Protecting Babies from RSV

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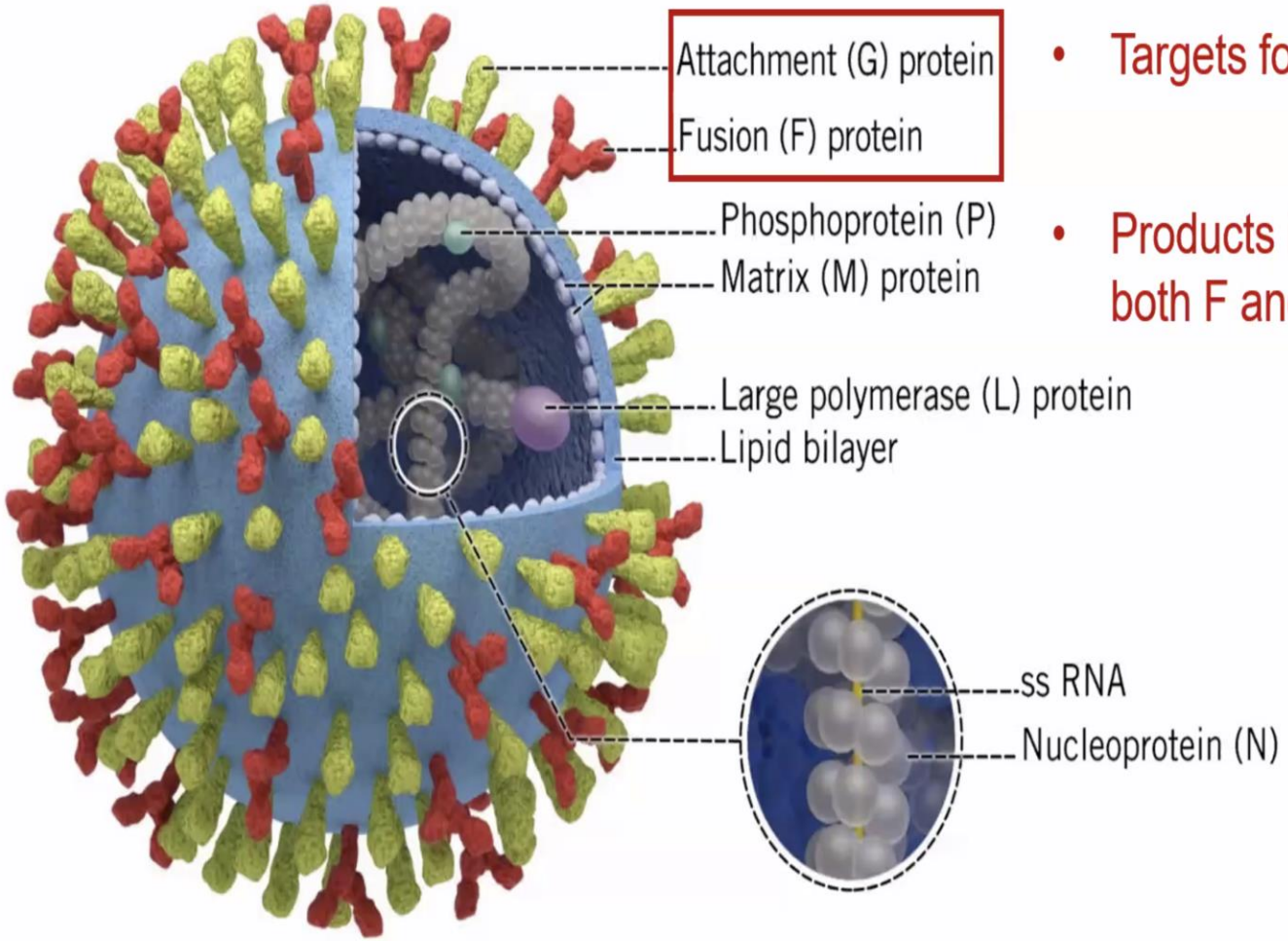
Maternal RSV vaccines

Virology

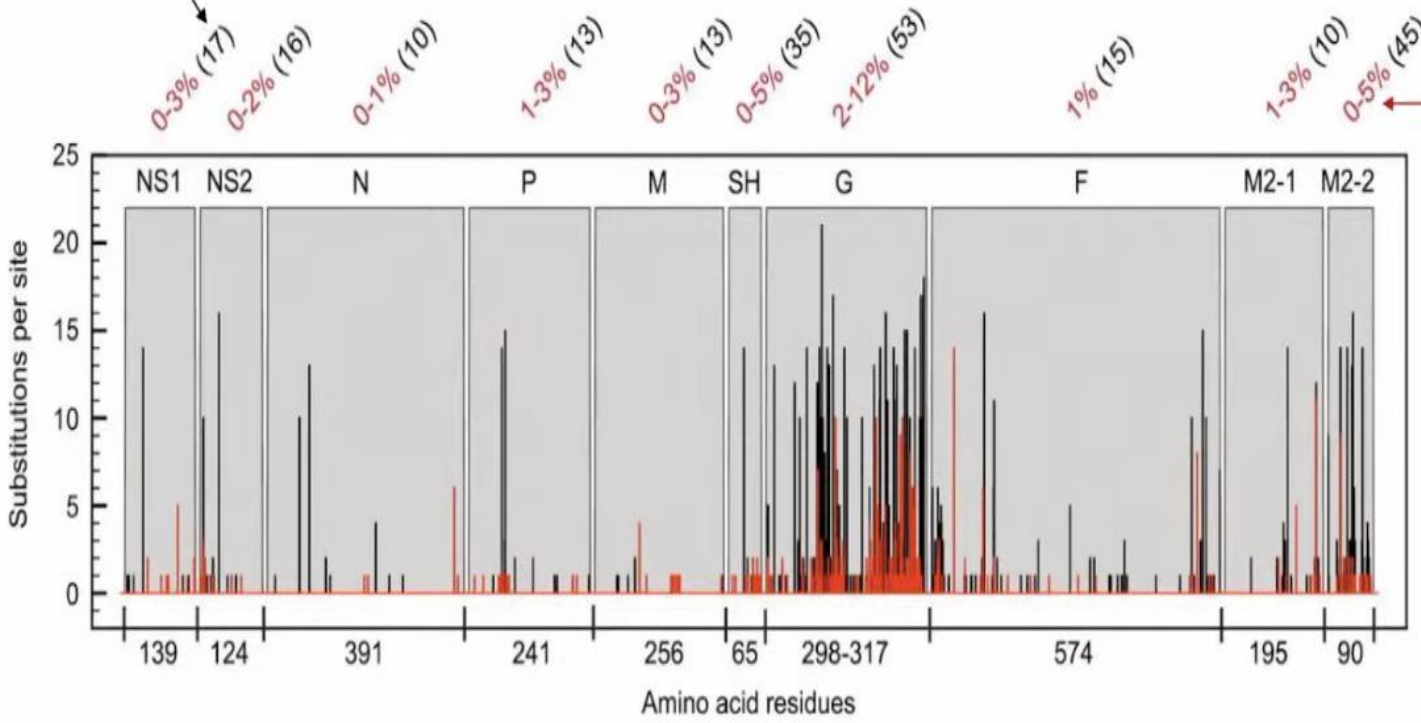
RSV – virion structure



- Targets for neutralizing antibodies
- Products in target F alone or have both F and G

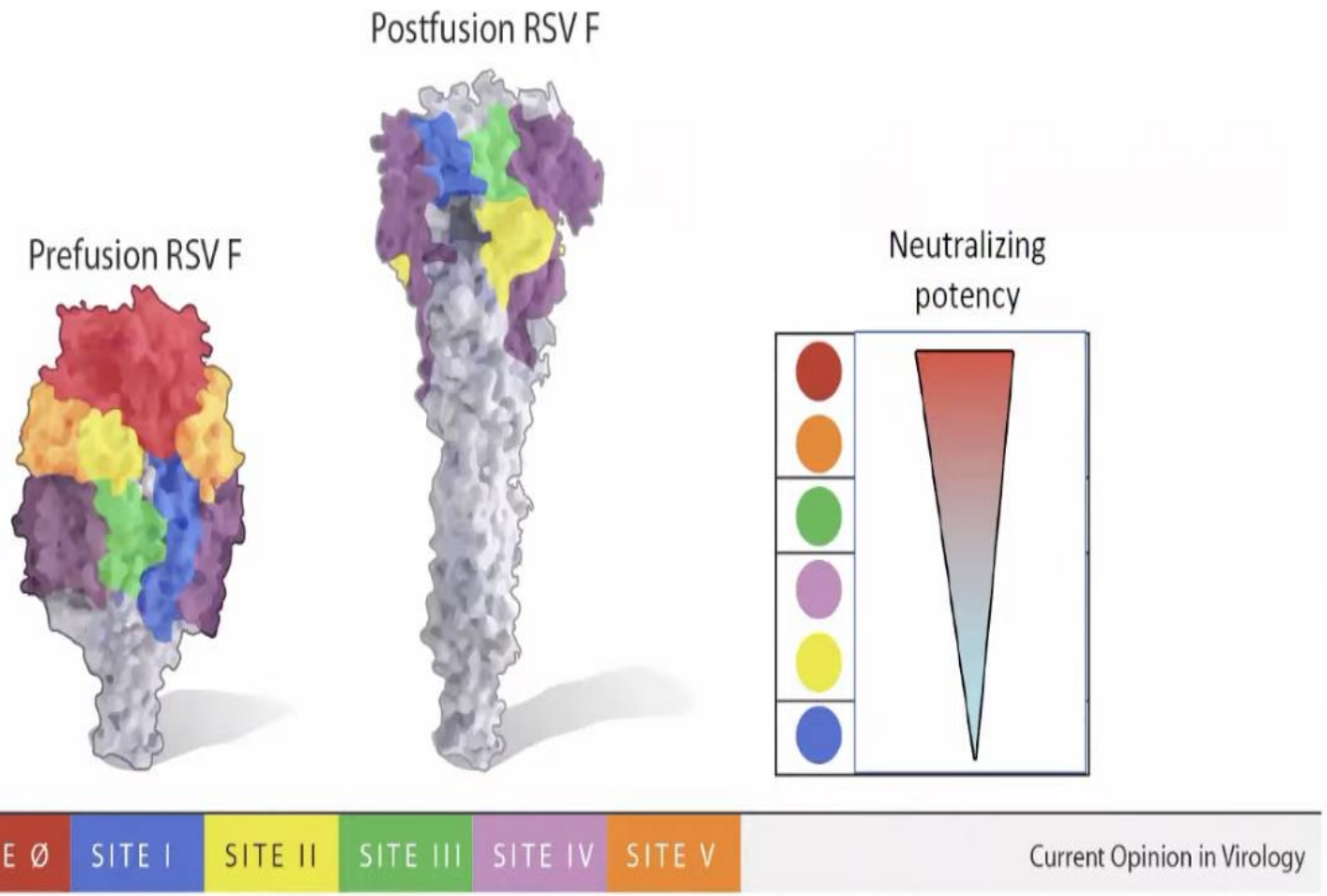
RSV G gene is the most variable in the genome (F is more conserved)

(Percent sequence variability between A and B)



Lydia Tan et al. J. Virol. 2013;87:8213-8226

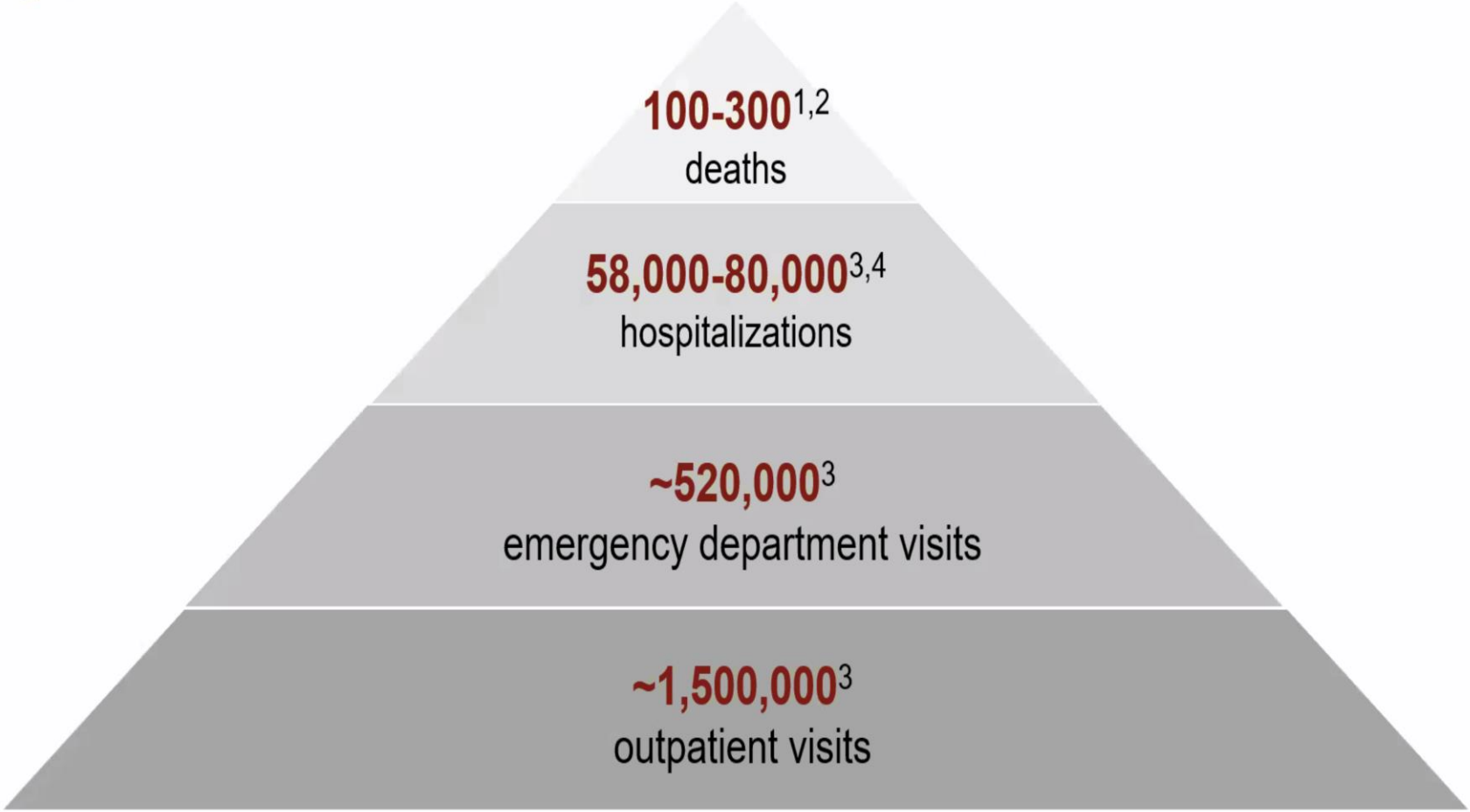
The fusion (F) protein exists in two or more structural forms exposes different antigenic regions



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

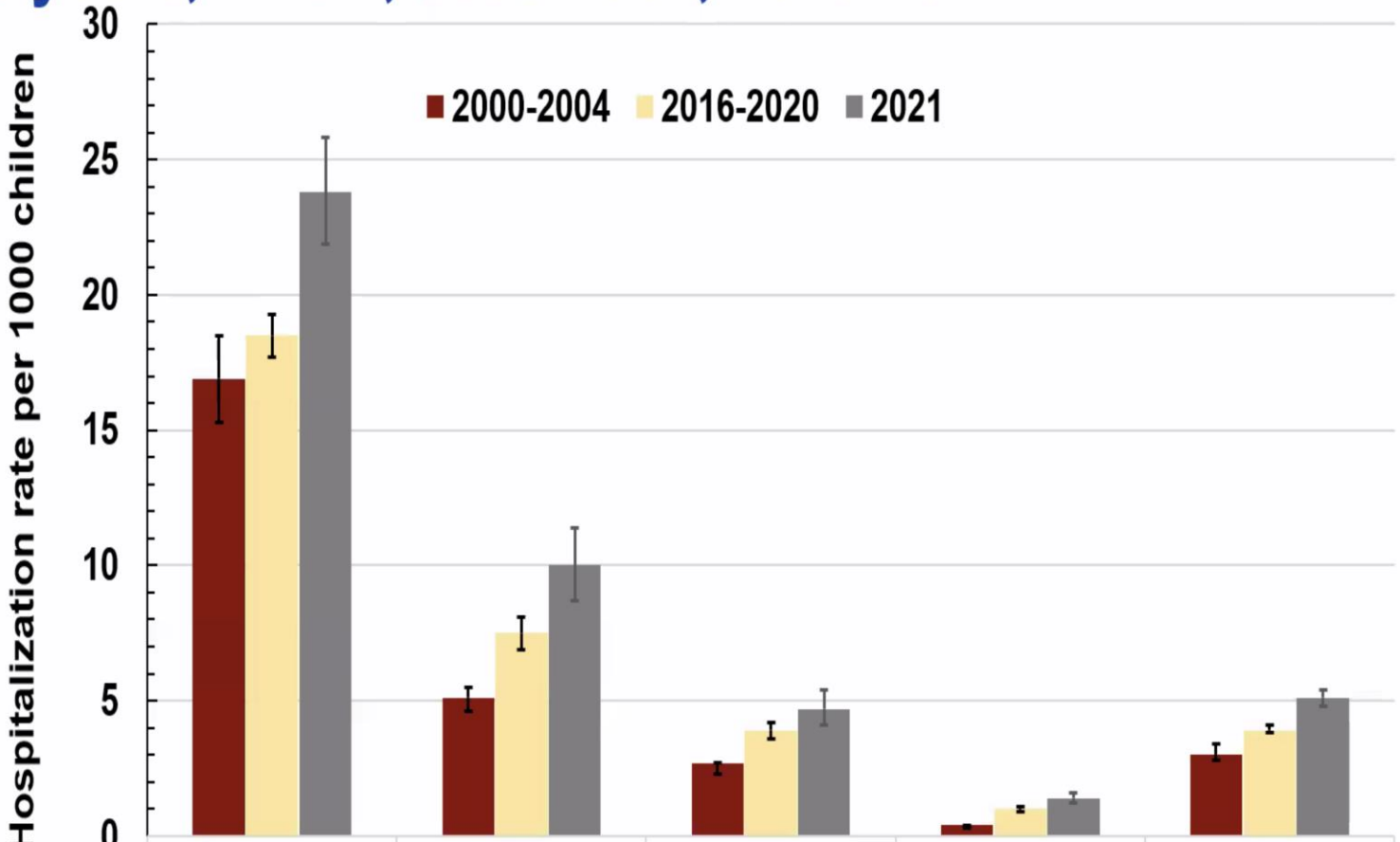
Epidemiology

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)

RSV-associated hospitalization rates in children aged <5 years, 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

All young infants are at risk of having severe disease with RSV

- Premature infants born at <30 weeks gestation had hospitalization rates ~3x higher than term infants[1]
- Children with chronic lung disease of prematurity and congenital heart disease are also at increased risk of severe RSV disease[2]
- 79% of children hospitalized with RSV aged <2 years had no underlying medical conditions[1]

[1]Hall et al, Pediatrics, 2013; [2]Langley & Anderson, PIDJ, 2011

RSV severity appears to be similar in pregnant and non-pregnant people

- Among 387 women aged 18-49 years were hospitalized with RSV in RSV-NET during October-April 2014-2018
  - 41 (12%) were pregnant
- Severe outcomes among pregnant women hospitalized with RSV were uncommon
  - 5 (12%) pregnant women vs. 82 (24%) non-pregnant women aged 18-49 years had severe outcomes (ICU admission/in-hospital death)
- Being pregnant was not a risk factor for a severe outcome with RSV hospitalization in multivariable analysis

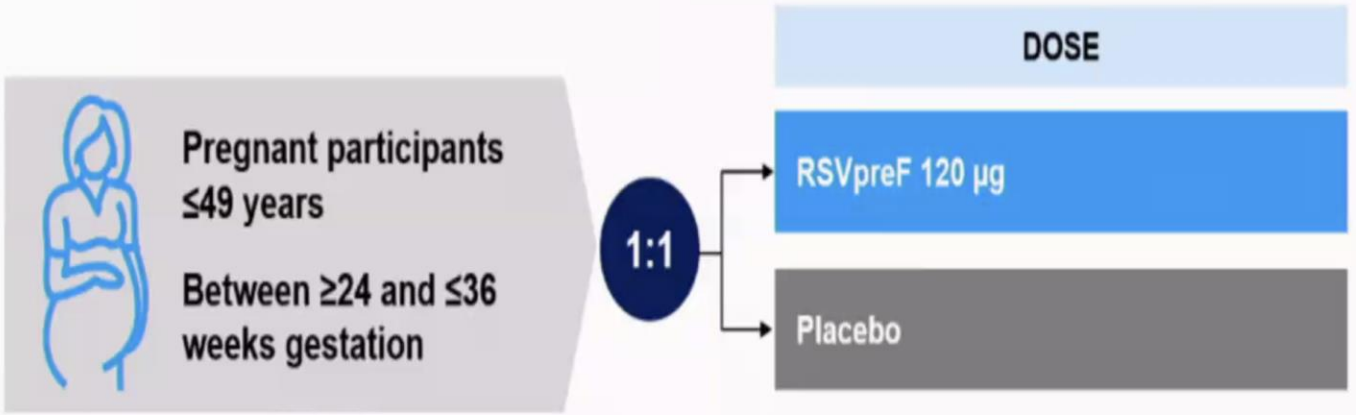
Milucky et al. Outcomes of pregnant women hospitalized with RSV infection, RSV-NET, 2014-2018. ReSViNet, 2023

Pfizer vaccine

Trial Design

MATISSE: Phase 3 Pivotal Maternal Vaccination Trial

Maternal Participants: Safety 6 Months after Delivery
Infants: Safety and Respiratory Surveillance up to 2 years



Analysis Included June 2020-September 2022

Efficacy

Phase 3 Efficacy Endpoints Defined

Weekly active surveillance for MA visit + RTI symptoms
Symptoms trigger nasal swab and visit

Primary Endpoints	Criteria used by the Adjudication Committee
RSV LRTI Medically attended visit and ≥1:	• Tachypnea (RR **≥60** (<2 M [60 days]) or **≥50** (≥2 to <12 M) • SpO2 measured **<95%** • Chest wall indrawing
Severe RSV LRTI Medically attended visit and ≥1:	• Tachypnea (RR **≥70** (<2 M [60 days]) or **≥60** (≥2 to <12 M) • SpO2 measured **<93%** • High-flow nasal cannula or mechanical ventilation • ICU admission for >4 hours • Unresponsive/unconscious

Positive validated RT-PCR

Medically attended (MA) visit: Infant participant taken to or seen by a healthcare provider (e.g., outpatient or inpatient visit, emergency room, urgent care, or home visit)
LRTI=Lower Respiratory Tract Illness; SpO2=peripheral capillary oxygen saturation

Outcome 1: Medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.5% or 97.58% CI)
0–90 days after birth[2]	24/3495	56/3480	57.3% (31.3, 73.5)	57.1% (14.7, 79.8)
0–120 days after birth	35/3495	81/3480	57.0% (36.2, 71.0)	56.8% (31.2, 73.5)
0–150 days after birth	47/3495	99/3480	52.7% (33.3, 66.5)	52.5% (28.7, 68.9)
0–180 days after birth	57/3495	117/3480	51.5% (33.7, 64.5)	51.3% (29.4, 66.8)

RR= relative risk, CI=confidence interval

[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). Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

[2] This outcome did not meet success criterion using manufacturer calculated VE (lower bound of CI was <20%)

Outcome 1: Severe medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.5% or 97.58% CI)
0–90 days after birth	6/3495	33/3480	81.9% (56.8, 92.4)	81.8% (40.6, 96.3)
0–120 days after birth	12/3495	46/3480	74.0% (51.1, 86.2)	73.9% (45.6, 88.8)
0–150 days after birth	16/3495	55/3480	71.0% (49.6, 83.4)	70.9% (44.5, 85.9)
0–180 days after birth	19/3495	62/3480	69.5% (49.1, 81.7)	69.4% (44.3, 84.1)

RR= relative risk, CI= confidence interval

[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).

Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

Safety

Maternal Participants - Adverse Events of Special Interest (AESI)

- AESI within 1 month of vaccination: 2.7% in RSVpreF group, 2.5% in placebo group
- **Premature delivery after vaccination**:
  - 206/3682 **(5.6%)** [95% CI: 4.9%, 6.4%] in RSVpreF group
  - 174/3675 **(4.7%)** [95% CI: 4.1%, 5.5%] in placebo group
- One maternal participant in the placebo group withdrew from the study due to premature delivery

FDA Approves First Vaccine for Pregnant Individuals to Prevent RSV in Infants

For Immediate Release: August 21, 2023

Español

Today, the U.S. Food and Drug Administration approved Abrysvo (Respiratory Syncytial Virus Vaccine), the first vaccine approved for use in pregnant individuals to prevent lower respiratory tract disease (LRTD) and severe LRTD caused by respiratory syncytial virus (RSV) in infants from birth through 6 months of age. Abrysvo is approved for use at 32 through 36 weeks gestational age of pregnancy. Abrysvo is administered as a single dose injection into the muscle. The FDA approved Abrysvo in May for the prevention of LRTD caused by RSV in individuals 60 years of age and older.

ACIP approves maternal RSV vaccine

Maternal RSV vaccine is recommended for pregnant people during 32 through 36 weeks gestation, using seasonal administration, to prevent RSV lower respiratory tract infections in infants.

Preterm birth in Pfizer RSVpreF vaccine phase 3 trial data, comparing trial vs approved dosing interval

	Trial dosing interval (24–36 weeks gestation)[1]				Approved dosing interval (32–36 weeks gestation)[1,2]			
	RSVpreF vaccine group N=3,568		Placebo group N=3,558		RSVpreF vaccine group N=1,628		Placebo group N=1,604	
	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)	n	% (95% CI)
Preterm birth (<37 weeks gestation)	202	**5.7%** (4.9%, 6.5%)	169	**4.7%** (4.1%, 5.5%)	68	**4.2%** (3.3%, 5.3%)	59	**3.7%** (2.8%, 4.7%)

1. Package Insert - ABRYSVO (STN 125768) (fda.gov)

2. Pfizer response to ACIP, unpublished data, August 2023. In package insert, approved dosing interval reported as: 4.2% (68/1,631) in the RSVpreF group and 3.7% (59/1,610) in the placebo group.

GSK vaccine

NEWS ANALYSIS

Maternal RSV vaccine: Further analysis is urged on preterm births

A "safety signal" in a similar respiratory syncytial virus (RSV) vaccine has led to trials being stopped and prompted calls for a cautious approach to using the vaccine in pregnant women, reports **Hristio Boytchev**

Hristio Boytchev

Experts have called for further analysis of trial data and post-approval monitoring of Pfizer's maternal RSV vaccine candidate after GSK's trials of a similar product were halted over a rise in preterm births and neonatal deaths.

An advisory committee from the US Food and Drug Administration (FDA) is set to discuss the vaccine on

explain the safety signal, including SARS-CoV-2 infections, Dieussaert said.

"Similar" vaccine

Pfizer's vaccine is similar to GSK's, although there may be differences in manufacturing, says Cody Meissner, professor of paediatrics and medicine at

Boytchev, H., *British Medical Journal* (2023) 381: 1021, published eight days before FDA VRBPAC meeting in May

GSK halts its trials

In February 2022, GSK halted enrolment and vaccination across three phase 3 trials of its maternal RSV vaccine candidate, citing a safety signal in one of them.[5] It emerged that the concern was about an increased risk of preterm birth in the vaccine arm.[6]

In a document submitted to the FDA, GSK's data showed 238 preterm births out of 3496 (6.8%) in the vaccine arm and 86 out of 1739 (4.9%) in the placebo arm—around one extra preterm birth for every 54 vaccinated mothers.[7] There were 13 neonatal deaths in the vaccine arm and three in the placebo arm.[7]

GSK said it is still investigating the cause of the preterm births and presented preliminary findings in a conference presentation earlier this year.[8]

GSK vaccine:

Lisbon, Portugal

May 7, 2023

Preterm births, overall and by economic region (infant cohort)

Preterm births	RSVPreF3 Mat		Placebo		Relative risk (95% CI)	*p-value*
	n/N	% (95% CI)	n/N	% (95% CI)		
Overall	238/3496	6.81 (5.99–7.69)	86/1739	4.95 (3.97–6.07)	1.38 (1.08–1.75)	0.0090
LMIC	173/1755	9.86 (8.50–11.35)	55/875	6.29 (4.77–8.10)	1.57 (1.17–2.10)	0.0026
HIC	65/1741	3.73 (2.89–4.73)	31/864	3.59 (2.45–5.05)	1.04 (0.68–1.58)	0.8528

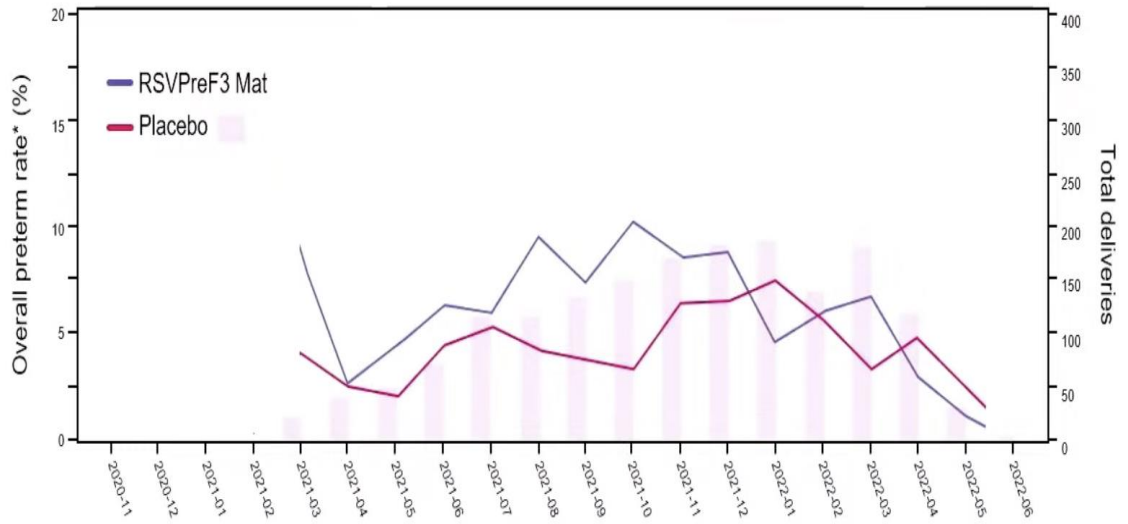
The imbalance in preterm birth between groups was greater in LMIC than in HIC

Examining the role of additional vaccinations on preterm birth by economic region (infant cohort)

	Categories	RSVPreF3 Mat n/N	RSVPreF3 Mat %	Placebo n/N	Placebo %	Relative risk (95% CI)
HIC	No additional vaccine(s)	21/457	4.60 (2.87–6.94)	11/225	4.89 (2.47–8.58)	0.94 (0.46–1.92)
	With additional vaccine(s)*	44/1284	3.43 (2.50–4.57)	20/639	3.13 (1.92–4.79)	1.09 (0.65–1.84)
LMIC	No additional vaccine(s)	80/625	12.80 (10.28–15.68)	30/298	10.07 (6.90–14.06)	1.27 (0.86–1.89)
	With additional vaccine(s)*	93/1130	8.23 (6.69–9.99)	25/577	4.33 (2.82–6.33)	1.90 (1.24–2.92)

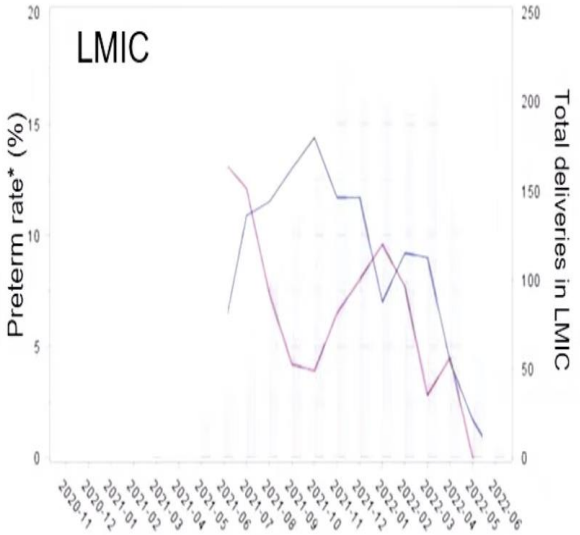
- In HIC and LMIC the preterm birth rate decreased with additional vaccination during pregnancy in both groups
- The imbalance in preterm birth between groups was the highest in LMIC when additional vaccines were administered during the 2nd and 3rd trimester

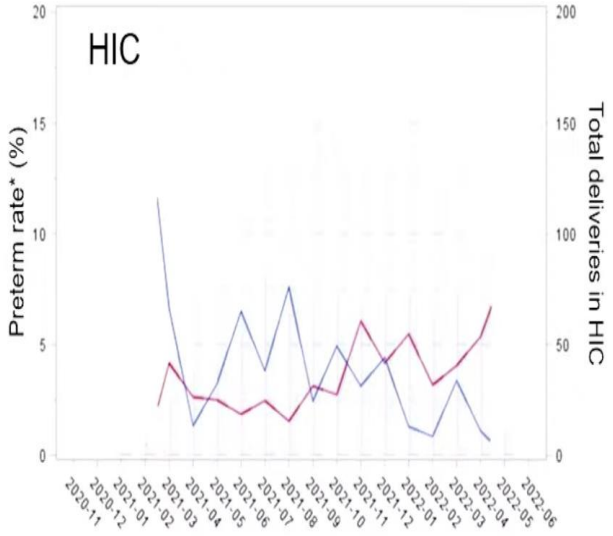
Monthly preterm birth rate and total births, overall and by economic region



The imbalance in preterm birth rates was consistently present between April and December 2021, and afterwards, the difference was not evident

The magnitude and temporal clustering of the imbalance in preterm birth between groups was greater in LMIC than in HIC during the same time period





Is it biologically plausible that the RSV Pre-F protein would cause prematurity?

RESEARCH ARTICLE

Respiratory Syncytial Virus Fusion Protein Promotes TLR-4–Dependent Neutrophil Extracellular Trap Formation by Human Neutrophils

Giselle A. Funchal[1,2,4], Natália Jaeger[2,4], Rafael S. Czepielewski[2,4], Mileni S. Machado[1,4], Stéfanie P. Muraro[1,4], Renato T. Stein[3,4], Cristina B. C. Bonorino[2,4], Bárbara N. Porto[1,3,4]*

1 Clinical and Experimental Immunology Laboratory, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil, **2** Cellular and Molecular Immunology Laboratory, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil, **3** Infant Center, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil, **4** Institute of Biomedical Research, Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS, Brazil

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Abstract

Acute viral bronchiolitis by Respiratory Syncytial Virus (RSV) is the most common respiratory illness in children in the first year of life. RSV bronchiolitis generates large numbers of hospi-

Funchal, G.A., et al. PLOS One (2015) doi: 10.1371/journal.pone.0124082.

Role of Toll-like receptor 4 in inflammation-induced preterm delivery

Liping Li[1], Jiali Kang, and Weihua Lei

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ABSTRACT: The aim of the present study was to investigate the potential role of Toll-like receptor 4 (TLR4) in lipopolysaccharide (LPS)-induced preterm delivery. Intraperitoneal injection of LPS in the presence or absence of previous TLR4 blockade was performed to establish a murine model of preterm delivery. The incidences of preterm delivery and fetal death were calculated. Flow cytometry was performed to examine the percentages of blood $CD45^+CD86^+$, $CD3^+CD69^+$, $CD19^+CD69^+$ and $CD49b^+CD69^+$ cell subsets, and the percentages of placenta $CD45^+CD86^+$, $CD45^+CD49b^+$ and $CD49b^+CD69^+$ cell subpopulations. In our study, an inflammation-induced preterm delivery model was established by intraperitoneal injection of LPS. Blocking TLR4 significantly decreased LPS-induced preterm delivery and fetal death. LPS treatment markedly up-regulated the percentages of blood $CD45^+CD86^+$, $CD3^+CD69^+$ and $CD49b^+CD69^+$ cells, and of placenta $CD45^+CD86^+$, $CD45^+CD49b^+$ and $CD49b^+CD69^+$ cells. TLR4 blockade almost completely abrogated LPS-induced elevated cell proportions. These data demonstrate that TLR4 plays a critical role in inflammation-induced preterm delivery.

Li, L., et al. *Molecular Human Reproduction* (2010) 16: 267-272.

REVIEW

Targeting Toll-like receptor-4 to tackle preterm birth and fetal inflammatory injury

Sarah A Robertson[1], Mark R Hutchinson[1,2], Kenner C Rice[3], Peck-Yin Chin[1], Lachlan M Moldenhauer[1], Michael J Stark[1], David M Olson[4] & Jeffrey A Keelan[5]

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[2]ARC Centre for Nanoscale Biophotonics and Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia
[3]Drug Design and Synthesis Section, National Institute on Drug Abuse and National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, Rockville, MD, USA
[4]Department of Obstetrics and Gynecology, Department of Physiology and Pediatrics, 220 HMRC, University of Alberta, Edmonton, AB, Canada
[5]Division of Obstetrics & Gynaecology, University of Western Australia, Perth, WA, Australia

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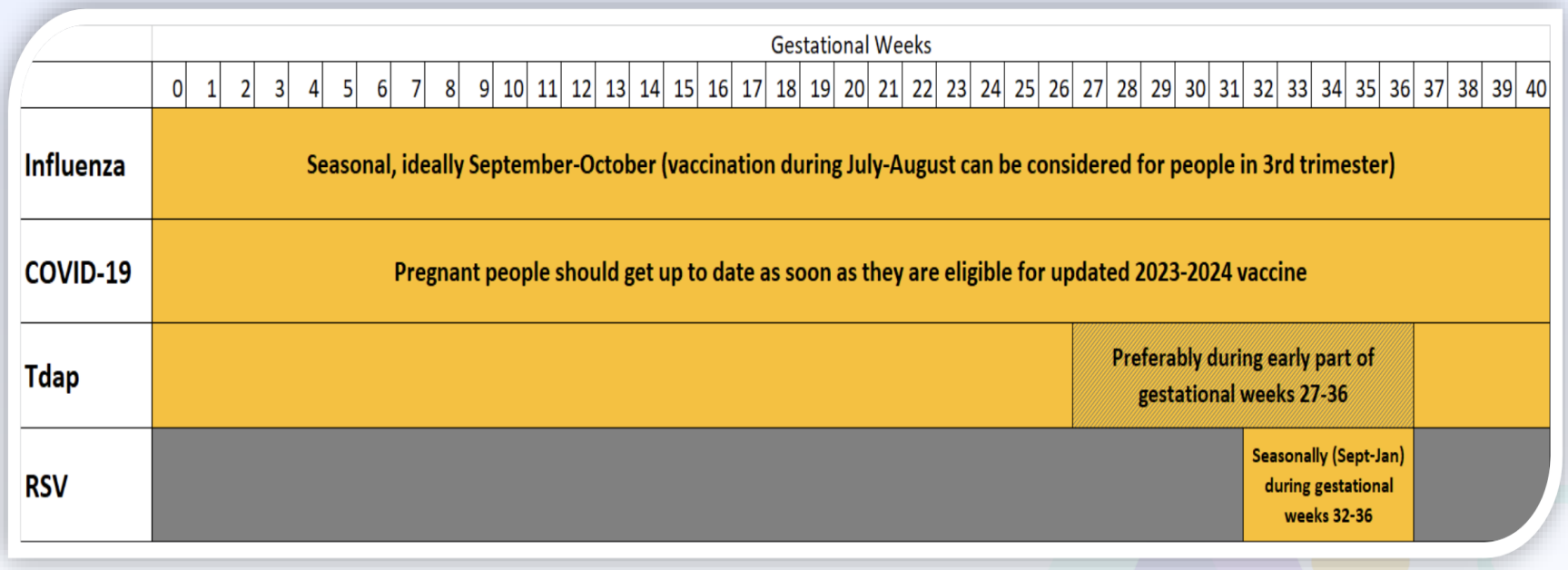
Abstract

Every year, 15 million pregnancies end prematurely, resulting in more than 1 million infant deaths and long-term health consequences for many children. The physiological processes of

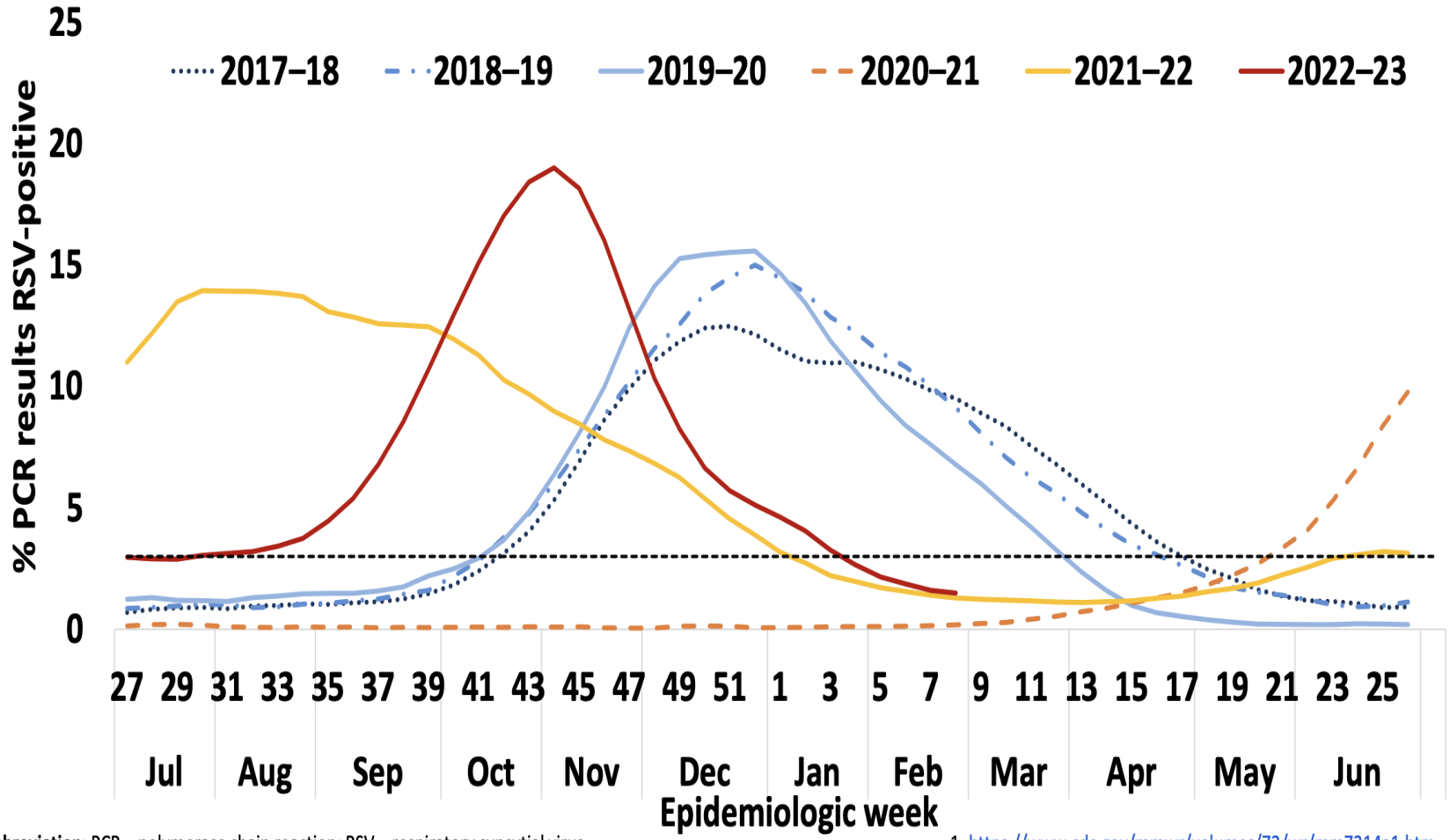
Robertson, S.A., et al., *Clinical and Translational Immunology* (2020) doi: 10.1002/cti2.1121.

Increasing Complexity of Maternal Immunization Schedule



- Increasingly complex maternal immunization schedule, with different timing of vaccines based on season and/or gestational age (with seasonal timing varying in some locations)
- Limited window for RSV vaccine administration
- Unclear willingness of pregnant people to accept multiple vaccines in pregnancy

Changes in seasonality of RSV transmission following SARS-CoV2 introduction— NREVSS[1], 2017–2023



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

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

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

A maternal RSV vaccine isn’t the only option available to prevent RSV disease in infants

Long-acting monoclonal antibody against RSV F protein:

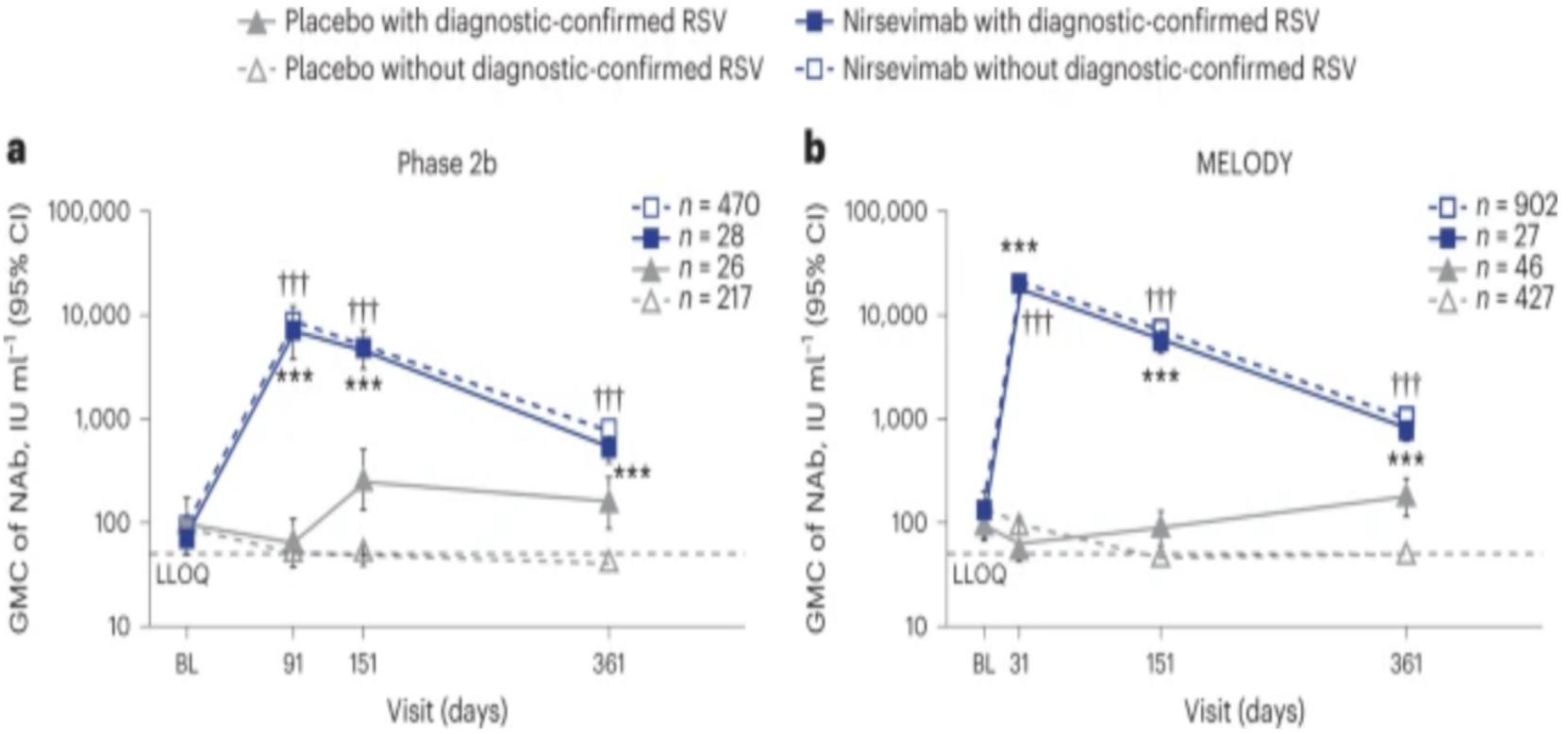
Nirsevimab (Beyfortus)

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

Source: California Department of Public Health

Fig. 4: RSV NAb GMC through day 361 by treatment and medically attended, diagnostic-confirmed RSV infection.



a, Phase 2b study NAbs. **b**, MELODY study NAbs. ***$P < 0.001$, nirsevimab versus placebo with diagnostic-confirmed RSV; †††$P < 0.001$, nirsevimab versus placebo without diagnostic-confirmed

HARMONIE preliminary results[1]

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

SaO2= oxygen saturation; AE= adverse event

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

Nirsevimab recommendations for infants and children at increased risk of severe RSV

- Nirsevimab is recommended for infants aged <8 months born during or entering their first RSV season, including those recommended to receive palivizumab by AAP[1]
- Nirsevimab is recommended for children aged 8–19 months who are at increased risk of severe RSV disease and entering their second RSV season, including those recommended to receive palivizumab by AAP[1]
- Per FDA label, children who have received nirsevimab should not receive palivizumab for the same RSV season[2]

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

[2]FDA label for nirsevimab

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

There is another option to prevent RSV in babies

Breastfeeding

Feeding in the first six months of life is associated with the probability of having bronchiolitis: a cohort study in Spain

Inés Gómez-Acebo[1,2*†], Carolina Lechosa-Muñiz[3†], María Paz-Zulueta[1], Trinidad Dierssen Sotos[1,2], Jéssica Alonso-Molero[1], Javier Llorca[2,4†] and María J. Cabero-Perez[1,3†]

Abstract

Background: Breastfeeding is associated with lower incidence and severity of lower respiratory tract disease. However, little is known about the relationship between feeding type and breastfeeding duration with bronchiolitis in a child's first year.

Methods: A prospective cohort study of 969 newborn babies were followed-up for 12 months to determine breastfeeding duration, feeding type, feeding trajectory, and bronchiolitis episodes at Marqués de Valdecilla

Gomez-Acebo, I., et al. *International Breastfeeding Journal* (2021) 16: 82.

Gomez-Acebo, et al. (2021)

- In Spain, 969 newborns were followed prospectively at 2, 4, 6, 9 and 12 months.
- About 26 percent of infants had at least one episode of bronchiolitis by 12 months of age.
- Exclusive breastfeeding for 2 months lowered the incidence of bronchiolitis by 45 percent compared with exclusive infant formula feeding.
- Exclusive breastfeeding for at least 6 months lowered the risk of bronchiolitis by 55 percent.

Outcome 1: Medically attended RSV-associated lower respiratory tract infection in infants (n=1 study)

Time period after birth	Events/Vaccine (n/N)	Events/Placebo (n/N)	Vaccine efficacy (1 – RR) (95% CI)	Manufacturer calculated vaccine efficacy[1] (99.5% or 97.58% CI)
0–90 days after birth[2]	24/3495	56/3480	57.3% (31.3, 73.5)	57.1% (14.7, 79.8)
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0–180 days after birth	57/3495	117/3480	51.5% (33.7, 64.5)	51.3% (29.4, 66.8)

RR= relative risk, CI=confidence interval

[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). Efficacy is from full phase 3 trial data, using trial dosing interval (24–36 weeks gestation).

[2] This outcome did not meet success criterion using manufacturer calculated VE (lower bound of CI was <20%)

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Breast Milk Prefusion F Immunoglobulin G as a Correlate of Protection Against Respiratory Syncytial Virus Acute Respiratory Illness

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Mazur, N.I., et al. *J Infect Dis* (2019) 219: 59-67.

Mazur, et al. (2019)

- Breast milk was obtained from 174 mothers 1-, 3-, and 6-months post-partum.
- Pre-fusion (F protein) IgG levels were significantly lower in mothers whose babies suffered RSV acute respiratory illness.
- The authors concluded that IgG directed against RSV pre-F protein in breast milk was a correlate of protection against RSV.

Breastfeeding prevents severe RSV disease, causing hospitalization

Breast-feeding protects against respiratory syncytial virus infections

M A P S DOWNHAM, R SCOTT, D G SIMS, J K G WEBB, P S GARDNER

British Medical Journal, 1976, **2**, 274-276

Summary

Eight out of 115 infants admitted to hospital with respiratory syncytial (RS) virus infection had been breast-fed compared with 46 out of 167 controls; this difference was statistically significant. Twenty-one specimens of same question was put to mothers of 167 infants interviewed without selection in the waiting rooms of Newcastle city child health clinics during the same RS virus epidemic. Follow-up of these control infants established that they had not been admitted to hospital with respiratory illness during that winter. All children were aged less than 12 months; the mean age of the children admitted with RS virus infection was 4·1 months and of the control children 4·7 months.

Downham, M.A.P.S., et al. *British Medical Journal* (1976) 2: 274-276.

Downham, et al. (1976)

- Incidence of breast feeding in the general population was about 28 percent (46 of 167).
- Of those babies admitted to the hospital with RSV infection, only 7 percent (5 of 115) were breast fed and all for less than one month.
- The authors concluded that “breastfeeding should be encouraged more widely.”

ARTICLE

Breastfeeding and the Risk of Hospitalization for Respiratory Disease in Infancy

A Meta-analysis

Virginia R. Galton Bachrach, MD, MPH; Eleanor Schwarz, MD, MS; Lela Rose Bachrach, MD, MS

Objective: To examine breastfeeding and the risk of hospitalization for lower respiratory tract disease in healthy full-term infants with access to modern medical care.

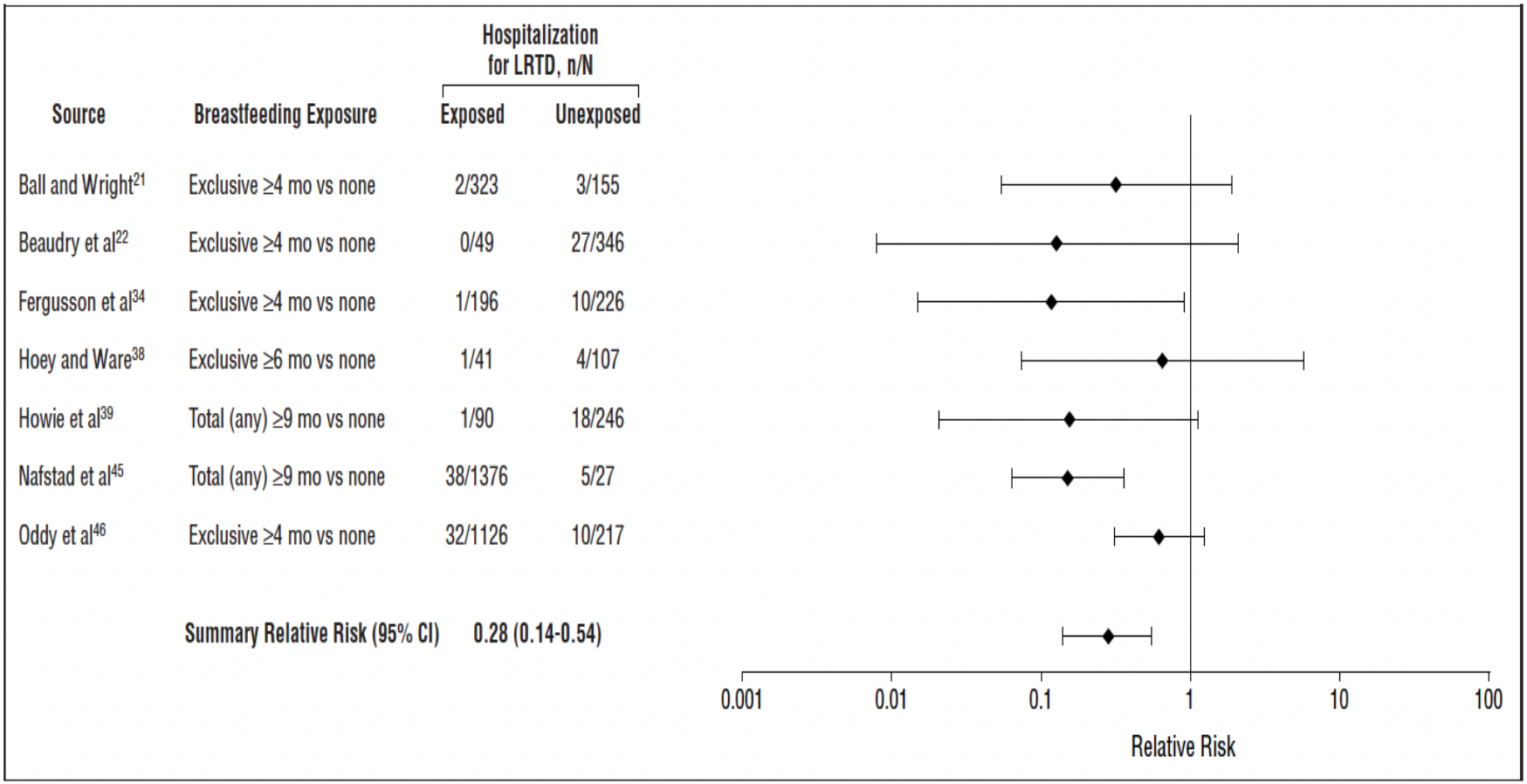
Data Sources: MEDLINE, personal communication with researchers, the OVID databases, Dissertation Abstracts Online, and BIOSIS.

Study Selection: The titles, abstracts, and text of studies from developed countries were explored for breastfeeding exposure measures and lower respiratory tract disease hospitalization rates. For summary statistics, we

Data Synthesis: Data from all primary material (33 studies) indicated a protective association between breastfeeding and the risk of respiratory disease hospitalization. Nine studies met all inclusion criteria, and 7 cohort studies were pooled. The feeding contrasts in these 7 studies were 4 or more months of exclusive breastfeeding vs no breastfeeding. The summary relative risk (95% confidence interval) was 0.28 (0.14-0.54), using a random-effects model. This effect remained stable and statistically significant after adjusting for the effects of smoking or socioeconomic status.

Bachrach, V.R.G., et al. *Arch Pediatr Adolesc* Med (2003) 157: 237-243.

Bachrach, et al. (2003)



Source	Breastfeeding Exposure	Hospitalization for LRTD, n/N: Exposed	Hospitalization for LRTD, n/N: Unexposed
Ball and Wright[21]	Exclusive ≥4 mo vs none	2/323	3/155
Beaudry et al[22]	Exclusive ≥4 mo vs none	0/49	27/346
Fergusson et al[34]	Exclusive ≥4 mo vs none	1/196	10/226
Hoey and Ware[38]	Exclusive ≥6 mo vs none	1/41	4/107
Howie et al[39]	Total (any) ≥9 mo vs none	1/90	18/246
Nafstad et al[45]	Total (any) ≥9 mo vs none	38/1376	5/27
Oddy et al[46]	Exclusive ≥4 mo vs none	32/1126	10/217
	Summary Relative Risk (95% CI)	0.28 (0.14-0.54)	

Figure 1. The risk of hospitalization for lower respiratory tract disease (LRTD) and breastfeeding exposure measures for 7 cohort studies. Breastfeeding diminishes the risk of hospitalization for respiratory disease.

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Original article

Positive association of breastfeeding on respiratory syncytial virus infection in hospitalized infants: a multicenter retrospective study

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Jang, M.J. et al., *Clinical and Experimental Pediatrics* (2020) 63: 135-140.

Jang, et al. (2020)

- Study of 411 infants hospitalized for RSV who had received either breast milk only, infant formula only, or mixed feeding.
- 4.3 percent of exclusively breast fed infants required oxygen compared with 13.5 percent of formula-fed infants.
- 1.1 percent of exclusively breast fed infants required ICU care compared with 4.5 percent of formula-fed infants.

BMJ Global Health

Impact of breastfeeding on the incidence and severity of respiratory syncytial virus (RSV)-associated acute lower respiratory infections in infants: a systematic review highlighting the global relevance of primary prevention

Gabriela M Mineva [1], Helen Purtill [2], Colum P Dunne [3], Roy K Philip [1,4]

Minerva, G.M., et al. BMJ Global Health (2023) doi: 10.1136/bmjgh-2022-009693

Minerva et al. (2023)

- Review of 19 studies involving 16,787 infants from 31 countries.
- Exclusive breast-feeding for 4-6 months decreased RSV-associated out-patient visits, emergency department visits, hospitalizations, and intensive care unit admissions.
- Both the WHO and UNICEF recommend that breast feeding be initiated in the first hour of the child's life and and continue exclusively for 6 months.

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