Evidence to Recommendations Framework: Clesrovimab

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April 16, 2025

Policy Question

- **Should clesrovimab be recommended for all infants <8 months of age born during or entering their first RSV season?**

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)
Public Health Problem	▪ Is the problem of public health importance?
Benefits and Harms	▪ How substantial are the desirable anticipated effects? ▪ How substantial are the undesirable anticipated effects? ▪ Do the desirable effects outweigh the undesirable effects?
Values	▪ Does the target population feel the desirable effects are large relative to the undesirable effects? ▪ Is there important variability in how patients value the outcome?
Acceptability	▪ Is the intervention acceptable to key stakeholders?
Feasibility	▪ Is the intervention feasible to implement?
Resource Use	▪ Is the intervention a reasonable and efficient allocation of resources?
Equity	▪ What would be the impact of the intervention on health equity?

EtR Domain: Public Health Problem

Is RSV-associated disease among infants <8 months of age of public health importance?

RSV burden is high in children <5 years of age

Each year in the United States, RSV leads to approximately*:

~2,000,000 medical encounters[1]

58,000–80,000 hospitalizations[1,2,3]

100–300 deaths[4,5,6]

*Data on the burden of RSV disease in children under 5 are from before the 2023-2024 RSV season, when RSV prevention products became available in the US.

References: 1) Hall et al, NEJM (2009): https://doi.org/10.1056/NEJMoa0804877 2) McLaughlin et al, J Infect Dis (2022): https://doi.org/10.1093/infdis/jiaa752 3) CDC RSV-NET, unpublished data. 4) Thompson et al, JAMA (2003): https://doi.org/10.1001/jama.289.2.179 5) Matias et al, Influenza Other Respi Viruses (2014): https://doi.org/10.1111/irv.12258 6) Hansen et al, JAMA Network Open (2022): https://doi.org/10.1001/jamanetworkopen.2022.0527

RSV is the leading cause of hospitalization in infants[1]

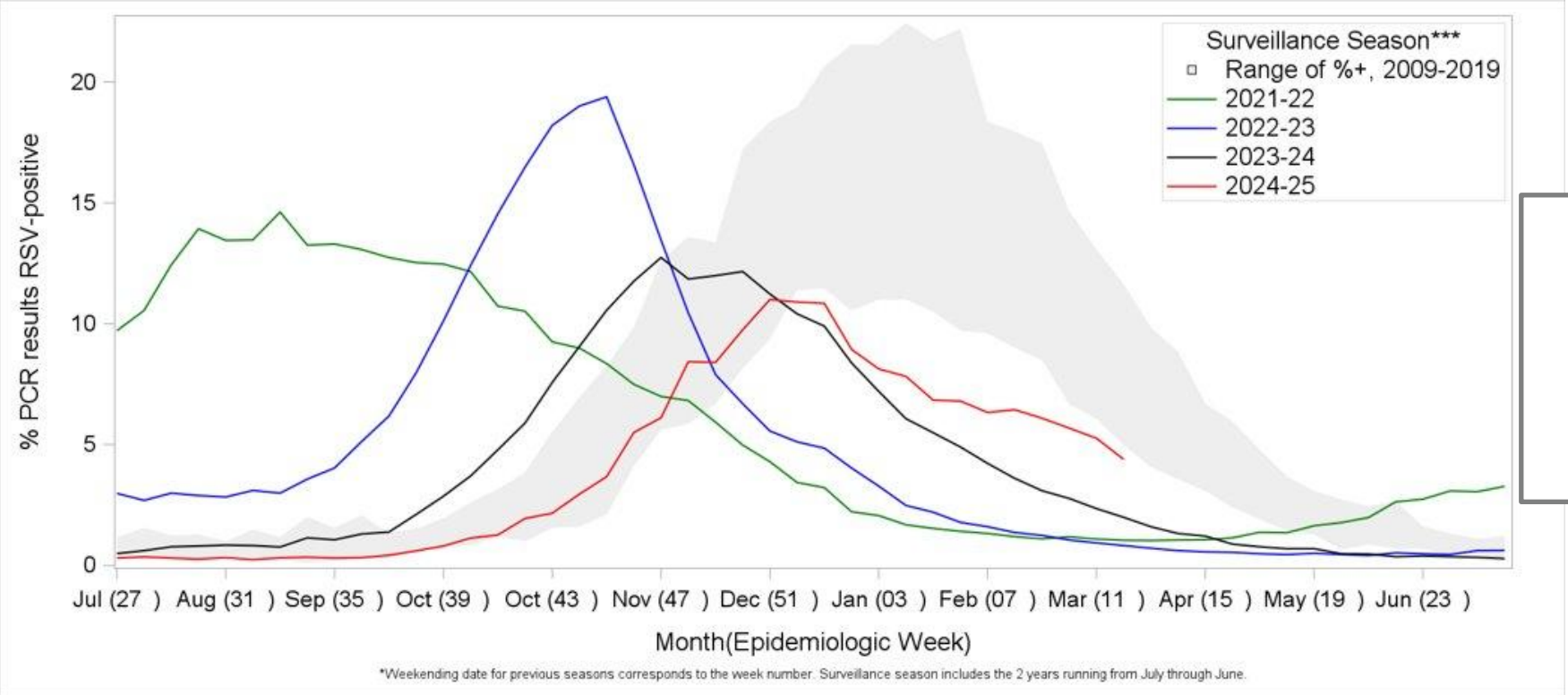
In the absence of RSV prevention products:

- **Most infants (68%) are infected in the first year of life and nearly all (97%) by age 2 years[2]**
- **2-3% of young infants are hospitalized for RSV[3,4,5]**
  - Highest rates occur in the first months of life, and risk declines with increasing age in early childhood[3,5]
  - 79% of children aged <2 years had no underlying medical conditions[3]
  - All infants are at risk for hospitalization

References: 1) Glezen et al, Arch Dis Child (1986): https://doi.org/10.1001/archpedi.1986.02140200053026 2) Suh et al. JID (2022): https://doi.org/10.1093/infdis/jiac120 3) Hall et al, Pediatrics (2013): https://doi.org/10.1542/peds.2013-0303 4) Langley & Anderson, PIDJ (2011): https://doi.org/10.1097/INF.0b013e3182184ae7 5) CDC NVSN data

2024–2025 RSV seasonality may be returning to pre-pandemic trends

Percentage* of polymerase chain reaction test results positive for respiratory syncytial virus, by MMWR week — National Respiratory and Enteric Virus Surveillance System, United States, July 2009–March 2025**



Pre-COVID-19 pandemic seasonality shown by grey shaded area

Notes: Report was last updated on 3/26/2025.
*All results presented are from nucleic acid amplification tests which represent >90% of the diagnostic tests reported to NREVSS. The last three weeks of data in 2023-24 may be less complete. NREVSS is an abbreviation for the National Respiratory and Enteric Virus Surveillance System. For more information on NREVSS, please visit National Respiratory and Enteric Virus Surveillance System | CDC.
**Respiratory syncytial virus types A and B are not shown separately in this report.
***The NREVSS surveillance season runs from the first week in July through June of the following year.

Public Health Problem - Work Group Interpretation

- **Is RSV-associated disease among infants <8 months of age of public health importance?**

No	Probably No	Probably Yes	**Yes**	Varies	Don't know

EtR Domain: Benefits and Harms

How substantial are the desirable anticipated effects?

How substantial are the undesirable anticipated effects?

Do the desirable effects outweigh the undesirable effects?

GRADE: PICO Question

Population	all infants <8 months of age born during or entering their first RSV season
Intervention	clesrovimab
Comparison	no immunization
Outcomes	<u>Benefits</u> 1. RSV-associated medically-attended lower respiratory tract infection (LRTI) 2. RSV-associated LRTI with hospitalization 3. RSV-associated LRTI with intensive care unit admission 4. All-cause medically-attended LRTI 5. All-cause LRTI with hospitalization <u>Harms</u> 1. Serious adverse events

Abbreviations: GRADE: Grading of Recommendations, Assessment, Development and Evaluation

GRADE: Outcomes, importance, and data sources

Outcome	Importance[1]	Data sources
Benefits		
1. RSV-associated medically-attended LRTI	Critical	Phase 2b/3 RCT[2]
2. RSV-associated LRTI with hospitalization	Critical	Phase 2b/3 RCT[2]
3. RSV-associated LRTI with ICU admission	Critical	Phase 2b/3 RCT[2]
4. All-cause medically-attended LRTI	Important	Phase 2b/3 RCT[2]
5. All-cause LRTI with hospitalization	Important	Phase 2b/3 RCT[2]
Harms		
6. Serious adverse events (SAEs)	Important	Phase 2b/3 RCT[2]

1. Three options: Critical; Important but not critical; Not important for decision making
2. Protocol 004: *A Phase 2b/3 Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Clesrovimab in Healthy Preterm and Full-Term Infants* – described in Zar et al., Open Forum Infectious Diseases (2025): https://doi.org/10.1093/ofid/ofae631.003; Sinha, presentation to ACIP (2024): https://www.cdc.gov/acip/downloads/slides-2024-10-23-24/02-RSV-Mat-Peds-Sinha-508.pdf; and unpublished data from manufacturer

Abbreviations: GRADE: Grading of Recommendations, Assessment, Development and Evaluation | LRTI: Lower respiratory tract infection | RCT: randomized controlled trial | ICU: intensive care unit

GRADE Benefits: Efficacy estimates and concerns in certainty assessment

Outcome	Vaccine efficacy estimate[1] % (95% CI)	Concerns in certainty assessment
Benefits, through 150 days of follow-up		
1. RSV-associated medically-attended LRTI	60.4 (44.1, 71.9)	Not serious (indirectness)[2]
2. RSV-associated LRTI with hospitalization	90.9 (76.2, 96.5)	Not serious (indirectness)[2]
3. RSV LRTI with ICU admission[3]	100.0 (24.0, 100.0)	Serious (imprecision)[4] Not serious (indirectness)[2]
4. All-cause medically-attended LRTI	13.1 (-0.6, 24.8)	Serious (imprecision)[5] Not serious (indirectness)[2]
5. All-cause LRTI with hospitalization	49.0 (26.7, 64.5)	Not serious (indirectness)[2]

1. Estimates and 95% CI were estimated from the modified Poisson regression with robust variance method.
2. Concern for indirectness: the trial excluded infants who were palivizumab-eligible and took place during a season with disrupted seasonality due to COVID-19. This was deemed not serious.
3. Outcome was not a trial endpoint and was assessed post-hoc.
4. Serious concern for imprecision: the number of study participants did not meet optimal information size.
5. Serious concern for imprecision: the confidence interval containing estimates for which different policy decisions might be considered.

Abbreviations: GRADE: Grading of Recommendations, Assessment, Development and Evaluation | CI: confidence interval | LRTI: lower respiratory tract infection | RCT: randomized controlled trial | ICU: intensive care unit

GRADE Harms: Relative risk of serious adverse events (SAEs) and concerns in certainty assessment

Outcome	Relative risk[1] (95% CI)	Concerns in certainty assessment
Harms		
Serious adverse events (SAEs)[2]	0.93 (0.77, 1.12)	Serious (imprecision)[3]

1. Relative risk was calculated as the risk of a serious adverse event in the clesrovimab arm divided by the risk of a serious adverse event in the placebo arm.
2. Adverse event resulting in death, hospitalization, significant disability, or requiring medical intervention. Serious adverse events may be related or unrelated to the study intervention.
3. Serious concern for imprecision: too few infants were included in the trial to capture rare events.

Abbreviations: GRADE: Grading of Recommendations, Assessment, Development and Evaluation | CI: confidence interval

Summary of GRADE for clesrovimab

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
1. RSV-associated medically-attended LRTI	Critical	RCT (1)	Clesrovimab is effective in preventing RSV-associated medically-attended LRTI	**High**
2. RSV-associated LRTI with hospitalization	Critical	RCT (1)	Clesrovimab is effective in preventing RSV-associated LRTI with hospitalization	**High**
3. RSV-associated LRTI with ICU admission	Critical	RCT (1)	Clesrovimab is effective in preventing LRTI with ICU admission	**Moderate**
4. All-cause medically-attended LRTI	Important	RCT (1)	Clesrovimab is not effective in preventing all cause medically-attended LRTI	**Moderate**
5. All-cause LRTI with hospitalization	Important	RCT (1)	Clesrovimab is moderately effective in preventing all cause hospitalization with LRTI	**High**
Harms				
6. Serious adverse events	Important	RCT (1)	SAEs were balanced between the clesrovimab group and the placebo group	**Moderate**

Abbreviations: LRTI: Lower respiratory tract infection | RCT: randomized control trial | ICU: intensive care unit | serious adverse events

Additional benefits of clesrovimab not included in GRADE: Efficacy for RSV-associated medically-attended LRTI and hospitalization observed through 180 days

Outcome	Follow-up time: 150 days			Follow-up time: 180 days		
	Events/ Clesrovimab (n/N)	Events/ Placebo (n/N)	Vaccine Efficacy % (95% CI)	Events/ Clesrovimab (n/N)	Events/ Placebo (n/N)	Vaccine Efficacy % (95% CI)
RSV-associated medically-attended LRTI	60/2398	74/1201	60.4 (44.1, 71.9)	64/2398	77/1201	59.5 (43.3, 71.1)
RSV-associated LRTI with hospitalization	5/2398	27/1201	90.9 (76.2, 96.5)	5/2398	28/1201	91.2 (77.2, 96.6)

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval

Additional benefits of clesrovimab not included in GRADE

- *If approved by FDA and recommended by CDC,* there will be two approved[1] and recommended[2] long-acting monoclonal antibodies for prevention of severe RSV disease in infants
- Multiple products with different binding sites are beneficial if resistance mutations develop to either product
- Multiple manufacturers in the same market allow for:
  - If one product has insufficient supply in the United States, the other product reduces the risk of a shortage.[3]
  - Competitive pricing of products may be created by market competition

1. In July 2023, the Food and Drug Administration (FDA) approved nirsevimab for the prevention of RSV–associated lower respiratory tract infection among infants and children aged <24 months. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf; 2. In August 2023, the Advisory Committee for Immunization Practices recommended nirsevimab infants aged <8 months born during or entering their first RSV season and for infants and children aged 8–19 months who are at increased risk of severe RSV disease entering their second RSV season. https://www.cdc.gov/mmwr/volumes/72/wr/mm7234a4.htm; 3. https://www.cdc.gov/han/2023/han00499.html

Additional harms of clesrovimab not included in GRADE: Solicited adverse events (AEs), days 1–5 post immunization

- **Injection-site and systemic reactions were comparable between the clesrovimab (29.9%) and placebo (30.9%) arms**
  - Irritability and somnolence were the most commonly reported solicited AEs
- **Mostly Grade 1 (mild) or 2 (moderate)**
  - The proportions of participants with solicited AEs of Grade 3 (severe) were low (≤0.2%) in both groups
  - No Grade 4 (potentially life-threatening) solicited AEs

Grade 1= mild; Grade 2= moderate; Grade 3=severe; Grade 4=potentially life threatening; https://www.fda.gov/media/73679/download

Additional harms of clesrovimab not included in GRADE: Fever*, days 1–5 post immunization

- **Rates of fever were comparable between the clesrovimab (3.7%) and placebo (4.0%) arms**

Study	Events*/Clesrovimab (n/N)	Events*/Placebo (n/N)
Protocol 004	89/2408[†] (3.7%)	48/1202 (4.0%)

*Fever defined as a temperature ≥ 100.4°F

[†] Total N=2409; 2408 had temperature data available per communication with manufacturer on March 9, 2025

Workgroup interpretation of benefits and harms of clesrovimab

Benefits

- Efficacious long-acting, monoclonal antibody that can prevent severe RSV disease in young infants during the duration of their first RSV season
- Second long-acting, monoclonal antibody RSV prevention product would mitigate the risk of manufacturing shortages and loss of efficacy due to resistance mutations

Harms

- Favorable safety profile with no observed increase in serious adverse events, local or systemic reactions, including fever
- Rare serious adverse events unlikely to be detected in a trial due to sample size

Benefits and Harms

- **How substantial are the <u>desirable</u> anticipated effects?**
  - How substantial are the anticipated effects for each main outcome for which there is a desirable effect?

Minimal	Small	Moderate	**Large**	Varies	Don’t know

Benefits and Harms

- **How substantial are the <u>undesirable</u> anticipated effects?**
  - How substantial are the anticipated effects for each main outcome for which there is an undesirable effect?

Minimal	**Small**	**Moderate**	**Large**	**Varies**	**Don’t know**

Benefits and Harms

- **Do the desirable effects outweigh the undesirable effects?**

Favors intervention (clesrovimab)
Probably favors the intervention (clesrovimab)
Probably favors the comparison (no immunization)
Favors the comparison (no immunization)
Unclear

EtR Domain: Values

Do parents and caregivers feel that the desirable effects of clesrovimab are large relative to the undesirable effects?

Is there important uncertainty about, or variability in, how much parents and caregivers value the prevention of severe RSV disease?

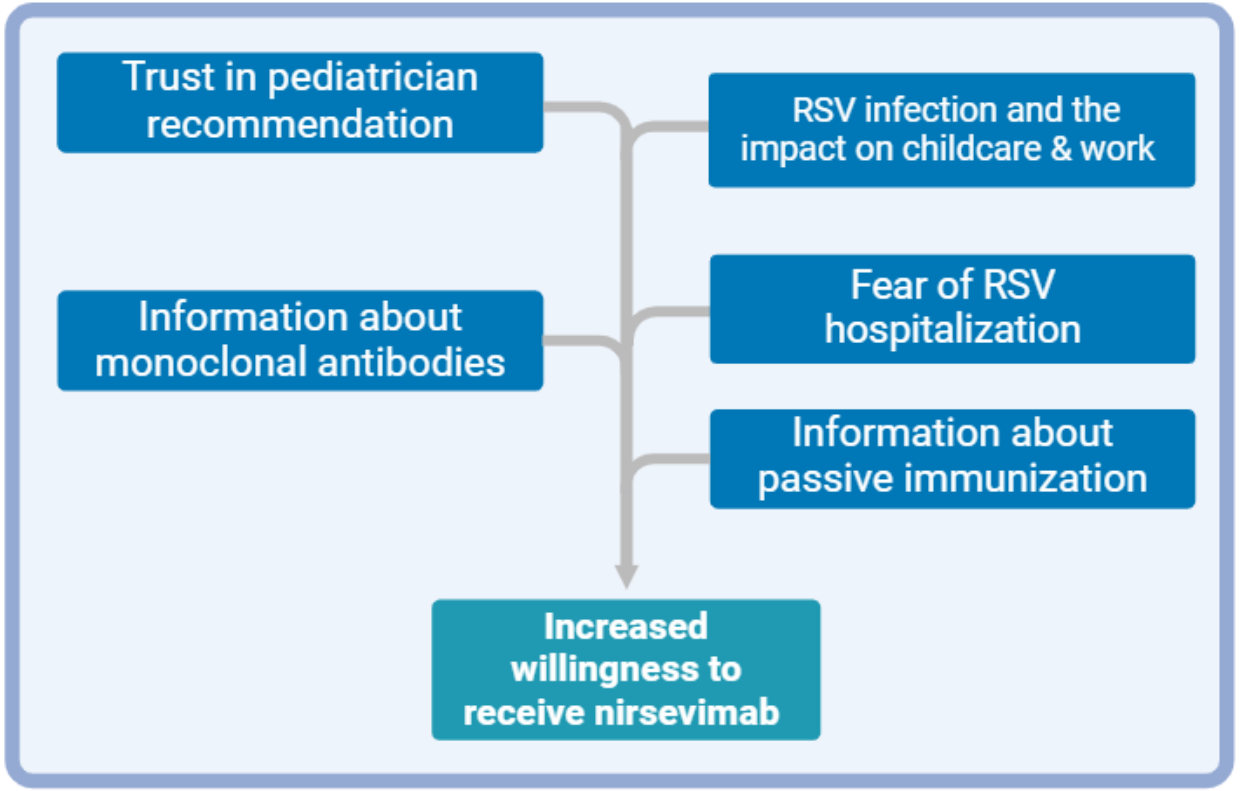
Parent attitudes about RSV disease

- 38% of respondents believe that their baby would have no symptoms or mild symptoms if they got sick with RSV
- 24% expressed uncertainty about the disease severity or treatability if their baby got sick with RSV
- Despite being unsure or perceiving RSV risk to be low, respondents were worried their baby would need to be hospitalized if they got sick with RSV (mean response 4 of 5 with 5 being most worried)

CDC and University of Iowa/RAND survey, unpublished. 523 women who were actively pregnant or pregnant within last 12 months; conducted: 12/2022—1/2023

Factors that may increase parental intent to receive RSV immunization products for their infant

- Trust in pediatrician's recommendation and fear of RSV infection was associated with increased intent to receive nirsevimab[1]
- Receiving information about monoclonal antibodies and passive immunization led to a positive impact (68%) on willingness to receive the immunization[2]



References: 1. Hinderstein et al., Pediatrics (2024): https://10.1542/peds.2024-067532; 2. Lee Mortensen et al., Expert Rev Vaccines (2022): https://10.1080/14760584.2022.2108799

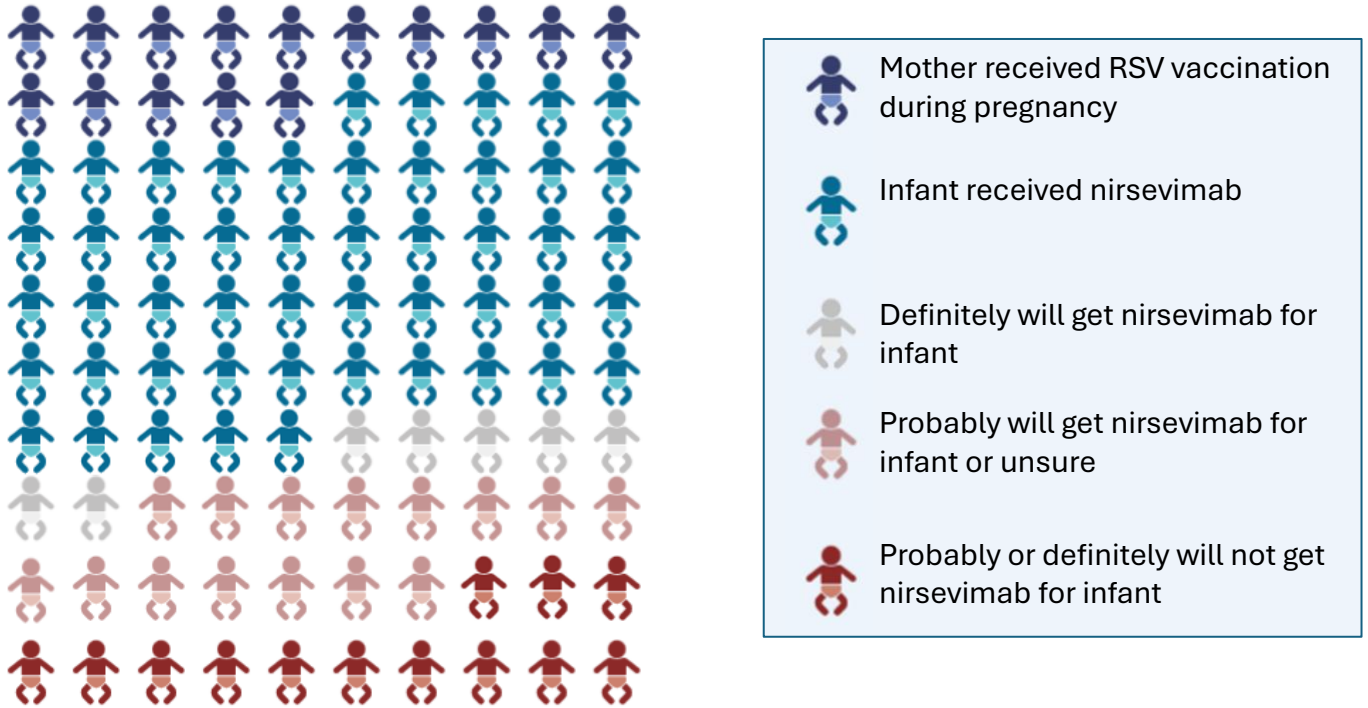
Factors that may decrease parental intent to receive RSV immunization products for their infant

- Parents deferring RSV immunization were concerned about adverse events and wanted to wait until the product had been available for longer, wanted more time to decide, or trusted their own prevention measures against RSV[1,2,3,4,5]

References: 1. Hinderstein et al., Pediatrics (2024): https://10.1542/peds.2024-067532; 2. Lee Mortensen et al., Expert Rev Vaccines (2022): https://10.1080/14760584.2022.2108799; 3. Wang et al., Vaccine (2025): https:/10.1016/j.vaccine.2024.126570; 4. Zornoza Moreno et al., Hum Vaccin Immunother (2024): https://10.1080/21645515.2024.2357439; 5. Ocana de Sentuary et al., EClinicalMedicine (2025): https://10.1016/j.eclinm.2024.102986

50% of women 18-49 years who have an infant <8 months received nirsevimab for their infant, February 2025, United States

Infant protection against RSV by maternal RSV vaccination* or receipt of nirsevimab†, and intent‡ for nirsevimab receipt by women aged 18–49 years who have an infant <8 months during the RSV season (born since April 1, 2024), February, United States

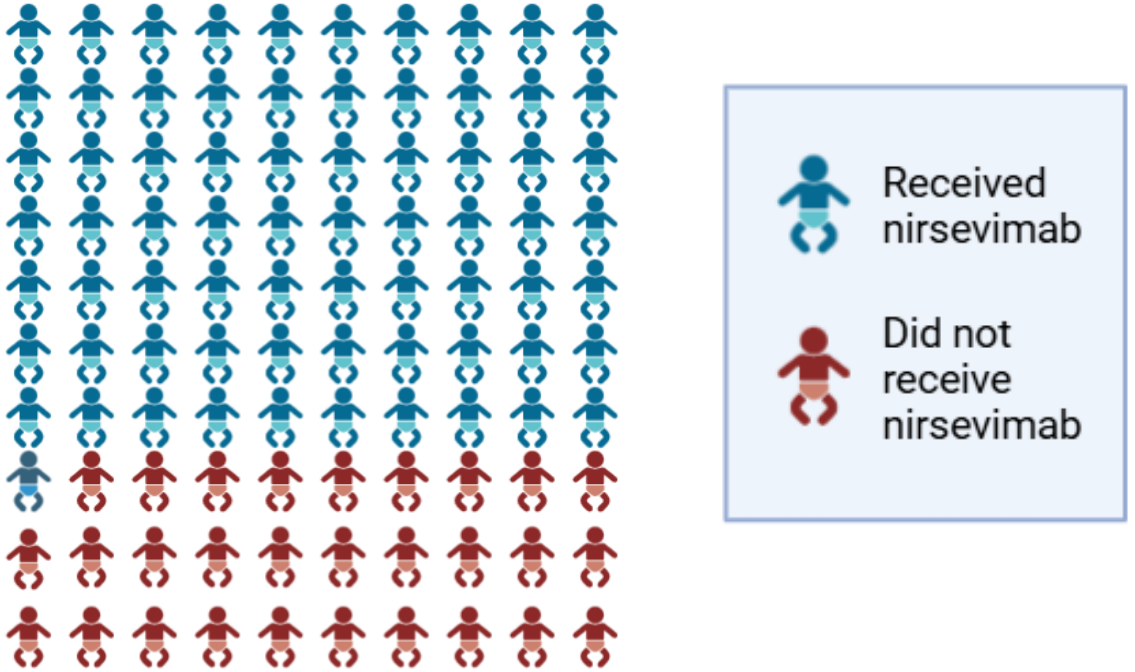


*Receipt of RSV vaccination during pregnancy was assessed by the NIS–ACM questionnaire among women 18–49 years who reported having an infant born since October 1, 2024. For infants born April 1, 2024, through September 30, 2024, maternal RSV vaccination was not assessed, and these infants were assumed to be protected against RSV only if infant was reported to have received nirsevimab. The estimates of receipt of RSV vaccination during pregnancy for infants born since April 1, 2024 are not an assessment of maternal RSV vaccination coverage among pregnant women eligible for vaccination as shown with the Vaccine Safety Datalink, as they are based on all infants eligible for nirsevimab or maternal vaccination rather than eligible pregnancies
†Estimates of nirsevimab receipt by infants born since April 1, 2024, include those who were born shortly before or are entering their first RSV season and do not account for the mother's RSV vaccination status during pregnancy
‡Intent for nirsevimab receipt is assessed among infants who had not received nirsevimab and whose mother did not receive RSV vaccination during pregnancy. Estimates of nirsevimab intent among women interviewed in August and September 2024 included all women who reported having an infant <8 months, and could include infants born in February and March 2024.

Data Source: National Immunization Survey – Adult COVID Module https://www.cdc.gov/rsvvaxview/dashboard/nirsevimab-coverage-infants.html

Nirsevimab uptake may be higher in settings of increased access

71% of newborns received nirsevimab at a US birthing center when it was universally offered[1]



References: 1. Puckett et al., Hosp Pediatr (2025): https://10.1542/hpeds.2024-008070.

Values

- **Do parents and caregivers feel that the desirable effects of clesrovimab are large relative to the undesirable effects?**

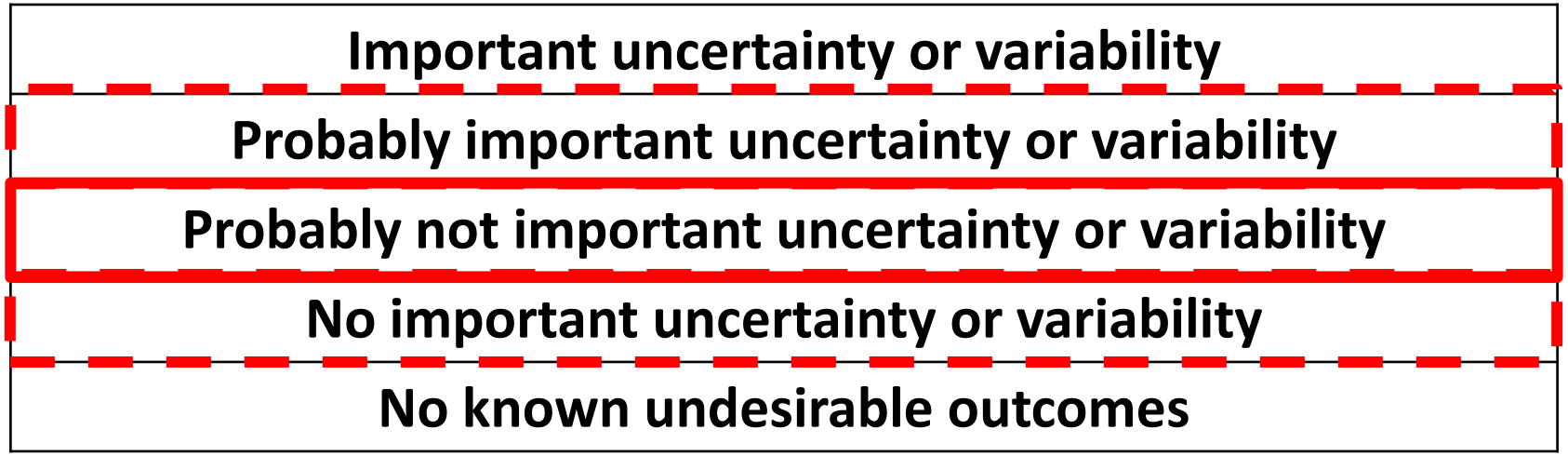
No	Probably No	Probably Yes	Yes	Varies	Don't know

Majority opinion

Minority opinion

Values

- **Is there important uncertainty about, or variability in, how much how much parents and caregivers value the prevention of severe RSV disease?**



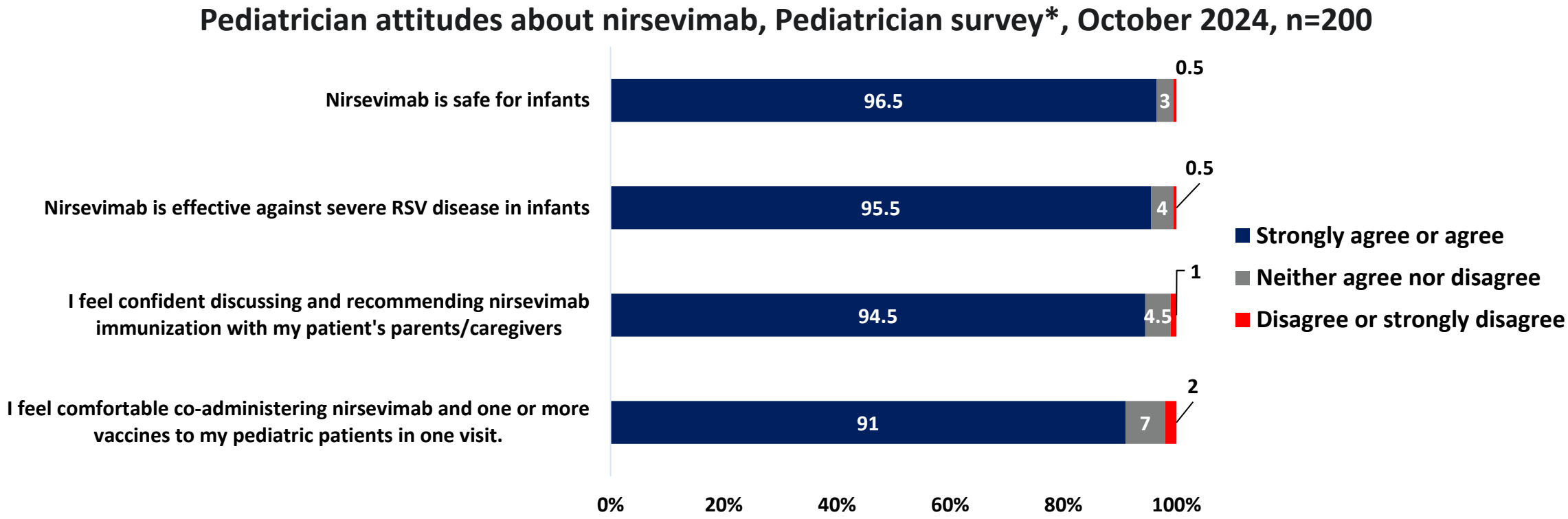
Majority opinion

Minority opinion

EtR Domain: Acceptability

Is clesrovimab acceptable to key stakeholders?

Pediatrician attitudes about nirsevimab may provide insight into their potential attitudes about clesrovimab



- **77% of pediatricians reported that their practice had ever offered nirsevimab**
- **The majority of pediatricians agreed that nirsevimab is safe for infants and effective against severe disease in infants**

*Porter Novelli View Health Care Practitioner survey was conducted from October 2-10, 2024, among 200 U.S. pediatricians who reported offering at least some routine pediatric vaccines to patients

Kang et al, CDC (2024); https://www.cdc.gov/rsvvaxview/publications/rsv-immunization-survey-2024.html

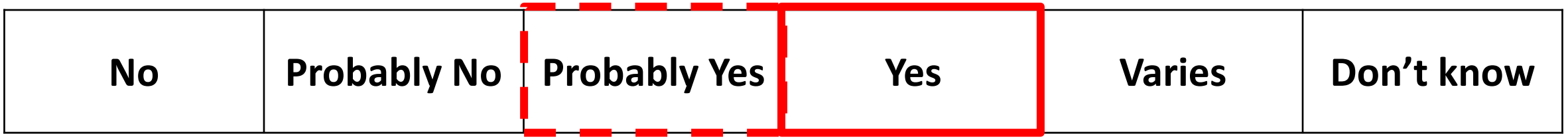
RSV prevention through long-acting, monoclonal antibodies endorsed by national organizations

- **Nirsevimab is recommended by**
  - American Academy of Pediatrics[1]
  - American Academy of Family Physicians[2]
  - National Foundation for Infectious Diseases[3]

1) https://publications.aap.org/redbook/resources/25379/AAP-Recommendations-for-the-Prevention-of-RSV?autologincheck=redirected
2) https://www.aafp.org/news/health-of-the-public/rsv-antibody-aafp-approval.html
3) https://www.nfid.org/resource/contagious-chronicles-updated-recommendations-for-respiratory-season/

Acceptability

- **Is clesrovimab acceptable to key stakeholders?**



Majority opinion

Minority opinion

EtR Domain: Feasibility

Is clesrovimab feasible to implement among all infants <8 months of age born during or entering their first RSV season?

Clesrovimab storage, handling, and administration

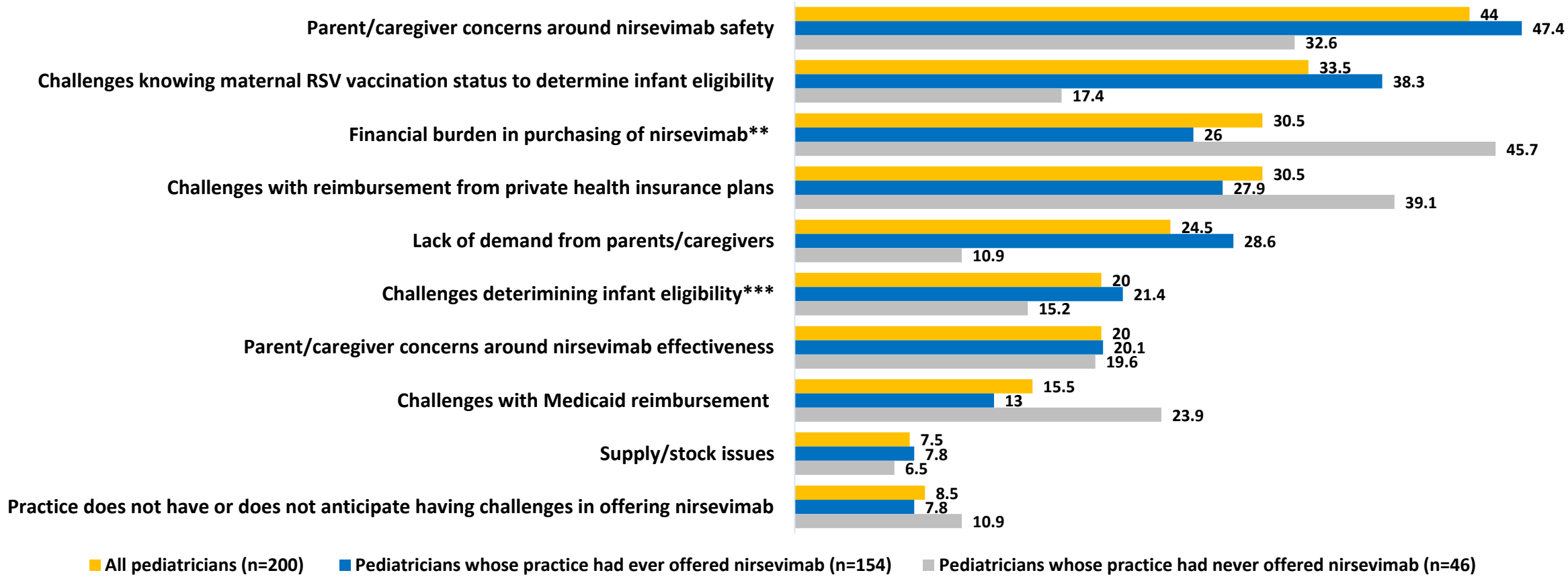
- Clesrovimab storage, handling, and administration is anticipated to be similar to other routine immunizations for children
- Administered as an intramuscular injection using a single-dose, prefilled syringe
- Stored at refrigerator temperature (2°C to 8°C)
- May be kept at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum of 48 hours.
  - After removal from the refrigerator, must be used within 48 hours or discarded
- Dosage is 0.7 mL for all infants born during or entering their first RSV season regardless of weight
- Can be administered simultaneously with other vaccines

Implementation and access

- The Vaccines for Children (VFC) program is a federally funded program that provides immunizations at no cost to children who might not otherwise be immunized because of inability to pay.[1]
  - If ACIP votes to include clesrovimab in VFC, it will be the second monoclonal antibody to be included in the VFC program.
- Implementation **pros and cons:**
  - Pro: Clesrovimab is a single dose regardless of weight
  - Con: Stocking clesrovimab may be challenging for providers who also need to stock nirsevimab for high-risk children 8 through 19 months entering their second RSV season and prefer to stock a **single** RSV monoclonal antibody

1. CDC. Vaccines for Children. https://www.cdc.gov/vaccines-for-children/about/index.html

Frequency of main challenges* pediatricians reported or anticipated in offering nirsevimab, Pediatrician survey, October 2024, n=200



*Respondents were instructed to select up to 3 response categories

** Private stock of nirsevimab for practices participating in the VFC (Vaccines for Children) program

*** Challenges knowing whether infant received nirsevimab at a birthing hospital

Yoonjae Kang, MPH; Fan Zhang, MD; Tara M Vogt, PhD, MPH; https://www.cdc.gov/rsvvaxview/publications/rsv-immunization-survey-2024.html

Birthing hospital barriers to monoclonal antibody administration

- **In a series of CDC Learning Collaborative calls hosted by the Association for Immunization Managers on nirsevimab administration in birthing hospitals, common barriers included:**
  - Determining maternal RSV vaccination status
  - Storage and handling
  - Billing
  - Cost of nirsevimab
  - Nirsevimab supply/shortages
  - Determining a newborn's VFC eligibility
  - Documenting nirsevimab receipt and care coordination
  - VFC requirements can be difficult to implement and enrollment is burdensome

VFC: Vaccines for Children

Feasibility

- **Is clesrovimab feasible to implement among all infants <8 months of age born during or entering their first RSV season?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

Majority opinion

Minority opinion

EtR Domain: Resource Use

Is clesrovimab a reasonable and efficient allocation of resources?

RSV-associated outcomes averted: 50% coverage with clesrovimab among an annual US birth cohort[1]

Comparison	Outpatient Visits Averted	ED Visits Averted	Hospital Admissions Averted	ICU Admissions Averted	Deaths Averted	QALYs Gained
Clesrovimab[2] vs. no RSV immunizations for most infants[3]	121,022	43,480	20,198	4,444	20	3,413

1. Estimates provided by an updated UM-CDC model, where updates included VE and cost/dose. Original model and methods described here: David W. Hutton, Lisa A. Prosser, Angela M. Rose, Kerra Mercon, Ismael R. Ortega-Sanchez, Andrew J. Leidner, Meredith L. McMorrow, Katherine E. Fleming-Dutra, Mila M. Prill, Jamison Pike, Jefferson M. Jones; Cost-Effectiveness of Nirsevimab for Respiratory Syncytial Virus in Infants and Young Children. Pediatrics December 2024; 154 (6): e2024066461. 10.1542/peds.2024-066461.
2. Clesrovimab has 50% coverage, and includes 50% palivizumab use for eligible high-risk babies that do not get clesrovimab
3. “No RSV immunizations for most infants" means the only RSV immunization is palivizumab for eligible high-risk infants

Abbreviations: ED: emergency department | ICU: intensive care unit | QALY: quality adjusted life year

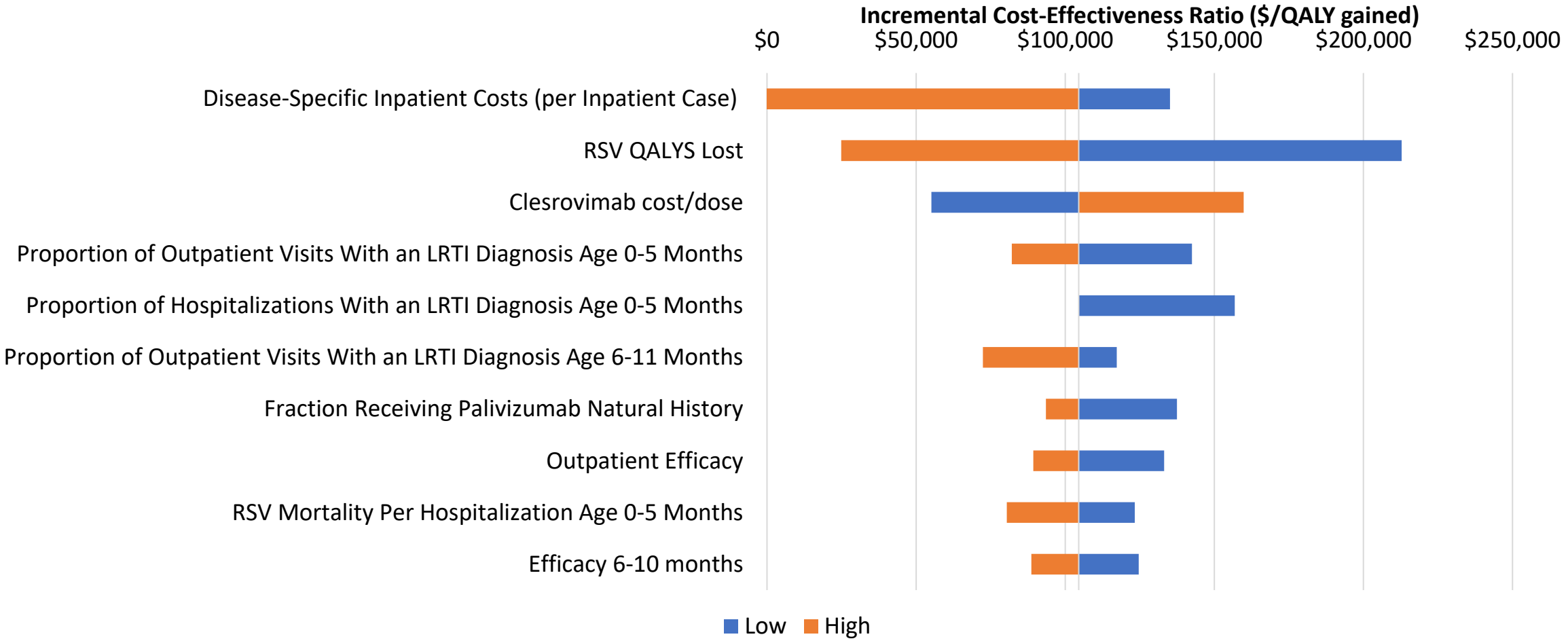
Incremental cost effectiveness ratios (ICERs): 50% coverage with clesrovimab among an annual US birth cohort[1]

Comparison	$/Outpatient Visit Averted	$/ED Visit Averted	$/Hospital Admission Averted	$/ICU Admission Averted	$/Death Averted	$/QALY Gained
Clesrovimab[2] vs. no RSV immunizations for most infants[3]	2,948	8,207	17,666	80,300	17,666,032	104,543

1. Estimates provided by an updated UM-CDC model, where updates included VE and cost/dose. Original model and methods described here: Hutton et al, Peds (2024);.https://doi.org/10.1542/peds.2024-066461.
2. Clesrovimab has 50% coverage, and includes 50% palivizumab use for eligible high-risk babies that do not get clesrovimab
3. “No RSV immunizations for most infants" means the only RSV immunization is palivizumab for eligible high-risk infants

Abbreviations: ED: emergency department | ICU: intensive care unit | QALY: quality adjusted life year

One-way sensitivity analysis: 50% coverage with clesrovimab among an annual US birth cohort[1]



1. Estimates provided by an updated UM-CDC model, where updates included VE and cost/dose. Original model and methods described here: David W. Hutton, Lisa A. Prosser, Angela M. Rose, Kerra Mercon, Ismael R. Ortega-Sanchez, Andrew J. Leidner, Meredith L. McMorrow, Katherine E. Fleming-Dutra, Mila M. Prill, Jamison Pike, Jefferson M. Jones; Cost-Effectiveness of Nirsevimab for Respiratory Syncytial Virus in Infants and Young Children. Pediatrics December 2024; 154 (6): e2024066461. 10.1542/peds.2024-066461.

Abbreviations: QALY: quality adjusted life year

Merck[1] and University of Michigan – CDC[2] Model Comparison

- **University of Michigan/CDC Model**
  - $/QALY gained: $104,543 (assumes $457/dose)
- **Merck Model**
  - $/QALY gained: $7,372 -$42,691 (assumes $423 - $493/dose); $36,636 (assumes $457/dose)
- **Key differences in inputs**
  - Initial efficacy and waning trajectory
  - Medical costs
  - Adverse events

1. Klodeta Kura, John C Lang, Dawei Wang, et al. Merck's technical report: Cost-effectiveness analysis of clesrovimab use in infants in the United states. (Version submitted to CDC and ACIP for review, January 27, 2025)
2. Estimates provided by an updated UM-CDC model, where updates included vaccine efficacy, vaccine efficacy waning trajectory, and cost/dose. Original model and methods described here: David W. Hutton, Lisa A. Prosser, Angela M. Rose, Kerra Mercon, Ismael R. Ortega-Sanchez, Andrew J. Leidner, Meredith L. McMorrow, Katherine E. Fleming-Dutra, Mila M. Prill, Jamison Pike, Jefferson M. Jones; Cost-Effectiveness of Nirsevimab for Respiratory Syncytial Virus in Infants and Young Children. Pediatrics December 2024; 154 (6): e2024066461. 10.1542/peds.2024-066461.

Abbreviations: QALY: quality adjusted life year

Resource use summary

- **Clesrovimab cost $104,543 per QALY gained in the base case, with sensitivity analyses ranging from cost saving to $215,000/QALY**
- **Cost effectiveness models sensitive to**
  - Inpatient costs
  - Clesrovimab cost/dose
  - QALYs lost due to RSV illness

Abbreviations: QALY: quality adjusted life year

Resource Use

- **Is clesrovimab use among all infants under 8 months of age born during or entering their first RSV season a reasonable and efficient allocation of resources with an estimated cost of $458 on average ($365 VFC / $560 other) per dose?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

Majority opinion

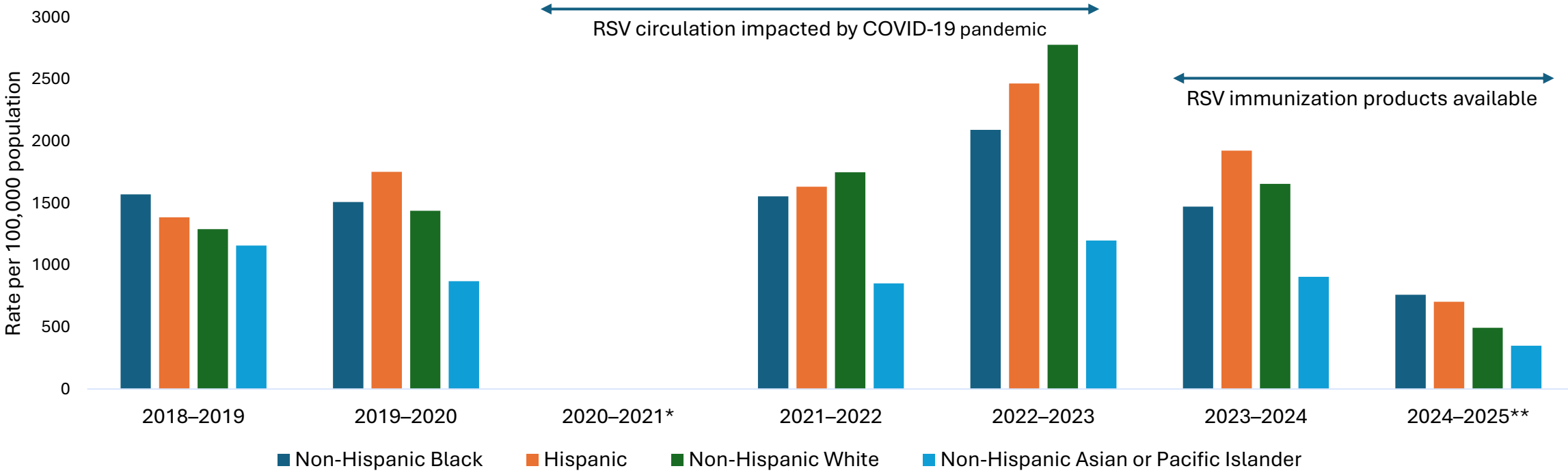
Minority opinion

Abbreviations: VFC: Vaccines for Children

EtR Domain: Equity

What would the impact of clesrovimab be on health equity for infants?

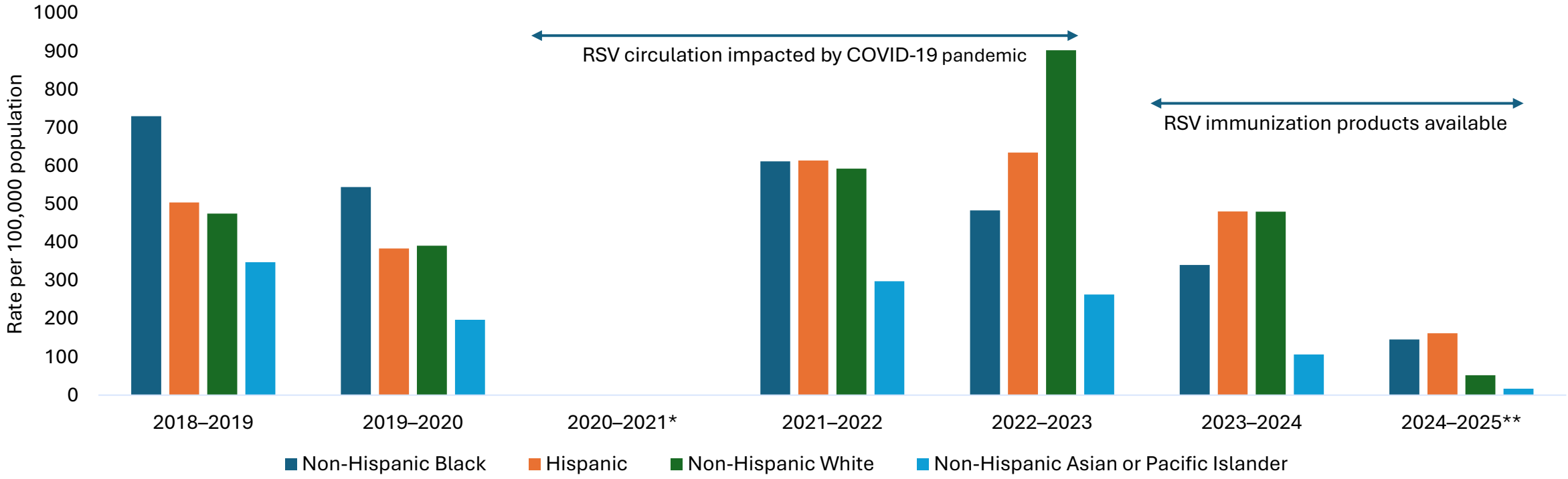
Adjusted population-based *hospitalization* rates among infants <6 months old with laboratory-confirmed RSV by race and ethnicity, RSV-NET, 2018–2019 to 2024–2025



Hospitalization rates among infants <6 months old differ by race and ethnicity but this difference varies by season

RSV-NET: unpublished data. Surveillance was conducted during October–April for the 2018–19 and 2019–20 seasons and during May–April for 2021–22 onwards. Rates were adjusted for RSV testing practices and test sensitivity. Black, White, Asian/Pacific Islander children were categorized as non-Hispanic; Hispanic children could be of any race.*2020–21 season experienced limited to no RSV circulation **2024–25 data available through February 1, 2025

Adjusted population-based *ICU admission* rates among infants <6 months old with laboratory-confirmed RSV by race and ethnicity, RSV-NET, 2018–2019 to 2024–2025



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*2020–21 season experienced limited to no RSV circulation; **2024–25 data available through February 1, 2025

RSV rates of severe disease by race and ethnicity

- **RSV hospitalization rates were up to 7x higher among Alaska Native and American Indian children compared to children aged less than 1 year[1]**
  - This study was limited to specific populations and might not be broadly representative of risk in all Alaska Native and American Indian children
- **National studies of death certificates found higher rates among non-Hispanic Black and Hispanic children compared to non-Hispanic White children[2]**
- **Hospitalization rates using NVSN data have shown mixed results[3]**
  - Several studies have shown no differences by race or ethnicity[4-7]
  - Even when significant, relative risk for non-Hispanic Black and Hispanic children mildly increased compared to non-Hispanic, White children (e.g., relative risk of 1.2-2.2)[6-7]

1. Atwell et al. 2023 Aug 1;152(2):e2022060435
2. Hansen J Infect Dis 2022 Aug 15;226(Suppl 2):S255-S266
3. NVSN analyses compared incidence rates of non-Hispanic Black, non-Hispanic White, and Hispanic children
4. Hall Pediatrics 2013 Aug;132(2):e341-8
5. Hall NEJM 2009;360(6):588–598
6. Iwane Pediatrics 2004 Jun;113(6):1758-64, findings differed by age group
7. Rha Pediatrics 2020 Jul;146(1):e20193611, findings differed by age group

Abbreviations: NVSN: New Vaccine Surveillance Network

Equity

- **What would be the impact of clesrovimab on health equity?**

Reduced
Probably reduced
Probably no impact
Probably increased
Increased
Varies
Don’t know

Majority opinion

Minority opinion

EtR Summary

Work group considerations and interpretation

- **Phase 2b/3 trial demonstrated high efficacy for prevention of severe RSV disease through 150 days**
- **Serious adverse events appeared balanced between the clesrovimab and placebo arms, however rare adverse events are unlikely to be detected in a trial of this size**
- **Work group discussion also highlighted:**
  - Clesrovimab has demonstrated a shorter half-life than nirsevimab (42[1] vs 71[2] days), however efficacy against severe RSV appeared sustained through 150 days
  - Clesrovimab and nirsevimab trial outcomes had different definitions, making direct comparisons in efficacy difficult

1. Maas et al. https://www.sciensano.be/sites/default/files/pk_sna_and_efficacy_against_rsv_malri_from_a_phase_1b2a_study_of_the_monoclonal_antibody_clesrovimab_mk-1654_in_infants.pdf
2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761328s000lbl.pdf

Work group considerations and interpretation, continued

- **The work group highlighted the benefits of multiple RSV antibody products and multiple manufacturers, including:**
  - If RSV develops resistance to one product or one product has insufficient supply, another is available
  - Potential for decrease in price
- **The leading cause of hospitalization in infants (RSV) can be prevented through immunization. However, for RSV immunizations to have public health impact, they must be administered early:**
  - For infants born outside the RSV season, high uptake prior to season onset is essential
  - For infants born during the RSV season, administration should be within the first week of life - *ideally during the birth hospitalization*

Evidence to Recommendations Framework
Summary

- What is the balance between the desirable effects relative to the undesirable effects?

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

Evidence to Recommendations Framework
Summary

- Should clesrovimab be recommended for all infants <8 months of age born during or entering their first RSV season?

Type of recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on shared clinical decision-making	We recommend the intervention

Acknowledgements

Jefferson Jones

Mila Prill

Meredith McMorrow

Ruth Link-Gelles

Monica Godfrey

Michael Melgar

Amadea Britton

Amber Kautz

Lauren Roper

Monica Patton

Fiona Havers

Ben Silk

Amber Winn

Alexa Churan

Melissa Shah

Amanda Payne

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Heidi Moline

Fatimah Dawood

Jenny Milucky

Coronavirus and Other Respiratory Viruses Division

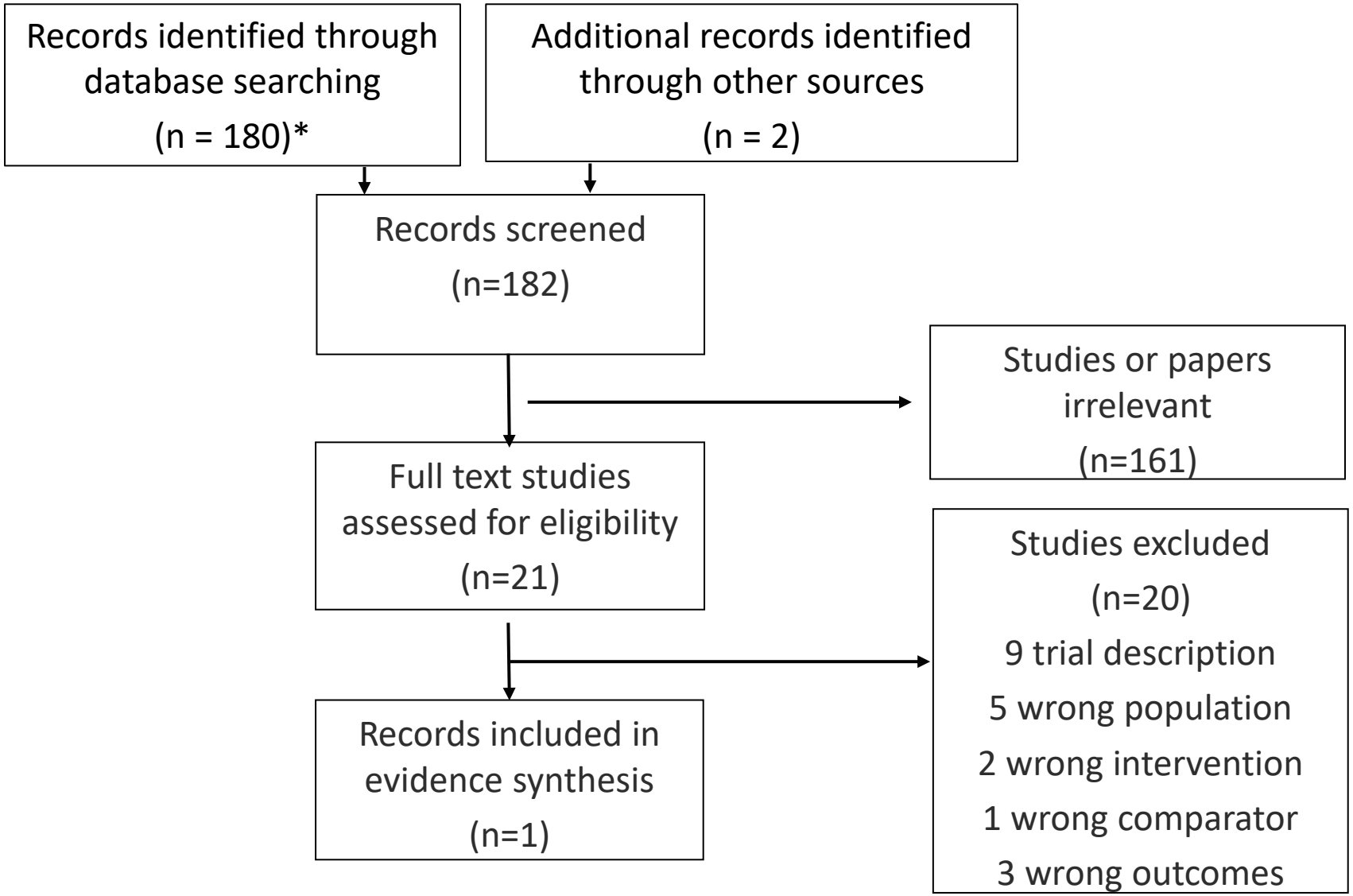
Immunization Services Division

RSV-NET

NIS-ACM

GRADE: Clesrovimab

Evidence retrieval, conducted as of December 3, 2024



*Medline (OVID), Embase (OVID), Cochrane Library, CINAHL (EbscoHost), Scopus, clinicaltrials.gov

Protocol 004: Phase 2b/3, double-blinded, placebo-controlled trial

- **3,614 healthy preterm infants (gestational age ≥29 weeks to <35 weeks) and full-term infants (GA ≥35 weeks) born during or entering their first RSV season**
  - Randomized 2:1 (2,411 clesrovimab, 1,203 placebo)
  - Enrolled at birth up to 1 year (median age at randomization: 3.1 months)
- **Multi-country: Argentina, Belgium, Canada, Chile, China, Colombia, Denmark, Finland, France, Italy, Japan, Korea, Malaysia, Mexico, Peru, Philippines, Poland, Thailand, Turkey, UK, USA, South Africa**
  - Over 2/3 of infants enrolled were from the Northern Hemisphere
- **Primary efficacy outcomes followed for 150 days, safety, and pharmacokinetics**
  - Secondary efficacy outcomes with follow-up through 150 and 180 days

GRADE evidence type

- **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty:** Our confidence in the effect estimate is limited. The true effect may be substantially different from the effect estimate.
- **Very low certainty:** We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

GRADE evidence type

- **Initial evidence type (certainty level) determined by study design**
  - Initial evidence is **high** certainty: A body of evidence from randomized controlled trials
  - Initial evidence is **low** certainty: A body of evidence from observational studies
- **Evidence type may be downgraded due to risk of bias, inconsistency, indirectness, and imprecision. Evidence type may be upgraded or downgraded due to other considerations including publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.**

NOTE: Evidence type is not measuring the quality of individual studies, but how much certainty we have in the estimates of effect across each outcome.

Benefits

Case definitions for benefits

Outcomes	≥ 1 signs/symptoms	AND ≥ 1 indicator of LRTI/severity	RSV-positive RT-PCR NP sample	Setting
1. RSV-associated medically-attended LRTI	At least one sign/symptom on examination: • Cough • Difficulty breathing	At least one of: • Rales/crackles • Wheezing • Chest wall indrawing/retractions • Hypoxemia* • Tachypnea** • Dehydration due to respiratory symptoms	Required	Outpatient or inpatient clinical setting
2. RSV-associated LRTI with hospitalization				Inpatient clinical setting
3. RSV-associated LRTI with ICU admission				Inpatient clinical setting
4. All-cause medically-attended LRTI			Not required	Outpatient or inpatient clinical setting
5. All-cause LRTI-associated hospitalization				Inpatient clinical setting

* Hypoxemia was defined as SpO2 <95% on room air at sea level, <92% on room air at altitude≥1800 m. In room air - oxygen saturation <95% at altitudes ≤1800 meters or <92% at altitudes >1800 meters

** Tachypnea was defined as RR≥60 breaths per minute for <2 months of age;≥50 breaths per minute for 2 to 12 months of age; or≥40 breaths per minute for >12 to 24 months of age

Abbreviations: LRTI: lower respiratory tract infection | ICU: intensive care unit | RT-PCR: reverse transcription polymerase chain reaction | NP: nasopharyngeal | RR: respiratory rate

Outcome 1: RSV-associated medically-attended LRTI[1] through 150 days of follow-up

Study	Events[1]/Clesrovimab n/N (%)	Events[1]/Placebo n/N (%)	Efficacy[2] (95% CI)
Protocol 004	60/2398[3] (2.5%)	74/1201[3] (6.2%)	60.4% (44.1, 71.9)

1. Defined by the presence of the following seen in an outpatient or inpatient clinical setting: cough or difficulty breathing AND ≥ 1 indicator of LRTI or severity (wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms); AND RSV positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) sample.
2. Estimates and 95% CI were estimated from the modified Poisson regression with robust variance method. The model included the following covariates: hemisphere at randomization, gestational age group and age group at randomization. The lower bound of the 95% CI was >25%, meeting the statistical criterion for success.
3. Patients were randomized 2:1 to the clesrovimab and placebo arms.

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval

GRADE: RSV-associated medically-attended LRTI through 150 days of follow-up (n=1 study)

- **Measure of effect**
  - Efficacy: 60.4% (95% CI: 44.1, 71.9)
    - Absolute risk (using 23.1% seasonal incidence[1]): 140 fewer cases per 1,000 immunized (166 fewer to 102 fewer)
      - Number needed to immunize: 7 (6 to 10)
    - Absolute risk (using 11.0% seasonal incidence[2]): 66 fewer cases per 1,000 immunized (79 fewer to 49 fewer)
      - Number needed to immunize: 15 (13 to 20)
    - Absolute risk (using 6.2% seasonal incidence [phase 2b/3 trial placebo arm]): 37 fewer cases per 1,000 immunized (44 fewer to 27 fewer)
      - Number needed to immunize: 27 (22 to 37)
- **Concerns in certainty assessment**
  - Not serious (indirectness): trial excluded infants who were palivizumab eligible
- **Final evidence type: High**

1. Lively 2019 JPIDS, 5 years from 3 NVSN sites from Nov-Apr season, included if with acute respiratory infection (ARI, not restricted to LRTI). 2. Assumes 47.5% of ARI are LRTI (Rainisch 2020 Vaccine)

Abbreviations: LRTI: lower respiratory tract infection | CI = confidence interval

Outcome 2: RSV-associated LRTI with hospitalization[1] through 150 days of follow-up

Study	Events[1]/Clesrovimab n/N (%)	Events[1]/Placebo n/N (%)	Efficacy[2] (95% CI)*
Protocol 004	5/2398[3] (0.2%)	27/1201[3] (2.2%)	90.9% (76.2, 96.5)

1. Defined by the presence of the following seen in an inpatient clinical setting: cough or difficulty breathing AND ≥ 1 indicator of LRTI (rhonchi, rales/crackles, wheezing) AND ≥1 indicator of severity (chest wall indrawing/retractions, hypoxemia, tachypnea, dehydration due to respiratory symptoms); AND RSV positive reverse transcriptase-polymerase chain reaction (RT-PCR) nasopharyngeal (NP) sample.
2. Estimates and 95% CI were estimated from the modified Poisson regression with robust variance method.
3. Patients were randomized 2:1 to the clesrovimab and placebo arms.

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval

GRADE: RSV-associated LRTI with hospitalization through 150 days of follow-up (n=1 study)

- **Measures of effect**
  - Efficacy: 90.9% (95% CI: 76.2, 96.5)
  - Absolute risk (using 1.3% seasonal incidence*): 12 fewer cases per 1,000 immunized (13 fewer to 10 fewer)
    - Number needed to immunize: 83 (77 to 100)
  - Absolute risk (using 2.2% seasonal incidence [phase 2b/3 trial placebo arm]): 20 fewer cases per 1,000 immunized (22 fewer to 17 fewer)
    - Number needed to immunize: 50 (45 to 59)
- **Concerns in certainty assessment**
  - Not serious (indirectness): trial excluded infants who were palivizumab eligible
- **Final evidence type: High**

*NVSN data 2016-2020 (unpublished), included if with acute respiratory infection

Abbreviations: LRTI: lower respiratory tract infection

Outcome 3: RSV-associated LRTI with ICU admission[1] through 150 days of follow-up

Study	Events[1]/Clesrovimab (n/N)	Events[1]/Placebo (n/N)	Efficacy[2] (95% CI)
Protocol 004	0/2398[3]	4[4]/1201[3]	100% (24, 100)

1. Defined as hospital admission for respiratory illness AND RSV-positive RT-PCR nasopharyngeal (NP) sample AND with evidence of admission in ICU in the associated serious adverse event (SAE) narrative by looking for one or more of these following key terms: ICU, PICU, NICU, mechanical ventilation, ventilator, intubation, intubated, intensive care, intensive care unit, intensive treatment unit, critical care unit.
2. Estimates and 95% CI were estimated by an exact method.
3. Patients were randomized 2:1 to the clesrovimab and placebo arms.
4. Onset of all 4 cases were prior to day 150. No cases occurred between days 150-180.

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval | ICU: intensive care unit | PICU: pediatric intensive care unit | NICU: neonatal intensive care unit

GRADE: RSV-associated LRTI with ICU admission through 150 days of follow-up (n=1 study)

- **Measures of effect**
  - Efficacy: 100% (95% CI: 24, 100)
  - Absolute risk (using 0.33% seasonal incidence [phase 2b/3 trial placebo arm]): 330 fewer per 100,000 (from 79 to 330 fewer)
    - Number needed to immunize: 303 (from 303 to 1,265)
- **Concerns in certainty assessment**
  - Not serious (indirectness): trial excluded infants who were palivizumab eligible
  - Serious (imprecision): number of study participants did not meet optimal information size for this outcome
- **Evidence type: Moderate**

Abbreviations: ICU: intensive care unite | LRTI: lower respiratory tract infection | CI: confidence interval

Outcome 4: All-cause medically attended LRTI[1] through 150 days of follow-up

Study	Events[1]/Clesrovimab n/N (%)	Events[1]/Placebo n/N (%)	Efficacy[2] (95% CI)
Protocol 004	526/2398[3] (21.9%)	296/1201[3] (24.6%)	13.1% (-0.6, 24.8)

1. Defined as outpatient and inpatient medically-attended LRTI due to any cause, defined by the presence of the following seen in an outpatient or inpatient clinical setting: cough or difficulty breathing AND 1 or more of the following: wheezing, chest wall in-drawing/retractions, rales/crackles, hypoxemia, tachypnea, dehydration due to respiratory symptoms.
2. Estimates and 95% CI were estimated from the modified Poisson regression with robust variance method.
3. Patients were randomized 2:1 to the clesrovimab and placebo arms.

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval

GRADE: All-cause medically-attended LRTI through 150 days of follow-up (n=1 study)

- **Measures of effect**
  - Efficacy: 13.1% (95% CI: -0.6, 24.8)
  - Absolute risk (using 24.6% seasonal incidence in phase 2b/3 controls): 26 fewer cases per 1,000 vaccinated (61 fewer to 1 more)
    - Number needed to immunize: 38 (16 to *)
- **Concerns in certainty assessment**
  - Not serious (indirectness): trial excluded infants who were palivizumab eligible
  - Serious (imprecision): width of the confidence interval contains estimates for which different policy decisions might be considered
- **Evidence type: Moderate**

*Upper bound of the confidence interval could not be calculated.

Abbreviations: LRTI: lower respiratory tract infection | | CI: confidence interval

Outcome 5: All-cause hospitalization with LRTI[1] through 150 days of follow-up

Study	Events[1]/Clesrovimab n/N (%)	Events[1]/Placebo (n/N)	Efficacy[2] (95% CI)
Protocol 004	60/2398[3] (2.5%)	58/1201[3] (4.8%)	49.0% (26.7, 64.5)

1. Defined by the presence of the following seen in an inpatient clinical setting: cough or difficulty breathing AND ≥ 1 indicator of LRTI (rhonchi, rales/crackles, wheezing) AND ≥1 indicator of severity (chest wall indrawing/retractions, hypoxemia, tachypnea, dehydration due to respiratory symptoms)
2. Estimates and 95% CI were estimated from the modified Poisson regression with robust variance method.
3. Patients were randomized 2:1 to the clesrovimab and placebo arms.

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval | RT-PCR: reverse transcription polymerase chain reaction | ICU: intensive care unit | PICU: pediatric intensive care unit | NICU: neonatal intensive care unit

GRADE: All-cause hospitalization with LRTI through 150 days of follow-up (n=1 study)

- **Measures of effect**
  - Efficacy: 49.0% (95% CI: 6.7, 64.5)
  - Absolute risk (using 4.1% seasonal incidence [phase 2b/3 trial controls]): 20 fewer cases per 1,000 immunized (27 fewer to 11 fewer)
    - Number needed to immunize: 50 (37 to 91)
- **Concerns in certainty assessment**
  - Not serious (indirectness): trial excluded infants who were palivizumab eligible
- **Evidence type: High**

Abbreviations: LRTI: lower respiratory tract infection | CI: confidence interval

Harms

Outcome 6: Serious adverse events (SAEs)[1] through 365 days post-dose

Study	Events[1]/Clesrovimab n/N (%)	Events[1]/Placebo n/N (%)	RR (95% CI)
Protocol 004	278/2409[2] (11.5%)	149/1202[2] (12.4%)	0.93 (0.77, 1.12)

1. Defined as an adverse event resulting in death, hospitalization, significant disability, or requiring medical intervention care, intensive care unit, intensive treatment unit, critical care unit. Serious adverse events may be related or unrelated to the study intervention.
2. Patients were randomized 2:1 to the clesrovimab and placebo arms.

Abbreviations: RR: risk ratio | CI: confidence interval

GRADE: Serious adverse events through 365 days post-dose (n=1 study)

- **Measures of effect**
  - Relative Risk: 0.93 (95% CI: 0.77 to 1.12)
  - Absolute risk: 9 fewer cases per 1,000 immunized (29 fewer to 16 more)
- **Concerns in certainty assessment**
  - Serious (imprecision): Too few infants included in the trial to capture rare serious adverse events
- **Evidence type: Moderate**

Abbreviations: CI: confidence interval

Summary of GRADE for clesrovimab

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
1. RSV-associated medically-attended LRTI	Critical	RCT (1)	Clesrovimab is effective in preventing RSV-associated medically-attended LRTI	**High**
2. RSV-associated LRTI with hospitalization	Critical	RCT (1)	Clesrovimab is effective in preventing RSV-associated LRTI with hospitalization	**High**
3. RSV-associated LRTI with ICU admission	Critical	RCT (1)	Clesrovimab is effective in preventing RSV-associated LRTI with ICU admission	**Moderate**
4. All-cause medically-attended LRTI	Important	RCT (1)	Clesrovimab is not effective in preventing all cause medically-attended LRTI	**Moderate**
5. All-cause LRTI with hospitalization	Important	RCT (1)	Clesrovimab is moderately effective in preventing all-cause hospitalization with LRTI	**High**
Harms				
6. Serious adverse events (SAEs)	Important	RCT (1)	SAEs were not more common in intervention group than placebo group	**Moderate**

Abbreviations: LRTI = lower respiratory tract infection | RCT = randomized controlled trial