Effectiveness of Nirsevimab Against RSV and RSV-Related Events in Infants

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abstract

BACKGROUND AND OBJECTIVES: Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease (LRTD) in infants and young children. In 2023, the Advisory Committee on Immunization Practices recommended nirsevimab for US infants to prevent RSV-associated LRTD. We assessed nirsevimab effectiveness against polymerase chain reaction (PCR)-confirmed RSV LRTD and RSV-associated health care utilization at Kaiser Permanente Northern California during the 2023–2024 RSV season.

METHODS: All nirsevimab-eligible, healthy term infants born April 2023 or later were included. Infants of RSV-vaccinated mothers or with high-risk conditions were excluded. We assessed nirsevimab effectiveness against RSV LRTD by Cox regression on a calendar timeline conditioned on birth month, adjusting for sex and race and/or ethnicity. Nirsevimab effectiveness was calculated as (1 − adjusted hazard ratio) × 100%. We estimated nirsevimab impact on the number of medical encounters per RSV LRTD by linear regression and odds of hospitalization by logistic regression.

RESULTS: The study included 31 900 infants; 15 647 (49.1%) received nirsevimab. There were 35 RSV LRTD episodes (6.10/1000 person-years) among nirsevimab-immunized infants vs 462 (58.51/1000 person-years) among nonimmunized infants. Nirsevimab effectiveness was 87.2% (CI, 81.7%–91.1%) against RSV LRTD, 98.0% (CI, 85.1%–99.7%) against hospitalized RSV LRTD, and 71.0% (CI, 65.3%–75.8%) against PCR-confirmed RSV. Nirsevimab-immunized infants with RSV LRTD had fewer encounters (adjusted means difference −0.86; $P = .001$) and lower odds of hospitalization (odds ratio, 0.11; CI, 0.01–0.85) than nonimmunized infants.

CONCLUSIONS: Nirsevimab was highly effective in protecting infants against RSV-associated LRTD as well as against milder RSV infection. Nirsevimab-immunized infants with RSV LRTD had significantly fewer medical encounters and were less likely to be hospitalized than were nonimmunized infants.

WHAT'S KNOWN ON THIS SUBJECT: Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease (LRTD) in infants and young children. In real-world studies, immunization with the long-acting monoclonal antibody nirsevimab has demonstrated effectiveness against hospitalized RSV LRTD.

WHAT THIS STUDY ADDS: Nirsevimab significantly reduced incidence of RSV LRTD, hospitalized RSV LRTD, and RSV infection regardless of LRTD. Among infants with RSV LRTD, those who were nirsevimab immunized had fewer medical encounters and were less likely to be hospitalized than were nonimmunized infants.

To cite: Hsiao A, Hansen J, Fireman B, et al. Effectiveness of Nirsevimab Against RSV and RSV-Related Events in Infants. *Pediatrics.* 2025;156(2):e2024069510

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Dr Hsiao drafted the initial manuscript, critically reviewed and revised the manuscript, contributed to the design of the study, and supervised data analysis. Mr Hansen critically reviewed and revised the manuscript, contributed to the design of the study, and supervised data analysis. Mr Fireman and Dr Klein conceptualized and designed the study and critically reviewed and revised the manuscript. Mr Timbol carried out the analyses and critically reviewed the manuscript. Dr Zerbo critically reviewed and revised the manuscript and contributed to the design of the study. Ms Mari and Drs Rizzo, La Via, and Izikson critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract disease (LRTD) among infants and young children, resulting in annual epidemics worldwide.[1–3] Nearly all children aged under 2 years are infected with RSV, with up to 40% having an LRTD (predominantly bronchiolitis or pneumonia).[4–8] All children, including healthy full-term infants, are at risk for severe RSV with LRTD, which is the leading cause of hospitalization in infants aged under 1 year.[5,6,9–11] Most medically attended health care visits for RSV-associated disease, however, occur in outpatient clinics, especially in healthy infants.[9,12–14]

Until recently, the only approved prophylaxis for preventing serious LRTD caused by RSV was the monoclonal antibody palivizumab, which requires monthly dosing during the RSV season and is only indicated for infants at high risk for RSV[15] (ie, infants born ≤ 35 weeks gestational age, those with bronchopulmonary dysplasia or hemodynamically significant congenital heart disease).[16] In July 2023, the US Food and Drug Administration approved nirsevimab, a long-acting monoclonal antibody, for the prevention of RSV-associated LRTD (RSV LRTD) in infants.[17] The Advisory Committee on Immunization Practices subsequently recommended nirsevimab for all infants aged < 8 months born during or entering their first RSV season and for children aged 8 to 19 months at high risk of severe RSV entering their second RSV season.[17]

Pooled estimates from the phase 2b and 3 MELODY trials in healthy infants born ≥ 29 weeks found that nirsevimab efficacy was 79.5% (CI, 65.9%–87.7%) against medically attended RSV lower respiratory tract infection (LRTI), 77.3% (CI, 50.3%–89.7%) against hospitalized RSV LRTI, and 86.0% (CI, 62.5%–94.8%) against RSV LRTI requiring intensive care unit (ICU) care.[18–20] The phase 3b HARMONIE randomized control trial demonstrated similar efficacy against hospitalized RSV-associated LRTI (83.2%; CI, 67.8%–92.0%) and very severe RSV-associated LRTI (75.7%; CI, 32.8%–92.9%).[21] Limited data are available on its effectiveness in the outpatient setting.[22]

To evaluate the real-world effectiveness of routinely administered nirsevimab, we conducted an observational cohort study in healthy term infants during the 2023–2024 RSV season at Kaiser Permanente Northern California (KPNC). Here, we report on nirsevimab effectiveness against the coprimary and select secondary outcomes from the Beyfortus (nirsevimab) Effectiveness Against Medically-Attended RSV Events in Infants Study (BEAR Study).[23]

METHODS

Setting

KPNC is an integrated health care delivery system with an annual membership of approximately 4.6 million and an annual birth cohort of approximately 40 000 infants. KPNC members are fully insured and receive nearly all health care at KPNC facilities, which include 259 medical clinics and 21 hospitals. KPNC's comprehensive electronic medical record captures all medical services, including immunizations, diagnoses, and laboratory tests. KPNC members comprise approximately one-third of Northern California's population and broadly represent insured individuals in Northern California with regard to racial, ethnic, and socioeconomic demographics, although those at the very lowest incomes are somewhat underrepresented.[24]

Routine nirsevimab administration at KPNC began October 19, 2023.[17] KPNC offered nirsevimab to all eligible infants born on or after this date prior to discharge, at urgent care, or at outpatient well-child visits. KPNC also contacted eligible infants born prior to this date for catchup dosing in outpatient clinics as part of routine care.

Since 2006, KPNC has used a multiplex reverse transcription polymerase chain reaction (PCR) assay (Cepheid GeneXpert PCR assay) to simultaneously test for RSV and influenza, with the addition of SARS-CoV-2 in recent years. For the 2023–2024 respiratory season, routine PCR testing began on October 1, 2023, to April 30, 2024. Pediatricians routinely order PCR testing in all health care settings, including outpatient clinics, based on clinical judgement.

The KPNC Institutional Review Board approved the study protocol with a waiver of written informed consent.

Study Population

This was a retrospective cohort study that included "healthy" infants born between April 1, 2023, and April 30, 2024.[23] Follow-up began on October 19, 2023, or date of birth, whichever was later. For study population inclusion, we required that infants be born at KPNC to mothers who received prenatal care at KPNC to ascertain maternal RSV vaccination status.

Infants met the "healthy" criteria for inclusion in the study population if they were born at ≥37 weeks gestational age without any high-risk diagnoses that would increase their risk of severe RSV disease (Supplemental Materials Table S1). Since higher-risk infants may have been more likely to receive nirsevimab, to seek care (and have their care escalated), and to be tested, infants with underlying medical conditions and those born preterm were excluded from the analysis to reduce bias.

We excluded infants whose mothers were vaccinated against RSV during pregnancy and infants with a record of a positive RSV PCR test result prior to October 19, 2023 (ie, a PCR-confirmed RSV infection between April 1, 2023, to October 18, 2023, prior to the start of follow-up).

Outcomes

The primary outcome was a first episode of PCR-confirmed RSV infection during follow-up with an LRTD diagnosis. An episode was defined as having at least 1 medical encounter

with an LRTD diagnosis in any setting in the 7 days before and up to 10 days after the positive RSV PCR test (Supplemental Materials Table S2). The episode start date was the date of the first medical encounter in this time range. We used International Classification of Diseases, Tenth Revision codes to identify all diagnoses. Episodes that included at least 1 hospitalization were considered a hospitalized RSV LRTD.

As a coprimary outcome, we counted the number of medical encounters within an episode of RSV LRTD. Each medical encounter was categorized as outpatient, emergency department (ED), inpatient, or ICU care. Inpatient stays were counted as a single encounter, regardless of length of stay, unless an infant was admitted more than once in the episode window. If an infant first had an ED visit followed by an inpatient stay on the same calendar date, the visits were considered the same encounter and categorized as an inpatient encounter, since infants who require hospitalization would first be triaged at the ED.

A secondary outcome was any PCR-confirmed RSV (with or without an LRTD diagnosis).

We also examined PCR-confirmed influenza as a negative control outcome because we hypothesized it would be unrelated to nirsevimab immunization.

We included all outcomes that occurred from October 19, 2023, to April 30, 2024.

Statistical Analysis

To examine the effectiveness of nirsevimab immunization against the primary outcome, we compared nirsevimab-immunized vs nonimmunized infants with respect to the hazard of RSV LRTD. We used Cox regression analysis to estimate the adjusted hazard ratio (HR_{Adj}) of a first episode of RSV LRTD. Nirsevimab effectiveness was estimated as 1 minus HR_{Adj}, expressed as a percentage, and interpreted as the percent difference in risk of the outcome in nirsevimab-immunized vs nonimmunized infants.

Nirsevimab immunization status could vary during follow-up. Follow-up began on October 19, 2023, or the infant's date of birth (whichever came later). Infants who received nirsevimab during follow-up were considered nonimmunized through the day of nirsevimab receipt and immunized thereafter. The Cox model used a calendar time scale; risk sets were conditioned on birth month and calendar day. As prespecified, the model included covariates adjusting for sex, and race and/or ethnicity (guardian reported, per the electronic medical record). Sex was included, as studies have reported an association between male sex and hospitalization for RSV.[9,25,26] Race and/or ethnicity as a social construct was included because RSV rates are higher for infants of Black, Hispanic, and other races when compared with non-Hispanic white infants.[27–29]

Similar Cox models were used for the secondary outcome of all PCR-confirmed RSV and a post hoc analysis of hospitalized RSV LRTD.

We censored infants who received nirsevimab aged ≥ 8 months.[17] Infants who did not receive nirsevimab were not censored and continued contributing nonimmunized follow-up time after age 8 months.

We examined the association of nirsevimab immunization with the number of medical encounters during an RSV LRTD episode (coprimary outcome) using linear regression. In post hoc analyses, we separately estimated the association of nirsevimab receipt with the odds of hospitalization and odds of an ED visit among infants with an RSV LRTD episode. Both linear and logistic regression analyses were adjusted for birth month, sex, and race and/or ethnicity.

To explore the number of days (if any) required to reach peak antibody concentrations after nirsevimab receipt, we conducted 2 sensitivity analyses in which we excluded cases that occurred < 2 days and < 7 days after immunization.[30] We also conducted a sensitivity analysis in which we did not censor infants who received nirsevimab aged ≥ 8 months.

To assess residual confounding, we similarly examined the association of nirsevimab with PCR-confirmed influenza. KPNC uses a multiplex PCR test that simultaneously tests for RSV and influenza. If present, we would expect residual confounders to have a similar effect on the nirsevimab-influenza association as on the nirsevimab-RSV association but that nirsevimab would not protect against influenza.

All data analyses were performed using SAS software version 9.4. Missing data were not imputed. Confidence intervals are 95% intervals.

RESULTS

Of the 49 680 infants born at KPNC between April 1, 2023, to April 30, 2024, 31 900 healthy term infants met the inclusion criteria, of whom 15 647 (49.1%) received nirsevimab (Figure 1). Nearly half of the study population were female (49.2%), and most were Hispanic (31.1%), white (30.4%), or Asian (23.2%).

Among immunized infants, most received nirsevimab in November (45.3%) or December (30.8%; Supplemental Materials Table S3 and Figure S1). The mean age at receipt was 2.6 months (standard deviation: 2.3 months). Except for Asian race, infant diet, and some infant birth months, the standardized difference in proportions of immunized vs nonimmunized infants was $< |0.2|$ (small effect size[31]; Table 1). Most infants received nirsevimab in outpatient clinics (87.5%). Nirsevimab-immunized infants were followed for up to 193 days after immunization (median, 148 days; interquartile range [IQR], 126–167). Among

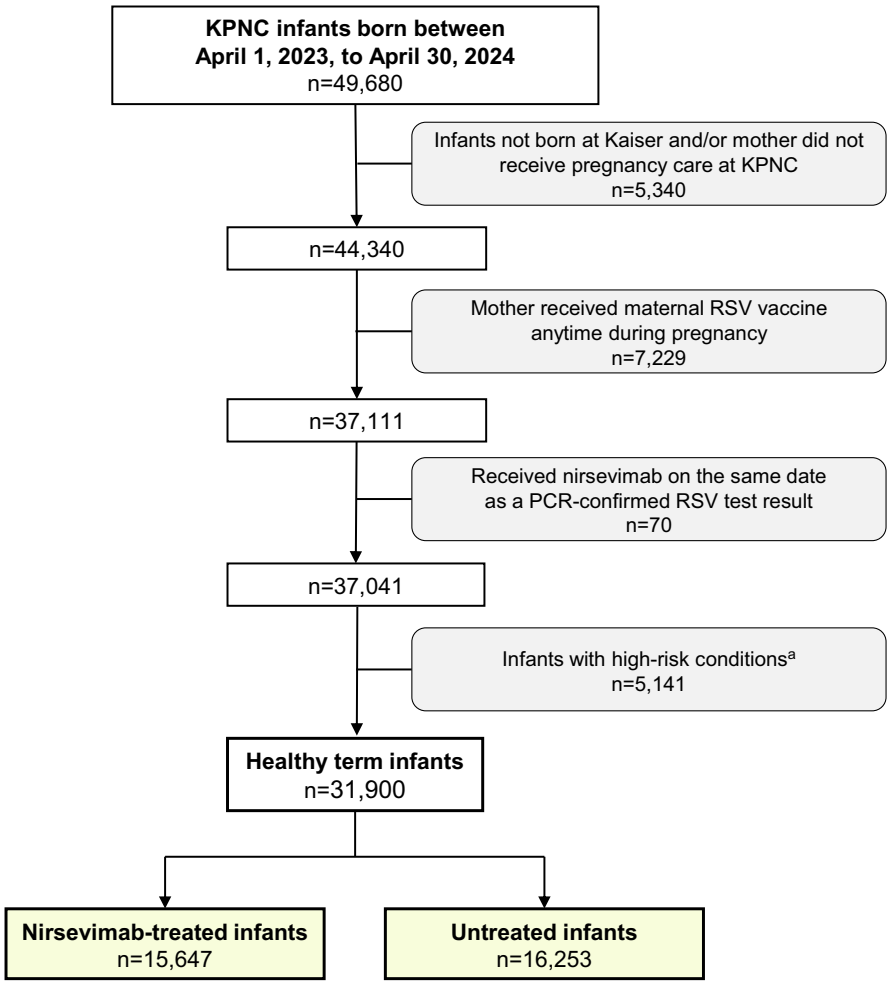

FIGURE 1.

KPNC study population of eligible infants. [a]Infants with high-risk conditions (n = 5141) included 2345 infants born before 37 weeks gestation, 952 infants born before 37 weeks gestation with a high-risk condition, and 1844 infants born after or at 37 weeks with a high-risk condition.
Abbreviations: KPNC, Kaiser Permanente Northern California; RSV, respiratory syncytial virus.

20 030 infants born before October 19, 2023, 48.3% (n = 9676) received nirsevimab (Supplemental Materials Table S4). Among 11 870 infants born on or after October 19, 2023, 50.3% (n = 5971) received nirsevimab.

In the study population, there were 5056 infants with at least 1 PCR test between October 19, 2023, to April 30, 2024, of whom 1114 (22.0%) were positive for RSV. RSV activity among the study population peaked in December (Figure 2). Thirty infants with PCR-confirmed RSV prior to October 19, 2023, were excluded from the analysis.

Nirsevimab Effectiveness

Coprimary Outcome: First Episode of RSV LRTD

There were 35 first episodes (6.10 episodes per 1000 person-years [PY]) of RSV LRTD among nirsevimab-immunized infants (Table 2), occurring between 2 to 113 days (median, 40 days; IQR, 23–52 days) after nirsevimab receipt.

There were 462 first episodes (58.51 episodes per 1000 PY) of RSV LRTD among nonimmunized infants (Table 2), occurring between 3 to 155 days (median, 46 days; IQR, 28–70 days) from the start of follow-up.

Nirsevimab receipt was associated with an adjusted effectiveness of 87.2% (CI, 81.7%–91.1%; $P < .0001$) against RSV LRTD when compared with no receipt (Table 2).

Other Outcomes

There were 158 PCR-confirmed RSV episodes with or without an LRTD diagnosis (27.53 episodes per 1000 PY) among nirsevimab-immunized infants vs 956 cases (121.00 episodes per 1000 PY) among nonimmunized infants (Table 2). When compared with no receipt, nirsevimab receipt was associated with an adjusted effectiveness of 71.0% (CI, 65.3%–75.8%; $P < .0001$) against any PCR-confirmed RSV (Table 2).

TABLE 1. Demographic and Baseline Characteristics of Healthy Term Infant Study Population by Nirsevimab Receipt

	Total N = 31 900, n (%)	Received Nirsevimab N = 15 647, n (%)	Did Not Receive Nirsevimab N = 16 253, n (%)	Standardized Difference[a]
Infant Month of Birth				
April 2023	2878 (9.0)	238 (1.5)	2640 (16.2)	−.53
May 2023	2992 (9.4)	977 (6.2)	2015 (12.4)	−.21
June 2023	3022 (9.5)	1365 (8.7)	1657 (10.2)	−.05
July 2023	3133 (9.8)	1877 (12.0)	1256 (7.7)	.14
August 2023	3211 (10.1)	1983 (12.7)	1228 (7.6)	.17
September 2023	3009 (9.4)	2044 (13.1)	965 (5.9)	.25
October 2023	3116 (9.8)	2142 (13.7)	974 (6.0)	.26
November 2023	2807 (8.8)	2049 (13.1)	758 (4.7)	.30
December 2023	1680 (5.3)	1055[b] (6.7)	625 (3.8)	.13
January 2024	1263 (4.0)	690[b] (4.4)	573 (3.5)	.05
February 2024	1194 (3.7)	600[b] (3.8)	594 (3.7)	.01
March 2024	1442 (4.5)	626 (4.0)	816 (5.0)	−.05
April 2024	2153 (6.7)	1 (0.0)	2152 (13.2)	−.55
Sex				
Female	15 710 (49.2)	7718 (49.3)	7992 (49.2)	.003
Male	16 190 (50.8)	7929 (50.7)	8261 (50.8)	−.003
Race and/or Ethnicity				
Asian	7396 (23.2)	4380 (28.0)	3016 (18.6)	.23
Black	1593 (5.0)	689 (4.4)	904 (5.6)	−.05
Hawaiian/Pacific Islander	275 (.9)	134 (.9)	141 (.9)	−.001
Hispanic	9926 (31.1)	4686 (29.9)	5240 (32.2)	−.05
Multiracial	900 (2.8)	465 (3.0)	435 (2.7)	.02
Native American/Alaskan	111 (.3)	61 (.4)	50 (.3)	.01
Unknown	1995 (6.3)	787 (5.0)	1208 (7.4)	−.10
White	9704 (30.4)	4445 (28.4)	5259 (32.4)	−.09
5-minute Apgar Score				
0–3	22 (.1)	13 (.1)	9 (.1)	.01
4–6	159 (.5)	89 (.6)	70 (.4)	.02
7–10	30 327 (95.1)	15 138 (96.7)	15 189 (93.5)	.15
Unknown	1392 (4.4)	407 (2.6)	985 (6.1)	−.17
Delivery Method				
Caesarean	7967 (25.0)	4138 (26.4)	3829 (23.6)	.01
Unknown	1384 (4.3)	404 (2.6)	980 (6.0)	.02
Vaginal	22 549 (70.7)	11 105 (71.0)	11 444 (70.4)	.15
Infant Diet in First 6 mos of Life				
Unknown	693 (2.2)	33 (.2)	660 (4.1)	−.27
Breast milk and formula fed	16 968 (53.2)	9111 (58.2)	7857 (48.3)	.20
Breast milk only	12 462 (39.1)	5647 (36.1)	6815 (41.9)	−.12
Formula only	1777 (5.6)	856 (5.5)	921 (5.7)	−.01
GA at Birth				
Early term: $37^{0/7}$–$38^{6/7}$ weeks GA	9231 (28.9)	4568 (29.2)	4663 (28.7)	.01
Full term: $39^{0/7}$–$40^{6/7}$ weeks GA	19 743 (61.9)	9664 (61.8)	10 079 (62.0)	−.01
Late term: $41^{0/7}$–$41^{6/7}$ weeks GA	2848 (8.9)	1385 (8.9)	1463 (9.0)	−.01
Post term: $\geq 42^{0/7}$ weeks GA	78 (.2)	30 (.2)	48 (.3)	−.02

(Continued on next page)

TABLE 1. Demographic and Baseline Characteristics of Healthy Term Infant Study Population by Nirsevimab Receipt (Continued)				
	Total N = 31 900, n (%)	Received Nirsevimab N = 15 647, n (%)	Did Not Receive Nirsevimab N = 16 253, n (%)	Standardized Difference[a]
Nirsevimab Administration Setting				
Hospital	N/A	1962 (12.5)	N/A	N/A
Outpatient	N/A	13 685 (87.5)	N/A	N/A

Abbreviations: GA, gestational age; N/A, not applicable.
[a] The standardized difference in proportions of immunized versus nonimmunized infants was calculated as the difference in the proportions divided by the standard error; imbalances were defined as an absolute value greater than 0.20 (small effect size).
[b] 16 infants (5 in December 2023, 10 in January 2024, 1 in February 2024) received nirsevimab between 8 to < 12 months of age. These infants contributed follow-up time as untreated infants and were censored in the analysis at time of nirsevimab receipt.

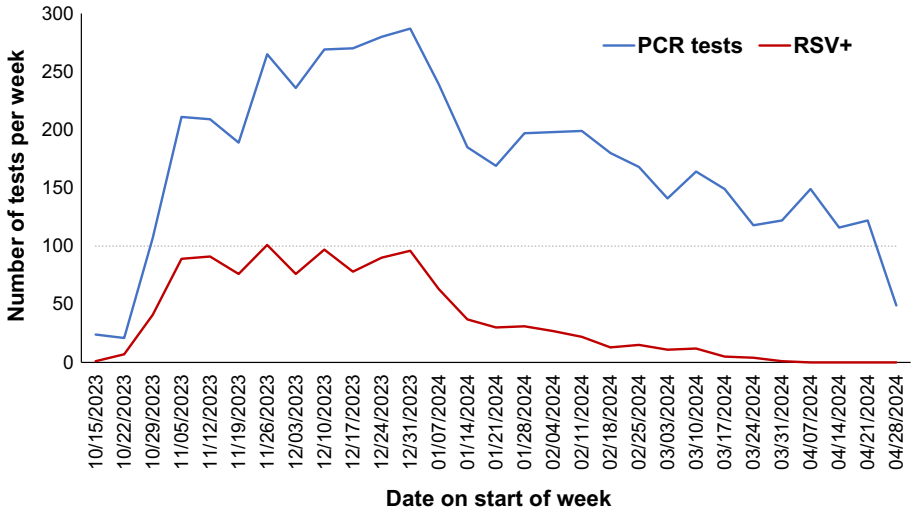

FIGURE 2.
PCR testing and RSV+ results in study population, 2023–2024 influenza season. For the purposes of this figure, only 1 test per infant (n = 5056) is captured. If an infant had multiple negative tests, the date of the first test is included in the figure. If an infant had a positive RSV result (n = 1114), the date of the first positive is included in the figure.
Abbreviations: PCR, polymerase chain reaction; RSV+, respiratory syncytial virus positive.

Table 2. Adjusted Hazard Ratio for First Occurrence of PCR-Confirmed RSV LRTD Episode and PCR-Confirmed RSV for Nirsevimab-Immunized Versus Nonimmunized Healthy Term Infants

	Received Nirsevimab N = 15 647		Did Not Receive Nirsevimab N = 16 253		Unadjusted RR	HR_{Adj}[a] (95% CI)	Estimated Treatment Effectiveness, % (95% CI)[b]	P Value[c]
	n (IP)	IR (95% CI)	n (IP)	IR (95% CI)				
Primary Outcome: First episode of PCR-confirmed RSV LRTD	35 (.002)	6.10 (4.38–8.49)	462 (.03)	58.51 (53.41–64.09)	.104 (.074–.147)	.128 (.089–.183)	87.2 (81.7–91.1)	< **.001**
Secondary Outcome: PCR-confirmed RSV	158 (.01)	27.53 (23.55–32.17)	956 (.06)	121.00 (113.60–129.00)	.227 (.192–.2697)	.290 (.242–.347)	71.0 (65.3–75.8)	< **.001**

Abbreviations: HR_{Adj}, adjusted hazard ratio; IP, incidence proportion; IR, incidence rate per 1000 person-years; LRTD, lower respiratory tract disease; PCR, polymerase chain reaction; RR, relative risk; RSV, respiratory syncytial virus.
[a] Cox regression on a calendar timeline adjusted for sex and race and/or ethnicity stratified by birth month.
[b] Estimated as $1 - HR_{Adj}$ expressed as a percentage.
[c] Test: H_0: $HR_{Adj} = 1$; results bolded where $P < .05$.

In a post hoc analysis, nirsevimab receipt was associated with an adjusted effectiveness of 98.0% (CI, 85.1%–99.7%; $P < .0001$) against hospitalized RSV LRTD when compared with no receipt (Supplemental Materials Table S5).

Nirsevimab Impact on Health Care Utilization

Coprimary Outcome: Number of Medical Encounters Associated with an RSV LRTD Episode

Among the 35 nirsevimab-immunized infants with RSV LRTD, there was a total of 75 medical encounters, most of which were in outpatient clinics (n = 57; 76%) followed by the ED (n = 17; 23%; Supplemental Material Table S6). Among the 462 nonimmunized infants with RSV LRTD, there was a total of 1241 medical encounters. Most of these encounters were also in outpatient clinics (n = 807; 65%) or the ED (n = 367; 30%).

Among infants with RSV LRTD, nirsevimab-immunized infants had an adjusted 0.86 fewer mean number of encounters than nonimmunized infants ($P = .001$; Table 3). Post hoc analysis of RSV episodes (with or without LRTD) also found that nirsevimab-immunized infants had 0.12 fewer mean number of encounters than nonimmunized infants ($P = .001$; Supplemental Material Table S7).

Hospitalizations, ED, ICU Care (Post Hoc Analyses)

Among infants with RSV LRTD, nirsevimab-immunized infants had lower adjusted odds of hospitalization than nonimmunized infants (odds ratio, 0.11; CI, 0.01–0.85; $P = .035$; Supplemental Material Table S6 and S8). Nirsevimab-immunized infants also had lower adjusted odds of an ED visit than nonimmunized infants (odds ratio, 0.30; CI, 0.13–0.67; $P = .003$; Supplemental Material Table S6 and S9).

Too few infants with hospitalized RSV LRTD required ICU care to estimate the odds of ICU care (Supplemental Material Table S6).

Sensitivity Analyses

Estimated effectiveness from sensitivity analyses that varied the time required to be considered "immunized" were consistent with the results of the main analysis (87.5% [CI, 82.0%–91.3%] waiting 2 days; 87.7% [CI, 82.0%–91.6%] waiting 7 days; Supplemental Material Table S5).

Estimated effectiveness did not change when we did not censor infants who received nirsevimab aged ≥ 8 months (n = 16; Supplemental Material Table S5).

Nirsevimab was not associated with PCR-confirmed influenza (P = .67), a finding that suggests our analyses were not biased by unmeasured factors that might affect the risk of both RSV and influenza infection (Supplemental Material Table S5).

DISCUSSION

In this large real-world study in a diverse population of healthy term infants during the 2023–2024 RSV season, we found that infants who received nirsevimab had an 87% reduction in the incidence of RSV LRTD and a 98% reduction in the incidence of hospitalized RSV LRTD when compared with infants who did not receive nirsevimab. Immunization with nirsevimab also demonstrated a 71% reduction in the incidence of RSV infection with or without an LRTD diagnosis. These findings suggest that nirsevimab was highly effective in protecting against RSV-associated lower respiratory tract disease as well as against milder RSV infection.

Nirsevimab-immunized infants with RSV LRTD, as well as RSV regardless of LRTD diagnosis (post hoc), had fewer medical encounters than nonimmunized infants, and most of their medical encounters were in the outpatient clinic. Nirsevimab-immunized infants with RSV LRTD were also less likely to be hospitalized or to have an ED visit. These results suggest that routine use of nirsevimab may reduce the burden of RSV-associated utilization in both the inpatient and outpatient settings.

Our findings were similar to 2 test-negative design studies from the 2023–2024 season in the United States and France.[22,30] The first, which included 765 infants aged < 8 months with PCR-confirmed RSV recruited from 7 US pediatric medical centers, estimated that nirsevimab effectiveness was 89% (CI, 79%–94%) against RSV-associated acute respiratory infections and 93% (CI, 82%–97%) against RSV-associated hospitalization.[30] The second study from France, which included 883 infants aged < 12 months with PCR-confirmed RSV and a more restrictive bronchiolitis diagnosis, estimated nirsevimab effectiveness as 79.7%

TABLE 3. Adjusted Difference in Mean Number of Medical Encounters per RSV LRTD Episode Among Nirsevimab-Immunized Versus Nonimmunized Healthy Term Infants

	Received Nirsevimab[a] Mean Number per Episode of RSV LRTD (Total Encounters/ Infants With RSV LRTD)	Did Not Receive Nirsevimab[a] Mean Number per Episode of RSV LRTD (Total Encounters/ Infants With RSV LRTD)	Unadjusted Difference in Means (95% CI)	Adjusted Difference in Means[b] (95% CI)	*P* Value[c]
Medical encounters	2.14 (75/35)	2.69 (1241/462)	−.54 (−1.04 to −.05)	−.86 (−1.36 to −.36)	**.001**

Abbreviations: LRTD, lower respiratory tract disease; RSV, respiratory syncytial virus.
[a] Mean age at episode (interquartile range) in days; treated population: 111 (53–172); untreated population: 143 (83–205).
[b] Linear regression model adjusted for birth month, sex, and race and/or ethnicity.
[c] Test: H_0: no difference in the mean number of medical encounters; results bolded where $P < .05$.

(CI, 67.7%–87.3%), which was consistent, although somewhat lower, than ours.[22]

Our post hoc estimate of 98% nirsevimab effectiveness against hospitalized RSV LRTD had a confidence interval (CI, 85.1%, 99.7%) that was in the range reported by other observational studies from Spain, France, Luxembourg, and the United States (70%–90%),[32–37] which used test-negative or other case-control designs. In contrast to our study, these studies included high-risk infants as well as newborns and very young infants due to nirsevimab shortages that led to preferential administration to infants at higher risk of severe RSV disease.[33,35]

A strength of our study was that 49% of eligible healthy term infants at KPNC received nirsevimab during the 2023–2024 season. At KPNC, nirsevimab was available in adequate quantities throughout the season for all eligible infants, including healthy term infants; unlike other studies, administration was not limited only to the youngest or highest-risk infants.[33–37] In our study population, we did not find strong evidence that nirsevimab was administered selectively or differentially based on an infant's risk or demographic profile. The demographic characteristics of infants who received nirsevimab were similar to those of infants who did not receive nirsevimab, except for small differences in the proportion of Asian infants and some infant birth months. Since many infants were immunized before RSV season peaked, we could estimate nirsevimab effectiveness with much precision (narrow confidence intervals).

Our study had several other strengths. First, especially in infants aged < 1 year, KPNC pediatricians routinely order PCR testing during the respiratory virus season when infants present with respiratory symptoms in all clinics and hospitals. Therefore, identification of RSV was not limited only to more severe cases, and nirsevimab effectiveness was less likely to be biased due to testing patterns. Second, we made use of KPNC's extensive data on the entire study population by implementing a cohort design rather than a test-negative design that would typically be limited to tested infants in the ED or hospital. We compared immunized vs nonimmunized infants in strata restricted to infants born in the same month and at risk on the same calendar date, with additional adjustment for sex and race and/or ethnicity. Third, a sensitivity analysis found no association between nirsevimab receipt and PCR-confirmed influenza, which gives us confidence that our results were not confounded by factors such as health care–seeking behavior that could yield a biased association between nirsevimab and influenza.

This study had limitations. We were unable to assess how soon after receipt nirsevimab protection occurs because few RSV LRTD cases occurred within 7 days. In addition, although KPNC performs a large amount of PCR testing, we did not quantify what proportion of infants with respiratory symptoms were tested; testing biases among RSV-positive infants were possible. Further, as an observational study, unmeasured confounders that increase one's risk of RSV (eg, lower socioeconomic status,[38,39] having siblings,[38,40] and/or daycare attendance[38]) could affect our results. We also did not include infants born before 37 weeks or with high-risk conditions, and our findings may not be generalizable to high-risk infants. Lastly, although KPNC has a large, diverse population, our findings may not be generalizable to populations elsewhere.

CONCLUSION

Nirsevimab was highly effective in protecting healthy term infants against RSV-associated LRTD as well as against milder RSV infection during the 2023–2024 season. These findings support the Advisory Committee on Immunization Practice's recommendation for eligible infants aged < 8 months entering their first RSV season to receive nirsevimab to reduce the risk of RSV infection.

ACKNOWLEDGMENTS

We would like to thank Lynn Schultz and in memory of Barbara Courssaris at Sanofi for their writing support of the study protocol.

ABBREVIATIONS

ED: emergency department
HR_{Adj}: adjusted hazard ratio
ICU: intensive care unit
KPNC: Kaiser Permanente Northern California
LRTD: lower respiratory tract disease
PCR: polymerase chain reaction
PY: person-years
RSV: respiratory syncytial virus

CONFLICT OF INTEREST DISCLOSURES: Nicola P. Klein reported receiving research support from GlaxoSmithKline, Merck, Pfizer, Seqirus, Moderna, and the US Centers for Disease Control and Prevention outside of the submitted work. Ousseny Zerbo reports receiving research support from Pfizer and Moderna outside the submitted work. Karine Mari, Christopher Rizzo, William La Via, and Ruvim Izikson are employed and compensated by Sanofi. The remaining authors report nothing to disclose.

FUNDING: This study was funded by Sanofi. All nirsevimab doses given as part of this study were donated by Sanofi and AstraZeneca. The Kaiser Permanente Vaccine Study Center did not receive direct research support for this study from AstraZeneca.

TRIAL REGISTRATION NUMBER: ClinicalTrials.gov NCT06325332

Accepted for Publication Date: April 17, 2025

https://doi.org/10.1542/peds.2024-069510

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