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Monitoring the Safety of Nirsevimab in Infants Birth through <8 Months

Preliminary Results from the Vaccine Safety Datalink for the 2024-2025 Season

Matthew F. Daley, MD

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Disclosures and Acknowledgments

- No conflicts of interest
- Presenting on behalf of the Vaccine Safety Datalink (VSD) team

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Background

Nirsevimab Overview

- Long-acting monoclonal antibody, licensed for prevention of lower respiratory tract disease in infants caused by RSV
- Recommendations for use:
  - All infants aged birth through <8 months (if no RSV vaccine during pregnancy)
  - High-risk infants aged 8-19 months
- High efficacy in phase 3 trial, high effectiveness post-licensure
- Severe shortage during 2023-2024 season
- RSV prevention (nirsevimab or vaccine): 72% uptake in VSD

Ref: 1) Muller WJ et al, N Engl J Med 2023;388(16):1533-1534; 2) Jones JM et al, MMWR 2023;72(34):920-925.
3) Moline HL et al, JAMA Pediatr 2025;179(2):179-187. 4) Irving SA et al, Pediatrics 2025;155(6):e2024070240.

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Nirsevimab Safety, Clinical Trials

- Across 3 randomized trials: n=3,184 received nirsevimab, n=1,284 received placebo, n=304 received palivizumab
- Adverse events generally balanced among infants who received nirsevimab versus comparator
- Adverse events of special interest included 7 nirsevimab-exposed infants with rashes, primarily papular or maculopapular
- No anaphylaxis, no serious hypersensitivity-type reactions reported
- No immune complex diseases reported

Ref: 1) Muller WJ et al, N Engl J Med 2023;388(16):1533-1534. 2) Mankad VS et al, Pathogens 2024;13(6):503.

Post-Licensure Safety of Nirsevimab

- Additional post-licensure safety data needed, including assessment of rare adverse events, and when nirsevimab given during routine care in a general patient population
- Objective: To investigate the safety of nirsevimab, by examining pre-specified adverse events among nirsevimab recipients in the Vaccine Safety Datalink (VSD)
- Nirsevimab is a passive immunization; CDC and ACIP requested that VSD evaluate its safety

Vaccine Safety Datalink (VSD)

- Collaboration between CDC and 13 healthcare organizations
- Observational; uses electronic health record (EHR) data
- Has ~15.5 million individuals overall; annual birth cohort ~115,000
- Data characteristics:
  - Electronic health records, claims, immunization information systems
  - Diagnoses, vaccines, medications ordered
  - Inpatient, emergency departments, outpatient
- VSD applies a range of analytic methods to address confounding, including self-controlled designs

Ref: 1) McNeil MM et al, Vaccine. 2014 Sep 22;32(42):5390-8.

VSD in 2025

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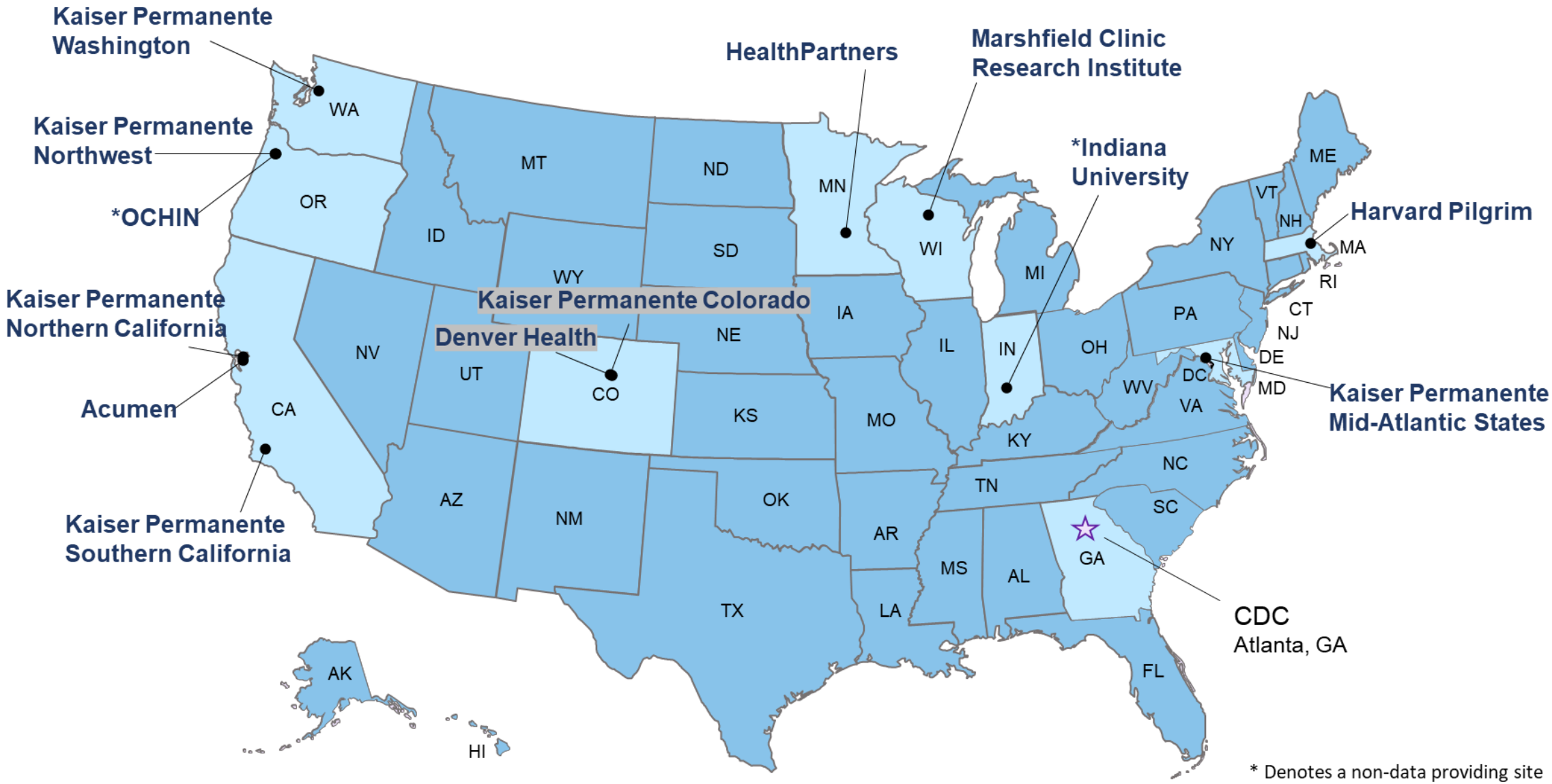

* Denotes a non-data providing site

Safety Results, VSD, 2023-2024 Season

- Received nirsevimab, n=36,719
- Adverse events monitored, self-controlled risk interval (SCRI):
  - All analyses stratified by age group (neonates; infants)
  - Seizures, ITP, drug reaction, fever or sepsis (neonate cohort only)
  - None showed elevated risk
- Exposure-dependent events: monitored case counts
  - Anaphylaxis: no cases detected
  - Non-anaphylactic allergic reactions: urticaria, often same day as nirsevimab

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Methods

Methods Overview

- Setting: all VSD data-contributing sites
- Population: all infants 0 days through <8 months of life who received nirsevimab between October 1, 2024, and February 1, 2025
- Same-day vaccines: study included all nirsevimab-exposed infants, regardless of whether they received vaccines same day as nirsevimab
- Health insurance enrollment: through control window
- Study design: primarily used SCRI
- Excluded infants born to someone who received RSV vaccine during pregnancy

Self-Controlled Designs in Safety Studies

- Self-controlled risk interval is a form of self-controlled case series study
- Commonly used design in vaccine safety studies
- Rationale: exposed (to vaccine, or to nirsevimab) often differ in important characteristics from unexposed; these characteristics typically not measured in electronic health record (EHR) data and can confound safety assessments
- These are within-individual designs; control for measured and unmeasured confounders that do not vary over time; example, a prevalent chronic condition

Ref: 1) Nie X et al, Expert Rev Vaccines 2022;21(3):313-324. 2) Weldeselassie YG et al, Epidemiol Infect 2011;139(12):1805-17. 3) Li R et al, J Biopharm Stat 2016;26(4):686-93. 4) Bots SH et al, Am J Epidemiol. 2025;194(1):208-219.

Age Effects

- Diagnoses in first month of life often related to pregnancy, delivery, newborn-specific conditions
- Health care utilization different in first month of life
- Lags in health insurance enrollment
- With the exception of birth dose of hepatitis B vaccine, earliest all other vaccines recommended: 38 days of age
- Separate safety analyses:
  - Newborns: defined as 0 days through 37 days of age
  - Infants (out of newborn period): 38 days through <8 months of age

Adverse Events Monitored

- Rationale for pre-specified adverse events:
  - Biologic plausibility
  - Clinical trial data
  - Expert opinion
  - Feedback from ACIP RSV Work Group
- Identified based on ICD-10 diagnosis codes, laboratory data (platelet counts)

Outcomes for Nirsevimab Safety Surveillance Study

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Adverse event	Design
Seizures	Self-controlled risk interval
Immune thrombocytopenia (ITP)	Self-controlled risk interval
Drug reaction	Self-controlled risk interval
Fever or sepsis (neonates only)	Self-controlled risk interval
Anaphylaxis	Counts monitored
Non-anaphylactic serious allergic reaction	Counts monitored
Autoimmune, immune complex disease	Outcomes rare, may have long latency; examine as case-control at end of surveillance

Self-Controlled: Risk and Control Windows

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Adverse event	Age at nirsevimab administration	Risk window (days)	Control window (days)	Setting
Seizure	0-37 days	0-7	8-21	Inpatient, ED
	38 days to <8 months	0-7	8-21	Inpatient, ED
Immune thrombocytopenia	0-37 days	1-21	22-42	Inpatient, ED, outpatient
	38 days to <8 months	1-21	22-42	Inpatient, ED, outpatient
Drug reaction	0-37 days	0-7	8-15	Inpatient, ED
	38 days to <8 months	0-7	8-15	Inpatient, ED
Fever or sepsis (neonates only)	0-37 days	0-7	8-15	Inpatient, ED

Exposure-Dependent Events: Case Counts Monitored

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Adverse event	Age at nirsevimab administration	Risk window (days)	Setting	Manual review
Anaphylaxis	0-37 days	0-2	Inpatient, ED	All cases will be manually reviewed
	38 days to <8 months	0-2	Inpatient, ED	All cases will be manually reviewed
Non-anaphylactic allergic reactions	0-37 days	0-7	Inpatient, ED	Cases reviewed if indicated
	38 days to <8 months	0-7	Inpatient, ED	Cases reviewed if indicated

Outcomes for Nirsevimab Safety Surveillance Study

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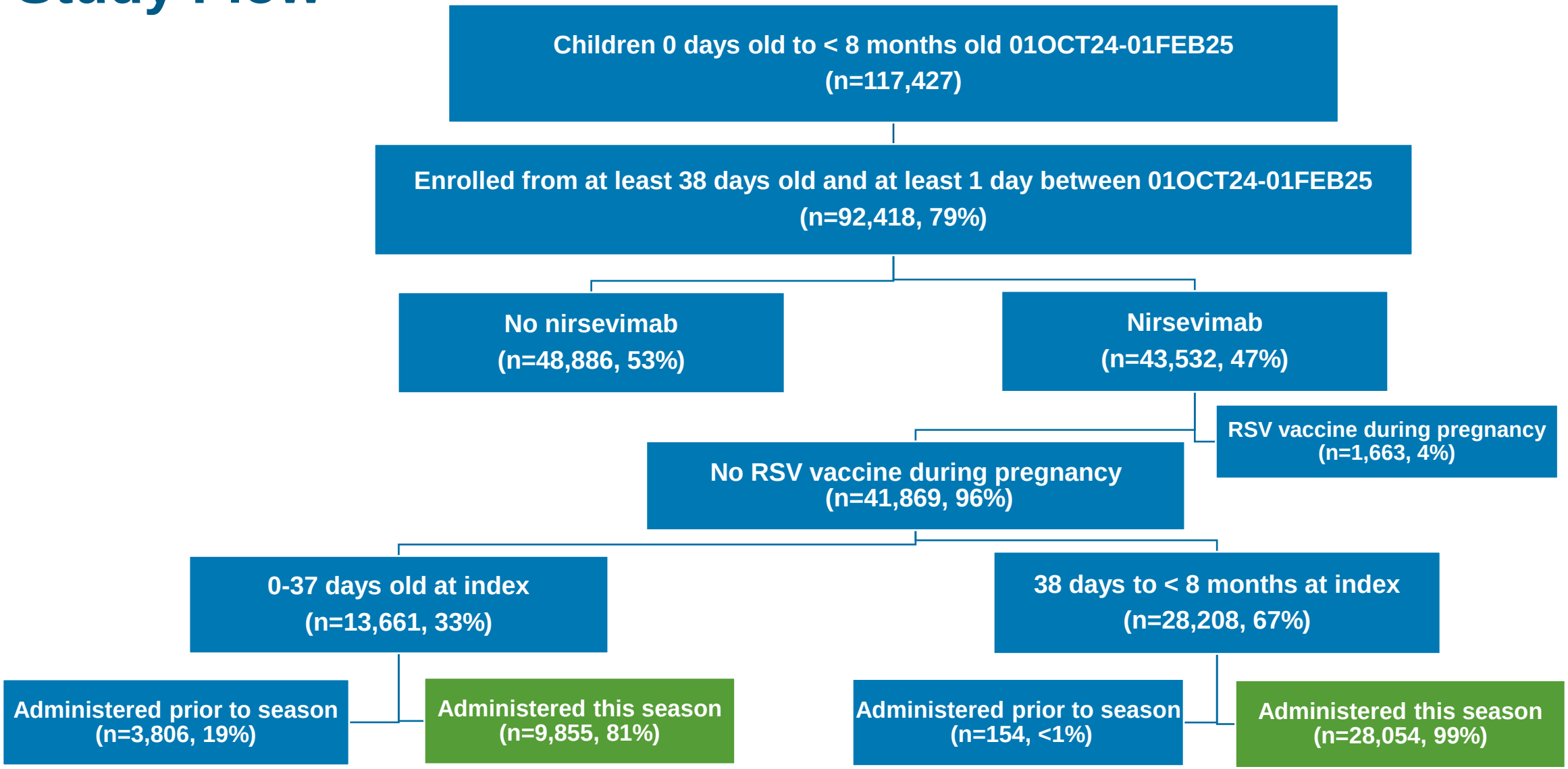
Adverse event	ICD-10 codes	Additional information
Seizure	G40, R56, P90	First episode in 30 days
Immune thrombocytopenia	D69.3, D69.6, P61.0	Also required platelets <50,000; first episode in 90 days
Drug reaction	P93, T80.22, T80.29, T80.8, T80.9	Example: “Infection following…therapeutic injection”; first episode in 30 days
Fever or sepsis (neonates only)	P36.9, R50.82, R50.83, R50.9, T81.1, T81.4	First episode in 30 days
Anaphylaxis	T80.5, T78.2, T88.6, P81.1	First episode in 30 days
Non-anaphylactic serious allergic reaction	T80.6, T78.3, L50.0, L50.1, L50.9, P83.88	First episode in 30 days

Analytic Methods: SCRI Analysis

- For each pre-specified outcome:
  - Identify cases that occur within either risk or control window
  - Two observations per individual: One per control window and risk window
  - Informative cases have outcome in one window but not the other
  - Cohort must have at least one outcome in each window to estimate effect
- Models stratified by age group
- Fixed-effects Poisson regression
  - Individual: Within person comparison across windows controls for measured and unmeasured time-invariant factors

Results

Study Flow


Children 0 days old to < 8 months old 01OCT24-01FEB25
(n=117,427)
Enrolled from at least 38 days old and at least 1 day between 01OCT24-01FEB25
(n=92,418, 79%)
No nirsevimab
(n=48,886, 53%)
Nirsevimab
(n=43,532, 47%)
RSV vaccine during pregnancy
(n=1,663, 4%)
No RSV vaccine during pregnancy
(n=41,869, 96%)
0-37 days old at index
(n=13,661, 33%)
38 days to < 8 months at index
(n=28,208, 67%)
Administered prior to season
(n=3,806, 19%)
Administered this season
(n=9,855, 81%)
Administered prior to season
(n=154, <1%)
Administered this season
(n=28,054, 99%)

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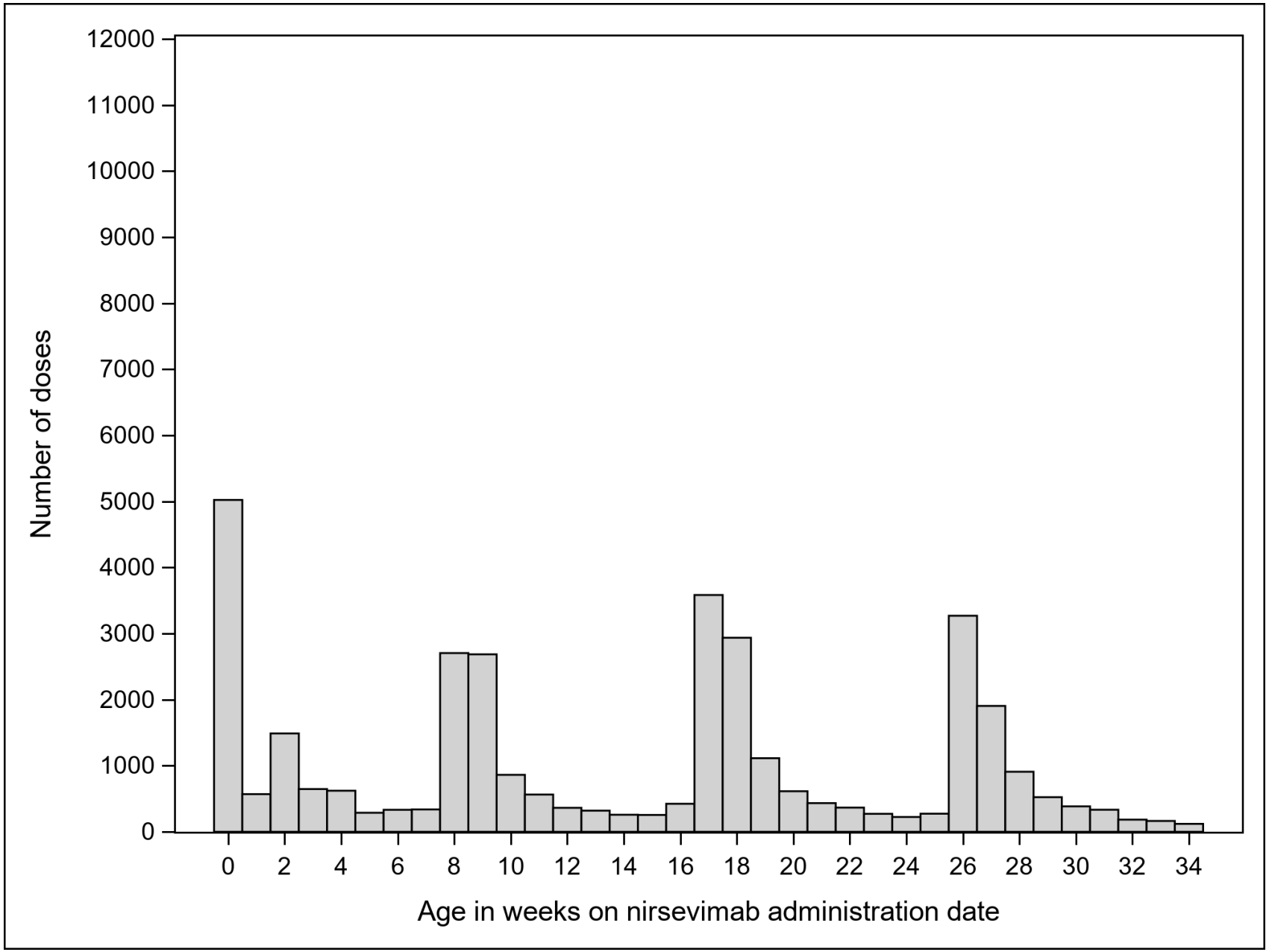
Doses by Week of Age



Note:
0 week=aged 0-6 days
1 week=aged 7-13 days
And so forth

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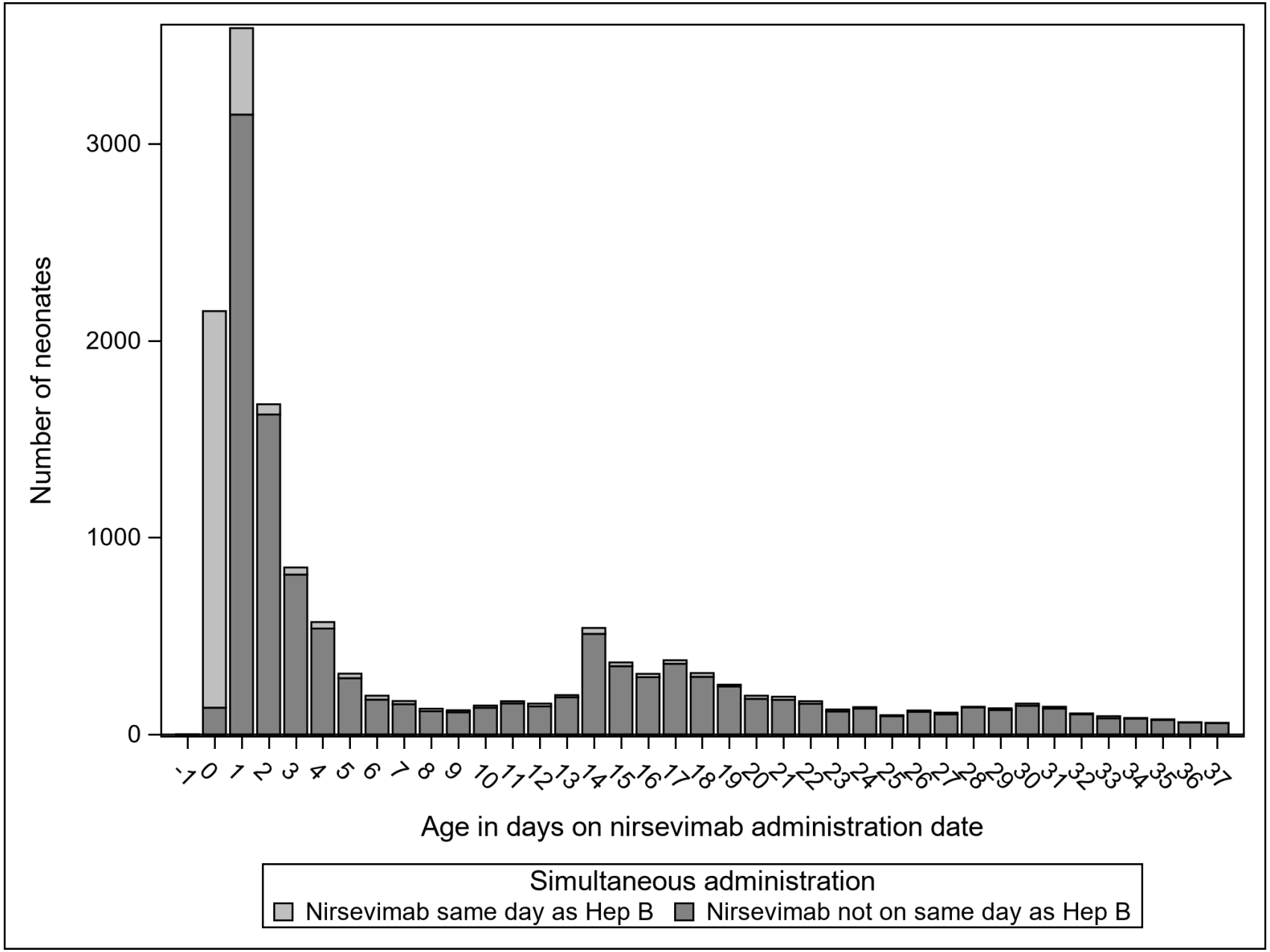
Neonate Cohort: Doses by Days of Age



Simultaneous (Same-Day) Receipt of Vaccines

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- Among neonates (0-37 days old) who received nirsevimab:
  - N=2,954 (20%): received on same day as hepatitis B vaccine
- Among infants 38 days through <8 months who received nirsevimab:
  - N=24,847 (84%): received on same day as vaccines
  - Most common combination: nirsevimab plus hepatitis B, rotavirus, DTaP, Hib, pneumococcal, and polio vaccines (n=15,252)

Self-controlled Risk Interval Results: Seizures

Adverse event	Age group	n	Risk window (days)	Control window (days)	N cases in risk window	N cases in control window	RR	95% CI	P-value
Seizures	0-37 days	9,855	0-7	8-21	4	2	3.50	0.64, 19.11	0.148
	38 days to <8 months	28,054	0-7	8-21	5	2	4.38	0.85, 22.55	0.078

- 2023-2024 season: non-significant also; no elevated risk of seizures

Self-controlled Risk Interval Results: ITP

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Adverse event	Age group	n	Risk window (days)	Control window (days)	N cases in risk window	N cases in control window	RR	95% CI	P-value
ITP	0-37 days	9,817	1-21	22-42	0	0	N/A	N/A	N/A
	38 days to <8 months	28,023	1-21	22-42	1	0	N/A	N/A	N/A

- Case definition required a diagnosis, and a platelet count below 50,000, within 21 days of each other, taking first of 2 dates

Self-controlled Risk Interval Results: Drug Reaction

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Adverse event	Age group	n	Risk window (days)	Control window (days)	N cases in risk window	N cases in control window	RR	95% CI	P-value
Drug reaction	0-37 days	9,855	0-7	8-15	0	0	N/A	N/A	N/A
	38 days to <8 months	28,054	0-7	8-15	0	0	N/A	N/A	N/A

Self-controlled Risk Interval Results: Sepsis and Fever

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Adverse event	Age group	n	Risk window (days)	Control window (days)	N cases in risk window	N cases in control window	RR	95% CI	P-value
Sepsis and fever	0-37 days	9,855	0-7	8-15	4	9	0.44	0.14, 1.44	0.18

- Only for newborn cohort (not conducted for 38 days to <8 months of age)
- Additional exploratory analysis performed to assess whether nirsevimab could cause fever, leading to sepsis workup (blood, CSF cultures)
  - An imbalance detected in cultures obtained in risk vs. control windows
  - Manual review of sample of charts showed no consistent pattern of concern (neonates typically had reasons other than fever for cultures being done)

Exposure-Dependent Events: Hypersensitivity Reactions

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Adverse event	Age group	n	Risk window (days)	N cases in risk window	Rate per 10K person month
Anaphylaxis	0-37 days	9,855	0-2	0	0
	38 days to <8 months	28,054	0-2	0	0
Other allergic reaction	0-37 days	9,855	0-7	14	54.93
	38 days to <8 months	28,054	0-7	4	5.46

- Anaphylaxis and other allergic reactions: exposure-induced outcomes; only assess within potential risk windows
- “Other allergic reaction” cases: n=17 with diagnosis code for urticaria and n=1 “serum reaction” (also for urticaria); majority on same day as nirsevimab

Summary

Summary

- Among a population of >74,000 (across two seasons) neonates and infants exposed to nirsevimab:
  - No evidence of increased risk of seizures, ITP, drug reaction, fever and sepsis
  - No cases of anaphylaxis
  - Small number of cases of non-anaphylactic allergic reactions in both years, primarily coded as urticaria
- Provides reassuring data regarding the safety profile of nirsevimab when used in routine clinical practice
- Additional data extraction needed for late-season nirsevimab use; findings preliminary

Surveillance Continues

- Three planned assessments
  - After 2023-2024 respiratory season
  - Preliminary assessment 2024-2025 season (through January, presented today)
  - End of surveillance assessment (data extraction July 2025)
- Manual record review of any anaphylaxis cases
- Planned case-control study of autoimmune and immune complex disease; however, appear to have too few cases to study this group of outcomes at present

Questions?

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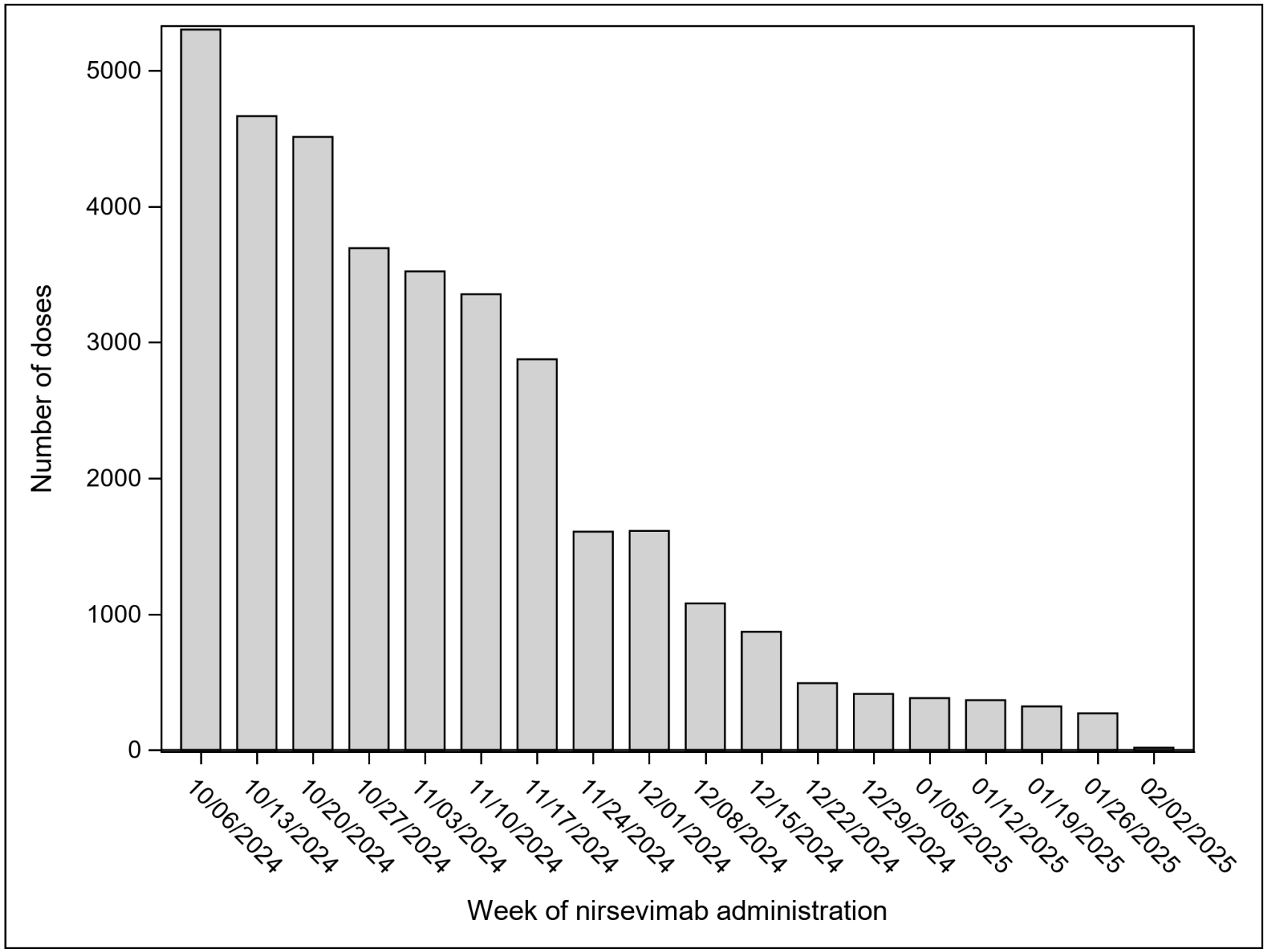
Doses by Week, All Formulations



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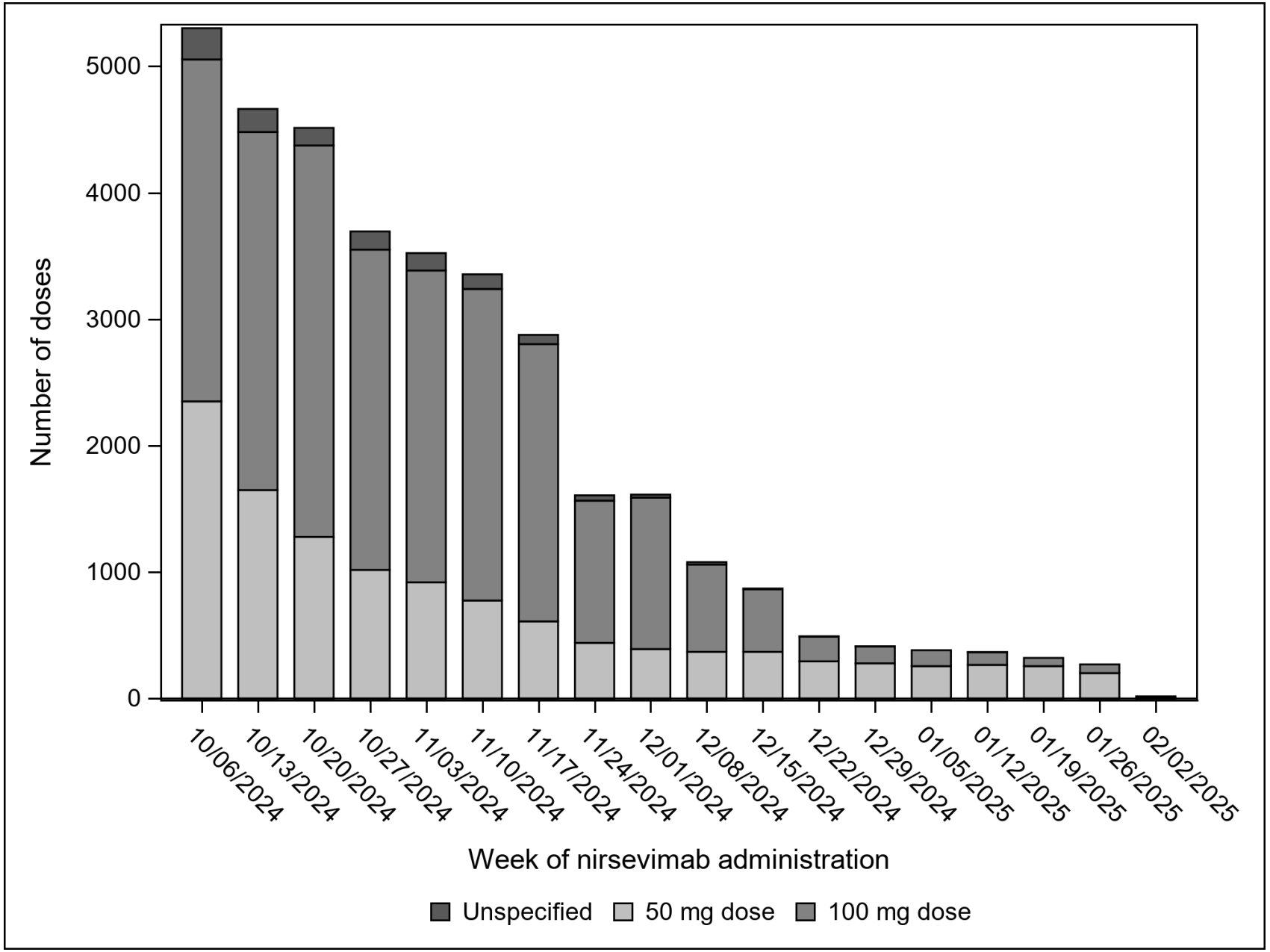
Doses by Week by Formulation



Other Nirsevimab Safety Surveillance

- SmartVax (Western Australia):
  - 4,340 parents texted hyperlink to report adverse events (27.5% responded)
  - 18 (1.5%) respondents sought medical attention within 3 days of nirsevimab
  - Symptoms at presentation included gastrointestinal issues, fatigue, local reaction, fever, refusal to feed, unsettled behavior
  - No serious adverse events reported
- Maternity department, French hospital
  - Exposed accepted nirsevimab (n=477); unexposed declined (n=40)
  - Surveyed at 2 hours, days 7, 14, 30
  - More frequent reports of regurgitation in nirsevimab-exposed on day 30

Ref: 1) Carcione D et al, PIDJ, 2025 (in press). 2) Ocana de Sentuary C et al, eClinicalMedicine 2025;79:102986

Study Limitations

- Misclassification of exposure: missing nirsevimab doses
- Misclassification of outcomes
- Safety assessment limited to pre-specified outcomes of interest
- Main analyses were regardless of vaccines received on same day; if positive safety signal, can be difficult to disentangle effect of vaccines from effect of nirsevimab
- Although risk and control windows are short, time-varying covariates could bias results
- In a population size of >74,000, unable to assess risk of very rare adverse events