Evidence to Recommendations Framework: Nirsevimab

Jefferson Jones MD MPH FAAP, CDR USPHS

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Evidence to Recommendations Framework

Nirsevimab is a form of passive immunization

- Active immunity results from infection or vaccination, which triggers an immune response

- Passive immunity is when a person receives antibodies from an external source
  - From mother to baby through transplacental or breastmilk transfer
  - Direct administration of antibodies, such as IVIG or monoclonal antibodies

https://www.cdc.gov/vaccines/vac-gen/immunity -types.htm

Evidence to Recommendations (EtR) Framework
Policy Questions

- Should one dose of nirsevimab be recommended a) at birth for all infants born during October to March and b) when entering first RSV season and <8 months of age for all infants born during April through September?
- Should one dose of nirsevimab be recommended for children <20 months of age with increased risk of severe disease entering their second RSV season?

Evidence to Recommendations (EtR) Framework

PICO Question 1

Population	All infants born during Apr-Sept who are <8 months of age when entering their first RSV season and infants born during Oct-Mar
Intervention	Nirsevimab (1 injection prior to start of RSV season or at birth if born during season, 50 mg if <5 kg or 100 mg if ≥5 kg)
Comparison	No nirsevimab prophylaxis
Outcomes	▪ Medically-attended RSV-associated lower respiratory tract infection (MA-LRTI) ▪ RSV-associated LRTI with hospitalization ▪ RSV-associated LRTI with ICU admission ▪ RSV-associated death ▪ All-cause MA-LRTI ▪ All-cause LRTI-associated hospitalization ▪ Serious adverse events

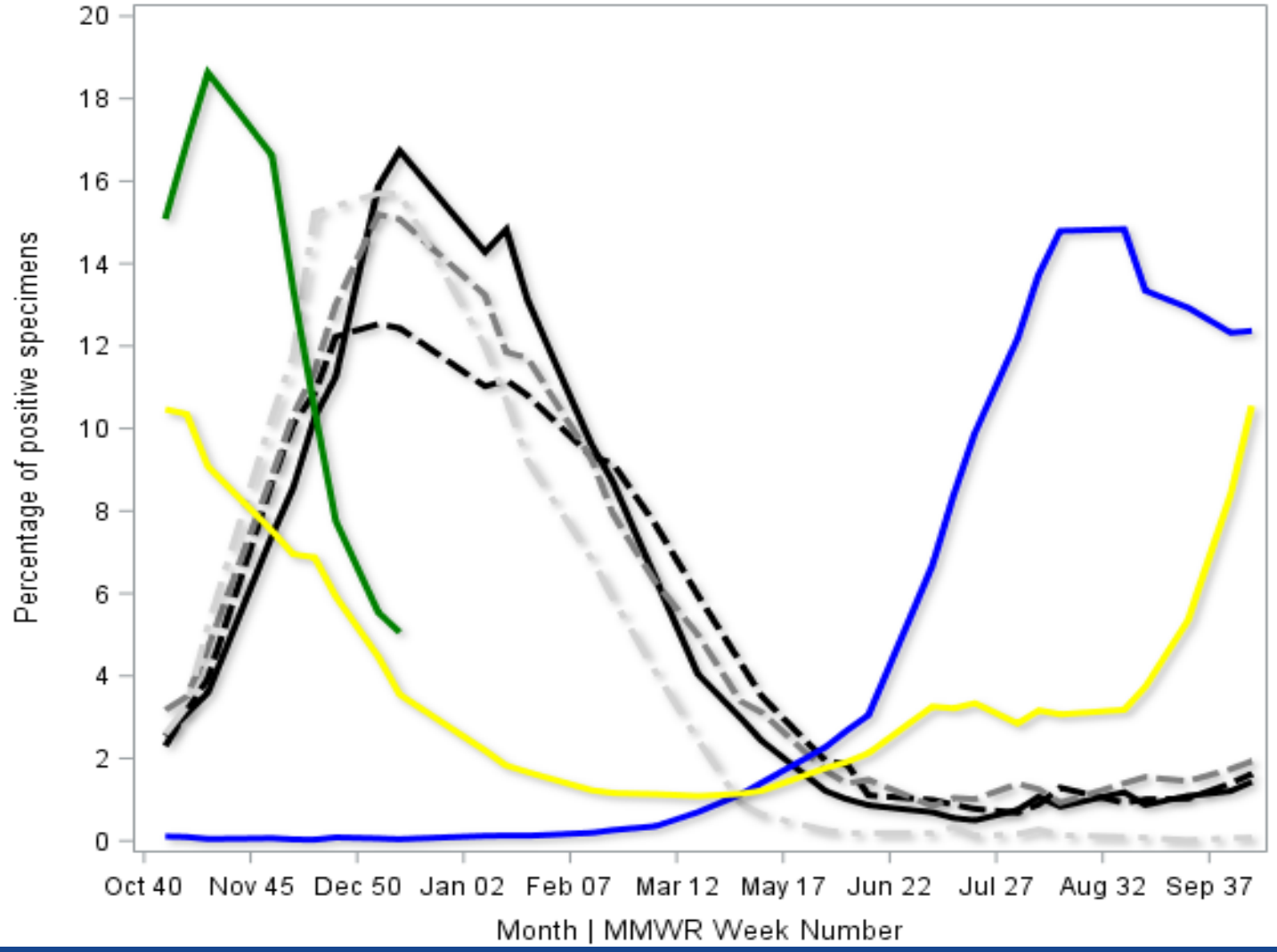
Evidence to Recommendations (EtR) Framework

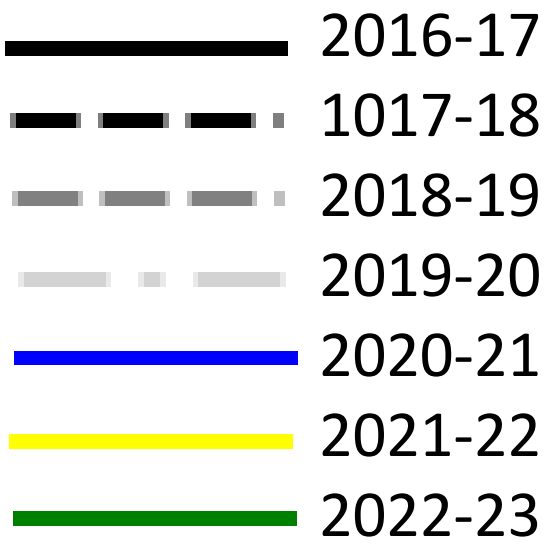
EtR Domain	Question(s)
Public Health Problem	▪ Is the problem of public health importance?
Benefits and Harms	▪ How substantial are the desirable anticipated effects? ▪ How substantial are the undesirable anticipated effects? ▪ Do the desirable effects outweigh the undesirable effects?
Values	▪ Does 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 entering their first RSV season and infants born during the RSV season of public health importance?

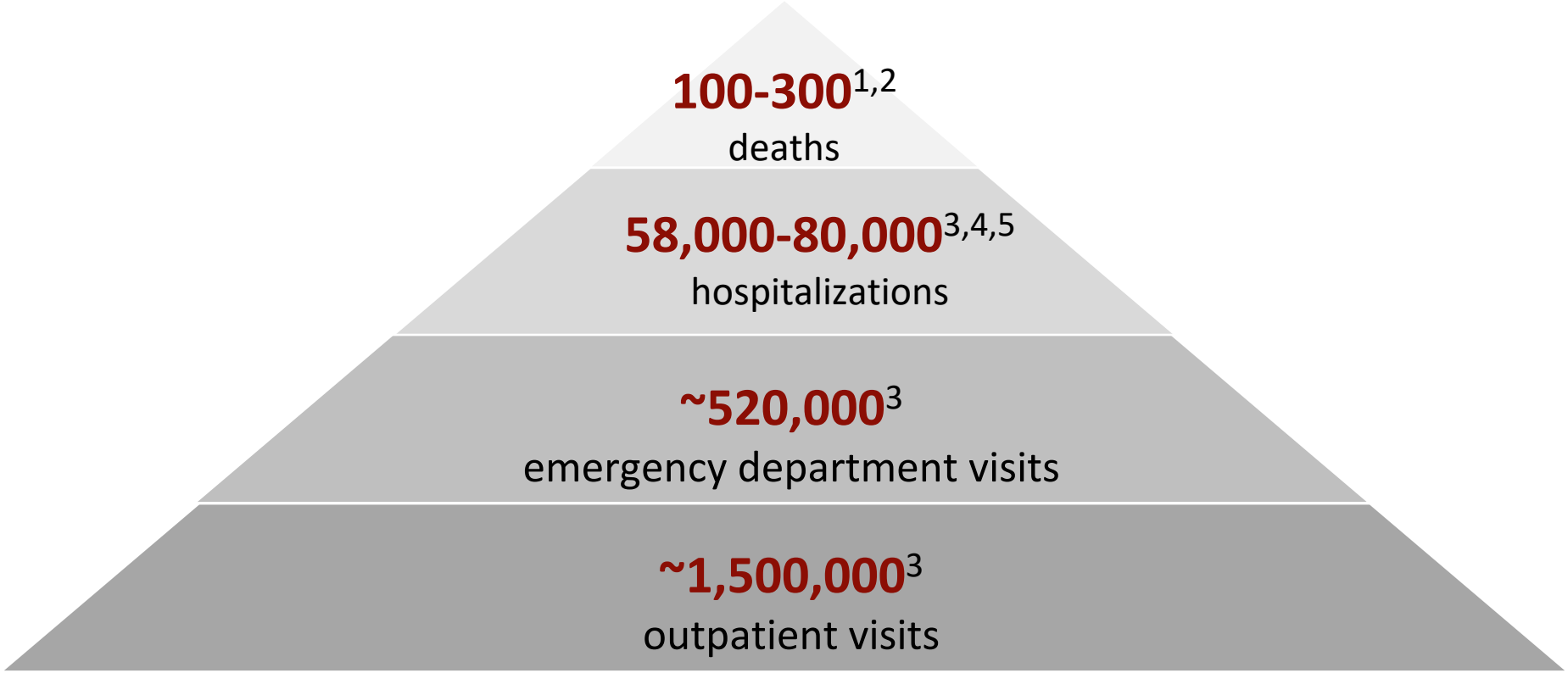
Changes in seasonality of RSV transmission following SARS-CoV2 introduction— NREVSS[1], 2016–2023





[1] Displayed results are among ~200 commercial, hospital, and state/local public health laboratories which consistently report RSV PCR tests at an annual average of ≥10 PCR tests and ≥30 weeks of the 12-month surveillance year. Testing is clinician-directed and results include all ages.

Each year among U.S. children aged less than 5 years, RSV is associated with…



[1]Thompson et al, JAMA, 2003; [2]Hansen et al, JAMA Network Open, 2022; [3]Hall et al, NEJM, 2009; [4]Rha et al., Peds, 2020; [5]McLaughlin et al, J Infect Dis, 2022; (*estimate 80,000 hospitalizations in infants <1y)

Epidemiology of RSV

- Pre-pandemic RSV seasonality is well defined with limited geographic variability in most of the U.S.
- RSV is the most common cause of hospitalization in U.S. infants
  - Highest hospitalization rates in first months of life
  - Risk declines by month with increasing age in infancy and early childhood
- Prematurity and other chronic diseases increase risk of RSV-associated hospitalization, but most hospitalizations are in healthy, term infants

Public Health Problem- Work Group Interpretation

- **Is RSV-associated disease among infants <8 months of age entering their first RSV season and infants born during the RSV season of public health importance?**

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

EtR Domain: Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

Outcomes, importance, and data sources

Outcome	Importance[a]	Data sources
Benefits		
Medically attended RSV LRTI	Critical	Phase 3 and phase 2b RCT[b]
RSV LRTI with hospitalization	Critical	Phase 3 and phase 2b RCT[b]
RSV LRTI with ICU admission	Critical	Phase 3 and phase 2b RCT[b]
Death due to RSV respiratory illness	Critical	No RSV deaths in trials
All-cause medically attended-LRTI	Important	Phase 3 and phase 2b RCT[b]
All-cause LRTI-associated hospitalization	Important	Phase 3 and phase 2b RCT[b]
Harms		
Serious Adverse Events (SAEs)	Important	Phase 3 and phase 2b RCT[b]

LRTI: Lower respiratory tract infection, RCT: randomized control trial, ICU: intensive care unit

[a] Three options: Critical; Important but not critical; Not important for decision making

[b] Includes 3012 participants in the phase 3 trials (born >34 weeks gestational age [GA]) and 860 participants in phase 2b trial (born 29-34 weeks GA). Among phase 2b trial participants, only those who received the recommended dose were included: infants ≥5 kg received a dose (50mg) that was determined to be too low to be efficacious for this weight

Efficacy estimates and concerns in certainty of assessment

Outcome	Efficacy estimate*	Concerns in certainty of assessment
Benefits		
Medically attended RSV LRTI	79.0% (95% CI: 68.5%–86.1%)	Not serious (indirectness)
RSV LRTI with hospitalization	80.6% (95% CI: 62.3%–90.1%)	Not serious (indirectness)
RSV LRTI with ICU admission	90.0% (95% CI: 16.4%–98.8%)	Serious (imprecision): Too few events Not serious (indirectness)
Death due to RSV respiratory illness	None recorded	N/A
All-cause medically attended-LRTI	34.8% (95% CI: 23.0–44.7%)	Not serious (indirectness)
All-cause LRTI-associated hospitalization	44.9% (95% CI:24.9%–59.6%)	Not serious (indirectness)

*Pooled phase 2b (excluding underdosed) and phase 3 trial estimate comparing nirsevimab arm to placebo arm

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All-cause LRTI-associated hospitalization	44.9% (95% CI:24.9%–59.6%)	Not serious (indirectness)

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All-cause LRTI-associated hospitalization	44.9% (95% CI:24.9%–59.6%)	Not serious (indirectness)

*Pooled phase 2b (excluding underdosed) and phase 3 trial estimate comparing nirsevimab arm to placebo arm

Relative risk of SAEs and concerns in certainty of assessment

Outcome	Relative risk[1]	Concerns in certainty of assessment
Harms		
Serious Adverse Events (SAEs)[2]	0.73 (95% CI: 0.59–0.89)	Serious (imprecision)

[1] Pooled phase 2b and phase 3 estimate comparing nirsevimab arm to placebo arm

[2] Adverse event resulting in death, hospitalization, significant disability, or requiring medical intervention. Adverse events include respiratory symptoms.

Summary of GRADE for nirsevimab

Outcome	Importance	Design (# of studies)	Findings	Level of certainty
Benefits				
Medically attended RSV LRTI	Critical	RCT (2)	Nirsevimab is effective in preventing medically attended RSV LRTI	**High**
RSV LRTI with hospitalization	Critical	RCT (2)	Nirsevimab is effective in preventing medically attended RSV LRTI with hospitalization	**High**
RSV LRTI with ICU admission	Critical	RCT (2)	Nirsevimab is likely effective in preventing medically attended RSV LRTI with ICU admission	**Moderate**
Death due to RSV	Critical	RCT (2)	No deaths reported	-
All-cause medically attended -LRTI	Important	RCT (2)	Nirsevimab is effective in preventing all cause medically attended LRTI	**High**
All-cause LRTI-associated hospitalization	Important	RCT (2)	Nirsevimab is effective in preventing all cause hospitalization with respiratory disease	**High**
Harms				
Serious adverse events	Critical	RCT (1)	SAEs were likely not more common in intervention group than placebo group	**Moderate**

[1] 1: High certainty; 2: Moderate certainty. 3: Low certainty; 4: Very low certainty.

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RSV LRTI with hospitalization	Critical	RCT (2)	Nirsevimab is effective in preventing medically attended RSV LRTI with hospitalization	**High**
RSV LRTI with ICU admission	Critical	RCT (2)	Nirsevimab is likely effective in preventing medically attended RSV LRTI with ICU admission	**Moderate**
Death due to RSV	Critical	RCT (2)	No deaths reported	-
All-cause medically attended -LRTI	Important	RCT (2)	Nirsevimab is effective in preventing all cause medically attended LRTI	**High**
All-cause LRTI-associated hospitalization	Important	RCT (2)	Nirsevimab is effective in preventing all cause hospitalization with respiratory disease	**High**
Harms				
Serious adverse events	Critical	RCT (1)	SAEs were likely not more common in intervention group than placebo group	**Moderate**

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RSV LRTI with ICU admission	Critical	RCT (2)	Nirsevimab is likely effective in preventing medically attended RSV LRTI with ICU admission	**Moderate**
Death due to RSV	Critical	RCT (2)	No deaths reported	-
All-cause medically attended -LRTI	Important	RCT (2)	Nirsevimab is effective in preventing all cause medically attended LRTI	**High**
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Harms				
Serious adverse events	Critical	RCT (1)	SAEs were likely not more common in intervention group than placebo group	**Moderate**

[1] 1: High certainty; 2: Moderate certainty. 3: Low certainty; 4: Very low certainty.

Overall evidence rating

- Overall evidence rating: moderate certainty
- Downgraded based on imprecision for protection against ICU admissions because of few recorded events and imprecision of SAEs because rare events are unlikely to be detected

Benefits and Harms

- How substantial are the desirable anticipated effects?
  - How substantial are the anticipated effect 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 undesirable anticipated effects?
  - How substantial are the anticipated effect 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?
  - What is the balance between the desirable effects relative to the undesirable effects?

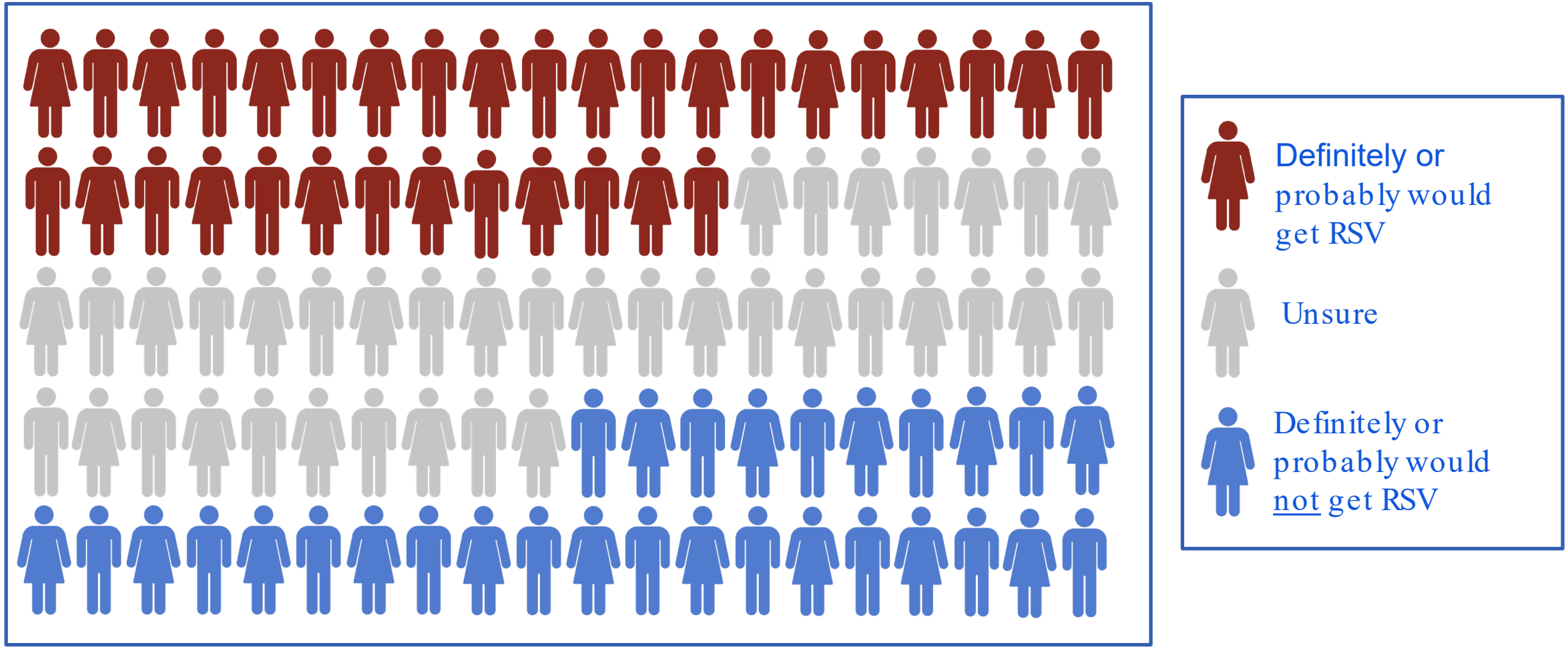
Favors intervention (Nirsevimab)
Favors comparison (No intervention)
Favors both
Favors neither
Unclear

EtR Domain: Values

Criterion 1: Does the target population feel that the desirable effects are large relative to undesirable effects?

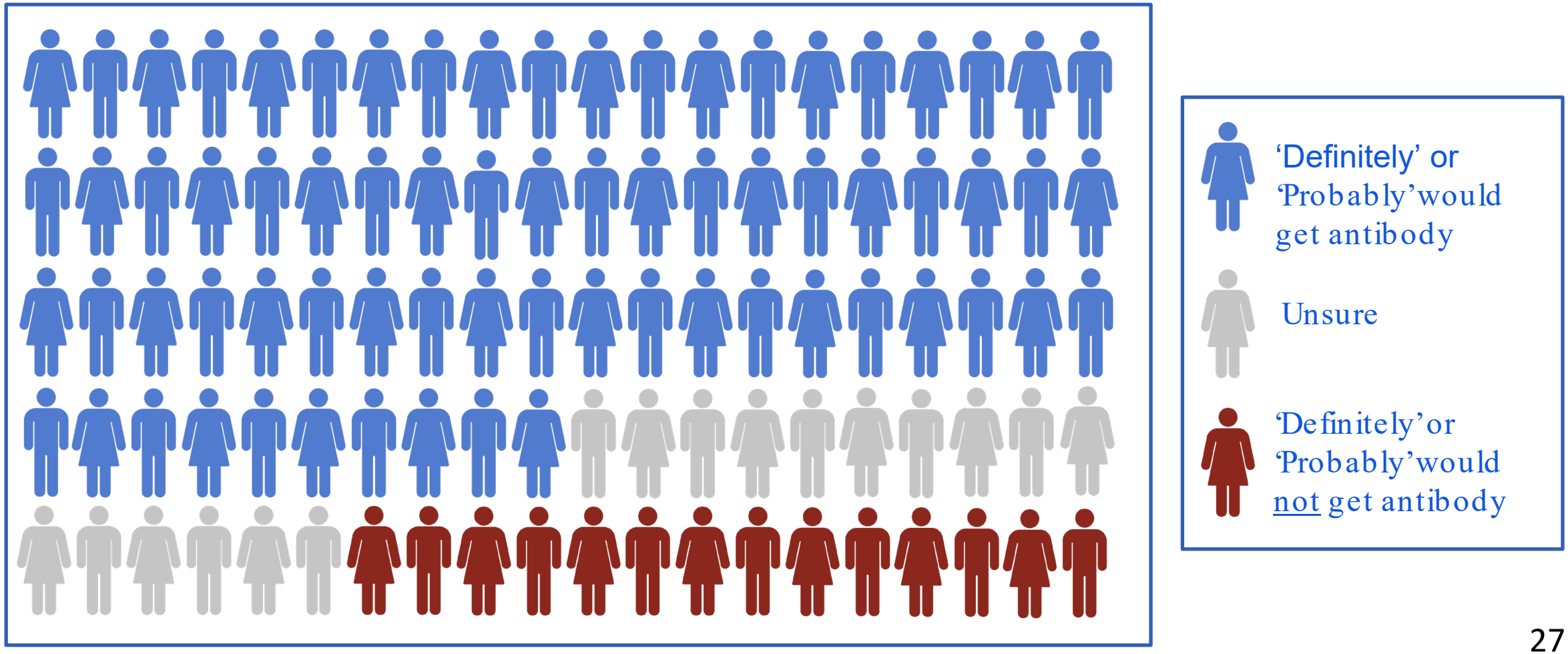
Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

About one-third (33%) of respondents thought their baby ‘definitely’ or ‘probably’ would get an RSV infection within one year after being born*



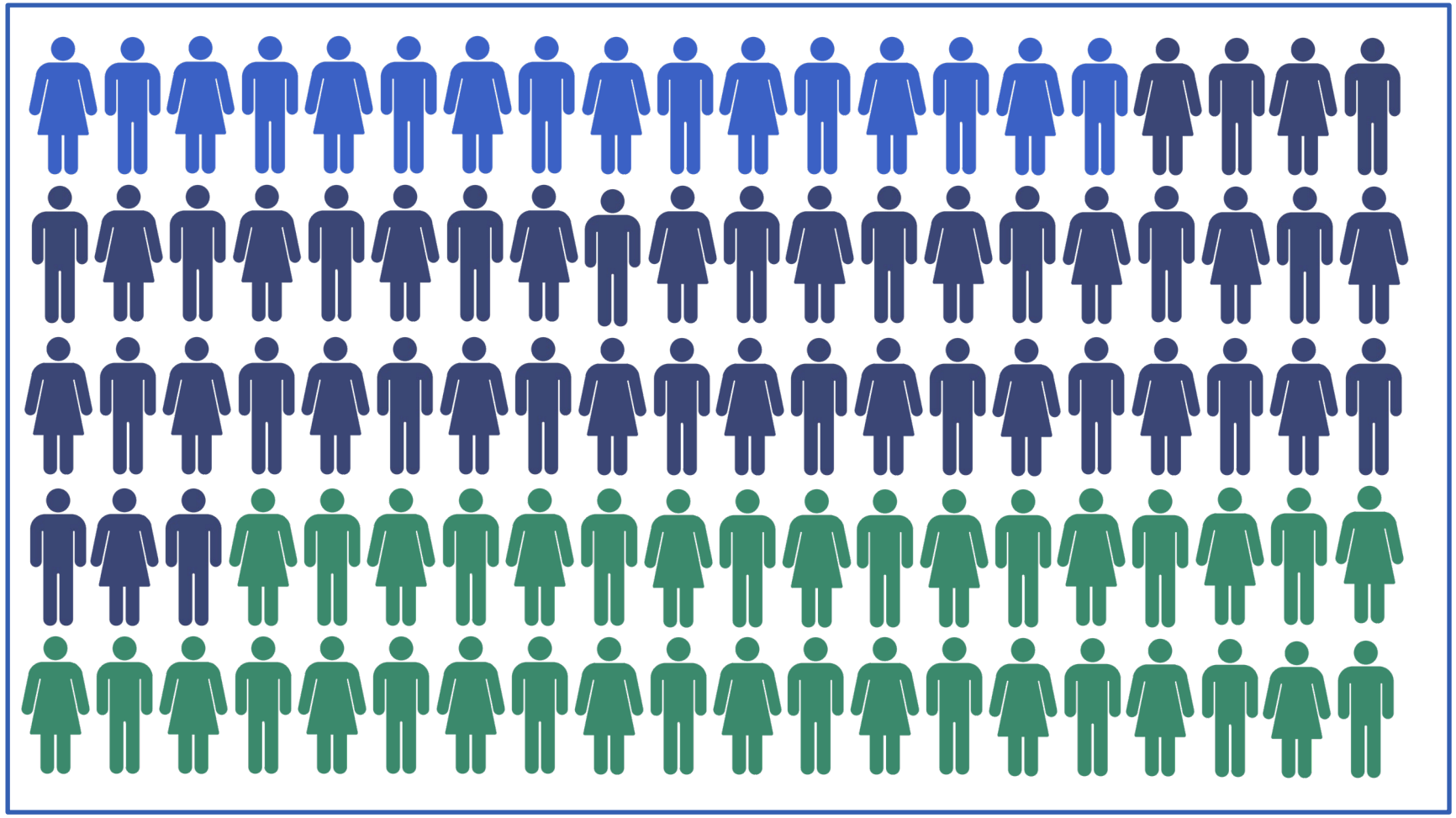
*CDC and University of Iowa/RAND survey, unpublished, of 523 people who were actively pregnant or pregnant within last 12 months; conducted during 12/2022–1/2023; 68% of respondents had previously heard of RSV.

70% of respondents said they ‘definitely’ or ‘probably’ would get an RSV antibody injection for their baby if safe and effective*



*If antibody injection was approved by FDA and recommended by CDC. CDC and University of Iowa/RAND survey, unpublished

63% of respondents said they were more worried or equally worried about their baby experiencing side effects from an RSV antibody injection vs. symptoms if sick with RSV



CDC and University of Iowa/RAND survey, unpublished

Parent attitudes about RSV

- 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

Values

- Criterion 1: Does the target population feel that the desirable effects are large relative to undesirable effects?

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

Values

- Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

Important uncertainty or variability
Probably important uncertainty or variability
Probably not important uncertainty or variability
No important uncertainty or variability
No known undesirable outcomes

EtR Domain: Acceptability

Is immunization with nirsevimab acceptable to key stakeholders?

Provider survey

- In survey by Alliance for Patient Access and National Coalition for Infant Health of 175 providers using YouGov to poll U.S. physicians
  - 99% agree that parents need more information about RSV
  - 86% report including RSV education as part of routine care
  - 97% said immunizations could help prevent RSV
  - 92% agreed that RSV immunization policy should ensure all children get access

https://admin.allianceforpatientaccess.org/wp-content/uploads/2023/01/AfPA-and-NCfIH_The-Indirect-Impact-of-RSV_Survey-Report_Jan-2023.pdf

Importance of RSV prevention recognized by relevant national organizations

- AAP states that development of safe and effective RSV immunization is a priority

- National Foundation for Infectious Disease roundtable agreed on the importance of rapid adoption and deployment of evidence-based RSV prevention
  - Included National Association of County and City Health Officials

AAP COID BGC Pediatrics 2014 Aug;134(2):405
https://www.nfid.org/wp-content/uploads/2022/04/NFID-RSV-Call-to-Action.pdf

Acceptability

- Is immunization with nirsevimab acceptable to key stakeholders?

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

EtR Domain: Feasibility

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

Administration and storage

- Administered as intramuscular injection using pre-filled, single-use syringe available in the following doses for infants born during or entering 1st RSV season:
  - 50mg (0.5mL) for infants weighing <5 kg or
  - 100mg (1.0 mL) for infants ≥5 kg
- For high-risk infants and children entering 2nd RSV season, dosing is 200mg (two 100 mg doses administered at the same time
- One dose of nirsevimab per season
- Storage at refrigerator temperatures (2°C - 8°C)
- May be kept at room temperature (20°C - 25°C) when protected from light for a maximum of 8 hours

Beyfortus summary of product characteristics. European Medicines Agency https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf

ACIP considerations

- Nirsevimab would be first passive immunization product to be independently included in CDC immunization schedule
- Proposed indication is for all infants and would result in population-level impacts
- Nirsevimab inclusion in Vaccines For Children (VFC) program undetermined

Considerations related to nirsevimab being classified as a drug

- Certain types of health care workers (e.g., medical assistants) can administer vaccines but might not be able to administer a monoclonal antibody depending on jurisdiction
- Adverse events would be reported to FDA Adverse Event Reporting System rather than the Vaccine Adverse Event Reporting System
- Billing and administration codes for nirsevimab have not been finalized
- Some state immunization information systems might not be able to include products that are considered drugs and not vaccines

Feasibility

- Is immunization with nirsevimab feasible to implement among all infants <8 months of age entering their first RSV season and infants born during the RSV season?

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Resource Use

Is nirsevimab immunization among all infants <8 months of age entering their first RSV season and infants born during the RSV season a reasonable and efficient allocation of resources?

Cost-effectiveness results

Cost of nirsevimab per infant [1]	ICER ($/QALY[2])
$300	$ 102,805
$500	$ 244,677

ICER: Incremental cost effectiveness ratio, QALY: quality-adjusted life year

[1] Cost includes cost of administration.

[2] Restricted to lower respiratory tract infection (i.e., upper respiratory infections from RSV excluded). Incorporated costs of outpatient, ED, inpatient, and death from RSV LRTI. Incidence of RSV-associated outpatient, ED, and inpatient events based on published and unpublished NVSN estimates. Nirsevimab efficacy based on phase 2b and phase 3 trial results. Other model assumptions from published literature. Cost of palivizumab not incorporated.

Resource Use

- Is nirsevimab immunuization among all infants <8 months of age entering their first RSV season and infants born during the RSV season a reasonable and efficient allocation of resources?

At $300 per infant

No	Probably No	Probably Yes	Yes	Varies	Don't know

At $500 per infant

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Equity

What would be the impact of nirsevimab on health equity?

Equity and payment

- Nirsevimab inclusion in Vaccines For Children (VFC) program undetermined

- If not included in VFC, state Medicaid, Medicaid expansion (Children's Health Insurance Programs), and private insurance would likely cover nirsevimab
  - Underinsured and uninsured would likely have reduced access

Seasonal incidence per 1,000 children of RSV-associated hospitalizations among American Indian and Alaska Native children <5 years of age, Nov 2019- May 2020 (SuNA)*

Age	Chinle, Arizona	Whiteriver, Arizona	Anchorage, Alaska	Yukon-Kuskokwim Delta, Alaska	NVSN** for comparison
0-5 Months	83.0 (52.0, 132.5)	70.4 (36.3, 136.6)	35.7 (20.4, 62.6)	132.3 (98.2, 178.1)	21.6 (20.0, 23.3)
6-11 Months	61.6 (35.9, 105.8)	90.1 (50.0, 162.3)	0.0 (0.0, 10.8)	91.6 (64.0, 131.0)	8.2 (7.1, 9.3)
0-11 Months	**71.8 (50.4, 102.4)**	**80.6 (51.9, 125.2)**	**19.2 (11.2, 33.0)**	**112.2 (89.3, 141.0)**	**14.9 (13.9, 16.0)**
12-23 Months	**42.1 (27.2, 65.3)**	**38.7 (22.0, 68.1)**	**15.6 (8.7, 27.7)**	**26.4 (16.6, 41.8)**	**4.5 (3.9, 5.2)**
24-59 Months	10.9 (6.8, 17.4)	8.2 (4.2, 16.0)	1.1 (0.3, 3.8)	5.9 (3.2, 10.9)	1.2 (1.2, 1.5)
0-59 Months	27.2 (21.4, 34.4)	25.4 (18.7, 34.5)	7.7 (5.3, 11.1)	32.7 (26.9, 39.7)	4.6 (4.3, 4.8)

*Hartman et al, RSV2022 12th International Symposium, Belfast 9/29/2022-10/2/2022; Atwell et al. (manuscript submitted, under peer-review) SuNA = RSV Surveillance among Native American Persons

**Incidence of RSV-associated hospitalization in 2019-2020 from Curns et al. (unpublished manuscript in preparation) included for comparison. NVSN = New Vaccine Surveillance Network.

RSV rates of severe disease by race and ethnicity

- National studies of death certificates found higher rates among non-Hispanic black compared with non-Hispanic White children[1]

- Hospitalization rates using New Vaccine Surveillance Network (NVSN) data have shown mixed results[2]
  - Several studies have shown no differences by race or ethnicity[3-5]
  - Even when significant, relative risk for non-Hispanic Black and Hispanic children mildly increased (e.g., relative risk of 1.2-2.2)[5-6]

1. Hansen J Infect Dis 2022 Aug 15;226(Suppl 2):S252-S266
2. NVSN analyses compared incidence rates of non-Hispanic Black, non-Hispanic White, and Hispanic children
3. Hall Pediatrics 2013 Aug;132(2):e341-e348
4. Hall NEJM 2009;360(6):588-598
5. Iwane Pediatrics 2004 Jun;113(6):1758-1764, findings differed by age group
6. Rha Pediatrics 2020 Jul;146(1):e20193611, findings differed by age group

Equity

- What would be the impact of nirsevimab on health equity?

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

EtR Summary: All infants 1st RSV season

EtR Domain	Question(s)	Work Group Judgments
Public Health Problem	▪ Is RSV-associated disease among infants <8 months of age entering their first RSV season and infants born during the RSV season of public health importance?	Yes
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?	Moderate to large Minimal to small Yes
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?	Yes/probably yes No consensus
Acceptability	▪ Is nirsevimab acceptable to key stakeholders?	Yes/probably yes
Feasibility	▪ Is the intervention feasible to implement?	Probably yes
Resource Use	▪ Is the intervention a reasonable and efficient allocation of resources?	Yes/probably yes (depends on price)
Equity	▪ What would be in the impact of the intervention on health equity?	—

Evidence to Recommendations Framework

Summary: Work Group Interpretations

All infants 1st RSV season

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: Work Group Interpretations

All infants 1st 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

2nd indication

Should one dose of nirsevimab be recommended for children <20 months of age with increased risk of severe disease entering their second RSV season?

Evidence to Recommendations (EtR) Framework

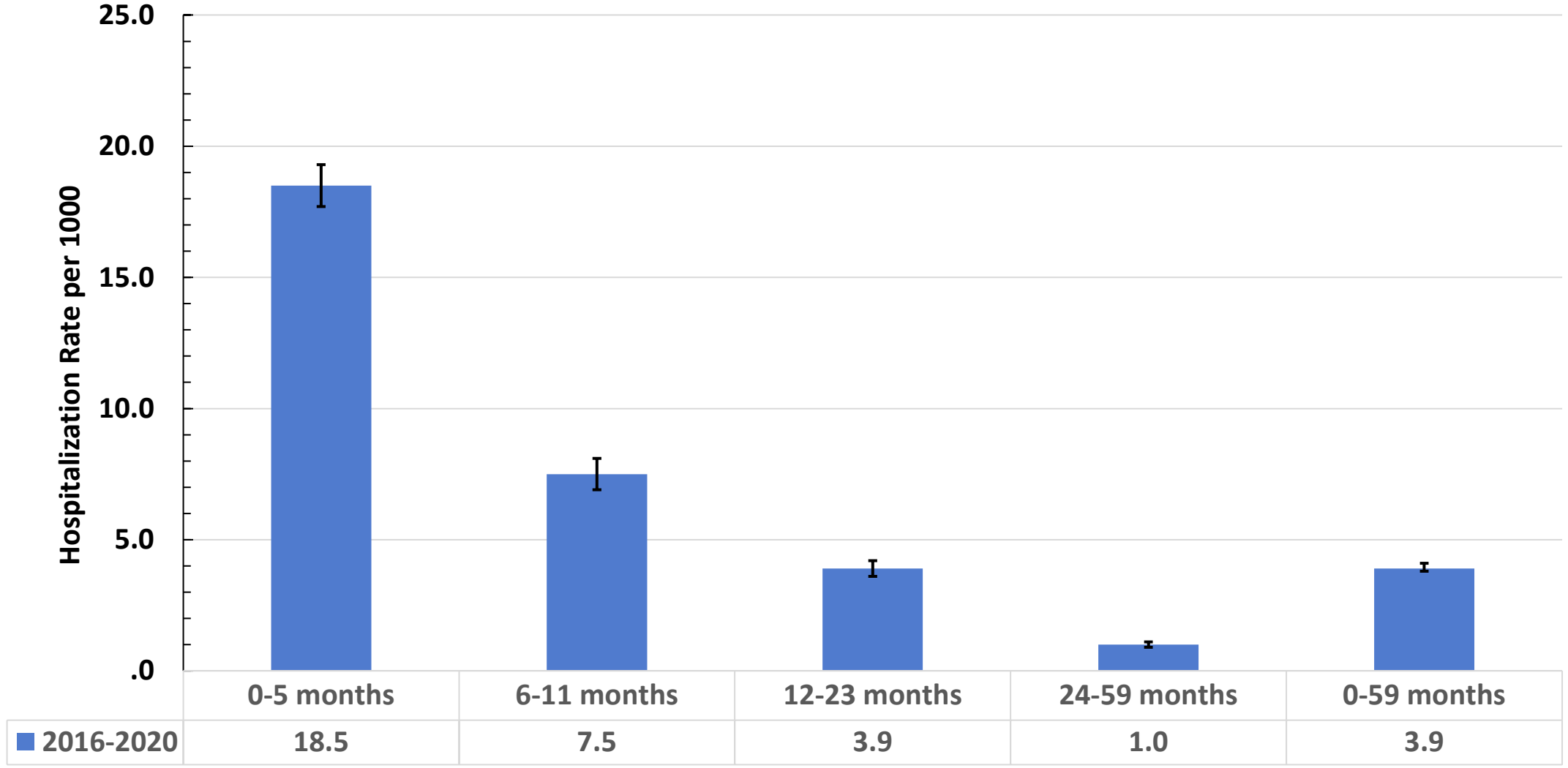
PICO Question

Population	Children **age <20 months who are at increased risk of severe disease** with RSV and who are entering their **second RSV season**
Intervention	Nirsevimab (**200 mg** [2 x 100 mg] injection prior to start of second RSV season)
Comparison	No nirsevimab prophylaxis
Outcomes	▪ Medically attended RSV associated lower respiratory tract infection (LRTI) ▪ Medically attended RSV associated LRTI with hospitalization ▪ Medically attended RSV associated LRTI with ICU admission ▪ RSV-associated death ▪ All-cause MA LRTI ▪ All-cause LRTI associated hospitalization ▪ Serious adverse events

EtR Domain: Public Health Problem

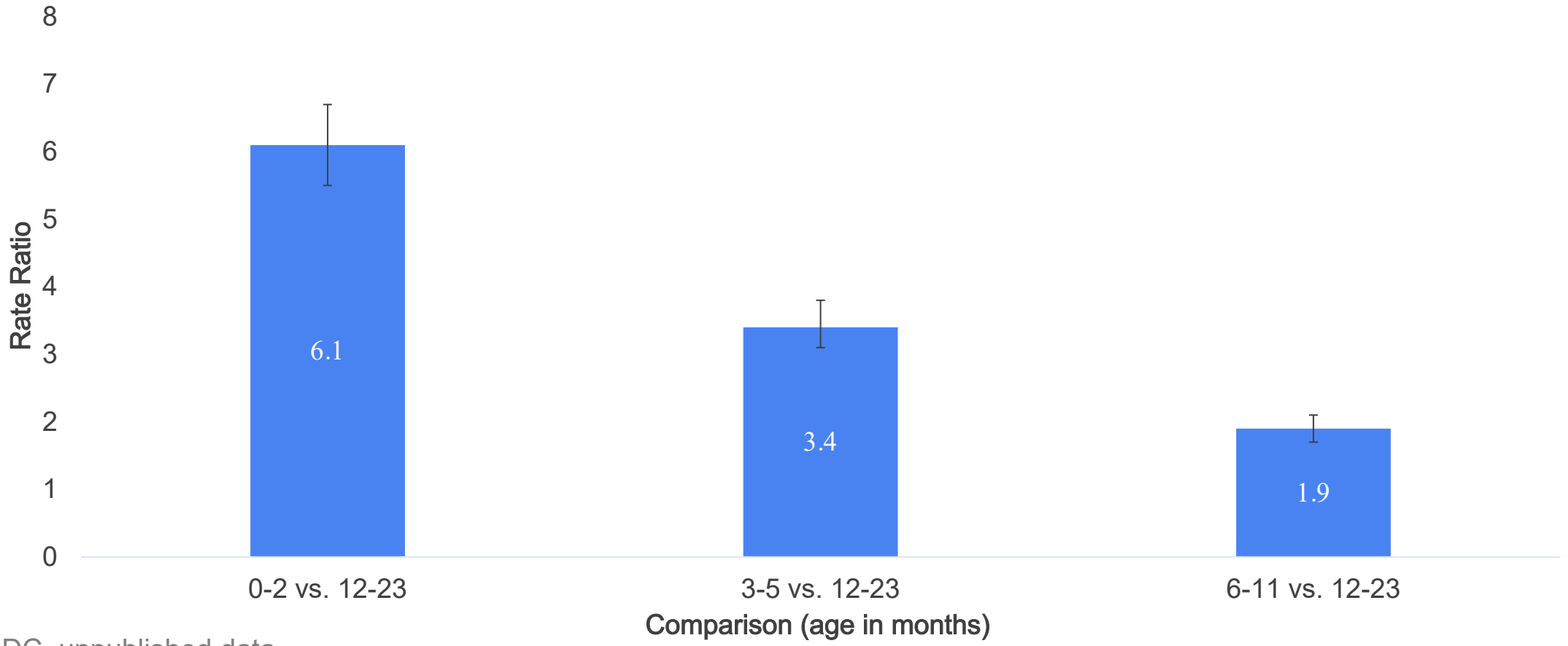
Is RSV disease among children who are at high risk of severe disease in their 2nd RSV season of public health importance?

RSV-associated hospitalization rates in children aged <5 years, New Vaccine Surveillance Network, 2016-2020



Relative risk in 1st RSV season compared with 2nd RSV season

Figure: RSV hospitalization rate ratios by age in months among children <2 years old, New Vaccine Surveillance Network, December 2016 through September 2020.



CDC, unpublished data

High-risk second season indications proposed by manufacturer

- Children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season, which may include but is not limited to children with:
  - Chronic lung disease of prematurity (CLD)
  - Hemodynamically significant congenital heart disease (CHD)
  - Immunocompromised states
  - Down syndrome
  - Cystic fibrosis
  - Neuromuscular disease
  - Congenital airway anomalies
- In MEDLEY study, palivizumab-eligible children with hemodynamically-significant CHD and CLD were included

Chronic conditions recommended by American Academy of Pediatrics (AAP) to qualify for palivizumab when entering 2nd RSV season

- Group recommended for palivizumab
  - CLD of prematurity if require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season
- Groups that can be considered for palivizumab
  - Profoundly immunocompromised
  - Cystic fibrosis if manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest XR or CT that persist when stable) or weight for length < 10th percentile.

American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415-20.

WG considerations for conditions and populations to be considered “high risk”

- Same children eligible for palivizumab when entering 2nd RSV season per American Academy of Pediatrics recommendations
  - Children with chronic lung disease of prematurity if require medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) during the 6-month period before the start of the second RSV season
  - Children who are profoundly immunocompromised
  - Children with cystic fibrosis with manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest XR or CT that persist when stable) or weight for length < 10th percentile
- Other conditions are under review

American Academy of Pediatrics Committee on Infectious Diseases and Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. Pediatrics. 2014;134(2):415-20.

Public Health Problem- Work Group Interpretation

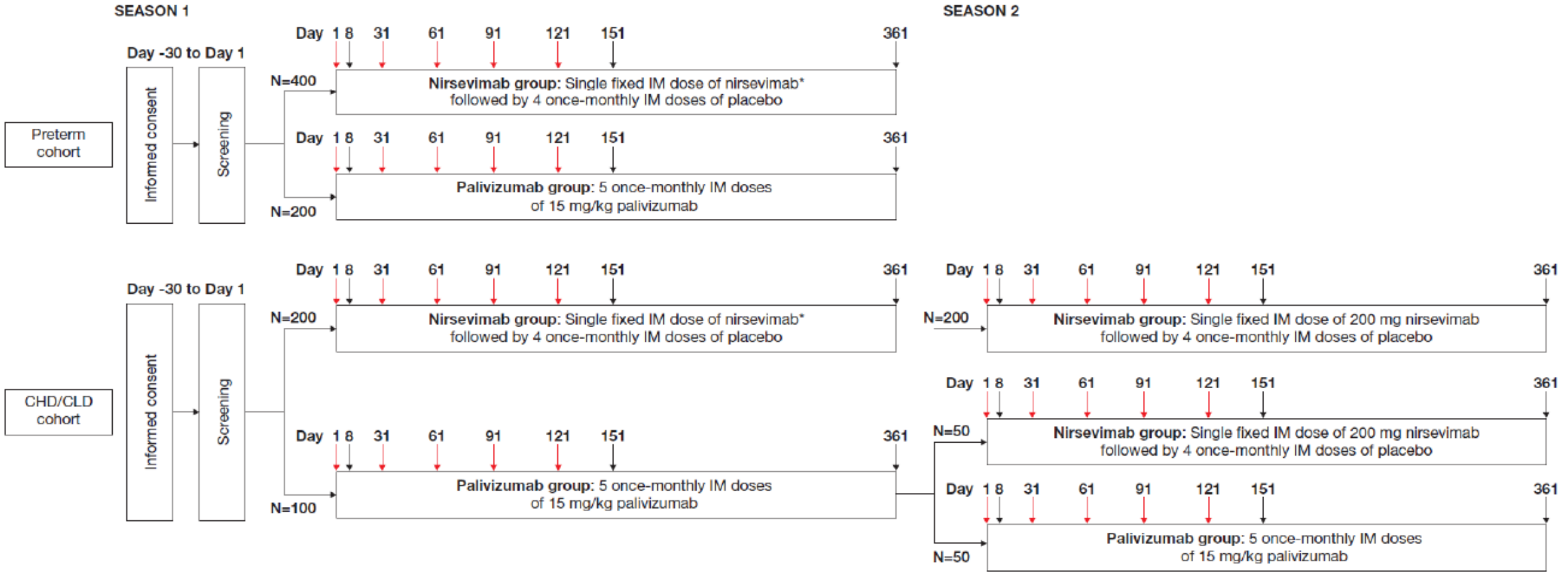
- **Is RSV disease among children who are at high risk of severe disease in their 2nd RSV season of public health importance?**

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

MEDLEY study: Dose for children ≤24 months with CLD/CHD entering their second RSV season



Domachowske et al. https://www.nejm.org/doi/full/10.1056/NEJMc2112186, https://clinicaltrials.gov/ct2/show/NCT03959488

Outcomes, importance, and data sources

Outcome	Importance[a]	Data sources
Benefits		
Medically attended RSV LRTI	Critical	MEDLEY, Domachowske et al.
RSV LRTI with hospitalization	Critical	No available data
RSV LRTI with ICU admission	Critical	No available data
Death due to RSV respiratory illness	Critical	No available data
All-cause medically attended-LRTI	Important	No available data
All-cause LRTI-associated hospitalization	Important	No available data
Harms		
Serious Adverse Events (SAEs)	Important	MEDLEY, Domachowske et al.

[a] Three options: Critical; Important but not critical; Not important for decision making

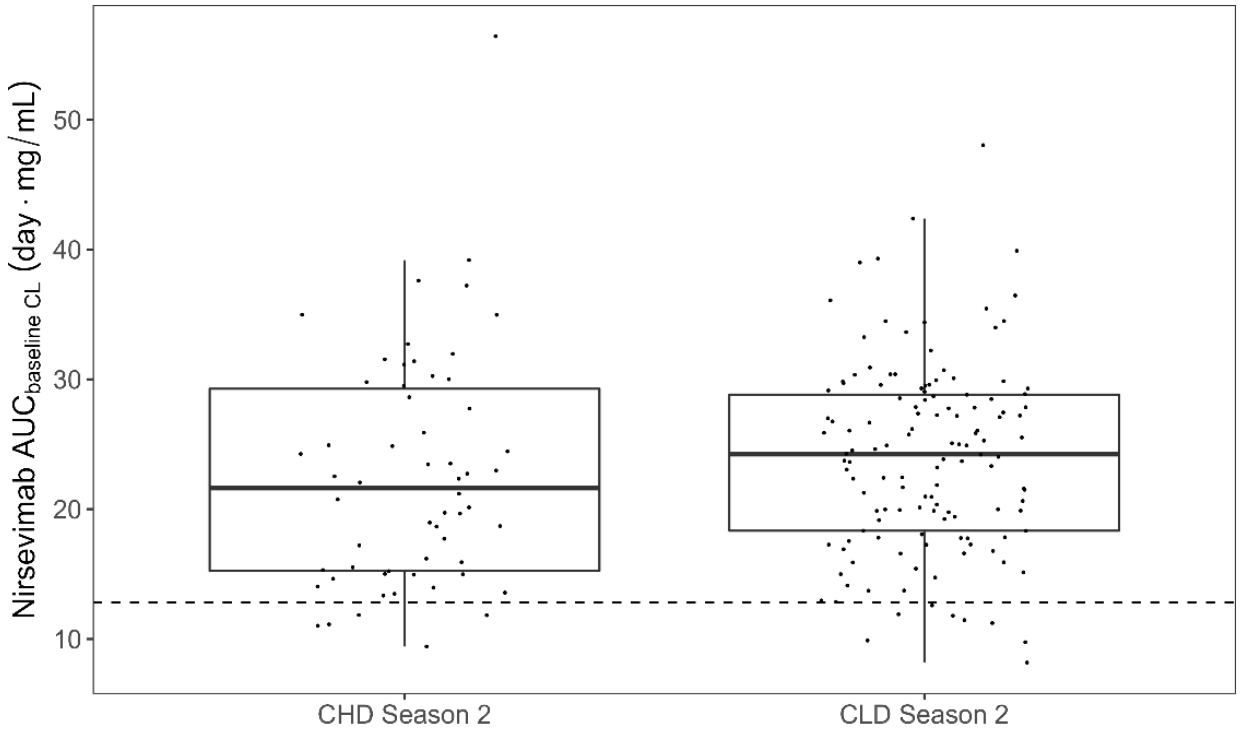
Medically attended (MA)* RSV LRTI

- MEDLEY designed as safety and pharmacokinetics (PK) study
- No clinical efficacy data available for children <24 months at high risk of severe RSV disease entering their second RSV season
- PK data from Phase 2b, Phase 3, and MEDLEY studies (i.e., among infants <12 months of age) were analyzed using population modelling
- Area under the curve ($AUC_{0-\infty}$) was derived using individual estimates as a measure of exposure to nirsevimab
- $AUC_{0-\infty}$ was then correlated to efficacy for prevention of the first episode of MA RSV LRTI in infants age <12 months from Phase 2b, Phase 3 and MEDLEY trials

*Medically attended means presented for medical care, either outpatient or inpatient

Pharmacokinetic data for children ≤24 months with CLD/CHD entering their second RSV season who received 200 mg of nirsevimab

	CHD (N=58)	CLD (N=132)	Total (N=190)
AUCbaseline CL ≥ Threshold	55 (94.8%)	127 (96.2%)	182 (95.8%)



Data from Sanofi/AstraZeneca

Dashed black line is the AUC Exposure-Response threshold (12.8 day*mg/mL)

Notes: black points are individual AUC predictions.

AUC = area under the serum concentration-time curve derived from dose and post-hoc clearance values at baseline from the final population PK model; CHD = congenital heart disease; CL = clearance; CLD = chronic lung disease; GA = gestational age

- Pre-determined threshold of 80% meeting PK criteria met

GRADE: medically attended RSV LRTI (n=1 study)

- Measures of effect:
  - Pharmacokinetic extrapolation from efficacy in infants <12 months of age for prevention of the first MA RSV LRTI to pharmacokinetic levels in children ≤24 months with CLD/CHD entering their second RSV season
- Concerns in certainty assessment:
  - Very serious (indirectness due to surrogate outcome, outcome established in 1st season, and population that does not match proposed indication)
- Evidence type:
  - Low certainty

Available safety data from children ≤24 months with CLD/CHD entering their second RSV season who received nirsevimab (200 mg) or palivizumab (15 mg/kg)

Subjects with	CLD/CHD Cohort		
	Palivizumab/ Palivizumab[1] (N=42) N (%)	Palivizumab / Nirsevimab[1] (N=40) N (%)	Nirsevimab / Nirsevimab[1] (N=180) N (%)
At least one adverse event[2]	29 (69.0)	29 (72.5)	126 (70.0)
At least one serious event[3]	0 (0.0)	4 (10.0)	17 (9.4)
At least one investigational product-related event	0 (0.0)	0 (0.0)	0 (0.0)
Any adverse event with outcome of death	0 (0.0)	0 (0.0)	0 (0.0)

[1] Palivizumab/ Palivizumab = Palivizumab in season 1 / Palivizumab in season 2; Palivizumab / Nirsevimab = Palivizumab in season 1 /Nirsevimab in season 2; Nirsevimab / Nirsevimab = Nirsevimab in season 1 / Nirsevimab in season 2

[2] Any untoward medical occurrence (e.g., unintended abnormal laboratory, symptom, or disease temporally associated with product, whether or not considered associated); [3] AE resulting in death, hospitalization, significant disability, or required medical intervention.

Data from Sanofi/AstraZeneca

GRADE: Serious adverse events (n=1 study)

- Measures of effect
  - Relative Risk: 8.4 (95% CI: 0.52-135.50)[1]
  - Absolute risk: 176 more cases per 1,000 immunized (95% CI: 11 fewer to 1,000 more)
- Concerns in certainty assessment
  - Serious (indirectness because comparison group is palivizumab recipients rather than placebo)
  - Very serious (imprecision)
- Evidence type:
  - Very low certainty

[1] Relative risk of a serious adverse event among children who received nirsevimab in their 2nd RSV season compared with children who received palivizumab their 2nd RSV season. Because no SAEs were reported in palivizumab group, 0.5 was added to both the nirsevimab and the palivizumab groups to calculate relative risk.

Summary of GRADE for nirsevimab dose for second season

Outcome	Importance	Design (# of studies)	Findings	Level of certainty
Benefits				
Medically attended (MA) RSV LRTI	Critical	3	Nirsevimab might be effective in preventing MA RSV LRTI	**Low**
RSV LRTI with hospitalization	Critical		No available data	
RSV LRTI with ICU admission	Critical		No available data	
RSV-associated death	Critical		No available data	
All cause medically attended LRTI	Important		No available data	
All cause hospitalization with respiratory disease	Important		No available data	
Harms				
Serious adverse events (SAEs)	Critical	1	SAEs might not be more common in intervention group than placebo group	**Very low**

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Overall evidence rating

- Overall evidence rating: Very low certainty

- Downgraded based on indirectness because pharmacokinetic data used as surrogate for efficacy, population did not include children that matches proposed indication, study small in size, and no placebo group was included for comparison

Benefits and harms of nirsevimab

- How substantial are the desirable 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 of nirsevimab

- How substantial are the undesirable anticipated effects?
  - How substantial are the anticipated effect for each main outcome for which there is an undesirable effect?

Minimal	Small	Moderate	Large	Varies	Don't know

Benefits and harms of nirsevimab

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

Favors intervention (Nirsevimab)
Favors comparison (No intervention)
Favors both
Favors neither
Unclear

EtR Domains: Values, Acceptability, and Feasibility

Values

- Criterion 1: Does the target population feel that the desirable effects are large relative to undesirable effects?

No	Probably No	Probably Yes	Yes	Varies	Don't know

Values

- Criterion 2: Is there important uncertainty about, or variability in, how much people value the main outcomes?

Important uncertainty or variability
Probably important uncertainty or variability
Probably not important uncertainty or variability
No important uncertainty or variability
No known undesirable outcomes

Acceptability

- Is RSV prevention with nirsevimab acceptable to key stakeholders?

No	Probably No	Probably Yes	Yes	Varies	Don't know

Feasibility

- Additional visit to provider might be needed for administration of nirsevimab prior to beginning of 2nd RSV season

- Is nirsevimab feasible to implement among high-risk children <20 months of age entering their second RSV season?

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Resource Use

Resource Use

- Is nirsevimab use among all high-risk children aged <20 months of age entering their second RSV season a reasonable and efficient allocation of resources?

$600 per child

No	Probably No	Probably Yes	Yes	Varies	Don't know

$1000 per child

No	Probably No	Probably Yes	Yes	Varies	Don't know

EtR Domain: Equity

Equity

- Equity issues differ by chronic condition among infants and young children
- Non-Hispanic Black populations experience higher rates of preterm birth than non-Hispanic White population[1]
- For children with cystic fibrosis, the majority are from non-Hispanic white populations[2]
- Hispanic populations may have higher prevalence of Down syndrome than non-Hispanic White populations[3]
- Hispanic and non-Hispanic American Indian and Alaska Native populations may have higher prevalence of neuromuscular disorders than non-Hispanic White populations[3]

1. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm
2. McGarry Pediatr Pulmonol 2021 Jun;56(6):1496-1503
3. Mai Birth Defects Res 2019 Nov 1;111(18):1420-1435

Equity

- What would be the impact of nirsevimab on health equity among high-risk children entering their 2nd RSV season?

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

Summary: Children at high risk entering 2nd RSV season

EtR Domain	Question(s)	Work Group Judgments
Public Health Problem	▪ Is RSV disease among children <20 months who are at high risk of severe disease of public health importance?	Yes
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?	Moderate Minimal Favors nirsevimab
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?	Probably yes Probably no
Acceptability	▪ Is nirsevimab acceptable to key stakeholders?	Probably yes
Feasibility	▪ Is the intervention feasible to implement?	Probably yes
Resource Use	▪ Is the intervention a reasonable and efficient allocation of resources?	$600: Probably yes $1000: Probably yes or probably no
Equity	▪ What would be in the impact of the intervention on health equity?	-

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Children at high risk entering 2nd RSV season

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: Work Group Interpretations

Children at high risk entering 2nd 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

Summary

1st RSV season

- The WG recommends nirsevimab a) at birth for all infants born during October to March and b) when entering first RSV season and <8 months of age for all infants born during April through September?

- Many expressed concerns about feasibility and equity, particularly because inclusion in VFC is unknown

- Some WG expressed concern that at higher prices, nirsevimab may not be a reasonable and efficient allocation of resources

2nd RSV season

- WG would like more time to consider which infants and children would be sufficiently high risk to warrant nirsevimab in their 2nd RSV season
  - Limited efficacy and safety data
  - Limited data to measure the risk of severe disease in the 2nd RSV season
  - At this time, WG recommended nirsevimab for those who are eligible for palivizumab in their 2nd RSV season, since assumed to be cost effective
  - WG will continue to evaluate other conditions

ACIP Policy Questions

- Should one dose of nirsevimab be recommended a) at birth for all infants born during October to March and b) when entering first RSV season and <8 months of age for all infants born during April through September?

- Should one dose of nirsevimab be recommended for children <20 months of age entering their second RSV season who are eligible for palivizumab in their second RSV season?

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Evelyn Twentyman
Rebecca Morgan
Doug Campos-Outcalt

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov