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Juliette Paireau, Cécile Durand, Sylvain Rimbault, Joséphine Cazaubon, Guillaume Mortamet, et al.. Nirsevimab effectiveness against cases of respiratory syncytial virus bronchiolitis hospitalised in pediatric intensive care units in France, September 2023 -January 2024. 2024. pasteur-04501286v1

HAL Id: pasteur-04501286

<https://pasteur.hal.science/pasteur-04501286v1>

Preprint submitted on 12 Mar 2024 (v1), last revised 11 Jun 2024 (v2)

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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.

Acknowledgements

We thank PICUs involved in the Pediatric Intensive Care Unit Registry-PICURE- and healthcare professionals of PICUs for cases management and case report

Dr Sylvain Balandier, Dr Jean Duval Destin, Service de réanimation pédiatrique- CHU de Lille ; Dr Bertrand Leboucher, Dr Gerald Boussicault, Dr Amandine Prenant, Dr Oriane Pauvert, Dr Mélanie Sicard, Dr Morgane Ollivier, Dr Alice de Pellegars, Services de réanimation pédiatrique et réanimation néonatale – CHU d’Angers ; Dr Sylvain Raimbault, Dr Leo Charrin, Service de réanimation pédiatrique – HFME Hôpital Femme mère enfant, HCL Bron ; Dr Yvonnick Boué, Service de réanimation polyvalente – CH de Mayotte; Dr Millet, Dr Makhoulouf, Dr Delacroix, Dr Maisonneuve, Dr Clos, Dr Desrumaux, Dr Gabriel, Dr Touraton, Pr Mortamet, Service de réanimation pédiatrique – CHU de Grenoble ; Dr Christophe Milesi, Dr Flora Le Roux, Dr Sophie Mounier, Dr Julien Frédéric Baleine, Service de réanimation pédiatrique – CHU de Montpellier; Dr Clémence Mougey, Pr Gérard Thiriez, Service de réanimation pédiatrique – CHU de Besançon ; Dr Julie Chantreuil, Dr Nadine Fakhri, Dr Claire Le Reun, Dr Nicolas Rouillet-Renoleau, Dr Barbaud, Dr Brigaud, Dr Reynier, Dr Rousseau, Service de réanimation pédiatrique – CHRU de Tours Clocheville ; Dr Benoit Colomb, Service de réanimation pédiatrique – CHU de Dijon ; Dr Jean-Michel Roue, Dr Iona Sicard-Cras, Service de réanimation pédiatrique – CHU de Brest ; Dr Noémie Vanel, Dr Solène Denante, Service de réanimation pédiatrique – AP-HM Timone enfants ; Dr Sébastien Barthelemy, Dr Nathalie Courtois, Service de réanimation pédiatrique – Hôpital pédiatrique Lenal CHU de Nice ; Dr Corseri, Dr Semeus, Dr Michau, unité de soins continu pédiatrique – CH Andrée Rosemond; Dr Sabrina Dessard, Service de réanimation pédiatrique – CHU Hôpital Sud

Rennes; Dr Buek, Dr Alexandra David, Dr Firah, Dr Mas, Service de réanimation pédiatrique - CH de Pau ; Dr Martine Roques-Gineste, Dr Sonia Pelluau, Service de réanimation pédiatrique - CHU Toulouse Hôpital enfant ; Dr Aurélie Garbi, Dr Gaëlle Sorin, Service de réanimation néonatale - APMH NORD - Neonat – Marseille; Dr Florence Villedieu, Service de réanimation pédiatrique – CHU de Caen ; Dr Chareyre, Dr Perez, Dr Ros, Service de réanimation pédiatrique – CHU Pellegrin ; Dr Gabilly-Benard, Service de réanimation pédiatrique – CHU de Poitiers; Dr Ranga, Dr Randrian, Service de réanimation néonatale – CH Andrée Rosemond ; Dr Mounier, Service de réanimation pédiatrique – CHU Estaing.

We thank colleagues at the Cellules régionales de Santé publique France (CR) for their contribution on case report : Thomas Benet, Tasnim Fareh – CR Auvergne Rhône-Alpes ; Romane Carpentier, Elise Daudens-Vaysse – CR Hauts-de-France ; Annabelle Lapostolle – CR Mayotte ; Séverine Bailleul, Jean-Loup Chappert, Cécile Durand – CR Occitanie ; Jean-Luc Lassalle, Isabelle Mertens-Rondelart – CR Provence Alpes Côte d’Azur ; Mariline Ciccardini, Sabrina Tessier – CR Bourgogne-Franche-Comté ; Claire Kerzerho, Bertrand Gagnière – CR Bretagne ; Gwenola Picard, Sophie Hervé – CR Pays de la Loire ; Virginie de Lauzun – CR Centre Val de Loire ; Marie Barrau - CR Guyane ; Anne Bernadou, Alice Herteau - CR Nouvelle-Aquitaine ; Sandrine Gautier - CR Normandie.

We thank also the National Reference Center for Viruses of Respiratory Infections for surveillance data and Vincent Auvigne for useful discussions.

Funding

This study was funded by Santé publique France and the Laboratoire d’Excellence Integrative Biology of Emerging Infectious Diseases program (grant ANR-10-LABX-62-IBEID).

Conflict of interest disclosure

All authors declare that they have no conflict of interest.

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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.

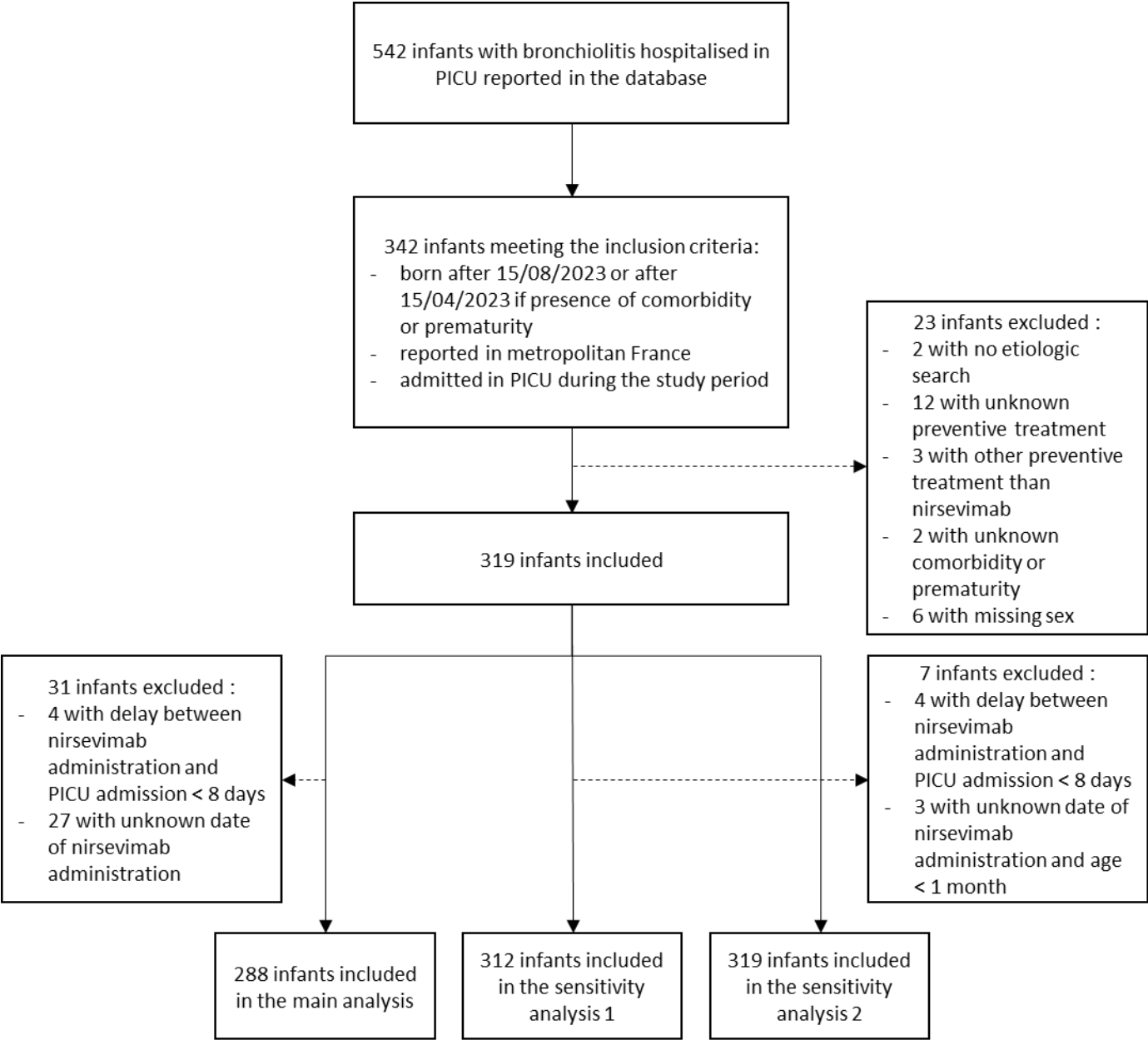


Table S1. Definition of the main analysis and the two sensitivity analyses (SA1 and SA2). The three analyses differ in the way they include/exclude infants who received nirsevimab based on the age and the time T between nirsevimab administration and PICU admission.

| 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" |