ORIGINAL ARTICLE

Nirsevimab and Hospitalization for RSV Bronchiolitis

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ABSTRACT

BACKGROUND

Respiratory syncytial virus (RSV) is the leading cause of bronchiolitis, resulting in 3 million hospitalizations each year worldwide. Nirsevimab is a monoclonal antibody against RSV that has an extended half-life. Its postlicensure real-world effectiveness against RSV-associated bronchiolitis is unclear.

METHODS

We conducted a prospective, multicenter, matched case–control study to analyze the effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis in infants younger than 12 months of age. Case patients were infants younger than 12 months of age who were hospitalized for RSV-associated bronchiolitis between October 15 and December 10, 2023. Control patients were infants with clinical visits to the same hospitals for conditions unrelated to RSV infection. Case patients were matched to control patients in a 2:1 ratio on the basis of age, date of hospital visit, and study center. We calculated the effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis (primary outcome) by means of a multivariate conditional logistic-regression model with adjustment for confounders. Several sensitivity analyses were performed.

RESULTS

The study included 1035 infants, of whom 690 were case patients (median age, 3.1 months; interquartile range, 1.8 to 5.3) and 345 were matched control patients (median age, 3.4 months; interquartile range, 1.6 to 5.6). Overall, 60 case patients (8.7%) and 97 control patients (28.1%) had received nirsevimab previously. The estimated adjusted effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis was 83.0% (95% confidence interval [CI], 73.4 to 89.2). Sensitivity analyses gave results similar to those of the primary analysis. The effectiveness of nirsevimab therapy against RSV-associated bronchiolitis resulting in critical care was 69.6% (95% CI, 42.9 to 83.8) (27 of 193 case patients [14.0%] vs. 47 of 146 matched control patients [32.2%]) and against RSV-associated bronchiolitis resulting in ventilatory support was 67.2% (95% CI, 38.6 to 82.5) (27 of 189 case patients [14.3%] vs. 46 of 151 matched control patients [30.5%]).

CONCLUSIONS

In a real-world setting, nirsevimab therapy was effective in reducing the risk of hospitalized RSV-associated bronchiolitis. (Funded by the National Agency for AIDS Research–Emerging Infectious Disease and others; ENVIE ClinicalTrials.gov number, NCT06030505.)

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Bronchiolitis is the most common lower respiratory tract infection among infants and young children. Respiratory syncytial virus (RSV) is the leading causative agent of bronchiolitis and is estimated to be responsible for 33.1 million cases of lower respiratory tract infection in children younger than 5 years of age annually, with 3.2 million hospitalizations and more than 100,000 deaths worldwide each year.[1-3]

Until 2023, palivizumab was the only approved agent for RSV prophylaxis, and its indications were limited to high-risk infants.[4] Nirsevimab is a monoclonal antibody against RSV that has enhanced neutralizing activity and an extended half-life in vivo, which enable its implementation in the general population.[5] Double-blind, randomized, placebo-controlled trials have shown the efficacy of nirsevimab therapy in reducing the risk of RSV-associated lower respiratory tract infection leading to medical care among healthy preterm and full-term infants over a 5-month period, with a favorable safety profile.[6,7] Nirsevimab was approved by the European Medical Agency in November 2022 and by the Food and Drug Administration in July 2023.[8] Given that the implementation of nirsevimab therapy started in the autumn of 2023 in only a few countries,[9] the postlicensure real-world effectiveness of nirsevimab in the prevention of RSV-associated bronchiolitis is unclear. We aimed to assess the real-world effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis among infants younger than 12 months of age.

METHODS

STUDY DESIGN AND OVERSIGHT

We conducted a prospective, multicenter, matched case–control study (Effectiveness of Nirsevimab against RSV-Associated Bronchiolitis Requiring Hospitalization in Children [ENVIE]) to assess the effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis among infants younger than 12 months of age. A matched case–control design was preferred to a test-negative design owing to a potential confounding bias related to the differential probability of nirsevimab exposure between RSV-associated and non–RSV-associated bronchiolitis. In France, nirsevimab was administered mainly to newborns or very young infants. Because previous studies showed that children who were hospitalized for RSV-associated bronchiolitis were younger than those hospitalized for non–RSV-associated bronchiolitis,[10,11] those with RSV infection would be much more likely to have received nirsevimab. In addition, the use of nirsevimab has increased rapidly nationwide since September 2023, so it was important to include both case and control patients concomitantly. Given that no other major respiratory virus is usually circulating concomitantly during an RSV outbreak, the inclusion of control patients with non–RSV-associated bronchiolitis would have been delayed, which would have thus increased their probability of receiving nirsevimab.

The ENVIE study protocol, which is available with the full text of this article at NEJM.org, was approved by the relevant ethics committee. Oral informed consent was obtained from each participant's parent or guardian. The study sponsors had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the study to the protocol.

NIRSEVIMAB PROGRAM

For the 2023–2024 RSV season, National French guidelines recommended free-of-charge administration of a single dose of nirsevimab to all children born in France after February 6, 2023.[12] The nirsevimab program started in metropolitan France on September 15, 2023.[9] Approximately 62,000 births occur in France each month.[13] Because shortages occurred during the national campaign, nirsevimab, after being recommended for all eligible children, was then preferentially administered to newborns or very young infants. In addition, national guidelines recommended that nirsevimab be administered to infants younger than 1 year of age who were eligible to receive palivizumab because of the similar efficacy and safety profile of nirsevimab to palivizumab, as well as its simpler administration regimen.[12] By December 15, 2023, approximately 230,000 doses had been administered. Maternal RSV vaccination was not implemented in France during the study period.

Information about RSV circulation over the study period is presented in Figure S1 in the Supplementary Appendix, available at NEJM.org.

PATIENTS AND SETTINGS

In this matched case–control study, we prospectively included all infants younger than 12 months of age who were hospitalized for RSV-associated bronchiolitis in six tertiary hospitals across metropolitan France (including four hospitals with pediatric intensive care units [PICUs]) between October 15 and December 10, 2023. On the basis of national and international guidelines, bronchiolitis was defined as the first wheezing attack with respiratory symptoms before 12 months of age or the second attack in infants without a personal or family history of asthma or atopy.[14-16] At all the participating centers, all the infants who had been admitted for bronchiolitis underwent nasopharyngeal sampling for RSV testing by means of polymerase-chain-reaction (PCR) assay at admission.

Case patients were defined as infants younger than 12 months of age who had been hospitalized for bronchiolitis with RSV detected by means of PCR assay with the use of a nasopharyngeal sample obtained during the study period at one of the six participating centers. Infants who had previously received palivizumab and those whose mother had been vaccinated against RSV during pregnancy were excluded from the study.

Control patients were defined as infants younger than 12 months of age who had visited the pediatric emergency department of a participating center for one of the following diagnoses: urinary tract infection without respiratory symptoms, acute gastroenteritis without respiratory symptoms, infantile colic without fever or respiratory symptoms, weight loss or feeding difficulties without fever or respiratory symptoms, neonatal jaundice without fever or respiratory symptoms, abnormal crying (based on parental subjectivity) without fever or acute respiratory symptoms, head trauma without fever or respiratory symptoms, or emergency surgery without fever or respiratory symptoms. These conditions were chosen because they classically affect children with a similar age as the case patients and because the incidence of these conditions is expected to be sufficiently high during the RSV season. Finally, these conditions were selected without respiratory symptoms in order to minimize the risk of misclassification with RSV infection.

To ensure that the availability of nirsevimab was similar in the two groups, case patients and control patients were matched at a 2:1 ratio according to age (within a window of ±1 month), calendar date of hospital visit (within a window of ±15 days), and participating center. The use of nirsevimab nationwide increased rapidly over the course of the study period, and shortages of nirsevimab led to preferential administration in newborns and very young infants. Thus, the probability of nirsevimab administration may have varied depending on the age of the patient, calendar date, and geographic location. This situation led us to match case patients and control patients on the basis of these three variables. Case and control patients were enrolled independently of information about their nirsevimab-receipt status. For each pair of case patients, the selected matched control patient was the eligible patient for whom the date and hour of the hospital visit was the closest to the admission dates and times of the matched case patients.

DATA COLLECTION

We collected data on demographic characteristics, including the French Deprivation index,[17] which is a previously validated index that assesses the social deprivation of the household (e.g., income, parents' educational level, and unemployment). We also collected data about RSV immunization status and history of RSV infection, previous hospitalization for bronchiolitis, risk factors for severe bronchiolitis, and clinical, microbiologic, and outcome data related to bronchiolitis.

OUTCOME AND EXPOSURE MEASURES

The main outcome was hospitalization for RSV-associated bronchiolitis in infants younger than 12 months of age. The treatment exposure was nirsevimab-receipt status among both case and control patients. We considered nirsevimab receipt to have occurred when administration had taken place at least 7 days before the date of the hospital visit, in order to account for the length

of incubation of RSV and the possible delay between the onset of symptoms and the pediatric emergency department visit or hospital admission.

We performed subgroup analyses according to age group (<3 months vs. ≥3 months), PICU admission (yes vs. no), ventilatory support (defined as invasive or noninvasive ventilatory support, including high-flow oxygen therapy with nasal cannula; yes vs. no), and at least one risk factor for severe bronchiolitis (yes vs. no) (Table S1). The risk factors were defined according to international guidelines as preterm birth (gestational age, ≤35 weeks), chronic lung disease of prematurity, hemodynamically significant congenital heart disease, and young chronologic age (<6 months).[18]

STATISTICAL ANALYSIS

On the basis of an expected nirsevimab coverage of 15% in the general population of infants younger than 12 months of age, we calculated the study-sample size to detect a 50% reduction in the odds of nirsevimab receipt among case patients with RSV-associated bronchiolitis relative to that of control patients. The calculation assumed a two-sided alpha of 0.05, a study power of 0.90, and a 2:1 matching ratio, which resulted in 642 case patients and 321 control patients (i.e., 963 patients in total) being required for the study.

The effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis was estimated with the use of a conditional logistic-regression model to test the association between nirsevimab-receipt status and case patient or control patient status, with the use of the following equation: effectiveness = 100% × (1 − adjusted odds ratio). The final multivariate regression model was adjusted for sex, gestational age at birth (as a continuous variable), birth weight, and risk factors for severe bronchiolitis as defined above (see the Method S1 section). To handle missing data in the multivariate analysis, we performed multiple imputation by means of a chained equation generating 20 replicates (see the Method S2 section).

Ten sensitivity analyses were performed. First, to assess the immediate protection conferred by passive immunization, we considered previous nirsevimab receipt regardless of the time between administration and the date of the hospital visit (instead of the minimal 7-day delay as defined in the primary analysis). Second, to account for potential misdiagnosis between bronchiolitis and asthma, bronchiolitis was defined solely as the first wheezing attack. Third, to better control for confounders related to nirsevimab exposure, we conducted a propensity-score analysis with the use of the inverse probability of treatment weighting method. Fourth, a complete case approach was used to handle missing data. Fifth, control patients with each diagnosis (urinary tract infection, acute gastroenteritis, infantile colic, weight loss or feeding difficulties, neonatal jaundice, abnormal crying, head trauma, or emergency surgery) were removed sequentially from the analysis to investigate whether the inclusion of infants with one of these diagnoses could have biased our estimates. Sixth, the conditional multivariate regression model was adjusted for previous RSV infection. Seventh, the conditional multivariate regression model was adjusted for the French Deprivation index to account for the socioeconomic level. Eighth, the matching covariates (patient age, date of admission, and study center) were included in the conditional multivariate regression model (in addition to sex, gestational age at birth, birth weight, and risk factors for bronchiolitis).[19] Ninth, we used a standard logistic-regression model that included both matched and unmatched patients to explore whether the exclusion of the unmatched patients could have influenced the results. Tenth, we analyzed a model that included gestational age at birth (≤35 weeks vs. >35 weeks) and birth weight (in quartiles) as categorical variables instead of as continuous variables. Details of these sensitivity analyses are provided in Table S2 and Figure S2.

All the statistical tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing. Statistical analyses were carried out with the use of R software, version 4.3.1 (R Foundation for Statistical Computing).

RESULTS

CHARACTERISTICS OF THE CASE AND CONTROL PATIENTS

During the study period, 1091 infants younger than 12 months of age were hospitalized for bronchiolitis, of whom 832 tested positive for RSV. Among the infants with RSV-positive bronchiolitis, 142 were excluded because the parent declined participation, the age of the patient was found to be 12 months or older (i.e., the patient had been included erroneously), data on parental consent or nirsevimab-receipt status were missing, palivizumab had been previously received, or matching was incomplete (Fig. 1). Overall, the study included 690 infants who had been hospitalized for RSV-associated bronchiolitis (case patients), who were matched with 345 control patients (Table S3 and Fig. S3).

The general characteristics of the matched case and control patients are shown in Table 1, and the representativeness of the study population is discussed in Table S4. The median age was 3.1 months (interquartile range, 1.8 to 5.3) among the case patients and 3.4 months (interquartile range, 1.6 and 5.6) among the control patients. At least one risk factor for severe bronchiolitis was present in 37 of 660 case patients (5.6%) and in 20 of 315 control patients (6.3%) (Table 1).

PRIMARY OUTCOME

A nirsevimab injection had been received previously by 60 of 690 case patients (8.7%) and by 97

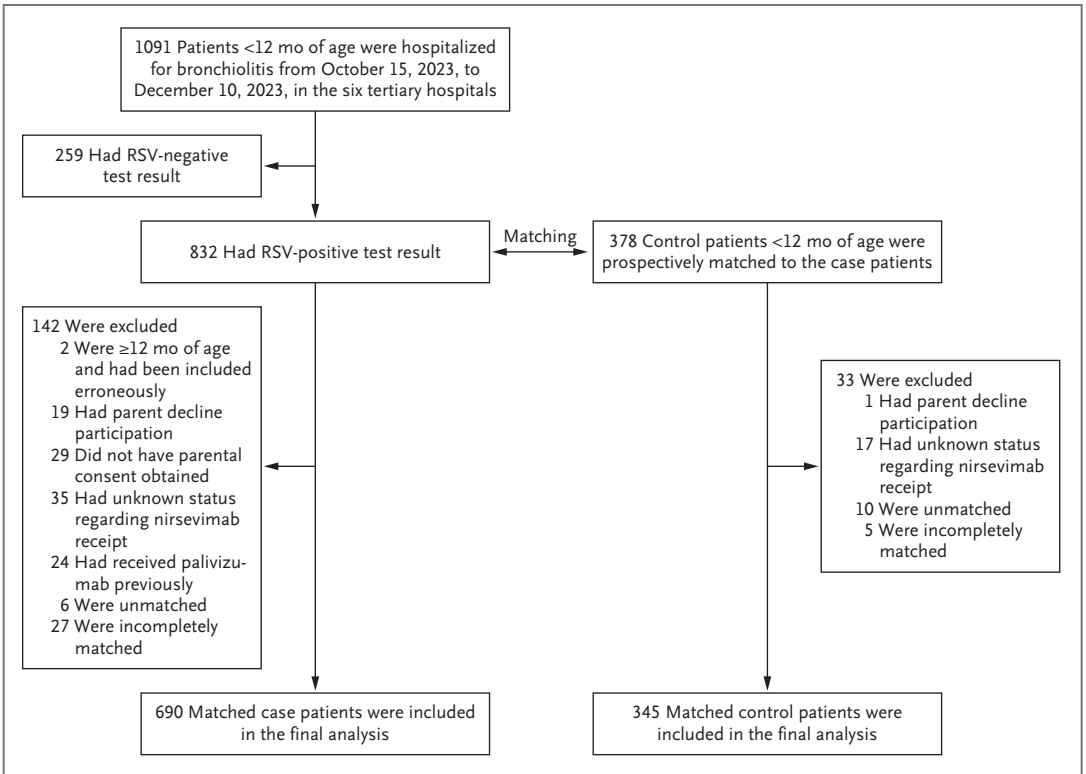

Figure 1. Study Population.

Case patients were infants younger than 12 months of age who were hospitalized for respiratory syncytial virus (RSV)–associated bronchiolitis between October 15 and December 10, 2023. Control patients were infants with clinical visits to the same hospitals for conditions unrelated to RSV infection. Case patients were matched to control patients in a 2:1 ratio on the basis of age, date of hospital visit, and study center. Infants who had been admitted for bronchiolitis underwent nasopharyngeal sampling for RSV testing by means of polymerase-chain-reaction assay at admission.

of 345 (28.1%) matched control patients (Table S5). The estimated adjusted effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis was 83.0% (95% confidence interval [CI], 73.4 to 89.2). All the sensitivity analyses gave results similar to those of the primary analysis (Fig. 2 and Table S6).

SUBGROUP ANALYSES

The effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis was similar among infants younger than 3 months of age and those 3 months of age or older (Fig. 2). The effectiveness of nirsevimab therapy against RSV-associated bronchiolitis leading to PICU admission was 69.6% (95% CI, 42.9 to 83.8) (27 of 193 case patients vs. 47 of 146 matched control patients) and leading to ventilatory support was 67.2% (95% CI, 38.6 to 82.5) (27 of 189 case patients vs. 46 of 151 matched control patients). Among infants with at least one risk factor for bronchiolitis, the effectiveness of nirsevimab therapy was 64.8% (95% CI, –17.2 to 89.4), although this analysis was limited by the small number of patients.

DISCUSSION

In this real-world study, we estimated the postlicensure effectiveness of nirsevimab therapy against hospitalization for RSV-associated bronchiolitis among infants younger than 12 months of age and found an overall effectiveness of 83.0%. This level of effectiveness was consistent across age groups. In addition, nirsevimab therapy was effective against the most severe forms of RSV-associated bronchiolitis — those leading to PICU admission and ventilatory support.

These results need to be put in perspective with the findings of the prelicensure phase 3 trials. The effectiveness of nirsevimab therapy in the present study appears to have been slightly higher than that in the MEDLEY and MELODY trials but similar to that in the HARMONIE trial.[7,18,20] Several differences between these trials and our study should be highlighted. First, the outcomes in the MEDLEY and MELODY trials were assessed on day 150.[7,18] By contrast, the implementation of nirsevimab started in France on September 15, 2023, and enrollment in the present study was stopped on December 10, 2023, when the sample size for the study was reached. Thus, the effectiveness in the present study was assessed within 3 months after the implementation of nirsevimab. The HARMONIE trial assessed outcomes on day 90 after administration.[20] Given that the protection conferred by nirsevimab may decrease over time, this situation may have contributed to the higher effectiveness found in our study than in the MEDLEY and MELODY trials. Overall, these findings suggest that campaigns that start each year at the beginning of the RSV outbreak, as is done for influenza, rather than continuous treatment of newborns throughout the year, may improve the usefulness of the nirsevimab program.

The present study took place after the epidemics in 2022 and 2023, which were marked by particularly high circulation of RSV.[21,22] Thus, the proportion of pregnant women who had been naturally infected with RSV may have been high, which would have provided very young children with natural protection against this pathogen.[23] Further studies to compare the effectiveness of nirsevimab in different contexts of RSV circulation are warranted.

Palivizumab, which was previously the only existing prophylaxis against RSV infection, is licensed for use only in infants born preterm or in those with chronic lung or congenital heart disease. Palivizumab requires monthly injections throughout the RSV season in order to provide sustained protection and, on a population basis, has only a limited effect on the incidence of RSV-associated hospitalizations.[4] In the present study, subgroup analyses showed substantial effectiveness among preterm infants and among infants with at least one risk factor for severe RSV bronchiolitis. On the basis of the current results, coupled with those from trials that showed safety in infants who were eligible to receive prophylaxis with palivizumab, nirsevimab may be a reasonable alternative to palivizumab in children with risk factors for severe bronchiolitis.[24]

Our study has several limitations. First, the observational case–control study design does not allow for the drawing of any causative conclusions. Further studies in other settings are needed to confirm these findings. Second, PCR

Table 1. Characteristics of the Included Matched Case and Control Patients.*

Characteristic	Case Patients (N = 690)	Control Patients (N = 345)
Demographic and clinical characteristics		
Age at admission		
Median (IQR) — mo	3.1 (1.8–5.3)	3.4 (1.6–5.6)
Distribution — no. (%)		
<3 mo	332 (48.1)	150 (43.5)
≥3 mo	358 (51.9)	195 (56.5)
Sex — no./total no. (%)		
Male	357/687 (52.0)	196/343 (57.1)
Female	330/687 (48.0)	147/343 (42.9)
Median gestational age at birth (IQR) — wk	39 (38–40)	39 (38–40)
Preterm birth — no./total no. (%)†	38/665 (5.7)	21/306 (6.9)
History of bronchiolitis — no./total no. (%)	67/685 (9.8)	14/341 (4.1)
Previous hospitalization for bronchiolitis — no./total no. (%)	25/686 (3.6)	3/342 (0.9)
Previous RSV infection — no./total no. (%)	11/678 (1.6)	7/336 (2.1)
Risk factor for severe bronchiolitis — no./total no. (%)	37/660 (5.6)	20/315 (6.3)
Preterm birth and age of <6 mo†	27/673 (4.0)	18/322 (5.6)
Chronic lung disease of prematurity‡	7/688 (1.0)	4/343 (1.2)
Congenital heart disease§	7/688 (1.0)	2/339 (0.6)
Median duration of hospitalization (IQR) — days	4 (3–6)	0 (0–1)
Clinical findings in case patients		
Lung sounds — no./total no. (%)		
Rales	79/669 (11.8)	—
Wheezing	427/688 (62.1)	—
Ronchi	195/680 (28.7)	—
Crackles	365/685 (53.3)	—
Other respiratory virus detected — no./total no. (%)	126/685 (18.4)	—
Influenza	2/126 (1.6)	—
Human parainfluenza virus	14/126 (11.1)	—
Human rhinovirus or enterovirus	109/126 (86.5)	—
Human metapneumovirus	3/126 (2.4)	—
Human bocavirus	3/126 (2.4)	—
Human adenovirus	19/126 (15.1)	—
SARS-CoV-2	13/126 (10.3)	—
Supplemental oxygen use — no./total no. (%)	97/689 (14.1)	—
Ventilatory support — no./total no. (%)	189/683 (27.7)	—
Noninvasive ventilation¶	135/688 (19.6)	—
Invasive ventilation	5/686 (0.7)	—

Table 1. (Continued.)

Characteristic	Case Patients (N = 690)	Control Patients (N = 345)
PICU admission — no./total no. (%)	193/688 (28.1)	—
Reason for hospital visit in control patients		
Urinary tract infection — no./total no. (%)	—	36/339 (10.6)
Acute gastroenteritis — no./total no. (%)	—	120/339 (35.4)
Weight loss or feeding difficulties — no./total no. (%)	—	28/339 (8.3)
Infantile colic — no./total no. (%)	—	15/339 (4.4)
Neonatal jaundice — no./total no. (%)	—	14/339 (4.1)
Abnormal crying — no./total no. (%)	—	53/339 (15.6)
Head trauma — no./total no. (%)	—	62/339 (18.3)
Emergency surgery — no./total no. (%)	—	11/339 (3.2)

* Case patients were infants younger than 12 months of age who were hospitalized for respiratory syncytial virus (RSV)–associated bronchiolitis between October 15 and December 10, 2023, and control patients were infants with clinical visits to the same hospitals for conditions unrelated to RSV infection. Case patients and control patients were matched at a 2:1 ratio according to age (within a window of 1 month), calendar date of hospital visit (within a window of 15 days), and participating center. Data on the gestational age at birth were missing for 64 participants (for 25 case patients and for 39 control patients), and data on the duration of hospitalization were missing for 66 participants (for 4 and 62, respectively). IQR denotes interquartile range, PICU pediatric intensive care unit, and SARS-CoV-2 severe acute respiratory syndrome coronavirus 2.
† Preterm birth was defined as birth at a gestational age of 35 weeks or less.
‡ Chronic lung disease of prematurity was defined as bronchopulmonary dysplasia in preterm infants younger than 32 weeks' gestation in whom supplemental oxygen was administered for at least the first 28 days of life.
§ Congenital heart disease was defined as hemodynamically significant congenital heart disease.
¶ Noninvasive ventilatory support included high-flow oxygen therapy with a nasal cannula.

testing for RSV was not performed in control patients, which may have influenced the study results (especially with regard to gastroenteritis and urinary tract infection, which may manifest with fever). We explored this possibility by conducting a sensitivity analysis in which we sequentially excluded the different categories of diagnoses in the control patients to assess the influence of each category on the effectiveness of nirsevimab therapy, and results similar to those of the primary analysis were obtained. Third, control patients were recruited among patients visiting pediatric emergency departments, whereas case patients were hospitalized. Despite this difference in the level of care and the potential confounding related to health behaviors, the baseline characteristics were similar in the case patients and the control patients. Furthermore, sensitivity analyses that excluded the specified conditions in the control patients, which do not usually result in hospital admission, such as infantile colic, showed similar results.

Fourth, the effectiveness of nirsevimab therapy was assessed very early after the start of the national program. Assessment of the potentially longer effectiveness of nirsevimab is warranted. Fifth, shortages that were experienced during the national campaign may have led to differential access to nirsevimab depending on socioeconomic level, which may have introduced a bias in our study. However, the sensitivity analysis that was adjusted on the basis of the French Deprivation index, which reflects the socioeconomic level, gave results similar to those of the primary analysis. Sixth, the study was powered to analyze the effectiveness of nirsevimab therapy against overall RSV-associated bronchiolitis leading to hospitalization. Subgroup analyses — in particular, the analysis involving infants with at least one risk factor for severe bronchiolitis — were underpowered and should be considered to be exploratory. Similarly, the slightly lower effectiveness of nirsevimab therapy with regard to the most severe forms of RSV-associated

Analysis	Case Patients	Control Patients	Effectiveness (95% CI)
	no. who received nirsevimab/total no. (%)		*percent*
Primary analysis	60/690 (8.7)	97/345 (28.1)	83.0 (73.4 to 89.2)
Sensitivity analyses			
Previous nirsevimab receipt regardless of time	75/690 (10.9)	120/345 (34.8)	86.6 (78.8 to 91.5)
Bronchiolitis defined as the first wheezing attack	56/618 (9.1)	96/327 (29.4)	84.9 (75.4 to 90.7)
Propensity-score analysis	60/690 (8.7)	97/345 (28.1)	78.2 (65.7 to 86.2)
Multivariate model with complete case analysis	56/624 (9.0)	90/284 (31.7)	84.8 (74.9 to 90.7)
Multivariate model adjusted for previous RSV infection	60/690 (8.7)	97/345 (28.1)	83.1 (73.5 to 89.2)
Multivariate model adjusted for socioeconomic level	60/690 (8.7)	97/345 (28.1)	83.4 (73.8 to 89.4)
Multivariate conditional regression model including matching covariates	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Standard logistic-regression model including unmatched patients	61/724 (8.4)	102/360 (28.3)	77.1 (67.4 to 84.0)
Multivariate model with gestational age at birth and birth weight as categorical variables	60/690 (8.7)	97/345 (28.1)	84.1 (74.9 to 90.0)
Subgroup analyses			
Age			
<3 mo	53/332 (16.0)	76/150 (50.7)	82.4 (69.3 to 89.9)
≥3 mo	7/358 (2.0)	21/195 (10.8)	82.7 (52.8 to 93.7)
≥1 Risk factor for severe bronchiolitis			
Yes	9/37 (24)	10/20 (50)	64.8 (−17.2 to 89.4)
No	50/623 (8.0)	83/295 (28.1)	78.2 (67.9 to 85.2)
RSV bronchiolitis with ventilatory support	27/189 (14.3)	46/151 (30.5)	67.2 (38.6 to 82.5)
RSV bronchiolitis with PICU admission	27/193 (14.0)	47/146 (32.2)	69.6 (42.9 to 83.8)

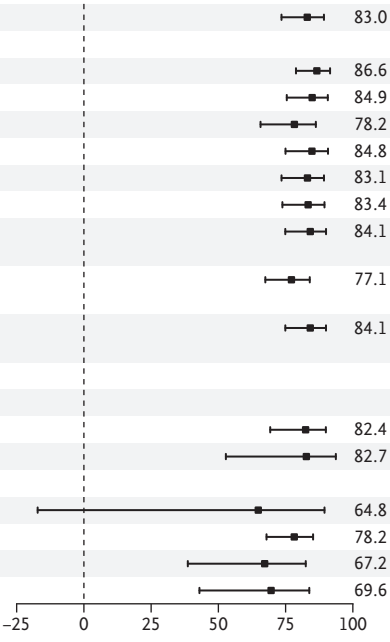

Figure 2. Effectiveness of Nirsevimab against Hospitalization for RSV-Associated Bronchiolitis.

The primary analysis assessed hospitalization for RSV-associated bronchiolitis in infants younger than 12 months of age, with the use of a multivariate conditional logistic-regression model with multiple imputation of missing data. Analyses of previous nirsevimab receipt regardless of time were conducted with the use of a multivariate conditional logistic-regression model with multiple imputation of missing data. All the sensitivity analyses were conducted with the use of multiple imputation of missing data, except the complete case analysis. Socioeconomic level was reflected by the French Deprivation index.[17] Matching covariates were age (within a window of ±1 month), calendar date of hospital visit (within a window of ±15 days), and participating center. The analysis that included unmatched patients was conducted with the use of standard multivariate logistic-regression model with multiple imputation of missing data. Risk factors for severe bronchiolitis were defined as preterm birth (gestational age, ≤35 weeks) and an age of younger than 6 months, chronic lung disease of prematurity, and hemodynamically significant congenital heart disease. Case patients who received ventilatory support and case patients who were in the pediatric intensive care unit (PICU) were matched to control patients on the basis of age, date, and study center and were not matched to control patients who were in the PICU or who received ventilator support. Effectiveness was calculated as 100% × (1 − adjusted odds ratio). The widths of the confidence interval have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

bronchiolitis (i.e., those resulting in critical care or ventilatory support) should be interpreted with caution, although a similar trend was observed in the HARMONIE trial.[20]

This real–world study evaluating the effectiveness of nirsevimab within 3 months of nationwide implementation indicated that nirsevimab prophylaxis was effective against RSV-associated bronchiolitis leading to hospitalization among infants younger than 12 months of age, including those with severe cases that led to PICU admission and ventilatory support.

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