Evidence to Recommendations Framework:

Nirsevimab Updates

Jefferson Jones MD MPH FAAP, CDR USPHS
Co-Lead, Respiratory Syncytial Virus Vaccines - Pediatric/Maternal Work Group
Coronavirus and Other Respiratory Viruses Division
National Center for Immunization and Respiratory Diseases
August 3, 2023

Evidence to Recommendations (EtR) Framework
Policy Questions

- Should one dose of nirsevimab be recommended for infants aged <8 months born during or entering their first RSV season (50 mg for infants <5 kg and 100 mg for infants ≥5 kg)?
- Should one dose of nirsevimab be recommended children aged 8–19 months who are at increased risk of severe RSV disease and entering their second RSV season (200 mg)?

- Given an average RSV season of 4–5 months, infants aged 8 months and children aged 20 months would be experiencing their second and third RSV seasons, respectively

Nirsevimab is a 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

IVIG= Intravenous Immunoglobulin Therapy

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

Evidence to Recommendations (EtR) Framework

PICO Question 1

Population	Infants aged <8 months born during or entering their first RSV season
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 (LRTI) ▪ RSV-associated LRTI with hospitalization ▪ RSV-associated LRTI with ICU admission ▪ RSV-associated death ▪ All-cause medically attended LRTI ▪ All-cause LRTI-associated hospitalization ▪ Serious adverse events

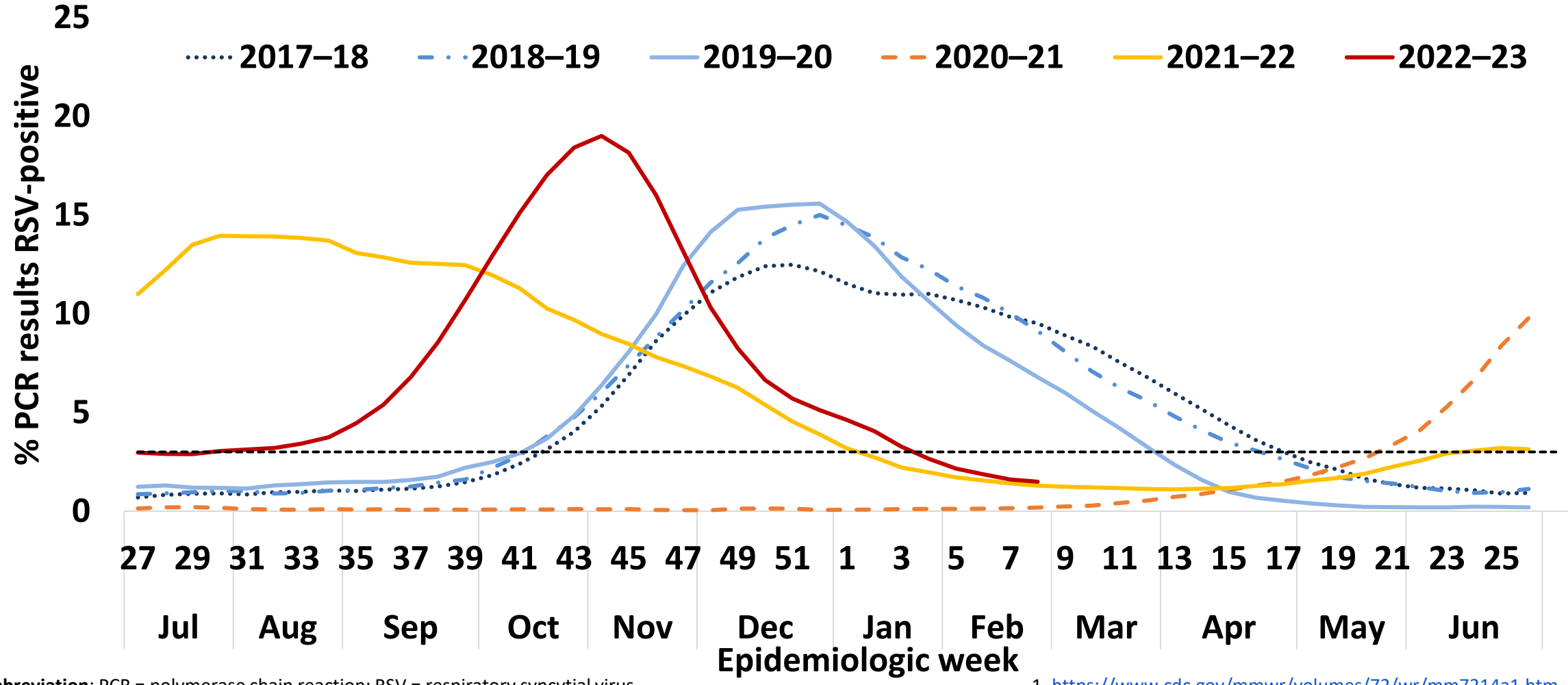
Evidence to Recommendations (EtR) Framework

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], 2017–2023



Abbreviation: PCR = polymerase chain reaction; RSV = respiratory syncytial virus.

1. https://www.cdc.gov/mmwr/volumes/72/wr/mm7214a1.htm

* 3-week centered moving averages of percentage of RSV-positive PCR results nationwide. The black dotted line represents the threshold for a seasonal epidemic (3% RSV-positive laboratory PCR results).

Epidemiology of RSV

- 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
- Work group felt that RSV-associated disease in infants born or entering their first RSV season is of public health importance

EtR Domain: Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

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%)	None
RSV LRTI with hospitalization	80.6% (95% CI: 62.3%–90.1%)	None
RSV LRTI with ICU admission	90.0% (95% CI: 16.4%–98.8%)	Serious (imprecision): Too few events
Death due to RSV respiratory illness	None recorded	N/A
All-cause medically attended-LRTI	34.8% (95% CI: 23.0–44.7%)	None
All-cause LRTI-associated hospitalization	44.9% (95% CI:24.9%–59.6%)	None

*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	Evidence type[1]
Benefits				
Medically attended RSV LRTI	Critical	RCT (2)	Nirsevimab is effective in preventing medically attended RSV LRTI	**High**
RSV-associted LRTI with hospitalization	Critical	RCT (2)	Nirsevimab is effective in preventing medically attended RSV LRTI with hospitalization	**High**
RSV-associated LRTI with ICU admission	Critical	RCT (2)	Nirsevimab is likely effective in preventing medically attended RSV LRTI with ICU admission	**Moderate**
RSV-associated death	Critical	RCT (2)	No RSV-associated 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 (2)	SAEs were likely not more common in intervention group than placebo group	**Moderate**

Additional safety data provided at Antimicrobial Drugs Advisory Committee meeting

- Most commonly reported adverse reaction were injection site reactions (0.3%) and rash (0.9%)

- FDA noted an imbalance in deaths between nirsevimab and the control arms but determined that the deaths were unlikely to be related to nirsevimab

https://www.fda.gov/advisory-committees/advisory-committee-calendar/june-8-2023-meeting-antimicrobial-drugs-advisory-committee-meeting-announcement-06082023

Nirsevimab phase 3b study (HARMONIE)[1]

- Enrolled 8,058 infants
  - Age at enrollment: 49% <3 month, 24% 3-5 months, 28% ≥6 months
  - 85% born at term, 50% born in season
- Conducted in France, UK, and Germany during August 8, 2022–February 28, 2023
- Randomized to nirsevimab or no injection
- Primary endpoint RSV hospitalization
  - LRTI hospitalization with positive RSV test
  - RSV tests ordered by clinician and not on all patients with LRTI
  - Participants followed for at least 12 months after randomization
- At end of RSV season, preliminary efficacy results released
  - Median post-randomization follow up time of 2.5 months

[1] Study not peer reviewed and information provided directly by sponsor; https://www.clinicaltrials.gov/study/NCT05437510

HARMONIE preliminary results[1]

- Efficacy
  - RSV hospitalization: 83% (95% CI 68%–92%)
  - Severe disease (SaO2 <90% and oxygen given): 76% (95% CI 33%–93%)
  - All-cause hospitalization with LRTI during RSV season: 58% (95% CI 40%–71%)
- Safety
  - Grade 1 AEs slightly higher in nirsevimab arm (29%) vs no intervention arm (25%)
  - Number of Grade 2 and Grade 3 AEs similar between nirsevimab and control arm

SaO2= oxygen saturation; AE= adverse event

[1] Study not peer reviewed and information provided directly by sponsor; https://www.clinicaltrials.gov/study/NCT05437510/. Results analyzed as of 2/28/2023 because RSV season had ended, and median duration of follow up was 2.5 months at that time.

Benefits and harms summary

- Overall GRADE evidence rating: moderate
- 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
- The work group felt that the:
  - Desirable anticipated effects of nirsevimab were moderate to large
  - Undesirable anticipated effects of nirsevimab were minimal to small
  - Desirable effects outweighed the undesirable effects and favored nirsevimab over no intervention

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?

Summary results of CDC and University of Iowa/RAND survey on RSV immunizations to prevent RSV disease in infants

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

Values summary

- The work group determined that the target population probably feels that the desirable effects are large relative to undesirable effects
- The work group varied in whether they felt there was important uncertainty about, or variability in, how much people value the main outcomes

*If antibody injection was approved by FDA and recommended by CDC.

CDC and University of Iowa/RAND survey, unpublished

EtR Domain: Acceptability

Is immunization with nirsevimab acceptable to key stakeholders?

Acceptability Summary

- In a survey of U.S. pediatric providers, over 85% agreed that parents need more information about RSV, that immunization could help prevent RSV, and that immunization policy should ensure all children get access[1]
- The American Academy of Pediatrics and National Foundation For Infectious Diseases Roundtable have stated the need for safe and effective RSV prevention products[2,3]
- The work group felt that passive immunization with nirsevimab was probably acceptable to key stakeholders

1. https://admin.allianceforpatientaccess.org/wp-content/uploads/2023/01/AfPA-and-NCfIH_The-Indirect-Impact-of-RSV_Survey-Report_Jan-2023.pdf
2. AAP COID BGC Pediatrics 2014 Aug;134(2):415-20.
3. https://www.nfid.org/wp-content/uploads/2022/04/NFID-RSV-Call-to-Action.pdf

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?

Work Group Feasibility Interpretation

- Considerations reviewed in separate presentation
- Work group felt that nirsevimab will probably be feasible to implement

EtR Domain: Resource Use

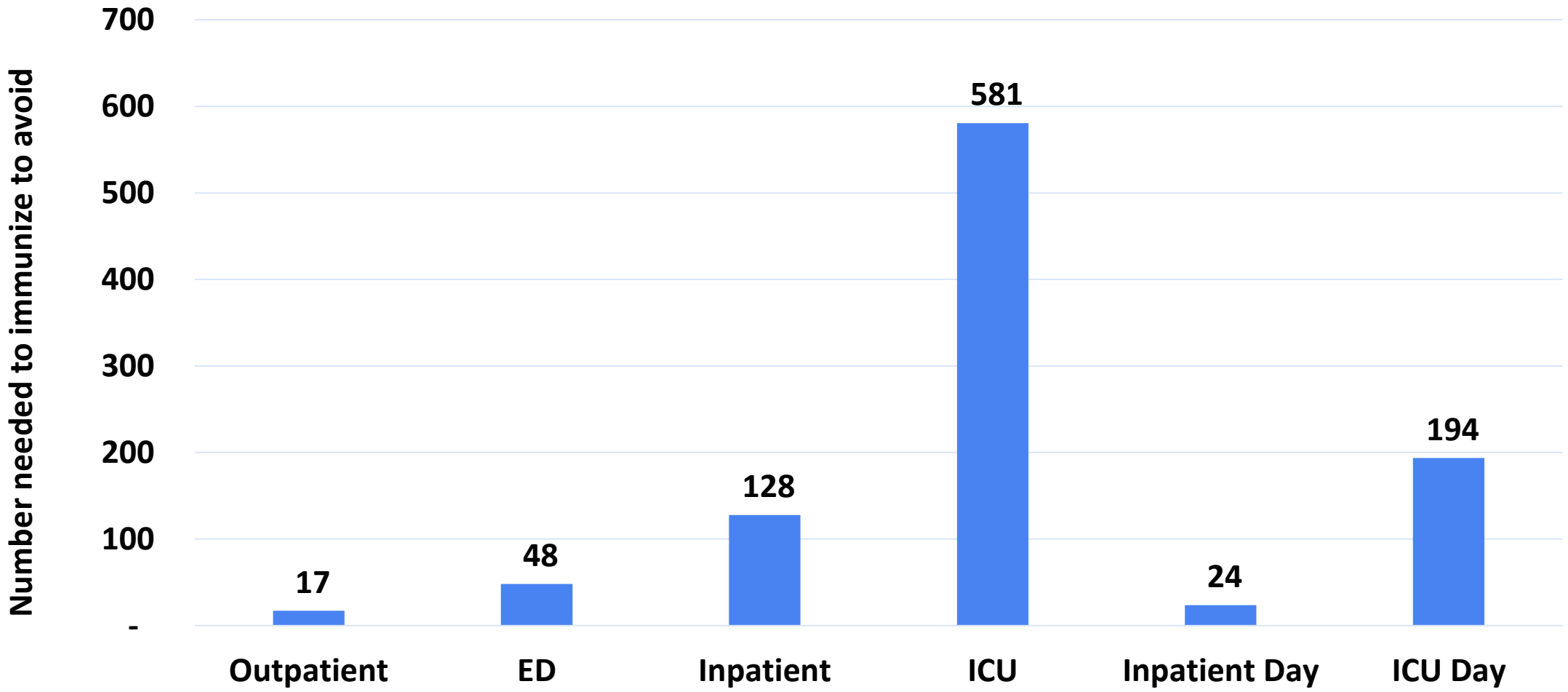
Is nirsevimab immunization among all infants <8 months of age entering their first RSV season and infants born during the RSV season a reasonable and efficient allocation of resources?

Updates to cost effectiveness model

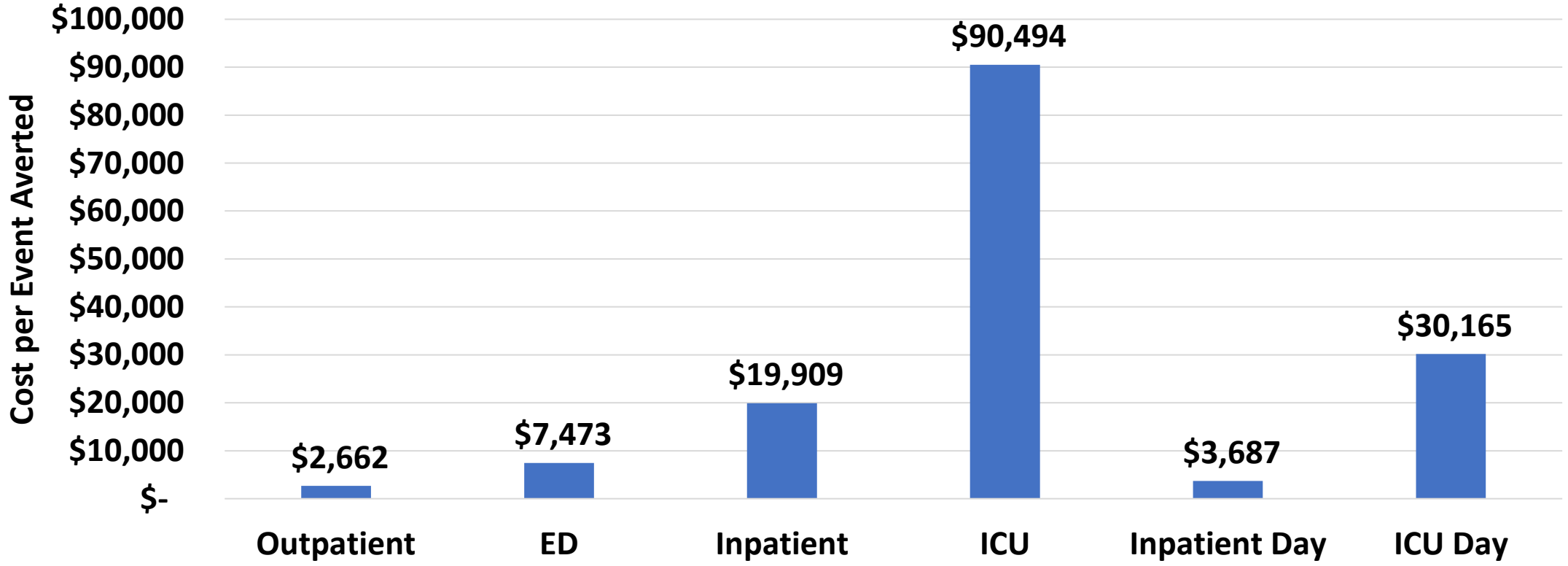
- Cost of product
  - $495 list price
  - $395 Vaccines for Children (VFC) program price
  - Assuming 50% VFC and 50% private insurance, average price of $445
  - Price not final
- Mortality assumptions modified to include individuals at increased risk of severe RSV disease
- Savings from not using palivizumab incorporated
- Other inputs unchanged[1]

[1] Other inputs unchanged from previous model presented at February 23, 2023 ACIP meeting

Number needed to immunize with nirsevimab to prevent one health outcome



Cost per health event averted



Cost of $445 per dose

Cost effectiveness result and Work Group Interpretation

- Updated base case result: **$102,811** per quality adjusted life year saved

- The work group felt nirsevimab is or probably is a reasonable and efficient use of resources

EtR Domain: Equity

What would be the impact of nirsevimab on health equity?

Equity Summary

- If recommended, ACIP will vote on VFC resolution for nirsevimab
- National studies of death certificates found higher rates among non-Hispanic black children compared with non-Hispanic White infants and children aged 1–4 years[1]
- ICU admission rates for RSV among Non-Hispanic Black infants <6 months old were 1.2–1.6x higher than among Non-Hispanic White infants[2]
- RSV hospitalization rates 4–10x higher among Alaska Native and American Indian children aged <24 months than the rate in the general population[3]
- Studies of RSV hospitalization by race and ethnicity have differing results[4–7]
- The work group felt that nirsevimab would increase health equity

1. Hansen J Infect Dis 2022 Aug 15;226(Suppl 2):S255-S266. 2. Unpublished data from RSV-NET, CDC. 3. Atwell Pediatrics 2023, e2022060435. 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

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
Equity	▪ What would be in the impact of the intervention on health equity?	Probably increased

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

Minority opinion – – –

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 8–19 months of age with increased risk of severe disease entering their second RSV season?

Evidence to Recommendations (EtR) Framework

PICO Question 2

Population	Children **aged 8–19 months who are at increased risk of severe RSV disease** and who are entering their **second RSV season**
Intervention	Nirsevimab (**200 mg** [2 x 100 mg] injection near 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 Medically attended 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 disease among children who are at increased risk of severe disease in their 2nd RSV season of public health importance?

Risk groups previously proposed to receive nirsevimab when entering second RSV season

- Based on American Academy of Pediatrics recommendations for palivizumab for a child's second RSV season[1]
- Assumed to be cost saving compared with palivizumab
- Proposed recommendation to receive nirsevimab when entering 2nd RSV season
  - 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 with severe immunocompromise
  - Children with cystic fibrosis if manifestations of severe lung disease (previous hospitalization for pulmonary exacerbation in the first year of life or abnormalities on chest imaging that persist when stable) or weight for length < 10th percentile

1. American Academy of Pediatrics. Committee on Infectious Diseases [Respiratory Syncitial Virus.] In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book : 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics, 2021.

Analyses conducted by CDC to evaluate risk factors for severe RSV disease during second RSV season

- Systematic review of literature
- Analysis of MarketScan national claims database

Systematic review of literature on risk factors for severe disease during second RSV season

- Included any studies that compared RSV hospitalization rates among children with risk factors to a healthy control group among children aged 6–24 months
- Among 3,825 abstracts, 6 studies identified
- Chronic lung disease, congenital heart disease, and neuromuscular disease analyzed in these studies
- Studies indicated increased risk of hospitalization for these risk factors
- No studies evaluating other risk factors identified

Analysis of MarketScan national claims database for select risk factors for severe RSV disease during second RSV season, 2015-2021

- Using ICD-9-CM/ICD-10-CM codes, identified children with and without select conditions (chronic lung disease, congenital heart disease, Down syndrome, neuromuscular disease, pulmonary malformations, immunodeficiency, cystic fibrosis) and children that were hospitalized with RSV
- Compared rates of RSV hospitalization among children with a chronic conditions to children without chronic condition
- Increased rates of hospitalization seen for all conditions
- RSV testing may be more common for children with risk conditions, inflating RSV-specific hospitalization rates

Increased incidence of RSV-associated severe disease in American Indian and Alaska Native children

- Several prior studies have documented increased incidence of RSV-associated hospitalizations among American Indian and Alaska Native children[1,2,3,4]
  - One study found that rates of RSV-associated hospitalization in AI/AN children were 4-10 times average rates of U.S. children aged 12-23 months from NVSN[1]
  - These studies have been conducted in specific populations and may not be broadly representative of risk in all AI/AN children
  - Findings of these studies do not separate environmental, sociocultural, or other factors that may increase severe disease risk
- Some AI/AN communities are also in remote areas that make transportation of children with severe RSV to appropriate healthcare facilities more challenging[5]

[1] Atwell 2023 Pediatrics 2023 Jul 14;e2022060435. [2] Karron et al. J Infect Dis 1999. [3] Holman et al. Pediatrics 2004. [4] Lowther et al. J Ped Infect Dis 2000 [5]American Academy of Pediatrics. Committee on Infectious Diseases [Respiratory Syncytial Virus.] In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, eds. Red Book : 2021 Report of the Committee on Infectious Diseases. Itasca, IL: American Academy of Pediatrics, 2021.

Public health problem work group interpretation

- Evidence for RSV burden among children aged 8–19 months entering their second with specific risk conditions is limited
- The work group felt nirsevimab should be recommended to the same groups that AAP recommends for palivizumab for the second RSV season
- The work group also felt that nirsevimab should be recommended to Alaska Native and American Indian children entering their second RSV season
- The work group felt that RSV disease among children who are at increased risk of severe disease[1] in their 2nd RSV season was of public health importance

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

EtR Domain: Benefits and Harms

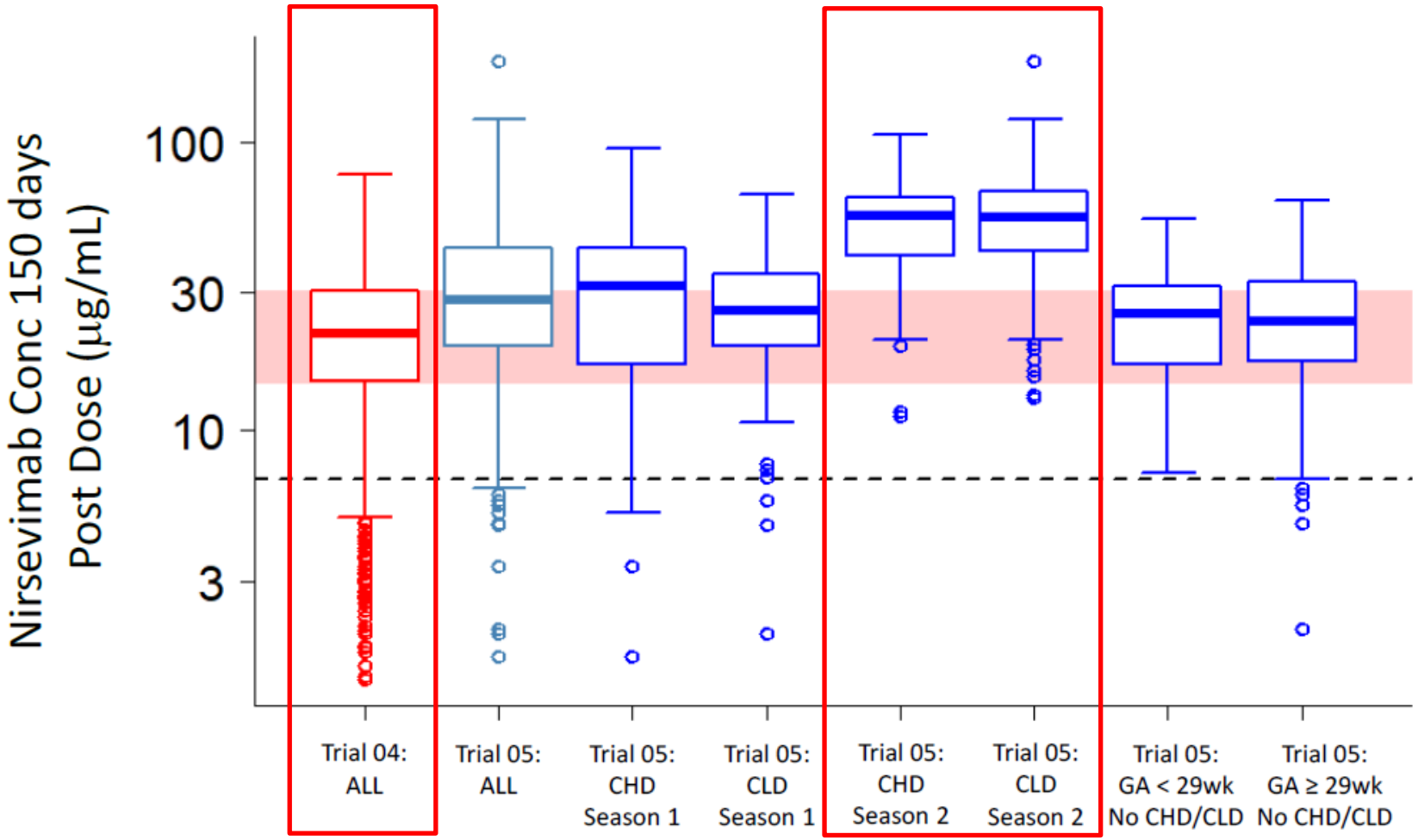
Do the desirable effects outweigh the undesirable effects?

Efficacy based on extrapolation of pharmacokinetic data

- A pharmacokinetic trial was conducted that randomized children at increased risk of severe RSV disease to palivizumab or nirsevimab
- In the second RSV season, 220 participants received nirsevimab and 42 received palivizumab
- Among those that received nirsevimab, two pharmacokinetic endpoints have been reported
  - Day 150 nirsevimab concentrations compared with phase 3 (Melody) efficacy trial among late pre-term and term infants that showed efficacy
  - Proportion of participants that had area under the curve nirsevimab concentrations above target based on efficacy trial data of 12.8 mg*day/ml

Domachowske J, Madhi SA, Simões EAF, Atanasova V, Cabañas F, Furuno K, et al. Safety of nirsevimab for RSV in infants with heart or lung disease or prematurity. *New England Journal of Medicine.* 2023;386(9): 892–894. doi: 10.1056/NEJMc2112186

Observed nirsevimab concentrations 150 days post-dose



- Among recipients of nirsevimab, day 150 concentrations higher in those who received 200 mg in second RSV season (labeled trial 05) than infants who received 50mg (if <5kg) or 100mg (if >5kg) in phase 3 Melody trial (labeled trial 04)

Source: FDA briefing document for Antimicrobial Drugs Advisory Committee June 8, 2023 meeting.
The dashed line is EC90 value of 6.8 µg/mL determined based on RSV challenge studies in cotton rat model.
Abbreviations: CHD, hemodynamically significant congenital heart disease; CLD, chronic lung disease of prematurity; EC90, 90% effective concentration; GA, gestational age. Trial 04: MELODY trial among late pre-term and term infants. Trial 05: Pharmacokinetics study among infants at increased risk of severe RSV disease.

Area under the curve (AUC) nirsevimab concentration and safety results

- Among recipients of nirsevimab in second season, most had AUC nirsevimab concentrations above the target threshold
  - 97.7% (129/132) of infants with chronic lung disease
  - 100% (58/58) of infants with congenital heart disease

- No adverse events judged as related to nirsevimab or palivizumab in second RSV season follow up period

Source: FDA briefing document for Antimicrobial Drugs Advisory Committee June 8, 2023 meeting

Summary of GRADE for nirsevimab dose for second season

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Medically attended (MA) RSV LRTI	Critical	1	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	Prevalence of SAEs was not significantly different in the intervention and control groups	**Very low**

Benefits and harms summary

- Overall evidence rating: Very low certainty (type 4)
- 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
- The work group felt[1] that the:
  - Desirable anticipated effects were moderate
  - Undesirable anticipated effects were minimal
  - Desirable effects outweighed the undesirable effects and favored nirsevimab over no intervention

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

EtR Domains: Values, Acceptability, and Feasibility

Values summary

- No additional data was available for values specific to populations at increased risk for severe disease
- The work group determined that the target population feels or probably feels that the desirable effects are large relative to undesirable effects[1]
- The work group also felt that there was probably not important uncertainty or variability in how much people valued the main outcomes[1]

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

Acceptability summary

- No additional data was available for acceptability specific to infants and young children at increased risk
- The work group felt that prevention with nirsevimab was, or probably was acceptable to key stakeholders[1]

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

Feasibility summary

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

- The work group felt that nirsevimab was probably feasible to implement among children aged 8–19 months at increased risk of severe RSV disease entering their second RSV season[1]

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

EtR Domain: Resource Use

Inputs to cost effectiveness model for second RSV season

- Theoretical groups of children with increased risk created with 2x, 4x, 6x, 10x higher risk than the general population aged 8–19 months in October
  - Increased incidence of RSV-associated hospitalization and increased mortality per hospitalization
  - Increased incidence of RSV-associated hospitalization but held mortality per hospitalization constant
  - No increase in incidence of outpatient and ED visits, healthcare costs, or quality adjusted life years lost with RSV disease[1]
- Cost updated to $890 nirsevimab costs (2x $445/dose)
- Mortality estimates modified to include high-risk individuals
- Other inputs unchanged[1]

[1]Same assumption as previous model presented at February 23, 2023 ACIP meeting

Updated cost effectiveness results for children 8–19 months entering second RSV season

	Incremental Cost-Effectiveness Ratio ($ / quality adjusted life year)	
Increased Risk category	RSV Hospitalization incidence increased	RSV hospitalization incidence and mortality per hospitalization increased
1x (base)	$1,557,544	$1,557,544
2x	$1,147,756	$836,270
4x	$726,983	$280,740
6x	$512,337	$118,912
10x	$294,775	$25,328

Resource Use Work Group Interpretation

- The work group felt that nirsevimab use among children aged 8–19 months entering their second RSV season who are at increased risk of severe disease[1] is probably a reasonable and efficient allocation of resources.

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

EtR Domain: Equity

Equity summary and Work Group interpretation

- Equity issues differ by chronic condition among infants and young children
- AI/AN children have higher hospitalization incidence rates than general population during second RSV season
- Non-Hispanic Black and Hispanic populations higher rates of preterm birth than non-Hispanic White population[1]
- The work group felt that nirsevimab use would probably increase health equity[2]

[1] https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm

[2] For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

Summary: Children at high risk entering 2nd RSV season

EtR Domain	Question(s)	Work Group Judgments
Public Health Problem	▪ Is RSV disease among children 8–19 months who are at increased 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?	Yes / Probably yes
Feasibility	▪ Is the intervention feasible to implement?	Probably yes
Resource Use	▪ Is the intervention a reasonable and efficient allocation of resources?	$890: Probably yes
Equity	▪ What would be in the impact of the intervention on health equity?	Probably increased

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Children at increased risk of severe disease entering 2nd RSV season[1]

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

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Children at increased risk of severe disease entering 2nd RSV season[1]

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

[1]For groups recommended to receive palivizumab in their second RSV season by the American Academy of Pediatrics and American Indian and Alaska Native children

Acknowledgements

Meredith McMorrow
Lauren Roper
Katherine Fleming-Dutra
Mila Prill
Amanda Payne
Danielle Moulia
Morgan Najdowski
David Hutton
Jamie Pike
Ismael Ortega-Sanchez
Andrew Leidner
Sara Oliver
Monica Godfrey
Evelyn Twentyman
Rebecca Morgan
Doug Campos-Outcalt
Sherry Farr
Karrie Finn-Downing
Melissa Glidewell
Eric Griggs
Emilia (Emily) Koumans
Matt Oster
Eghosa (Ivy) Oyegun
Francena Scott
Olga Varechtchouk
Lori Moore
Roua El Kalach
Eric Larson
Harris LaTreace
Michelle Ruslavage
Hannah Rosenblum
James Singleton
Carla Black
Sarah Meyer
Derrell Powers
Raigan Wheeler
Michael Melgar
Amadea Britton
Erica Reott
Samuel Graitcer
Jeanne Santoli
Jill Moses
Jamie Mells
Dawona Hough
Paul Lucas
Michelle Banks
Arthur Bayo
Nancy Fenlon
Rebecca Miller
Elizabeth Walker
Suzanne Johnson-DeLeon
JoEllen Wolicki
Elizabeth Greene
Neil Murthy
Patricia Wodi
Sarah Cutchin
Elisha Hall
Sarah Schillie
Andrew Kroger
Melissa Barnett
Dale Babcock
Rosa Herrera
Richard Quartarone
Stuart Myerburg
Melissa Taylor
Sarah Morales
Barbara Mahon
All members of the ACIP Mat/Peds RSV Work Group

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

Back up slides

GRADE

Indication: one dose of nirsevimab for infants aged <8 months born during or entering their first RSV season

GRADE: Medically attended RSV LRTI (n=2 studies)

- Measures of effect
  - Efficacy: 79.0% (68.5% to 86.1%)
  - Absolute risk (using 23.1% seasonal incidence*): 177 fewer cases per 1,000 immunized (195 fewer to 152 fewer)
    - Number needed to immunize: 6 (5 to 7)
  - Absolute risk (using 11.0% seasonal incidence**): 86 fewer cases per 1,000 immunized (94 fewer to 74 fewer)
    - Number needed to immunize: 12 (11 to 14)
  - Absolute risk (using 5.4% seasonal incidence [phase 3 trial controls]): 42 fewer cases per 1,000 immunized (46 fewer to 37 fewer)
    - Number needed to immunize: 24 (22 to 27) 67
- Concerns in certainty assessment
  - None
- Evidence type: **High (type 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). **Assumes 47.5% of ARI are LRTI (Rainisch 2020 Vaccine)

GRADE: RSV-associated LRTI with hospitalization (n=2 studies)

- Measures of effect
  - Efficacy: 80.6% (62.3% to 90.1%)
  - Absolute risk (using 1.3% seasonal incidence*): 10 fewer cases per 1,000 immunized (12 fewer to 8 fewer)
    - Number needed to immunize: 100 (83 to 125)
  - Absolute risk (using 2% seasonal incidence [phase 3 trial controls]): 16 fewer cases per 1,000 immunized (18 fewer to 12 fewer)
    - Number needed to immunize: 63 (56 to 83) [68]
- Concerns in certainty assessment
  - None
- Evidence type: **High (type 1)**

*NVSN data 2016-2020 (unpublished), included if with ARI

GRADE: RSV-associated LRTI with ICU admission (n=2 studies)

- Measures of effect
  - Efficacy: 90.0% (16.4% to 98.8%)
  - Absolute risk (using 0.35% seasonal incidence*): 3 fewer cases per 1,000 immunized (3 fewer to 1 fewer)
    - Number needed to immunize: 317 (289 to 1,754)
  - Absolute risk (using 0.1% seasonal incidence [phase 3 trial controls]): 0.9 fewer cases per 1,000 immunized (1.0 fewer to 0.2 fewer)
    - Number needed to immunize: 1,111 (1,010 to 6,250)
- Concerns in certainty assessment
  - Serious (imprecision): Too few events
- Evidence type: **Moderate (type 2)**

*Arriola 2019 JPIDS for proportion of hospitalizations admitted to ICU, NVSN data 2016-2020 (unpublished), included if with ARI

GRADE: All-cause medically attended LRTI (n=2 studies)

- Measures of effect
  - Efficacy: 34.8% (23.0 to 44.7%)
  - Absolute risk (using 13.9% seasonal incidence [phase 3 trial controls]): 46 fewer cases per 1,000 immunized (60 fewer to 30 fewer)
    - Number needed to immunize: 21 (17 to 33)
- Concerns in certainty assessment
  - None
- Evidence type: **High (type 1)**

70

GRADE: All-cause LRTI-associated hospitalization (n=2 studies)

- Measures of effect
  - Efficacy: 44.9% (24.9% to 59.6%)
  - Absolute risk (using 3.7% seasonal incidence in phase 3 controls): 16 fewer cases per 1,000 vaccinated (22 fewer to 9 fewer)
    - Number needed to immunize: 63 (45 to 111)
- Concerns in certainty assessment
- Evidence type: **High (type 1)**

71

GRADE: SAEs (n=2 studies)

- Measures of effect
  - Relative Risk: 0.73 (0.59 to 0.89)
  - Absolute risk: 28 fewer cases per 1,000 immunized (43 fewer to 12 fewer)
- Concerns in certainty assessment
  - Serious (imprecision)
- Evidence type: **Moderate (type 2)**

72

GRADE

Indication: one dose of nirsevimab for children aged 8-19 months who are at increased risk of severe RSV disease and entering their second RSV season

GRADE Summary

Certainty assessment							No of patients		Effect		Certainty	Importance
No of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nirsevimab**	**Palivizumab**	**Relative (95% CI)**	**Absolute (95% CI)**		
Medically attended lower respiratory tract infection												
1	randomized trial	not serious	not serious	not serious	very serious[a]	none	Pharmacokinetic extrapolation was used and based on comparable pharmacokinetic levels from efficacy in infants <12 months of age for prevention of the first medically attended RSV LRTI to pharmacokinetic levels in children ≤24 months with chronic lung disease (CLD) or congenital heart disease (CHD) entering their second RSV season[b]		n/a	n/a	⨁⨁◯◯ Low	CRITICAL
Serious adverse events												
1	randomized trial	not serious	not serious	serious[c]	very serious[d]	none	21/220[e]	0/42 (0%)	**RR 8.4** (0.52 to 135.5)[f]	**86 more per 1,000 (from 6 fewer to 1,000 more)[g]**	⨁◯◯◯ Very low	Important

a Very serious concern for indirectness, due to use of a surrogate outcome, the was surrogate established in 1st season while trial is in 2nd season, and population that does not match proposed indication.

b Pharmacokinetic extrapolation was used and based on comparable pharmacokinetic levels from efficacy in infants <12 months of age for prevention of the first medically attended RSV LRTI to pharmacokinetic levels in children ≤24 months with chronic lung disease (CLD) or congenital heart disease (CHD) entering their second RSV season. Based on pharmacokinetic and efficacy data from the phase 2b and phase 3 (MELODY) trials, a target area under the curve nirsevimab concentration of > 12.8 mg*day/ml was established. For the CLD cohort, 129/132 (98%) participants met the target nirsevimab concentration, and for the CHD cohort, 58/58 (92%) participants met the target. Additionally, the concentration of nirsevimab 150 days after injection was higher compared with the 150-day concentration in the phase 3 trial nirsevimab arm population.

c Serious concern for indirectness as the comparison group is palivizumab rather than placebo.

d Very serious concern for imprecision due to the width of the confidence interval containing estimates for which different policy decisions might be considered.

e 180 trial participants received nirsevimab in both the first and second season. 40 received palivizumab in the first season and nirsevimab in the second season

Updated cost effectiveness analysis

Economic Analysis of Nirsevimab in Pediatric Populations

David W. Hutton, PhD, MS

Associate Professor, Health Management and Policy, School of Public Health

Associate Professor of Global Public Health, School of Public Health

Associate Professor, Industrial and Operations Engineering, College of Engineering

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MICHIGAN

University of Michigan

SUSAN B. MEISTER CHILD HEALTH EVALUATION AND RESEARCH CENTER
MICHIGAN MEDICINE

Highlighted portions of presentation represent changes from Feb 2023 ACIP presentation

Research Team

University of Michigan

- David Hutton, PhD
- Lisa Prosser, PhD
- Angela Rose, MPH
- Kerra Mercon, MS
- Jefferson Jones, MD, MPH, FAAP
- Mila Prill, MSPH
- Meredith McMorrow, MD, MPH, FAAP
- Jamison Pike, PhD
- Katherine Fleming-Dutra, MD, FAAP
- Ismael Ortega-Sanchez, PhD
- Fiona Havers, MD
- Betsy Gunnels, MSPH
- Andrew Leidner, PhD

Conflicts of interest statements

- Authors have no known conflict of interests.

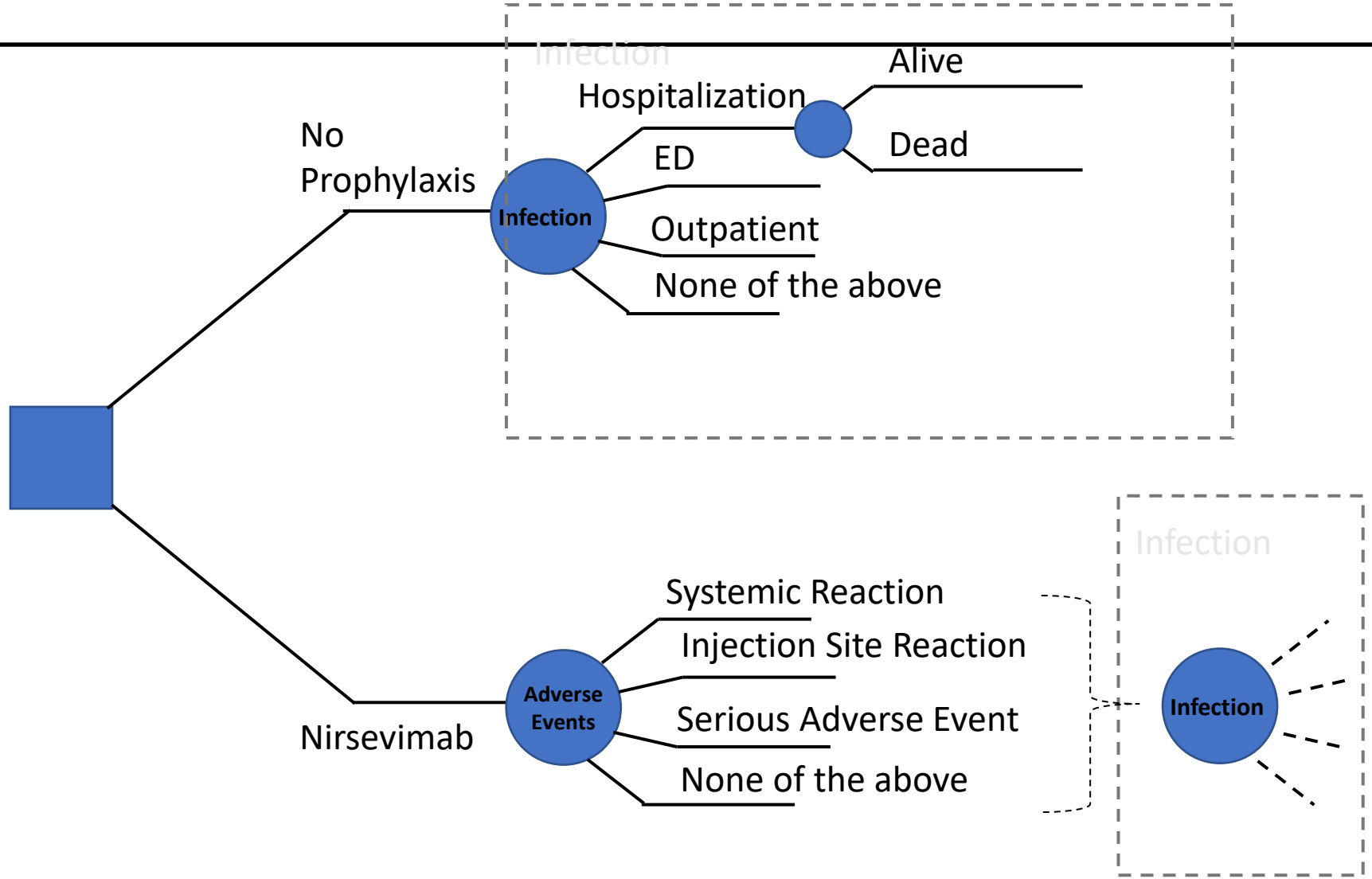
Methods: Study question

- Determine the cost-effectiveness of nirsevimab by:
  - Evaluating the population burden of disease in pediatric US population in terms of
    - annual resource utilization
    - total cases
    - total costs
    - deaths
    - quality-adjusted life years
  - Comparing the incremental cost-effectiveness ratio of nirsevimab to no prevention.
  - Running scenario analyses outcomes that explore key areas of uncertainty.
- Perspective: Societal

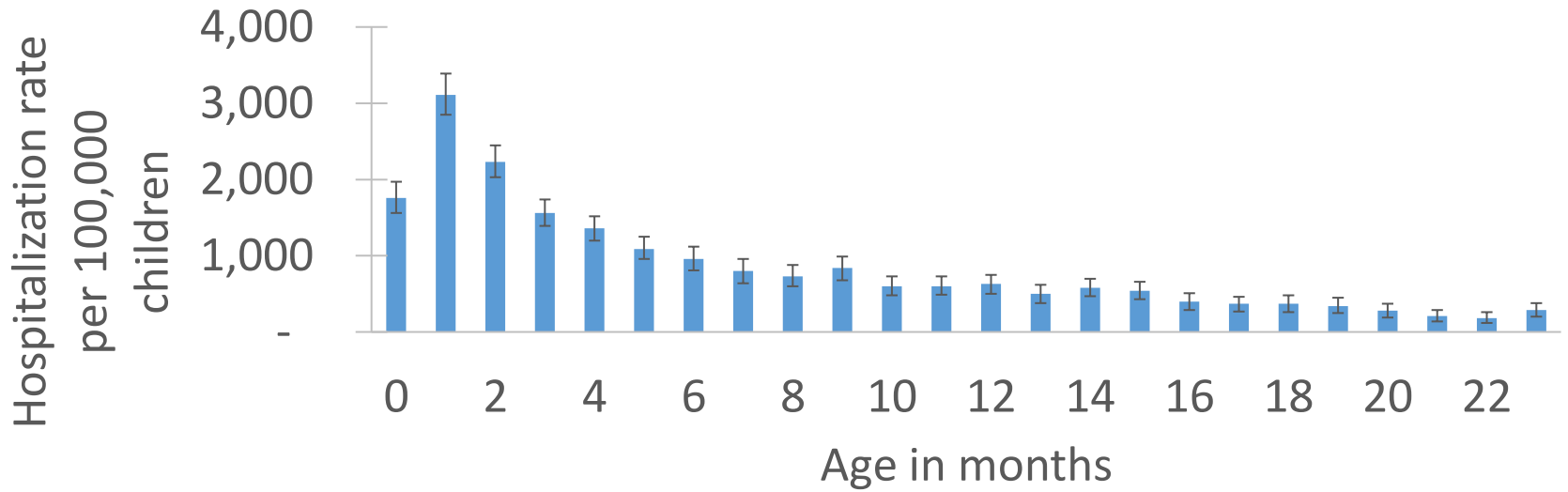
Methods: Intervention(s)

- Target population: US pediatric < 7 months of age entering their first RSV season
  - Secondary analysis high-risk infants in their second RSV season (7-18 months old)
- Interventions:
  1. No nirsevimab (Natural history)
  2. Nirsevimab against RSV illness
- Time horizon: 1 RSV season
- Analytic horizon: lifetime
- Discount rate: 3%

Methods: Decision Tree Model



Methods: Epidemiology Hospitalization



	Base Case	Range	Source
Respiratory syncytial virus (RSV) incidence, per 100,000	See Above	See Above	CDC NVSN, December 2016 to September 2020
Proportion with LRTI			
Age 0-5 months	1.0	0.5-1.0	Rainisch, 2020
Age 6-11 months	1.0	0.5-1.0	Rainisch, 2020

CDC New Vaccine Surveillance Network (NVSN) hospitalization rates for children under 2 years of age from December 2016 to September 2020

Methods: Epidemiology
ED and Outpatient

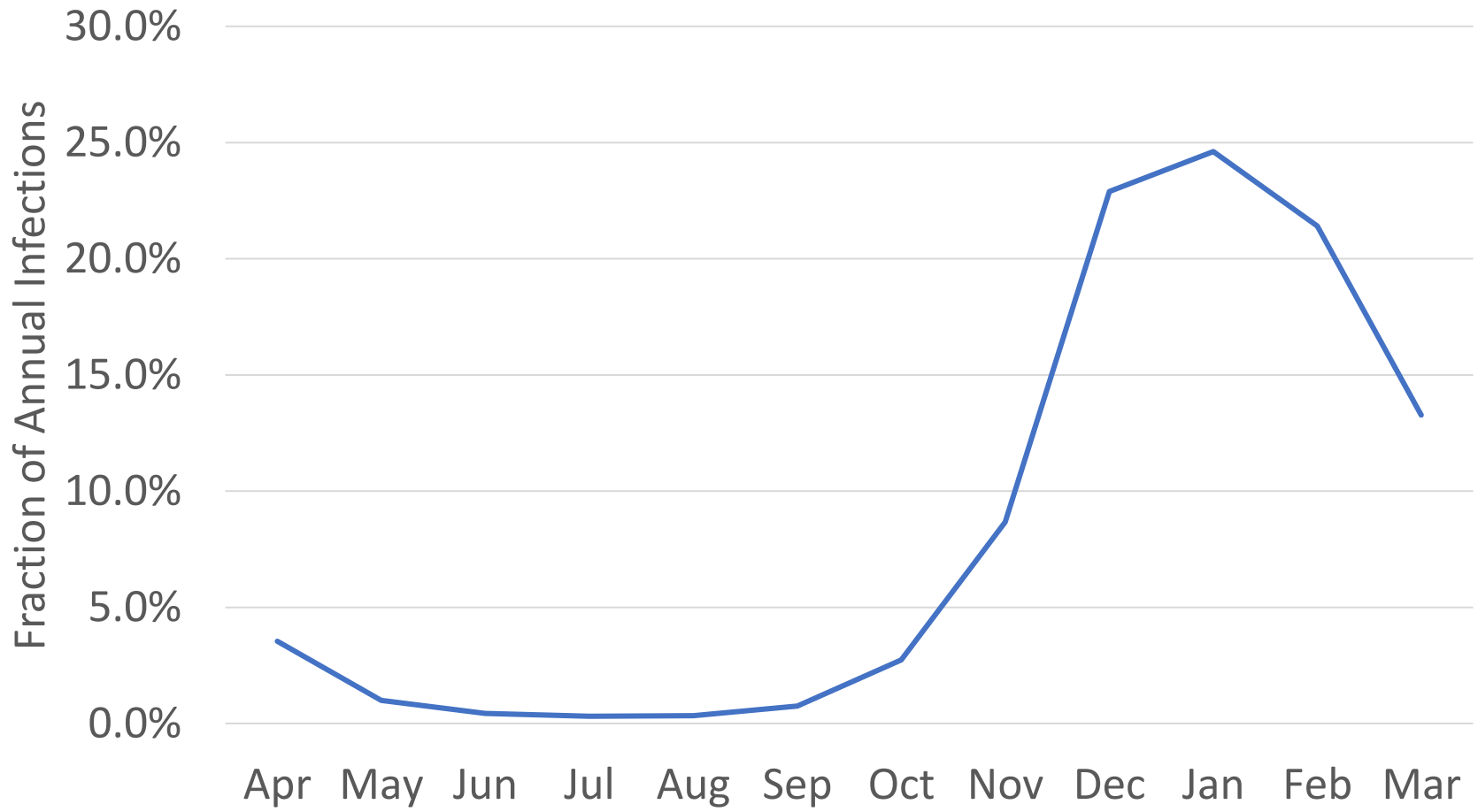
Respiratory syncytial virus (RSV) incidence, per 100,000	Base Case	Range	Source
Emergency Department			
Age 0-5 months	7,500	5,500 – 7,500	Lively 2019 (base case and range)[5], Hall 2009 (range)[6]
Age 6-11 months	5,800	5,700 – 5,800	
Age 12 -23 months	3,200	3,200 – 5,300	Hall 2009 (base case and range)[6], Lively 2019 (range)[5]
Proportion with LRTI			
Age 0-5 months	0.65	0.25-1.0	Rainisch, 2020[4]
Age 6-11 months	0.5	0.25-1.0	Rainisch, 2020[4]
Medically attended outpatient			
Age 0-5 months	21,600	13,200 – 21,600	Lively 2019 (base case and range)[5], Hall 2009 (range)[6]
Age 6-11 months	24,600	17,700 – 24,600	
Age 12 -23 months	18,440	6,600 – 29,620	Jackson 2021 (base case and range)[7], Hall 2009 (range)[6]
Proportion with LRTI			
Age 0-5 months	0.65	0.25-1.0	Rainisch, 2020[4]
Age 6-11 months	0.3	0.1-1.0	Rainisch, 2020[4]

Methods: Epidemiology
Mortality

	Base Case	Range	Source
RSV mortality per hospitalization			
Age 0-5 months	0.10%	0.04-0.20%	Hansen 2022, Doucette 2016
Age 6-11 months	0.10%	0.04-0.20%	Hansen 2022, Doucette 2016
Age 12-23 months	0.3%	0.28%-0.34%	Gupta 2016

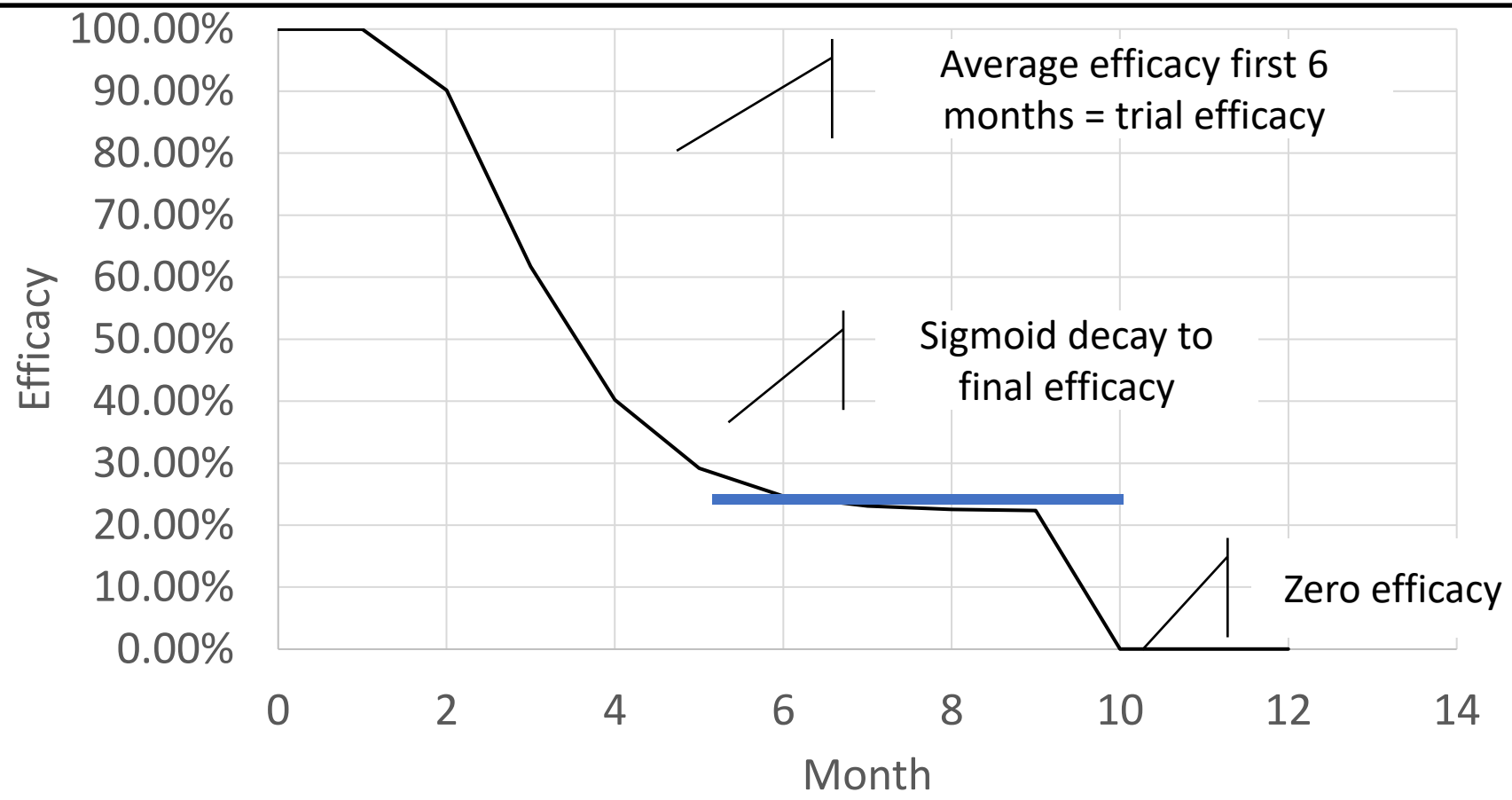
New Mortality estimates are based on recent study by Hansen to be appropriate for the entire US population instead of just non-high-risk individuals.

Seasonality



Source: National Respiratory and Enteric Virus Surveillance System (NREVSS) (2015-2019)

Methods: Nirsevimab Efficacy



Methods: Efficacy

Variable	Base case value	Range for sensitivity analysis	Source
Nirsevimab			
Initial efficacy (months 0-5) against RSV-associated LRTI	79.0%	68.5% -86.1%	
Efficacy months 6-10	25.0%	0.0% - 50.0%	
Efficacy after 10 months	0.0%		

Methods: Provision of Nirsevimab

- Base case:
  - At birth for those born
    - October 1 – March 31
  - October for those born in
    - April (~6-month visit)
    - June (~4-month visit)
    - August (~2-month visit)
  - November for those born in
    - May (~6-month visit)
    - July (~4-month visit)
    - September (~2-month visit)
  - 50% coverage in the population

Methods: Medical Costs

Variable	Value	Range	Source
Disease-specific hospitalization costs (per hospitalization)			
Age 0-11 months	$11,487	4,804 - 86,646	Bowser 2022
Age 12- 23 months	$11,469	4,804 - 86,646	
Disease-specific ED costs (per ED visit)	$563	544 – 581	Bowser 2022
Disease-specific outpatient costs (per outpatient visit)	$82	46-118	Bowser 2022

- Bowser, 2022 is a systematic review using studies from 2014-2021
- Funded by Sanofi
- All numbers updated to 2022 dollars using GDP Deflator

Methods: Productivity Costs

Variable	Value	Range	Source
Productivity burden of RSV Disease (caregiver losses)			
Days of lost productivity			
Outpatient*	2.5	0-5	Fragaszy, 2018; Petrie, 2016; Van Wormer, 2017
ED*	2.5	0-5	Fragaszy, 2018; Petrie, 2016; Van Wormer, 2017
Hospitalization^	7.4	0-14	
Lifetime productivity for those <1 year old (lost from death)	1,795,936		Grosse, 2019

*Productivity for outpatient and ED based on adult influenza
^Hospitalization productivity loss = length of hospitalization + 2 days

Methods: Intervention Cost

Variable	Value	Range	Source
Immunization-related costs			
Nirsevimab, per dose	$445	$50-$600	Assumption

Manufacturer has suggested $495 list price and $395 for VFC
We assume 50% VFC*

Both assume no additional visits, but do include costs of administration

** 50% VFC based on:*
Benefits from Immunization During the Vaccines for Children Program Era — United States, 1994–2013

Methods: Palivizumab

- Assumption: Nirsevimab policy will lead to 100% reduction in palivizumab use.
- Savings assumptions: current Palivizumab use
  - 1.6% are high-risk (palivizumab-eligible)
  - 75% uptake in high-risk
  - 4.17 palivizumab doses/person on average
  - $1,228/palivizumab dose

Methods: RSV
Health-Related Quality-of-Life

Measured in
Days Lost

LRTI quality adjusted life DAYS lost	Base	Lower (Regnier)	Upper (JIVE)
Outpatient: Child	3.1	1.8	16.6
Outpatient: Caregiver	1.5	0	9.1
ED: Child	4.9	2.9	16.6
ED: Caregiver	2.5	0	9.1
Hospitalized: Child	6.2	3.7	26.5
Hospitalized: Caregiver	2.4	0	13.6

Methods: Additional Inputs

- Also included nirsevimab adverse events
  - Systemic reactions
  - Injection site reactions
  - Serious adverse events
  - Medical costs
  - Productivity costs
  - Quality-adjusted life-years lost

Methods: Uncertainty analyses

- One-way sensitivity

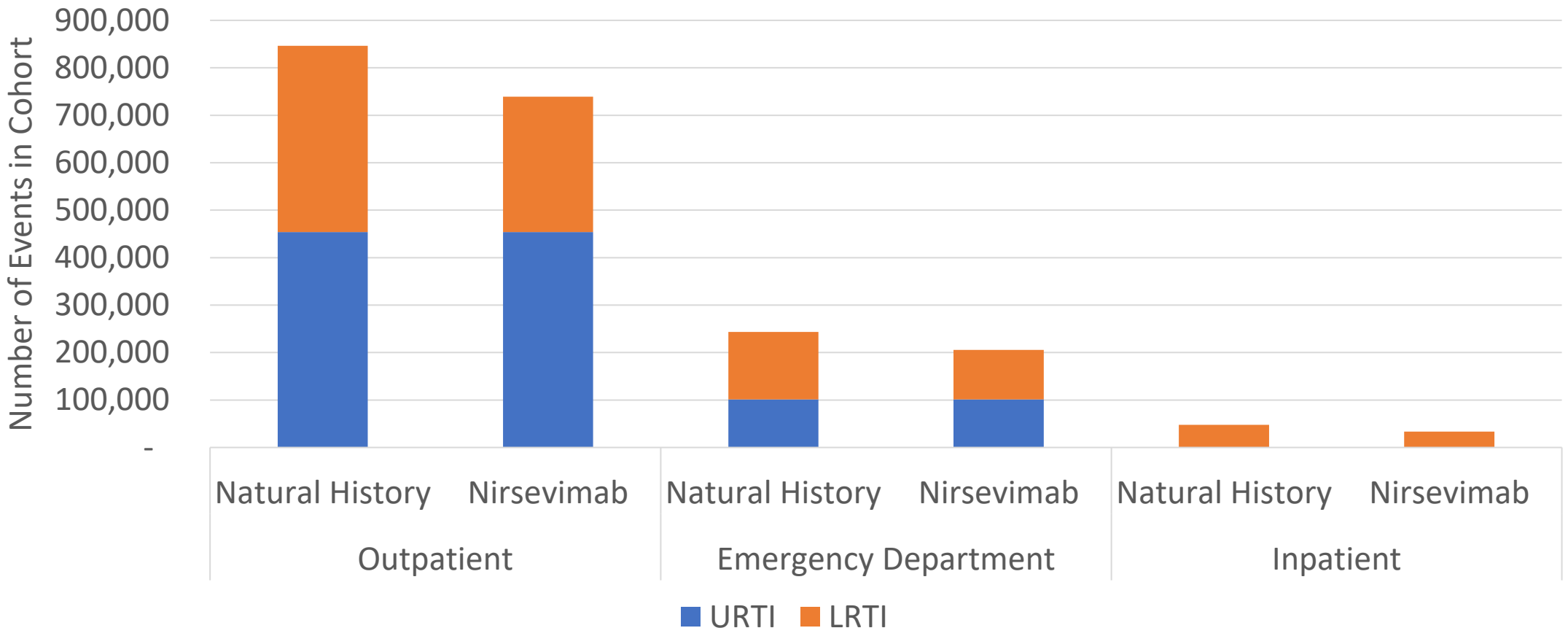
- Scenarios:
  - Upper respiratory infection effect
  - Timing of administration

- Additional Scenario:
  - High-risk children entering the second RSV season

Results: Base Case

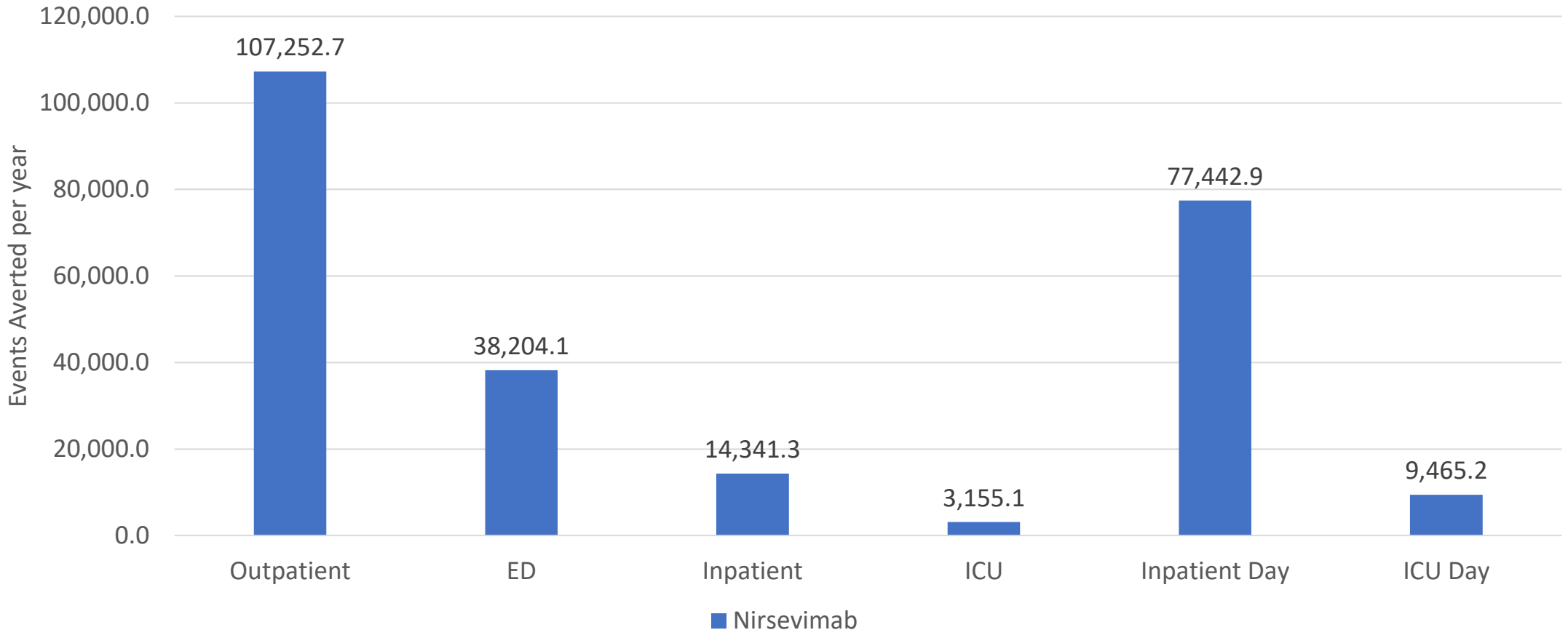
- Base Case:
  - Population of 1,000 births
  - 50% uptake in the nirsevimab group
  - First RSV season
  - $500/dose
  - Nirsevimab only impacts LRTI

Results: Health outcomes



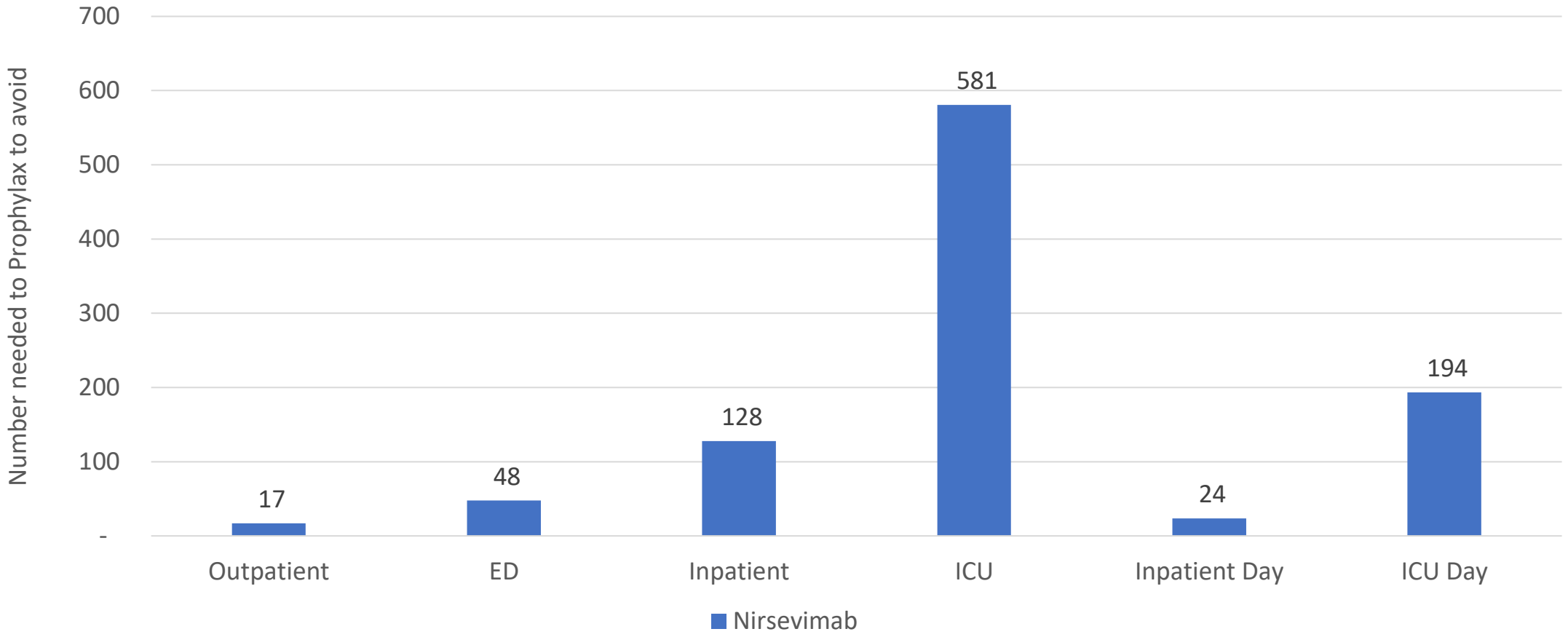
Cohort:1,000 nirsevimab and 1,000 natural history, assuming 50% uptake in nirsevimab group
URTI- Upper respiratory tract infection; LRTI- Lower respiratory tract infection

Results: Health outcomes

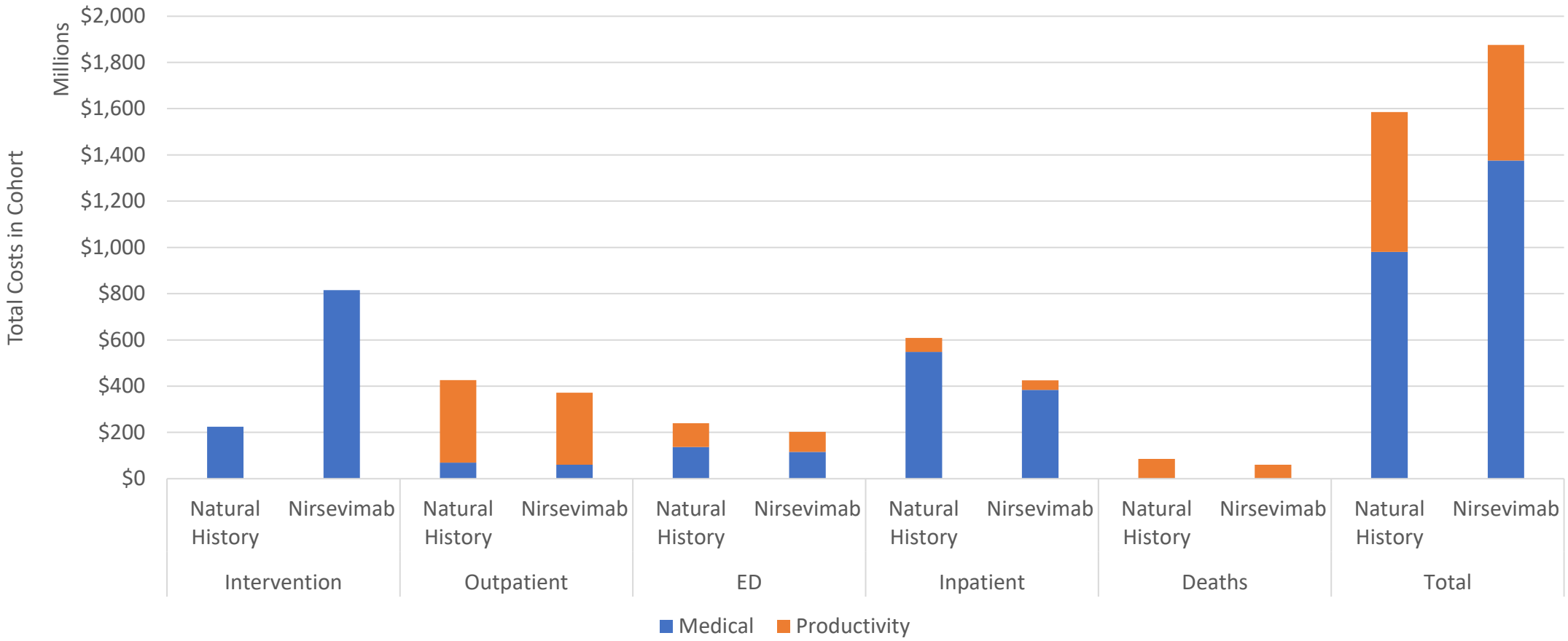


Cohort:1,000 nirsevimab and 1,000 natural history, assuming 50% uptake in nirsevimab group

Results: Health outcomes



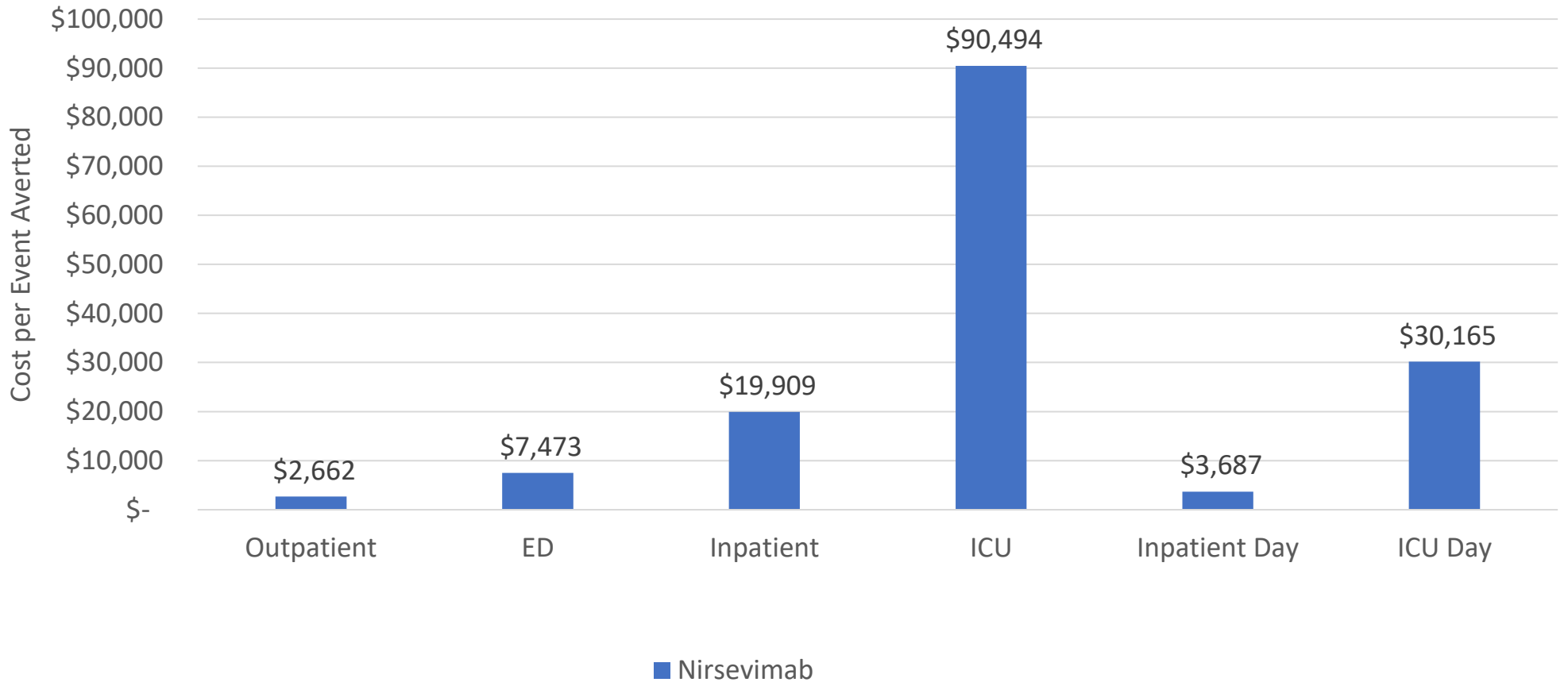
Results: Costs



Cohort: 3.66 million births, assuming 50% uptake in nirsevimab group

Base costs of nirsevimab: $445/dose, Cost of palivizumab for high-risk included in “Natural History”

Results: Health outcomes



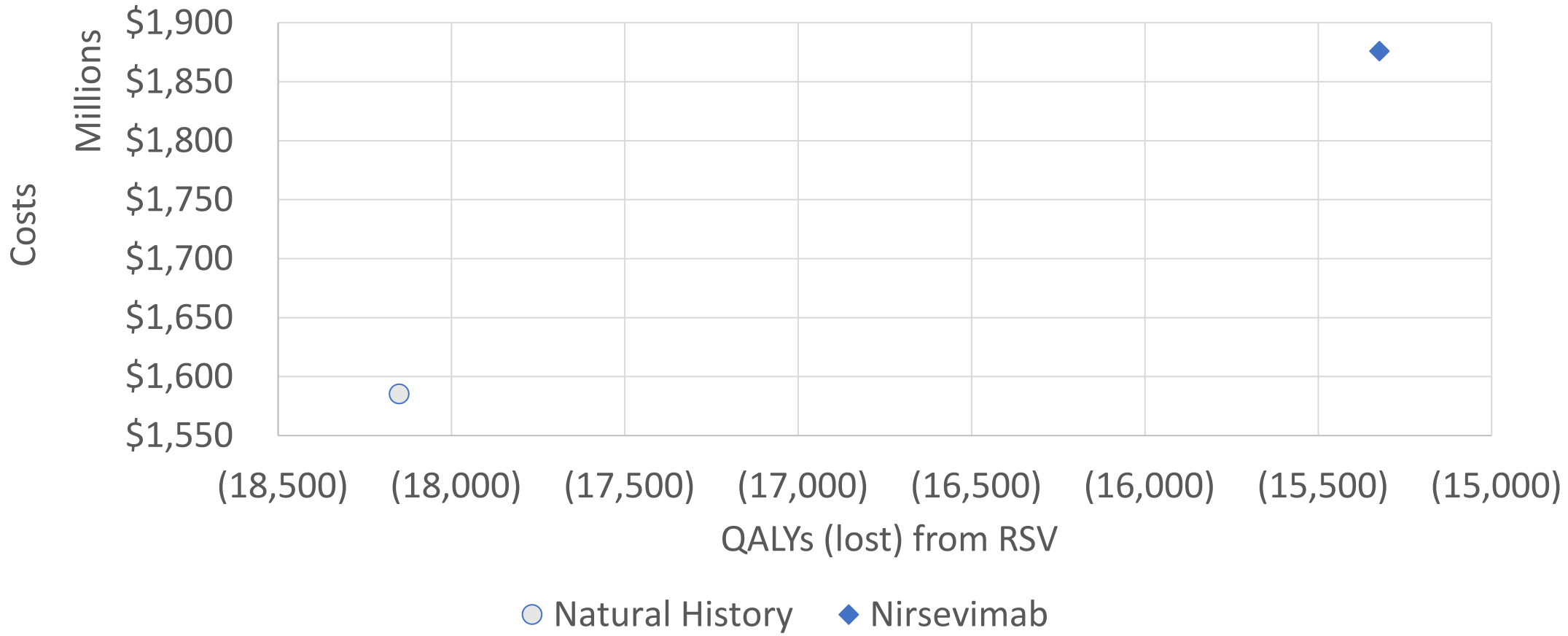
Base costs of nirsevimab: $445/dose

Results: QALYs lost

	Adverse Events	Outpatient		ED		Inpatient		Deaths	Total		Grand
		Child	Caregiver	Child	Caregiver	Child	Caregiver	Child	Child	Caregiver	Total
Natural History		7,153	3,580	3,290	1,645	807	320	1,356	12,606	5,545	18,151
Nirsevimab	52	6,246	3,127	2,774	1,387	565	224	949	10,586	4,738	15,324

Cohort: 3.66 million births, assuming 50% uptake in nirsevimab group

Results: Cost-effectiveness



Cohort: 3.66 million births, assuming 50% uptake in nirsevimab group

Base costs of nirsevimab: $445/dose, Cost of palivizumab for high-risk included in “Natural History”

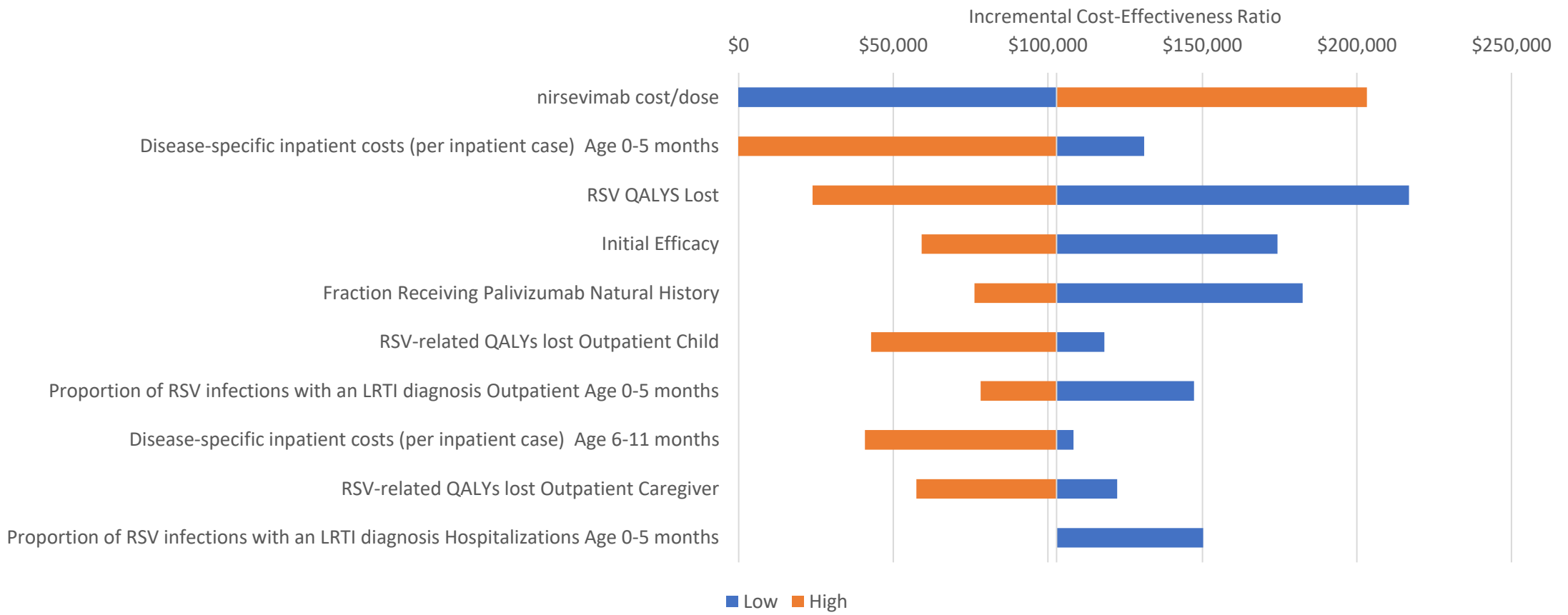
Results: Cost-effectiveness

Overall	Costs ($)	QALYs	ICER ($/QALY) Vs. NH
Natural History	1,585,172,002	18,151	
Nirsevimab	1,875,840,158	15,324	102,811

Cohort: 3.66 million births, assuming 50% uptake in nirsevimab group

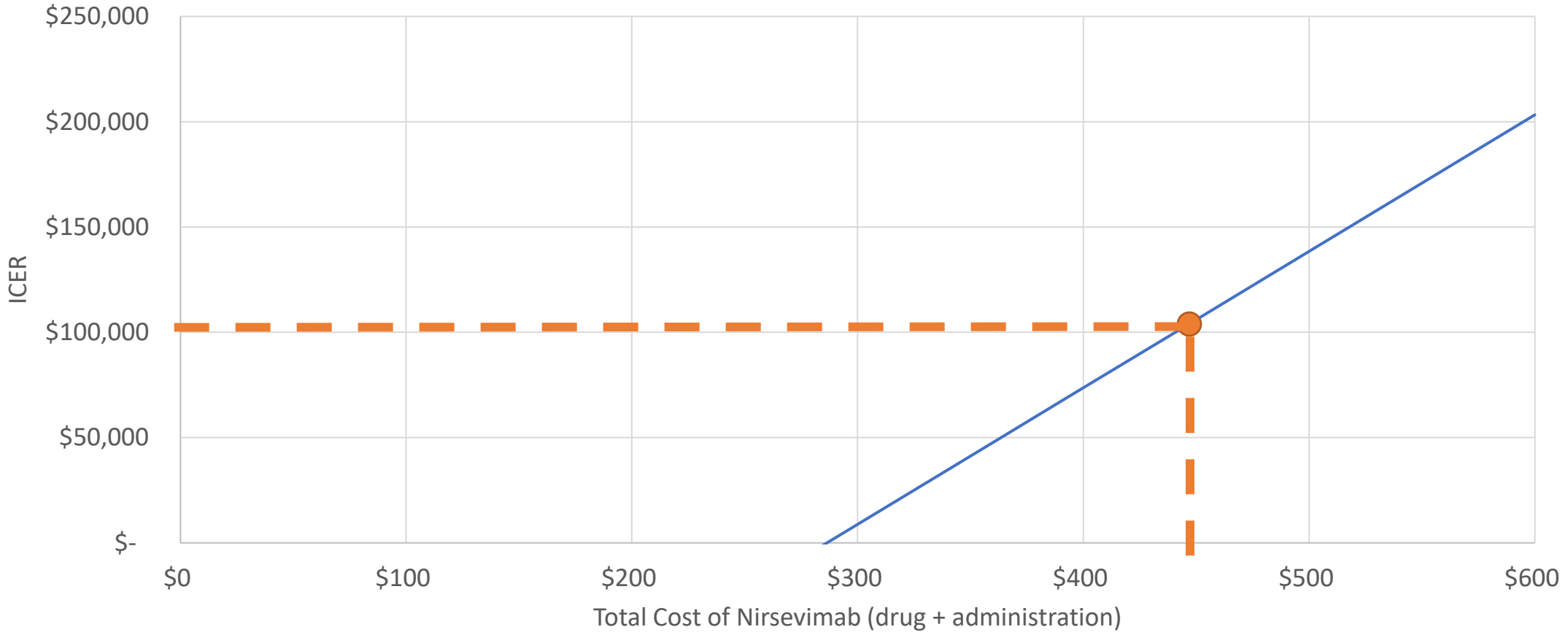
Base costs of nirsevimab: $445/dose, Cost of palivizumab for high-risk included in “Natural History”

Sensitivity: Tornado nirsevimab



Base cost of $445/dose

Sensitivity: Cost nirsevimab



Base cost of $500/dose

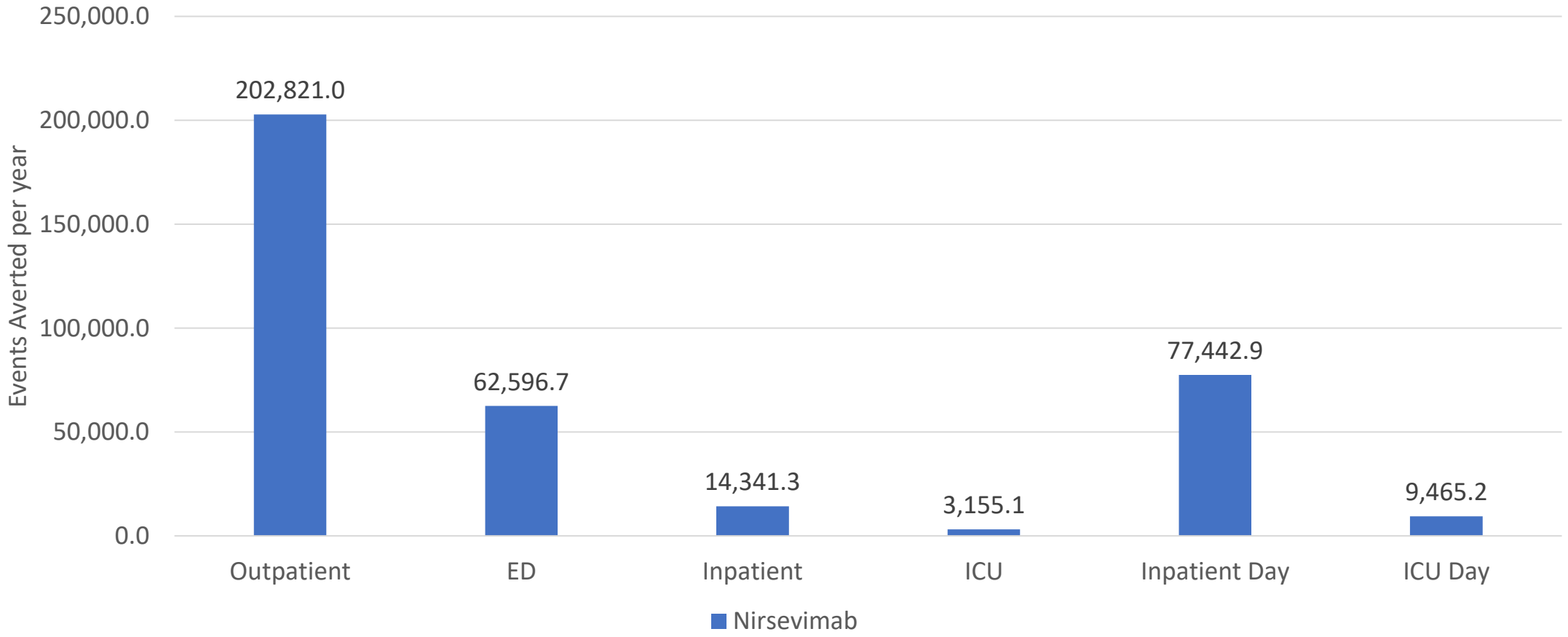
Results: Alternative Scenarios

	No Palivizumab Savings	Palivizumab Savings
Low-Risk Mortality	$205,639	$118,522
Overall Average Mortality	$182,397	$102,811

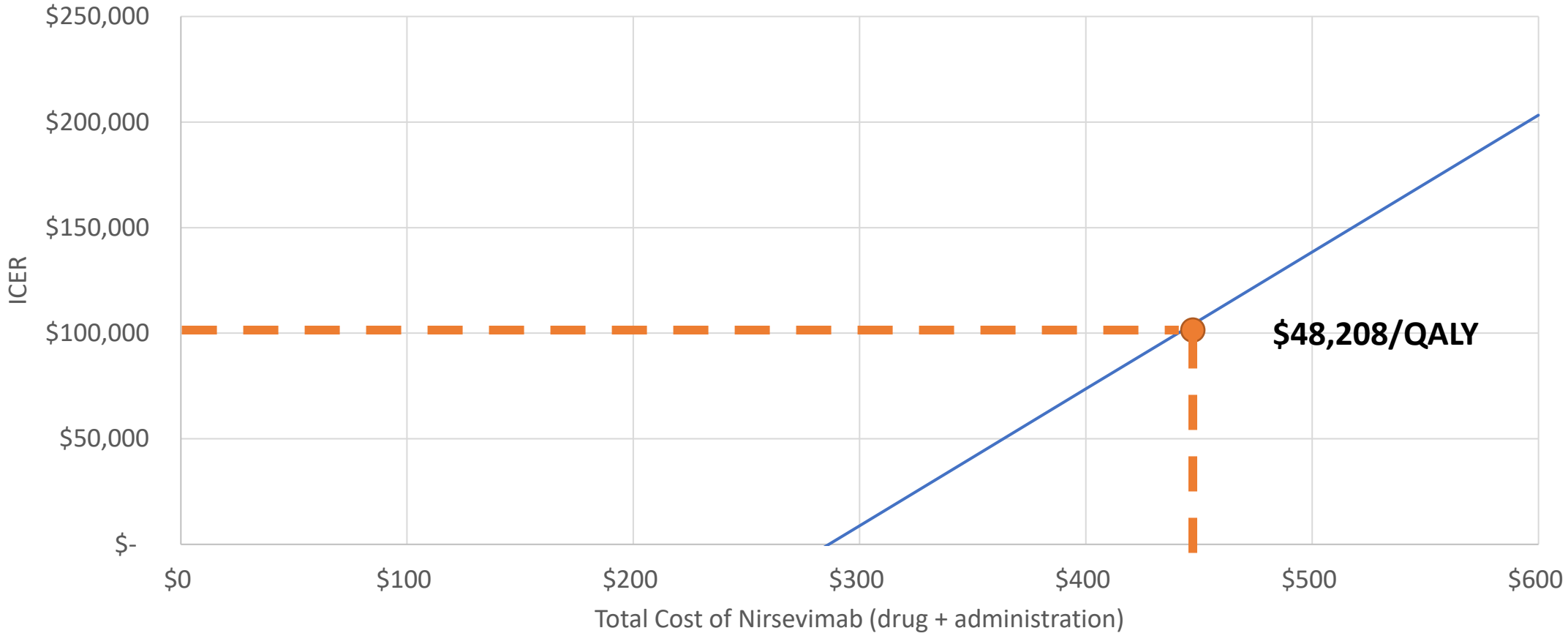
Cohort: 3.66 million births, assuming 50% uptake in nirsevimab group

Base costs of nirsevimab: $445/dose, Cost of palivizumab for high-risk included in “Natural History”

Scenario: Upper respiratory infection effect



Scenario: Upper respiratory infection effect



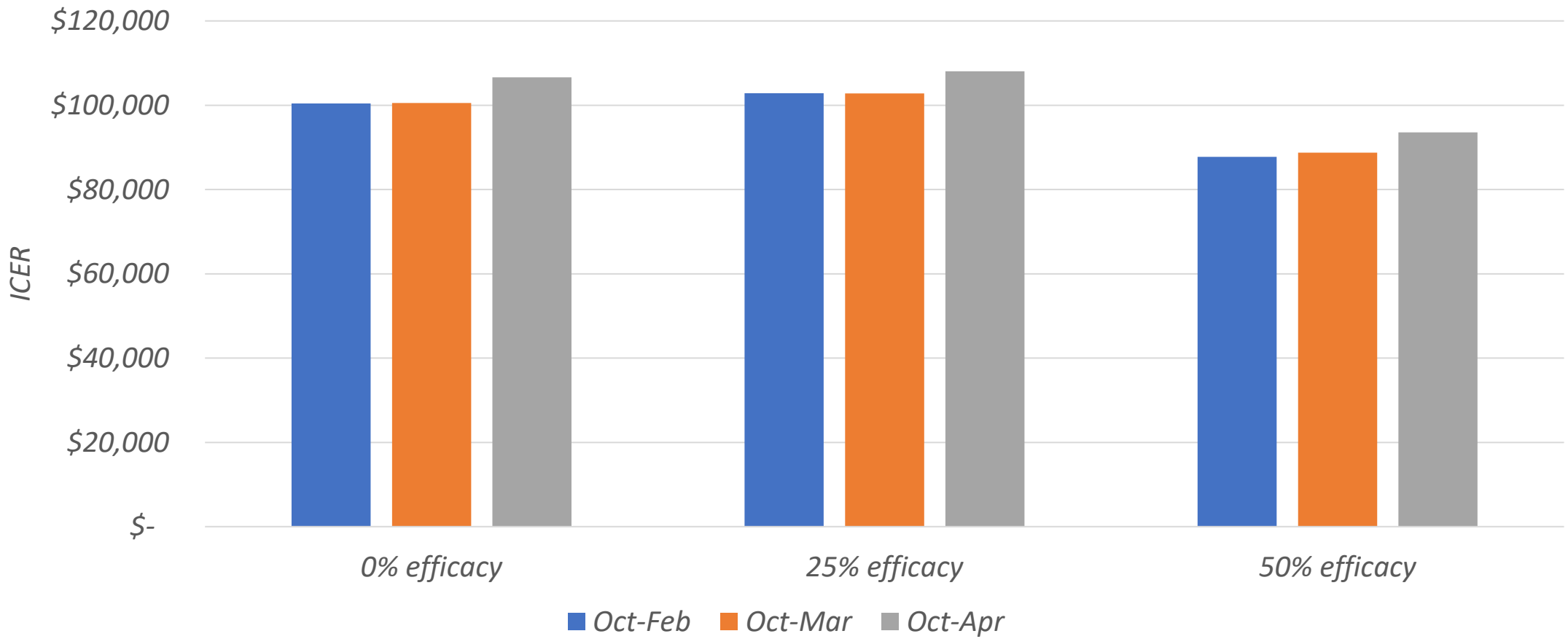
Nirsevimab is assumed to be equally efficacious in preventing upper respiratory tract infections as lower respiratory tract infections.

Scenario: Timing analysis

- Cost-effectiveness of an infant receiving nirsevimab as a newborn in
  - Oct-Feb
  - Oct-March
  - Oct-April
- With varying efficacy in months 6-10
  - 0%
  - 25%
  - 50%

Cohort:1,000 nirsevimab and 1,000 natural history, assuming 50% uptake in nirsevimab group

Scenario: Timing and efficacy in months 6-10



Very minor differences, Slightly higher ICERs for Oct-Apr

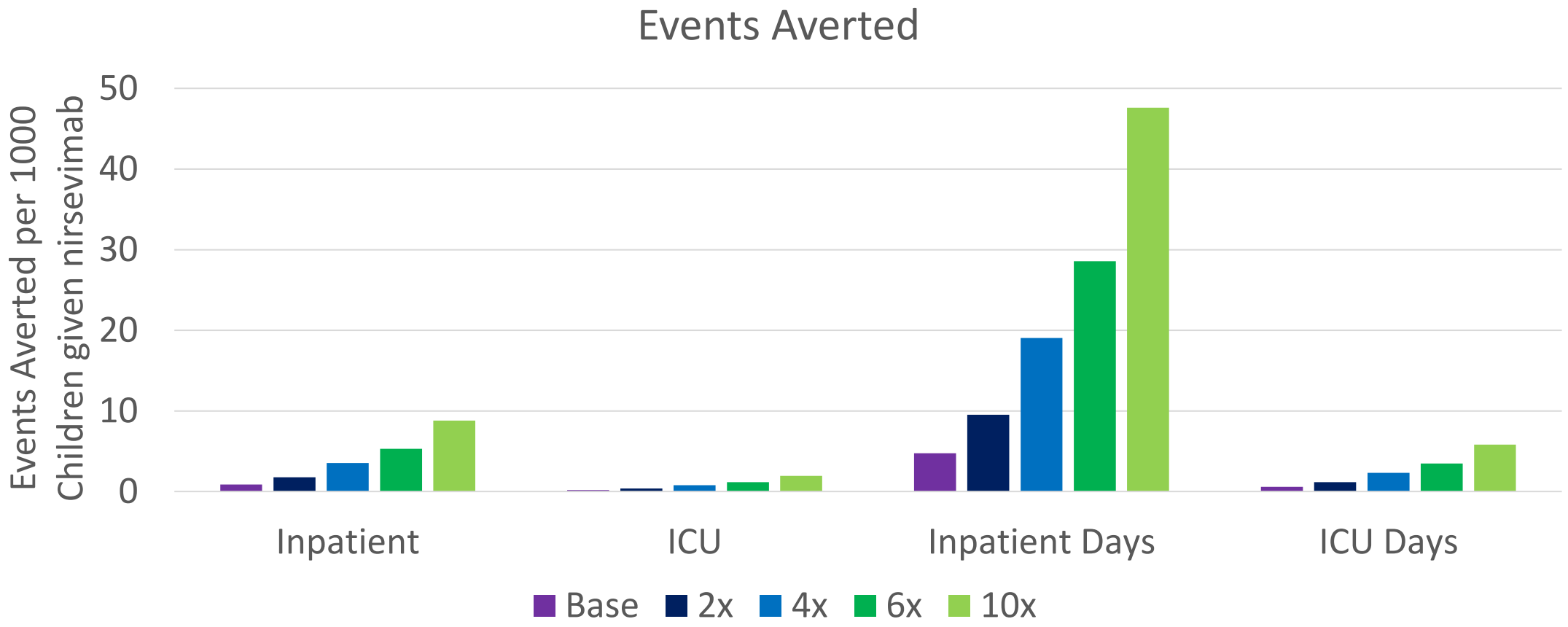
Base cost of $445/dose
ICER= Incremental cost-effectiveness ratio

Higher-risk children entering the second RSV season

- Immunization in October (under 19 months old in October)
- Incidence of RSV-associated hospitalization and mortality per hospitalization:
  - 1x, 2x, 4x, 6x, 10x higher
- Cost
  - $890 nirsevimab costs (2x $445/dose)

Cohort:1,000 nirsevimab and 1,000 natural history, assuming 50% uptake in nirsevimab group

Second Season, High-Risk



Second Season, High-Risk

Increased Risk	Incidence	Incidence and mortality, given hospitalization
1x (base)	$1,557,544	$1,557,544
2x	$1,147,756	$836,270
4x	$726,983	$280,740
6x	$512,337	$118,912
10x	$294,775	$25,328

Cost is $890 per overall course, 2 doses @ $445 each

Limitations

- Model Structure
  - No risk groups
  - No dynamic transmission. No impact of the vaccine on transmission and indirect effects
- Uncertain inputs
  - Nirsevimab cost
  - QALYs lost
  - Upper respiratory tract infections
  - Palivizumab utilization

Summary

- Nirsevimab has the potential to be cost-effective
- Results sensitive to:
  - Cost per dose (Cost-Saving – 200,000 $/QALY)
  - Inpatient costs (Cost-saving – 125,000 $/QALY)
  - Efficacy (45,000 – 170,000 $/QALY)
    - URTI/LRTI
      - Proportion of infections with LRTI
      - Or efficacy of nirsevimab against URTI
  - QALYs lost (20,000 – 200,000 $/QALY)
    - Hospitalization, Outpatient, ED
    - Child, Parent

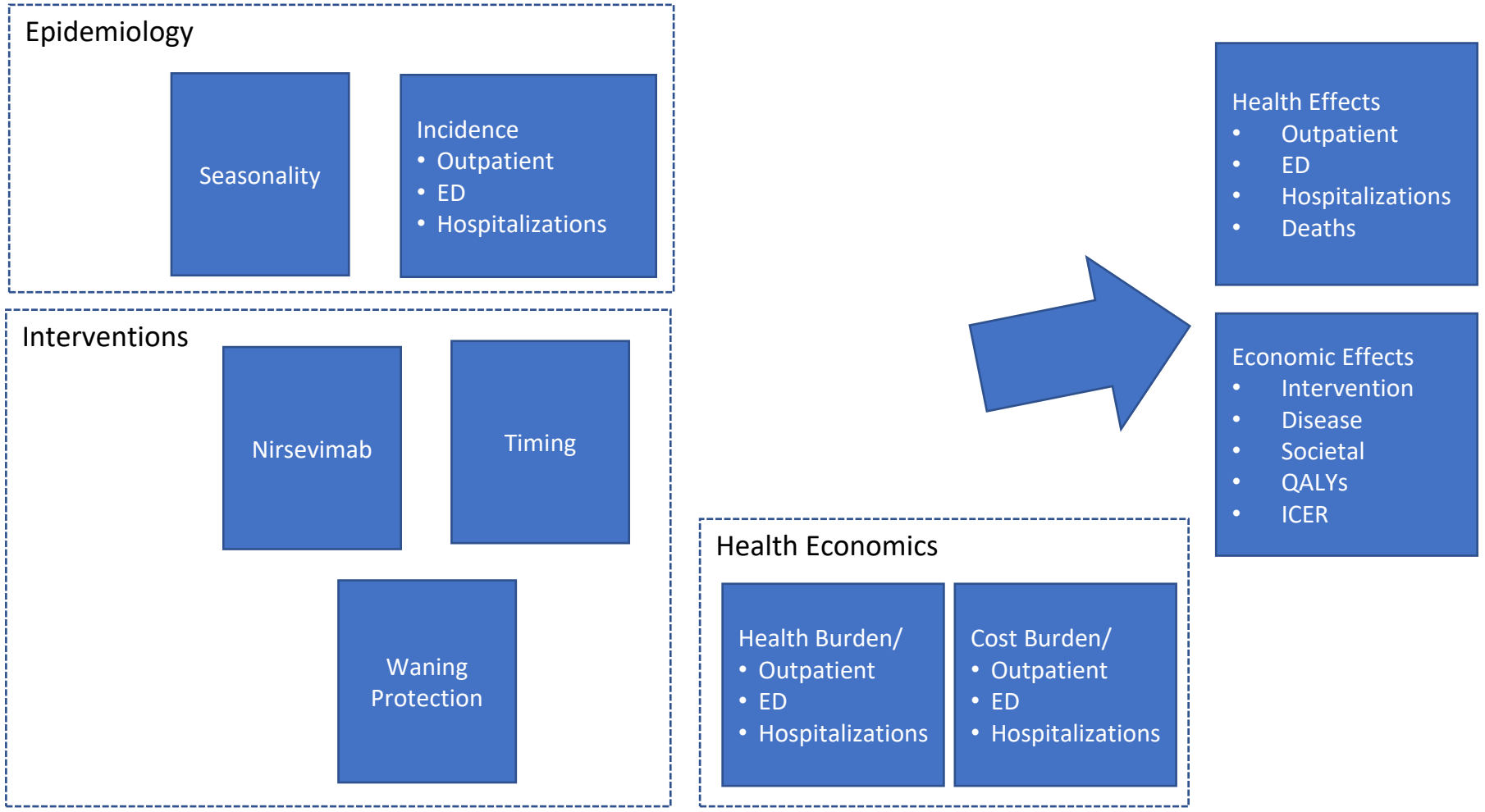
URTI: Upper Respiratory Tract Infection
LRTI: Lower Respiratory Tract Infection
QALY: Quality-Adjusted Life-Year

Thank You

- Please send comments to:
- dwhutton@umich.edu

Appendix

Methods: Epidemiological model



Methods: Inputs

- Incidence
  - Raw reported incidence may be underreported because of imperfect PCR sensitivity, so we consider an additional scenario in sensitivity analysis:
    - based on CDC Unpublished re-analysis of raw data from Zhang et al study which found decreased RSV PCR sensitivity in light of paired serology testing (adjustment factor: 87.6%).

Methods: Inputs

Variable	Value	Range	Source
Probabilities of Pediatric Adverse Events: Nirsevimab			
Systemic Reaction	0.005		Sanofi/AstraZeneca ACIP data request
Probability of outpatient visit given Systemic Reaction	1x Outpatient Visit	-	Assumption; Deluca et al (under review)
Anaphylaxis	0	0 – 0.0000010	Sanofi/AstraZeneca ACIP data request
Injection Site Reaction	0.002		Sanofi/AstraZeneca ACIP data request
Probability of outpatient visit given Injection Site Reaction	0.1		Assumption; Deluca et al (under review)
Serious Adverse Event	0.000001		Prosser, 2006[12]

* ISR grade 3 not reported by arm. We assumed the ISR grade 3 rates by arm were proportional to ISR of any severity by arm. Range is based on 95% CI based on binomial proportion from the base value.

Methods: Inputs

Variable	Value	Range	Source
Pediatric Quality-Adjusted Life-Years lost due to adverse events			
Systemic reaction	0.0056	0.00051-0.0061	Deluca et al (under review)
Anaphylaxis	0.0137	0.0135-0.0139	
Serious Adverse Event	0.141	0.092-0.199	(Guillain-Barre) Prosser, 2006[12]

* No SAEs were reported in the nirsevimab trial. Values in the table above are based on the incidence of Guillian-Barre syndrome following influenza vaccination.

Methods: Inputs

Variable	Value	Range	Source
Costs due to adverse events^			
Medical Costs			
Cost of outpatient visit for systemic reaction	$313	$27 - $1,337	Marketscan unpublished; Deluca et al (under review)
Cost of outpatient visit for injection site reaction	$326	$48 - $1,101	Marketscan unpublished; Deluca et al (in Press)
Anaphylaxis medical costs	$7,706	$89 - $23,414	Marketscan unpublished; Deluca et al (In Press)
Serious Adverse Event	$36,163.76	$10372.31 - $122,145.60	Prosser, 2006[12]
Productivity Costs			
Recipient time for office visit (fraction of day)	0.25		
Parent time for anaphylaxis (days)	1	1-3	Shimabukuro, 2021[13]
Daily productivity	190	169.41 – 211.03	Grosse, 2019[14]

* Daily productivity rate calculated by dividing mean annual total productivity (both market and non-market) for each age group by 365.25 days

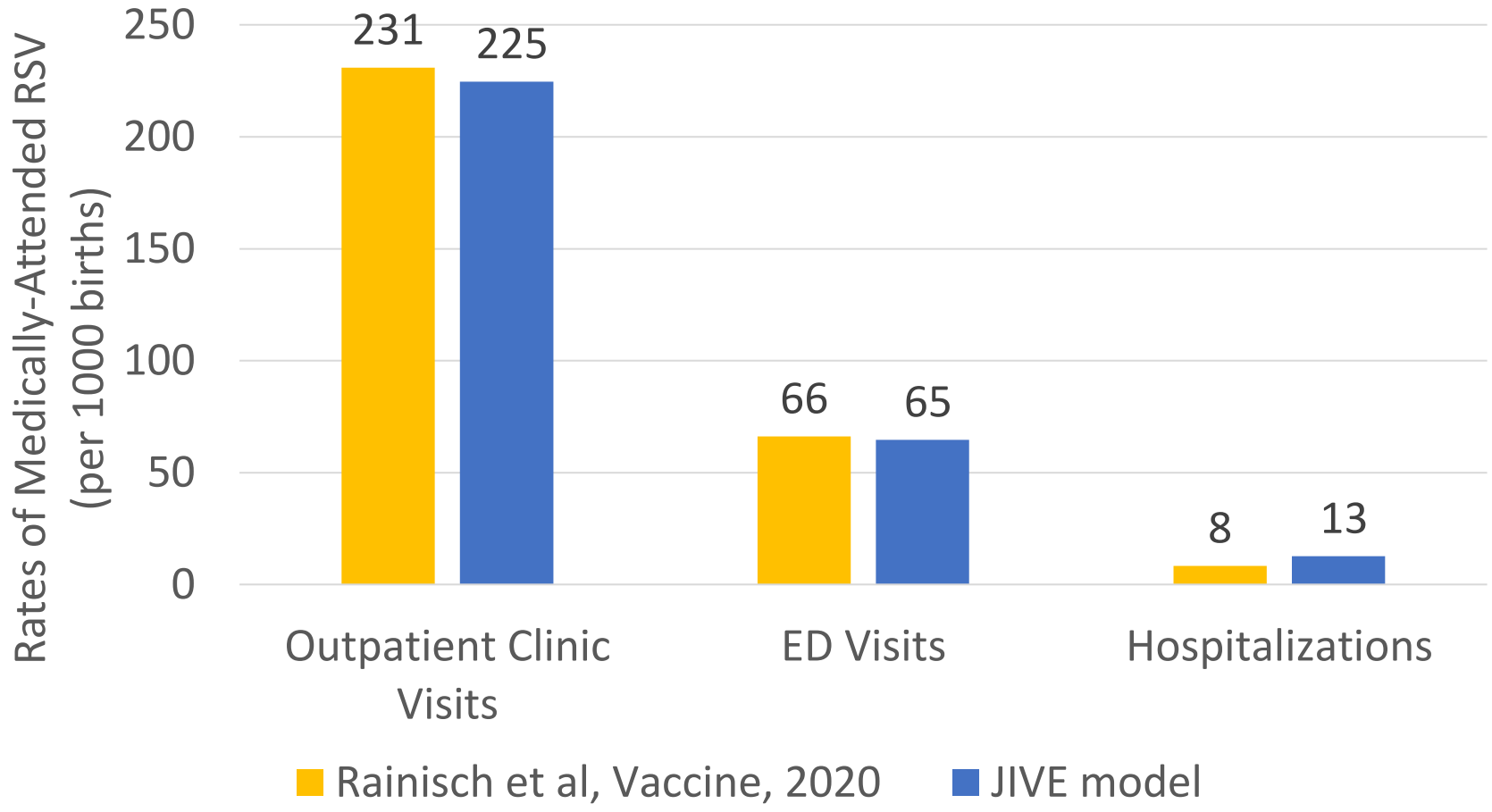
^ Costs updated to 2022$ using GDP deflator

Deluca EK, Gebremariam A, Rose A, Biggerstaff M, Meltzer MI, Prosser LA. Cost-Effectiveness of Routine Annual Influenza Vaccination by Age and Risk Status. Vaccine. 2023. In press

Health-Related Quality-of-Life

- Sources
  - Glaser (2022)
    - Estimate based on comparison of utility losses between premature children who had RSV vs. premature children without RSV and their caregivers
    - Used as base case for hospitalization for children and their caregivers
  - Regnier (2013)
    - Estimate QALY losses for hospitalization, ED visits, and outpatient visits for children with pertussis
    - Use relative QALYs between hospitalization, ED, and outpatient to estimate base losses for ED and outpatient in base case
  - JIVE RSV Utilities Survey (2021)
    - Estimates QALY losses for hospitalization and outpatient visits for child and caregiver
    - Estimates may be impacted by COVID-related concerns about respiratory viruses
    - Inform upper bound of range

Validation


Rates of Medically-Attended RSV (per 1000 births)
250
200
150
100
50
0
231
225
66
65
8
13
Outpatient Clinic Visits
ED Visits
Hospitalizations
Rainisch et al, Vaccine, 2020
JIVE model

Results: Costs

	Medical						Productivity					
	Intervention	Outpatient	ED	Inpatient	Total RSV Medical	Total Health System	Outpatient	ED	Inpatient	Deaths	Total Productivity	Total
Natural History	225,005,528	69,409,019	137,189,260	548,601,655	755,199,934	980,205,462	356,863,932	102,733,556	59,598,851	85,770,201	604,966,541	1,585,172,002
Nirsevimab	815,695,065	60,614,296	115,680,370	383,861,494	560,156,160	1,375,851,225	311,646,183	86,626,721	41,701,850	60,014,178	499,988,933	1,875,840,158

Cohort:entire annual US birth cohort, assuming 50% uptake in nirsevimab group

Base cost of $445/dose