VRS : a che punto siamo ?

Paolo Manzoni

Professore Associato di Pediatria e Neonatologia

Università degli Studi di Torino

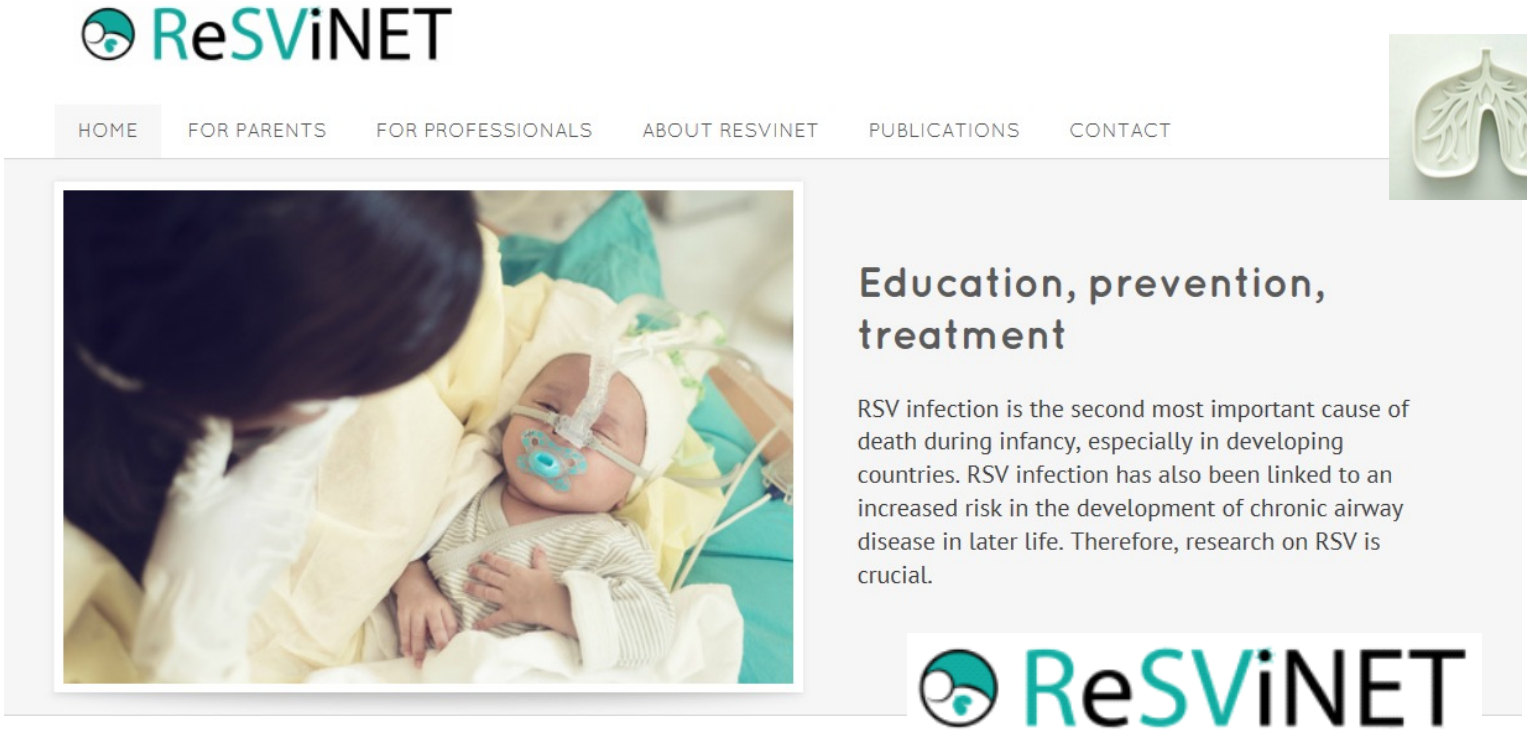
Disclosure

Speaker fees/Advisory Boards fees per:

- AstraZeneca, Sanofi, Pfizer, Moderna, GSK

Membro fondatore dell’Expert International Network on RSV «RESVINET»

Disclosures (2)



ReSViNET is a fully independent research network.

The **mission** is to support performance of high quality research, to improve knowledge of RSV epidemiology, and to develop safe and effective therapeutic and preventive interventions.

http://www.resvinet.org/

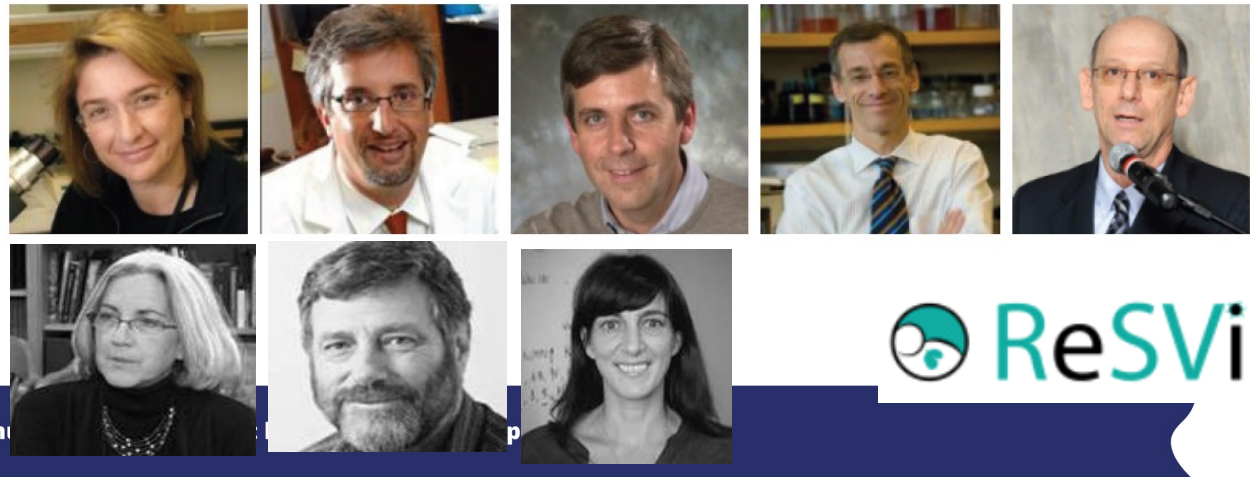
JOINED IN 2014

Board

- Netherlands (1)
- UK (3)
- Italy (2)
- Spain (1)
- Greece (1)
- France (1)
- Finland (1),
- United States (2)
- Argentina (1)
- Brazil (1)
- Australia (1)
- South Africa (1)

RESVINET Board Members

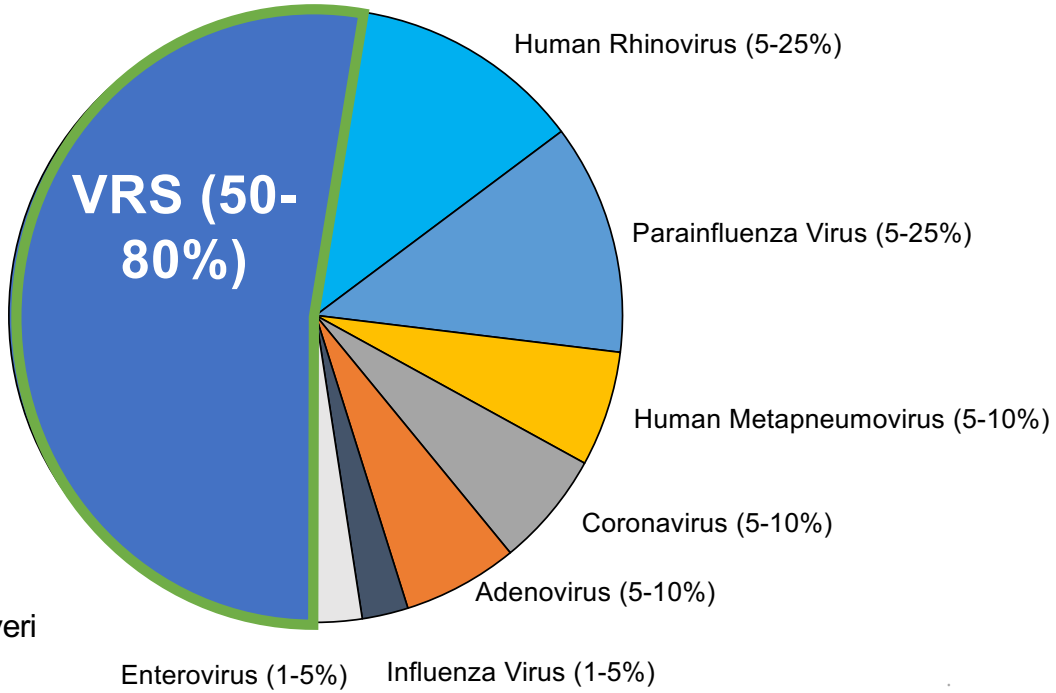
JOINED IN 2015



ReSViNET

Il VRS è la principale causa virale di infezioni del tratto respiratorio inferiore in bambini di età inferiore a 5 anni negli Stati Uniti e nel mondo

Frequenza approssimativa di identificazione del virus in bambini ricoverati con bronchiolite[1]
I tassi di ricovero associato a VRS sono 3 volte superiori a quelli associati ai virus influenzali o parainfluenzali[2]

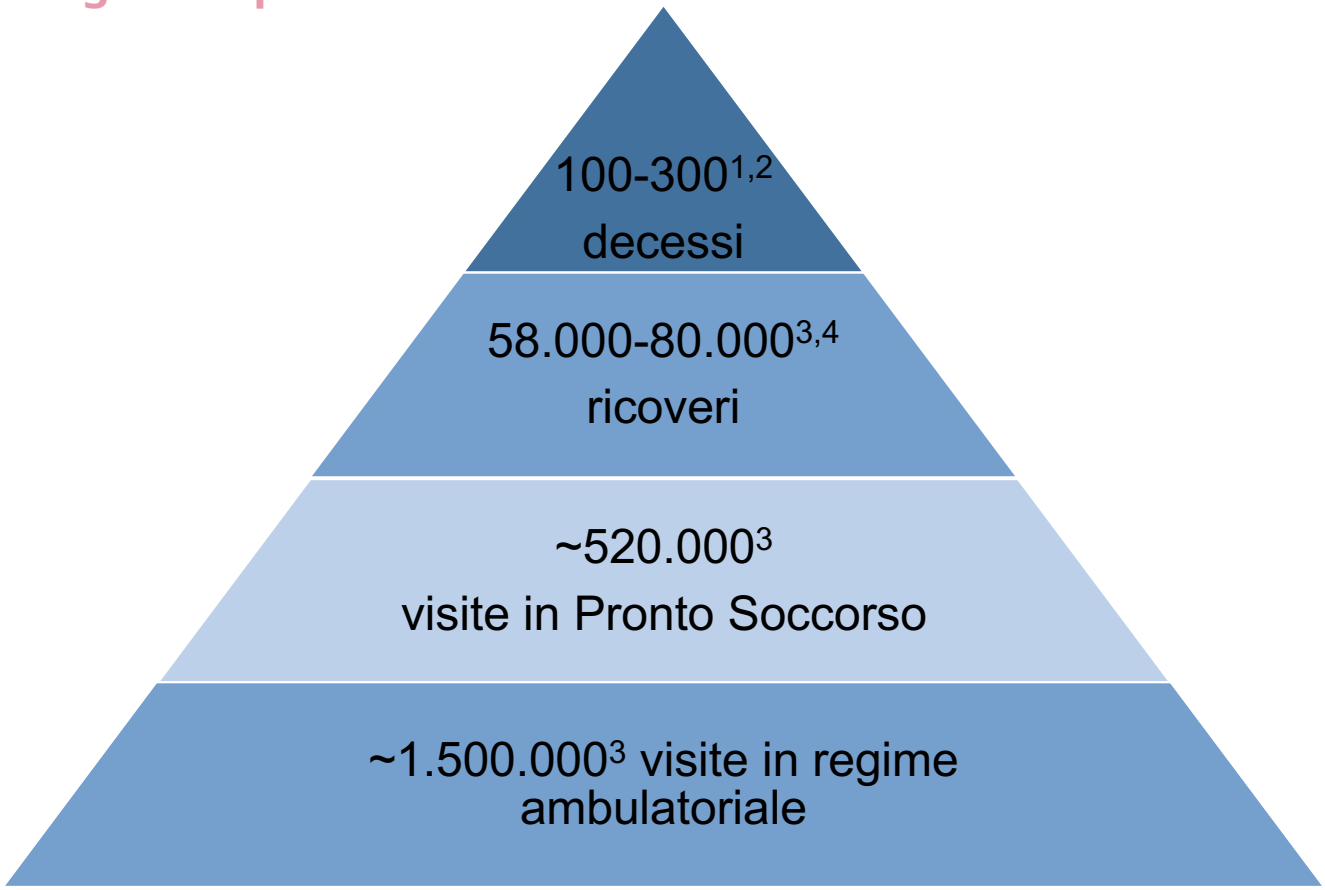


*Esiste una certa variabilità geografica e annuale nella percentuale segnalata di ricoveri per bronchiolite attribuibili a ciascun virus

Nota: dimensionamento del grafico a torta in base al punto medio di ciascun intervallo di frequenza di identificazione segnalato

1. Meissner HC. NEJM. 2016; 374:62-72.

Oltre 2,1 milioni di bambini di età inferiore a 5 anni richiedono assistenza medica ogni anno negli USA per un'infezione da VRS[3]



McMorrow M. RSV seasonality in the United States and the burden of RSV in children. ACIP June 23, 2022. Adattato da: 1. Thompson WW et al. JAMA, 2003. 2. Hansen CL et al. JAMA Network Open, 2022. 3. Hall CB et al. NEJM. 2009, 360(6): 588-98. 4. McLaughlin JM et al. J Infect Dis, 2022 (*80.000 ricoveri stimati in lattanti <1 anno).

Burden di morbidità legato all'infezione da VRS nei bambini negli Stati Uniti: massimo nei molto piccoli

- **La maggior parte (68%) dei lattanti contrae l'infezione nel primo anno di vita e quasi tutti (97%) entro i due anni di età[1]**
- **Il VRS è la causa principale di ricovero nei bambini[2]**
  - Il VRS rende conto del 50-80% di tutti i ricoveri per bronchiolite[3]
  - L'1-2% di tutti i lattanti <6 mesi viene ricoverato per VRS[4]

Gruppi di età	Ricoveri[4] Incidenza per 1.000 (CI)	Visite in regime ambulatoriale	
		Visite in PS[5] Incidenza per 1.000 (CI)	Visite in ambulatorio pediatrico[5] Incidenza per 1.000 (CI)
<2 mesi	18,9 (17,0-20,9)	--	--
<6 mesi	14,7 (13,6-15,9)	74,8 (64,0-85,6)	215,7 (179,8-251,5)
<2 anni	6,3 (5,9-6,7)	59,6 (50,9-68,3)	205,7 (169,5-241,9)

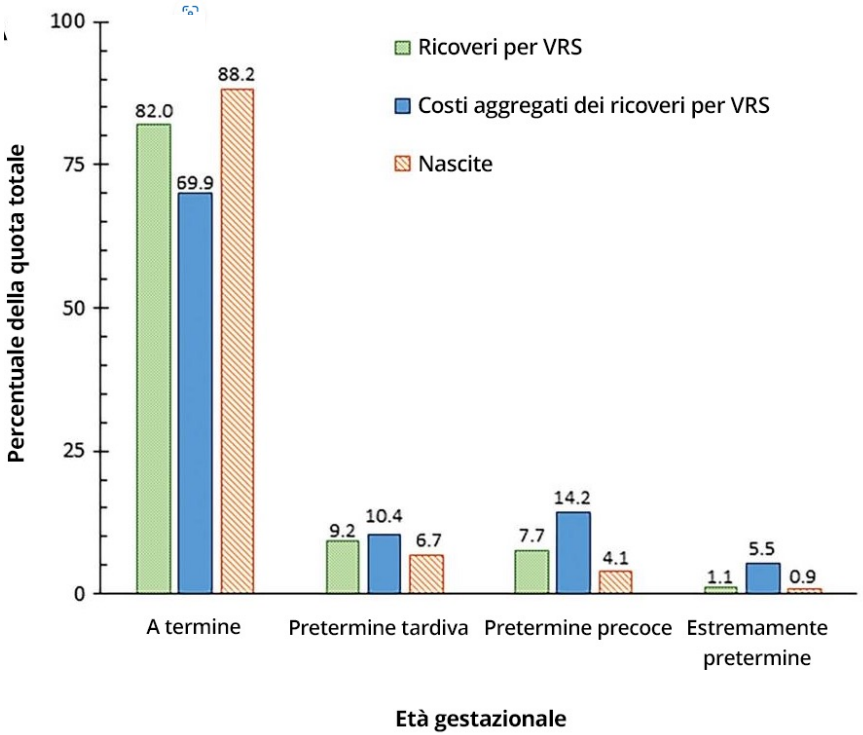
1. Glezen WP. Am J Dis Child 1986; 140:543-6. 2. Hall et al. Pediatrics, 2013. 3. Meissner C. NEJM 2016. 4. Rha B et al. Pediatrics. 2020. 5. Lively J. Journal of Pediatr Infect Dis. 2019.

La maggior parte dei costi aggregati di ricovero per VRS è attribuibile alla cura dei lattanti a termine

- **Revisione sistematica della letteratura statunitense sui ricoveri per VRS nel periodo 2014-2021 in lattanti <1 anno[1]**

- Il VRS rappresenta oltre 39.000 ricoveri/anno, per un costo di 472 milioni di dollari* (11.973 USD/ricovero*)
- I lattanti a termine rappresentano:
  - ~80% dei ricoveri
  - ~70% dei costi di ricovero
- Lattanti estremamente prematuri:
  - Rappresentano i costi di ricovero più elevati per episodio di VRS (5,6 volte quelli dei lattanti a termine)
  - Rappresentano l'1,1% dei ricoveri per VRS e il 5,5% dei costi di ricovero

- **Distribuzione dei ricoveri per VRS di lattanti, costi aggregati e nascite per età gestazionale alla nascita[1]**

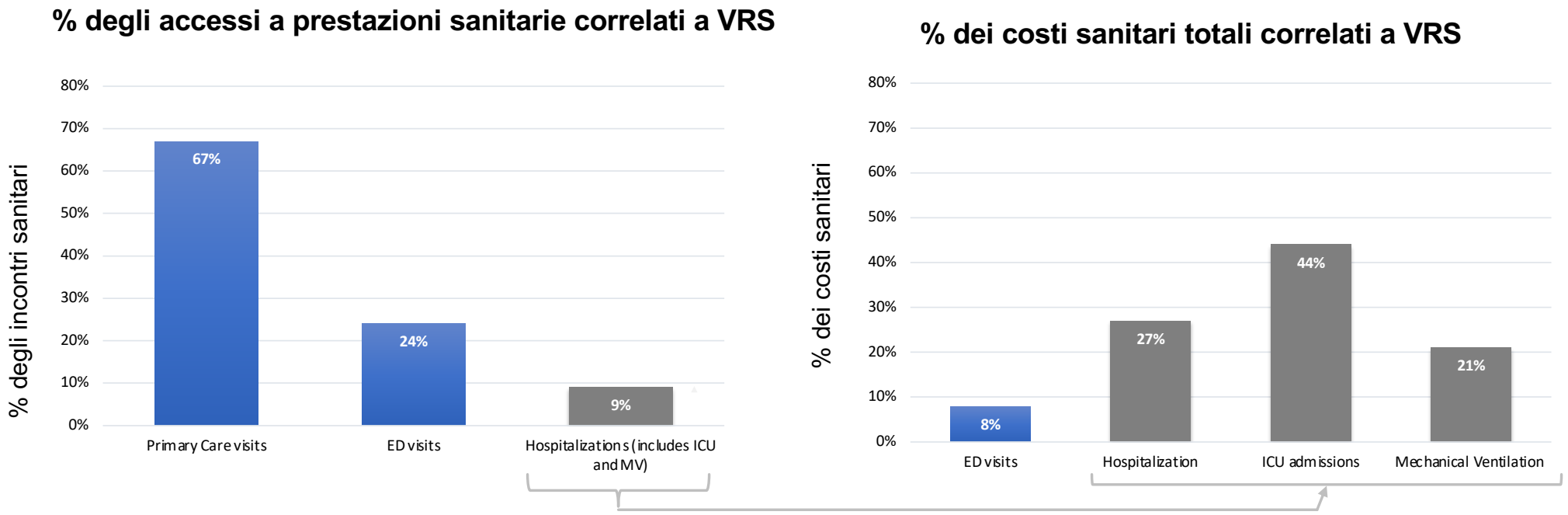


* con aggiustamento al valore del dollaro statunitense a gennaio 2020

1. Bowser DM. JID J Infect Dis 2022;

Il ricovero è il fattore chiave dei costi sanitari legati all'infezione da VRS nei lattanti

- In uno studio, un modello decisionale analitico statico ha stimato i costi totali negli Stati Uniti (visite in regime ambulatoriale, visite in PS e ricoveri) per infezioni da VRS a 1,2 miliardi di dollari (USD 2021)



I ricoveri per VRS costituiscono il 9% degli incontri sanitari legati a VRS e il 92% dei costi sanitari correlati a VRS

1. Kieffer A. J Infect Dis 2022; 226(S2):S282-92.

MATERNAL RISK FACTORS FOR RESPIRATORY SYNCYTIAL VIRUS LOWER RESPIRATORY TRACT INFECTION (RSV-LRTI) IN OTHERWISE HEALTHY PRETERM AND TERM INFANTS : A SYSTEMATIC REVIEW

- **Paolo Manzoni[1], Elsa Viora[2], Marcello Lanari[3], Raffaella Iantomasi[4], Eva Agostina Montuori[4], Barry Rodgers-Gray[5], Nicola Waghorne[5], Bianca Masturzo[6]**
- [1]University of Torino School of Medicine, Department of Maternal-Infant Medicine, "Degli Infermi" Hospital, Ponderano (Biella), Italy; [2]Città della Salute e della Scienza S. Anna Hospital, Torino, Italy (retired); [3]Alma Mater Studiorum - University of Bologna, Pediatric Emergency Unit, Department of Medical & Surgical Sciences, IRCCS- S. Orsola Hospital, Bologna, Italy; [4]Pfizer, Rome, Italy; [5]Violicom Medical Limited, Aldermaston, United Kingdom; [6]Obstetrics and Gynecology Department, Biella Hospital, Italy

- *MANZONI P ET AL. RSVVW'23 | FEBRUARY 22 – 24, 2023 | LISBON, PORTUGAL*

- **OBJECTIVE → To undertake a systematic literature review (SLR) to answer the research question:**
  - ***What maternal risk factors are associated with an increased risk of RSV-LRTI in infants?***

PECOS	Inclusion criteria	Exclusion criteria
Population	- Pregnant or post-partum women	- Not meeting inclusion criteria
Exposure	- Confirmed RSV-LRTI in otherwise healthy* premature/term infants (≤1 year)	- Mixed infections with RSV in otherwise healthy* premature/term infants (≤1 year)
Comparator	- No RSV-LRTI in otherwise healthy* premature/term infants (≤1 year)	- Other (non-RSV) LRTI in otherwise healthy* premature/term infants (≤1 year)
Outcomes	- Association between maternal risk factors and RSV-LRTI	- Not meeting inclusion criteria
Study Design	- Any relevant study design *e.g.* clinical trials, observational studies, systematic reviews *etc.*	- Preclinical studies, case studies, protocols

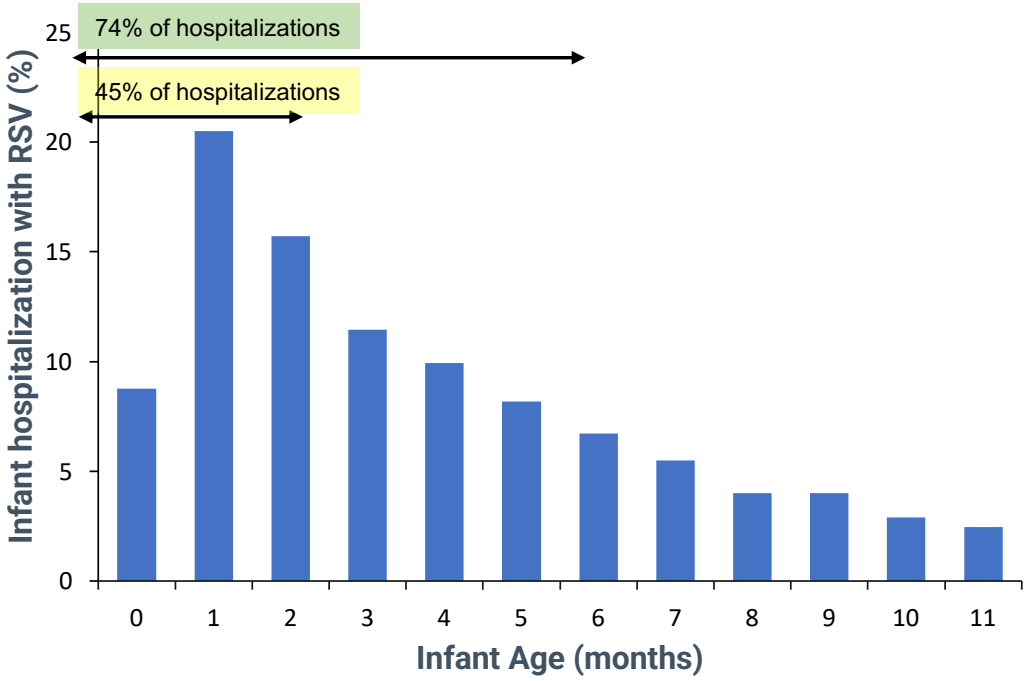
- **RESULTS**
- 50 eligible studies, the majority had a low risk of bias (93%; 41/44),

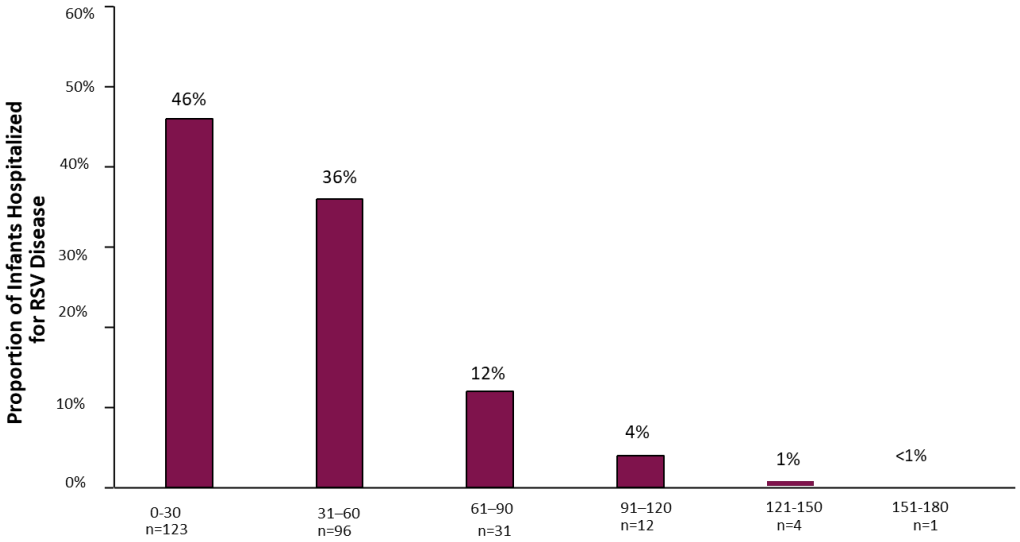
- ***Maternal risk factors***
- In total, 20 maternal risk factors associated with RSV-LRTI were reported in multivariate analyses of the 41 individual studies identified (Table 2)[15-55]
- The most commonly reported risk factor was multiparity (22 studies), albeit the increased risk of RSV-LRTI is likely associated with siblings being a vector for viral transmission
- Three other key risk factors linked with increased rates of RSV-LRTI were smoking while pregnant (8 studies), younger (typically recorded as <25 years) mothers (7 studies), and delivery by caesarean section (6 studies)
- The most notable protective maternal risk factor was breastfeeding for >4 months (8 studies)
-
- Interestingly, multiple birth was associated with both an increased (2 studies) and decreased (3 studies) risk of RSV-LRTI, which is perhaps linked, in part, to younger gestational age exacerbating disease *versus* increased parental shielding of these infants

- Excluding multiparity due to its potential confounding with siblings, the two maternal risk factors reported with a significant association with RSV-LRTI in meta-analyses are:

1. **Smoking while pregnant: OR 1.4-1.7**
2. **No breastfeeding: OR 2.2**

I neonati sono più vulnerabili per VRS nei primi 6 mesi di vita e Il Timing tra la nascita e l'ospedalizzazione per RSV è spesso molto breve (meno di 60 giorni)





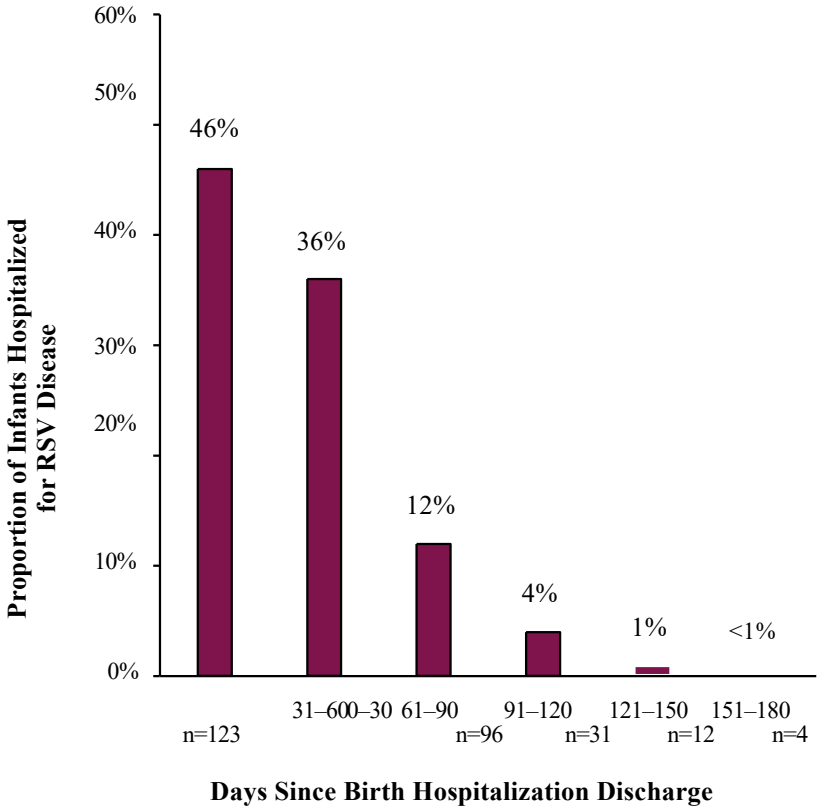
Study Design: Observational study of RSVH in the first year of life among US Infants born 29-35 wGA who were not receiving RSV immunoprophylaxis (2014-2015 RSV season).

ICU: intensive care unit; IMV: invasive mechanical ventilation; NICU; neonatal ICU; wGA: weeks gestational age.

Reeves RM, et al. J Infect. 2019;78(6):468-475.

Anderson EJ et al. Am J Perinatol. 2017;34:51-61.

Infants need anti-RSV antibodies immediately after birth: Timing Between In-Season Birth Discharge and RSV Hospitalization is very short (less than 60 days)



For infants discharged from birth hospitalization during the RSV season (Nov-Mar):

- 46% of all RSV-confirmed hospitalizations occurred within 30 days of birth hospital discharge
- 82% of all RSV-confirmed hospitalizations occurred within 60 days of birth hospital discharge

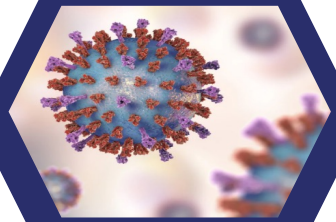
Study Design: Observational study of RSVH in the first year of life among US Infants born 29-35 wGA who were not receiving RSV immunoprophylaxis (2014-2015 RSV season).

ICU: intensive care unit; IMV: invasive mechanical ventilation; NICU; neonatal ICU; wGA: weeks gestational age.

Anderson EJ et al. *Am J Perinatol.* 2017;34:51-61.

Incidenza RSV nei neonati e bambini alla loro prima stagione epidemica

Infezione da RSV



~ 100%

Incidenza infezione[1]

Visite ambulatoriali per infezione da RSV

>20%

Incidenza assistenza medica ambulatoriale[1-2]

Accessi in Pronto Soccorso per infezione da RSV

6%

Incidenza accesso in PS[1-2]

Ospedalizzazione per infezione da RSV

4%

Incidenza ricovero in ospedale[1,3]

Azzari C, Baraldi E, Bozzola E, Bonanni P, Coscia A, Lanari M, Mazzone T, Piacentini G, Mosca F, et al. Epidemiology and prevention of RSV in Italy. Ital J Pediatr 47, 198 (2021).
Lively JY, Curns AT, Weinberg GA, et al. Respiratory Syncytial Virus-Associated Outpatient Visits Among Children Younger Than 24 Months. J Pediatric Infect Dis Soc. 2019;8(3):284-286.
Heppe Montero M, et al. Burden of severe bronchiolitis in children up to 2 years of age in Spain from 2012 to 2017. Hum Vaccin Immunother. 2022 Dec 31;18(1):1883379.

Current and Potential Strategies for RSV Disease Prevention in Infants

NOT-SPECIFIC MEASURES

- Hygiene measures
- Breastfeeding
- Vitamin D

Active immunisation

- Live attenuated virus
- Subunit vaccine

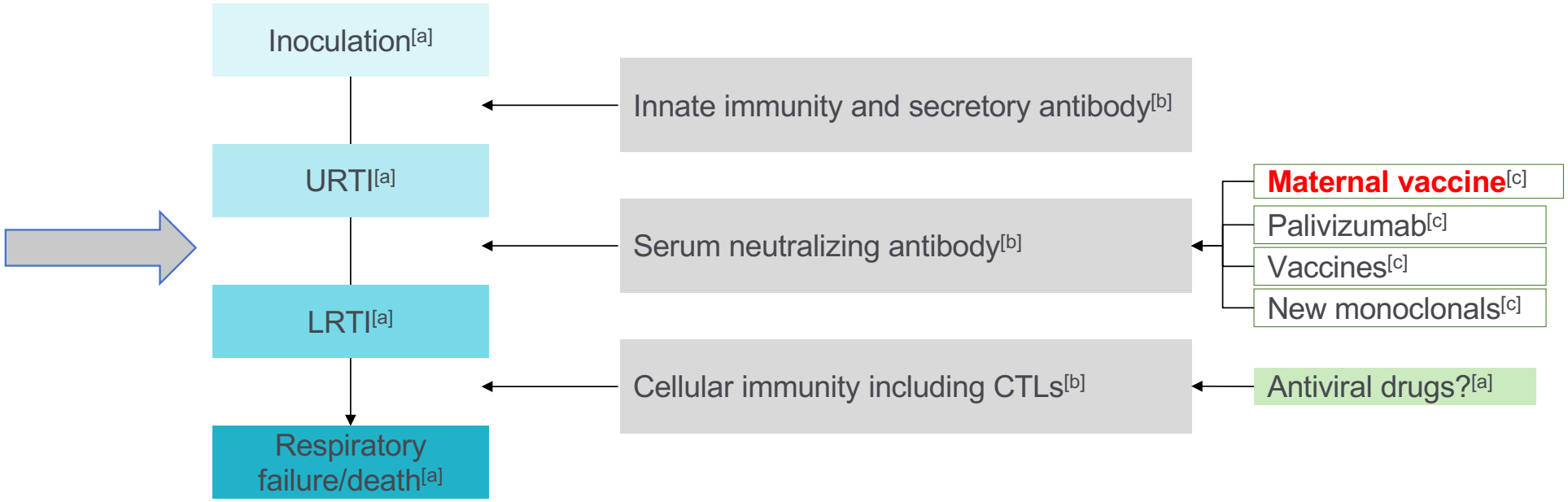
Passive immunisation

- Maternal immunisation
- Palivizumab
- Long-acting monoclonal antibodies

Abrysvo, vaccino anti RSVpreF, Classe Cnn Medicinale in commercio dal 1° Marzo 2024

Mazur NI, et al. Lancet Infect Dis. 2023;23(1):e2-e21. 2. Esposito S et al. Front Immunol. 2022;13:880368.

Mechanisms of Progression of RSV Infection in Infants

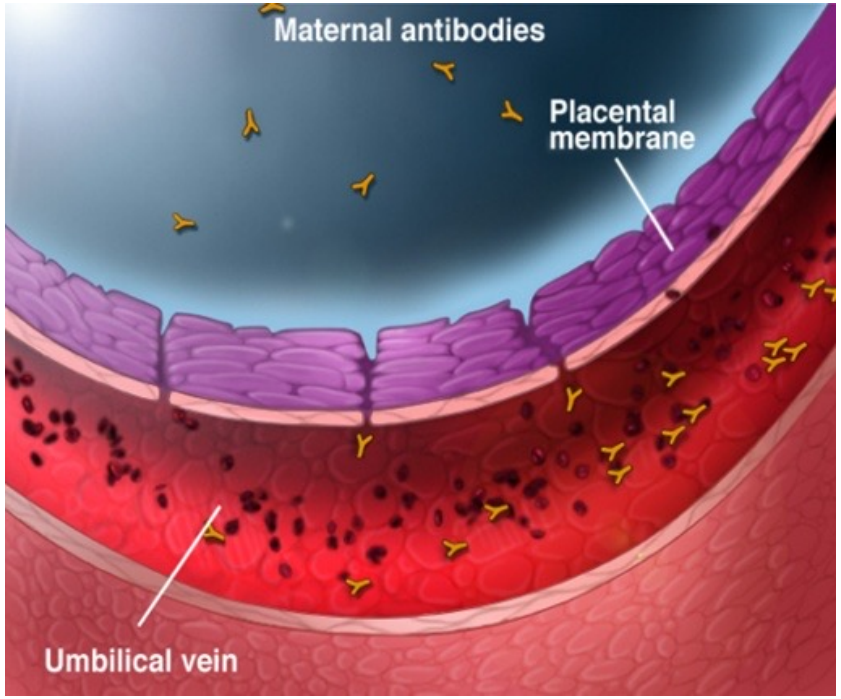


CTL, cytotoxic T-lymphocyte; LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; URTI, upper respiratory tract infection.

a. Jain H, et al. Respiratory Syncytial Virus Infection. In: StatPearls [Internet]. StatPearls Publishing; 2023. Updated Nov 8, 2022. Accessed January 30, 2023. https://www.ncbi.nlm.nih.gov/books/NBK459215/; b. Russell CD, et al. Clin Microbiol Rev. 2017;30:481-502; c. Gunatilaka A, et al. Hum Vaccin Immunother. 2021;17:4542-4548.

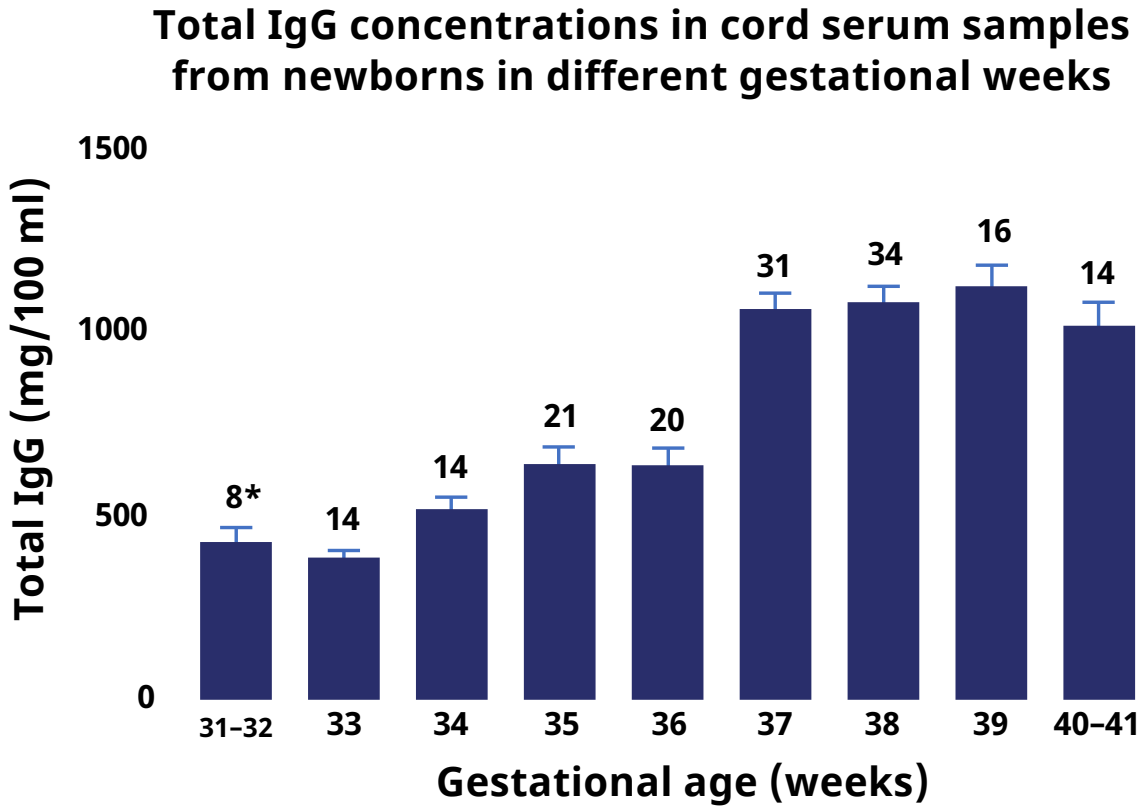
Maternal anti-RSV Antibody Placental transfer during pregnancy

- Anti-RSV Antibody transfer occurs during the third trimester (after 28 weeks)
- Antibody levels at birth are proportional to gestational age
- Antibody levels are also influenced by birthweight, independent of gestational age



Yeung CY, Hobbs JR. Lancet. 1968
Okoko JB, et al. Trop Med Int Health. 2001

Transfer of maternal anti-RSV IgG is linearly associated with gestational age at birth



*Number of samples in each period.
IgG, immunoglobulin G.

Figure adapted from Palmeira P, et al. Clin Dev Immunol. 2012;2012:985646.

Palmeira P, et al. Clin Dev Immunol. 2012;2012:985646

RSV Transplacental Antibody Transfer and Kinetics in Mother-Infant Pairs

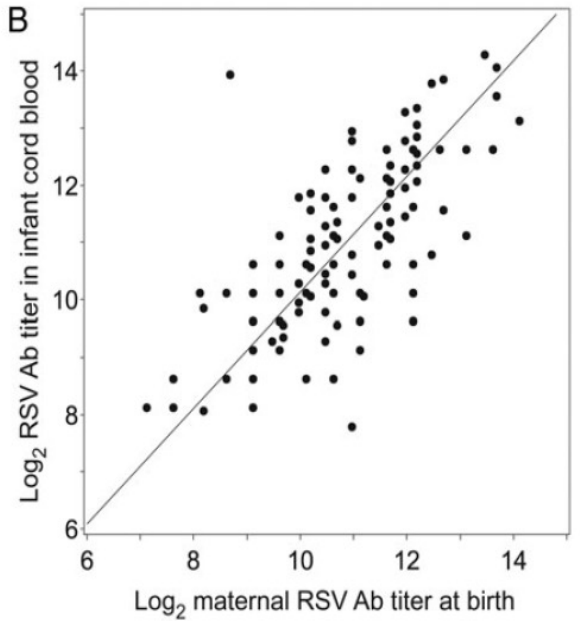
149 mother-infant pairs in Bangladesh

A microneutralization assay, RSV/A2, ELISA endpoint

Ratio of infant cord blood to maternal serum RSV Nt Ab titer was 1.01; 95% CI: 0.99-1.03

Antibody half-life: 38 days; (95% CI, 36-42 days)

Median time to reduction of titer below a potentially protective level : 17 weeks



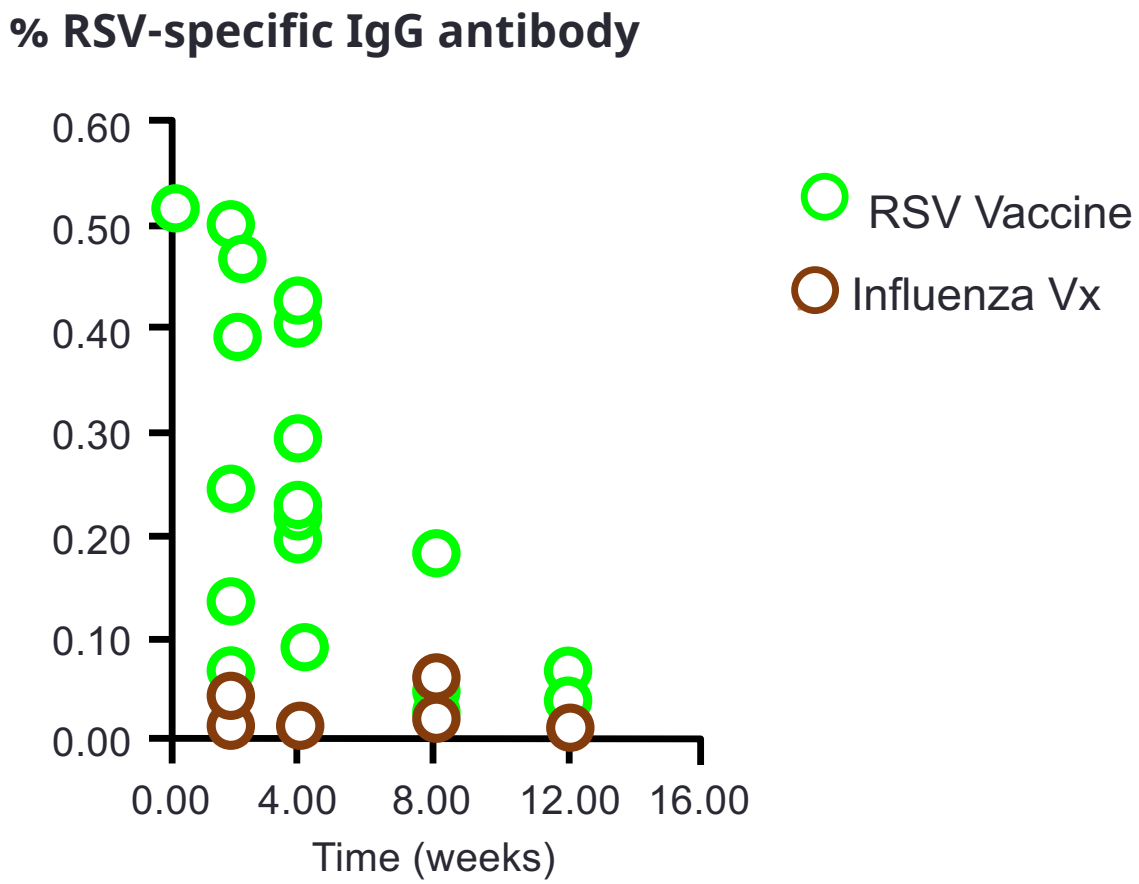
Chu HY, et al. *J Infect Dis* 2014; 210: 1582–9.

Serum concentrations of specific anti-RSV antibodies in the newborn: a serum concentration of specific antibodies 2 to 4 times lower in infants who have RSV disease is observed, compared with those who do not get sick from RSV

RSV Antibody Titer		Assay Method	Article
No RSV disease	RSV disease		
652.6	198.1	Membrane Fluores-cent Antibody Test	Ogilvie, J Med Vir 1981 7:263 Maternal Ab & RSV
92	9.5	Neutralizing Ab	Glezen, J Ped 1981 98:708
40.00 44.16	11.08 11.37	MFAT Neutralizing Ab	Roca, J Med Vir 2002 67:616 IgG Mozambique
238.9	68.6	Neutralizing Ab	Piedra, Vaccine 2003 21:3479 Correlates of imm
538.0	392.1	Neutralizing Ab	Eick, Ped Inf Dis J 2008 27:207 Native Americans
1047	646	ELISA	Ochola, PLOS One 2009 4:e8088 Infants in Kenya

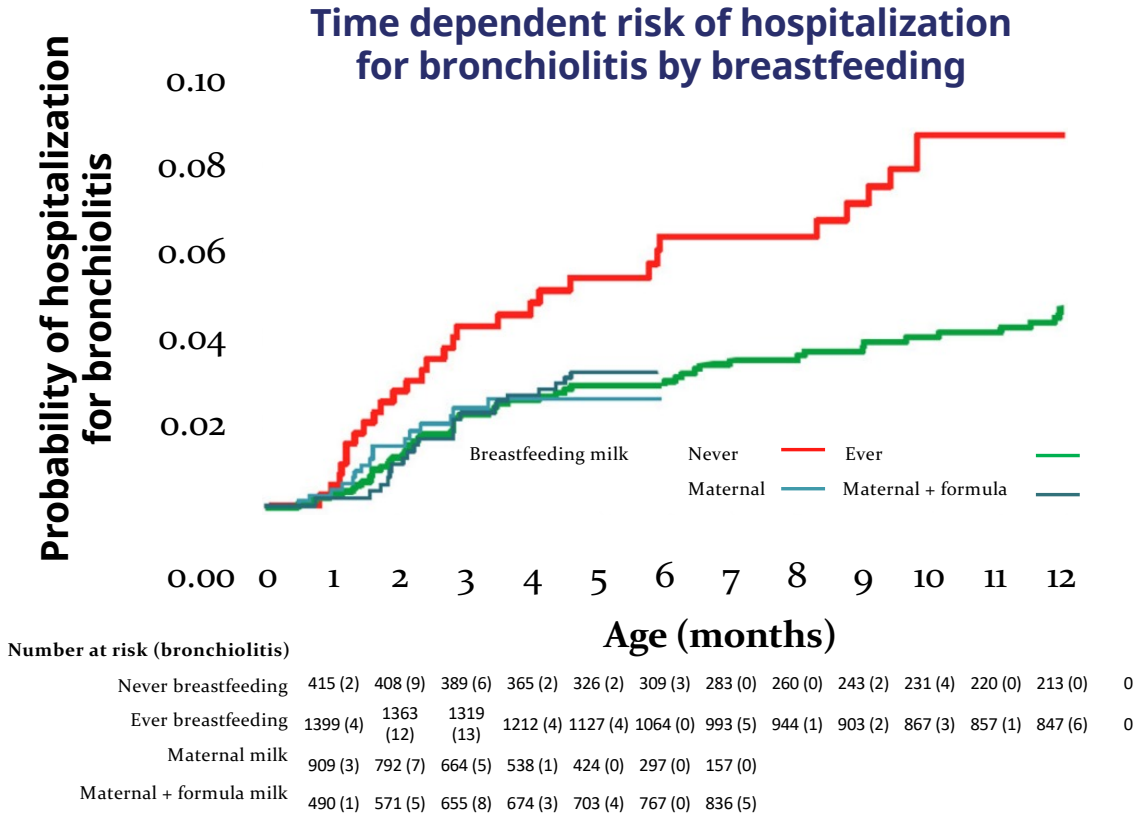
Reduced incidence of RSV disease in neonates during the first several months after birth correlates with higher concentrations of RSV-specific maternal antibodies

Role of Breast Feeding:
Breast milk IgG following RSV PFP-2 or TIV in Postpartum women



Glezen, WP, Vaccine 2003

Maternal milk protects infants against bronchiolitis during the first year of life: results from an Italian cohort of newborns



- Prospective database of 30 neonatology units
- 1,814 preterms >33 wGA
- Follow-up interview at 12 months
- “Never breastfed” at multivariate analysis = OR 1.57 (95% CI: 1–2.48)

CI, confidence interval; OR, odds ratio; wGA, weeks gestational age.
Lanari M, et al. Early Hum Dev. 2013;89 Suppl 1:S51–57.

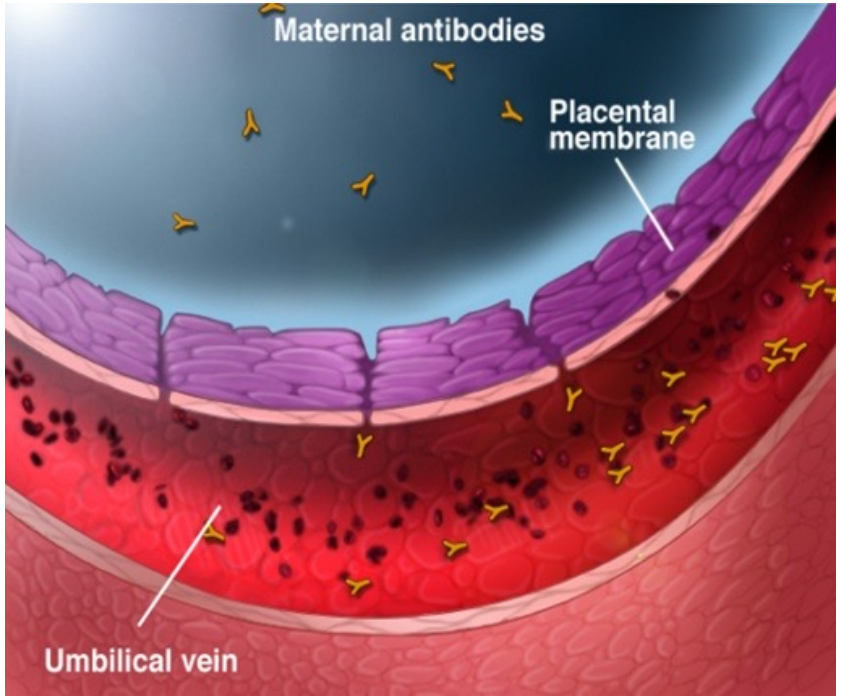
Rationale of Maternal immunization

Mechanisms of protection of the infant

1. **Transplacental transfer** (TAT) of vaccine-derived maternal antibody: direct fetal/infant protection against infection via the transport of specific antibodies to the fetus prior to birth
2. **Cocooning (**i.e., protect the mother directly against RSV infections, and hence her baby)
3. Transfer of maternal antibody also after birth, through **breast-milk**.

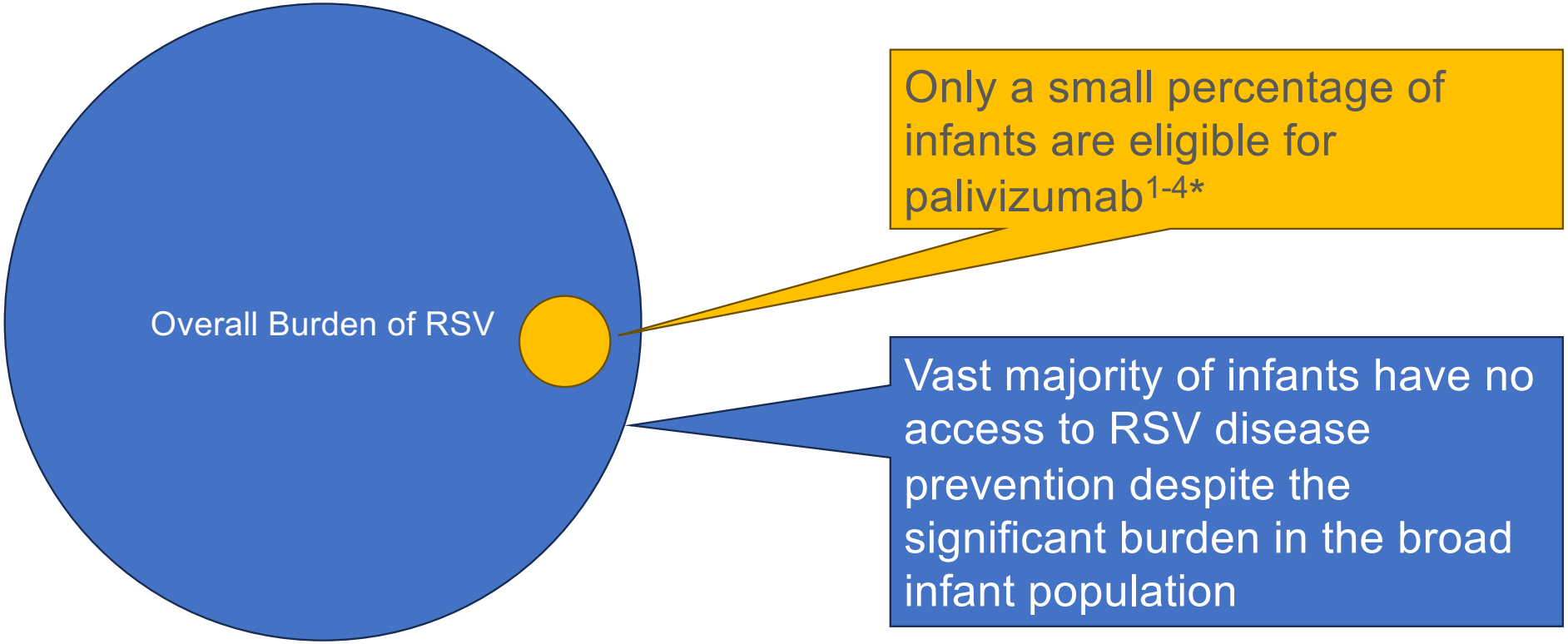
Maternal Antibody Placental transfer during pregnancy

- Antibody transfer occurs during the third trimester (after 28 weeks)
- Antibody levels at birth are proportional to gestational age
- Antibody levels are also influenced by birthweight, independent of gestational age



Yeung CY, Hobbs JR. Lancet. 1968
Okoko JB, et al. Trop Med Int Health. 2001

Current prevention strategies for RSV: Monoclonal antibodies as a prophylaxis for specific high-risk pediatric populations



MAT-GLB-2302467 (v1.0) June 2023

*<5% based on the US recommendation. Recommendations vary by country/geography.

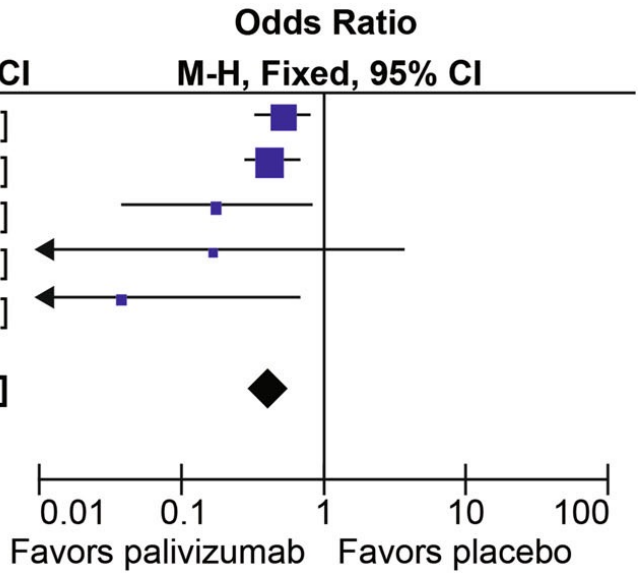
1. Synagis (SmPC). 2022. **2.** American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. *Pediatrics*. 2014;134(2):e620-e638. **3.** Hall CB, et al. *N Engl J Med*. 2009;360(6):588-598. **4.** Rha B, et al. *Pediatrics*. 2020;146(1):e20193611.

Efficacy of Palivizumab on RSV-Hospitalisation
Systematic Reviews

Study or Subgroup	Palivizumab Events	Palivizumab Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Cardiac 2003	34	639	63	648	39.5%	0.52 [0.34, 0.80]
IMpact-RSV 1998	48	1002	53	500	44.9%	0.42 [0.28, 0.64]
MAKI 2013	2	214	11	215	7.2%	0.17 [0.04, 0.80]
Subramanian 1998	0	22	2	20	1.7%	0.16 [0.01, 3.64]
Tavsu 2014	0	39	10	41	6.7%	0.04 [0.00, 0.67]
Total (95% CI)		**1916**		**1424**	**100.0%**	**0.41 [0.31, 0.55]**
Total events	84		139			

Heterogeneity: $Chi^2=5.34$, df=4 ($P = 0.25$); $I^2=25\%$

Test for overall effect Z=6.08 ($P < 0.00001$)



Authors' Conclusion (most recent Cochrane Review):

"Palivizumab is effective in reducing the frequency of hospitalizations due to RSV ie. the incidence of serious lower respiratory tract RSV disease in children with chronic lung disease, congenital heart disease, or ***those born preterm***"[b]

M-H, Mantel-Haenszel method; RSV, respiratory syncytial virus.

a. Wegzyn C, et al. Infect Dis Ther. 2014;3(2):133-158; b. Andabaka T, et al. Cochrane Database Syst Rev. 2013;(4):CD006602.

Systematic Review of Real-World Studies of RSV Hospitalizations Among Moderate/Late Preterm Infants Exposed or Not Exposed to Palivizumab

Study	Study design and dates	Gestational age, weeks	Infants, n	RSVH, n/N (%)		Rate ratio	*P* value	Reported, OR (95% CI)	Reported compliance
				With palivizumab	Without palivizumab				
Pedraz et al, 2003, Spain	Prospective cohort vs historical control, 1998–2002	29–32	2467	30/1170 (2.5%)	129/1297 (9.9%)	4.0	< .0000	3.86 (2.83–5.25)	91%
Banerji et al, 2014, Canada	Prospective cohort, 2009–2010	29–35	101	2/91 (2.2%)	5/10 50%	22.7	.0005	22.3 (3.8–130)	Implied
Priante et al, 2019, Italy	Retrospective cohort, multicenter, 2015–2017	29-35	536	3/148 (2.0%)	16/388 (4.1%)	2.1	–	–	NA
Newby and Sorokan, 2017, Canada	Retrospective cohort, single center, 2008–2011	29–32	297	2/46 (4.3%)	14/251 (5.6%)	1.3	–	–	NA
Cetinkaya et al, 2017, Turkey	Prospective cohort, 2015–2016	29–35	110	0/9 (0%)	19/101 (18.8%)	–	–	–	Required
Rajah et al, 2017, USA	Retrospective cohort, single center, 2013–2015	29–35	91	5	86	NA	–	–	NA

NA, not available; OR, odds ratio; RSVH, RSV-related hospitalization.
Manzoni P, et al. Am J Perinatol. 2022;39(suppl S1):S7-S13.

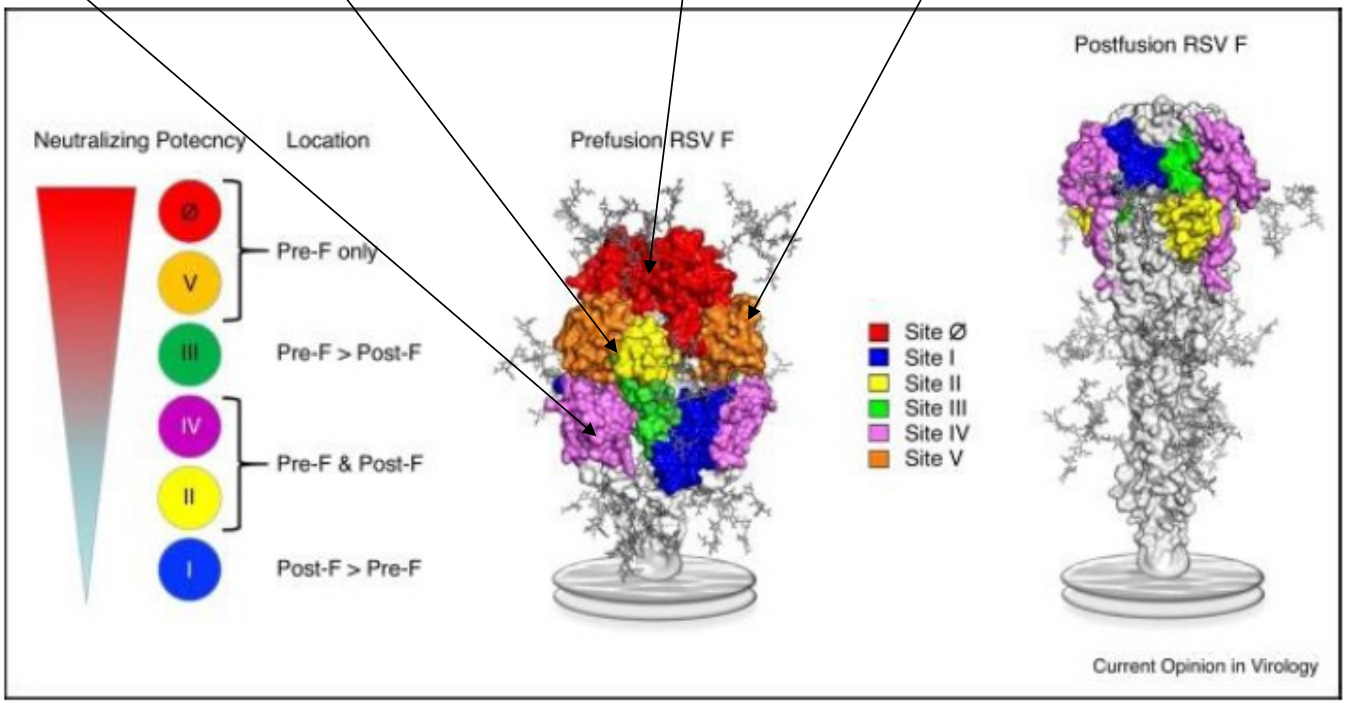
What Are the Targets for the mAbs Against RSV?

CLESROVIMAB
Site IV

PALIVIZUMAB
Site II

NIRSEVIMAB
Site 0

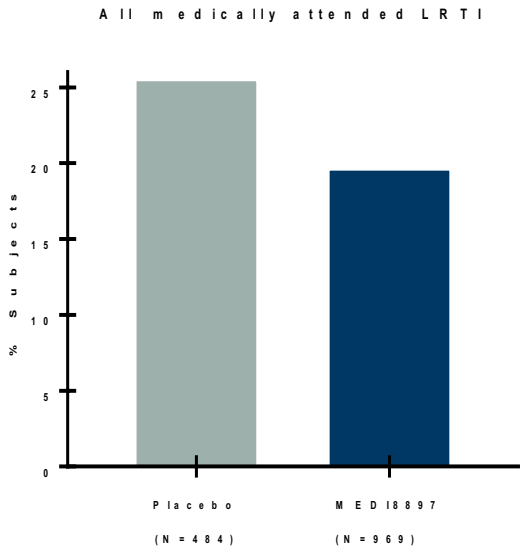
SUPTAVUMAB
Site V

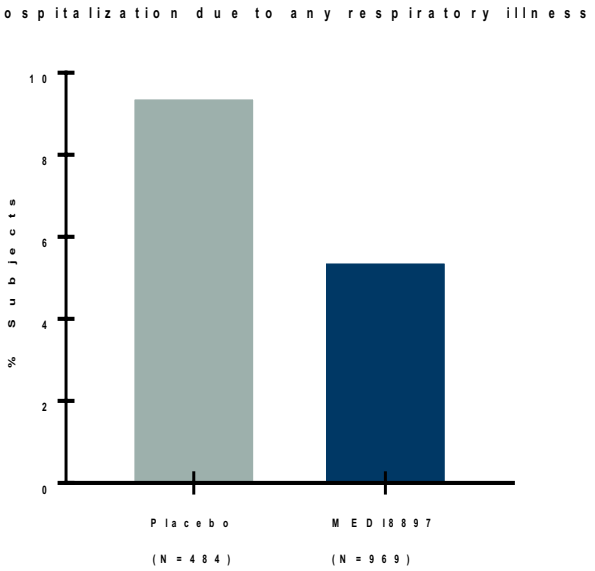


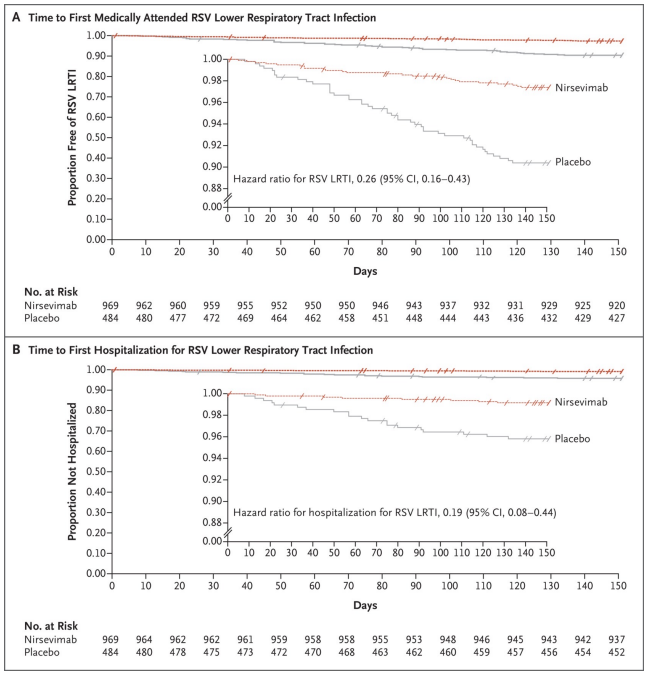
Palivizumab, investigational mAb candidates like clesrovimab and nirsevimab, and most RSV vaccine candidates share this mechanism - targeting the RSV Fusion (F) protein

Graham BS, et al. Curr Opin Virol. 2017 ;23:107-112; Swanson KA, et al. Proc Natl Acad Sci U S A. 2011;108:9619-24; McLellan JS, et al. Science. 2013 ;342:592-8

Passive Prophylaxis against RSV in Neonates transates into a significant decrease of hospitalizations due to <u>any</u> respiratory illness in the first 5 months of life







Griffin et al, NEJM 2019

November 4 , 2022

EMA Approval for Nirsevimab use for ALL neonates and infants

Press Release

sanofi

European Commission grants first approval worldwide of Beyfortus® (nirsevimab) for prevention of RSV disease in infants

- Beyfortus is the first and only broadly protective option against RSV for newborns and infants
- Results from the clinical development program reinforce Beyfortus' consistency in reducing RSV infections requiring medical care, including hospitalizations

Paris, November 4, 2022. The European Commission has approved Beyfortus® (nirsevimab) for the prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in newborns and infants during their first RSV season. RSV is a common and highly contagious seasonal virus, infecting nearly all children by the age of two.[1,2] Beyfortus is the first and only single-dose RSV protective option for the broad infant population, including those born healthy, at term or preterm, or with specific health conditions. Beyfortus is being developed jointly by Sanofi and AstraZeneca.

Nirsevimab use in Spain 2023-24

Recomendaciones de utilización de nirsevimab frente a virus respiratorio sincitial para la temporada 2023-2024

Ponencia de Programa y Registro de Vacunaciones 2023

Julio 2023

Consejo Interterritorial
SISTEMA NACIONAL DE SALUD

GOBIERNO DE ESPAÑA
MINISTERIO DE SANIDAD

Therefore, after conducting a literature review and an evaluation of the use of nirsevimab in the population under 1 year of age, nirsevimab is recommended in the following population groups only for this season 2023-2024, prioritised as follows:

1. **Paediatric population at high risk of developing serious disease from RSV infection**, including: (a) preterm infants with <35 weeks gestational age (a single dose should be administered before 12 months of age); (b) patients with congenital heart disease (cyanotic and non-cyanotic) with significant hemodynamic involvement, (c) patients with bronchopulmonary dysplasia, and (d) patients with other underlying diseases with high risk of developing serious RSV bronchiolitis (see diseases in the recommendations section). In patients with underlying risk conditions b, c and d, nirsevimab should be administered before each RSV season before 24 months of age at the time of immunisation.
2. **Under 6 months of age** at the start of or during RSV season: For the 2023-2024 season, nirsevimab is recommended in children under 6 months of age born from 1 April 2023 until 31 March 2024. Priority will be given to immunise those born during the season and those born previously will be immunised as early as possible (October).

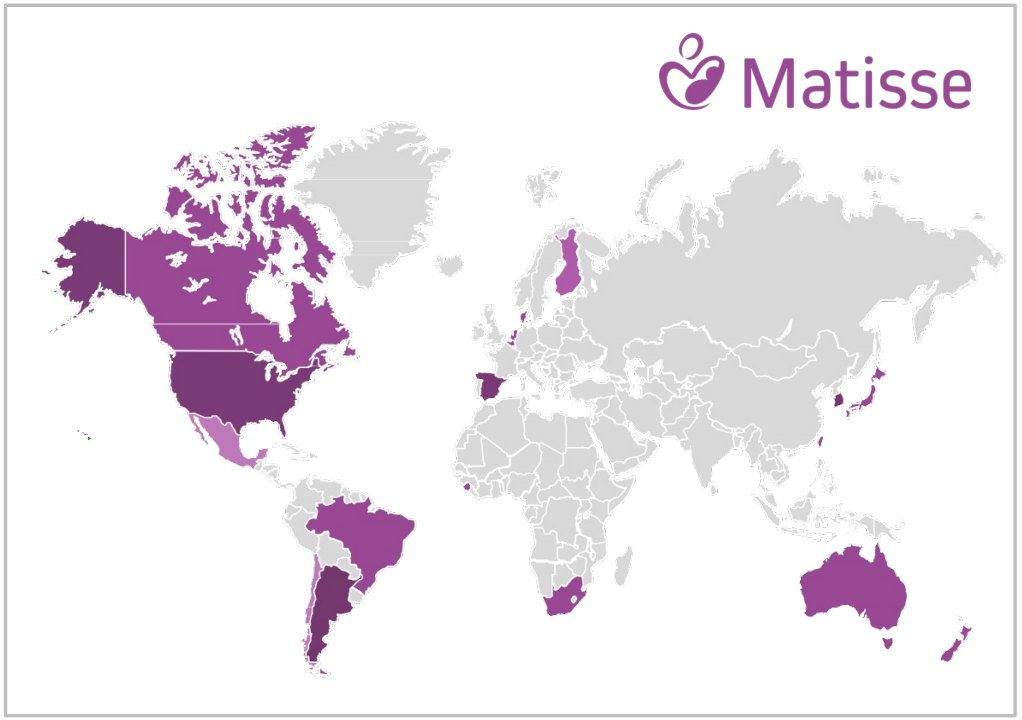
The majority of the target population should be immunised at the beginning of the RSV season (in October). In addition, those born during RSV season (October - March) should receive nirsevimab very early from birth (preferably within the first 24-48 hours from birth) due to the increased risk of developing serious disease from RSV infection in the first days of life.

MATISSE: A Phase 3 Trial to Evaluate the Efficacy and Safety of RSVpreF in Infants Born to Women Vaccinated During Pregnancy

7,392 Maternal Participants in 18 Countries
Randomized 1:1 RSVpreF 120µg or Placebo

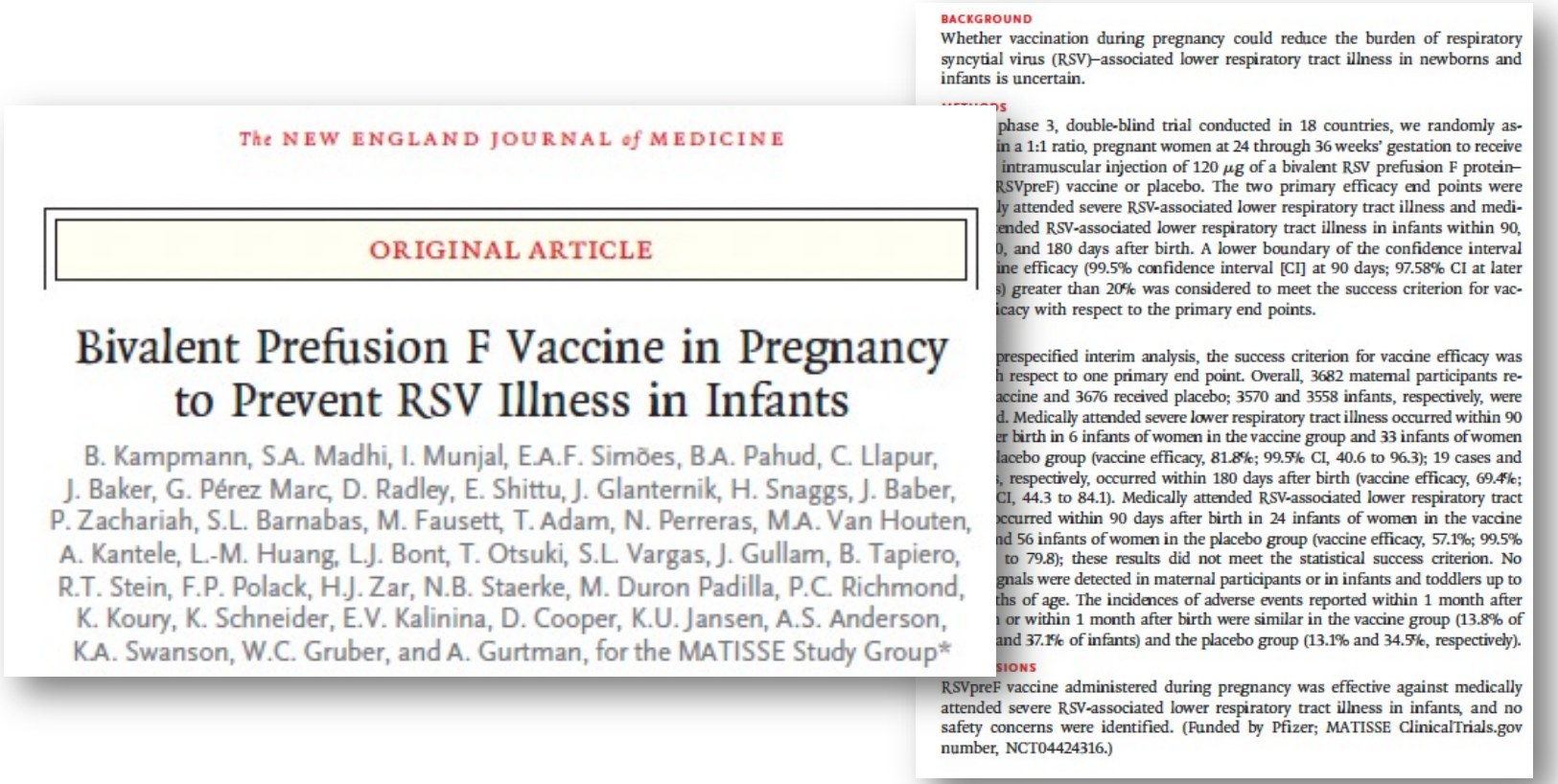
Pregnant persons ≤49 years between ≥24 and ≤36 weeks gestation

7,128 Infants enrolled



Source: A Trial to Evaluate the Efficacy and Safety of RSVpreF in Infants Born to Women Vaccinated During Pregnancy. NCT04424316

Results published in February 2023



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

B. Kampmann, S.A. Madhi, I. Munjal, E.A.F. Simões, B.A. Pahud, C. Llapur, J. Baker, G. Pérez Marc, D. Radley, E. Shittu, J. Glanternik, H. Snaggs, J. Baber, P. Zachariah, S.L. Barnabas, M. Fausett, T. Adam, N. Perreras, M.A. Van Houten, A. Kantele, L.-M. Huang, L.J. Bont, T. Otsuki, S.L. Vargas, J. Gullam, B. Tapiero, R.T. Stein, F.P. Polack, H.J. Zar, N.B. Staerke, M. Duron Padilla, P.C. Richmond, K. Koury, K. Schneider, E.V. Kalinina, D. Cooper, K.U. Jansen, A.S. Anderson, K.A. Swanson, W.C. Gruber, and A. Gurtman, for the MATISSE Study Group*

BACKGROUND

Whether vaccination during pregnancy could reduce the burden of respiratory syncytial virus (RSV)–associated lower respiratory tract illness in newborns and infants is uncertain.

phase 3, double-blind trial conducted in 18 countries, we randomly as-
in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive
intramuscular injection of 120 μg of a bivalent RSV prefusion F protein–
RSVpreF) vaccine or placebo. The two primary efficacy end points were
ly attended severe RSV-associated lower respiratory tract illness and medi-
ended RSV-associated lower respiratory tract illness in infants within 90,
0, and 180 days after birth. A lower boundary of the confidence interval
ine efficacy (99.5% confidence interval [CI] at 90 days; 97.58% CI at later
s) greater than 20% was considered to meet the success criterion for vac-
icacy with respect to the primary end points.

prespecified interim analysis, the success criterion for vaccine efficacy was
h respect to one primary end point. Overall, 3682 maternal participants re-
accine and 3676 received placebo; 3570 and 3558 infants, respectively, were
d. Medically attended severe lower respiratory tract illness occurred within 90
r birth in 6 infants of women in the vaccine group and 33 infants of women
lacebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and
, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%;
CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract
ccurred within 90 days after birth in 24 infants of women in the vaccine
nd 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5%
to 79.8); these results did not meet the statistical success criterion. No
gnals were detected in maternal participants or in infants and toddlers up to
ths of age. The incidences of adverse events reported within 1 month after
or within 1 month after birth were similar in the vaccine group (13.8% of
and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).

SIONS

RSVpreF vaccine administered during pregnancy was effective against medically attended severe RSV-associated lower respiratory tract illness in infants, and no safety concerns were identified. (Funded by Pfizer; MATISSE ClinicalTrials.gov number, NCT04424316.)

Phase 3, double-blind, randomised, placebo-controlled trial that was conducted over four RSV seasons to evaluate the efficacy and safety of maternal RSVpreF immunisation against MA-LRTI in infants followed for 1–2 years. Eligible participants were healthy women, ≤49 years, at 24 through 36 weeks' gestation on the day of planned injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications. Eligible women were randomly assigned, in a 1:1 ratio, to receive a single IM injection of 120 μg of RSVpreF vaccine (60 μg each of RSV A and RSV B antigens) or placebo.

IM, intramuscular; RSVpreF, respiratory syncytial virus prefusion F protein.

Kampmann B, et al. *N Engl J Med*. 2023. doi: 10.1056/NEJMoa2216480

The MATISSE TRIAL
Bivalent Prefusion F Vaccine

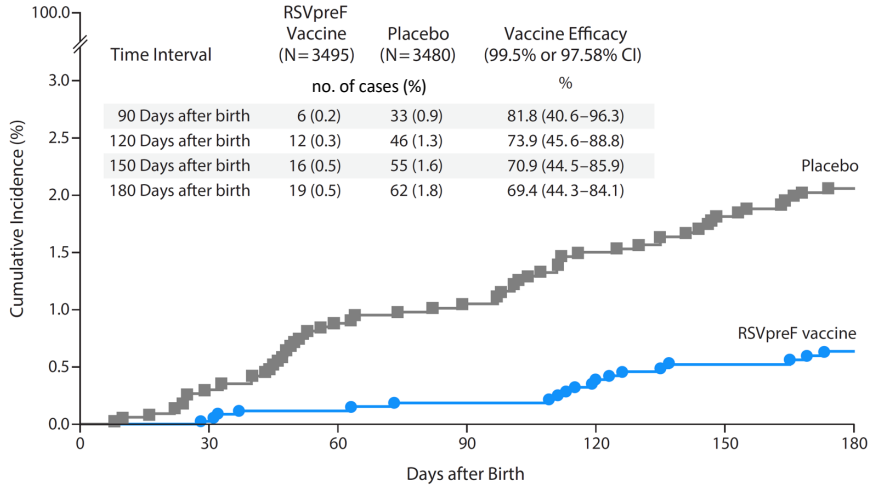
- Phase 3, randomised, double-blind, placebo-controlled trial
- International - 18 countries, over 4 RSV seasons
- Eligible participants were healthy women, ≤49 years, at 24 through 36 weeks' gestation on the day of planned injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications
- Infants were followed for 1–2 years for efficacy outcomes.
- Total participants > 7,500 : 3682 pregnant women received RSVpreF vaccine, and 3676 received placebo

• Kampmann B, et al. N Engl J Med. 2023;388:1451-1464

MATISSE Study:
Maternal RSV Vaccine in Infants <6 Months

Medically Attended Severe RSV-Associated LRTI Within 90, 120, 150, and 180 Days After Birth

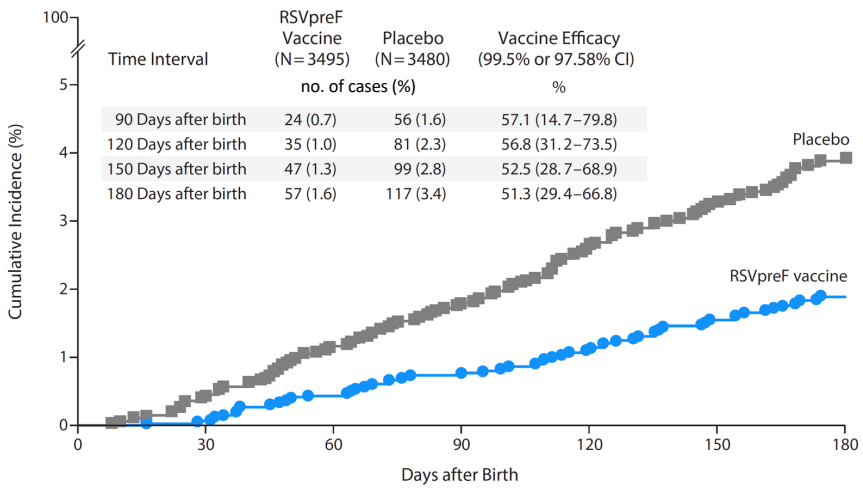
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6–96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6–88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5–85.9)
180 Days after birth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

Medically Attended RSV-Associated LRTI Within 90, 120, 150, and 180 Days After Birth

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

- **Success criteria for the primary efficacy endpoints was met for MA severe RSV-associated LRTI**

Phase 3, double-blind, randomised, placebo-controlled trial that was conducted over 4 RSV seasons to evaluate the efficacy and safety of maternal RSVpreF immunisation against MA-LRTI in infants followed for 1-2 years. Eligible participants were healthy women, ≤49 years, at 24 through 36 weeks' gestation on the day of planned injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications. Eligible women were randomly assigned, in a 1:1 ratio, to receive a single IM injection of 120 µg of RSVpreF vaccine (60 µg each of RSV A and RSV B antigens) or placebo.

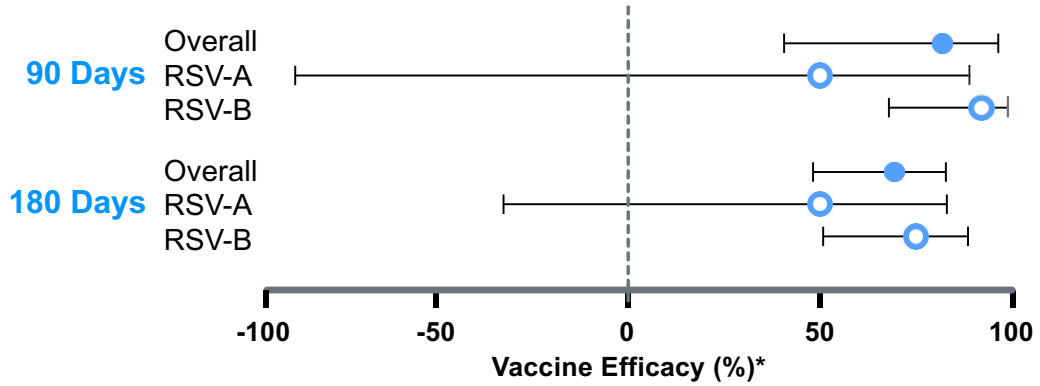
IM, intramuscular; LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus; RSVpreF, respiratory syncytial virus prefusion F protein.

Kampmann B, et al. *N Engl J Med*. 2023;388(16):1451-1464.

Immunizzazione materna per proteggere sin dal primo respiro

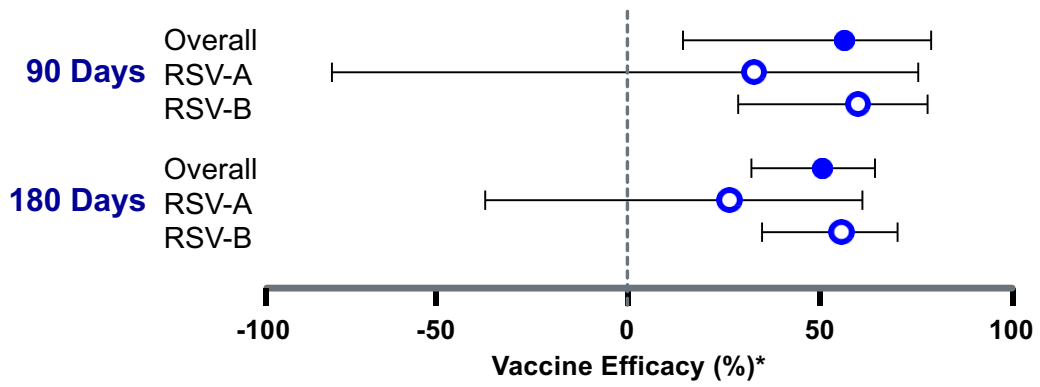
Consistent Efficacy Was Observed Across RSV Subgroup A and B*

RSV Severe MA-LRTI 90, 180 Days



	Case Split (RSVpreF/Placebo)	VE
90 Days	6:33	81.8%
	4:8	50.0%
	2:25	92.0%
180 Days	19:62	69.4%
	7:14	50.0%
	11:44	75.0%

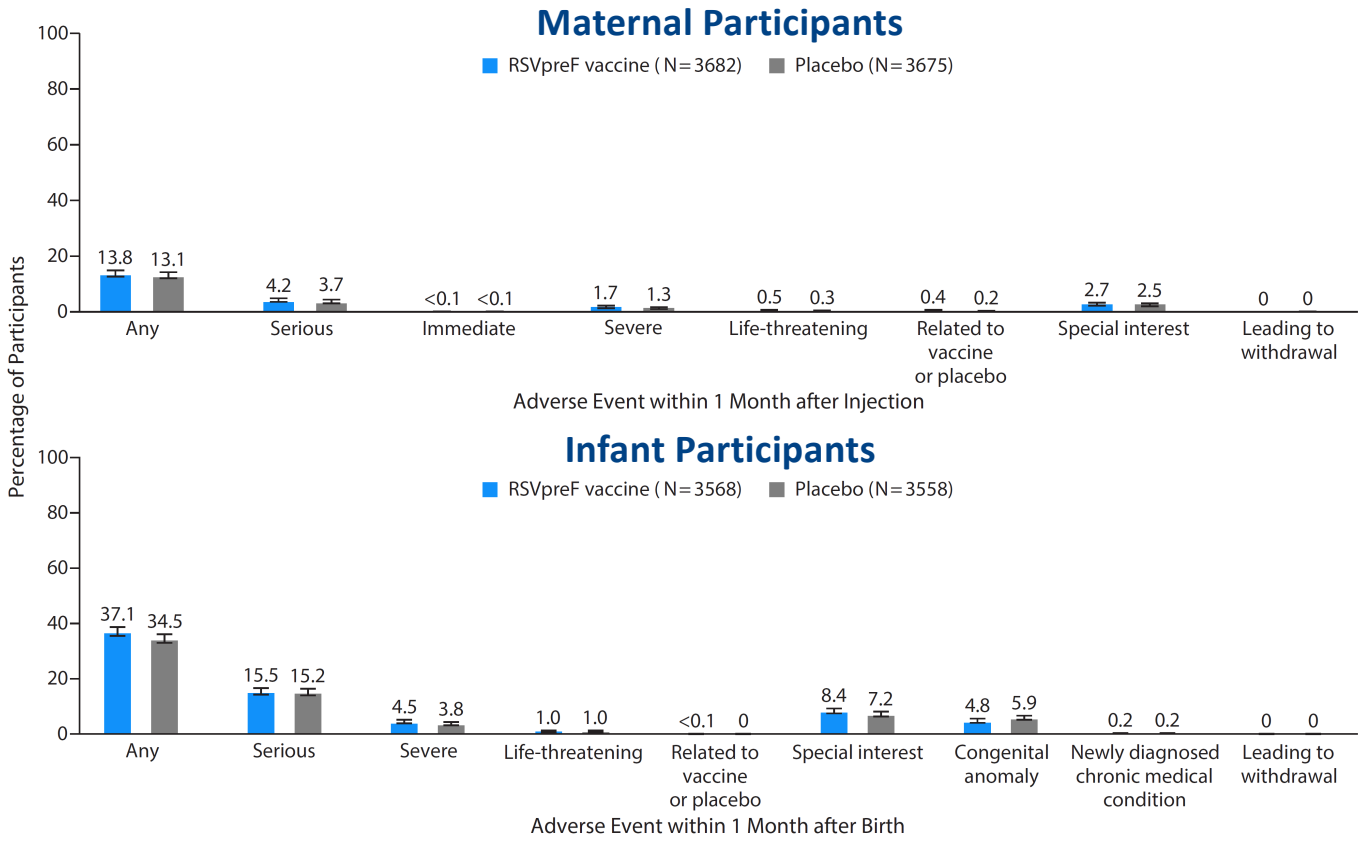
RSV MA-LRTI 90, 180 Days



	Case Split (RSVpreF/Placebo)	VE
90 Days	24:56	57.1%
	8:12	33.3%
	17:43	60.5%
180 Days	57:117	51.3%
	19:26	26.9%
	38:87	56.3%

Note: *Exploratory Endpoint – no prespecified criterion for RSV A and B, 95% CI. **Abbreviations**: MA: Medically Attended; LRTI: Lower Respiratory Tract Illness; VE: Vaccine Efficacy. **Source:** Kampmann et al. New England Journal of Medicine (2023); NCT04424316

MATISSE Study: Safety



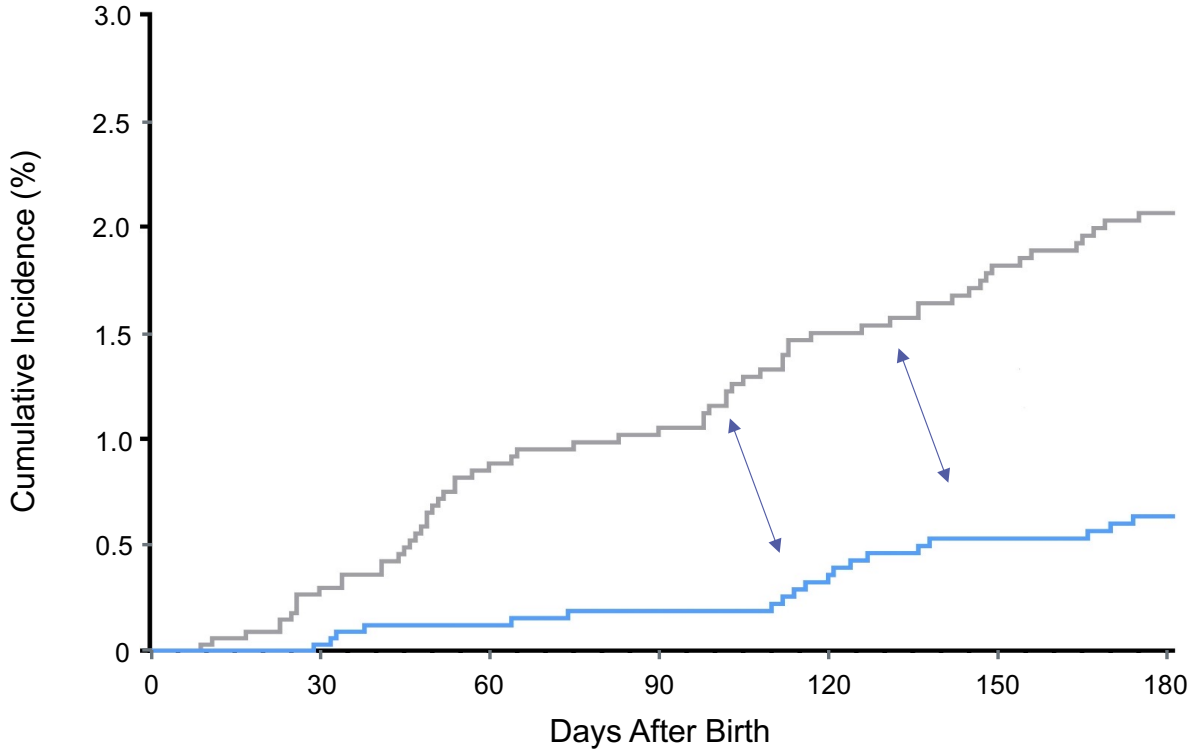
- Among the infant participants, the incidences of AEs of special interest and newly diagnosed chronic medical conditions were similar in the 2 groups
- Among maternal participants, the incidences of SAEs through 6 months after injection were similar in the 2 groups
- The incidences of premature delivery were similar in the 2 groups (0.8% in the vaccine group and 0.6% in the placebo group)

Phase 3, double-blind, randomised, placebo-controlled trial that was conducted over four RSV seasons to evaluate the efficacy and safety of maternal RSVpreF immunisation against MA-LRTI in infants followed for 1-2 years. Eligible participants were healthy women, ≤49 years, at 24 through 36 weeks' gestation on the day of planned injection, with an uncomplicated, singleton pregnancy and no known increased risk of pregnancy complications. Eligible women were randomly assigned in a 1:1 ratio, to receive a single IM injection of 120 µg of RSVpreF vaccine (60 µg each of RSV A and RSV B antigens) or placebo.

AE, adverse event; IM, intramuscular; LRTI, lower respiratory tract infection; MA, medically attended; RSV, respiratory syncytial virus; RSVpreF, respiratory syncytial virus prefusion F protein; SAE, serious adverse event.

Kampmann B, et al. *N Engl J Med*. 2023;388(16):1451-1464.

Cumulative Incidence of RSV Severe MA-LRTIs; 180 Days After Birth



Number of Cases						
RSVpreF	1	4	6	12	16	19
Placebo	10	28	33	46	55	62

Abbreviation: MA: Medically Attended; LRTI: Lower Respiratory Tract Illness

The (positive) gap between vaccinated and unvaccinated tends to stop enlarging after 90 days

The option of Maternal Immunisation : the pediatrician's and neonatologist's view (1)

- **Is this a reasonable approach ? YES**
- **Is the vaccine pregnancy platform working? YES → Vaccination during pregnancy has had successes and we have solid data to support this approach:**
  - Tetanus
  - Influenza
  - Tdap
  - RSV
- **Are there data that might –in turn - disconfirm this approach ? Currently NO**

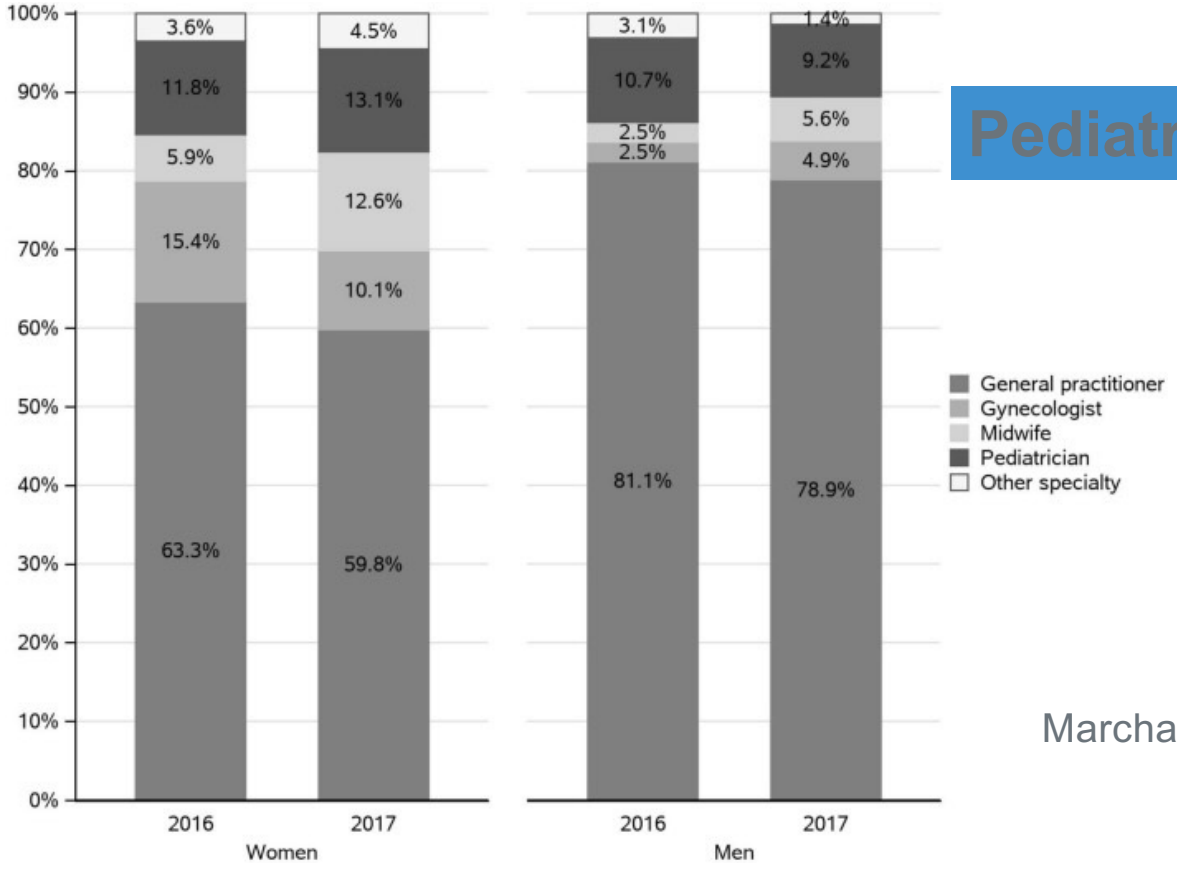
TAKE HOME MESSAGES

1. **Il Burden di morbidità infantile attribuobile al VRS è ingente**
2. **Non esiste trattamento specifico**
3. **Le strategie di prevenzione plausibili sono inevitabilmente legate al fornire Anticorpi anti –VRS fin dalla nascita**
4. **La vaccinazione materna in gravidanza vs VRS è sicuramente una strategia efficace nel ridurre la patologia da VRS nel neonato e lattante, e per enfatizzare il transfer di anticorpi attraverso il latte materno**

Thank you for your attention!

paolomanzoni@hotmail.com

Chi prescrive e raccomanda la vaccinazione in gravidanza? Francia, Pertosse, 2016-2017



Pediatri meno del 10%

Marchal C et al, Front Ped 2022