Evidence to Recommendations Framework:
Nirsevimab Updates

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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

<table>
<thead>
<tr>
<th>Population</th>
<th>Infants aged &lt;8 months born during or entering their first RSV season</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Nirsevimab (1 injection prior to start of RSV season or at birth if born during season, 50 mg if &lt;5 kg or 100 mg if ≥5 kg)</td>
</tr>
<tr>
<td>Comparison</td>
<td>No nirsevimab prophylaxis</td>
</tr>
</tbody>
</table>
| 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

<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question(s)</th>
</tr>
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<tbody>
<tr>
<td><strong>Public Health Problem</strong></td>
<td>- Is the problem of public health importance?</td>
</tr>
</tbody>
</table>
| **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\textsuperscript{1}, 2017–2023

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

* 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).

\textsuperscript{1}\url{https://www.cdc.gov/mmwr/volumes/72/wr/mm7214a1.htm}
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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Efficacy estimate*</th>
<th>Concerns in certainty of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically attended RSV LRTI</td>
<td>79.0% (95% CI: 68.5%–86.1%)</td>
<td>None</td>
</tr>
<tr>
<td>RSV LRTI with hospitalization</td>
<td>80.6% (95% CI: 62.3%–90.1%)</td>
<td>None</td>
</tr>
<tr>
<td>RSV LRTI with ICU admission</td>
<td>90.0% (95% CI: 16.4%–98.8%)</td>
<td>Serious (imprecision): Too few events</td>
</tr>
<tr>
<td>Death due to RSV respiratory illness</td>
<td>None recorded</td>
<td>N/A</td>
</tr>
<tr>
<td>All-cause medically attended-LRTI</td>
<td>34.8% (95% CI: 23.0–44.7%)</td>
<td>None</td>
</tr>
<tr>
<td>All-cause LRTI-associated hospitalization</td>
<td>44.9% (95% CI: 24.9%–59.6%)</td>
<td>None</td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Relative risk(^1)</th>
<th>Concerns in certainty of assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events (SAEs)(^2)</td>
<td>0.73 (95% CI: 0.59–0.89)</td>
<td>Serious (imprecision)</td>
</tr>
</tbody>
</table>

\(^1\) 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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence type¹</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically attended RSV LRTI</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>Nirsevimab is effective in preventing medically attended RSV LRTI</td>
<td>High</td>
</tr>
<tr>
<td>RSV-associated LRTI with hospitalization</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>Nirsevimab is effective in preventing medically attended RSV LRTI with hospitalization</td>
<td>High</td>
</tr>
<tr>
<td>RSV-associated LRTI with ICU admission</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>Nirsevimab is likely effective in preventing medically attended RSV LRTI with ICU admission</td>
<td>Moderate</td>
</tr>
<tr>
<td>RSV-associated death</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>No RSV-associated deaths reported</td>
<td>-</td>
</tr>
<tr>
<td>All-cause medically attended LRTI</td>
<td>Important</td>
<td>RCT (2)</td>
<td>Nirsevimab is effective in preventing all cause medically attended LRTI</td>
<td>High</td>
</tr>
<tr>
<td>All-cause LRTI-associated hospitalization</td>
<td>Important</td>
<td>RCT (2)</td>
<td>Nirsevimab is effective in preventing all cause hospitalization with respiratory disease</td>
<td>High</td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>Critical</td>
<td>RCT (2)</td>
<td>SAEs were likely not more common in intervention group than placebo group</td>
<td>Moderate</td>
</tr>
</tbody>
</table>
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
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

- **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/](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.
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.

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

<table>
<thead>
<tr>
<th>Setting</th>
<th>Number Needed to Immunize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>17</td>
</tr>
<tr>
<td>ED</td>
<td>48</td>
</tr>
<tr>
<td>Inpatient</td>
<td>128</td>
</tr>
<tr>
<td>ICU</td>
<td>581</td>
</tr>
<tr>
<td>Inpatient Day</td>
<td>24</td>
</tr>
<tr>
<td>ICU Day</td>
<td>194</td>
</tr>
</tbody>
</table>
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

### EtR Summary: All infants 1st RSV season

<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question(s</th>
<th>Work Group Judgments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Public Health Problem</strong></td>
<td>- Is RSV-associated disease among infants &lt;8 months of age entering their first RSV season and infants born during the RSV season of public health importance?</td>
<td>Yes</td>
</tr>
</tbody>
</table>
| **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**

<table>
<thead>
<tr>
<th>Balance of consequences</th>
<th>Undesirable consequences</th>
<th>Undesirable consequences</th>
<th>The balance between desirable and undesirable consequences</th>
<th>Desirable consequences</th>
<th>Desirable consequences</th>
<th>There is insufficient evidence to determine the balance of consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>clearly outweigh</em></td>
<td><em>probably outweigh</em></td>
<td><em>closely balanced or uncertain</em></td>
<td><em>clearly outweigh</em></td>
<td><em>clearly outweigh</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td>desirable consequences</td>
<td>desirable consequences</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>in most settings</td>
<td>in most settings</td>
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</tr>
</tbody>
</table>

Minority opinion
**Evidence to Recommendations Framework**

**Summary: Work Group Interpretations**

All infants 1st RSV season

<table>
<thead>
<tr>
<th>Type of recommendation</th>
<th>We do not recommend the intervention</th>
<th>We recommend the intervention for individuals based on shared clinical decision-making</th>
<th>We recommend the intervention</th>
</tr>
</thead>
</table>


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

<table>
<thead>
<tr>
<th>Population</th>
<th>Children <em>aged 8–19 months who are at increased risk of severe RSV disease</em> and who are entering their <em>second RSV season</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Nirsevimab (<em>200 mg</em> [2 x 100 mg] injection near start of second RSV season)</td>
</tr>
<tr>
<td>Comparison</td>
<td>No nirsevimab prophylaxis</td>
</tr>
<tr>
<td>Outcomes</td>
<td>▪ Medically attended RSV associated lower respiratory tract infection (LRTI)</td>
</tr>
<tr>
<td></td>
<td>▪ Medically attended RSV associated LRTI with hospitalization</td>
</tr>
<tr>
<td></td>
<td>▪ Medically attended RSV associated LRTI with ICU admission</td>
</tr>
<tr>
<td></td>
<td>▪ RSV-associated death</td>
</tr>
<tr>
<td></td>
<td>▪ All-cause Medically attended LRTI</td>
</tr>
<tr>
<td></td>
<td>▪ All-cause LRTI associated hospitalization</td>
</tr>
<tr>
<td></td>
<td>▪ Serious adverse events</td>
</tr>
</tbody>
</table>
## Evidence to Recommendations (EtR) Framework

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

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\textsuperscript{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\textsuperscript{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\textsuperscript{5}

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.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance</th>
<th>Design (# of studies)</th>
<th>Findings</th>
<th>Evidence type</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benefits</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medically attended (MA) RSV LRTI</td>
<td>Critical</td>
<td>1</td>
<td>Nirsevimab might be effective in preventing MA RSV LRTI</td>
<td>Low</td>
</tr>
<tr>
<td>RSV LRTI with hospitalization</td>
<td>Critical</td>
<td></td>
<td>No available data</td>
<td></td>
</tr>
<tr>
<td>RSV LRTI with ICU admission</td>
<td>Critical</td>
<td></td>
<td>No available data</td>
<td></td>
</tr>
<tr>
<td>RSV-associated death</td>
<td>Critical</td>
<td></td>
<td>No available data</td>
<td></td>
</tr>
<tr>
<td>All cause medically attended LRTI</td>
<td>Important</td>
<td></td>
<td>No available data</td>
<td></td>
</tr>
<tr>
<td>All cause hospitalization with respiratory disease</td>
<td>Important</td>
<td></td>
<td>No available data</td>
<td></td>
</tr>
<tr>
<td><strong>Harms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious adverse events (SAEs)</td>
<td>Critical</td>
<td>1</td>
<td>Prevalence of SAEs was not significantly different in the intervention and control groups</td>
<td>Very low</td>
</tr>
</tbody>
</table>
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 stakeholders¹

¹For 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

- Cost updated to $890 nirsevimab costs (2x $445/dose)
- Mortality estimates modified to include high-risk individuals
- Other inputs unchanged

1Same assumption as previous model presented at February 23, 2023 ACIP meeting
Updated cost effectiveness results for children 8–19 months entering second RSV season

<table>
<thead>
<tr>
<th>Increased Risk category</th>
<th>RSV Hospitalization incidence increased</th>
<th>RSV hospitalization incidence and mortality per hospitalization increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x (base)</td>
<td>$1,557,544</td>
<td>$1,557,544</td>
</tr>
<tr>
<td>2x</td>
<td>$1,147,756</td>
<td>$836,270</td>
</tr>
<tr>
<td>4x</td>
<td>$726,983</td>
<td>$280,740</td>
</tr>
<tr>
<td>6x</td>
<td>$512,337</td>
<td>$118,912</td>
</tr>
<tr>
<td>10x</td>
<td>$294,775</td>
<td>$25,328</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>EtR Domain</th>
<th>Question(s)</th>
<th>Work Group Judgments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Public Health</td>
<td>▪ Is RSV disease among children 8–19 months who are at increased risk of severe disease of public health importance?</td>
<td>Yes</td>
</tr>
<tr>
<td>Problem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benefits and Harms</td>
<td>▪ How substantial are the desirable anticipated effects?</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>▪ How substantial are the undesirable anticipated effects?</td>
<td>Minimal</td>
</tr>
<tr>
<td></td>
<td>▪ Do the desirable effects outweigh the undesirable effects?</td>
<td>Favors nirsevimab</td>
</tr>
<tr>
<td>Values</td>
<td>▪ Does the target population feel the desirable effects are large relative to the undesirable effects?</td>
<td>Probably yes</td>
</tr>
<tr>
<td></td>
<td>▪ Is there important variability in how patients value the outcome?</td>
<td>Probably no</td>
</tr>
<tr>
<td>Acceptability</td>
<td>▪ Is nirsevimab acceptable to key stakeholders?</td>
<td>Yes / Probably yes</td>
</tr>
<tr>
<td>Feasibility</td>
<td>▪ Is the intervention feasible to implement?</td>
<td>Probably yes</td>
</tr>
<tr>
<td>Resource Use</td>
<td>▪ Is the intervention a reasonable and efficient allocation of resources?</td>
<td>$890: Probably yes</td>
</tr>
<tr>
<td>Equity</td>
<td>▪ What would be in the impact of the intervention on health equity?</td>
<td>Probably increased</td>
</tr>
</tbody>
</table>
### Evidence to Recommendations Framework

**Summary: Work Group Interpretations**

Children at increased risk of severe disease 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 |

---

1For 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 |

¹For 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
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Eghosa (Ivy) Oyegun
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Nancy Fenlon
Rebecca Miller
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Dale Babcock
Rosa Herrera
Richard Quartarone
Stuart Myerburg
Melissa Taylor
Sarah Morales
Barbara Mahon
All members of the ACIP Mat/Peds RSV Work Group
Back up slides
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)

- **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)
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)**
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)
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

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>No of patients</th>
<th>Effect</th>
<th>Certainty</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

**Medically attended lower respiratory tract infection**

| 1 | randomized trial | not serious | not serious | very serious | 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. | n/a | n/a | ⬤🥈◯◯ | Low | CRITICAL |

**Certainty assessment**

- **No of patients**
- **Effect**
- **Certainty**
- **Importance**

---

**Serious adverse events**

| 1 | randomized trial | not serious | not serious | serious | very serious | none | 21/220 | 0/42 (0%) | RR 8.4 (0.52 to 135.5) | 86 more per 1,000 (from 6 fewer to 1,000 more) | ⬤◯◯◯ | 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.

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

University of Michigan

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

- No Prophylaxis
  - Infection
    - Hospitalization
      - ED
    - Outpatient
    - None of the above
  - Alive
  - Dead

- Nirsevimab
  - Adverse Events
    - Systemic Reaction
    - Injection Site Reaction
    - Serious Adverse Event
    - None of the above
## Methods: Epidemiology

### Hospitalization

#### Base Case

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

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

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

#### Mortality

<table>
<thead>
<tr>
<th>RSV mortality per hospitalization</th>
<th>Base Case</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-5 months</td>
<td>0.10%</td>
<td>0.04-0.20%</td>
<td>Hansen 2022, Doucette 2016</td>
</tr>
<tr>
<td>Age 6-11 months</td>
<td>0.10%</td>
<td>0.04-0.20%</td>
<td>Hansen 2022, Doucette 2016</td>
</tr>
<tr>
<td>Age 12-23 months</td>
<td>0.3%</td>
<td>0.28%-0.34%</td>
<td>Gupta 2016</td>
</tr>
</tbody>
</table>

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

Methods: Nirsevimab Efficacy

Average efficacy first 6 months = trial efficacy
Sigmoid decay to final efficacy
Zero efficacy
## Methods: Efficacy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Base case value</th>
<th>Range for sensitivity analysis</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nirsevimab</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial efficacy (months 0-5) against RSV-associated LRTI</td>
<td>79.0%</td>
<td>68.5% - 86.1%</td>
<td></td>
</tr>
<tr>
<td>Efficacy months 6-10</td>
<td>25.0%</td>
<td>0.0% - 50.0%</td>
<td></td>
</tr>
<tr>
<td>Efficacy after 10 months</td>
<td>0.0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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

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

- 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

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

*Productivity for outpatient and ED based on adult influenza

^Hospitalization productivity loss = length of hospitalization + 2 days
## Methods: Intervention Cost

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunization-related costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nirsevimab, per dose</td>
<td>$445</td>
<td>$50-$600</td>
<td>Assumption</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>LRTI quality adjusted life DAYS lost</th>
<th>Base</th>
<th>Lower (Regnier)</th>
<th>Upper (JIVE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient: Child</td>
<td>3.1</td>
<td>1.8</td>
<td>16.6</td>
</tr>
<tr>
<td>Outpatient: Caregiver</td>
<td>1.5</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td>ED: Child</td>
<td>4.9</td>
<td>2.9</td>
<td>16.6</td>
</tr>
<tr>
<td>ED: Caregiver</td>
<td>2.5</td>
<td>0</td>
<td>9.1</td>
</tr>
<tr>
<td>Hospitalized: Child</td>
<td>6.2</td>
<td>3.7</td>
<td>26.5</td>
</tr>
<tr>
<td>Hospitalized: Caregiver</td>
<td>2.4</td>
<td>0</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Measured in Days Lost

Most Likely
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
Cohort: 1,000 nirsevimab and 1,000 natural history, assuming 50% uptake in nirsevimab group
Results: Health outcomes

Number needed to Prophylax to avoid Nirsevimab

- Outpatient: 17
- ED: 48
- Inpatient: 128
- ICU: 581
- Inpatient Day: 24
- ICU Day: 194
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

<table>
<thead>
<tr>
<th></th>
<th>Adverse Events</th>
<th>Outpatient</th>
<th>ED</th>
<th>Inpatient</th>
<th>Deaths</th>
<th>Total</th>
<th>Grand</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Child</td>
<td>Caregiver</td>
<td>Child</td>
<td>Caregiver</td>
<td>Child</td>
<td>Caregiver</td>
</tr>
<tr>
<td>Natural History</td>
<td></td>
<td>7,153</td>
<td>3,580</td>
<td>3,290</td>
<td>1,645</td>
<td>807</td>
<td>320</td>
</tr>
<tr>
<td>Nirsevimab</td>
<td></td>
<td>52</td>
<td>6,246</td>
<td>3,127</td>
<td>2,774</td>
<td>1,387</td>
<td>565</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Overall</th>
<th>Costs ($)</th>
<th>QALYs</th>
<th>ICER ($/QALY) Vs. NH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural History</td>
<td>1,585,172,002</td>
<td>18,151</td>
<td></td>
</tr>
<tr>
<td>Nirsevimab</td>
<td>1,875,840,158</td>
<td>15,324</td>
<td>102,811</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th></th>
<th>No Palivizumab Savings</th>
<th>Palivizumab Savings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low-Risk Mortality</strong></td>
<td>$205,639</td>
<td>$118,522</td>
</tr>
<tr>
<td><strong>Overall Average Mortality</strong></td>
<td>$182,397</td>
<td>$102,811</td>
</tr>
</tbody>
</table>

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

![Graph showing events averted per year for different settings with Nirsevimab]
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

Inpatient

ICU

Inpatient Days

ICU Days

Events Averted per 1000 Children given nirsevimab

Events Averted

- Base
- 2x
- 4x
- 6x
- 10x
## Second Season, High-Risk

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

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

Epidemiology
- Seasonality
  - Incidence
    - Outpatient
    - ED
    - Hospitalizations

Interventions
- Nirsevimab
- Timing
- Waning Protection

Health Effects
- Outpatient
- ED
- Hospitalizations
- Deaths

Economic Effects
- Intervention
- Disease
- Societal
- QALYs
- ICER

Health Economics
- Health Burden/
  - Outpatient
  - ED
  - Hospitalizations
- Cost Burden/
  - Outpatient
  - ED
  - Hospitalizations
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

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

* 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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pediatric Quality-Adjusted Life-Years lost due to adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic reaction</td>
<td>0.0056</td>
<td>0.00051-0.0061</td>
<td>Deluca et al (under review)</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>0.0137</td>
<td>0.0135-0.0139</td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>0.141</td>
<td>0.092-0.199</td>
<td>(Guillain-Barre) Prosser, 2006¹²</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Costs due to adverse events</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical Costs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost of outpatient visit for systemic reaction</td>
<td>$313</td>
<td>$27 - $1,337</td>
<td>Marketscan unpublished; Deluca et al (under review)</td>
</tr>
<tr>
<td>Cost of outpatient visit for injection site reaction</td>
<td>$326</td>
<td>$48 - $1,101</td>
<td>Marketscan unpublished; Deluca et al (in Press)</td>
</tr>
<tr>
<td>Anaphylaxis medical costs</td>
<td>$7,706</td>
<td>$89 - $23,414</td>
<td>Marketscan unpublished; Deluca et al (In Press)</td>
</tr>
<tr>
<td>Serious Adverse Event</td>
<td>$36,163.76</td>
<td>$10372.31 - $122,145.60</td>
<td>Prosser, 2006¹²</td>
</tr>
<tr>
<td><strong>Productivity Costs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recipient time for office visit (fraction of day)</td>
<td>0.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parent time for anaphylaxis (days)</td>
<td>1</td>
<td>1-3</td>
<td>Shimabukuro, 2021¹³</td>
</tr>
<tr>
<td>Daily productivity</td>
<td>190</td>
<td>169.41 – 211.03</td>
<td>Grosse, 2019¹⁴</td>
</tr>
</tbody>
</table>

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

¹ Costs updated to 2022$ using GDP deflator

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)

- Outpatient Clinic Visits: 231
- ED Visits: 66, JIVE model 65
- Hospitalizations: 8, JIVE model 13

Rainisch et al, Vaccine, 2020

JIVE model
## Results: Costs

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Medical</th>
<th>Productivity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Outpatient</td>
<td>ED</td>
</tr>
<tr>
<td>Natural History</td>
<td>225,005,528</td>
<td>69,409,019</td>
</tr>
<tr>
<td>Nirsevimab</td>
<td>815,695,065</td>
<td>60,614,296</td>
</tr>
</tbody>
</table>

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

Base cost of $445/dose