Centers for Disease Control and Prevention
National Center for Immunization and Respiratory Diseases

Clinical considerations for maternal RSVPreF vaccine and nirsevimab

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Outline

- RSV epidemiology in children
- Efficacy and safety of maternal RSVpreF vaccine (Abrysvo) and nirsevimab (Beyfortus)
- Clinical considerations for use of maternal RSV vaccine and nirsevimab

RSV epidemiology in children

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

- Most (68%) infants are infected in the first year of life and nearly all (97%) by age 2 years[2]
- 2–3% of young infants will be hospitalized for RSV[3,4,5]
- RSV is a common cause of lower respiratory tract infection in infants
- Highest RSV hospitalization rates occur in first months of life and risk declines with increasing age in early childhood[3,5]
- 79% of children hospitalized with RSV aged <2 years had no underlying medical conditions[3]

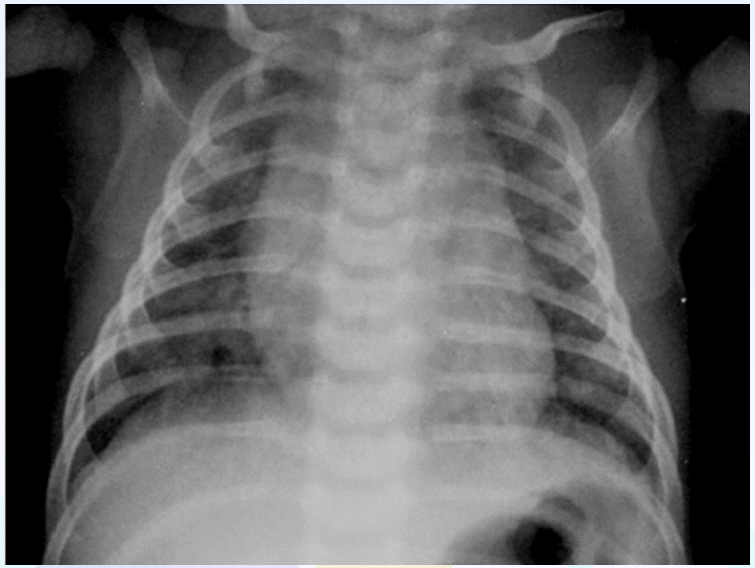
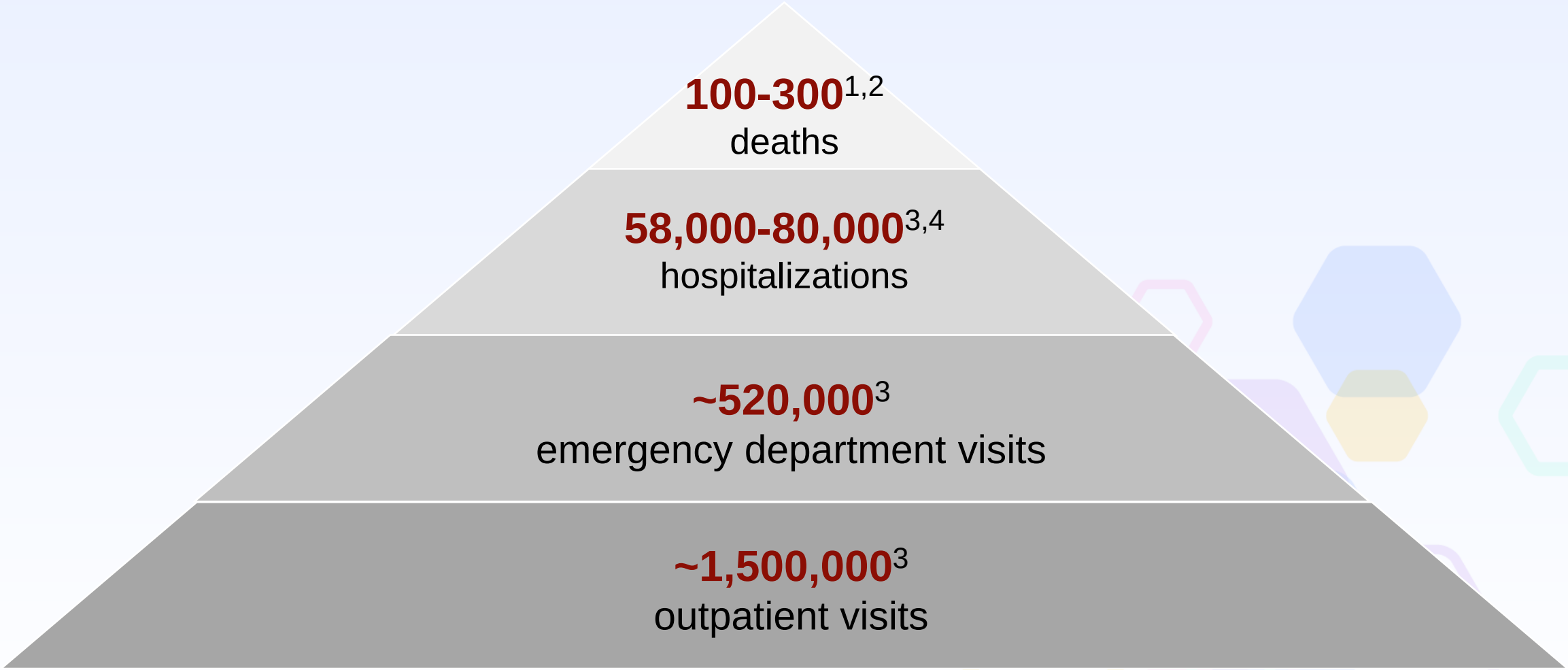


Image: Goncalves et al. Critical Care Research and Practice 2012

[1]Suh et al. JID 2022; [2]Glezen et al, Arch Dis Child, 1986; [3]Hall et al, Pediatrics, 2013; [4]Langley & Anderson, PIDJ, 2011; [5]CDC NVSN data

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



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

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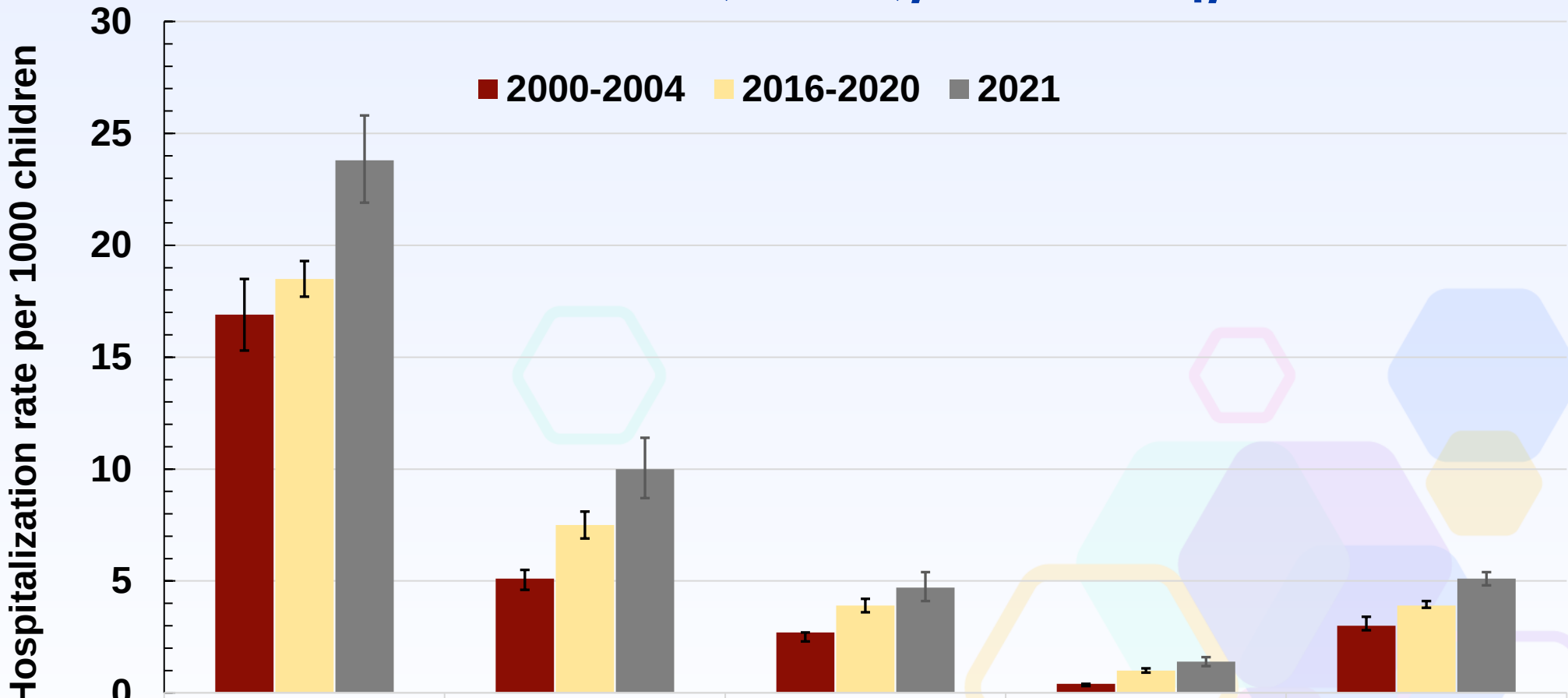
RSV-associated hospitalization rates in children aged <5 years, New Vaccine Surveillance Network (NVSN), 2000-2004, 2016-2021



	0-5 months	6-11 months	12-23 months	24-59 months	0-59 months
2000-2004	16.9	5.1	2.7	0.4	3
2016-2020	18.5	7.5	3.9	1.0	3.9
2021	23.8	10.0	4.7	1.4	5.1

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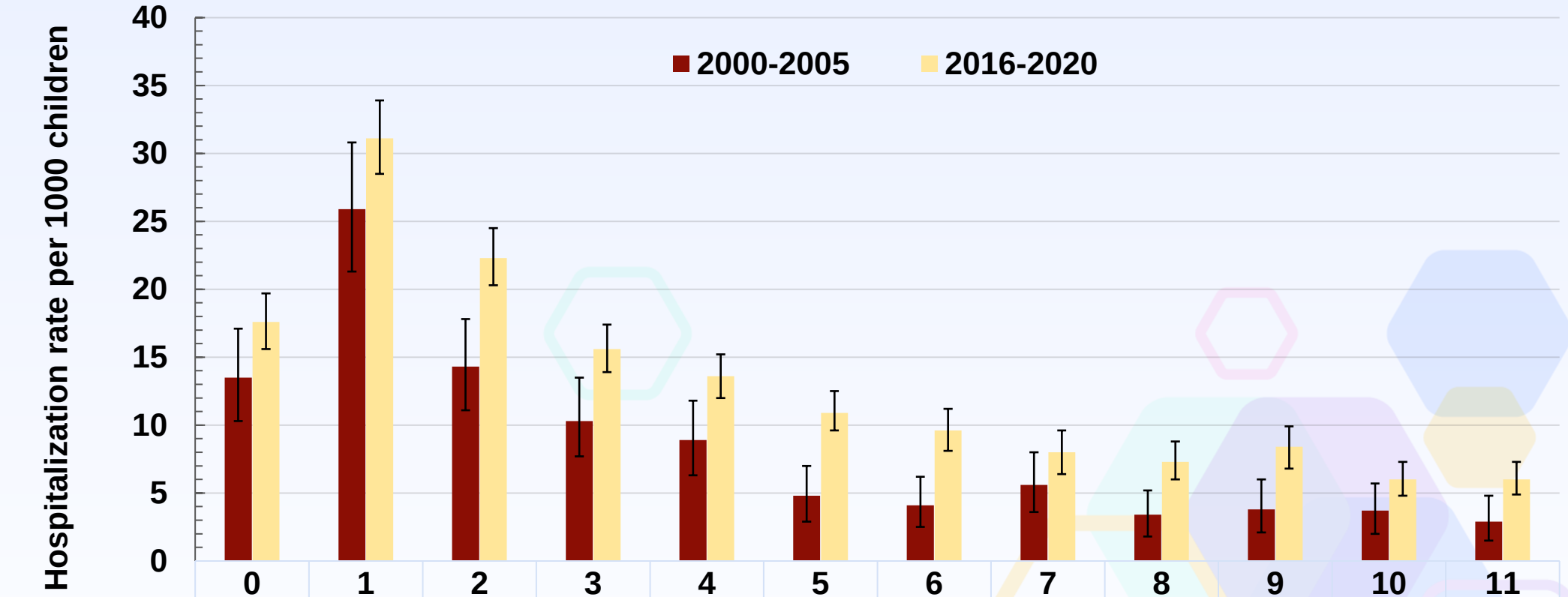
RSV-associated hospitalization rates in children aged 0–11 months, NVSN, 2000–2005 and 2016–2020



	0	1	2	3	4	5	6	7	8	9	10	11
2000-2005	13.5	25.9	14.3	10.3	8.9	4.8	4.1	5.6	3.4	3.8	3.7	2.9
2016-2020	17.6	31.1	22.3	15.6	13.6	10.9	9.6	8.0	7.3	8.4	6.0	6.0

2000–2005: Adapted from Hall et al, Pediatrics 2013,
2016–2020: CDC unpublished data

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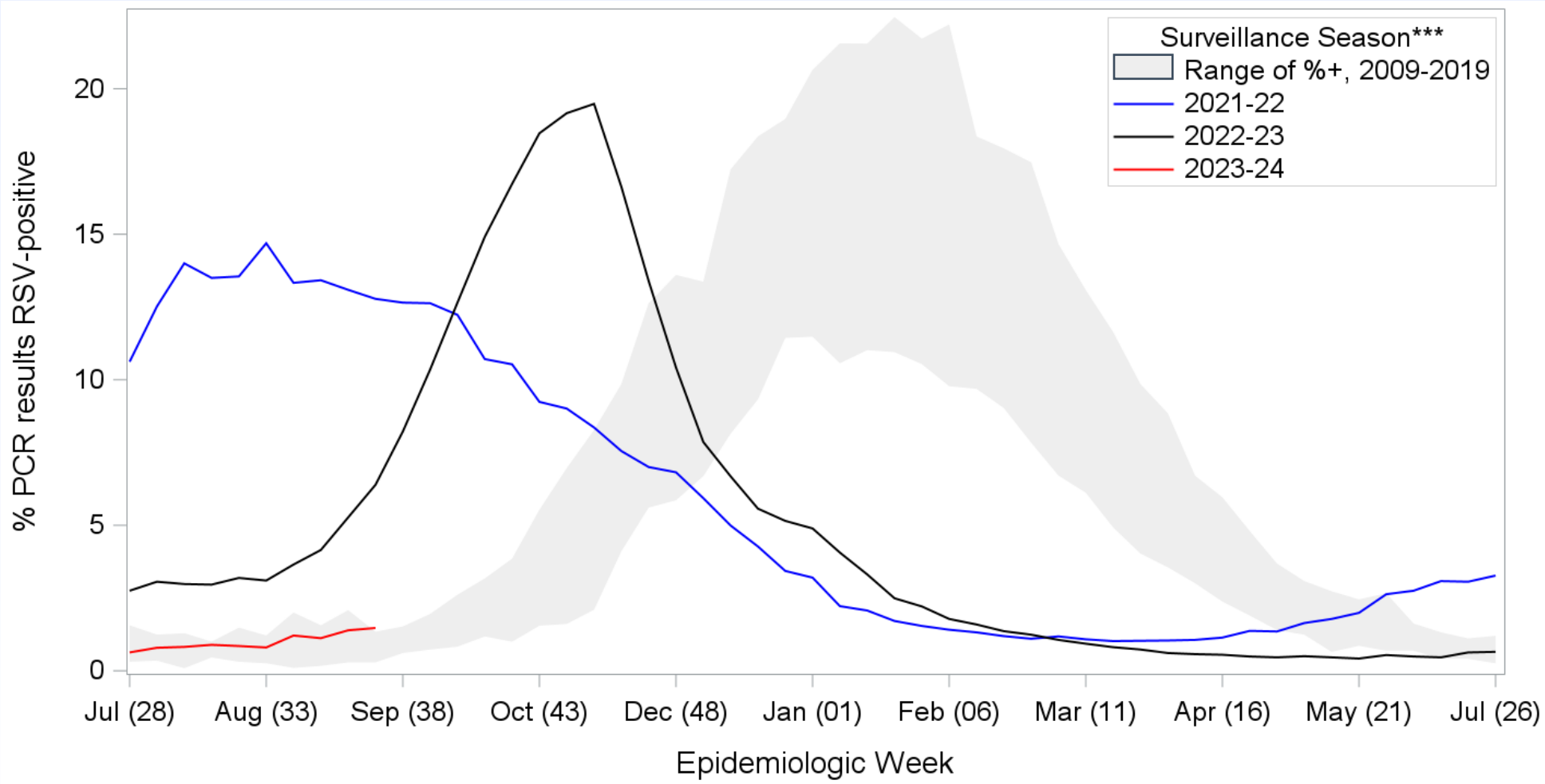
Percentage* of polymerase chain reaction test results positive for respiratory syncytial virus**, by MMWR week — National Respiratory and Enteric Virus Surveillance System, United States, July 2009–September 2023



Report was last updated on: 9/20/2023.
*All results presented are from nucleic acid amplification tests which represent >90% of the diagnostic tests reported to NREVSS. The last three weeks of data in 2023-24 may be less complete. NREVSS is an abbreviation for the National Respiratory and Enteric Virus Surveillance System. For more information on NREVSS, please visit National Respiratory and Enteric Virus Surveillance System | CDC.
**Respiratory syncytial virus types A and B are not shown separately in this report.
***The NREVSS surveillance season runs from the first week in July through June of the following year.

Efficacy and safety of maternal RSVpreF vaccine and nirsevimab

Relative risk of SAEs and concerns in certainty of assessment: nirsevimab

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.

Efficacy estimates and concerns in certainty of assessment: nirsevimab

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

Effect estimates, harms: Pfizer maternal RSVpreF vaccine comparing trial vs approved dosing interval

Outcome	Trial dosing interval[1] (24–36 weeks)	Approved dosing interval[1] (32–36 weeks)
	Relative Risk[2] (95% CI)	Relative Risk[2] (95% CI)
Harms		
Serious adverse events in pregnant people	1.06 (0.95, 1.17)	1.02 (0.87, 1.20)
Reactogenicity (grade 3+) in pregnant people	0.97 (0.72, 1.31)	0.98 (0.62, 1.54)
Serious adverse events in infants	1.01 (0.91, 1.11)	1.04 (0.90, 1.20)
Preterm birth (<37 weeks)	1.20 (0.99, 1.46)	1.15 (0.82, 1.61)

CI= confidence interval

1 Phase 3 and 2b trials

2 Pooled relative risk estimates were independently calculated using counts of events and participants in the phase 3 trial interim analysis, and phase 2b trial among those who received the phase 3 vaccine formulation

Effect estimates, benefits: Pfizer maternal RSVpreF vaccine comparing trial vs approved dosing interval

Outcome	Trial dosing interval (24–36 weeks gestation)	Approved dosing interval (32–36 weeks gestation)
	Manufacturer calculated vaccine efficacy (CI)[1]	Manufacturer calculated vaccine efficacy (95% CI)[2]
Benefits		
Medically attended RSV-associated lower respiratory tract infection in infants (0–180 days)	51.3% (97.58% CI: 29.4, 66.8)	57.3% (95% CI: 29.8, 74.7)
Hospitalization for RSV-associated lower respiratory tract infection in infants (0–180 days)	56.8% (99.17% CI: 10.1, 80.7)	48.2% (95% CI: -22.9, 79.6)
ICU admission from RSV hospitalization in infants (0–180 days)	42.9% (95% CI: -124.8, 87.7)	1 event in the vaccine group 2 events in the placebo group
Mechanical ventilation from RSV hospitalization in infants (0–180 days)	100% (95% CI: -9.1, 100)	0 events in the vaccine group 2 events in the placebo group
All-cause medically attended lower respiratory tract infection in infants (0–180 days)	2.5% (99.17%: -17.9, 19.4)	7.3% (95% CI: -15.7, 25.7)
All-cause hospitalization for lower respiratory tract infection in infants (0–180 days)	28.9% (95% CI: -2.0, 50.8)	34.7% (95% CI: -18.8, 64.9)

CI= confidence interval; ICU=Intensive care unit

1 Vaccine efficacy was calculated as 1–(P/[1–P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using the Bonferroni procedure and accounting for the primary endpoints results. Confidence intervals that are not 95% were adjusted using the Bonferroni procedure and accounting for the primary endpoints results.

2 Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

Phase 3 trial vaccine efficacy against severe medically attended RSV-associated LRTI, co-primary trial endpoint

Time period after birth	Trial dosing interval (24–36 weeks gestation) Vaccine efficacy[1] (99.5% or 97.58% CI)	Approved dosing interval (32–36 weeks gestation) Vaccine efficacy[2] (95% CI)
0–90 days after birth	81.8% (40.6, 96.3)	91.1% (38.8, 99.8)
0–180 days after birth	69.4% (44.3, 84.1)	76.5% (41.3, 92.1)

Within 0-180 days after birth

- Among 81 infants with severe medically attended RSV LRTI, 50 (62%) were hospitalized
- Among 63 infants hospitalized with RSV, 50 (79%) had severe medically attended RSV LRTI

1 Vaccine efficacy was calculated as 1−(P/[1−P]), where P is the number of cases of illness in the RSVpreF group divided by the total number of cases of illness. At 90 days, 99.5% confidence intervals (CIs) were used (determined by the alpha-spending function and adjusted with the use of the Bonferroni procedure), and at later intervals, 97.58% CIs were used (based on a two-sided alpha level of 0.0483 adjusted with the use of the Bonferroni procedure).

2 Vaccine efficacy was calculated as 1-(hP/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases and h is the ratio of number of participants at risk in the placebo group to the number of participants at risk in the RSVpreF group.

1. Kampmann et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants - PubMed (nih.gov)
2. Vaccines and Related Biological Products Advisory Committee May 18, 2023 Meeting Briefing Document- FDA

Clinical considerations for use of maternal RSV vaccine and nirsevimab

Clinical considerations for use of maternal RSV vaccine

- Maternal vaccine recommended for pregnant people during 32 through 36 weeks gestation, with seasonal administration
  - During September through January in most of the continental United States
  - In jurisdictions with seasonality that differs from most of the continental United States (e.g., Alaska, jurisdictions with tropical climates), providers should follow state, local, or territorial guidance on timing of administration
- Maternal RSVpreF vaccine may be simultaneously administered with other indicated vaccinations [1]

[1] https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/index.html.

Clinical considerations for maternal RSV vaccine and nirsevimab

- Either maternal vaccination or use of nirsevimab in the infant is recommended to prevent RSV lower respiratory tract infection, but administration of both products is not needed for most infants
- Healthcare providers of pregnant people should provide information on both products and consider patient preferences when determining whether to vaccinate the pregnant patient or to not vaccinate and rely on administration of nirsevimab to the infant after birth

Relative risks and benefits of maternal vaccination and nirsevimab

Both products are safe and effective in preventing RSV lower respiratory infection in infants

Maternal RSV vaccine	Nirsevimab
Benefits • Provides protection immediately after birth • May be more resistant to virus mutation • Avoids injection of infant **Risks** • Protection reduced if fewer antibodies produced or are transferred from mother to baby (e.g., mother immunocompromised or infant born soon after vaccine) • Potential risk of preterm birth	**Benefits** • Studies of antibody levels suggest that protection might wane more slowly • Can provide antibodies directly if infant receives less antibodies from mother • No risk of adverse pregnancy outcomes **Risks** • Potentially limited availability during 2023-2024 RSV season

Recommendations for use of nirsevimab in setting of an available maternal RSV vaccine

- Nirsevimab is recommended for infants aged <8 months born during or entering their first RSV season if
  - Mother did not receive RSV vaccine or unknown if mother received RSV vaccine
  - Mother vaccinated but infant born <14 days after vaccination
- Nirsevimab is not needed for most infants born ≥14 days after maternal vaccination

Timing of nirsevimab

- Providers should target administration[1]:
  - In the first week of life for infants born shortly before and during the season
  - Shortly before the start of the RSV season for infants aged <8 months
  - Shortly before the start of the RSV season for children aged 8–19 months who are at increased risk of severe RSV disease
- Based on pre-pandemic patterns, this means nirsevimab could be administered in most of the continental United States from October through the end of March
- Because timing of the onset, peak, and decline of RSV activity may vary, providers can adjust administration schedules based on local epidemiology

[1] While optimal timing for nirsevimab administration is shortly before the season, nirsevimab may be given at any time during the RSV season for age-eligible infants and children who have not yet received a dose

Timing of nirsevimab for infants born shortly before or during RSV season

- Nirsevimab should be administered within 1 week of birth.
  - Administration can be during the birth hospitalization or in the outpatient setting

- Infants with prolonged birth hospitalizations due to prematurity or other causes should receive nirsevimab shortly before or promptly after discharge

Tropical climates and Alaska

- Tropical climates may have seasonality that differs from most of the continental United States or is unpredictable
  - May include southern Florida, Hawaii, Guam, Puerto Rico, U.S. Virgin Islands, and U.S.-Affiliated Pacific Islands
- In Alaska, RSV seasonality is less predictable, and the duration of RSV seasons is often longer than the national average
- Providers in these jurisdictions should consult state, local, or territorial guidance on timing of nirsevimab administration

Circumstances for which nirsevimab can be considered when mother has received RSV vaccine ≥14 days prior to birth

- Nirsevimab can be considered in rare circumstances when, per the clinical judgment of the healthcare provider, the potential incremental benefit of administration is warranted
  - Infants born to pregnant people who may not mount an adequate immune response to vaccination (e.g., people with immunocompromising conditions) or have conditions associated with reduced transplacental antibody transfer (e.g., people living with HIV infection)[1]
  - Infants with cardiopulmonary bypass, leading to loss of maternal antibodies
  - Infants with substantial increased risk for severe RSV disease (e.g., hemodynamically significant congenital heart disease, intensive care admission and requiring oxygen at discharge)

[1] Palmerira Clin Dev Immunol 2012.

Nirsevimab administration algorithm for children aged <8 months on the day of administration

Meet all 3 following criteria? (yes/no)

1. Either mother did not receive RSV vaccine during pregnancy ≥14 days prior to birth or maternal RSV vaccine status unknown[1]
2. Day of nirsevimab administration during October through March[2]
3. Never previously received dose of nirsevimab[3]

Yes
All 3 criteria met

No
Any criteria not met

Nirsevimab recommended

Nirsevimab not needed

Nirsevimab administration algorithm for children aged <8 months on the day of administration footnotes

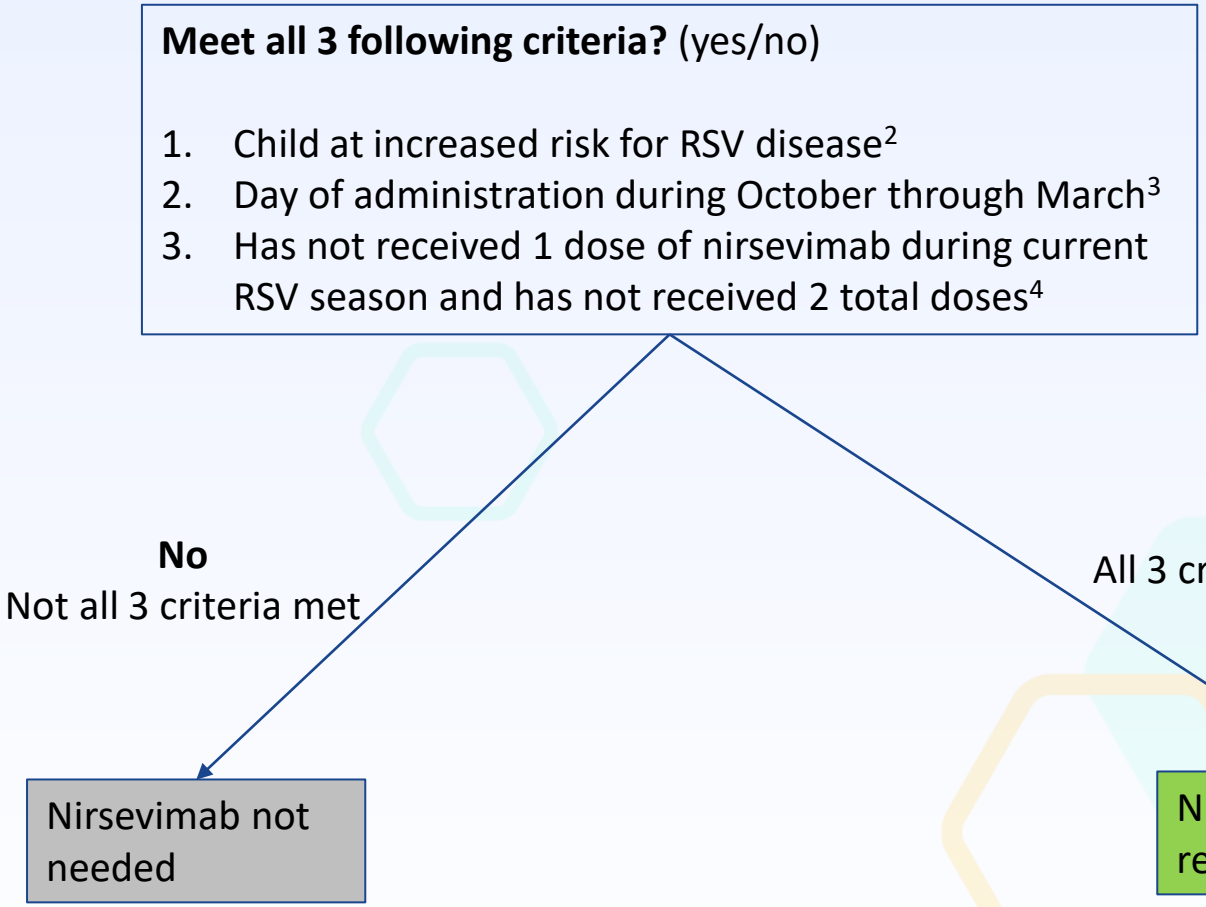
[1]For most infants age <8 months whose mother received RSV vaccine 14 or more days prior to birth, nirsevimab is not needed. Nirsevimab can be considered in rare circumstances when, per the clinical judgment of the healthcare provider, the potential incremental benefit of administration is warranted. These may include pregnant people who may not mount an adequate immune response to vaccination (e.g., people with immunocompromise) or have conditions associated with reduced transplacental antibody transfer (e.g., people living with HIV infection), infants with cardiopulmonary bypass leading to loss of RSV antibodies, and infants with substantial increased risk for severe RSV disease (e.g., hemodynamically significant congenital heart disease, intensive care admission and requiring oxygen at discharge).

[2]While the timing of the onset and duration of RSV season may vary, nirsevimab may be administered October through the end of March in the majority of the continental United States. Providers may adjust timing of administration based on guidance from public health authorities (e.g., CDC, health departments) or regional medical centers. Although optimal timing of administration is just before the start of the RSV season, nirsevimab may also be administered during the RSV season to infants and children who are age-eligible. Infants born shortly before or during RSV season should receive nirsevimab within one week of birth. Nirsevimab administration can occur during the birth hospitalization or in the outpatient setting. Infants with prolonged birth hospitalizations related to prematurity or other causes should receive nirsevimab shortly before or promptly after hospital discharge.

Children aged 8–19 months recommended to receive nirsevimab when entering their second RSV season because of increased risk of severe disease

- Children with chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season
- Children with severe immunocompromise
- Children with cystic fibrosis who have 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
- American Indian and Alaska Native children

Nirsevimab administration algorithm for children aged 8 through 19 months on day of administration[1]



Nirsevimab administration algorithm for children aged 8 through 19 months on day of administration footnotes

[1]Children at increased risk for severe disease aged <8 months of age and entering their second RSV season should receive nirsevimab. For example, a child born in March should receive their first RSV dose shortly after birth; they may be entering their second RSV season at 7 months of age in October and should not wait until 8 months of age to receive nirsevimab.

[2]Children aged 8–19 months recommended to receive nirsevimab during their second RSV season by ACIP:

-Children with chronic lung disease of prematurity who required medical support (chronic corticosteroid therapy, diuretic therapy, or supplemental oxygen) any time during the 6-month period before the start of the second RSV season

-Children with severe immunocompromise

-Children with cystic fibrosis who have either 1) 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 2) weight-for-length <10th percentile

-American Indian and Alaska Native children

Nirsevimab administration algorithm for children aged 8 through 19 months on day of administration footnotes

[3]While the timing of the onset and duration of RSV season may vary, nirsevimab may be administered October through the end of March in the majority of the continental United States. Providers may adjust timing of administration based on guidance from public health authorities (e.g., CDC, health departments) or regional medical centers. Although optimal timing of administration is just before the start of the RSV season, nirsevimab may also be administered during the RSV season to infants and children who are age-eligible. Infants born shortly before or during RSV season should receive nirsevimab within one week of birth. Nirsevimab administration can occur during the birth hospitalization or in the outpatient setting. Infants with prolonged birth hospitalizations related to prematurity or other causes should receive nirsevimab shortly before or promptly after hospital discharge.

[4]Children at increased risk for severe disease should not receive more than two doses of nirsevimab (one dose [50mg or 100 mg depending on weight] for the first RSV season and one dose [two 100 mg injections] for the second RSV season). Only one dose of nirsevimab is recommended per season (with exception for children who undergo cardiac surgery with cardiopulmonary bypass). Nirsevimab is recommended for children at increased risk for severe disease (as defined in footnote 4) during their first RSV season, including if aged 8-11 months if the child has not received nirsevimab during that RSV season.

Nirsevimab coadministration with routine childhood vaccines

- In accordance with CDC's general best practices for immunizations, simultaneous administration of nirsevimab with age-appropriate vaccines is recommended
- In clinical trials, when nirsevimab was given concomitantly with routine childhood vaccines, the safety and reactogenicity profile of the coadministered regimen was similar to the childhood vaccines given alone[1]
- When coadministered, nirsevimab is not expected to interfere with the immune response to vaccines[2]

[1]FDA label for nirsevimab ; [2]Espocito Front Immunol. 2021 Aug 11;12:708939

Consumers and health care providers reporting suspected adverse reactions for nirsevimab

- Report suspect adverse reactions following the administration of nirsevimab without coadministration with any vaccine to MedWatch
  - Reports can be submitted to MedWatch online at www.fda.gov/medwatch or by phone at 1-800-FDA-1088

- Report suspect adverse reactions following co-administration of nirsevimab with any vaccine to the Vaccine Adverse Event Reporting System (VAERS)
  - Please specify that the patient received nirsevimab on the VAERS form, specifically, in Section 9: 'Prescriptions, over-the-counter medications, dietary supplements, or herbal remedies being taken at the time of vaccination'

Vaccine Storage, Handling, and Administration of Maternal RSVpreF Vaccine

- Overall clinical implementation similar to other vaccines
  - Stored at 2◦ to 8◦ C
  - Administered as a single dose through intramuscular route

- Additional steps required for dilution, including reconstitution of the lyophilized antigen component with the sterile water diluent component (administered immediately or stored at room temperature for up to 4 hours)

Package Insert - ABRYSVO (STN 125769/26) (fda.gov)

Insurance Coverage of Maternal RSV Vaccine

- The Affordable Care Act (ACA) requires insurers to cover all ACIP-routinely recommended immunizations for plan years that begin on or after the date that is one year after the date of the recommendation[1]

- The Inflation Reduction Act (IRA) requires coverage of ACIP-recommended vaccines without cost sharing for Medicaid and Children's Health Insurance Program, starting October 1, 2023[2]
  - ~42% of mothers have Medicaid at the time of birth[3]

- ACIP passed a Vaccines for Children resolution for maternal RSV vaccine in people aged <19 years

1. 42 U.S. Code § 300gg–13 - Coverage of preventive health services. https://www.law.cornell.edu/uscode/text/42/300gg-13
2. Anniversary of the Inflation Reduction Act: Update on CMS Implementation | CMS
3. Medicaid Coverage for Women | KFF

Nirsevimab Storage, Handling, and Administration

- Similar to other routine vaccines for children
- Administered as intramuscular injection using single-dose pre-filled syringe
  - Can be administered simultaneously with other childhood vaccines
- Dosed by weight/age
  - 50 mg if <5 kg
  - 100 mg if ≥5 kg
  - 200 mg (2x100 mg) for high-risk children entering 2nd RSV season
- Stored in refrigerator at 2-8° C
- May be kept at room temperature (20-25° C) for up to 8 hours

Insurance Coverage for Infant Nirsevimab

- ACIP has recommended nirsevimab as a routine immunization. Therefore, it will be covered under the ACA without cost sharing by the patient starting in the effective plan year[1]

- Nirsevimab is included in the Vaccines for Children Program[2]
  - Eligible children (~50% of U.S. children) will be able to access nirsevimab at no cost

42 U.S. Code § 300gg–13 - Coverage of preventive health services. https://www.law.cornell.edu/uscode/text/42/300gg-13
Advisory Committee on Immunization Practices, Vaccines for Children Program (cdc.gov)

Supply and Availability of Maternal RSV Vaccine and Nirsevimab During 2023-2024 RSV Season

- No anticipated supply/demand mismatch
- Because the Pfizer maternal RSV vaccine is the same product in use for adults aged ≥60 years, availability is expected shortly after ACIP recommendations
- Nirsevimab will likely be available late September/early October, but may not be available in all pediatric settings this season
  - Efforts underway to increase number of birthing hospitals who will administer nirsevimab

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Karen Broder

Naomi Tepper

Heidi Moline

Amber Winn

Monica Patton

Jenny Milucky

Fiona Havers

Rebecca Morgan

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Patricia Wodi

Sascha Ellington

Megan Lindley

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ACIP and maternal-pediatric RSV WG members