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E. Jeziorski, A. Ouziel, M. Cotillon, C. Bridonneau, E. Bizot, et al.. Impact of nirsevimab on respiratory syncytial virus bronchiolitis in hospitalized infants: a real-world study.. The Pediatric Infectious Disease Journal, 2024, The Pediatric Infectious Disease Journal, 10.1097/INF.0000000000004630 . hal-04872610

HAL Id: hal-04872610
https://hal.univ-lille.fr/hal-04872610v1

Submitted on 8 Jan 2025

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IMPACT OF NIRSEVIMAB ON RESPIRATORY SYNCYTIAL VIRUS BRONCHIOLITIS IN HOSPITALIZED INFANTS

A REAL-WORLD STUDY

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Abstract: Regarding nirsevimab immunization status, among 1085 infants hospitalized for bronchiolitis, the odds of hospitalization for respiratory syncytial virus bronchiolitis were 4.7 times higher for nonimmunized children. Immunized infants were less likely to require oxygen supplementation (20.2% vs. 30.6%, $P = 0.02$) and had a 1-day shorter hospital stay. Respiratory syncytial virus bronchiolitis was less frequent and less severe in infants immunized with nirsevimab.

Key Words: immunization, nirsevimab, respiratory syncytial virus, bronchiolitis, hospitalization

Accepted for publication September 12, 2024

E.J. received personal fees from Pfizer, GSK and Sanofi and nonfinancial support from MSD, Sanofi outside the submitted work. R.C. received personal fees and nonfinancial support from Pfizer and personal fees from Merck, GSK, Sanofi and AstraZeneca outside the submitted work. C.L. received personal fees and nonfinancial support from Pfizer and Merck outside the submitted work. S.A. and R.K. are employed at Sanofi and hold shares of the company. The other authors have no conflicts of interest to disclose.

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This work was funded by Sanofi Vaccines and AstraZeneca.

E.J., R.C., S.B. and C.L.: study conception. E.J., A. O., M.C., C.B., E.B., C.B., A.P., F.D., S.B., L.D., C. J., V.G., E.L., R.B. and Y.G.: data collection. E.J, R.C, S.B. and C.L.: data analysis and interpretation. E.J., R.C., S.B. and C.L.: drafting the manuscript. All authors: revising the manuscript for important intellectual content and approved the final version submitted. R.C., E.J., S.B. and C.L.: study supervision.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

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DOI: 10.1097/INF.0000000000004630

Nirsevimab, a monoclonal antibody against respiratory syncytial virus (RSV) showed good efficacy in reducing hospitalizations for lower respiratory tract infections caused by RSV in healthy preterm and full-term infants.[1] All countries that had introduced nirsevimab immunization in the 2023–2024 season (eg, US, France, Spain and Luxembourg) confirmed its high effectiveness.[2–6] The impact of nirsevimab on RSV bronchiolitis severity was suggested in a Luxembourg study with a decrease in hospitalization duration by historical comparison.[5] However, the cohort involved few children, and the study did not cover the full RSV season.

France had introduced nirsevimab for all infants entering their first RSV epidemic season starting in mid-September 2023. Although the recommendation was to immunize infants born after February 6, 2023, because of the high level of parental acceptance of the immunization program and to provide doses to this target population throughout the epidemic season, in early October, the decision was to restrict the nirsevimab vaccination to neonates in maternity wards.[7] In France, the estimated immunization coverage for infants born after September 15, 2023, was about 85%.

In this context, we performed a prospective study of children hospitalized for all-cause bronchiolitis to evaluate changes in disease severity according to RSV and nirsevimab status.

METHODS

We conducted a national multicentre prospective study (called OVNI) involving 6 pediatric wards throughout France. From October 27, 2023, to February 29, 2024, we enrolled all infants ≤12 months of age who were hospitalized for acute bronchiolitis. Bronchiolitis was defined as the presence of signs of a viral upper respiratory infection, with one of the following examination findings: wheezing, crackles, diminished vesicular murmur and breathing difficulties. All the centers followed the same standardized hospitalization criteria.[8] We excluded infants who had received nirsevimab from 0 to 7 days before the onset of symptoms and those who had palivizumab immunization (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/F821).[6]

An electronic case report form was completed on a secure database. Information collected included demographic, clinical and biologic data; risk factors of severe bronchiolitis (eg, bronchopulmonary dysplasia, prolonged neonatal ventilation, congenital heart disease, immune deficiencies)[8]; nirsevimab status; treatments; and death. RSV diagnosis was defined as positive by polymerase chain reaction (PCR), comprising respiratory multiplex PCR (BioFire respiratory panel and FilmArray Biomérieux, Marcy-l'Étoile, France, Cepheid's GeneXpert systems, Maurens-Scopont, France; and Panel SARS-CoV-2/Flu A/B/RSV Assay, Panther Fusion System, Hologic, Tremblay-en-France, France) or rarely, a rapid antigen test.

The study evaluated the number of RSV-positive and RSV-negative bronchiolitis cases requiring hospitalization in infants overall, as well as those with risk factors for bronchiolitis. We also aimed to identify any clinical differences associated with nirsevimab status. Because the immunization program started on September 15, 2023, we conducted an additional analysis for infants born after this date.

Data were entered in the electronic case report form (PHP/MySQL) and analyzed by using Stata/SE 18 (2023; StataCorp LLC, College Station, TX). Quantitative data were compared by Student's t test and categorical data by χ^2 or Fisher exact test. Odds ratios (ORs) were estimated. Confidence intervals (95% CIs) were calculated by using an exact binomial method (Clopper–Pearson). All tests were 2-sided, and the results were considered significant at $P < 0.05$. Multivariate logistic regression models were developed

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Table 1. Characteristics of Infants ≤12 Months of Age According to RSV and Nirsevimab Status Overall

Characteristics	RSV-positive (N = 724)				RSV-negative (N = 291)			
	With Nirsevimab, n = 102 (14.1%)	Without Nirsevimab, n = 609 (82.9%)	*P*‡	Total (N = 711*)	With Nirsevimab, n = 128 (44.9%)	Without Nirsevimab, n = 157 (54.0%)	*P*†	Total (N = 285*)
Age at diagnosis (mo)								
Mean±SD	1.8±1.1	4.1±2.7	<0.001	3.8±2.6	2.5±2	4.6±2.9	<0.001	3.7±2.8
Median	1.5	3.6		3.3	1.8	4.4		2.9
Age group, n (%) (mo)								
<3	87 (85.3)	229 (37.6)	<0.001	316 (44.4)	89 (69.5)	57 (36.3)	<0.001	146 (51.2)
≥3–5	15 (14.7)	227 (37.3)		242 (34.0)	26 (20.3)	53 (33.8)		79 (27.7)
≥6	0	153 (25.1)		153 (21.5)	13 (10.2)	47 (29.9)		60 (21.1)
Sex: male, n (%)	64 (62.8)	334 (54.9)	0.16	398 (56.1)	87 (68.5)	88 (56.1)	0.037	175 (61.6)
Preterm birth, n (%) (weeks)*								
<32	2 (2.0)	9 (1.5)	0.62	11 (1.6)	10 (8.1)	4 (2.8)	0.042	14 (5.2)
≥32 to <37	10 (10)	43 (7.4)		53 (7.8)	17 (13.7)	12 (8.3)		29 (10.8)
≥37	88 (88)	532 (91.1)		620 (90.6)	97 (78.2)	129 (89.0)		226 (84.0)
At least 1 risk factor of severe bronchiolitis, n (%)	6 (5.9)	29 (4.8)	0.63	35 (4.9)	20 (15.6)	14 (8.9)	0.082	34 (11.9)
Ventilatory support†								
No	34 (33.3)	138 (22.7)	0.003	172 (24.2)	60 (46.9)	61 (38.9)	0.02	121 (42.5)
Oxygen therapy	23 (22.6)	238 (39.1)		261 (36.8)	34 (26.6)	67 (42.7)		101 (35.5)
Support	45 (44.1)	232 (38.2)		277 (39.0)	34 (26.6)	29 (18.5)		63 (22.1)
Intensive care unit	15 (14.7)	63 (10.3)	0.192	78 (11.0)	9 (7.0)	6 (3.8)	0.227	15 (5.3)
Length of hospitalization >8 d*	5 (4.9)	61 (10.1)	0.138	66 (9.3)	15 (11.7)	9 (5.8)	0.09	24 (8.5)
Length of hospitalisation (d)*	4.0±3.1	4.3±3.0	0.405	4.3±3.1	4.5±5.1	3.6±3.1	0.06	4.0±4.1
Mean±SD	4	4		4	3	3		3
Median								

*RSV and nirsevimab available data.
†On available data.
‡*P* comparing nirsevimab groups.

with RSV-positive bronchiolitis and ventilation support as dependent variables.

Although our study was not designed to calculate the effectiveness of nirsevimab against hospitalization for RSV-positive bronchiolitis, we conducted a post-hoc analysis with a test-negative design (cases were defined as RSV-positive bronchiolitis and controls as RSV-negative bronchiolitis) using the following equation: effectiveness = 100% × (1 − OR of logistic regression model for RSV infection).

No written consent was required for this study, but parents were informed, and all data were analyzed unless parents expressed their refusal to participate to the pediatrician. The study was approved by an ethics committee (CHI Créteil Hospital, France) and was registered at ClinicalTrials.gov (NCT06112132).

RESULTS

Overall Population

Among the 1105 infants hospitalized for bronchiolitis, data for 1085 were analyzed (Figure, Supplemental Digital Content 1, http://links.lww.com/INF/F821). Mean age was 3.9 ± 2.7 months (median: 3.3). Many (43.8%) infants were aged <3 months, followed by those ≥3–6 months (33.3%) and ≥6 months (23.0%). Preterm births accounted for 11.1% of cases; <32 weeks, 2.6%; and 32–36 weeks, 8.5%. Overall, 7.1% of infants had at least 1 risk factor for severe bronchiolitis. The mean length of hospitalization was 4.1 ± 3.4 days (median: 3.0), and in 8.7% of cases, infants were hospitalized in an intensive care unit. Oxygen supplementation and ventilatory support were required for 36.7% and 32.5% of cases, respectively. No death was reported during the study.

The RSV-positive rate was 71.3% (724/1015) and RSV was most often diagnosed by PCR (92.1% of cases, n = 667). The RSV-positive rate was lower for infants aged <3 months than older children (68.4%, 316/462 vs. 74.0%, 395/534, $P = 0.052$). The difference in RSV-positive rate between infants <3 months old versus older children was more marked for children who received nirsevimab immunization (49.4% vs. 80.1%, $P < 0.001$).

For 61.6% (170/276) of RSV-negative cases, other viruses were reported: rhinovirus or enterovirus in 92 cases, followed by metapneumovirus (n = 58), SARS-CoV-2 (n = 31), influenza (n = 17), parainfluenza (n = 14), adenovirus (n = 9) and bocavirus (n = 2). For 53 of these patients more than 1 virus was detected. For 17.1% (123/718) of RSV-positive cases, other viruses were reported. In preterm infants and/or infants with at least 1 risk factor for severe bronchiolitis, other viruses were reported in 73.3% (44/60) of RSV-negative and 26.7% (23/86) in RSV-positive bronchiolitis cases ($P < 0.001$).

Population With RSV Results and Nirsevimab Status

Children who had received nirsevimab represented 14.4% of RSV-positive cases and 44.9% of RSV-negative cases (102/711 vs. 128/285, $P < 0.001$) (Table 1). Nirsevimab was more frequent in infants with than without at least 1 risk factor for severe bronchiolitis (37.7%, 26/69 vs. 22.0%, 204/927, $P = 0.003$). In this population of infants with at least 1 risk factor, the rate of RSV positivity was lower with than without nirsevimab (23.1%, 6/26 vs. 67.5%, 29/43, $P < 0.001$).

The estimated nirsevimab effectiveness against RSV-positive bronchiolitis was 79.5% [95% CI: 71.4–85.3; 14.3% (102/711 cases) vs. 44.9% (128/285 controls)].

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Infants Born After September 15, 2023, With RSV Results and Nirsevimab Status

In this population, mean age was 1.6 ± 1.0 months (median: 1.3) and the age distribution did not differ by nirsevimab status or RSV results (Table, Supplemental Digital Content 2, http://links.lww.com/INF/F822). Nirsevimab was significantly more frequent in infants with at least 1 risk factor for severe bronchiolitis in both RSV-positive and RSV-negative groups, and infants with than without nirsevimab had a lower length of hospitalization (4.1 ± 3.1 vs. 5.2 ± 3.5 days, $P = 0.01$) and oxygen supplementation (20.2%, 19/94 vs. 30.6%, 59/193, $P = 0.02$).

Multivariate Analysis

RSV-positive bronchiolitis was higher (adjusted OR=4.7, 95% CI: 3.5–6.5) for children without nirsevimab, adjusted on the presence of bronchiolitis risk factor. Ventilatory support was higher (adjusted OR=2.2, 95% CI: 1.6–3.1) in RSV-positive cases and in children <2 months old (adjusted OR=2.2, 95% CI: 1.5–3.1).

DISCUSSION

To our knowledge, this multicentre prospective study of 1085 infants hospitalized for bronchiolitis is the largest in the context of the first nirsevimab immunization program. The odds of hospitalization was 4.7 times higher for children not immunized for RSV-positive bronchiolitis than those immunized. In France, nirsevimab doses were reserved for newborns in maternity wards,[7] which explains the younger age in the nirsevimab group we observed in our study. Although the rate of RSV-positive bronchiolitis in children aged <3 months can exceed 70%, we found a lower rate for those immunized with nirsevimab (49.4%).[9]

Because the criteria for hospitalization are nationally standardized, we were able to analyze the severity of RSV-positive bronchiolitis in hospitalized infants.[8] In the target population of children born after nirsevimab launch, the proportion of those requiring oxygen supplementation was significantly lower for children with than without nirsevimab (20.2% vs. 30.6%, $P = 0.02$).[10] Moreover, in this population, children immunized and hospitalized for RSV-positive bronchiolitis, hospitalization length was reduced by 1 day (4.1 ± 3.1 vs. 5.2 ± 3.5 days, $P = 0.01$). Our findings strongly suggest that the RSV-positive bronchiolitis course was less severe for children with nirsevimab. Even if our study was not designed for medicoeconomic analysis, we can assume that reducing hospital stays by 1 day could have significant economic consequences.

Our data confirm that nirsevimab immunization was more frequent in infants with a risk factor for severe bronchiolitis.[6] This finding is not surprising because those infants were immunized first and therefore were more protected, because we reported only 23.1% of RSV-positive cases in this population. Indeed, in this population, our data confirm that other viruses were implicated (73.3% of RSV-negative bronchiolitis).

Although our study was not designed to calculate the effectiveness of nirsevimab against hospitalization for RSV-positive bronchiolitis, we estimated an effectiveness of 79.5% (95% CI: 71.4–85.3), similar to that observed in other countries.[2–6]

As a limitation, we were unable to observe a change in the age distribution of hospitalized infants because we did not include retrospective data for past seasons. However, we will continue our surveillance during the second year of nirsevimab introduction to evaluate its impact in the context of a broader and earlier immunization program and to investigate a cohort of children previously immunized for their second RSV epidemic season.

In conclusion, with this large prospective multicentre study, we found a significant protective effect of nirsevimab on hospitalization for RSV-positive bronchiolitis. Because in immunized infants, RSV-positive bronchiolitis was less frequent and less severe with a significant reduction of hospitalization length than in nonimmunized infants, we can expect significant savings, which should be evaluated.

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