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Epidemiology of Respiratory Syncytial Virus in U.S. Children

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Vaccines and Related Biological Products Advisory Committee Meeting
December 12, 2024

Outline

- RSV disease burden and seroprevalence in U.S. children
- RSV immunization recommendations
- Immune response after RSV immunization with nirsevimab
- Unmet medical needs and data gaps for pediatric RSV prevention

RSV disease burden and seroprevalence in U.S. children

RSV burden is high in children <5 years of age

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

~2,000,000 medical encounters[1]

58,000–80,000 hospitalizations[1,2,3]

100–300 deaths[4,5,6]

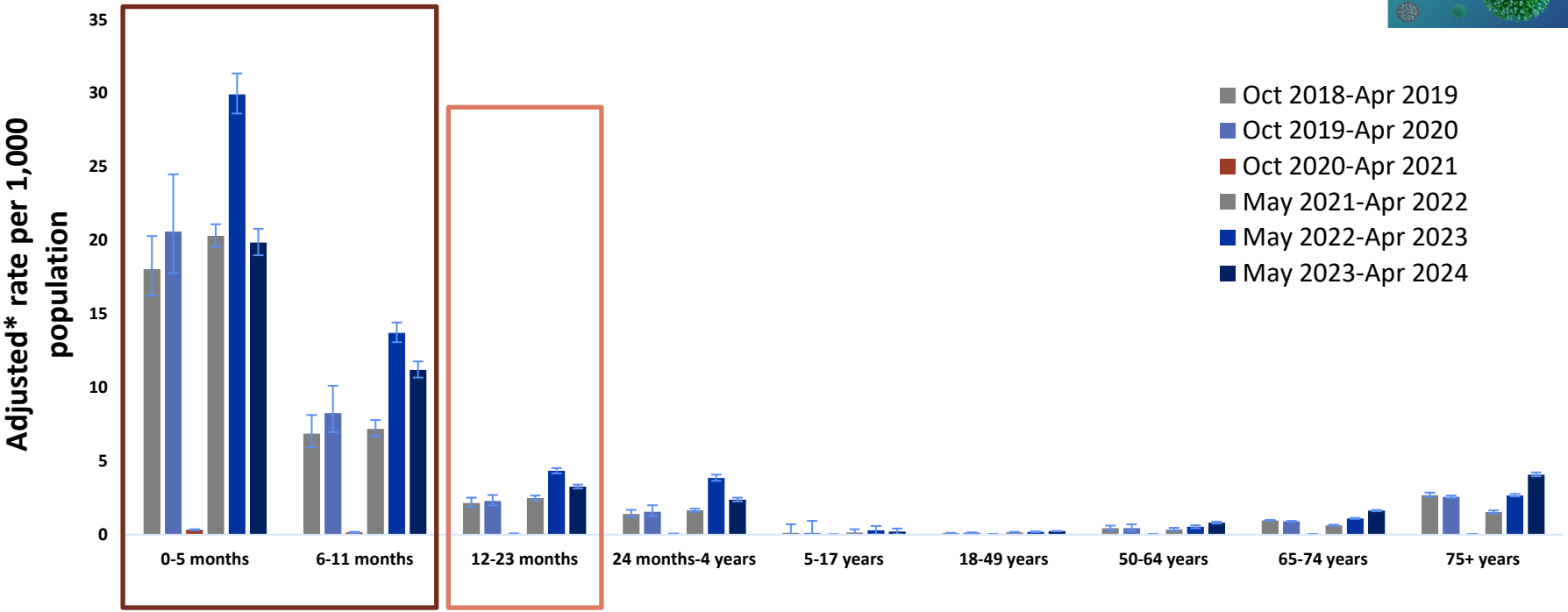
1. Hall et al, NEJM (2009): https://doi.org/10.1056/NEJMoa0804877
2. McLaughlin et al, J Infect Dis (2022): https://doi.org/10.1093/infdis/jiaa752
3. CDC RSV-NET, unpublished data.
4. Thompson et al, JAMA (2003): https://doi.org/10.1001/jama.289.2.179
5. Matias et al, Influenza Other Respi Viruses (2014):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

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

- 2-3% of young infants will be hospitalized for RSV[2,3,4]
- All infants are at risk for hospitalization
- Highest RSV hospitalization rates occur in the first months of life and risk declines with increasing age in early childhood[2,4]
- Certain conditions confer an increased risk of severe RSV disease in infants or young children
    - Prematurity[3]
    - Chronic lung disease[4]
    - Congenital heart disease[4]

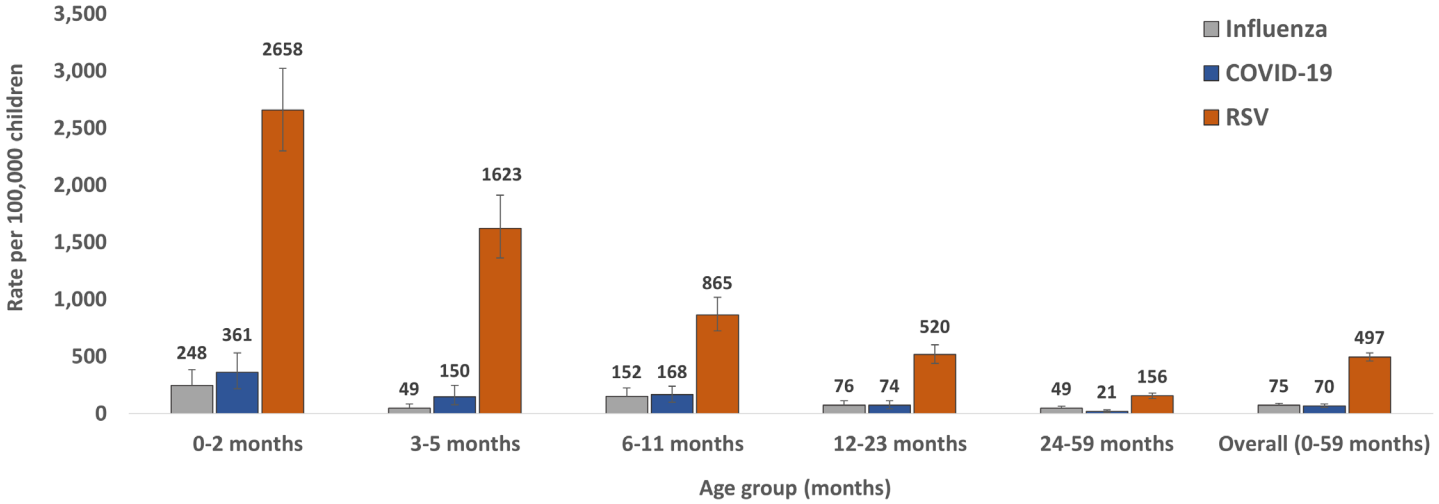
[1]Suh et al. JID 2022; [2]Hall et al, Pediatrics, 2013; [3]Langley & Anderson, PIDJ, 2011; [4]Curns et al. Pediatrics, 2024;

RSV-associated hospitalization rates across the lifespan are highest in young children



Adult RSV rates through 2022–23 adapted from Havers, et al. "The Burden of Respiratory Syncytial Virus Hospitalizations and In-Hospital Deaths in U.S. Adults, October 2016 through September 2023," *JAMA Network Open.* 2024;7(11):e2444756. Other data: RSV-NET unpublished data.
*Rates adjusted for undertesting and test sensitivity.

RSV-associated hospitalization rates exceed rates of other immunization-preventable respiratory viruses in young children (2023-2024 season)



Bar labels indicate the incidence rate per 100,000 children during September-April of 2023-2024. Rates were calculated using county-specific denominators from the 2020 US bridged-race population estimates, and population-based numerators based on the observed number of hospitalizations at each site adjusted to account for weeks with <7 days of surveillance, the proportion of eligible children not enrolled and each site's estimated market share of ARI hospitalizations by age. Error bars denote 95% confidence intervals determined based on 1000 bootstrap samples for each rate.

Cumulative incidence of RSV infection in longitudinal birth cohorts of U.S. children with molecular surveillance and seroprevalence data

Cohort	Years	No. of children	% RSV infection by 1 year of age	% RSV infection by 2 years of age
Houston Family Study[1]	1975-1980	125	68%	99%
INSPIRE[2] (Tennessee)	2012-2014	1,680	53%	–
PREVAIL[3] (Ohio)	2017-2020	245*	–	75%

INSPIRE Cohort: Infant Susceptibility to Pulmonary Infections and Asthma Following RSV Exposure Cohort
PREVAIL Cohort: Pediatric Respiratory & Enteric Virus Acquisition & Immunogenesis Longitudinal Cohort
***Cumulative incidence estimated among 194 children with high adherence to weekly swab collection for molecular testing (collection ≥70% of weekly swabs)**
[1] Glezen et al, Arch Dis Child, 1986 [2] Cacho et al, Emerg Infect Dis. 2024 [3] Unpublished preliminary data.

Houston Family Study, 1975-2000

- RSV reinfection was common in children <5 years of age
- RSV reinfection risk was inversely associated with RSV neutralizing antibody titer
- Reinfections were generally milder than primary infections

Table 4.—Risk of Reinfection With Respiratory Syncytial Virus Related to Preexisting Neutralizing Antibody Titer*

Titer (Reciprocal)	No. of Children	No. (Rate/100 Child-Years) Reinfected†	No. (Rate/100 Child-Years) With LRD‡
≤8	46	38 (82.6)	10 (21.7)
16-64	60	32 (53.3)	6 (10.0)
≥128	17	2 (11.8)	0 (0)
Total	**123**	**72** (58.5)	**16** (13.0)

*Houston Family Study, 1975 through 1980.
†$P<.01$.
‡LRD indicates lower respiratory tract disease ($.05<P<.1$).

Glezen et al, Arch Dis Child, 1986;

Summary

- RSV infection is common in infants and young children
  - At least half of infants have an RSV infection by 1 year of age
  - At least three quarters by 2 years of age
- RSV is the most common cause of hospitalization in U.S. infants
  - Highest hospitalization rates are in infants, followed by children 12-23 months of age
- Most hospitalizations in children <2 years of age are in healthy infants and children

RSV immunization recommendations

Two products are recommended to protect infants and young children from RSV lower respiratory tract infection through passive immunization

All infants in their first RSV season through either:

Maternal RSV Vaccine (Pfizer, Abrysvo)

for pregnant people at 32-36 weeks gestation

OR

Nirsevimab

for infants <8 months entering or born during the season

Some children in their second RSV season

Nirsevimab

for children 8-19 months entering the season at increased risk for severe RSV disease

Use of the Pfizer Respiratory Syncytial Virus Vaccine During Pregnancy for the Prevention of Respiratory Syncytial Virus–Associated Lower Respiratory Tract Disease in Infants: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR

Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)

Recommendations regarding additional RSV vaccine doses in subsequent pregnancies

- **People who received a maternal RSV vaccine during a previous pregnancy are not recommended to receive additional doses during future pregnancies**
- **Infants born to people who were vaccinated only during a prior pregnancy should receive nirsevimab**
- **Recommendations can be updated in the future if additional data are available**

https://www.cdc.gov/mmwr/volumes/72/wr/mm7241e1.htm

RSV prevention in children aged 8-19 months at increased risk for severe RSV disease in their second season

Children with chronic lung disease of prematurity who required medical support any time during the 6-month period before the start of the second RSV season

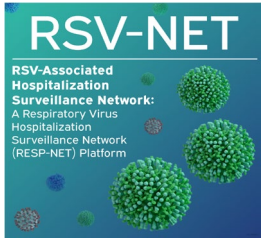
Children with severe immunocompromise

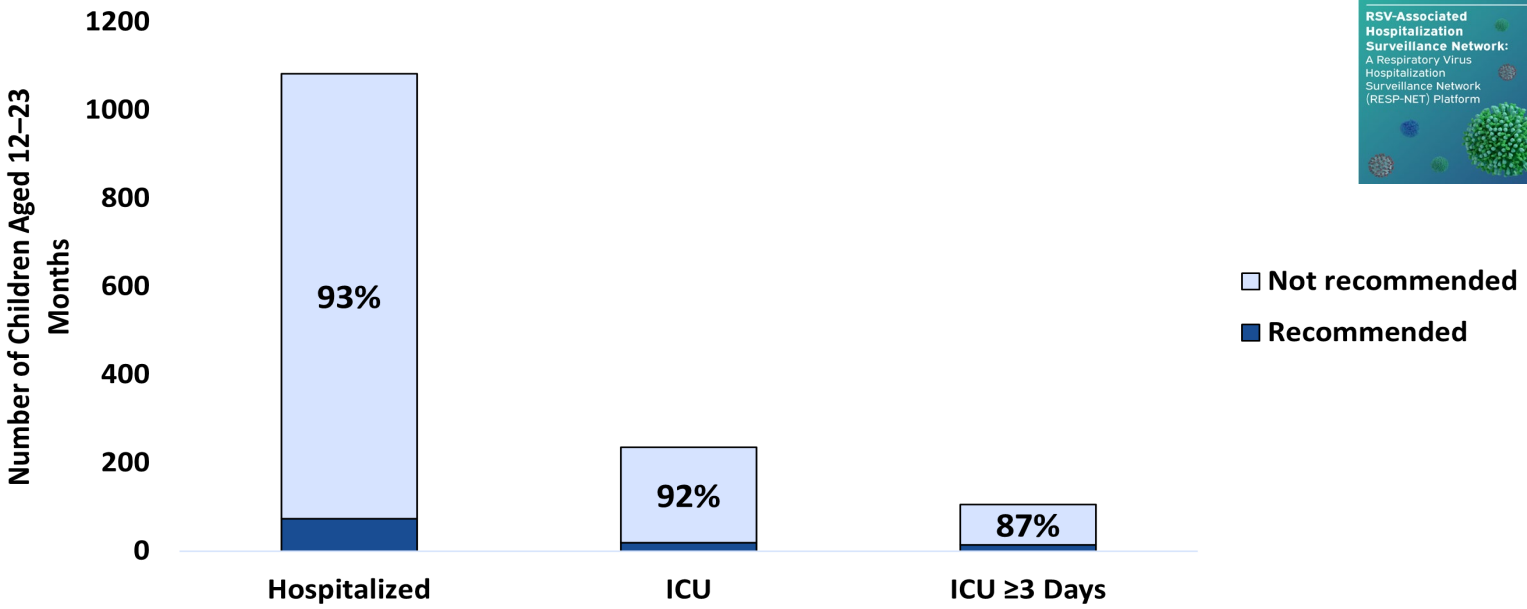
Children with cystic fibrosis who have manifestations of severe lung disease or weight-for-length <10th percentile

American Indian and Alaska Native children

Use of Nirsevimab for the Prevention of Respiratory Syncytial Virus Disease Among Infants and Young Children: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023 | MMWR (cdc.gov)

Most children 12-23 months of age hospitalized with RSV disease are not recommended* to receive nirsevimab in their second RSV season (2022-2023 season)

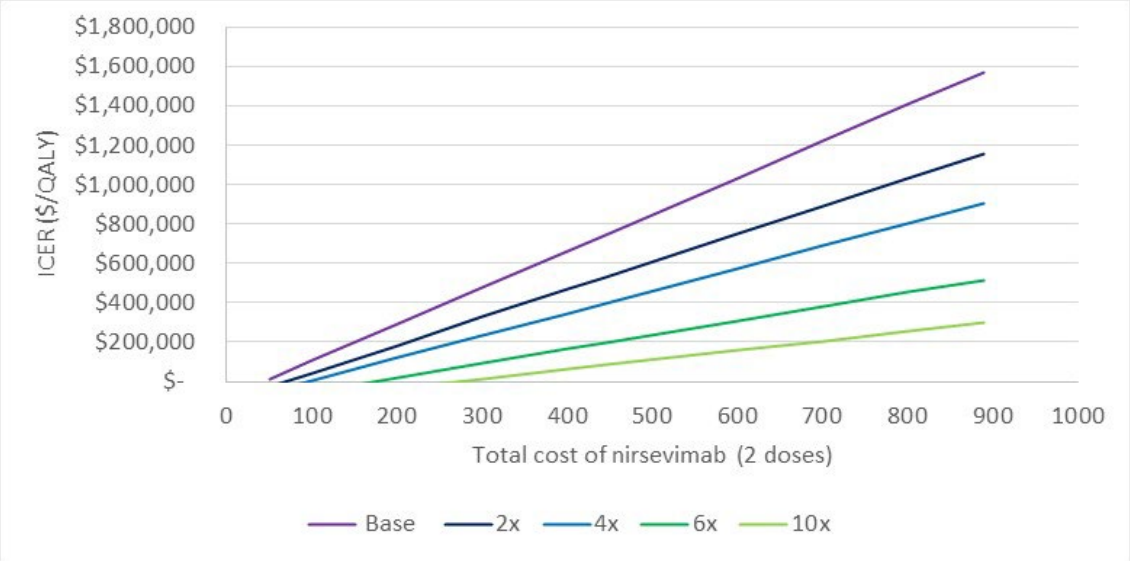




*Recommended defined as any chronic lung disease of prematurity, immunocompromising condition, or cystic fibrosis or American Indian or Alaska Native descent

Wang D, et al. Characteristics of Children Aged <24 Months Hospitalized with Laboratory-Confirmed Respiratory Syncytial Virus—RSV-NET, United States, October 2022–April 2023. National Immunization Conference; 2024 August 12-14, Atlanta, GA.

Incremental cost effectiveness ratio (ICER) of nirsevimab for children in their second RSV season varies by product cost and RSV hospitalization risk



QALY: Quality adjusted life year

Base case cost assumption for nirsevimab of $890 for two 100mg doses that comprise the recommended dose for children in their second RSV season (2 X $445).

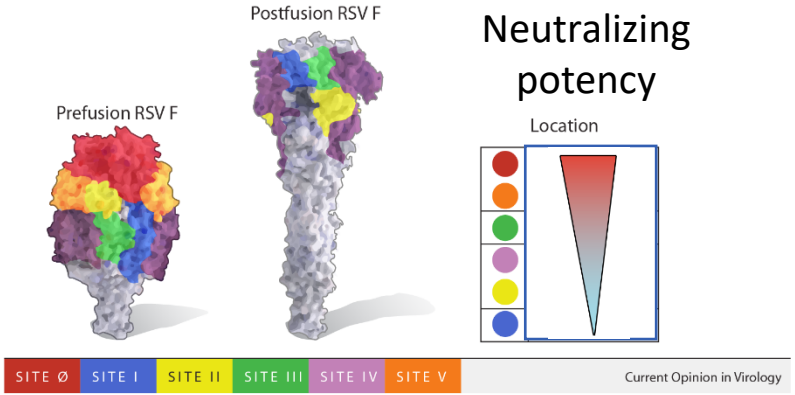
Analysis focuses on children not already eligible for palivizumab; savings from palivizumab were not included in this analysis.

Hutton et al. Cost-Effectiveness of Nirsevimab for Respiratory Syncytial Virus in Infants and Young Children. Pediatrics 2024; e2024066461.

Immune response after RSV immunization with nirsevimab

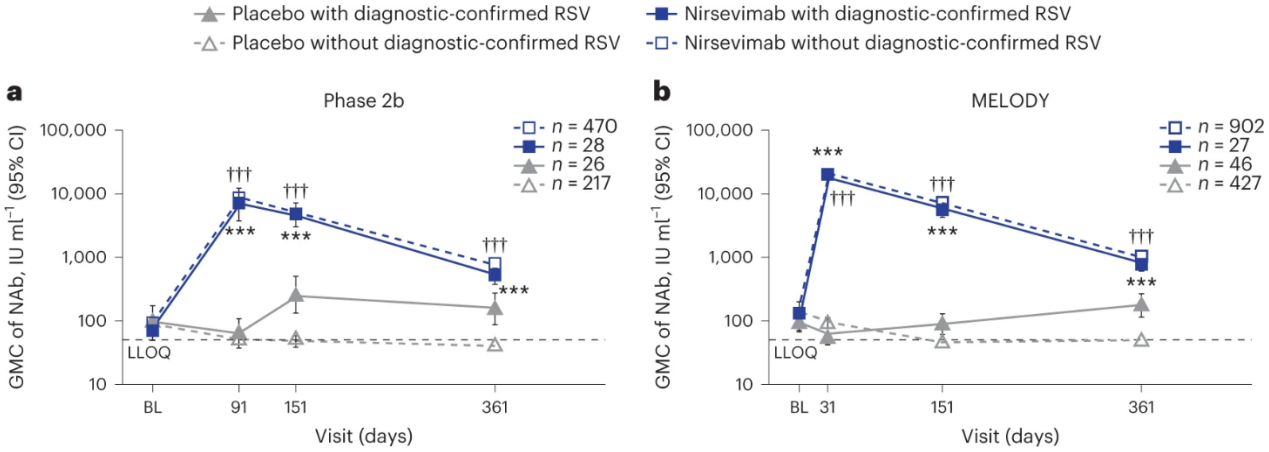
RSV Fusion Glycoprotein (F Protein)

- Facilitates virus entry into host cells
- Exists in 2 key states
  - **Pre-fusion** conformation – target of most neutralizing antibody after natural infection and target of vaccines and monoclonal antibodies
  - **Post-fusion** conformation – antibodies to post-F protein can be used to differentiate responses to natural infection versus immunization



Graham B. Current Opinion in Virology 2017; 23: 107-112

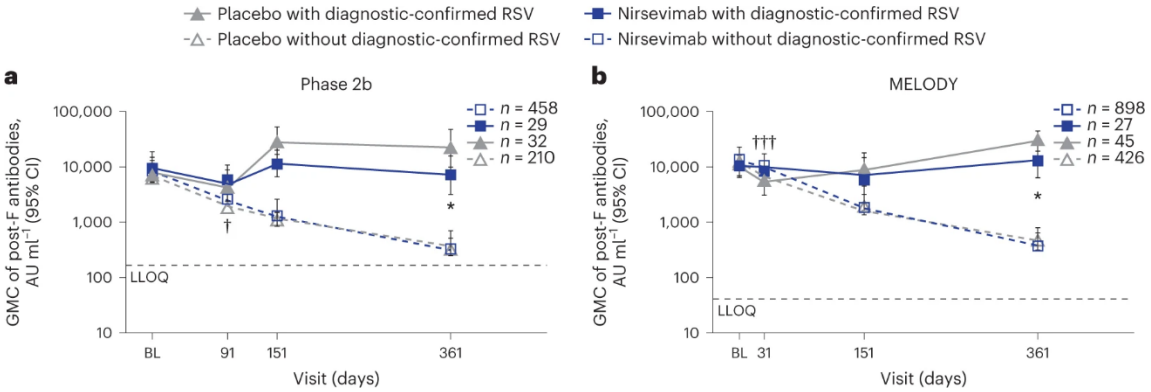
Post-immunization RSV neutralizing antibody titers are higher and durable through 1 year in nirsevimab versus placebo recipients irrespective of RSV infection status (phase 2b and 3 nirsevimab trials)



a, Phase 2b study. b, MELODY study. ***P < 0.001, nirsevimab versus placebo with diagnostic-confirmed RSV; †††P < 0.001, nirsevimab versus placebo without diagnostic-confirmed RSV. n denotes number of infants who had a serum sample available at baseline. Data are presented as GMCs ± 95% CIs, which were calculated assuming log normal distribution. Two-sided P values were calculated based on the F statistic from ANOVA, without adjustment. In a, all were P < 0.0001, except for day 361 with diagnostic-confirmed RSV, which was P = 0.0005. In b, all were P < 0.0001. BL, baseline.

Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants | Nature Medicine

After RSV exposure, nirsevimab immunized infants mount antibody responses to RSV post-F protein, indicating immune responses to natural infection



- Rates of post-F antibody responses were similar in nirsevimab and placebo recipients
  - 69-70% in healthy preterm infants (phase 2b)
  - 63-68% in term and late term infants (phase 3)

a, Phase 2b study post-F IgG antibodies. b, MELODY study post-F IgG antibodies. *P < 0.05, nirsevimab versus placebo with diagnostic-confirmed RSV; †P < 0.05, †††P < 0.001, nirsevimab versus placebo without diagnostic-confirmed RSV. n denotes number of infants who had a sample available at baseline. Data are presented as GMCs ± 95% CIs, which were calculated assuming log normal distribution. Two-sided P values were calculated from the F statistic from ANOVA, without adjustment. a, At day 91 without diagnostic-confirmed RSV, P = 0.0227, and at day 361 with diagnostic-confirmed RSV, P = 0.0458. b, At day 31 without diagnostic-confirmed RSV, P < 0.0001, and at day 361 with diagnostic-confirmed RSV, P = 0.0391.

Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants | Nature Medicine

Summary

- Data from prelicensure nirsevimab trials suggest
  - Nirsevimab results in higher neutralizing antibody titers than natural infection in infants, and titers remain elevated through at least 1 year
  - Nirsevimab does not reduce rates of infant antibody response (post-F) to natural infection, although antibody responses to natural infection after nirsevimab receipt may be lower compared to placebo
    - 63-70% of all infants (nirsevimab and placebo recipients) had sero-response to RSV exposure at end of their first RSV season

Unmet needs and data gaps for pediatric RSV prevention

Unmet Medical Needs and Data Gaps for RSV Prevention Products

- Unmet need
  - Low cost and effective RSV immunizations to expand protection to a broader population of U.S. children in their second RSV season
- Data gaps
  - Safety, immunogenicity, and effectiveness of additional doses of maternal RSV vaccine (after the first lifetime dose) during subsequent pregnancies
  - Population-level immune landscape in infants and young children in the era of new RSV prevention products

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  - Erica Rose
  - Ben Silk
  - Natalie Thornburg
  - Amber Winn

  And many others

- Partners/Collaborators
  - New Vaccine Surveillance Network
  - PREVAIL Cohort
  - RSV-Net

Questions?

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

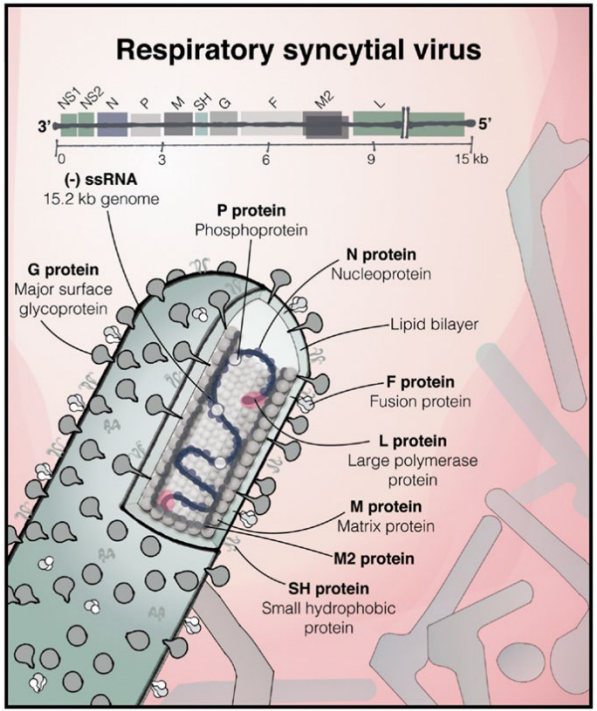
Extra Slides

Respiratory Syncytial Virus (RSV)

- Enveloped, non-segmented RNA virus
  - Two subgroups (A and B)

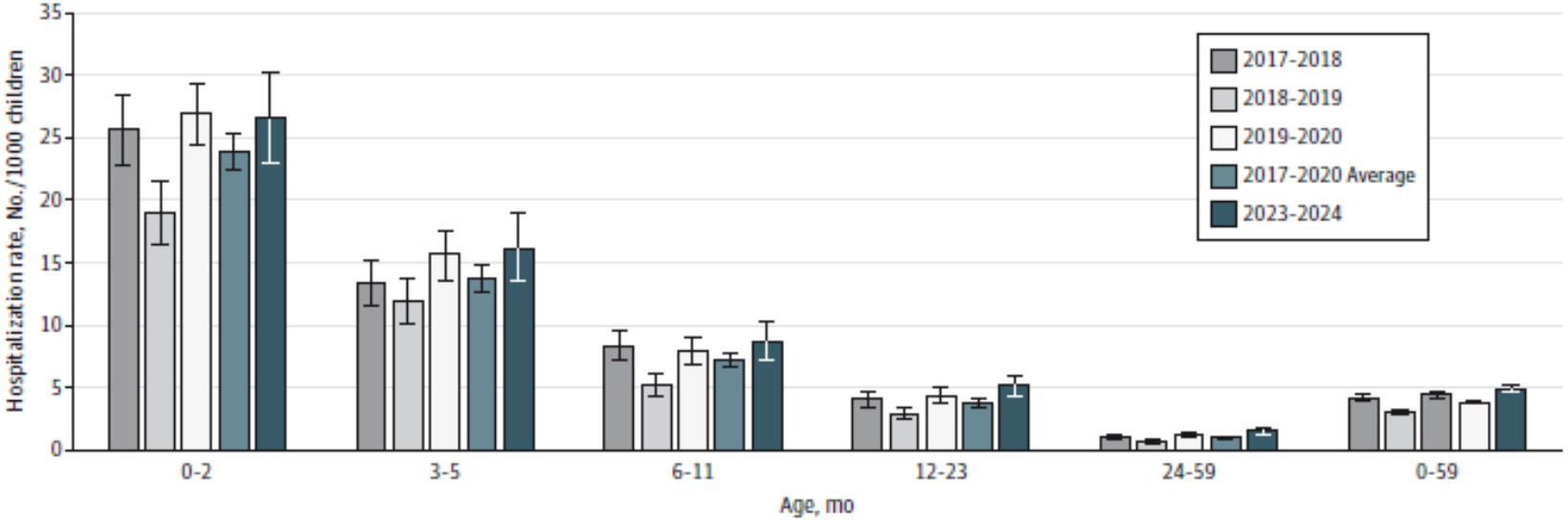
- Two major surface glycoproteins
  - F (fusion) – target of most vaccines and monoclonals
  - G (attachment) – highly variable, role in immune evasion and reinfection, used for classification of subgroups

- Usually causes mild, cold-like symptoms; can cause severe illness, particularly in infants and older adults



Lambert et al Frontiers in Immunology 2014
https://doi.org/10.3389/fimmu.2014.00466

RSV-associated hospitalization rates are highest in infants, followed by children 12-23 months of age



Bar labels indicate the incidence rate per 1,000 children during September-April of 2023-2024 and 2017-2018. Rates were calculated using county-specific denominators from the 2020 US bridged-race population estimates, and population-based numerators based on the observed number of hospitalizations at each site adjusted to account for weeks with <7 days of surveillance, the proportion of eligible children not enrolled, sensitivity of respiratory syncytial virus reverse-transcription polymerase chain reaction testing compared to serology, and each site's estimated market share of ARI hospitalizations by age. Error bars denote 95% confidence intervals determined based on 1000 bootstrap samples for each rate.

Moline et al. JAMA Pediatrics. 2024

Houston Family Study, 1975-2000

- Longitudinal birth/household cohort of children followed until 5 years of age
- Weekly symptom surveys and nasal wash collection for RSV testing with illness episodes; periodic serum collection

Table 1.—Frequency of Respiratory Syncytial Virus (RSV) Infection Among Children Studied From Birth*

Age, mo	No. of Child-Years	No. With RSV Infection: Primary	No. With RSV Infection: Reinfection	Total (Rate/100 Child-Years)	LRD† (Rate/100 Child-Years)	LRD Rate per 100 Infections
0-12	125	85	1	**86** (68.8)	28 (22.4)	32.6
13-24	92	33	43	**76** (82.6)	12 (13.0)	15.8
25-36	65	1	29	**30** (46.2)	7 (10.8)	23.3
37-48	39	0	13	**13** (33.3)	3 (7.7)	23.1
49-60	24	0	12	**12** (50.0)	0 (0)	. . .
Total	**345**	**119**	**98**	**217** (62.9)	**50** (14.5)	23.0

*Houston Family Study, 1975 through 1980.
†LRD indicates lower respiratory tract disease.

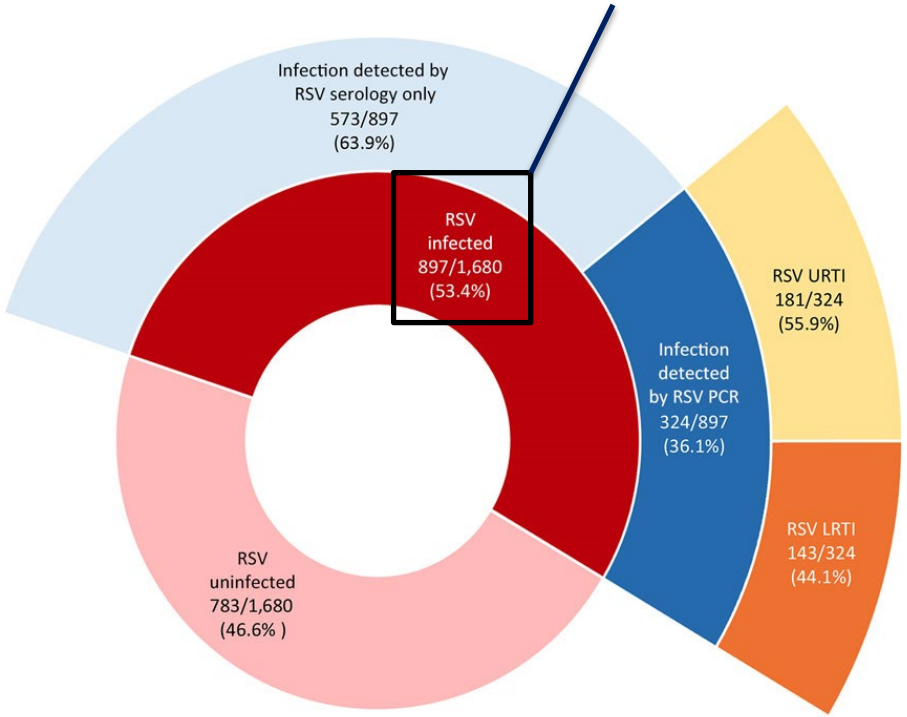
- By 12 months, 68% of infants had RSV infection
- By 24 months, all but 1 child had ≥1 RSV infection
- Reinfection was common; 44/58 (76%) children with primary infection by 12 months had reinfection by 24 months

Glezen et al, Arch Dis Child, 1986

INSPIRE Cohort

- Longitudinal birth cohort of 1,680 children in Tennessee followed until 5 years of age, enrolled 2012-2014
- Follow-up: Symptom surveys every two weeks and nasal swab collection for RSV testing with illness episodes; serum collection at 1 year of age
- Serum testing: ELISA for RSV antibodies

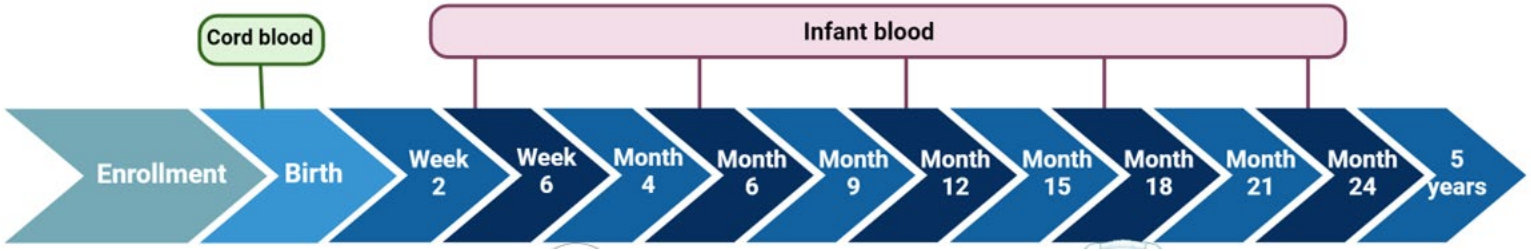
53% of infants with evidence of RSV infection by 1 year of age



Cacho F, Gebretsadik T, Anderson LJ, Chappell JD, Rosas-Salazar C, Ortiz JR, et al. Respiratory Syncytial Virus Prevalence and Risk Factors among Healthy Term Infants, United States. Emerg Infect Dis. 2024;30(10):2199-2202. https://doi.org/10.3201/eid3010.240609

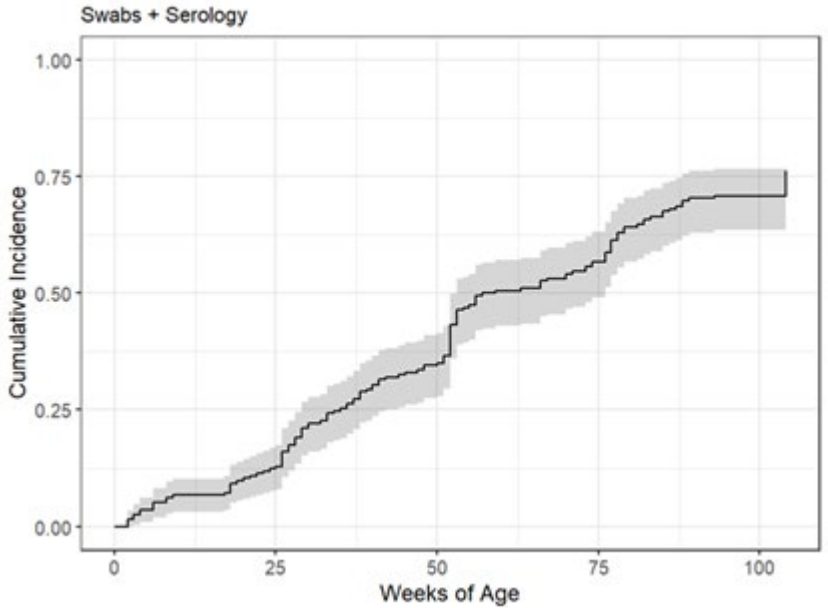
PREVAIL Cohort

- Longitudinal birth cohort that followed children until 2 years of age, 2017-2020
- Follow-up: weekly text surveys; weekly and ARI nasal swabs; periodic serum collection
- Serum testing: Meso Scale Discovery for RSV pre-F IgG and IgA



PREVAIL Cohort: Pediatric Respiratory & Enteric Virus Acquisition & Immunogenesis Longitudinal Cohort; ARI: acute respiratory illness

Approximately 75% of children had molecular or serologic evidence of a prior RSV infection by 2 years of age*, PREVAIL Cohort



- **Median age at first RSV infection 40 weeks (by molecular detection)**

PREVAIL Cohort: Pediatric Respiratory & Enteric Virus Acquisition & Immunogenesis Longitudinal Cohort

*Restricted to 194 children with high adherence to weekly swab collection for molecular testing defined as collection of ≥70% of weekly swabs

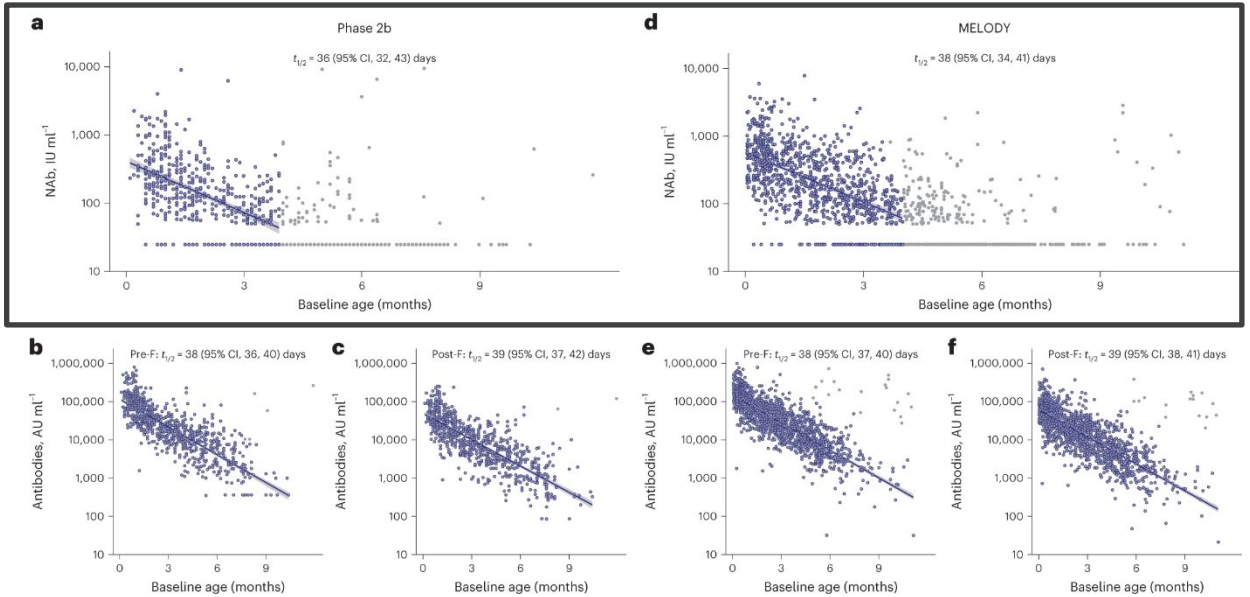
WG considerations for needed data to make RSV vaccine recommendations during subsequent pregnancies

- **Additional data are needed prior to recommending RSV vaccine during each pregnancy (i.e., during subsequent pregnancies)**
  - Antibody data in pregnant people and infants with vaccination during subsequent pregnancies
  - Safety data (e.g., reactogenicity) with vaccination during subsequent pregnancies
  - Safety data of RSV vaccine during the first pregnancy it is administered, particularly regarding outcomes of preterm birth and hypertensive disorders of pregnancy

Additional RSV vaccine doses in subsequent pregnancies are not currently recommended

- **ACIP recommendations for Pfizer RSV maternal vaccine state that**
  - *Currently, no data are available on either the efficacy of the first lifetime dose to protect infants born after subsequent pregnancies or the safety of additional doses given during subsequent pregnancies. Additional data are needed to determine whether additional seasonal doses during subsequent pregnancies are indicated, and ACIP might update recommendations in the future, as data become available.*
- **Still no data on additional RSV vaccine doses in subsequent pregnancies**
- **There are potentially people who received an RSV vaccine during pregnancy for the 2023-24 RSV season who could have a subsequent pregnancy during the 2024-2025 RSV season**

High variability in pre-season RSV neutralizing antibody titers in infants entering first RSV season (phase 2b and 3 nirsevimab trials)



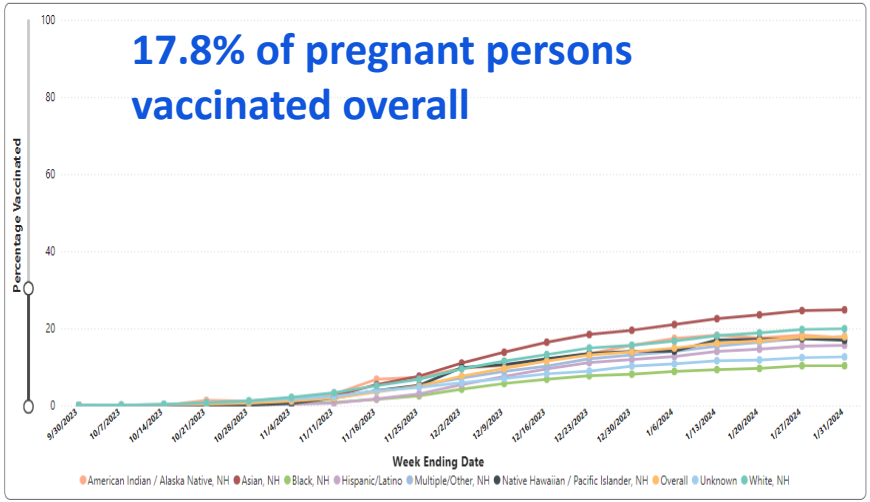
- >1,000-fold difference in pre-season neutralizing antibody titers
- Pre-season titers decrease with increasing infant age (consistent with waning)
- 25% of term infants had unmeasurable pre-season neutralizing antibody

a, Phase 2b study NAbs. b, Phase 2b study pre-F IgG antibodies. c, Phase 2b study post-F IgG antibodies. d, MELODY NAbs. e, MELODY pre-F IgG antibodies. f, MELODY post-F IgG antibodies. Blue circles denote data included in the analysis; gray circles denote data that were excluded (as described in Methods section). The gray band surrounding each line represents the 95% CI. t½, half-life.

Durability of neutralizing RSV antibodies following nirsevimab administration and elicitation of the natural immune response to RSV infection in infants | Nature Medicine

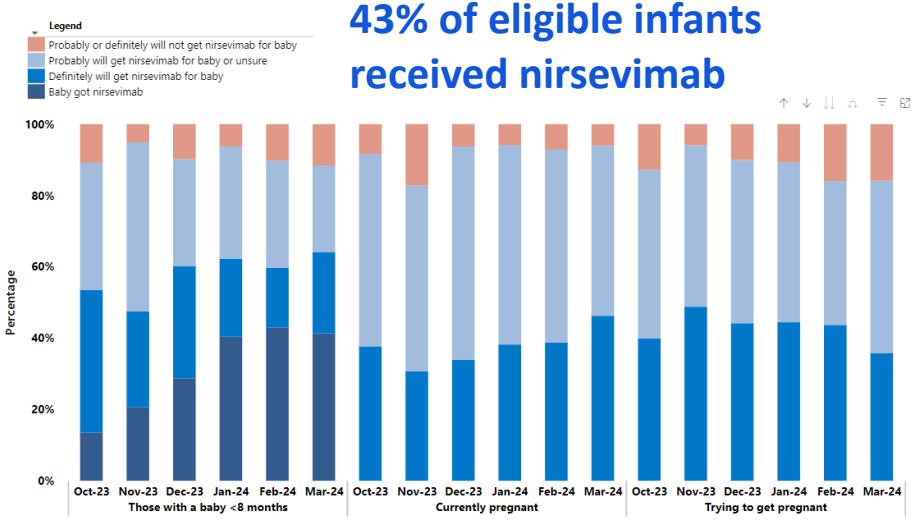
Estimated 51% of infants protected from RSV by either nirsevimab or maternal RSV vaccination by the end of the 2023-2024 season

Percent of pregnant persons ages 18–49 years vaccinated with RSV vaccine, Vaccine Safety Datalink



NH=Non-Hispanic

Monthly nirsevimab receipt and intent among women ages 18–49 years who have an infant, National Immunization Survey



2023-24 Respiratory Syncytial Virus (RSV) Vaccination Coverage, Pregnant Persons | RSVVaxView | CDC

2023-24 Nirsevimab Receipt and Intent for Infants | RSVVaxView | CDC