that in our study, no significant differences were found between immunized and non-immunized patients requiring respiratory support once hospitalized. In the subgroup analysis of healthy patients, we only observed a significant reduction in the need for low-flow oxygen therapy among immunized patients. However, the proportion of NIV or CMV remained similar in both groups. This finding, which has not been previously reported in the literature, is noteworthy. The existing literature focuses mainly on outcomes such as medically attended episodes and hospital admissions, and it was previously suggested that immunized patients experience less severe conditions once admitted.[15,17] Further studies should assess the clinical progress of inpatients to understand better the impact of nirsevimab on the natural progression of RSV infection in inpatients.

When comparing severity variables, we found that lower age and weight were the main variables associated with the requirement of NIV/CMV. However, the only risk factor associated with severity in our multivariate analysis was lower weight, not age or non-immunized status. Regardless of prematurity, lower weights at hospitalization traditionally heightened the risk of PICU admission.[28] On the other hand, the MELODY study reported a tendency for higher mean serum levels of nirsevimab in infants who received 100 mg (recommended from 5 kg) compared to those administered

TABLE 4 Demographic, clinical, and microbiological characteristics of patients with RSV infection who were eligible for immunization.

	Patients with RSV infection eligible for immunization				Patients with RSV infection eligible for immunization without comorbidities			
	Total	Not immunized	Immunized		Total	Not immunized	Immunized	
	n = 94	*n* = 54	*n* = 40	*p*-value*	*n* = 67	*n* = 42	*n* = 25	*p*-value*
Gender (male)	58 (62%)	32 (59%)	26 (65%)	.571	42 (63%)	26 (62%)	16 (64%)	.864
Age (months)	2.1 (1.3–4.2)	2.8 (1.4–5.0)	1.8 (1.3–3.7)	.090	2.0 (1.3–3.9)	2.1 (1.3–4.1)	1.9 (1.2–3.9)	.604
0–89 days (*n*)	56 (60%)	28 (52%)	28 (70%)	.143	41 (61%)	25 (60%)	16 (64%)	.853
90–179 days (*n*)	28 (30%)	18 (33%)	10 (25%)		22 (33%)	14 (33%)	8 (32%)	
180–364 days (*n*)	10 (11%)	8 (15%)	2 (5%)		4 (6%)	3 (7%)	1 (4%)	
Weight (kg)	5.1 (4.2–6.7)	5.4 (4.4–7.1)	4.7 (4.0–6.1)	.018	5.2 (4.3–7.0)	5.2 (4.3–7.0)	4.8 (4.4–6.8)	.721
RSV type								
A	38/55 (69%)	14/23 (61%)	24/32 (75%)	.263	28/38 (74%)	11/17 (65%)	17/21 (81%)	.293
B	18/55 (33%)	9/23 (39%)	9/32 (28%)	.391	11/38 (29%)	6/17 (35%)	5/21 (24%)	.491
Viral codetections (*n*)	23/90 (25%)	15/51 (29%)	8/39 (20%)	.337	16/65 (25%)	10/40 (25%)	6/25 (24%)	.927
RV	13/90 (14%)	10/51 (20%)	3/39 (8%)	.111	9/65 (14%)	7/40 (18%)	2/25 (8%)	.463
Other viral detections	13/90 (14%)	6/51 (12%)	7/39 (18%)	.408	7/65 (11%)	3/40 (8%)	4/25 (16%)	.414
BROSJOD upon hospital admission	8.0 (6.0–9.0)	8.0 (6.8–8.3)	8.0 (6.0–9.0)	.582	8 (6–9)	8 (6–9)	9 (8–10)	.068
Respiratory support (*n*)								
LFNC	85 (90%)	52 (96%)	33 (83%)	.034	60 (90%)	40 (95%)	20 (80%)	.049
HFNC	68 (72%)	41 (76%)	27 (68%)	.367	51 (76%)	33 (79%)	18 (72%)	.542
Non-invasive ventilation	36 (38%)	18 (33%)	18 (45%)	.250	24 (36%)	13 (31%)	11 (44%)	.281
Mechanical ventilation	8 (9%)	4 (7%)	4 (10%)	.719	6 (9%)	3 (7%)	3 (12%)	.664
Antibiotic prescription (*n*)	18 (19%)	10 (19%)	8 (20%)	.857	14 (21%)	8 (19%)	6 (24%)	.630
PICU LOS (days)	5.0 (3.0–10.0)	4.5 (3.0–12.0)	5.0 (3.5–7.0)	.800	5 (3–10)	4 (3–11)	5 (4–9)	.857
Hospital LOS (days)	5 (3.5–7.5)	5.0 (3.8–7.0)	5.0 (3.0–8.0)	.928	5 (4–7)	5 (4–7)	5 (3–6)	.925
CRP on admission (mg/L)	9.5 (3.9–28.7)	11.3 (3.9–31.5)	9.1 (2.9–26.0)	.572	10.3 (3.7–37.3)	11.6 (4.9–33.0)	9.1 (1.5–66.0)	.777
PCT on admission (ng/mL)	0.09 (0.06–0.22)	0.11 (0.06–0.39)	0.08 (0.06–0.16)	.215	0.11 (0.06–0.23)	0.11 (0.06–0.23)	0.11 (0.06–0.23)	.676
Comorbidities (*n*)								
None	67 (71%)	42 (78%)	25 (63%)	.106				
Prematurity < 36 wga	19 (20%)	7 (13%)	12 (30%)	.042				
Congenital heart disease	1 (1%)	0	1 (3%)	.426				

Abbreviations: BROSJOD, Bronchiolitis Score of Sant Joan de Déu; CRP, C-reactive protein; HFNC, high-flow nasal cannula; LFNC, low-flow nasal cannula; LOS, length of stay; PCT, procalcitonin; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; RV, rhinovirus.

*Comparisons between patients who were immunized and those who were not among the eligible individuals.

a 50 mg dose (recommended up to 5 kg), but the difference was not significant.[15] It is yet to be determined if there is a dose–response relationship that could explain the variability in efficacy and effectiveness concerning weight. Depending on future observations, immunization strategies should focus more on weight than the age range of the patients.

Regarding viral etiologies, RSV remains the most common cause of bronchiolitis in all patients, just before the immunization programs.[1,3] A minor difference was observed, with a higher rate of RSV-A detections in immunized patients. However, the lack of statistical significance in this difference reaffirms the findings of previous literature that nirsevimab is effective in neutralizing both RSV-A and RSV-B subtypes.[14,16] RV is still the second most common detection and is the primary virus coinfecting with RSV.[29] Interestingly, the rate of RV detections did not increase in immunized patients. In the MELODY and HARMONIE trials, immunization also decreased the incidence of hospitalization due to any cause of LRTI[15,17] without any immediate replacement. Moreover, patients immunized against RSV did not show a higher rate of coinfections when compared to non-immunized ones, suggesting that RSV had been an incidental codetection in the immunized patients. Coinfections were only more prevalent in patients not eligible for immunization, as multiple viral detections are more common in older patients, as previously described.[29,30]

For context, in Catalonia, the immunization coverage for the eligible population was 54% at the start of the study period and increased to 79% by the end.[23] In contrast, Andorra had much lower immunization rates due to the later initiation of immunization for low-risk patients. However, once the program was established, coverage for those immunized at birth exceeded 98%. It was noted that patients immunized at birth had significantly better immunization rates than those treated with nirsevimab as outpatients (catch-up). However, the study did not investigate the reasons why eligible children were not immunized. Observations suggest that parents may lack confidence in immunizing their newborns, and practical issues such as work schedules, language barriers or the need for active patient search may impede catch-up immunization. These factors, while not directly studied, could potentially influence the acceptability of immunization and should be considered in the development of future strategies for RSV prevention. Additionally, mother's vaccination for RSV prevention in very young infants is another alternative available.[20] Beyond acceptance, cost-effectiveness studies should be conducted to aid decision-making.

This study has several limitations, including its observational design and the homogeneous population across three hospitals. This may limit its applicability to other settings, notably in low-middle-income countries. Epidemiological differences and patient type variations between public and private settings, as well as in less populated areas like Andorra, may also exist. While we considered the "hospital" factor in the multivariable models calculating effectiveness, we were unable to conduct a detailed analysis by region or setting due to limited patient numbers from HUGC and HNSM. Despite these limitations, the inclusion of children from diverse settings enhances the generalizability of our results. Lastly, it is important to note that the test-negative design only estimates nirsevimab's effectiveness in preventing hospitalizations, not other outcomes like medically attended disease.

To conclude, this study provides real-world evidence of the effectiveness of nirsevimab in preventing RSV-LRTI hospitalization and severe disease in infants during their first RSV season following a systematic immunization program. Immunization's effectiveness can be demonstrated not only for those under 3 months old but also for those aged 3 to 6 months. Patients who were immunized and required hospital admission did not exhibit a higher rate of viral coinfections nor differences in clinical severity, such as the need for NIV/CMV or LOS.

AUTHOR CONTRIBUTIONS

Marta Agüera: Conceptualization; investigation; validation; data curation; methodology; writing – original draft; writing – review and editing; formal analysis. **Aleix Soler-Garcia:** Conceptualization; investigation; methodology; validation; formal analysis; data curation; writing – original draft; writing – review and editing. **Carme Alejandre:** Investigation; writing – review and editing; data curation. **Sara Moussalam-Merino:** Investigation; writing – review and editing. **Pere Sala Castellví:** Investigation; writing – review and editing; data curation. **Gemma Pons:** Investigation; writing – review and editing. **Daniel Penela-Sánchez:** Investigation; writing – review and editing; data curation. **Carla González-Grado:** Investigation; writing – review and editing. **Judit Alsina-Rosell:** Investigation; writing – review and editing. **Carme Climent:** Investigation; writing – review and editing; data curation; supervision. **Cristina Esteva:** Investigation; methodology; writing – review and editing; resources. **Clàudia Fortuny:** Methodology; investigation; writing – review and editing; resources. **Mariona-F de-Sevilla:** Investigation; writing – review and editing; resources. **Juan-José García-García:** Investigation; writing – review and editing; resources. **Pedro Brotons:** Investigation; conceptualization; methodology; formal analysis; data curation; writing – review and editing; writing – original draft. **Albert Balaguer:** Writing – review and editing; supervision; investigation. **Josep Estrada:** Investigation; writing – review and editing; supervision. **Iolanda Jordan:** Investigation; conceptualization; methodology; writing – original draft; writing – review and editing; formal analysis; supervision; resources. **Carmen Muñoz-Almagro:** Resources; formal analysis; methodology; writing – review and editing; conceptualization; investigation; writing – original draft. **Cristian Launes:** Conceptualization; resources; formal analysis; writing – review and editing; writing – original draft.

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