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Clinical and Non-Clinical Aspects of RSV Vaccine Safety in Young Children

PEDRO A PIEDRA, MD
PROFESSOR
MOLECULAR VIROLOGY AND MICROBIOLOGY, AND PEDIATRICS
BAYLOR COLLEGE OF MEDICINE,
HOUSTON, TX

DISCLOSURE STATEMENT

Affiliation / Financial Interest	Organization
Grants in the field of RSV prevention and treatment	GSK, Icosavax, Merck
Consultant in the field of RSV prevention and treatment	Merck, Moderna, Pfizer and Sanofi

OBJECTIVES

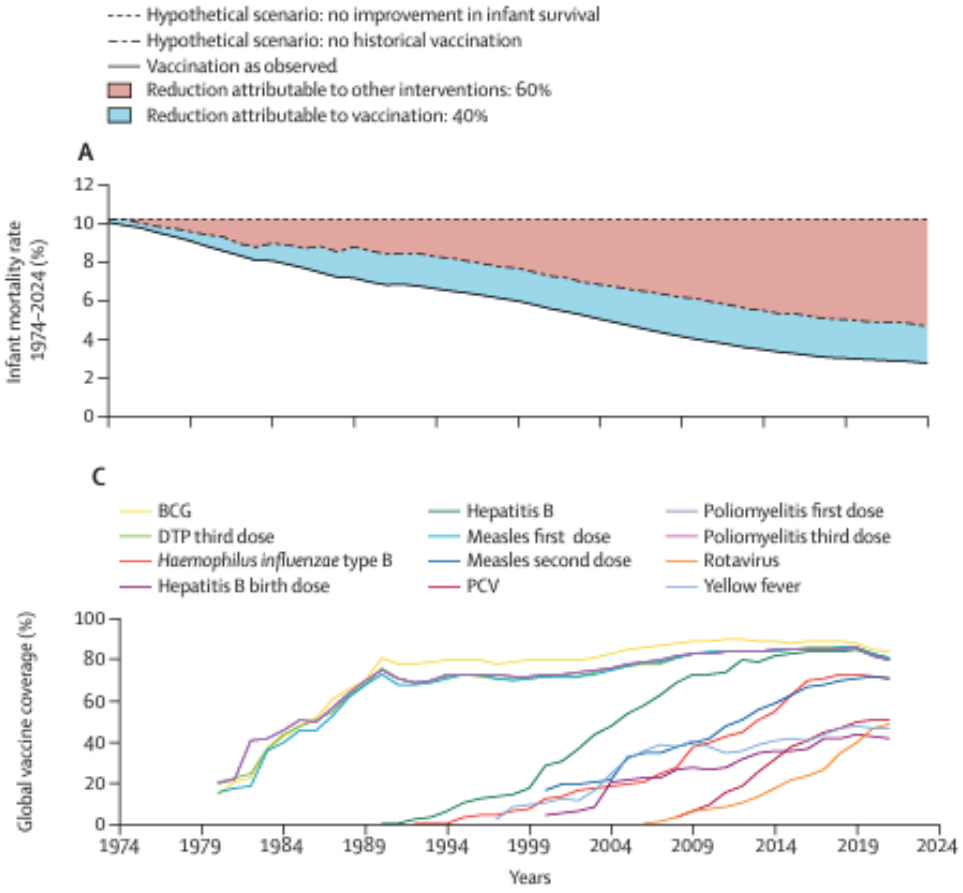
- Vaccines in general
- Clinical significance of RSV in children under 5 years of age
- History of the 1960's experience with FI-RSV vaccines
- The Virus
- Immunology and animal models of Vaccine Enhanced Disease (VED)
- Promising vaccines in development
- Potential impact of maternal vaccination and monoclonal antibody prophylaxis
- Outline of safety parameters and vaccine characteristics
  - RSV inexperience versus RSV experienced

Every ten seconds, one child is saved by a vaccine against a fatal disease.

Vaccines have saved 146 million children younger than 5 years of age over the last 50 years

EXPANDED PROGRAMME ON IMMUNIZATION (EPI)

- EPI launched in 1974 to make vaccines available globally.
- In this modeling study, it estimated the global impact of 50 years of vaccination against 14 pathogens in EPI.
- **Vaccination accounted for 40% of the observed decline in global infant mortality.**
- Measles vaccination was the single greatest driver of lives saved by vaccination.



AJ Shattock et al., Lancet 2024;203:2307-2316

Global causes of mortality in children under 5 years of age: 2019

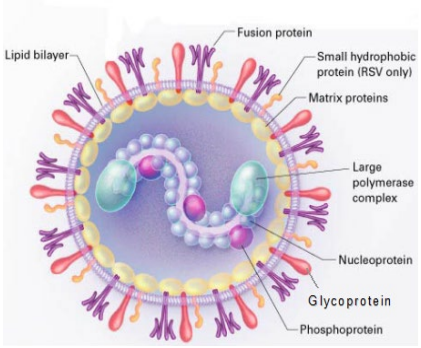
LEADING CAUSES OF DEATH
5.3 million deaths ◦ Preterm birth complications ◦ Lower respiratory tract infections ◦ intrapartum related events 2.44 million deaths among neonates (0-28 days) **2.61 million due to infectious causes** 21.7% were from vaccine preventable deaths

ESTIMATED NUMBER OF DEATH BY LEADING CAUSES IN CHILDREN 1-59 MONTHS

Causes	Number in million (95% uncertainty range)	Mortality rate per 1000 live births (95% uncertainty range)
LRTI	**0.54 (0.43, 0.61)**	**3.84 (3.05, 4.40)**
Diarrhea	0.45 (0.37, 0.51)	3.23 (2.65, 3.68)
Malaria	0.42 (0.34, 0.50)	2.98 (2.40, 3.56)

J Perin et al., Lancet 2022;6:106-115

One in every 15 deaths was caused by RSV among infants 28 days to < 6 months



RSV disease in young children

RSV is a major global pathogen

33.1 (21.6-50.3) million cases annually of RSV-ALRI

3.2 (2.7-3.8) million cases annually of severe RSV-ALRI

31-37% of pneumonia hospitalization in the Africa, Asia, & U.S

Leading cause of bronchiolitis

55,000 to 200,000 deaths annually attributed to RSV

Most of the deaths in developing countries occur in young children

Individuals are re-infected throughout their lifetime

Protective immunity is incomplete

Nair et al., Lancet 2010;375:1545-55, Shi et al., Lancet. 2017;390:946-58; PERCH Study Group. Lancet 2019;394:757-79, Jain et al., NEJM. 2015;372:835-45, Blau et al., CID. 2021;73(S3):S218-28.

There is a major need for a safe and efficacious vaccine for children under 5 years of age.

However, the experience of the 1960's that resulted in vaccine enhanced disease upon natural RSV infection has delayed vaccine development for young children.

Back to the beginning

ROBERT CHANOCK, M.D.

Dr. Robert Chanock, Chief of the Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, provided outstanding scientific leadership during his years of service to CARD. His demonstration that the adenoviruses that cause ARD of recruits will induce an asymptomatic, immunizing infection when administered live by the enteric route provided the basis for the successful adenovirus vaccine now given to all military recruits. He and his associates confirmed that the causative agent of atypical pneumonia *Mycoplasma pneumoniae* is a pleuropneumonia-like organism and were the first to cultivate it on an artificial medium.

Recovery of cytopathogenic agent from chimpanzees with coryza and from infants with respiratory illness: 1956-1957

It was recognized early after its discovery that RSV was a major respiratory pathogen of infants and young children.

Recovery of Cytopathogenic Agent from Chimpanzees with Coryza (JA Morris et al., Proc Soc Exp Biol Med 1956;92:544)

Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent. I. Isolation prperties and characterization (RR Chanock & L Finberg, Am J Hygiene 1957;66:281)

Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent. II. Epidemiologic aspects of infection in infants and young children (RR Chanock & L Finberg, Am J Hygiene 1957;66:291)

Lessons from the past: the Pfizer Formalin Inactivated RSV (FI-RSV) vaccine experience of the 1960s

Children 2 to 23 months of age				
RSV-outcome	**Vaccinated group**	**Control group**	**Time between last dose and outcome**	**Reference**
pneumonia	9/13 (69%)	4/47 (9%)	Median 54 days (range 15 to 236 days)	Kapikian
hospitalization	9 cases	2 cases	Not provided	Chin
hospitalization	16/31 (52%)	1/40 (2.5%)	23 d to 11 mo	Kim
hospitalization	10/111 (9%)	2/173 (1.2%)	Not provided	Fulginiti

Kapikian et al, AJE 1969;89:405-421
Chin et al,AJR 1969;89:449-463 (<1yr & 1-4 yrs: FI-RSV 43 & 99; FI-PIV 43 & 91)
Kim et al, AJE 1969;89:422-433 (2 infants died at 14 and 16 months; vaccinated at 2 and 5 months, respectively; both received 3 doses)
Fulginiti et al., AJE 1969;89:435-448

Clinical findings in FI-RSV vaccinated and nonvaccinated children following RSV infection

AZ KAPIKIAN ET AL.

Findings	FI-RSV vaccine (n=13)	Not vaccinated (N=11)
Coryza	13 (100%)	11 (100%)
Cough	13 (100%)	7 (64%)
Wheezing	10 (77%)	4 (36%)
Rales	13 (100%)	11 (100%)
X-ray evidence of pneumonia	10 of 11 (91%)	5 of 7 (71%)
Hospitalized	5 (38%)	1 (9%)

HW KIM ET AL.

Findings	FI-RSV vaccine (n=31)	PIV vaccinated (N=40)
GMNAT	48	8
RSV infection	20 (65%)	21 (53%)
Hospitalized	16 of 20 (80%)	1 of 21 (5%)
Mean length of hospitalization	10.5 days	6.7 days (age-matched)
Pneumonia or bronchiolitis	19 (95%)	4 (19%)
Death	2 (10%)	0

Kapikian et al., Am J Epi. 1969; 1969;89:405-421., Kim et al, AJE 1969;89:422-433

Vaccine enhanced disease was not observed in children 24 months of age and older at the time of vaccination

Age group (month)	Vaccine	Total number	No. Hospitalized	Attack rate per 100 at risk
6-11	**FI-RSV**	**51**	**7**	**13.7**
	FI-TPV	65	1	1.5
12-23	**FI-RSV**	**60**	**3**	**5**
	FI-TPV	108	1	0.92
>24	**FI-RSV**	**353**	**1**	**0.28**
	FI-TPV	361	0	0

Fulginiti et al., Am J Epi. 1969;89:435-448
TPV: trivalent parainfluenza vaccine

Merck FI-RSV vaccine trials of the 1960s

Simian cell-derived; whole virus; formalin-inactivated; concentrated 5-25-folds, alum absorbed
Vaccine enhanced disease was NOT observed upon natural infection

Vaccine type	Age group, Y	Outcome	Vaccine	Control	Ref.
RSV-PIV1-3	5-11	Poor Nt Ab	53	0	Potash
RSV-PIV1-3-Myco	3-10	Poor Nt Ab*	21	28	Sweet
RSV-PIV1-3-Myco-Flu A-B	1-10	Poor Nt Ab	29	7	Woodhour
RSV-PIV1-3-Myco-Flu A-B	3-5 (35% seronegative)	no enhanced disease	199	208	Weibel
RSV	3-5 (40% seronegative)	8% ↓ in severe RS disease	164	220	Weibel

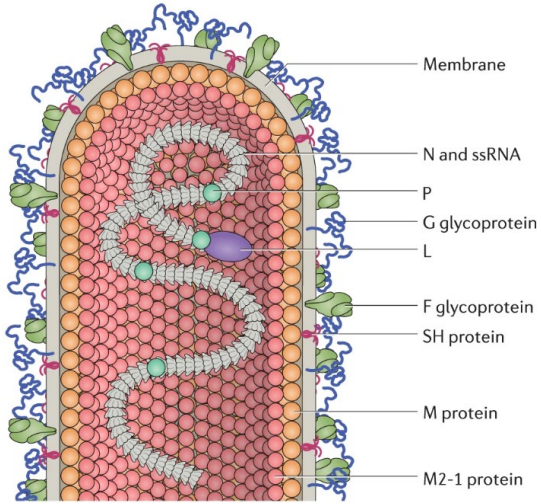
Potash et al., Am Rev Res Dis 1966;93:536-48
Sweet et al., Am Rev Res Dis 1966;94:340-49 (*2 seronegative developed GMT of 1:160)
Woodhour et al., Am Rev Res Dis 1966;94:350-61 (1of 4 seronegative elicited Nt Ab)
Weibel et al., Am Rev Res Dis 1966;94:362-79
Weibel et al., Am Rev Res Dis 1967;96:724-39

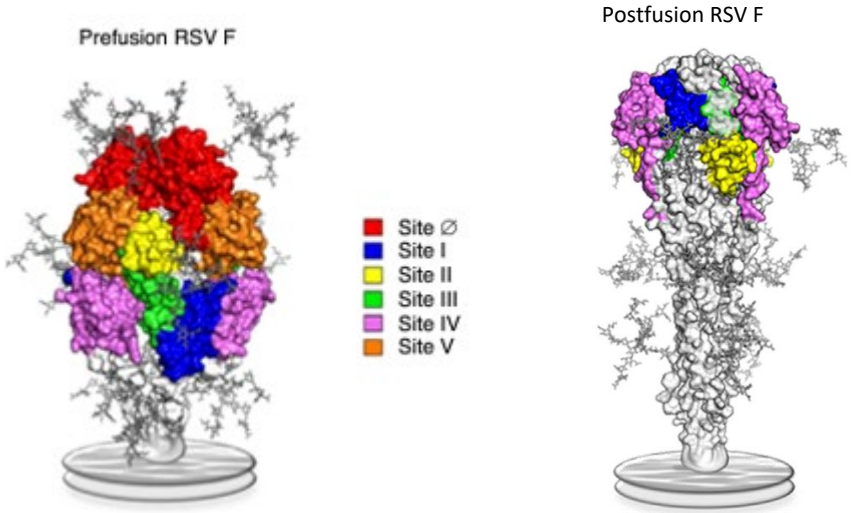
To date a clear mechanistic understanding of the FI-RSV vaccine enhanced disease has not been established, although there are leading immunological mechanisms that are considered plausible.

But first about the virus to better understand the immune response and vaccine development.

The Virus

- RSV is an enveloped, negative-sense, single-stranded RNA virus that belongs to the *Orthopneumovirus* genus in the family *Pneumoviridae*
- The genome contains 10 genes that encode 11 proteins.
- **The viral surface proteins F and G are the primary targets for host-neutralizing antibodies**
- Glycoprotein G is heavily glycosylated and mediates attachment of the virus to the ciliated epithelial cells of the respiratory tract
- The F protein mediates fusion of the viral lipid envelope with the plasma membrane of the cell





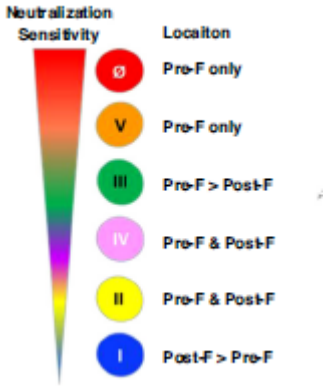
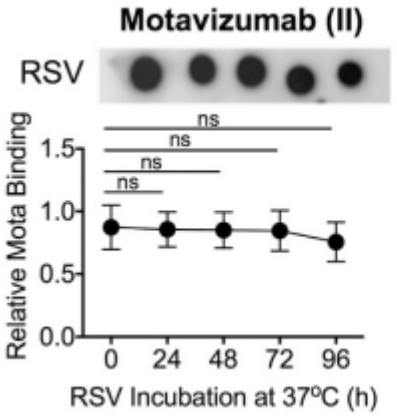


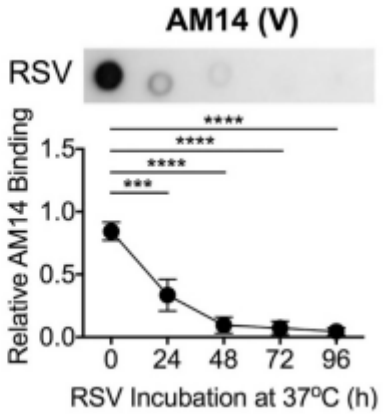
Illustration adapted from BS Graham. Current Opinion Immunol. 2019;59:57-64.

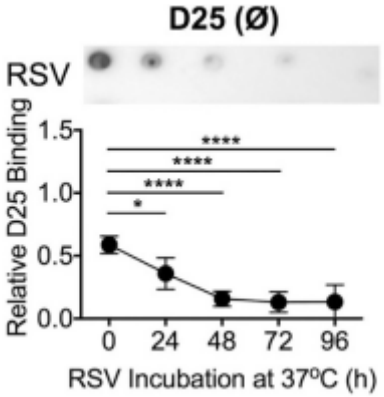
Pre-fusion F conformation is absent on the surface of FI-RSV

Instability of pre-F during FI-RSV production: infectious RSV is incubated at 37 °C with a 0.025% concentration of formalin for 72 hours

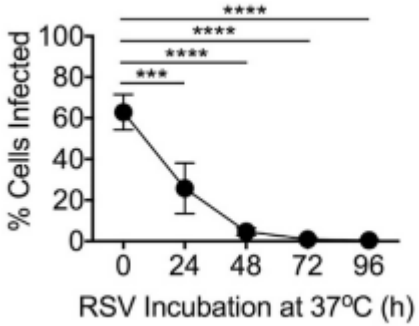
Antigenicity







Infectivity



Killikelly et al., Scientific Reports. 2016:34108 | DOI: 10.1038/srep34108 1

The antibody response as an unlikely cause of the FI-RSV vaccine enhanced disease.

Dissociation between serum neutralizing and binding antibody to F and G glycoproteins in children who received the FI-RSV vaccine

		Mean titer in reciprocal log_{10}		Ratio of anti-F IgG to Nt Ab titer
Group	Assay	Preinjection or acute	3 wks after 3rd injection or infection	Ratio of anti-F IgG to Nt Ab titer
FI-RSV (2-7 mo.) n=21	ELISA F	4.2 ± 0.3	4.1 ± 0.1	2.4 (251:1)
	ELISA G	3.6 ± 0.2	2.7 ± 0.1	
	Neutralization	2.4 ± 0.2	1.7 ± 0.1	
FI-PIV-1 (2-7 mo.) n=9	ELISA F	2.7 ± 0.2	2.1 ± 0.3	1.0 (10:1)
	ELISA G	3.1 ± 0.1	2.3 ± 0.1	
	Neutralization	1.5 ± 0.2	1.1 ± 0.2	
Natural infection (1-8 mo.) n=11	ELISA F	2.9 ± 0.2	3.5 ± 0.3	1.1 (12.6:1)
	ELISA G	2.8 ± 0.3	3.5 ± 0.1	
	Neutralization	1.7 ± 0.2	2.4 ± 0.2	

Murphy et al., J Clin Microbiol. 1986;24(2):197-202.

The antibody response as an unlikely cause of the FI-RSV vaccine enhanced disease

FI-RSV induced high titers of binding antibody with weak to moderate neutralizing and fusion-inhibitory activity consistent with low avidity antibody response.

These antibodies in the context of large antigen load is thought to have led to immune complex deposition and complement activation in airways upon subsequent RSV infection.

Vaccine enhanced pathology can be mediated by immune complexes and abolished in complement component C3 and B cell–deficient mice.

The two infants who died from vaccine enhanced disease had peribronchiolar deposition of C4d, a complement cleavage marker of complement activation by the classical pathway.

However, cell-bound C3 is present during the convalescent phase of natural RSV infection and RSV antigen-containing immune complexes are detectable in the upper airways of infected infants from 3 days after and up to 36 days after illness onset.

Antibodies induced by FI-RSV vaccine either passively administered or maternally transferred are not associated with vaccine enhanced pathology in cotton rat and mouse models of vaccine enhanced pathology.

Polack et al., J Exp Med. 2002;196(6):859-65. Kaul et al., J Clin Lab Immunol. 1984;15:187-90., Blanco et al., Vaccine 2017;35:3951-58. Kwon et al., Antiviral Research. 2014;104:1-6.

Safety and immunogenicity of RSV purified fusion protein-2 (PFP-2) vaccine in pregnant women

FIRST EVER RSV-F VACCINE STUDY IN PREGNANT WOMEN

35 women participated.

Randomized to receive PFP-2 (50µg) or saline placebo at a ratio of 4:3.

Vaccine administered at 30-34 weeks of gestation.

The vaccine was poorly immunogenic in pregnant women eliciting high anti-F IgG antibodies and low neutralizing antibodies against RSV/A and RSV/B.

No safety concerns or vaccine enhanced disease were observed in infants during their first RSV season.

RSV/A NEUTRALIZING ANTIBODY

	Placebo GMT log 2 (95% CI)	Vaccine GMT log 2 (95% CI)
Pre-vac	6.7 (5.8, 7.6)	6.9 (6.2, 7.6)
Delivery	7.0 (6.0, 8.0	7.5 (7.0, 8.0)
Infant cord	7.1 (6.1, 8.1)	7.7 (7.2, 8.2)
Infant -2 mo.	5.4 (4.7, 6.1)	6.1 (5.6, 6.6)
Infant -6 mo.	3.5 (3.0, 4.0)	4.5 (4.0, 5.0)
Infant-12 mo.	4.5 (3.6, 5.4)	3.2 (2.6, 3.8)

Munoz et al., Vaccine 2003;21:3465-67

The cellular immune response as a potential cause of the FI-RSV vaccine enhanced disease.

Lymphoproliferative response to RSV induced by FI-RSV vaccine or by infection

Lymphocytes from children were collected 2-14 months after FI-RSV vaccine administration. Twelve of 21 FI-RSV vaccinees were infected with RSV before lymphocyte collection.

			% transformation & mitotic activity of cultured lymphocytes for 7 days Mean (SE)			Serum antibody (mean)	
Vaccine	Natural RSV infection	No. tested	Exposed to RSV	Exposed to MK antigen	Unstimulated	Plaque reduction	Complement fixation
FI-RSV	yes	12	24.9 (4.8)	1.1 (0.6)	0.1 (0.1)	2,002	235
	no	9	20.7 (4.8)	0.9 (0.6)	0.5 (0.4)	1,181	91
FI-PIV-1	yes	14	5.6 (1.7)	0.4 (0.2)	0.1 (0.1)	1,369	41
	no	5	1.4 (0.8)	0.9 (0.8)	0.8 (0.7)	35	<4

Kim et al., Pediatr Res. 1976;10:75-8.

The cellular immune response as a potential cause of the FI-RSV vaccine enhanced disease

It is thought that FI-RSV induced a Th2-biased CD4 T cell response and after natural RSV infection resulted in eosinophilic parabronchial infiltrates and neutrophilic alveolitis resulting in the vaccine enhanced disease phenotype.

The Balb-c mouse, cotton rat, and African green monkey models have been used to study vaccine enhanced pathology. These models are semi-permissive to RSV and require high titers of infectious virus to infect.

FI-RSV priming in RSV naïve mice has been linked to an imbalance Th2 response with production of IL-4 and IL-5 with a pulmonary eosinophilic response upon experimental RSV infection with induce mucus production, airway hyperresponsiveness, and reduction of cellular cytotoxic activity.

Th2 biased immune response mediates airway hyperactivity and mucus hypersecretion, and CD4 cells producing TNF-α result in airway obstruction.

Recombinant RSV G protein vaccine induced vaccine enhance pathology with increased cellular infiltrates in the lungs and Th2-cell mediated IL-13 induced mucin hypersecretion.

Memory CD8 T cells with high IFN-γ production in the absence of RSV specific CD4 T cells and antibodies can result in viral clearance but lethal immunopathology.

In animal models enhanced pathology result from an unbalanced T cell priming rather than infection enhancing or sensitizing antibodies.

BS Graham. Current Opinion Immunol. 2019;59:57-64., Prince et al., J Gen Virol 2001;82:2881-88., Openshaw et al., Vaccine 2002;20:S27-S31., Knudson et al., Plos Pathogens 2015;11(3):e1004757., Schmidt et al., Plos Pathogens. 2018;14(1):e1006810., Kawahara et al, Vaccines 2024;9:187.

Vaccines not associated with vaccine enhanced disease

Vaccine enhanced disease was not observed with a live RSV vaccine administered subcutaneously

A two year follow-up study (1979-1980) was conducted in 510 children 6-47 months who were vaccinated 1:1 with a live RSV vaccine ($10^{3.9}$ TCID) or WI-38 tissue culture fluid as a single 0.5 ml sc dose.

- Live RSV vaccine: 146 (63%) of 233 children were under 24 months of age
- WI-38 tissue culture fluid control: 169 (61%) of 277 children were under 24 months of age

Antibody response to vaccine was determined by an ELISA assay

- An antibody response was significantly more frequent among seronegative live RSV vaccinees compared to seronegative placebo recipients.

Neither protection against RSV disease or development of vaccine enhanced disease after infection was detected among the RSV vaccinees.

- 93 RSV infections
- Live RSV vaccine: 11/233 RSV related hospitalization (47 cases per 1000 vaccinated children)
- WI-38 tissue culture fluid control: 12/277 RSV related hospitalization (43 cases per 1000 vaccinated children)

Belshe et al., JID. 1982;145(3):311-19.

Vaccine enhanced disease has not been observed with live RSV vaccines administered intranasally

Studies conducted from 1994-2002 with one of seven different live RSV vaccines administered intranasally.

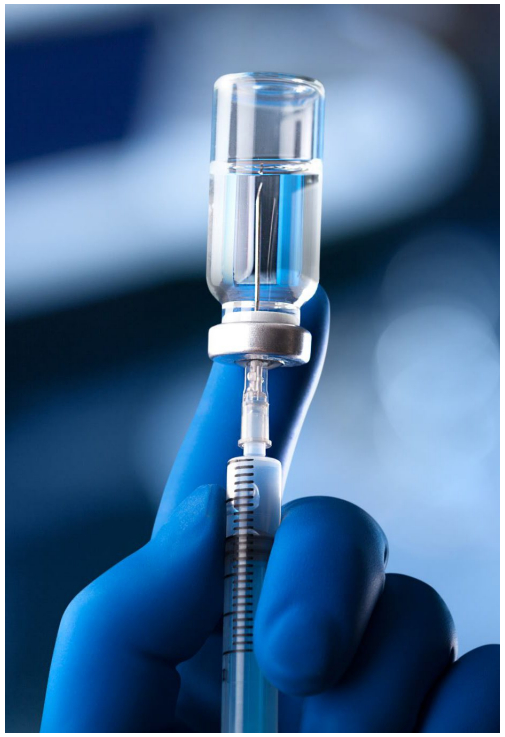
Cpts 248/955; cpts 530/1009; cpts 248/404; rA2cp 248/404/1030/ΔSH; rA2cp 248/404/ΔSH; rA2cp 530/1009/ΔNS2; rA2cp 248/404/ΔNS2

Age	Group	Number	All URI N (%; 95% CI)	RSV-URI N (%; 95% CI)	All-LRI N (%; 95% CI)	RSV-LRI N (%; 95% CI)
1-3 months (2 doses)	Vaccinees	62	32 (52%; 39-64)	10 (16%; 9-25)	5 (8.1%; 1.3-15)	3 (4.8%; 0-10)
	Controls	60	35 (58%; 46-71)	15 (25%; 14-36)	7 (12%; 3.6-20)	2 (3.3%; 0-7.8)
6-24 months (one dose)	Vaccinees	113	59 (52% 43-61)	16 (14%; 7.7-20.6)	5 (4.4%; 0.6-8.2)	3 (2.6%; 0-5.6)
	Controls	153	109 (71%; 64-78)	30 (20%; 13-26)	11 (7.2%; 3-11.3)	5 (3.3%; 0-7.8)

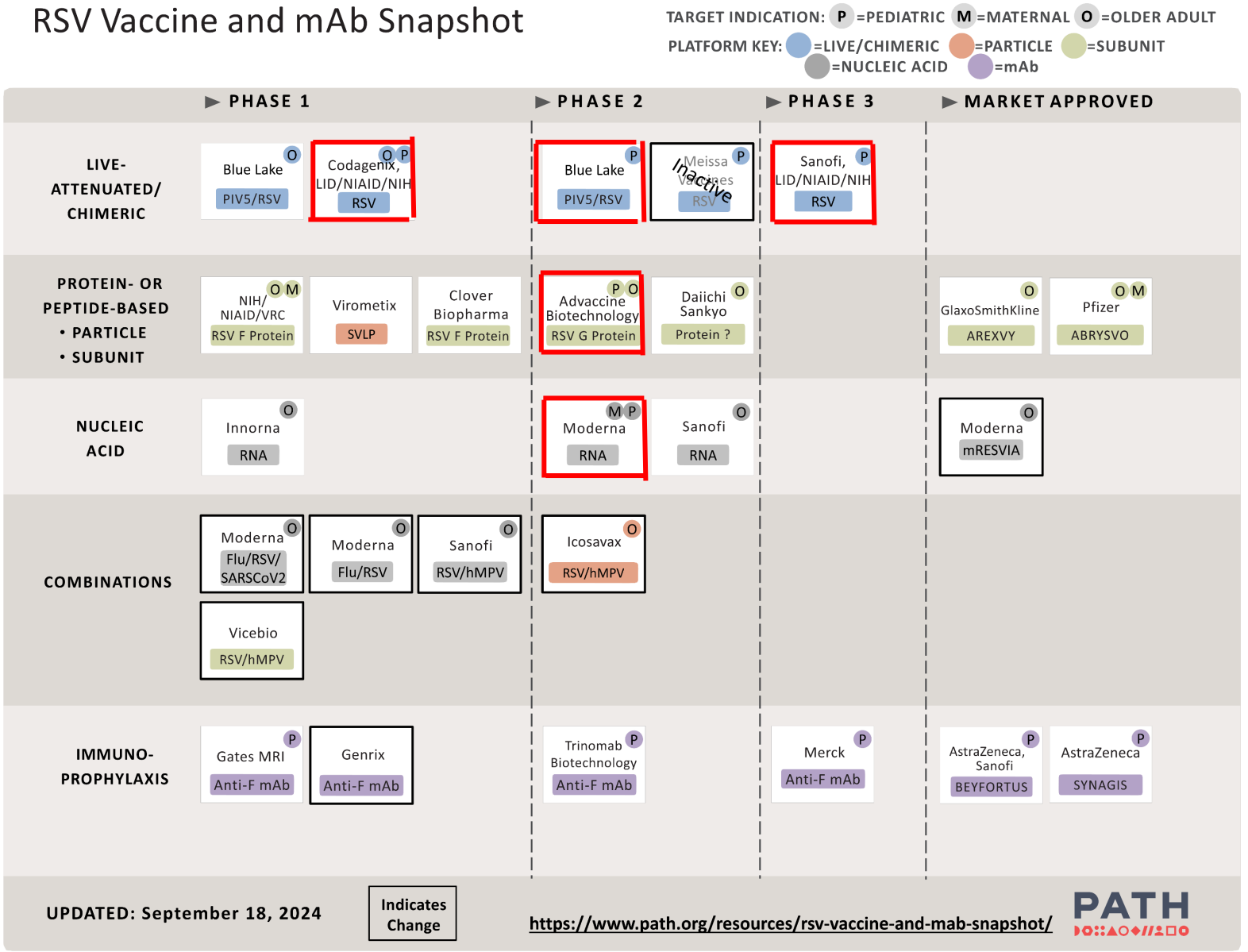
Wright et al., Vaccine. 2007;25:7372-78.

Prevention

- In 2023 two new preventative measures were approved by the US FDA to protect infants against RSV.
  - maternal RSVpreF vaccine (Abrysvo®) that contains the preF conformation of RSV A and RSV B F proteins
  - long-acting monoclonal antibody called nirsevimab (Beyfortus®) that targets site Ø on the preF form of the F protein
- Additionally, two RSVpreF vaccines (Arexvy® and Abrysvo®) and one mRNA vaccine (mResvia®) were approved for the prevention of severe RSV infection in adults 60 years of age and older



RSV Vaccine and mAb Snapshot



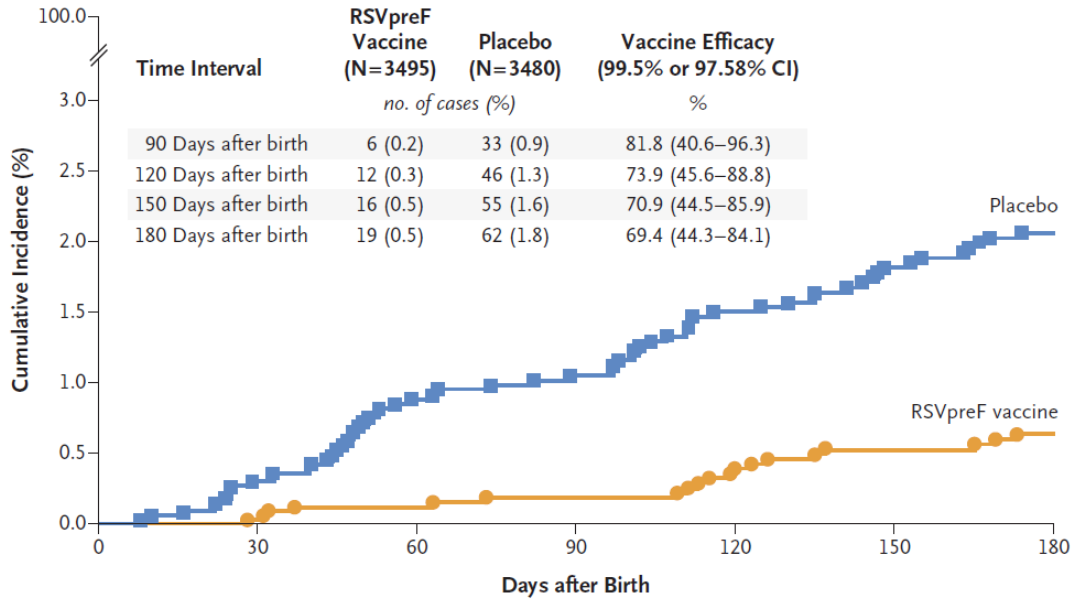
Will need to study RSV vaccine immunogenicity that target young children in the context of other preventative measures that protect infants against severe RSV infection.

Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants

Eligibility criteria: Healthy women 49 years of age and younger at 24 through 36 weeks gestation.

A Medically Attended Severe RSV-Associated Lower Respiratory Tract Illness

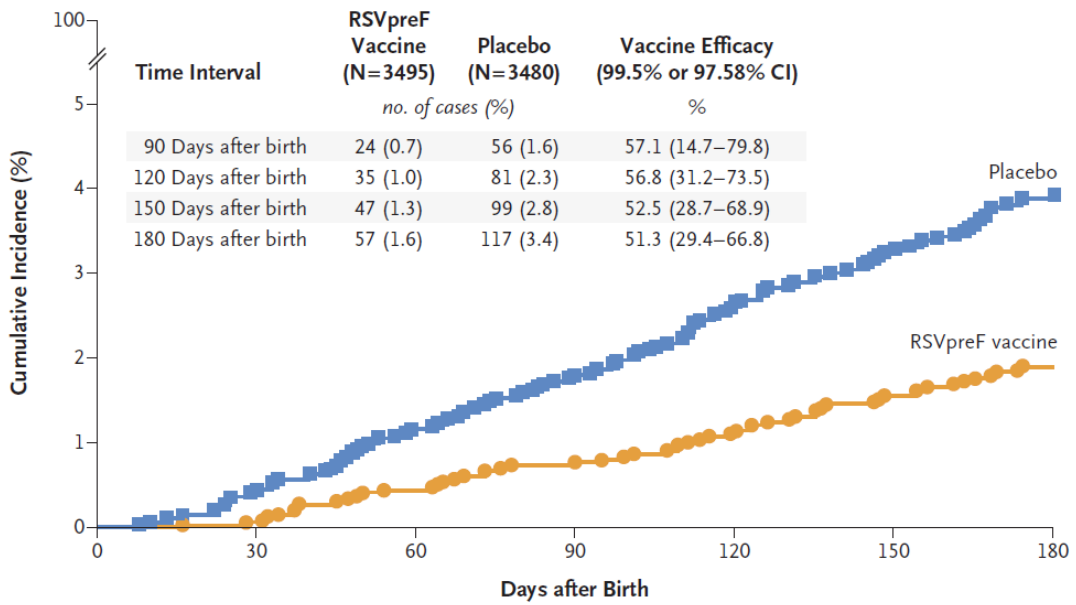
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	6 (0.2)	33 (0.9)	81.8 (40.6–96.3)
120 Days after birth	12 (0.3)	46 (1.3)	73.9 (45.6–88.8)
150 Days after birth	16 (0.5)	55 (1.6)	70.9 (44.5–85.9)
180 Days after birth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

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)



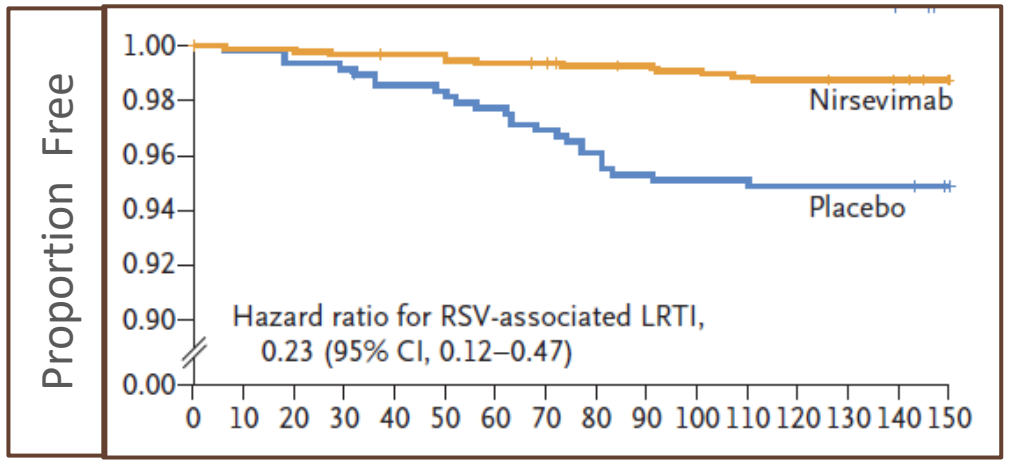
No. at Risk							
Placebo	3480	3288	2964	2879	2804	2738	2700
RSVpreF vaccine	3495	3348	3035	2968	2898	2845	2792

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants

Laura L. Hammitt, M.D., Ron Dagan, M.D., Yuan Yuan, Ph.D., Manuel Baca Cots, M.D., Miroslava Bosheva, M.D., Shabir A. Madhi, Ph.D., William J. Muller, Ph.D., Heather J. Zar, Ph.D., Dennis Brooks, M.D., Amy Grenham, M.Sc., Ulrika Wählby Hamrén, Ph.D., Vaishali S. Mankad, M.D., Pin Ren, Ph.D., Therese Takas, B.Sc., Michael E. Abram, Ph.D., Amanda Leach, M.R.C.P.C.H., M. Pamela Griffin, M.D., and Tonya Villafana, Ph.D., for the MELODY Study Group*



Medically attended RSV-LRTI. 74.5%
(95% CI, 49.6 to 87.1; P<0.001)
Hospitalization for RSV LRTI: 62.1%
(95% CI-8.8 to 86.8; P=0.07)
Antidrug antibodies:
6.1% nirsevimab group & 1.1% placebo

Hammitt LL et al., NEJM 2022;386(9):837-46.

Risk versus benefit ratio of RSV vaccines for young children

Define the immune profile and safety in preclinical animal models

The vaccine formulation should be determined or nearly settled before going into the pediatric population

Need to ensure the vaccine formulation is stable

- Also, non-transmissible

Need to establish an acceptable reactogenicity profile

- First in adults
- Progress into children

Ensure no significant safety signals are observed for participants followed during one to two RSV seasons

- First in RSV experienced children
- Followed by RSV inexperienced infants

Should induce an immune response associated with protection

- Need to determine if RSV maternal vaccination or nirsevimab immunoprophylaxis will attenuate or interfere with the RSV vaccine induced immune response

What are some of the major safety concerns of RSV vaccines in young children?

Vaccine enhanced disease upon natural infection

- Observed in the 1960s with the FI-RSV vaccine in children under 2 years of age

Adverse events of special interest: will likely be platform dependent

- Febrile seizure, possibly with adjuvanted or high dose vaccines or during co-administration
- Autoimmunity with new adjuvants
- Wheezing illness or respiratory distress with live attenuated vaccines or intranasally administered vaccines
- Systemic illness with vector-based or mRNA vaccines

Characteristics for RSV vaccines for children

- **Safety**: Safety profile demonstrates no or mild transient reactogenicity
- No evidence of vaccine enhanced disease
- **Efficacy**: 70% against confirmed severe RSV disease caused by RSV/A and RSV/B subgroups over one or more years
- Determine the impact on non-severe RSV disease, recurrent wheezing, and other respiratory viruses
- **Immunogenicity**: establish immune profile of vaccine and correlates of protection
- **Co-administration with other vaccines**: demonstrate safety and non-inferior immunogenicity
- **Preventive measures**: Assess interference between maternally acquired and monoclonal antibodies on vaccine immunogenicity

WHO 2017 http://www.who.int/immunization/documents/en