RSV Prevention 2024

Protecting More Babies with Fewer Pokes

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Conflicts of Interest

- Planning Committee & Faculty Disclosure: The Planning Committee and Faculty have no relevant financial relationships with commercial interests to disclose.

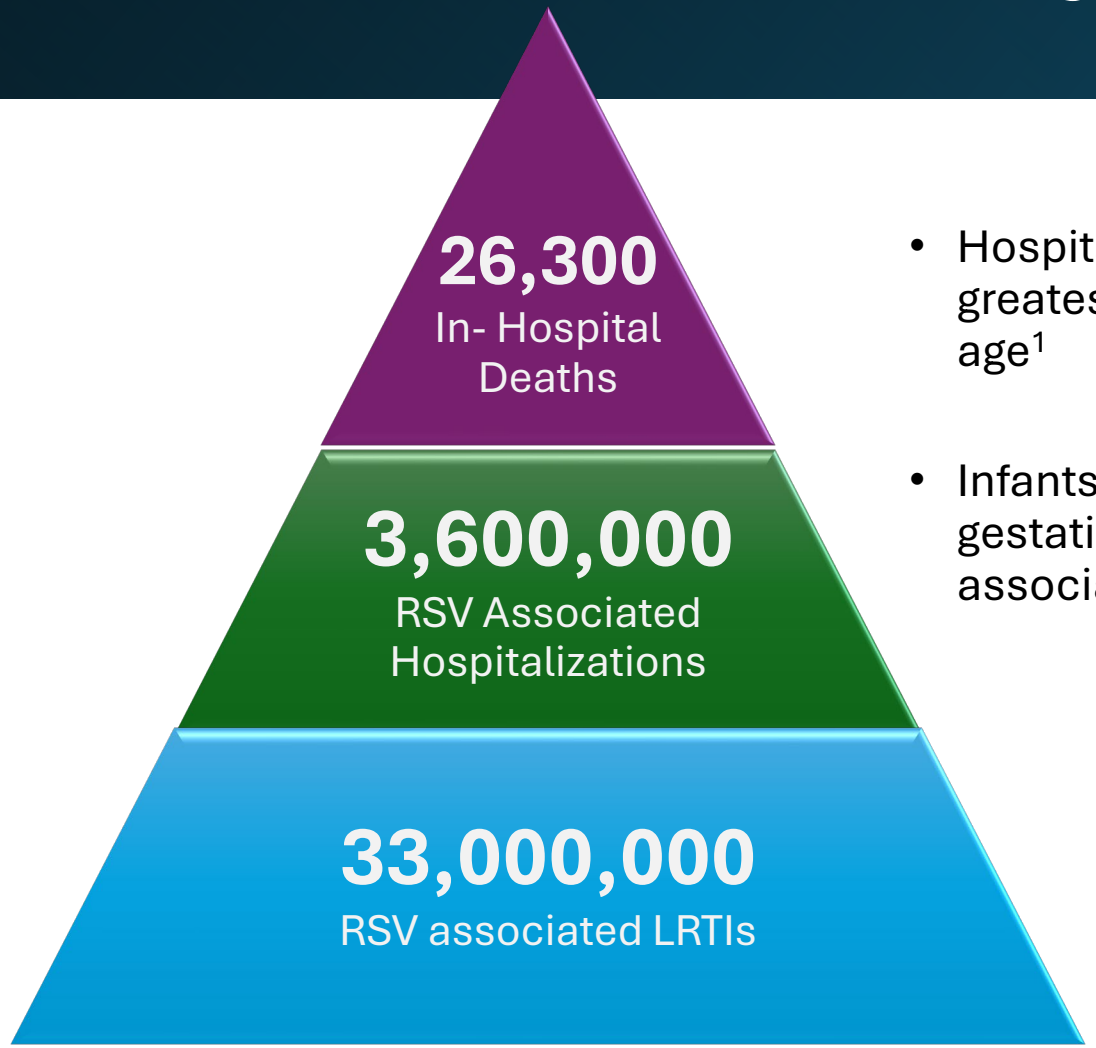
Objectives

- Describe RSV epidemiology, clinical impact, and financial burden nationwide
- Understand the risks, benefits, and indications for maternal vaccination with the RSV PreF vaccine (Abrysvo®)
- Compare palivizumab (Synagis®) indications with nirsevimab (Beyfortus®)
- Describe preliminary data on safety and effectivenss from the first season of nirsevimab and RSV PreF vaccine use worldwide

Definitions

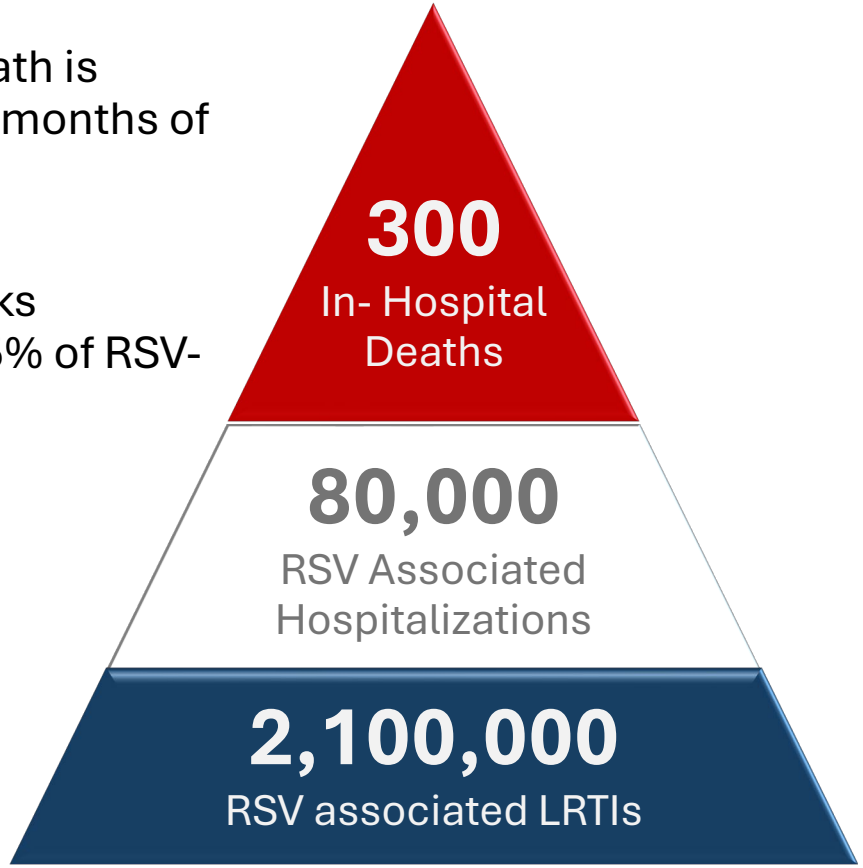
- **Immunization –** process of being made resistant to an infectious disease
  - **Active Immunity**
    - Response to being exposed to a disease-causing organism
    - Vaccine – a preparation that is administered to stimulate the body's immune response against a specific agent and imitates an infection *(RSV preF Vaccine)*
  - **Passive Immunity**
    - Antibody transfer from the mother in the final months of pregnancy *(RSV preF Vaccine)*
    - Administration of antibody containing products derived from human or animal sources *(palivizumab/nirsevimab)*
- **Efficacy:** degree to which immunization prevents disease under ideal and controlled conditions (clinical trial)
- **Effectiveness:** degree to which immunization prevents disease under real world conditions (observational studies)

World-Wide vs. US Burden of RSV in Children Less than 5 years



WORLD-WIDE[1]

- Hospitalization and risk of death is greatest in infants less than 6 months of age[1]
- Infants born less than 32 weeks gestation account for up to 25% of RSV-associated hospitalizations[1]



UNITED STATES[2]

US RSV Financial Impact

Static, decision-analytic model developed to estimate financial impact from RSV related health events and immunization strategies[3]

- Entire US birth cohort during its first RSV season (term, preterm, and high-risk)
- Model estimated a full 6-month RSV season and all RSV-Associated Medically Attended Lower Respiratory tract Illness (MA-LRTI)
  - $1.2 Billion direct economic impact (in 2021 US Dollars)
    - Primary Care Visits & ER Visits $100 Million US Dollars
    - Hospitalizations $1.1 billion
  - Breakdown
    - 93% of hospitalizations were from patients that were not deemed high risk for severe disease
    - 43% of total costs were for patients born outside of RSV season

Course of Disease[1]

4-6 Days

Initial Symptoms
- Runny Nose
- Decreased Appetite
- Cough

4-6 Days

Severe Symptoms
- Retractions
- Wheezing
- Tachypnea
- Hypoxemia
- Lethargy
- Apnea
- Feeding Difficulties

Treatments studies have failed because they're not initiated in time to prevent viral replication

Which patients are going to progress to severe disease?

Treatment Options Lacking

Supportive Care

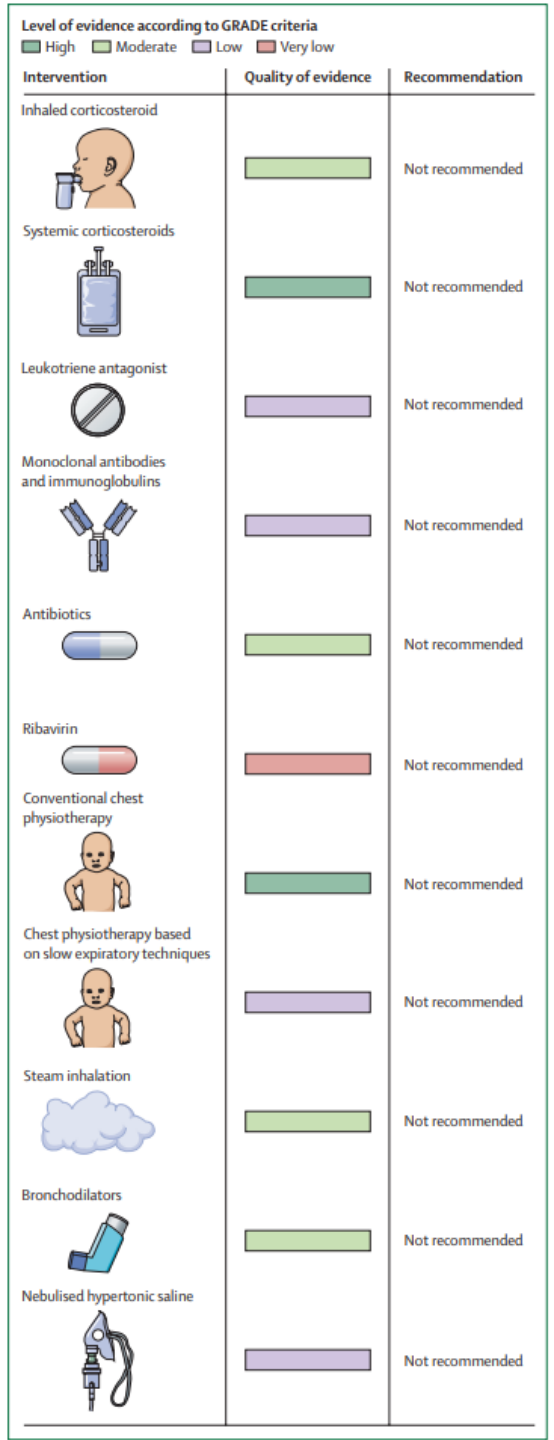


***Figure 3*: Evidence-based treatment of severe RSV infection**
The intervention and recommendation for use in hospital management (recommended or not recommended) are listed, and the quality of evidence for this recommendation is presented (ie, high, moderate, low, or very low). Quality of evidence was assessed based on GRADE-criteria and if possible, taken from Cochrane review of the literature.[67–75] GRADE= Grading of Recommendations, Assessment, Development, and Evaluations. RSV=respiratory syncytial virus.

Lancet. 2024 Sept 21;404(10458):1143-1156.

Long Term Implications – Wheeze

- **Drakenstein Child Health Study[4]**
  - Longitudinal Birth Cohort Study – Outside Cape Town, South Africa
    Assess wheezing in low and middle-income countries

    - 1143 Live Births were identified for the study and 950 children were followed for 5 years with complete data

    - Questionnaires at 14 scheduled visits and all LRTI presentations included a PCR nasopharyngeal swab

	Phenotype 2: early transient wheeze		Phenotype 3: late-onset wheeze		Phenotype 4: recurrent wheeze	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
LRTI						
Number of LRTI episodes	1·69 (1·27–2·30)	0·00053	1·60 (1·13–2·28)	0·0081	2·79 (2·05–3·81)	<0·0001
Hospital admission (*vs* no hospital admission)	1·40 (0·43–1·54)	0·52	0·84 (0·38–1·82)	0·66	1·01 (0·51–2·02)	0·97
Respiratory syncytial virus-LRTI (*vs* respiratory syncytial virus-negative)	3·34 (1·82–6·26)	<0·0001	2·82 (1·32–6·01)	0·0071	2·59 (1·30–5·15)	0·0067
Rhinovirus-LRTI (*vs* rhinovirus-negative)	1·39 (0·74–2·59)	0·31	1·79 (0·87–3·73)	0·12	1·64 (0·83–3·22)	0·15
Adenovirus-LRTI (*vs* adenovirus-negative)	0·87 (0·42–1·77)	0·71	1·56 (0·73–3·43)	0·21	1·11 (0·53–2·30)	0·78
Influenza (type A, B, or C)-LRTI *vs* influenza negative	1·36 (0·46–2·77)	0·78	1·38 (0·51–3·73)	0·52	0·74 (0·27–1·95)	0·54
Parainfluenza (type 1, 2, 3, or 4)-LRTI *vs* parainfluenza negative	1·05 (0·41–2·62)	0·92	1·75 (0·63–4·81)	0·27	1·15 (0·45–2·92)	0·76

Long Term Implications – Asthma

- Studies have shown a 2-12% increased risk of developing asthma following RSV LRTI or Bronchiolitis[5]
- **INSPIRE[6]**
  - US Birth Cohort Study – 1946 Infants
    - Patients were observed during their first year for either PCR(+) RSV during an acute respiratory infection or RSV positive serology at 1 year.
    - 5 – year follow up for the development of asthma
      - 26% lower risk of asthma at 5 years if RSV was avoided in infancy

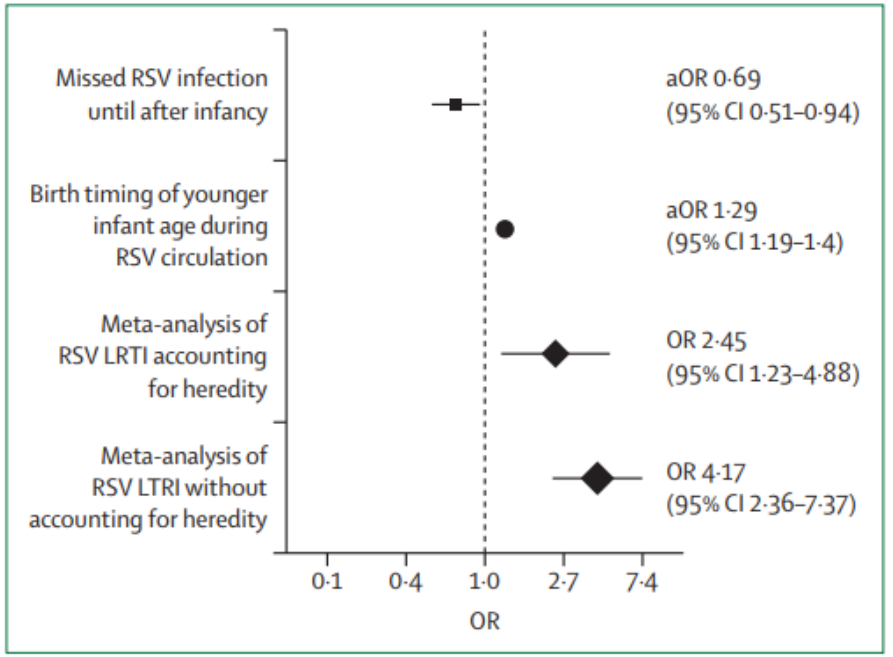
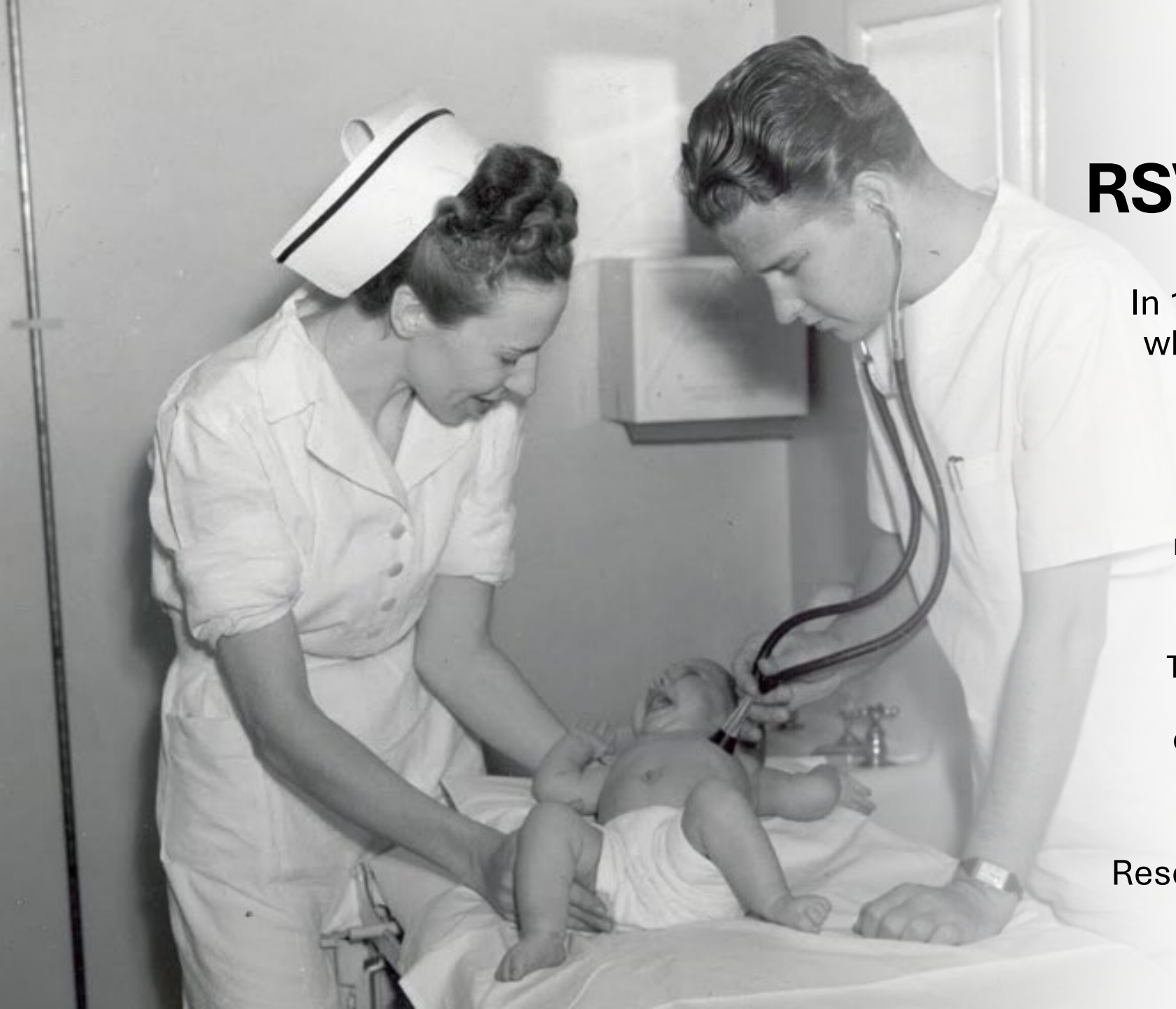


***Figure 1:* Association of RSV with asthma**
Forest plot of the compiled results of observational studies assessing the association of RSV with asthma in studies of: (1) the protective effect of delayed RSV infection until after infancy,[43] (2) timing of birth with younger infant age during first year of life RSV circulation,[46] (3) RSV LRTI with adjustment for heredity,[13] and (4) RSV LRTI without adjustment for heredity.[13] Data are presented as effect ratios and 95% CIs. Diamonds represent ORs from meta-analyses, ovals and rectangles represent ORs from individual studies, and bars represent 95% CIs. The x-axis is on the log scale. aOR=adjusted odds ratio. LRTI=lower respiratory tract infection. OR=odds ratio. RSV=respiratory syncytial virus.

Prevention is the Key



RSV Vaccine History

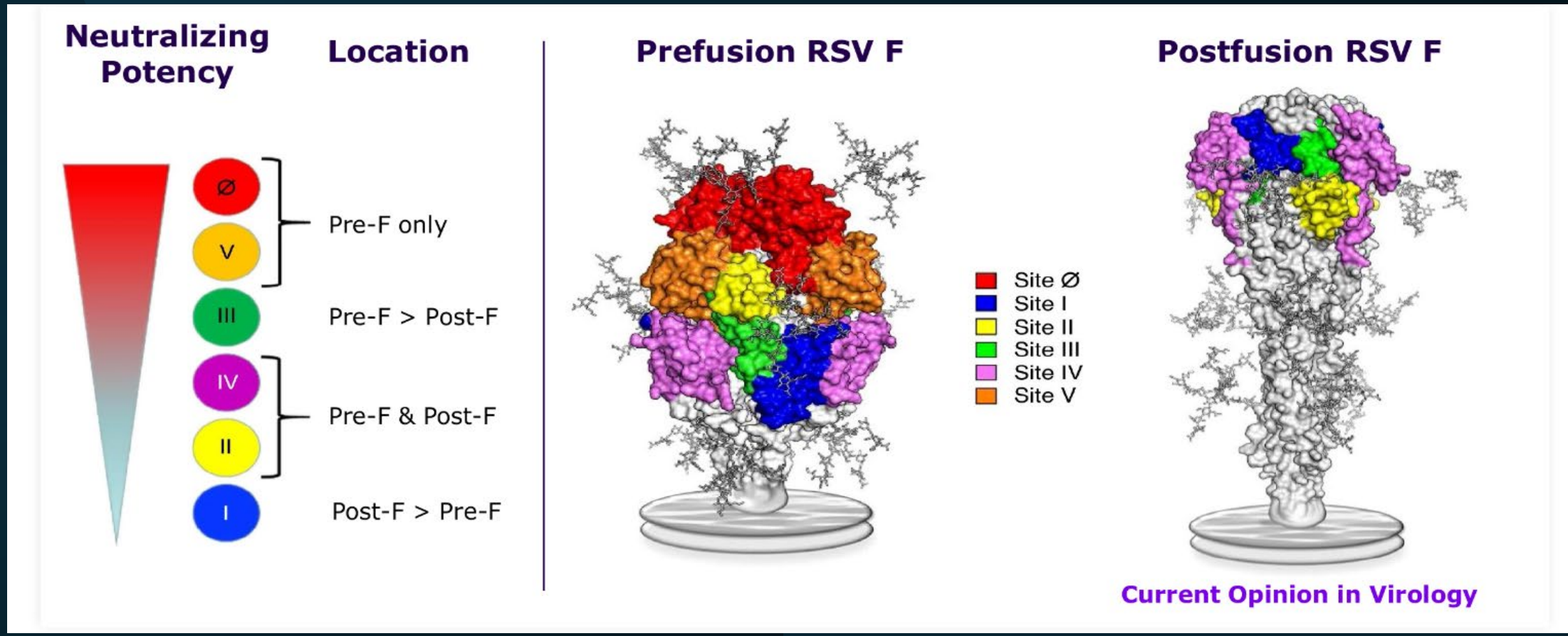
In 1965-1966 a formalin-inactivated whole RSV vaccine was studied in children[7,8,9]

31 infants received the vaccine, 20 of those became infected with RSV, 16 required hospitalization and 2 died (14 and 16 months old).

The clinical response to RSV was much more severe in the vaccinated infants compared to infants who had received parainfluenza vaccines

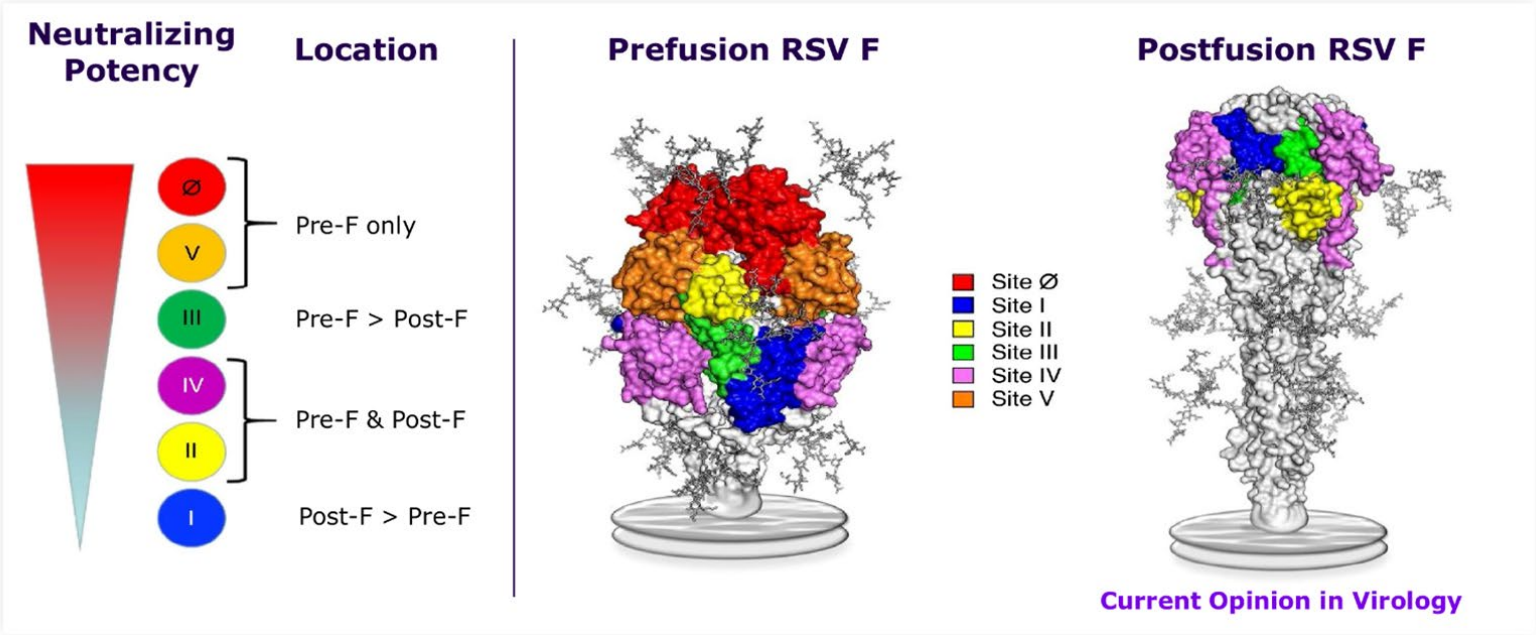
Research into RSV vaccine paused for decades

Targets for Therapy[10]



Monocolonal Antibody Against RSV – Palivizumab[12]

- Recombinant humanized monoclonal antibody
- Palivizumab binds a highly conserved region on the extracellular domain of mature RSV F, referred to as antigenic site II



Double-blind, placebo-controlled study at 139 centers in high income countries that included 1502 infants with prematurity (≤ 35 weeks) or bronchopulmonary dysplasia (BPD)

- 55% reduction in hospitalization (10.6% placebo vs. 4.8% palivizumab)
- Premature infants without BPD had a 78% reduction hospitalization for RSV (8.1% vs. 1.8%)
- Infants with BPD had a 39% reduction in hospitalization for RSV (12.8% vs. 7.9%)

IMPact-RSV Study published in 1998[13]

SYNAGIS®
PALIVIZUMAB

American Academy of Pediatrics (AAP) Palivizumab immunoprophylaxis (IP) guidance

- Following FDA approval in 1998, use has been limited by high-cost and recommendations from the American Academy of Pediatrics have guided administration and insurance coverage nationwide.
    - 15mg/kg IM injection given monthly for 5 months during RSV season
        - Half-Life 20-24.5 days[12]

<5% of patients were ever eligible for palivizumab[14]

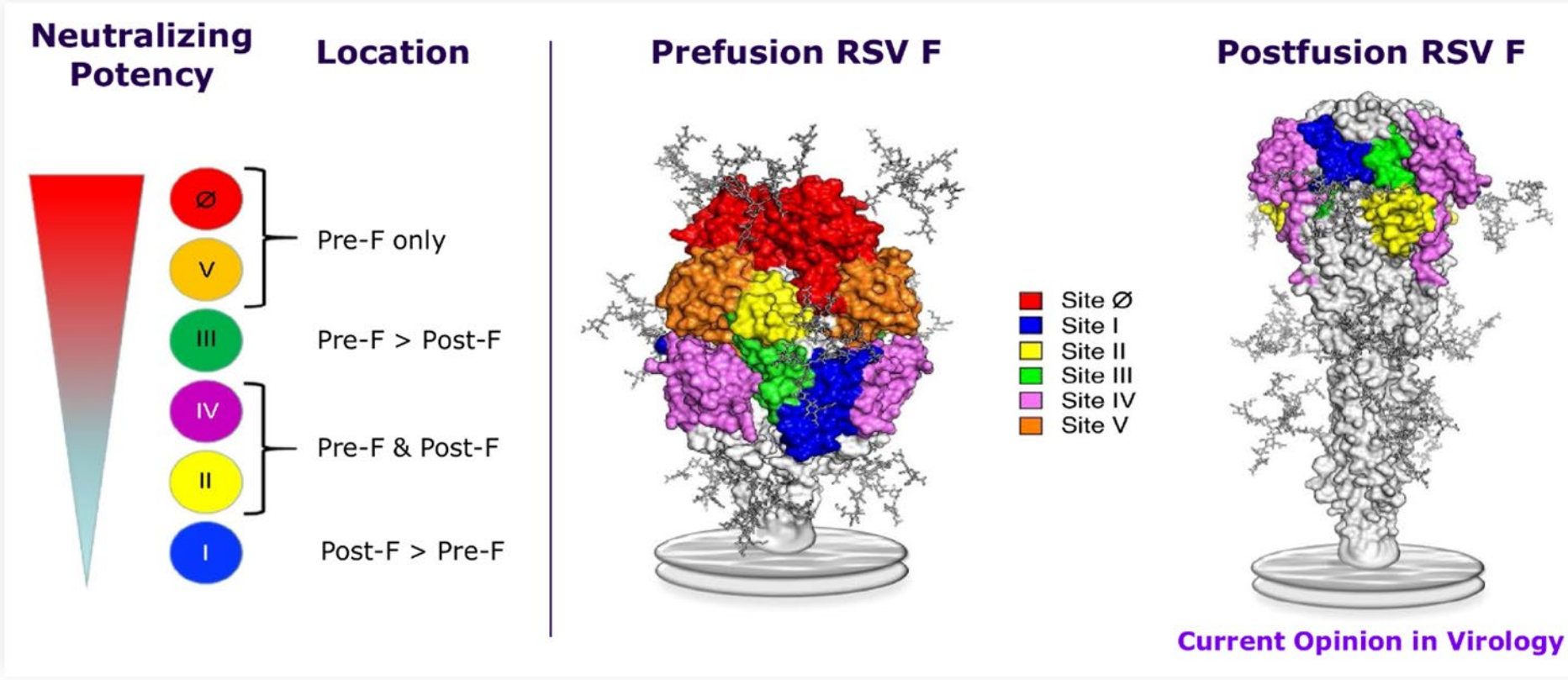
- Cost for a full 5-month course of palivizumab can range from $10,000-30,000 depending on the weight of the patient[12]

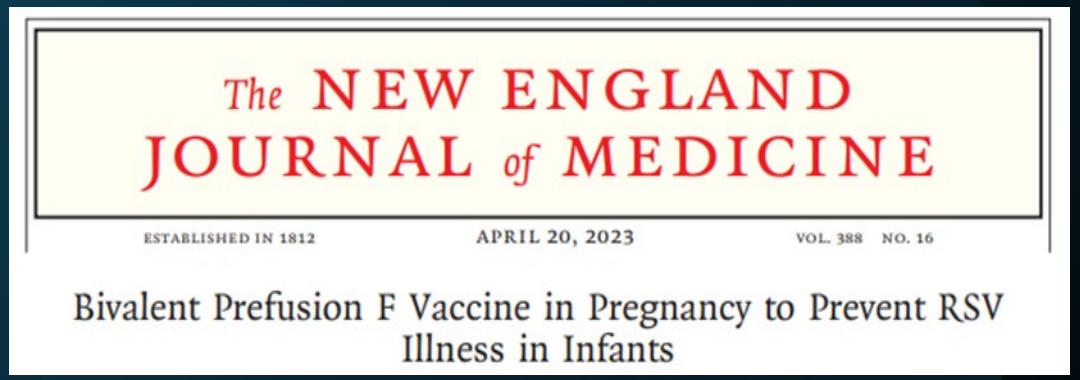
- Since the FDA approval of palivizumab the AAP has updated its RSV management guidance four times and in 2014 AAP, stopped recommending RSV IP use for ≥ 29 weeks' gestational age infants[15].

Goal of Prophylaxis for Larger Population via Maternal Vaccination

Maternal RSV preF Vaccine Development

Antibodies Targeting the Prefusion Conformation of RSV F Protein are the Most Potent at Neutralizing RSV





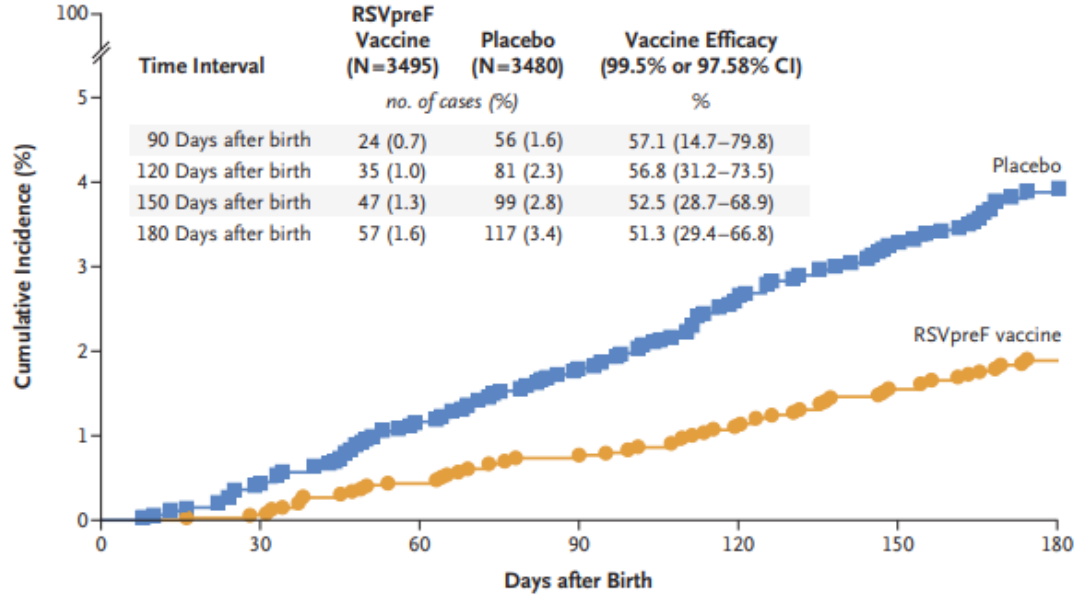
- MATISSE Study, phase 3, double-blind, placebo-controlled trial in 18 countries over both hemispheres[16]
  - Included pregnant women 24 to 36 weeks gestation
    - Uncomplicated, singleton pregnancies, no known risk factors for pregnancy complications
  - Primary end points
    - Incidence of medically attended severe RSV associated lower respiratory tract illness (MA-SLRTI)
    - Incidence of medically attended RSV associated lower respiratory tract illness (MA-LRTI)
  - 7358 participants received vaccine or placebo in the study which provided data on 7128 infants

RSV preF Vaccine Efficacy

All Infants were evaluated for the incidence of primary endpoints at 90, 120, 150, and 180 days after birth[16]

B Medically Attended RSV-Associated Lower Respiratory Tract Illness

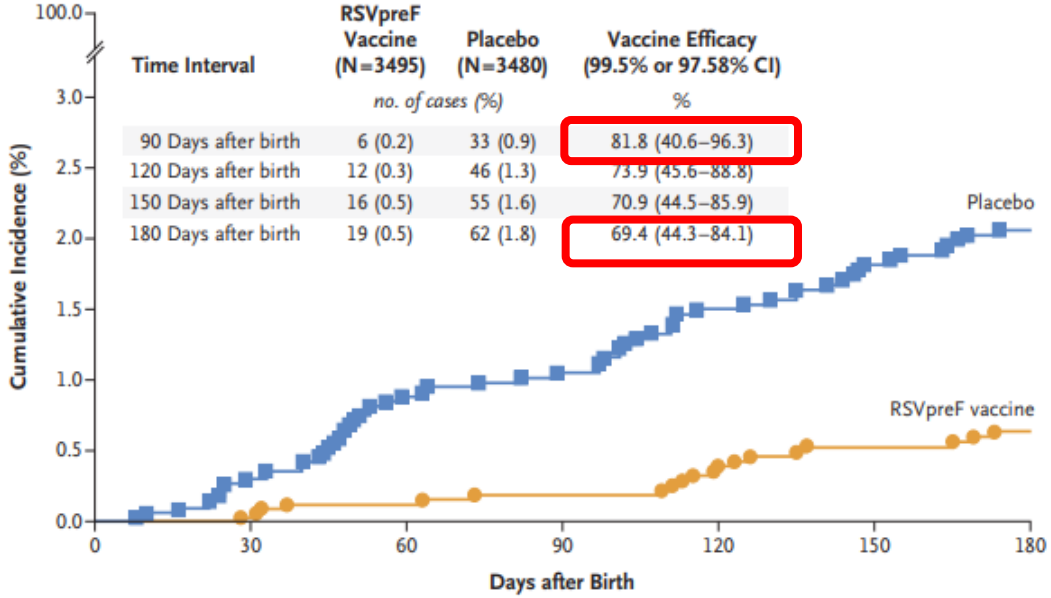
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7–79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2–73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7–68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4–66.8)



No. at Risk							
Placebo	3480	3288	2964	2879	2804	2738	2700
RSVpreF vaccine	3495	3348	3035	2968	2898	2845	2792

A Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness

Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6–96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6–88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5–85.9)
180 Days after birth	19 (0.5)	62 (1.8)	69.4 (44.3–84.1)

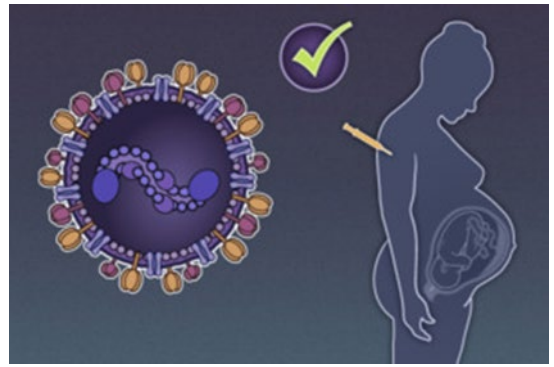


No. at Risk							
Placebo	3480	3292	2973	2899	2833	2776	2749
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	2820

RSV preF Vaccine Safety

Maternal Adverse Events:

- Majority of adverse events were minor and not different than placebo during the first 7 days following injection
- Preeclampsia was noted to be higher in the vaccine group 1.8% vs. 1.4%



Infant Adverse Events:

- Low birth weight - (< 2500g) 5.1% vs. 4.4%
- Neonatal Jaundice - 7.2% vs. 6.7%
- ***Preterm birth (<37 weeks) - 201 (5.7%) vs. 169 (4.7%), not statistically significant, but numerically higher**
  - **Additional information was requested by the CDC on this adverse event**

RSV Vaccine – GSK Preterm Birth

GSK maternal RSV vaccine clinical trial and preterm birth

- Trial of a similar GSK maternal RSV vaccine (stabilized prefusion F protein vaccine without an adjuvant) was halted due to an imbalance of preterm births with higher numbers in the vaccine vs placebo group

Outcome	Vaccine group, n (%) N=3,496	Placebo group, n (%) N=1,739	Relative Risk (95% CI)
Preterm birth (<37 weeks gestation)	238 (6.81%)	86 (4.95%)	1.38 (1.08, 1.75)
Neonatal death	13 (0.37%)	3 (0.17%)	2.16 (0.62, 7.55)

- Imbalance of neonatal deaths was a consequence of preterm birth imbalance
- Imbalance in preterm births was seen in low and middle-income countries (RR: 1.57, 95% CI: 1.17, 2.10) but not high-income countries (RR: 1.04, 95% CI: 0.68, 1.58)
- Imbalance was observed from April–December 2021, but not consistently after December 2021
- Reason for the imbalance remains unclear

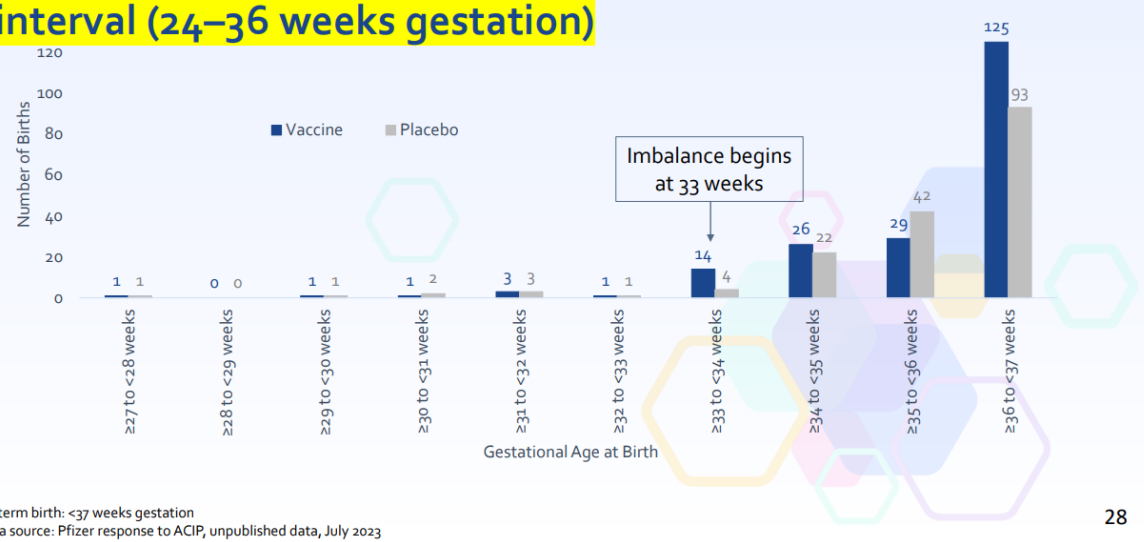
Study vaccine given at 24 0/7 to 34 0/7 weeks gestation

Vaccines and Related Biological Products Advisory Committee February 28 - March 1, 2023 Meeting Briefing Document- Sponsor GSK (fda.gov)

Images obtained from EtR Framework Updates: Pfizer Maternal RSVpreF Vaccine presented on September 22, 2022 ACIP General Meeting. Accessed 12/27/23.

RSV preF Vaccine and Preterm Birth

Number of births by gestational age, preterm births (<37 weeks gestation) only: Pfizer phase 3 trial, trial dosing interval (24–36 weeks gestation)



Preterm birth: <37 weeks gestation
Data source: Pfizer response to ACIP, unpublished data, July 2023

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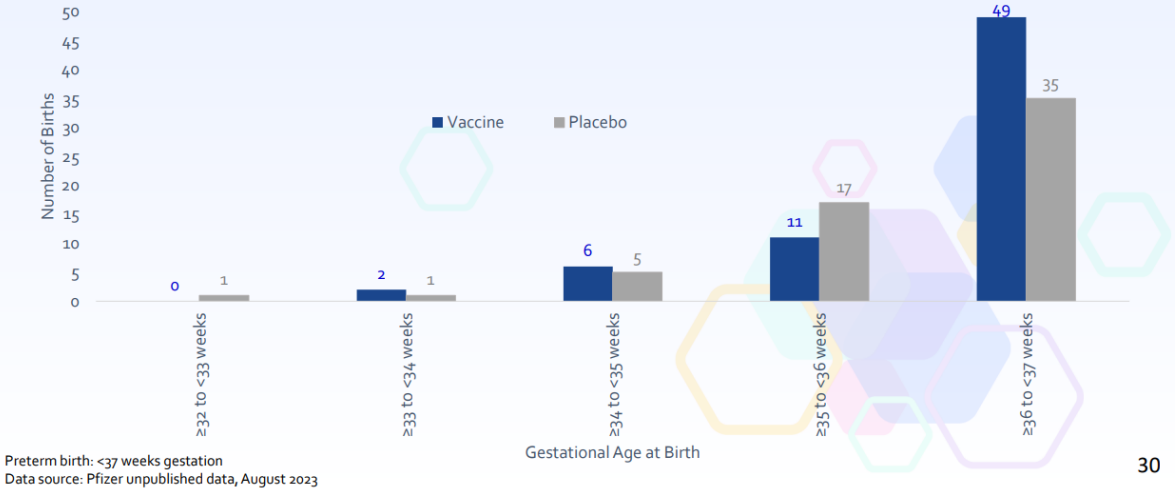
Number of births by gestational age, preterm births (<37 weeks gestation) only: Pfizer Phase 3 trial, approved dosing interval (32–36 weeks gestation)



Preterm birth: <37 weeks gestation
Data source: Pfizer unpublished data, August 2023

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Additionally, when reviewed by country, in the United States (the largest contributing country in the study), the rates of preterm birth were higher in the placebo group when assessing the FDA approved dosing interval

Images obtained from EtR Framework Updates: Pfizer Maternal RSVpreF Vaccine presented on September 22, 2022 ACIP General Meeting. Accessed 12/27/23.

RSV preF Vaccine and Preterm Birth

ACIP Work Group Members ultimately found data reassuring for premature birth

- In the full clinical trial interval, most preterm births occurred more than 30 days after vaccination
- In reviewing the approved dosing-interval the imbalance was still present, but lessened and most preterm births were at 36 weeks
- For the data from the US, the imbalance in preterm births reversed in the approved dosing interval
- The majority of the work group felt the risk of preterm birth was reduced and potential risk for complications was reduced when using the approved dosing interval of 32 – 36 weeks gestation.

Information obtained from EtR Framework Updates: Pfizer Maternal RSVpreF Vaccine presented on September 22, 2022 ACIP General Meeting. Accessed 12/27/23.

RSV preF Vaccine Efficacy in Clinical Trial Interval vs. Approved Interval

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.

Images obtained from EtR Framework Updates: Pfizer Maternal RSVpreF Vaccine presented on September 22, 2022 ACIP General Meeting. Accessed 12/27/23.

RSV preF Vaccine (Abrysvo®)

- Abrysvo® is indicated for pregnant women during weeks 32 through 36 of pregnancy with seasonal administration between the months of September and January.
  - *Alaska, Florida, and many of the US islands have different seasonality and recommendations for timing of administration may vary*

- Manufacturer Labeling
  - *"available data are insufficient to establish or exclude a causal relationship between preterm birth and Abrysvo. To avoid the potential risk of preterm birth with use of Abrysvo before 32 weeks gestation, administer Abrysvo as indicated in pregnant individuals at 32 through 36 weeks gestational age"*

Abrysvo® – First Full Season Summary

- Effectiveness
  - Due to limited uptake of the maternal vaccine, and late roll out effectiveness was not able to be assessed following the 2023-24 RSV season
  - 17.8% of all pregnant women received Abrysvo® according to Vaccine Safety Datalink

- Vaccine Safety Datalink
  - Collaborative effort between the CDC and 12 additional healthcare organizations across the country
  - Monitors the safety of vaccines through observational studies

Abrysvo®– Safety

- Safety
  - Matched Cohort Analysis of Vaccinated vs. Unvaccinated Pregnant women
    - Preterm Birth (<37 weeks due to imbalance in previous studies)
    - Small for Gestational age (< 10th percentile as low birth weight was identified in the original RSV vaccine study

	Matched pairs, N	RSV vaccinated		Unvaccinated match		Risk Ratio (95% CI)
		N events*	Percent %	N events*	Percent %	
Preterm birth[a]	13,965	563	4.0	628	4.5	0.90 (0.80–1.00)
Small for gestational age[b]	11,819	799	6.8	774	6.5	1.03 (0.94–1.14)

[a]Preterm birth = birth <37 weeks gestational age [b]SGA at birth = "Small for Gestational Age"; birthweight <10th percentile for gestational age compared with a U.S. reference population[2]
*Events only included through date of censoring when unvaccinated pair crosses over to vaccinated

  - RSV Vaccine was not associated with increased risk of preterm birth or small for gestational age infants

Images obtained from RSVpreF Vaccine, Preterm Birth, and Small for Gestational Age at Birth. Preliminary results from the Vaccine Safety Datalink presented on October 23, 2024 ACIP General Meeting. Accessed 10/25/2024.

Abrysvo®– Safety

- July 2024, Son et al. published on perinatal outcomes following maternal RSV vaccination at 2 NYC Hospitals in one health system[17]

- 2973 patients enrolled in the study with 1011 receiving the vaccine and 1962 without vaccination during the 2023-2024 season
  - There were some differences in baseline characteristics including age, race, insurance type, and in-vitro fertilization

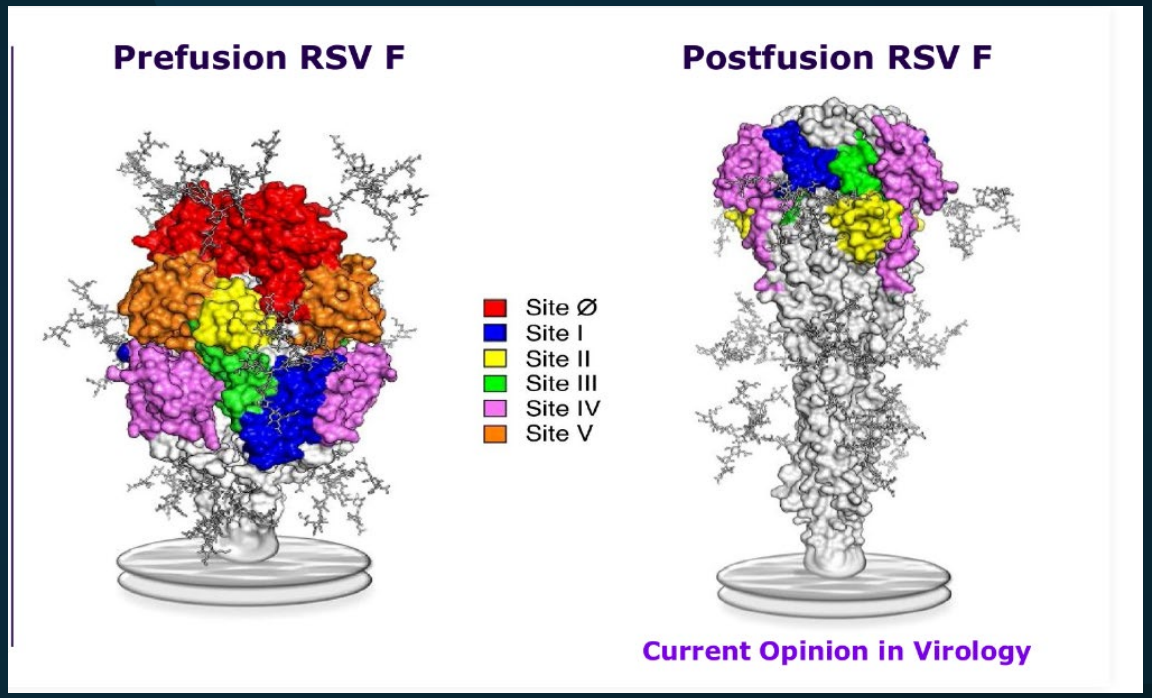
- Results
  - Preterm birth was not statistically different 5.9% vaccinated vs 6.7% unvaccinated
  - Hypertensive disorders of pregnancy (HDP) were higher in the vaccinated group at 20.1% vs. 18.1% [HR 1.43 (1.16-1.77)] in a time-dependent model
    - Differences in HDP and SGA were also associated with insurance type and hospital site, so further investigation is warranted particularly into HDP.
  - No differences in neonatal outcomes

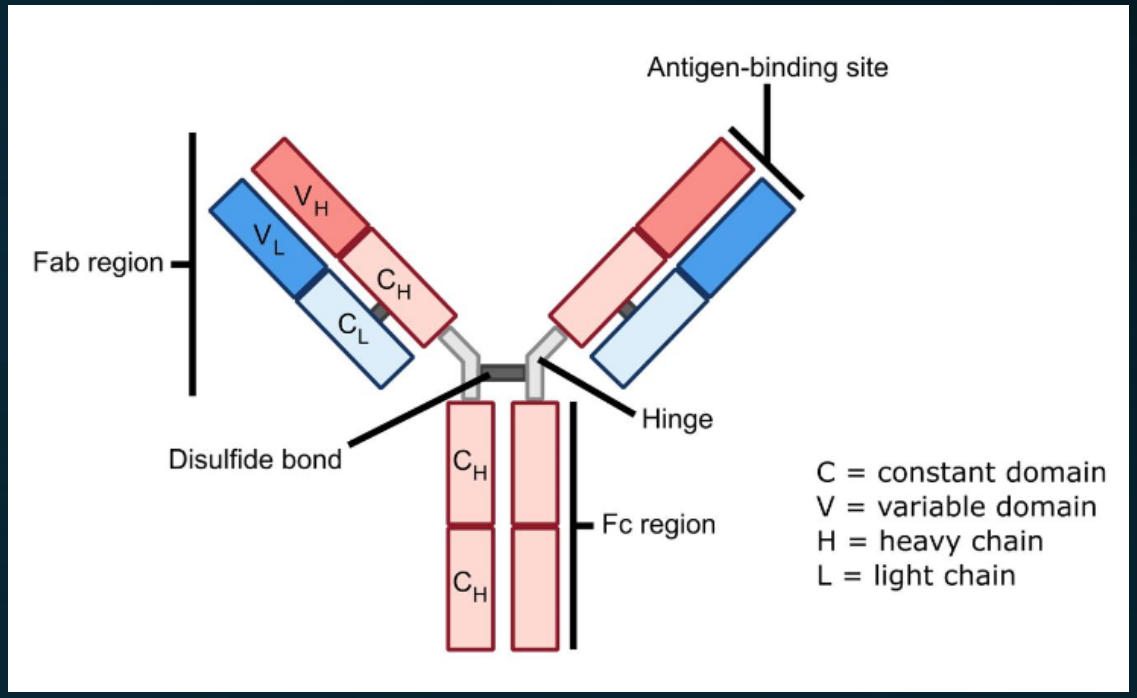
- Safety Signal of HDP is difficult to interpret. Hypertension may begin prior to 32 weeks, but not noted in the medical record until later.
  - CDC is working to determine the best plan for analyzing this maternal outcome

Abrysvo® – Summary after 1st Season

- RSVpreF vaccine (Abrysvo®) for maternal use continues to be indicated for prevention of RSV in infants.
  - Administration is recommended between 32-36 weeks gestation and seasonally between September and January
- Recent data suggests no increased risk of preterm birth, though continued monitoring is warranted
- Due to continued review of hypertension disorders of pregnancy, repeated vaccination in subsequent pregnancies are NOT currently recommended
  - Infants born to women vaccinated in a prior pregnancy should be protected by nirsevimab and the mother should not receive an additional RSVpreF vaccine

Fusion Protein and Targets for Therapy[18]





Nirsevimab Preliminary Data – NIRSEVIMAB

- Phase 2b, Randomized, Placebo-Controlled Clinical Trial [19]
  - Published NEJM July 2020; 164 sites and 23 countries were included
  - Premature infants 29 weeks to 34 weeks 6 days gestation and less than 1 year of age entering their first RSV season
  - 1453 infants matched 2:1 nirsevimab *(50 mg)* vs. placebo and followed for 150 days
    - MA-LRTI (2.6% vs 9.5%)
    - Hospitalization (0.8% vs 4.1%)

Table 2. Medically Attended Lower Respiratory Tract Infection and Hospitalization Associated with Respiratory Syncytial Virus (RSV) through 150 Days after Dose.*

End Points and Analyses	Nirsevimab (N=969)	Placebo (N=484)	Relative Difference (95% CI)	P Value
	number (percent)		%	
Medically attended RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			70.1 (52.3–81.2)	<0.001
Observed events	25 (2.6)	46 (9.5)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	25 (2.6)	46 (9.5)	72.9 (56.5–83.1)	<0.001
Hospitalization for RSV-associated lower respiratory tract infection				
Poisson regression with robust variance			78.4 (51.9–90.3)	<0.001
Observed events	8 (0.8)	20 (4.1)		
Participants with imputation of data†	24 (2.5)	11 (2.3)		
Cochran–Mantel–Haenszel test: observed events	8 (0.8)	20 (4.1)	80.0 (55.0–91.1)	<0.001

* Data are for the intention-to-treat population. The case definition for inclusion of the lower respiratory tract infection in the analysis of the end point required a positive result for RSV in a real-time, reverse-transcriptase–polymerase-chain-reaction assay performed at a central laboratory, a physical examination finding indicating involvement of the lower respiratory tract, and at least one indicator of clinical severity. CI denotes confidence interval.

† Data were imputed for participants who had no events and were not followed through 150 days after administration of the dose of nirsevimab or placebo.

Nirsevimab Preliminary Data - MELODY

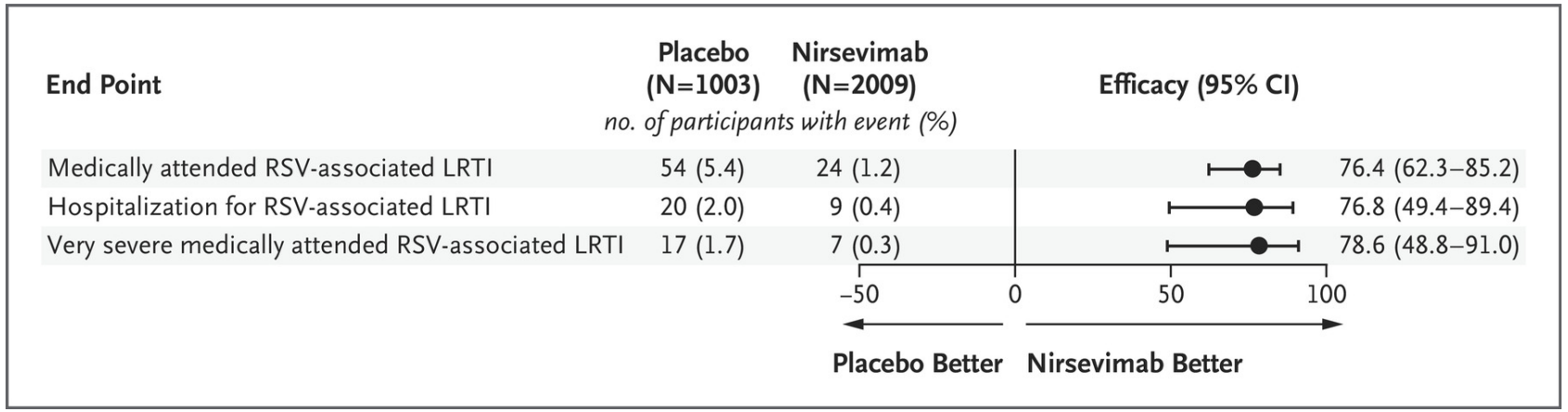
- Phase 3 Randomized, Double-Blind, Placebo Controlled Clinical Trial[20]
  - Published NEJM 2022, 160 sites and 21 countries
  - Late Preterm and Term Infants greater than 35 weeks gestation and less than 1 year entering their first RSV season
  - 1490 infants matched 2:1 nirsevimab *(50mg for patients < 5kg;100mg for patients ≥ 5kg)* vs. placebo and followed for 150 days
    - MA-LRTI (1.2% vs 5%)
    - Hospitalization (0.6% vs 1.6%)
  - COVID Pandemic haulted enrollment

Table 2. Medically Attended Lower Respiratory Tract Infections and Hospitalizations Associated with Respiratory Syncytial Virus (RSV) through 150 Days after the Injection.*

End Point and Analysis	Nirsevimab (N=994)	Placebo (N=496)	Efficacy (95% CI)†	P Value
	no. (%)			
Medically attended RSV-associated lower respiratory tract infection			74.5 (49.6 to 87.1)	<0.001
Poisson regression with robust variance				
Observed events	12 (1.2)	25 (5.0)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		
Hospitalization for RSV-associated lower respiratory tract infection			62.1 (−8.6 to 86.8)	0.07
Poisson regression with robust variance				
Observed events	6 (0.6)	8 (1.6)		
Participants with imputation of data‡	15 (1.5)	6 (1.2)		

Nirsevimab Preliminary Data - MELODY

- Full Melody Trial Cohort Post COVID Pandemic[21]
  - Published NEJM April 2023
  - 3012 infants matched 2:1 nirsevimab *(50mg for patients < 5kg;100mg for patients ≥ 5kg)* vs. placebo and followed for 150 days
    - MA-LRTI (1.2% vs 5%)
    - Hospitalization (0.6% vs 1.6%)



End Point	Placebo (N=1003)	Nirsevimab (N=2009)	Efficacy (95% CI)
	no. of participants with event (%)		
Medically attended RSV-associated LRTI	54 (5.4)	24 (1.2)	76.4 (62.3–85.2)
Hospitalization for RSV-associated LRTI	20 (2.0)	9 (0.4)	76.8 (49.4–89.4)
Very severe medically attended RSV-associated LRTI	17 (1.7)	7 (0.3)	78.6 (48.8–91.0)

Nirsevimab Preliminary Data – HARMONIE

- HARMONIE Trial, Open-Label, Clinical Trial[22]
  - Published NEJM 2023, 235 sites in UK, Germany, France
  - 8058 infants, ≥ 29 weeks gestation and less than 1 year of age entering first RSV season
  - Matched 1:1 nirsevimab *(50mg for patients < 5kg;100mg for patients ≥ 5kg)* vs. no intervention
    - Hospitalization for RSV-associated LRTI (0.3% vs 1.5%)
      - Greatest efficacy in infants less than 3 months 89.6%
    - Hospitalization for Very Severe LRTI (0.1% vs 0.5%)
      - 75.7% efficacy

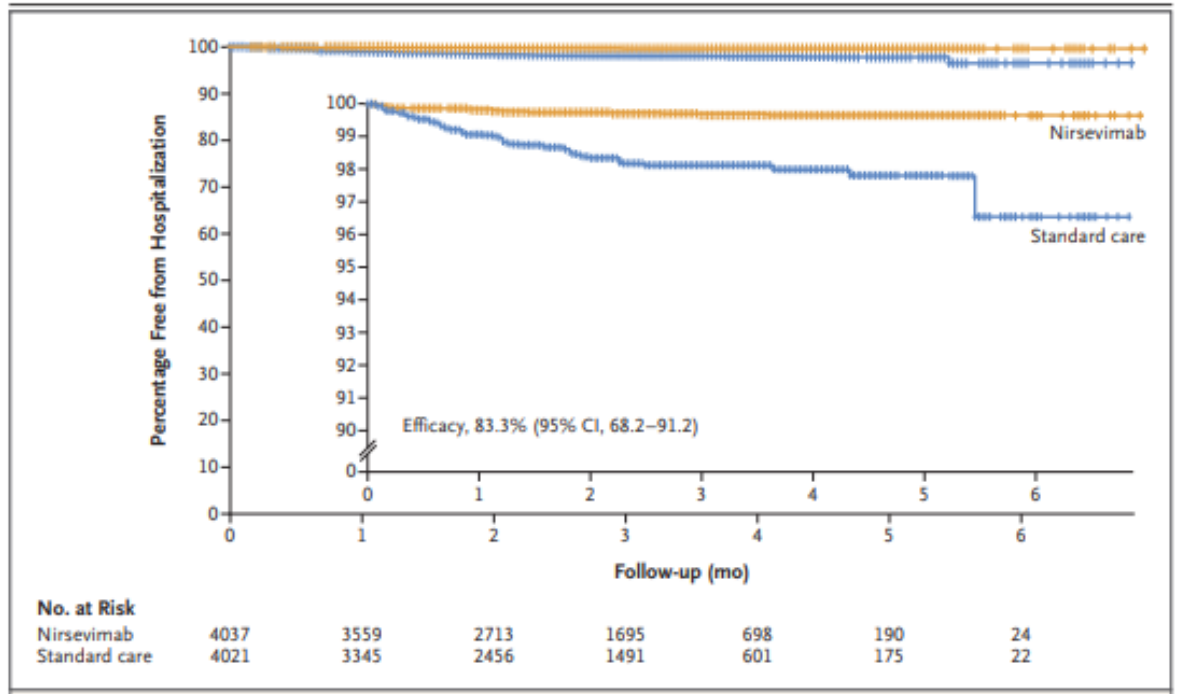


Figure 1. Hospitalization for RSV-Associated Lower Respiratory Tract Infection.

Shown are Kaplan–Meier curves of the time to hospitalization for respiratory syncytial virus (RSV)–associated lower respiratory tract infection, defined as hospital admission and an RSV-positive test result, in all the infants randomly assigned to receive nirsevimab or standard care. The efficacy was calculated as 1 minus the hazard ratio (expressed as a percentage) from a Cox proportional-hazards model, with stratification according to age group and country at randomization. The inset shows the same data on an expanded y axis.

- In July 2023, the FDA approved **nirsevimab** (Beyfortus™, Sanofi and AstraZeneca), a long-acting monoclonal antibody, for passive immunization to prevent RSV-associated lower respiratory tract disease among infants and young children.

ACIP and AAP Recommendations for the Use of Nirsevimab for the Prevention of RSV Disease

- August 3, 2023, recommendations were provided with anticipated start of nirsevimab administration on October 1, 2023

- All infants younger than 8 months born during or entering their first RSV season if:
  - The mother did not receive vaccine during pregnancy or vaccination status is unknown
  - The baby was born less than 14 days following maternal vaccination

- Infants and children aged 8 through 19 months who are at increased risk of severe RSV disease entering their second season*

- Administration may occur during the birth admission or as outpatient shortly after discharge for babies born during RSV season, and shortly before RSV season for those born outside of RSV season

***Risk factors for severe disease**

- Children with CLD 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 who are severely immunocompromised
- 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 have weight-for-length that is <10 percentile
- American Indian and Alaska Native children (*this is a new group for 2nd season prophylaxis in contrast to current palivizumab recommendations)

Limited Nirsevimab Supply in 2023–2024 RSV Season

On October 23, 2023, CDC released a health advisory notice to communicate interim recommendations regarding the limited supply of nirsevimab, the new preventive antibody to protect infants against severe RSV.

Read more: Limited Availability of Nirsevimab in the United States—Interim CDC Recommendations

- Prioritize **nirsevimab** 100mg doses for infants at the highest risk for severe RSV disease:
  - Young infants (age <6 months) and infants with conditions that place them at highest risk for severe RSV disease.

- Suspend using **nirsevimab** in **palivizumab-eligible** children aged 8–19 months for the 2023–2024 RSV season.

- Prenatal care providers should discuss potential nirsevimab supply concerns when counseling pregnant people about RSVpreF vaccine (Abrysvo, Pfizer)

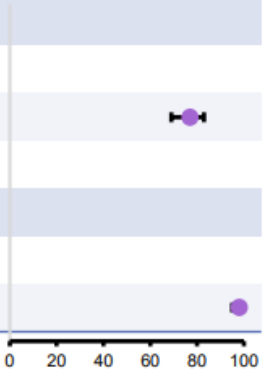
https://emergency.cdc.gov/han/2023/han00499.asp

VISION Data – Nirsevimab

- Virtual SARS-CoV-2, Influenza, and Other respiratory viruses Network (VISION)
  - Data from 127 EDs and 107 hospitals
- Population:
  - Infants < 8 months as of 10/1/2023 or born after 10/1/2023 and more than 7 days of age
    - Presented to and ED or was hospitalized with an RSV-like illness and had a positive RSV test within 10 days prior or 72 hours following presentation

First season nirsevimab product effectiveness (PE) against RSV-associated ED encounters and hospitalization – VISION, October 8, 2023 – March 31, 2024

Outcome | Nirsevimab dosage pattern	Total encounters	RSV-positive encounters N (Row %)	Median days since dose (IQR)	Adjusted PE (95% CI)*
RSV-associated ED encounter				
No nirsevimab doses	4,610	1,988 (43)	N/A	ref
Nirsevimab, ≥7 days prior	442	63 (14)	53 (27-84)	77 (69-83)
RSV-associated hospitalization				
No nirsevimab doses	927	601 (65)	N/A	ref
Nirsevimab, ≥7 days prior	93	4 (4)	48 (25-84)	98 (95-99)



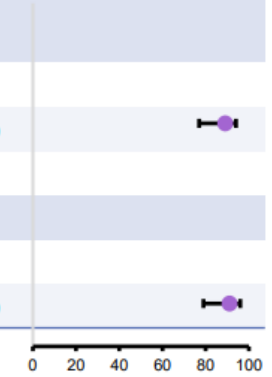
Images obtained from Summary of effectiveness of nirsevimab in infants. Presented on June 23, 2024 ACIP General Meeting. Accessed 10/26/2024.

NVSN Data – Nirsevimab

- New Vaccine Surveillance Network (NVSN)
  - Prospective, population-based surveillance network for pediatric acute respiratory illness
- Population:
  - Infants < 8 months as of 10/1/2023 or born after 10/1/2023
    - Presented to participating medical center with evidence of an acute respiratory illness (ARI) between October 2023 and March 2024
- Initial data from October 2023 to February 2024 was published in the CDC Morbidity and Mortality Weekly Report on March 7, 2024[23]
  - Data to the right includes additional data through March 2024

First season nirsevimab product effectiveness (PE) against medically attended RSV-associated ARI and RSV-associated hospitalization – NVSN, October 2023 – March 2024*

Outcome | Nirsevimab dosage pattern	Total encounters	RSV-positive encounters N (Row %)	Median days since dose (IQR)	Adjusted PE (95% CI)†
Medically Attended RSV-associated ARI episode‡				
No nirsevimab doses	1,575	755 (48)	N/A	ref
Nirsevimab, ≥7 days prior§	120	9 (8)	42 (21-73)	89 (77-94)
RSV-associated hospitalization				
No nirsevimab doses	807	526 (65)	N/A	ref
Nirsevimab, ≥7 days prior	63	6 (10)	38 (15-67)	91 (79-96)



Images obtained from Summary of effectiveness of nirsevimab in infants. Presented on June 23, 2024 ACIP General Meeting. Accessed 10/26/2024.

RSV Vaccine – NIRSE-GAL Study

- Longitudinal Population Based 3-year study out of Galicia Spain, published in Lancet Infectious Diseases April 2024[24]
  - Universal Prophylaxis Campaign began on Sept 25, 2023 and ended March 31, 2024
  - Initial data published was after 3 months of implementation
  - 9408 infants out of 10,259 that were eligible received nirsevimab (91%)
    - Nirsevimab effectiveness against:
      - RSV Related Hospitalization: 82%
        - 0.3% nirsevimab vs. 1.9% unimmunized
      - Severe RSV related LRTI requiring oxygen therapy: 86.9%
        - 0.16% nirsevimab vs. 1.2%
      - All Cause LRTI Hospitalizations: 69.2%
      - All Cause Hospitalizations: 66.2%
  - All adverse events were monitored through the Galician pharmacovigilance system.
  - Throughout the initial trial period there were 5 adverse events out of 9408 administrations classified as severe, but none were considered related to nirsevimab

Nirsevimab Universal Prophylaxis and ED Episodes

- Bronchiolitis Episodes in Pediatric ED in Spain
  - Universal Coverage for infants born during RSV season
  - Extended offering to infants less than 3 or 6 months of age at the start of RSV season in some regions with no extended coverage in others.
  - No maternal vaccination in Spain
  - 15 ED departments
  - Only reviewed episodes in infants less than 6 months of age

TABLE 1 Results According to the Implementation Strategy Followed

	Encounters in the PED for Infants Younger than 6 mo			Bronchiolitis-Related Admissions in Infants Younger than 6 mo	
	All Encounters	Lower Respiratory Tract Infections	Bronchiolitis	Hospital	PICU
	The decrease in encounters/admissions in 2023–2024 from the prenirsevimab seasons, % decrease (95% CI)				
Extended catch-up strategy	22.5 (21.9–23.1)	61.4 (60.1–62.6)	62.8 (61.5–64.0)	65.5 (63.2–67.7)	66.5 (61.1–71.5)
Limited catch-up strategy	14.8 (12.6–17.2)	34.7 (29.0–40.7)	34.0 (28.2–40.1)	46.5 (37.6–55.5)	41.4 (23.5–61.1)
No catch-up strategy	+ 2.4 (1.5–3.4)	4.8 (2.7–7.8)	6.9 (4.2–10.5)	31.4 (20.9–43.6)	40.9 (20.7–63.6)
Overall	20.9 (20.4–21.5)	57.7 (56.5–58.8)	59.2 (57.9–60.4)	63.1 (60.9–65.2)	63.1 (58.1–67.9)

PED, pediatric emergency department; RSV, respiratory syncytial virus.
Extended catch-up strategy: 13 hospitals from 7 regions that immunized babies born during RSV season and infants younger than 6 mo at the beginning of RSV season.
Limited catch-up strategy: 1 hospital from 1 region that immunized babies born during RSV season and infants younger than 3 mo at the beginning of RSV season.
No catch-up strategy: 1 hospital from 1 region that immunized babies born during RSV season without any catch-up.

Nirsevimab and Hospitalizations

Study	Population	Efficacy/Effectiveness against Hospitalization
Phase 2b Nirsevimab	Premature Infants ≥ 29 weeks though 34 weeks 6 days	78.4% (51.9 - 90.3)
Phase 3 Melody (full trial results)	Term and Late preterm Infants ≥ 35 weeks	76.8% (49.4 – 89.4)
HARMONIE Trial	Infants ≥ 29 weeks	83.3% (68.2 – 91.2)
VISION Network Data	Infants < 8 months entering 1st RSV Season and those born during RSV Season in the US post-FDA Approval	98% (95 - 99)
NVSN Network Data	Infants < 8 months entering 1st RSV Season and those born during RSV Season in the US post-FDA Approval	91% (79 – 96)

Nirsevimab Safety

- Comprehensive Summary of all Safety Data from Pivotal Trials[25]
  - Phase 2b Nirsevimab Study Group
  - Phase 3 MELODY Trial
  - Phase 2/3 MEDLEY Trial (data included patients with congenital heart disease, chronic lung disease of prematurity, and those born less than 35 weeks gestation)

Table 2. Most commonly observed Aes (reported in ≥10% of any treatment group during the first RSV season) through 360 days post-dose by preferred term in healthy term and preterm infants born ≥29 wGA. [a] Infants with CHD/CLD or preterm infants born ≤35 weeks 0 days GA without CHD/CLD, and children with CHD/CLD entering their second RSV season [b].

	Healthy Term and Preterm Infants Born ≥29 wGA [a]		Infants Eligible for Palivizumab Entering Their First RSV Season				Children with CHD/CLD Entering Their Second RSV Season [b]		
			Preterm Infants Born ≤35 Weeks 0 Days GA without CHD or CLD		Infants with CHD/CLD				
Preferred Term, *n* (%)	**Nirsevimab (*n* = 2570)**	**Placebo (*n* = 1284)**	**Nirsevimab (*n* = 406)**	**Palivizumab (*n* = 206)**	**Nirsevimab (*n* = 208)**	**Palivizumab (*n* = 98)**	**Nirsevimab/ Nirsevimab (*n* = 180)**	**Palivizumab/ Nirsevimab (*n* = 40)**	**Palivizumab/ Palivizumab (*n* = 42)**
Upper respiratory tract infection	869 (33.8)	417 (32.5)	110 (27.1)	56 (27.2)	39 (18.8)	23 (23.5)	48 (26.7)	8 (20.0)	9 (21.4)
Nasopharyngitis	523 (20.4)	292 (22.7)	36 (8.9)	20 (9.7)	21 (10.1)	19 (19.4)	26 (14.4)	7 (17.5)	9 (21.4)
Pyrexia	348 (13.5)	152 (11.8)	54 (13.3)	33 (16.0)	29 (13.9)	10 (10.2)	23 (12.8)	9 (22.5)	6 (14.3)
Gastroenteritis	284 (11.1)	128 (10.0)	17 (4.2)	14 (6.8)	8 (3.8)	2 (2.0)	14 (7.8)	2 (5.0)	3 (7.1)
Dermatitis diaper	271 (10.5)	126 (9.8)	17 (4.2)	3 (1.5)	11 (5.3)	3 (3.1)	8 (4.4)	0	1 (2.4)
Rhinitis	252 (9.8)	126 (9.8)	48 (11.8)	27 (13.1)	27 (13.0)	13 (13.3)	29 (16.1)	6 (15.0)	6 (14.3)
Constipation	112 (4.4)	55 (4.3)	16 (3.9)	10 (4.9)	21 (10.1)	10 (10.2)	5 (2.8)	2 (5.0)	2 (4.8)

Nirsevimab Safety

- Serious Adverse Events
  - Hypersensitivity
    - There were no episodes consistent with immediate hypersensitivity reactions or anaphylaxis in these 3 clinical trials
    - No hypersensitivity reactions noted from HARMONIE or NIRSE-GAL studies
  - Deaths
    - No deaths were considered related to nirsevimab treatment

- FDA Adverse Event Reporting system (FAERS)
  - Most commonly reported events include breakthrough RSV infections
  - Cases of serious hypersensitivity reactions were identified in post-marketing surveillance, so product labeling was updated
    - “Serious hypersensitivity reactions have been reported following BEYFORTUS administration. These reactions included urticaria, dyspnea, cyanosis, and or hypotonia.”

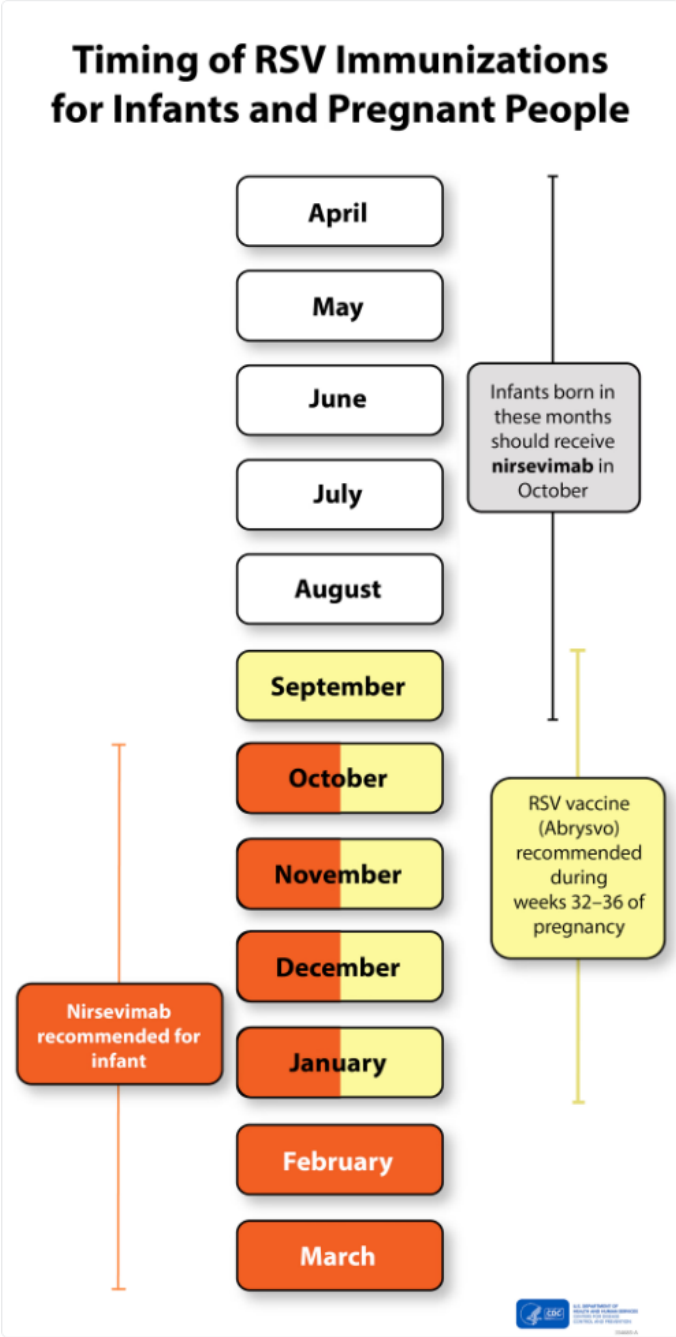
Nirsevimab and Fever

Does nirsevimab increase risk of fever and infectious rule-out?

- Phase 2b Nirsevimab Study
  - Pyrexia was reported 11.5% of nirsevimab vs. 13.4% of placebo recipients
- HARMONIE Trial
  - Pyrexia was reported 2.5% of nirsevimab recipients vs. 1.9% with no intervention

Immunization Options

Name	Recipient	Number of Injections	Dose	Half-Life	Anticipated Duration of Protection	Cost for Season
Palivizumab (Synagis®)	High Risk Infants Only	5 (monthly x 5 doses)	15mg/kg	20-24 days	1 month per injection	$10,000-$30,000
RSV preF Vaccine (Abrysvo®)	Mother 32-36 weeks gestation	1	120 mcg/ 0.5mL	N/A	6 months post-delivery	~$300
Nirsevimab (Beyfortus)	All Infants entering 1st RSV Season and High-Risk Infants entering 2nd RSV Season	*1st Season* 1 *2nd Season* 2 (simultaneously)	*1st Season* < 5kg = 50mg ≥ 5kg = 100mg *2nd Season* All patients = 200 mg	71 days	6 months post-administration	*1st Season* ~$500 *2nd Season* ~$1,000



Overall Immunization Plan

- Maternal Vaccination
  - Low risk pregnancies
  - No history of hypertensive disorders
  - Conversation with OB
- Infant Immunization
  - Unvaccinated or administration less than 14 days prior to delivery
  - Premature infants
  - Infants with high-risk conditions

Outstanding Questions

- Effectiveness for high-risk patients entering their second season
  - Congenital heart patients excluded in AAP recommendations
- Insurance coverage has caused variation in practice nationwide
  - Will the DRG increase to include coverage of nirsevimab for all patients?
  - Will additional states create a universal vaccination program?
  - Will private payors create carve outs for immunizations?
- Acceptance of infant immunization and maternal vaccination
- Safety outcomes and effectiveness for maternal vaccination
- Identification of maternal vaccination in infant medical records

Future Directions for RSV Prevention

- Clesrovimab (MK-1654)
  - Recent Data from Phase 2b/3 Studies were presented to the ACIP
    - Humanized monoclonal antibody with affinity for site IV on the RSV Fusion Protein and a half life of approximately 44 days
    - Preliminary data suggests it is highly effective at preventing RSV associated hospitalizations by over 90% through 6 months
    - Well tolerated with a safety profile comparable to all controls
- Sanofi is currently completing a Phase 3 study of live-attenuated intranasal RSV vaccine for infants and toddlers and assessing co-administration with other vaccines

Questions

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