Summary of effectiveness of nirsevimab in infants

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June 28, 2024

Agenda

- Real-world vaccine/product effectiveness methods
- Effectiveness of nirsevimab in the United States
  - RSV-associated emergency department encounters & hospitalization, VISION
  - RSV-associated medical encounters and hospitalization, NVSN
- Effectiveness of nirsevimab globally
- Conclusions

Real-world vaccine/product effectiveness context and methods

Efficacy ≠ effectiveness

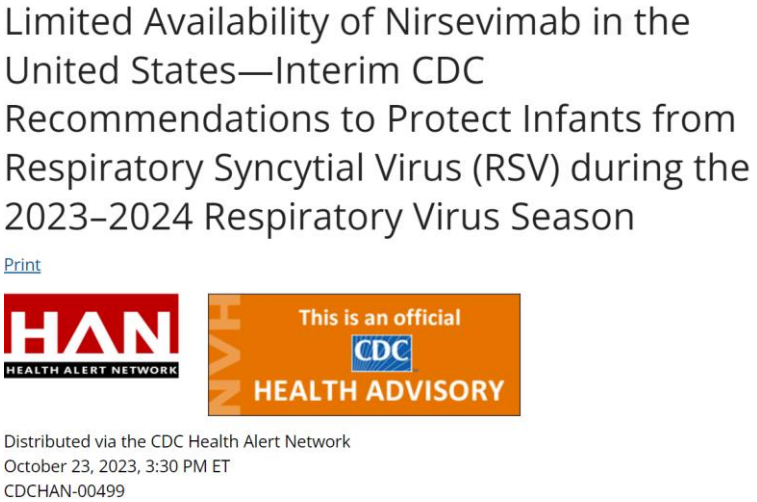
- **Efficacy:** the degree to which an immunization prevents disease **under ideal and controlled conditions** (i.e., measured in clinical trials)

- **Effectiveness:** the degree to which an immunization prevents disease **under real-world conditions** (i.e., measured in post-licensure observational studies)

In this presentation,
we'll discuss **product effectiveness ("PE")**
from real-world data.

Insufficient supply of nirsevimab to meet demand in 2023-2024 season

- Limited supply of nirsevimab (100mg and 50mg formulations) meant clinicians were uncertain how to ration or prioritize few available doses
- CDC issued an official Health Advisory notice via the Health Alert Network to prioritize available doses to high-risk infants and younger infants
- By January, demand had decreased and additional supply was available allowing return to original recommendations


Limited Availability of Nirsevimab in the United States—Interim CDC Recommendations to Protect Infants from Respiratory Syncytial Virus (RSV) during the 2023–2024 Respiratory Virus Season

Print

HAN HEALTH ALERT NETWORK

This is an official CDC HEALTH ADVISORY

Distributed via the CDC Health Alert Network
October 23, 2023, 3:30 PM ET
CDCHAN-00499

Health Alert Network (HAN) - 00499 | Limited Availability of Nirsevimab in the United States—Interim CDC Recommendations to Protect Infants from Respiratory Syncytial Virus (RSV) during the 2023–2024 Respiratory Virus Season

Observational effectiveness measured in a test-negative design (TND) study

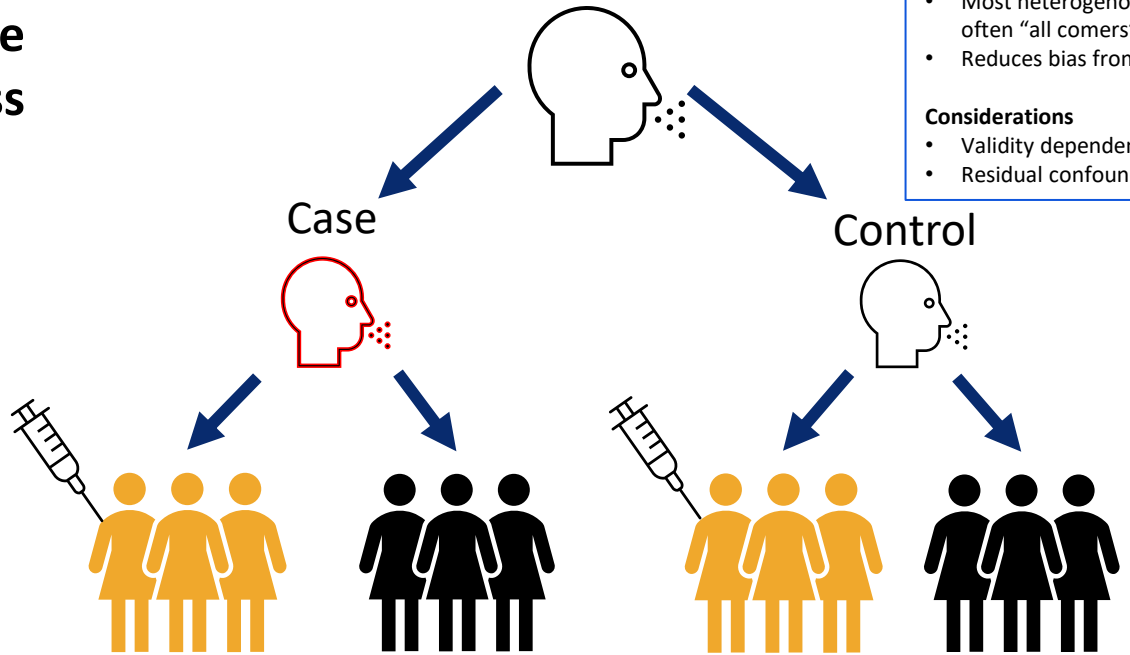
Key features of a TND
- Real-world circumstances
- Most heterogenous study population, often "all comers"
- Reduces bias from health-care seeking behavior

Considerations
- Validity dependent on test performance
- Residual confounding is possible

Person with acute respiratory illness

RSV test

RSV immunization status



Effectiveness = 1 – (odds ratio) x 100% Odds ratio = $\frac{Odds\ of\ immunization_{cases}}{Odds\ of\ immunization_{controls}}$

Chua H, Feng S, Lewnard JA, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. *Epidemiology* 2020;31:43-64.

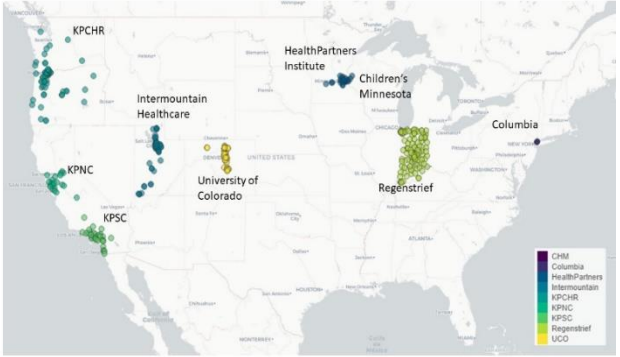
Slide courtesy of Ruth Link-Gelles, PhD MPH

Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)

VISION Multi-Site Network of Electronic Health Records (EHRs)

127 emergency rooms and 107 hospitals

- **Population:** Visiting a participating ED for or hospitalized with RSV-like illness (RLI)*
- **Immunization data:** Infant and maternal RSV immunization status documented by electronic health records, state and city registries, and claims data (subset of sites)
- **Covariate data:** Documented in electronic health records
  - Underlying medical conditions: ICD-10 discharge diagnosis codes at time of RLI encounter
  - Patient characteristics
    - Date of birth
    - Census tract of residence
    - Sex

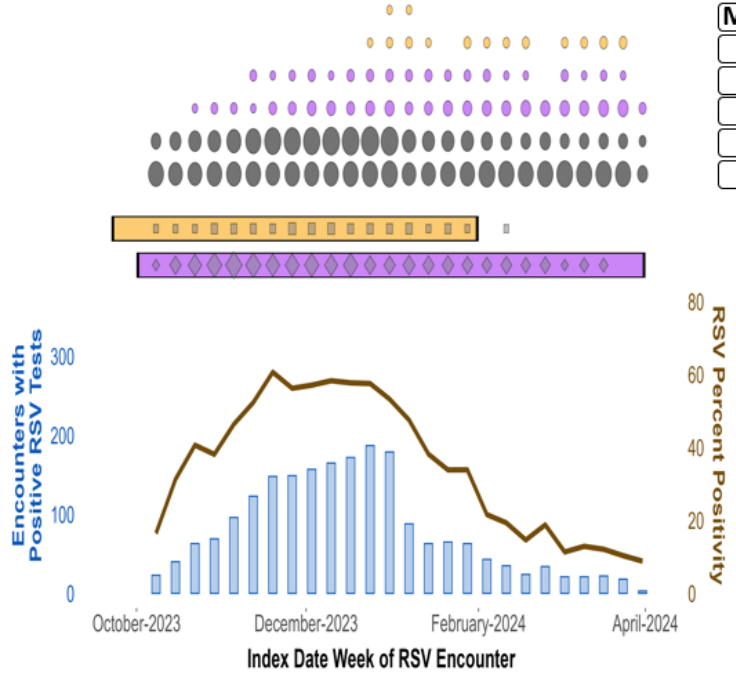


VISION 2.0 partners included in this analysis –
ED: Columbia, HealthPartners Institute, Intermountain Healthcare, KPSC, KPCHR, Regenstrief
Inpatient: Columbia, HealthPartners Institute, Intermountain, KPSC, KPCHR, Regenstrief

*≥1 ICD-10 discharge diagnosis code indicating RSV-like illness (RLI)
ED = emergency department

ED Encounters and Hospitalizations for RSV-like illness* among infants in their first RSV season, by immunization and RSV positivity status – VISION, October 2023 – March 2024

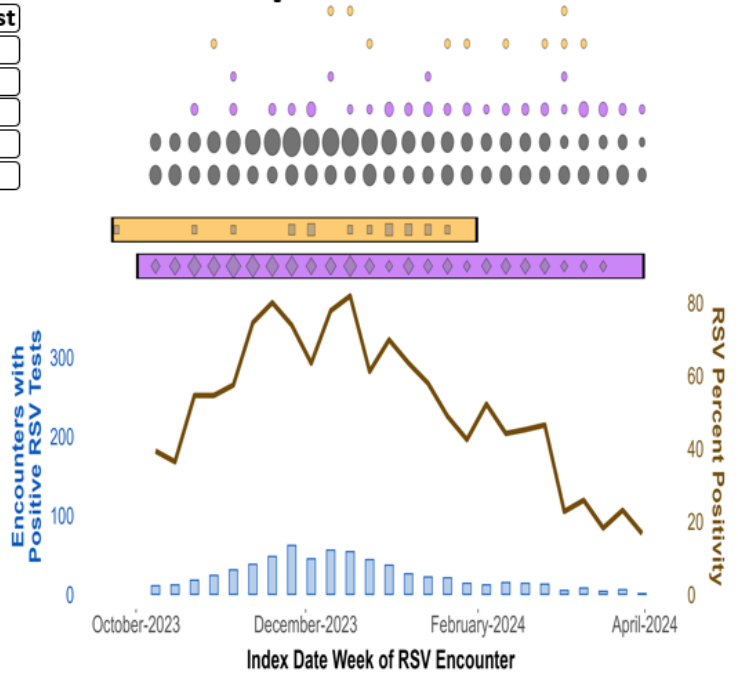
ED Encounters



Maternal RSV Vaccine / Positive RSV Test
Maternal RSV Vaccine / Negative Test
Nirsevimab / Positive RSV Test
Nirsevimab / Negative RSV Test
Unimmunized / Positive Test
Unimmunized / Negative Test

Maternal RSV Vaccine Administration
Nirsevimab Administration

Hospitalizations



- Encounters by immunization status and RSV test result§
- Dates of nirsevimab administration among included encounters§
- Dates of maternal RSV vaccine receipt among included encounters§
- RSV percent positivity
- Counts of positive RSV encounters

§ Size of shape corresponds to number of encounters or immunizations on a given date

* ≥1 ICD-10 discharge diagnosis code indicating RSV-like illness (RLI)
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ED Encounters and Hospitalizations for RSV-like illness* among infants in their first RSV season, by immunization and RSV positivity status – VISION, October 2023 – March 2024

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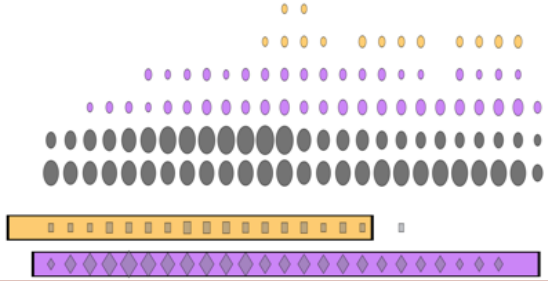

Maternal RSV Vaccine / Positive RSV Test
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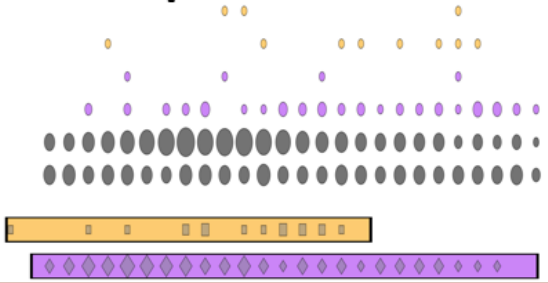
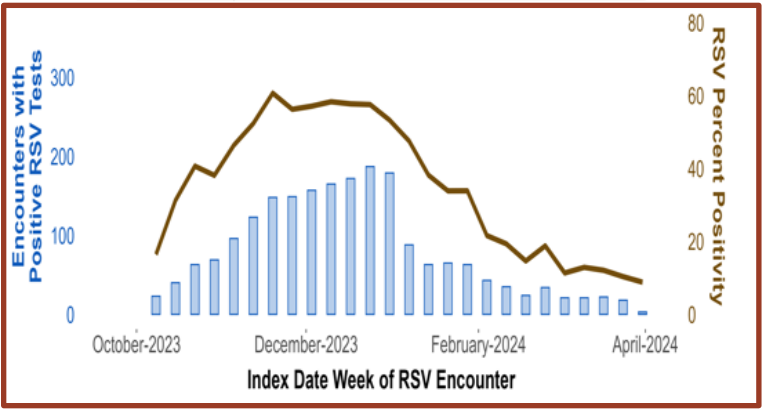
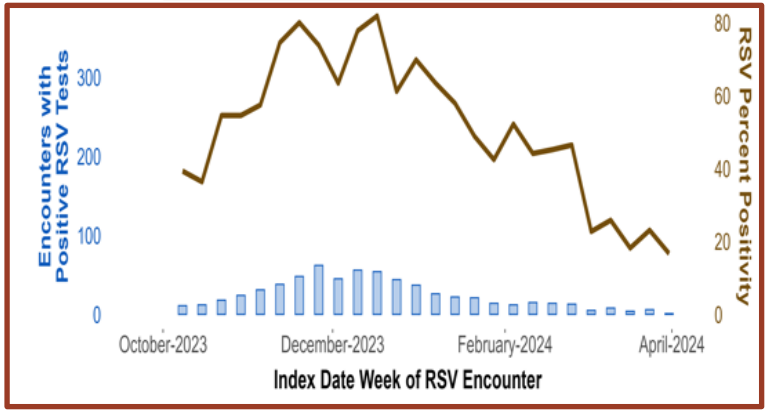
Maternal RSV Vaccine Administration
Nirsevimab Administration



Hospitalizations





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ED = Emergency Department

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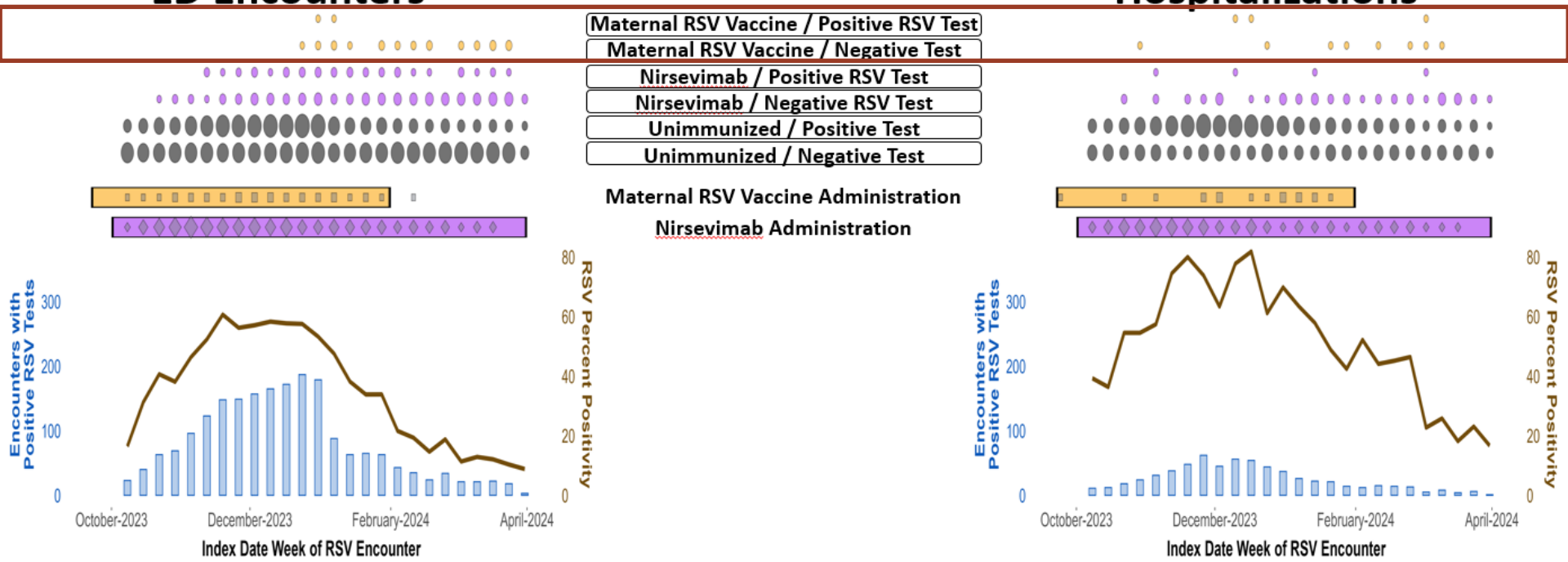

Encounters by immunization status and RSV test result§

Dates of nirsevimab administration among included encounters§

Dates of maternal RSV vaccine receipt among included encounters§

RSV percent positivity

Counts of positive RSV encounters

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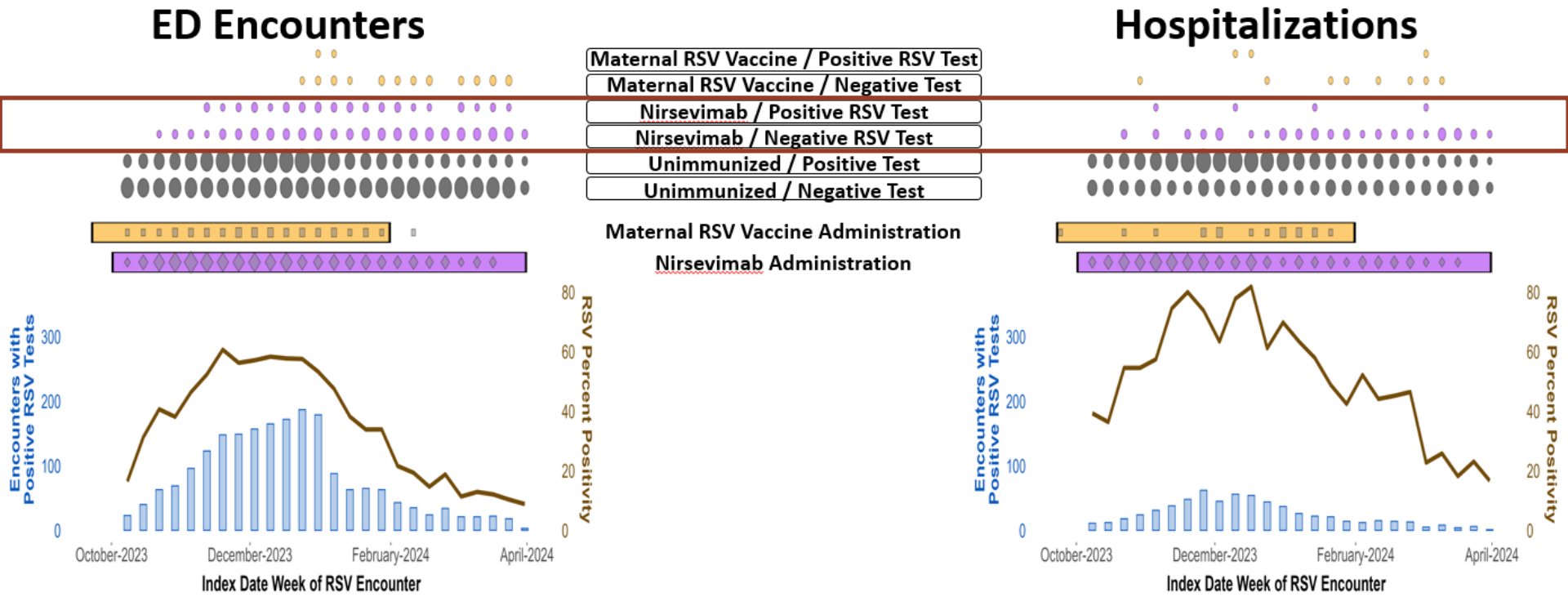

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Test-negative design (TND) analysis of first season nirsevimab product effectiveness (PE) against RSV-associated ED encounters and hospitalization – VISION, October 8, 2023 – March 31, 2024

- **Population:**
  - Infants aged <8 months as of October 1, 2023, or born after October 1, 2023
  - Visiting a participating ED for or hospitalized with RSV-like illness (RLI)
  - With RSV test result within 10 days before or 72 hours after encounter
    - **Cases:** RLI with *positive* RSV antigen or NAAT test*
    - **Controls:** RLI with negative RSV NAAT test

- **Study period:** October 8, 2023 – March 31, 2024

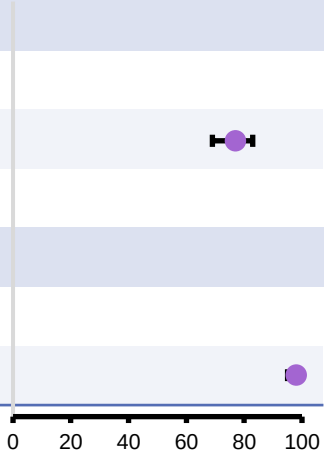
- **Exclusion criteria:**
  - Children aged <7 days
  - Children born after September 22, 2023, without linkage to maternal records
  - Evidence of maternal RSV vaccination or palivizumab administration
  - Receipt of unrecommended nirsevimab dose(s)†
  - <7 days between nirsevimab dose and RLI encounter
  - Indeterminate RSV test result

- **Statistical Analysis:** Adjusted OR comparing odds of immunization‡ among cases vs. controls estimated using multivariable logistic regression models, adjusting for age, race and ethnicity, sex, calendar day (days since Oct 8, 2023), and geographic region → **PE = (1-aOR) X 100%**

*RSV-positive encounters with positive SARS-CoV-2 and/or influenza test result were (i.e., coinfections) were excluded.
† Unrecommended nirsevimab dose(s) defined as: nirsevimab doses administered on or before October 1, 2023, and receipt of >1 nirsevimab dose. Nirsevimab doses in older children may be administered as 2 injections on the same day; this was considered one 'dose'.
‡Immunization defined as one nirsevimab dose ≥7 days prior to encounter index date.
NAAT = nucleic acid amplification test | OR = odds ratio | aOR = adjusted odds ratio | PE = product effectiveness

First season nirsevimab product effectiveness (PE) against RSV-associated ED encounters and hospitalization – VISION, October 8, 2023 – March 31, 2024

Outcome | Nirsevimab dosage pattern	Total encounters	RSV-positive encounters N (Row %)	Median days since dose (IQR)	Adjusted PE (95% CI)*
RSV-associated ED encounter				
No nirsevimab doses	4,610	1,988 (43)	N/A	ref
Nirsevimab, ≥7 days prior	442	63 (14)	53 (27-84)	77 (69-83)
RSV-associated hospitalization				
No nirsevimab doses	927	601 (65)	N/A	ref
Nirsevimab, ≥7 days prior	93	4 (4)	48 (25-84)	98 (95-99)



Nirsevimab was effective against RSV-associated ED encounters and hospitalization among infants in their first RSV season.

*Odds ratio used to calculate VE estimate was adjusted for age, race and ethnicity, sex, calendar day (days since Oct 8, 2023), and geographic region
N/A = not applicable | ref = reference group

Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus–Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season — New Vaccine Surveillance Network, October 2023–February 2024

Heidi L. Moline, MD[1]; Ayzsa Tannis, MPH[1]; Ariana P. Toepfer, MPH[1]; John V. Williams, MD[2,3]; Julie A. Boom, MD[4,5]; Janet A. Englund, MD[6]; Natasha B. Halasa, MD[7]; Mary Allen Staat, MD[8,9]; Geoffrey A. Weinberg, MD[10]; Rangaraj Selvarangan, PhD[11]; Marian G. Michaels, MD[2,3]; Leila C. Sahni, PhD[4,5]; Eileen J. Klein, MD[6]; Laura S. Stewart, PhD[7]; Elizabeth P. Schlaudecker, MD[8,9]; Peter G. Szilagyi, MD[10]; Jennifer E. Schuster, MD[12]; Leah Goldstein, MPH[1]; Samar Musa, MPH[2,3]; Pedro A. Piedra, MD[4,5]; Danielle M. Zerr, MD[6]; Kristina A. Betters, MD[7]; Chelsea Rohlfs, MBA[9]; Christina Albertin, MPH[10]; Dithi Banerjee, PhD[12]; Erin R. McKeever, MPH[1]; Casey Kalman, MPH[1]; Benjamin R. Clopper, MPH[1]; New Vaccine Surveillance Network Product Effectiveness Collaborators; Meredith L. McMorrow, MD[1,*]; Fatimah S. Dawood, MD[1,*]

Update to Moline HL, Tannis A, Toepfer AP, et al. Early Estimate of Nirsevimab Effectiveness for Prevention of Respiratory Syncytial Virus–Associated Hospitalization Among Infants Entering Their First Respiratory Syncytial Virus Season — New Vaccine Surveillance Network, October 2023–February 2024. MMWR Morb Mortal Wkly Rep 2024;73:209–214. DOI: http://dx.doi.org/10.15585/mmwr.mm7309a4

New Vaccine Surveillance Network (NVSN)

NVSN is a prospective, population-based surveillance network for pediatric acute respiratory illness (ARI) at 7 U.S. medical centers.

Children <18 years of age with ARI are enrolled year-round in the **outpatient, urgent care, emergency department (ED), and hospital** settings.

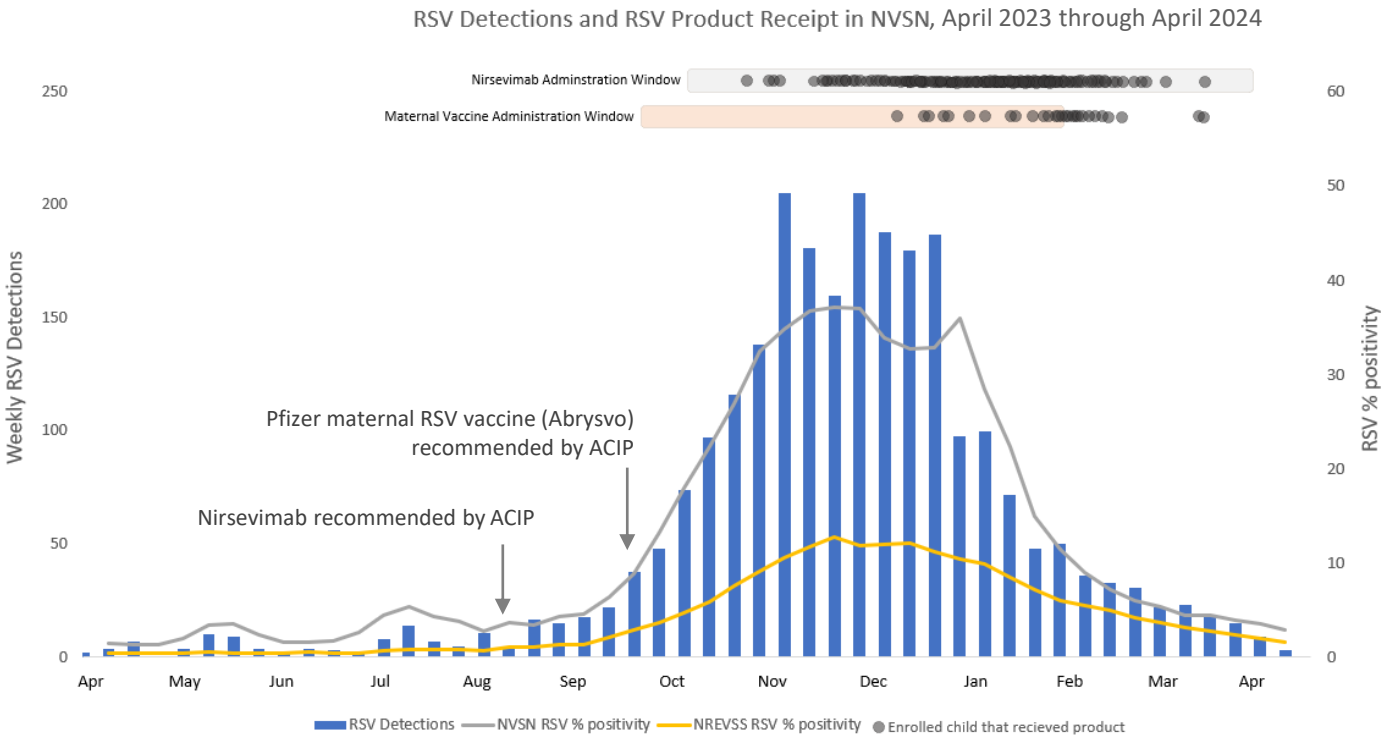
Surveillance Objectives:

- Determine the **etiology and burden** of laboratory-confirmed acute viral respiratory diseases in children
- Characterize the **clinical and epidemiologic factors** of pediatric ARI and associated syndromes
- Evaluate **vaccine effectiveness (VE)** using a test-negative design (TND) and impact of vaccines and other immunoprophylaxis products.

NVSN Data Collection

- **Caregiver interview**
  - Race and ethnicity, preterm status, date of symptom onset, breastfeeding status
- **Specimens**
  - Mid-turbinate nasal swab collected from all children for RSV testing by reverse-transcription polymerase chain reaction; results of both clinical and surveillance testing are collected
  - Sequencing of RSV-positive specimens to monitor for substitutions in the nirsevimab binding site
- **Medical chart abstraction**
  - Age, underlying medical conditions, clinical course of illness, insurance status
- **Immunization status (nirsevimab, palivizumab, and maternal RSV vaccine)**
  - Ascertained by parent report and confirmed with state immunization information system, electronic health record, or birth record

During 2023-2024, RSV prevention products became available in the U.S. after the RSV season started



ACIP = Advisory Committee on Immunization Practices
NVSN = New Vaccine Surveillance Network
NREVSS = National Respiratory and Enteric Virus Surveillance System

All NVSN sites had **some nirsevimab availability by mid-October**

Among 2,383 infants in their first RSV season

- 11.1% received nirsevimab
- 2.2% received palivizumab
- 3.4% (of 1,542 infants <6 months of age at enrollment) had history of maternal RSV vaccination

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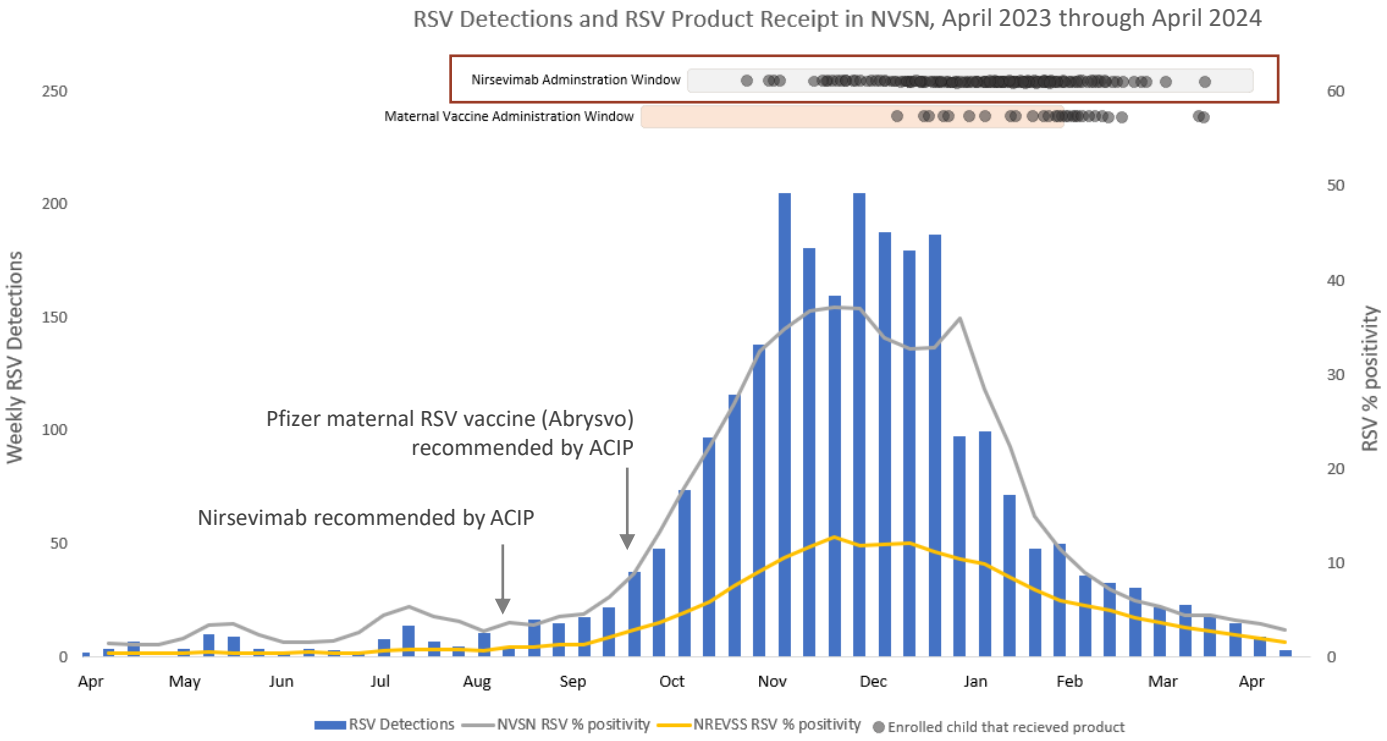

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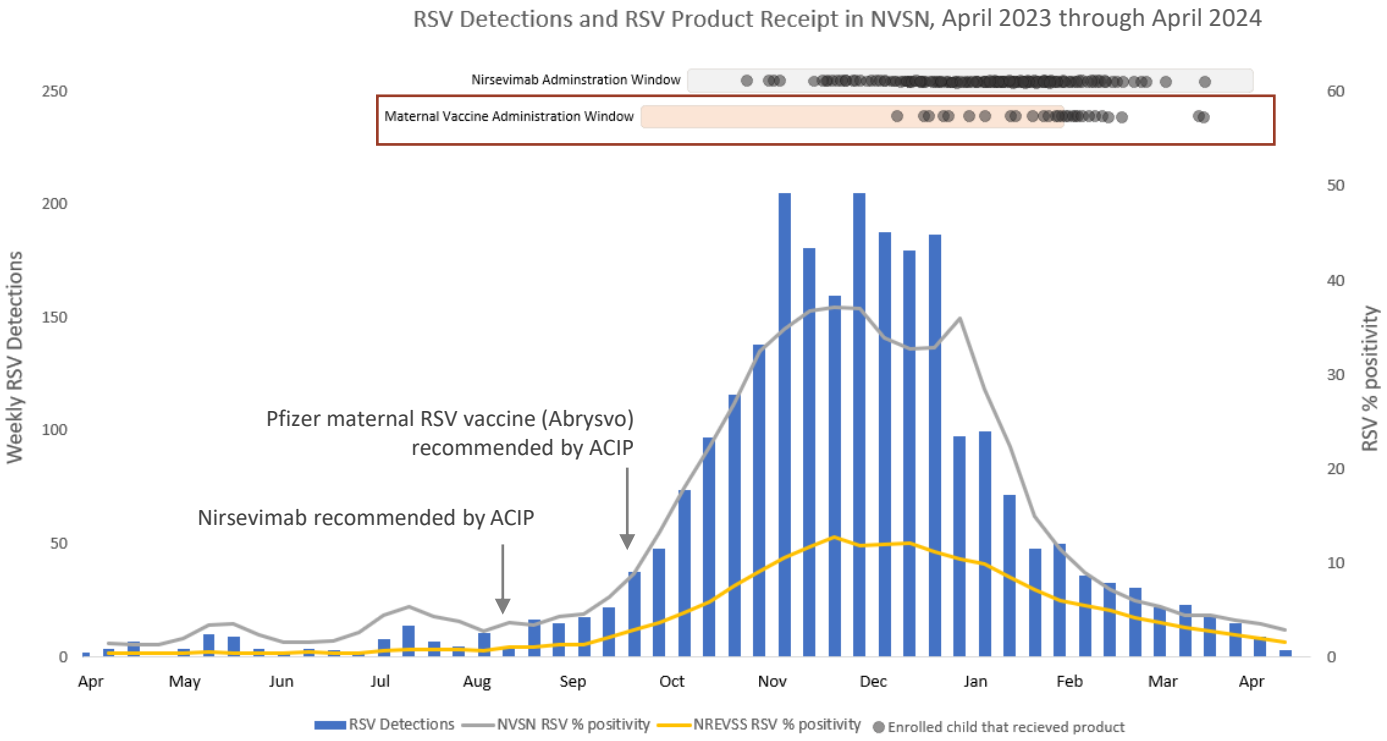

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Test-negative design (TND) analysis of first season nirsevimab product effectiveness (PE) against medically attended RSV-associated ARI episodes and RSV-associated hospitalization – NVSN, October 2023 – March 2024

- **Population:**
  - Infants <8 months as of October 1, 2023, or born after October 1, 2023
  - Enrolled from participating medical center
  - ARI*
    - **Case patients** – children with medically attended ARI who tested positive for RSV by surveillance or clinical testing
    - **Control patients** – children with medically attended ARI who tested negative for RSV by surveillance or clinical testing

- **Study period:** October 2023 – March 2024†

- **Exclusion criteria:**
  - Chart review incomplete for underlying conditions, preterm status, insurance status, highest level of care, clinical course of illness
  - Immunization status unverified for nirsevimab and palivizumab receipt and maternal RSV vaccination
  - Receipt of palivizumab or history of maternal RSV vaccination during pregnancy
  - Unknown or inconclusive RSV test result
  - Receipt of nirsevimab <7 days prior to ARI symptom onset

- **Statistical Analysis:** Adjusted OR comparing odds of immunization‡ among cases vs. controls estimated using multivariable logistic regression models, adjusting for site, age in months, month of enrollment, and presence of >1 high-risk medical condition for severe RSV disease → **PE = (1-aOR) X 100%**

*Acute respiratory illness (ARI) defined as >1 of the following sign/symptoms: fever, cough, earache, nasal congestion, runny nose, sore throat, vomiting after coughing, shortness of breath (rapid or shallow breathing), wheezing, apnea, or apparent life-threatening event or brief resolved unexplained event

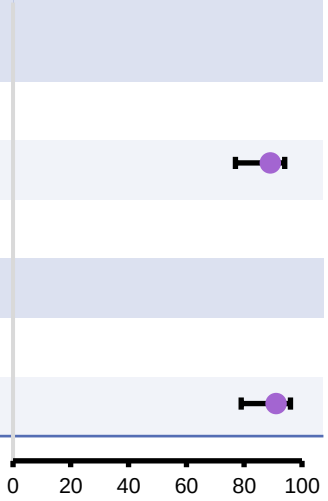
†State-level RSV RT-PCR percent positivity thresholds of 3% were used to define the beginning and end weeks of the analysis by site

‡Immunization defined as one nirsevimab dose ≥7 days prior to symptom onset.

OR = odds ratio | aOR = adjusted odds ratio | PE = product effectiveness

First season nirsevimab product effectiveness (PE) against medically attended RSV-associated ARI and RSV-associated hospitalization – NVSN, October 2023 – March 2024*

Outcome | Nirsevimab dosage pattern	Total encounters	RSV-positive encounters N (Row %)	Median days since dose (IQR)	Adjusted PE (95% CI)†
Medically Attended RSV-associated ARI episode‡				
No nirsevimab doses	1,575	755 (48)	N/A	ref
Nirsevimab, ≥7 days prior§	120	9 (8)	42 (21-73)	89 (77-94)
RSV-associated hospitalization				
No nirsevimab doses	807	526 (65)	N/A	ref
Nirsevimab, ≥7 days prior	63	6 (10)	38 (15-67)	91 (79-96)



Nirsevimab was effective against medically attended RSV-associated ARI episodes and RSV-associated hospitalization.

*State-level RSV RT-PCR percent positivity thresholds of 3% were used to define the beginning and end weeks of the analysis by site

†Multivariable logistic regression models compared the odds of vaccination among RSV case and control patients while adjusting for site, age in months, month of enrollment, and presence of >1 high-risk medical condition for severe RSV disease.

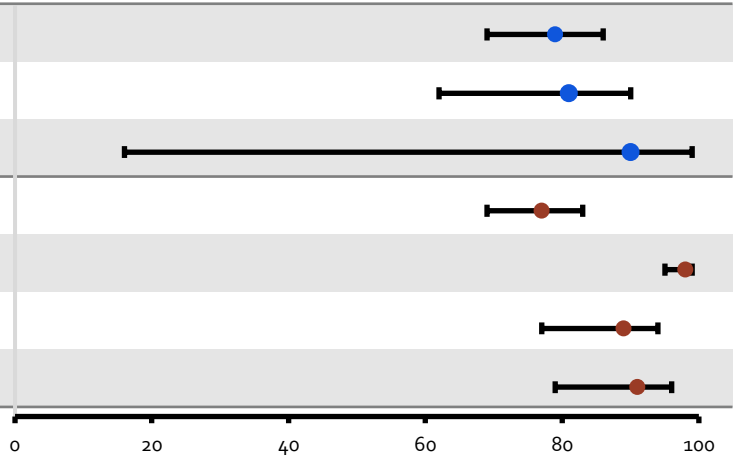
§Immunization defined as one nirsevimab dose ≥7 days prior to symptom onset.

ARI = acute respiratory illness | N/A = not applicable | ref = reference group

Summary of US data

Observational data indicate nirsevimab is working as expected (vs. RCT results) during the first RSV season after approval among infants in their first RSV season

Outcome/Analysis	Vaccine efficacy/effectiveness (%)
Clinical trial, RSV-associated LRTI	79 (69-86)
Clinical trial, RSV-associated LTRI with hospitalization	81 (62-90)
Clinical trial, RSV-associated LRTI with ICU admission	90 (16-99)
VISION, RSV-associated emergency department visits	77 (69-83)
VISION, RSV-associated hospitalization	98 (95-99)
NVSN, medically attended RSV-associated ARI episode	89 (77-94)
NVSN, RSV-associated hospitalization	91 (79-96)



Results may not be comparable across studies due to differences in outcome definitions, timing, and other factors.

https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm

RCT = randomized clinical trial | ARI = acute respiratory illness

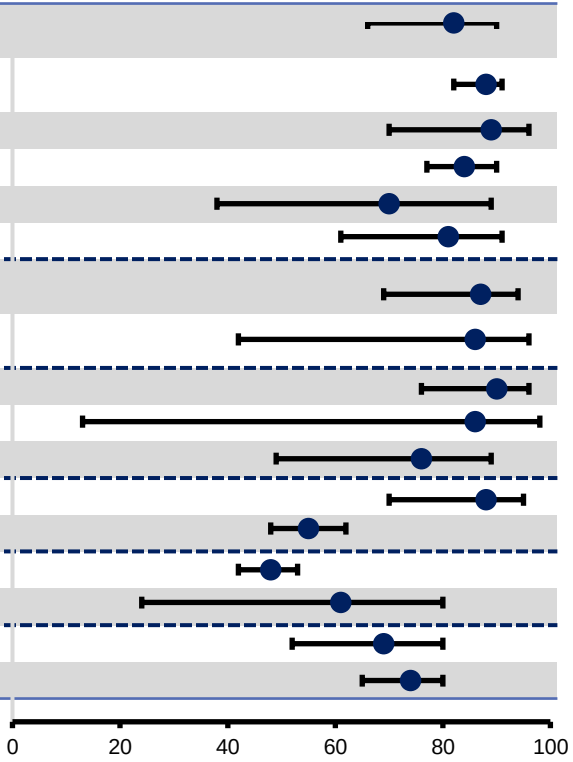
Limitations of test-negative design (TND) analyses of first season nirsevimab product effectiveness (PE), October 2023 – March 2024

- **High product effectiveness should be interpreted with caution**
  - Short interval from administration to respiratory illness onset
  - Unable to assess duration of protection during the 2023-2024 RSV season
- **Residual confounding was possible**
- **Misclassification of RSV immunization status was possible**
- **These results only reflect PE among infants in their first RSV season (not among children at increased risk in their second RSV season)**
- **VISION:**
  - Cases may have sought care for something other than RSV
  - All RSV testing was clinician-directed
  - EHR data may not fully capture all underlying medical conditions, which may be associated with likelihood of immunization and risk of severe RSV disease
- **NVSN:**
  - May not be nationally representative

Nirsevimab effectiveness – evidence from literature

Nirsevimab product effectiveness (PE) among infants in their first RSV season – Data* from Spain and France

Study Endpoint	PE (95% CI)†
RSV-associated hospitalization	82 (66 - 90)
	88 (82 - 91)
	89 (70 - 96)
	84 (77 - 90)†
	70 (38 - 89) †
	81 (61 - 91)
RSV-associated LRTI requiring oxygen	87 (69 – 94)
	86 (42 - 96)
RSV-associated ICU admission	90 (76 – 96)
	86 (13 – 98)
	76 (49 – 89)
RSV and/or bronchiolitis attended in the ED	88 (70 – 95)
	55 (48 – 62)
Bronchiolitis or viral pneumonia attended in primary care setting	48 (42 – 53)
	61 (24 – 80)
Medically attended RSV infection	69 (52 – 80)
	74 (65 – 80)



*References provided on backup slide 32.
†PE estimates generated from the same study, using different methods.
LRTI = lower respiratory tract infection | ICU = intensive care unit

Conclusions

Conclusions

- **Nirsevimab was effective against RSV-associated ED encounters and hospitalization among infants in their first RSV season during the 2023-2024 RSV season**

- **Due to timing of authorization/recommendation of RSV prevention products and RSV activity during the 2023-2024 RSV season:**
  - US-based analyses may be subject to residual confounding due to prioritization of nirsevimab doses
  - Short time between nirsevimab administration and outcomes, limiting ability to assess duration of protection
  - Limited ability to assess effectiveness of maternal RSV vaccines

- **Ongoing monitoring of post-licensure nirsevimab and maternal RSV vaccine effectiveness will continue**

Acknowledgements

CDC
Amadea Britton
Allison Ciesla
Benjamin Clopper
Fatimah S. Dawood
Monica Dickerson
Katherine Fleming-Dutra
Sascha Ellington
Shikha Garg
Leah Goldstein
Casey Kalman
Amber Kautz
Ruth Link-Gelles
Josephine Mak
Erin McKeever
Meredith McMorrow
Morgan Najdowski
Lakshmi Panagiotakopoulos
Caitlin Ray
Ayzsa Tannis
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Ariana Toepfer
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Patrick Mitchell
Sarah Reese
Elizabeth Rowley
Janet Watts
Zack Weber

Columbia University
Karthik Natarajan

HealthPartners
Malini B. DeSilva

Intermountain Health
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Hospitalized population comparison for VISION and NVSN

Characteristic	VISION, no. (col %)			NVSN, no. (col %)		
	Total no. of patients	RSV case-patients	RSV control-patients	Total no. of patients	RSV case-patients	RSV control-patients
All hospitalizations	1,020	605	415	870	532	338
Median age, months (IQR)	4 (1-7)	3 (1-6)	4 (1-7)	3 (1-6)	3 (1-5)	3 (1-6)
Gestational age						
Preterm (<37 weeks)	133 (13)	59 (10)	74 (18)	180 (21)	102 (19)	78 (23)
Term (≥37 weeks)	508 (50)	323 (53)	185 (45)	687 (79)	428 (81)	259 (77)
Unknown	379 (37)	223 (37)	156 (38)	3 (0)	2 (0)	1 (0)
Race/ethnicity						
Black or African American, Non-Hispanic	77 (8)	48 (8)	29 (7)	113 (13)	56 (11)	57 (17)
White, Non-Hispanic	437 (43)	268 (44)	169 (41)	390 (45)	266 (50)	124 (37)
Hispanic or Latino	394 (39)	234 (39)	160 (39)	248 (29)	146 (27)	102 (30)
Other, Non-Hispanic	75 (7)	33 (6)	42 (10)	107 (12)	58 (11)	49 (14)
Unknown	37 (4)	22 (4)	15 (4)	12 (1)	6 (1)	6 (2)
High risk conditions for severe RSV disease						
None	796 (78)	529 (87)	267 (64)	832 (96)	520 (99)	281 (83)
≥1	224 (22)	76 (13)	148 (36)	38 (4)	12 (2)	26 (8)
Immunization status						
No nirsevimab	927 (91)	601 (99)	326 (79)	807 (93)	526 (99)	281 (83)
Nirsevimab, ≥7 days earlier	93 (9)	4 (1)	89 (21)	63 (7)	6 (1)	57 (17)

Empirical studies* on nirsevimab product effectiveness (PE) among infants in their first RSV season

Citation	Country	Sample Size (Number of Infants)	Study Design	PE (95% Confidence Interval)
Ares-Gomez et al., 2024	Spain	10,259	Prospective Cohort	Hospitalization for RSV-related LRTI: 82% (95% CI: 66% - 90%) Severe RSV-related LRTI requiring oxygen support: 87% (95% CI: 69% - 94%) All-cause LRTI hospitalizations: 69% (56% - 78%) All-cause hospitalizations: 66% (56% - 74%)
Coma et al., 2024	Spain	26,525	Retrospective Cohort	Hospital admission for RSV-related disease: 88% (95% CI: 82% - 91%) Hospital ER visits due to bronchiolitis: 55% (95% CI: 48% - 62%) Medically attended RSV infection: 69% (95% CI: 52% - 80%) Primary care attended bronchiolitis: 48% (95% CI: 42% - 53%) Viral pneumonia diagnosed in primary care: 61% (95% CI: 24% - 80%) ICU admission for RSV-related disease: 90% (95% CI: 76%- 96%)
Estrella-Porter et al., 2024	Spain	27,362	Retrospective Cohort	Medically attended RSV infection: 74% (95% CI: 65% - 80%)
Ezpeleta et al., 2024	Spain	1,177	Prospective Cohort	Hospitalization due to RSV: 89% (95% CI: 70% - 96%) RSV infection attended in the ER: 88% (95% CI: 70% - 95%) RSV ICU admission: 86% (95% CI: 13% - 98%)
Lopez-Lacort et al., 2024	Spain	166	Screening and Test negative case control	RSV-LRTI hospital admission (pooled data across several regions): Screening methods: 84% (95% CI: 77% - 90%) Test negative design: 70% (95% CI: 38% - 89%)
Paireau et al., 2024	France	288	Test negative case control	RSV bronchiolitis hospitalized In the pediatric ICU: 76% (95% CI: 49% - 89%)
Aguera et al., 2024	Spain	181	Test negative case control	Hospitalization for RSV-related LRTI: 81% (95% CI: 61% - 91%) Severe RSV-related LRTI requiring NIV/CMV: 86% (95% CI: 42% - 96%)

*Published during June 20, 2023, through June 21, 2024

LRTI = lower respiratory tract infection | ER = emergency room | ICU = intensive care unit | CI = confidence interval | NIV: noninvasive ventilation | CMV: continuous mandatory ventilation