Nirsevimab effectiveness against cases of respiratory syncytial virus bronchiolitis hospitalised in pediatric intensive care units in France, September 2023 - January 2024

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Abstract

In September 2023, France was one of the first countries that started a national immunization campaign with nirsevimab, a new monoclonal antibody against respiratory syncytial virus (RSV). Using data from a network of pediatric intensive care units (PICUs), we aimed to estimate nirsevimab effectiveness against severe cases of RSV bronchiolitis in France. We conducted a case-control study based on the test-negative-design and included 288 infants reported by 20 PICUs. We estimated nirsevimab effectiveness at 75.9% (48.5-88.7) in the main analysis, and 80.6% (61.6-90.3) and 80.4% (61.7-89.9) in two sensitivity analyses. These real-world estimates confirmed the efficacy observed in clinical studies.

Main text

1 Introduction

Respiratory syncytial virus (RSV) infections, which mainly present in the form of bronchiolitis in children under the age of one, are a major cause of hospitalisation in children worldwide [1]. In France, hospitalisations with RSV represents 28% of all-cause hospitalisations in children under the age of one during the RSV season [2]. Seasonal RSV epidemics in France usually span from mid-November to the end of January. After the emergence of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in 2020 and the implementation of control measures, these epidemics have experienced significant disruptions in many countries [3]. In France, the 2020-2021 season was particularly low, with a late peak, while the subsequent seasons of 2021-2022 and 2022-2023 showed higher impacts and earlier peaks [4, 5].

Nirsevimab, a new long-acting anti-RSV monoclonal antibody, has been authorised by the European Medicines Agency (EMA) in October 2022, for the prevention of RSV lower respiratory tract disease in newborns and infants during their first RSV season [6]. On 19 July 2023, the French National Authority for Health (HAS) approved the reimbursement of nirsevimab [7]. On 15 September 2023, France was one of the few European countries that started a national immunization campaign [8, 9]. Because of very high adherence rates in France, nirsevimab was preferentially allocated for the immunization of newborns in maternity wards before discharge and for newborns under one month old in hospital wards starting from 26 September [8]. On 26 December 2023, 173,000 and 64,000 doses of nirsevimab 50 mg and 100 mg were distributed respectively [10].

Nirsevimab had been shown to provide good efficacy in clinical trials [11, 12] but its effectiveness needed to be evaluated in real-world settings. Using surveillance data from a network of volunteer pediatric or neonatal intensive care units (PICUs), we aimed to estimate nirsevimab effectiveness against severe cases of RSV bronchiolitis hospitalised in PICU in metropolitan France from 15 September 2023 to 31 January 2024.

2 Materials and methods

2.1 Surveillance data

In France, in response to the increased intensity of recent RSV epidemics, bronchiolitis surveillance has been strengthened for the 2023-2024 season through a multicentric network of volunteer PICUs coordinated by Santé publique France. Most PICUs were involved in the Pediatric Intensive Care Unit Registry (PICURe). The following cases had to be reported to Santé publique France: infants < 2 years old presenting a severe form of bronchiolitis requiring intensive care, regardless of the virus causing the infection. The collected variables included: age (month), sex, viral identification, administration of a preventive treatment, date and type of treatment, comorbidities (including cardiac, pulmonary, renal, liver, neuromuscular or metabolic pathologies, cancer, immunodepression and diabetes), prematurity and gestational age, date of PICU admission, respiratory support during the stay in PICU and death.

2.2 Study design

Using surveillance data from this network, we conducted a case-control study based on the test-negative-design (TND) to estimate nirsevimab effectiveness against cases of RSV bronchiolitis hospitalised in PICU in metropolitan France, from 15 September 2023 to 31 January 2024. Infants who

tested positive for RSV were enrolled as cases and those who tested negative for RSV were enrolled as controls.

We included infants aged less than 1 month at the start of the study, so that cases and controls could have received nirsevimab in accordance with recommendations. However, nirsevimab was also given to older infants who had comorbidities. Thus, we extended our inclusion criteria to infants with comorbidities who were aged less than 5 months at the start of the study.

Exclusion criteria were: no etiologic search, unknown preventive treatment against RSV, administration of another preventive treatment against RSV than nirsevimab (i.e. palizivumab), unknown comorbidities/prematurity or unknown sex.

In the main analysis, we excluded infants who received nirsevimab < 8 days prior to hospitalisation in PICU (taking into account RSV incubation period and time from symptom onset to PICU admission) or whose date of nirsevimab administration was unknown. In a first sensitivity analysis (SA1), infants whose date of nirsevimab administration was unknown and who were aged ≥ 1 month were included and considered as treated with nirsevimab more than 8 days before hospitalisation in PICU, since most doses were given at the maternity (before 1 month). In a second sensitivity analysis (SA2), we included as treated all infants who received nirsevimab, whatever the delay between administration of treatment and PICU admission (Supplementary Table S1).

We defined two periods based on RSV detection rates in hospital laboratories (Renal Network): (1) period of low RSV circulation from 15 September 2023 to 29 October 2023 and from 8 January 2024 to 31 January 2024, (2) period of high RSV circulation from 30 October 2023 to 7 January 2024.

Effectiveness of nirsevimab on PICU hospitalisation for RSV bronchiolitis was estimated with a logistic regression model. The odds ratio (OR) comparing the odds of nirsevimab administration among cases to the odds among controls was adjusted for age group (0-3 months, > 3 months), sex, presence of comorbidities, prematurity and time period. Effectiveness was estimated as (1-OR)*100%.

3 Results

Among the 542 reported cases of severe bronchiolitis, a total of 288 infants hospitalised in 20 PICUs were included in the main analysis (Supplementary figure S1), of whom 263 (91%) were aged 0-3 months and 157 (55%) were male (Table 1). RSV was identified for 238 (83%) infants (including 19 (8%) in association with another pathogen). In total, 238 cases and 50 controls were included. Among controls, rhinovirus was the most frequently identified pathogen (48%). Cases were younger than controls (p<0.001), with a lower proportion of males (52% vs 68%, p=0.035). Over the study period, 58 (20%) infants had received nirsevimab ≥ 8 days prior to hospitalisation in PICU (mean delay: 35 days, range: 9-70). They were more likely to be premature than untreated infants (29% vs 10%, p<0.001).

In the main analysis, we estimated that adjusted nirsevimab effectiveness against cases of RSV bronchiolitis hospitalised in PICU was 75.9% (95% confidence interval (CI) 48.5-88.7). In the sensitivity analyses, nirsevimab effectiveness was estimated at 80.6% (61.6-90.3) for SA1 and 80.4% (61.7-89.9) for SA2 (Table 2).

4 Discussion

Our results point towards a high effectiveness of nirsevimab in preventing severe RSV bronchiolitis in infants requiring PICU admission, from 75.9% (48.5-88.7) to 80.6% (61.6-90.3) depending on the assumptions. These real-world estimates are in line with the efficacy observed in clinical studies: efficacy of nirsevimab was evaluated in clinical trials against very severe medically attended RSV lower respiratory tract disease between 64.2% (-12.1-88.6) and 87.5% (62.9-95.8) depending on gestational age [6, 11] and at 75.7% (32.8-92.9) in a pragmatic trial [12]. This strong effectiveness is also consistent with a Spanish study looking at RSV-related hospitalisations [13] and French surveillance data showing a reduced impact of the 2023-2024 bronchiolitis epidemic on hospitalisations of infants under 3 months compared to previous years and in contrast to older infants [14].

To our knowledge, this study is the first to provide real-world estimates of nirsevimab effectiveness against severe cases of RSV bronchiolitis hospitalised in PICU. The strength of our study is the use of the TND, which allows timely estimation of effectiveness based on relatively limited surveillance data and reduces confounding bias due to differences in behaviour and access to care between cases and controls. Bias may still exist if healthcare use differs between infants treated or not with nirsevimab with relatively less severe or more severe illness [15]. However, this bias appears very limited in an analysis focusing only on severe cases admitted to PICU. The main limitation of our study is the small sample size, especially for the controls, which does not allow for subgroup analyses or matching of cases and controls. In addition, bias may exist if the preventive treatment and administration dates were less frequently reported when the pathogen was not RSV, leading to an underestimation of effectiveness. We attempted to mitigate this potential bias through sensitivity analyses.

Nirsevimab seems to be able to occupy a significant position in the therapeutic arsenal for preventing RSV infections, although it must be compared to other preventive treatments in development.

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Conflict of interest disclosure

All authors declare that they have no conflict of interest.

References

1. Li Y, Wang X, Blau DM, Caballero MT, Feikin DR, Gill CJ, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. Lancet. 2022;399(10340):2047-64. https://doi.org/10.1016/S0140-6736(22)00478-0

2. Demont, C., Petrica, N., Bardoulat, I. et al. Economic and disease burden of RSV-associated hospitalizations in young children in France, from 2010 through 2018. BMC Infect Dis 21, 730 (2021). https://doi.org/10.1186/s12879-021-06399-8

3. Meslé MMI, Sinnathamby M, Mook P; WHO European Region Respiratory Network Group; Pebody R et al. Seasonal and inter-seasonal RSV activity in the European Region during the COVID-19 pandemic from autumn 2020 to summer 2022. Influenza Other Respir Viruses. 2023 Nov 20;17(11):e13219. doi: 10.1111/irv.13219. PMID: 38025589; PMCID: PMC10661829.

4. Vaux S, Viriot D, Forgeot C, Pontais I, Savitch Y, Barondeau-Leuret A, et al. Bronchiolitis epidemics in France during the SARS-CoV-2 pandemic: The 2020-2021 and 2021-2022 seasons. Infect Dis Now. 2022;52(6):374-8. https://doi.org/10.1016/j.idnow.2022.06.003

5. Santé publique France. Bulletin épidémiologique bronchiolite. Bilan de la surveillance 2022-2023. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/bronchiolite/documents/bulletin-national/bulletin-epidemiologique-bronchiolite.-bilan-de-la-surveillance-2022-2023 Accessed March 5, 2024.

6. European Medicines Agency (EMA). Beyfortus (nirsevimab) - An overview of Beyfortus and why it is authorised in the EU. Amsterdam: EMA; 2023. https://www.ema.europa.eu/en/documents/overview/beyfortus-epar-medicine-overview_en.pdf Accessed March 5, 2024.

7. Haute Autorité de Santé. BEYFORTUS (nirsévimab), Virus respiratoire syncytial. Avis sur les médicaments. Adopté par la Commission de la transparence le 19 juillet 2023. https://www.has-sante.fr/upload/docs/evamed/CT-20356_BEYFORTUS_PIC_INS_AvisDef_CT20356.pdf Accessed March 5, 2024.

8. Ministère de la Santé et de la prévention. Direction générale de la Santé. DGS-Urgent n° 2023-19, 26 september 2023. Beyfortus (Nirsevimab) : priorisation temporaire des patients à immuniser [Beyfortus (Nirsevimab): temporary prioritisation of patients to be immunised]. dgs-urgent_-19_mise_a_disposition_beyfortus.pdf (sante.gouv.fr) Accessed March 5, 2024.

9. De Luca D, Sanchez-Luna M, Schettler K, Bont L, Baraldi E. Universal infant immunisation against respiratory syncytial virus and European inequalities: the pandemics lesson has not been learnt. Lancet Reg Health Eur. 2023;34:100753. https://doi.org/10.1016/j.lanepe.2023.100753 PMID: 37927432

10.Ministère de la Santé et de la prévention. Direction générale de la Santé. MINSANTE n°38, 26 december 2023. Beyfortus (Nirsevimab) : fin de campagne de distribution (Beyfortus (Nirsevimab): end of distribution campaign].

11. Hammitt LL, Dagan R, Yuan Y, Baca Cots M, Bosheva M, Madhi SA, et al ; MELODY Study Group. Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants. N Engl J Med. 2022 Mar 3;386(9):837-846. doi: 10.1056/NEJMoa2110275. PMID: 35235726.

12. Drysdale SB, Cathie K, Flamein F, Knuf M, Collins AM, Hill HC, et al. , HARMONIE Study Group. Nirsevimab for Prevention of Hospitalizations Due to RSV in Infants. N Engl J Med. 2023;389(26):2425-35. https://doi.org/10.1056/NEJMoa2309189 PMID: 38157500

13. López-Lacort M, Muñoz-Quiles C, Mira-Iglesias A, López-Labrador F X, Mengual-Chuliá B, Fernández-García C, et al. Early estimates of nirsevimab immunoprophylaxis effectiveness against hospital admission for respiratory syncytial virus lower respiratory tract infections in infants, Spain, October 2023 to January 2024. Euro Surveill. 2024;29(6):pii=2400046. https://doi.org/10.2807/1560-7917.ES.2024.29.6.2400046

14. Santé publique France. Bronchiolitis activity by age group. Description of data for children under 1 year old. https://www.santepubliquefrance.fr/media/files/01-maladies-et-traumatismes/maladies-et-infections-respiratoires/infections-respiratoires-aigues/annexe_bronchio_france_1-12_mois_20240124. Accessed March 5, 2024.

15. Lewnard JA, Patel MM, Jewell NP, Verani JR, Kobayashi M, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. Epidemiology. 2021 Jul 1;32(4):508-517. doi: 10.1097/EDE.0000000000001366.

Tables

Table 1. Descriptive statistics of the study population for the main analysis of nirsevimab effectiveness, France, September 2023 - January 2024 (N = 288 infants)

Characteristic		RSV Testing			Treatment by nirsevimab		
	Overall (N=288)	Test-negative (Control) (N=50)	Test-positive (Case) (N=238)		Untreated (N=230)	Treated (N=58)	
	n (%)[a]	n (%)[a]	n (%)[a]	p-value[b]	n (%)[a]	n (%)[a]	p-value[b]
Age group (months)				<0.001			0.3
0-3	263 (91%)	38 (76%)	225 (95%)		208 (90%)	55 (95%)	
4-8	25 (9%)	12 (24%)	13 (5%)		22 (10%)	3 (5%)	
Sex				0.035			0.3
Female	131 (45%)	16 (32%)	115 (48%)		108 (47%)	23 (40%)	
Male	157 (55%)	34 (68%)	123 (52%)		122 (53%)	35 (60%)	
Viral identification[c]							
RSV	238 (83%)	0 (0%)	238 (100%)	<0.001	201 (87%)	37 (64%)	<0.001
Rhinovirus	42 (15%)	24 (48%)	18 (8%)	<0.001	26 (11%)	16 (28%)	0.002
Metapneumovirus	6 (2%)	5 (10%)	1 (0%)	<0.001	3 (1%)	3 (5%)	0.10
Other virus	23 (8%)	23 (46%)	0 (0%)	<0.001	14 (6%)	9 (16%)	0.028
Not identified	12 (4%)	12 (24%)	0 (0%)	<0.001	8 (3%)	4 (7%)	0.3
Period of PICU admission				0.007			0.8
15 Sept. 2023 – 29 Oct. 2023	30 (10%)	10 (20%)	20 (8%)		24 (10%)	6 (10%)	
30 Oct. 2023 – 7 Jan. 2024	251 (87%)	37 (74%)	214 (90%)		201 (87%)	50 (86%)	
8 Jan. 2024 – 31 Jan. 2024	7 (2%)	3 (6%)	4 (2%)		5 (2%)	2 (3%)	
Comorbidities[d]				0.014			0.2
No	254 (88%)	39 (78%)	215 (90%)		206 (90%)	48 (83%)	
Yes	34 (12%)	11 (22%)	23 (10%)		24 (10%)	10 (17%)	
Prematurity				<0.001			<0.001
No	249 (86%)	34 (68%)	215 (90%)		208 (90%)	41 (71%)	
Yes	39 (14%)	16 (32%)	23 (10%)		22 (10%)	17 (29%)	
If prematurity, gestational age (mean (sd) – wk)	33 (4)	32 (5)	34 (2)	0.7	34 (3)	32 (4)	0.8
Nirsevimab				<0.001			<0.001
No	230 (80%)	29 (58%)	201 (84%)		230 (100%)	0 (0%)	
Yes	58 (20%)	21 (42%)	37 (16%)		0 (0%)	58 (100%)	

Respiratory support				>0.9			0.6
Non Invasive ventilation	209 (73%)	36 (72%)	173 (73%)		165 (72%)	44 (76%)	
High flow nasal cannula	57 (20%)	10 (20%)	47 (20%)		48 (21%)	9 (16%)	
Invasive ventilation	18 (6%)	3 (6%)	15 (6%)		13 (6%)	5 (9%)	
Extracorporeal assistance	0 (0%)	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
None/Not specified	4 (1%)	1 (2%)	3 (1%)		4 (2%)	0 (0%)	
Death	0 (0%)	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA

[a] n (%): percentages may not total 100 due to rounding.

[b] p-values from Pearson's Chi-squared test and Fisher exact test for categorical variables, and Wilcoxon rank sum test for continuous variables.

[c] Percentages do not total 100 due to co-infections by several pathogens.

[d] Include cardiac, pulmonary, renal, liver, neuromuscular or metabolic pathologies, cancer, immunodepression and diabetes.

Table 2. Estimated effectiveness of nirsevimab against cases of RSV bronchiolitis hospitalised in PICU, France, September 2023 - January 2024.

Analysis	**Controls not treated by nirsevimab**	**Controls treated by nirsevimab**	**Cases not treated by nirsevimab**	**Cases treated by nirsevimab**	**Unadjusted effectiveness (95%CI)**	**Adjusted effectiveness (95%CI)**
Main analysis (N=288)	29	21	201	37	74.4 % (50.5 – 86.8)	75.9 % (48.5 – 88.7)
Sensitivity analysis 1 (N=312)	29	35	201	47	80.5 % (65.0 – 89.1)	80.6 % (61.6 – 90.3)
Sensitivity analysis 2 (N=319)	29	38	201	51	80.5 % (65.4 – 89.0)	80.4 % (61.7 – 89.9)

Supplementary material

Figure S1. Flowchart of study inclusion and exclusion criteria.

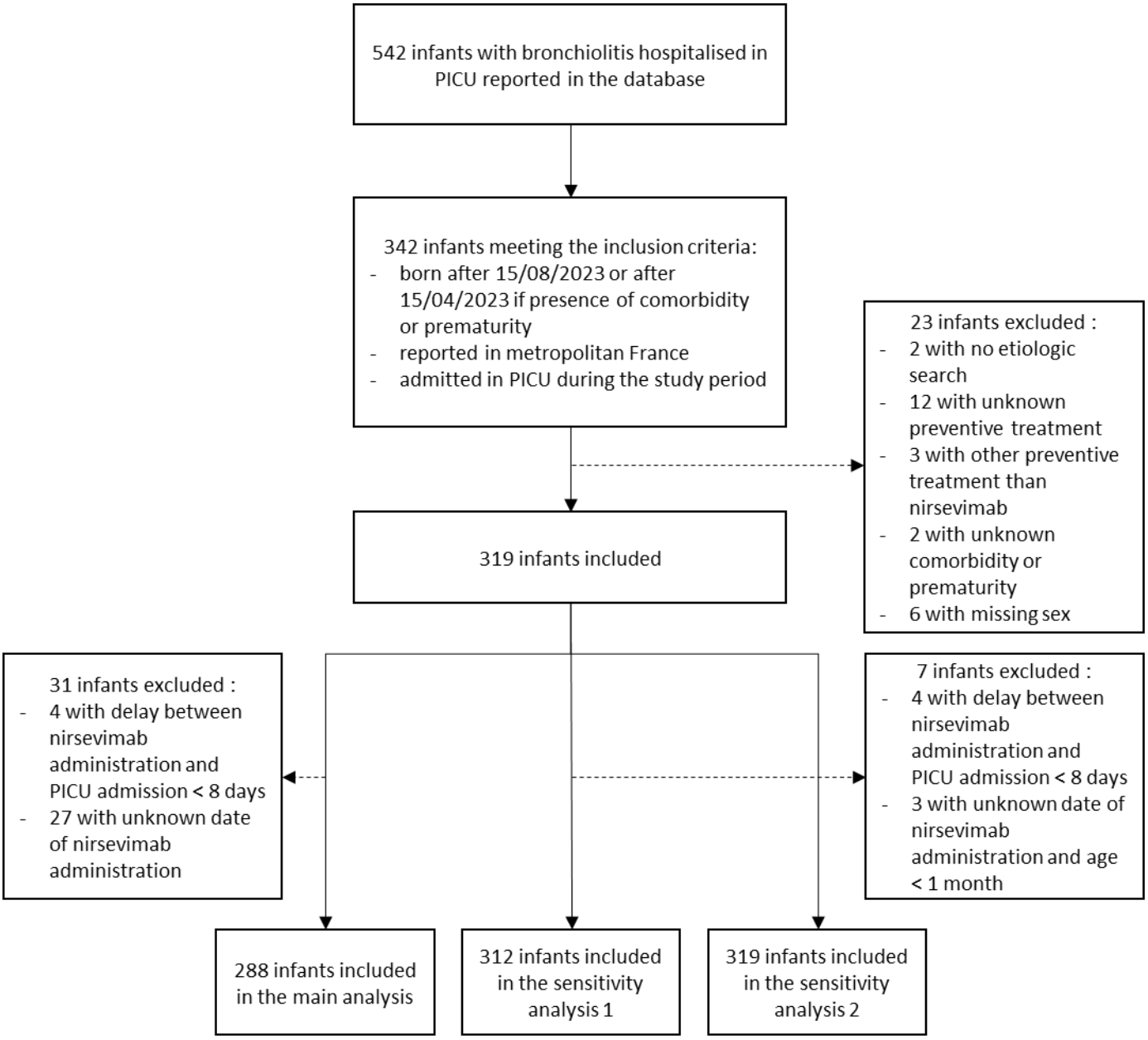

Table S1. Definition of the main analysis and the two sensitivity analyses (SA1 and SA2). The three analyses differ in the way they include/exclude infants who received nirsevimab based on the age and the time T between nirsevimab administration and PICU admission.

Analysis	Definition				
	Did not receive nirsevimab	Received nirsevimab			
		T ≥ 8 days	T < 8 days	Unknown date of nirsevimab administration and age = 0 month	Unknown date of nirsevimab administration and age ≥ 1 month
Main	Included as "untreated"	Included as "treated"	Excluded	Excluded	Excluded
SA1			Excluded	Excluded	Included as "treated"
SA2			Included as "treated"	Included as "treated"	Included as "treated"