RSV Updates

DATE: Nov 24, 2024

Lorne Walker, MD PhD

Objectives

- Characterize the strategies for RSV prevention (past and future)
- Describe the current and anticipated impact of RSV prevention
- Know the current consensus guidelines for RSV prevention

Part One: How did we get here?

RSV

- Each year
  - 2.1 million pediatric outpatient visits
  - 58-80,000 pediatric hospitalizations
  - 100-300 deaths

https://www.cdc.gov/rsv/php/surveillance/
https://www.aap.org/Respiratory-Syncytial-Virus-RSV-Brochure-50pk-Brochure

Timeline of Early RSV Preventative Strategies

1956: RSV was isolated in chimpanzees with upper respiratory tract infection. In 1957 RSV was detected in children with upper respiratory tract infection by Robert M. Chanock

1966: The first RSV vaccine trial with a formalin inactive RSV vaccine candidate did not provide protection, instead led to enhanced respiratory disease in infants

F-protein

1985: Surface glycoprotein G (attachment) and F (fusion) protein were isolated. 1980's was focused on improving the understanding of the immune response to RSV

1991: Recognition of neonatal protection from maternal IgG antibodies led to use of polyclonal intravenous immunoglobulins (IVIG). Though safe, IVIG was not protective.

RespiGam

1996: RespiGam, a polyclonal hyperimmune RSV immunoglobulin was licensed for monthly use in high risk infants

Palivizumab

1998: Palivizumab, a humanized monoclonal antibody was licensed for monthly use in high risk infants

Motavizumab

2010: Motavizumab, a second-generation humanized monoclonal antibody derived from palivizumab was withdrawn due to non-inferiority and concern of increased side effects

Noor et al. J Pediatric Infect Dis Soc. 2024 Jul 12;13(Supplement_2):S103-S109.

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Robert Chanock, MD

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JAMA

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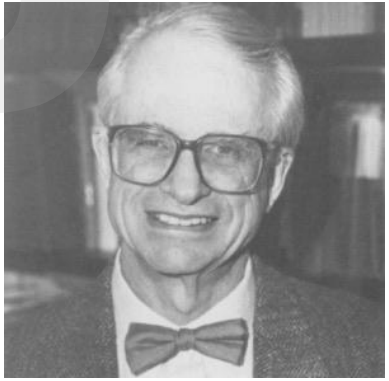
CHICAGO, ILLINOIS
MAY 27, 1961

Respiratory Syncytial Virus

I. Virus Recovery and Other Observations During 1960 Outbreak of Bronchiolitis, Pneumonia, and Minor Respiratory Diseases in Children

Robert M. Chanock, M.D., Bethesda, Md., Hyun Wha Kim, M.D., Andrew J. Vargosko, Ph.D., Ann Deleva, M.S., Washington, D.C., Karl M. Johnson, M.D., Christine Cumming, R.N., Bethesda, and Robert H. Parrott, M.D., Washington, D.C.



Chanock RM, et al. JAMA. 1961 May 27:176:647-53.
https://history.nih.gov/pages/viewpage.action?pageId=11600072

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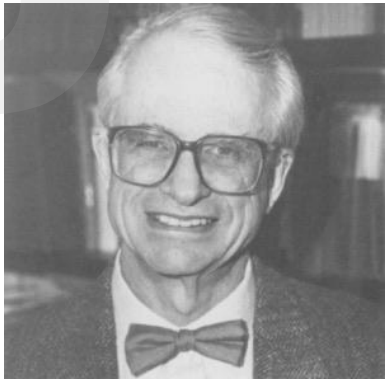
Robert Chanock, MD

Table 2.—Influence of Age upon Recovery of RS Virus from Patients with Upper or Lower Respiratory Disease

Category	Virus Recovery from Individuals of Indicated Age*																	
	0-6 Mo.			7-12 Mo.			13-24 Mo.			25-48 Mo.			49 Mo. or More			Total		
		Positive			Positive			Positive			Positive			Positive			Positive	
	Tested	No.	%	Tested	No.	%	Tested	No.	%	Tested	No.	%	Tested	No.	%	Tested	No.	%
Bronchiolitis	27	16	59	15	3	20	6	1	17	...	...	...	...	...	...	48	20	42
Pneumonia	13	7	54	15	3	20	16	2	12	4	...	...	10	2	20	58	14	24
Total	**40**	**23**	**57**	**30**	**6**	**20**	**22**	**3**	**14**	**4**	...	...	**10**	**2**	**20**	**106**	**34**	**32**
Minor respiratory illness	32	6	19	24	4	17	30	3	10	40	5	12	33	1	3	159	19	12
No respiratory illness	79	...	...	32	1	3	56	1	2	58	1	2	47	1	2	272	4	1

*March through July, 1960.



Chanock RM, et al. JAMA. 1961 May 27:176:647-53.
https://history.nih.gov/pages/viewpage.action?pageId=11600072

The first RSV vaccine (1965)

Live Bennett-strain RSV

Grown in tissue culture

Inactivated with formaldehyde

Inactivated virus particle

Vaccine performed well in guinea pig and monkey models

Noor et al. J Pediatric Infect Dis Soc. 2024 Jul 12;13(Supplement_2):S103-S109.
Kim HW, et al. Am J Epidemiol. 1969 Apr;89(4):422-34.

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 89, No. 4

Printed in U.S.A.

RESPIRATORY SYNCYTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE[1, 2]

HYUN WHA KIM, JOSE G. CANCHOLA[3], CARL D. BRANDT, GLORIA PYLES, ROBERT M. CHANOCK, KEITH JENSEN, AND ROBERT H. PARROTT[4]

(Received for publication August 8, 1968)

- Infants immunized with RSV or non-RSV (PIV) vaccines in the 1965-66 and 1966-67 respiratory season
- After 3 doses 91% of the RSV-vaccinated group developed RSV-specific antibodies

Noor et al. J Pediatric Infect Dis Soc. 2024 Jul 12;13(Supplement_2):S103-S109.
Kim HW, et al. Am J Epidemiol. 1969 Apr;89(4):422-34.

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TABLE 5

RS virus infection and serious illness in comparable groups of infants receiving one or more injections of inactivated RS and parainfluenza vaccines

Vaccine	Category of infants	No. and age of infants during designated time period of RS virus prevalence				Total No. infants
		1965–1966		1966–1967		
		No. infants	Age§ (mo.)	No. infants	Age§ (mo.)	
RS lot 100	At risk*	20	5.1	25‡	12.7	31
	RS infection†	5		15		20 (65%)‖
	Hospitalized	4		12		16 (80%) ¶
Total parainfluenza	At risk*	20	5.0	37	11.8	40
	RS infection†	2		19		21 (53%)‖
	Hospitalized			1		1 (5%) ¶

Two fatal cases in vaccinees at 14 and 16 months

Noor et al. J Pediatric Infect Dis Soc. 2024 Jul 12;13(Supplement_2):S103-S109.
Kim HW, et al. Am J Epidemiol. 1969 Apr;89(4):422-34.

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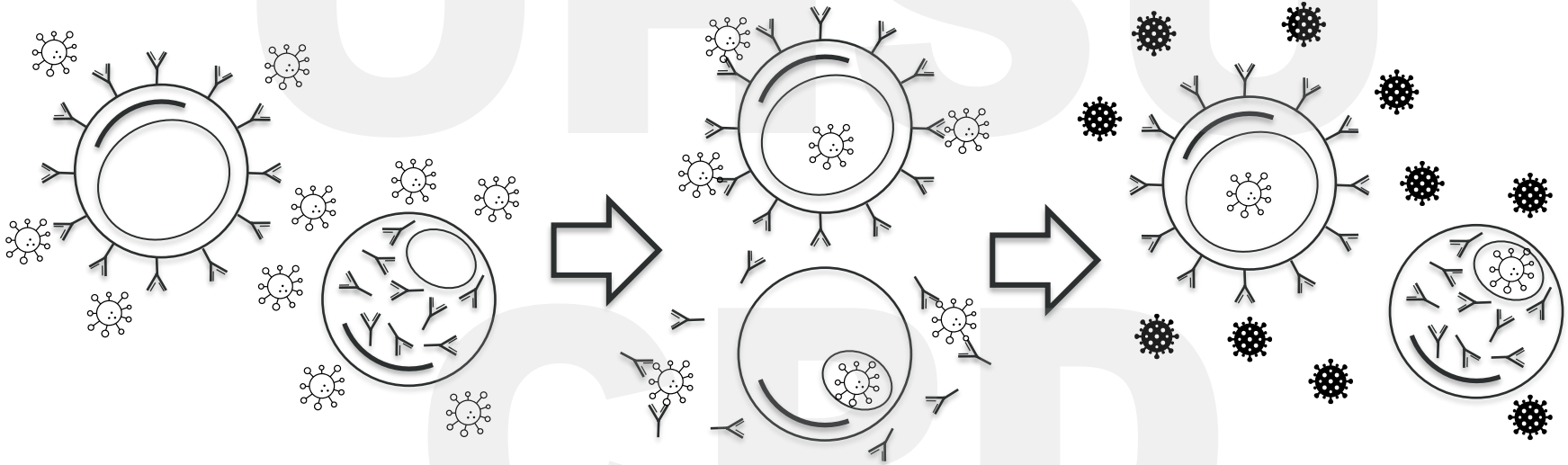
Original antigenic sin



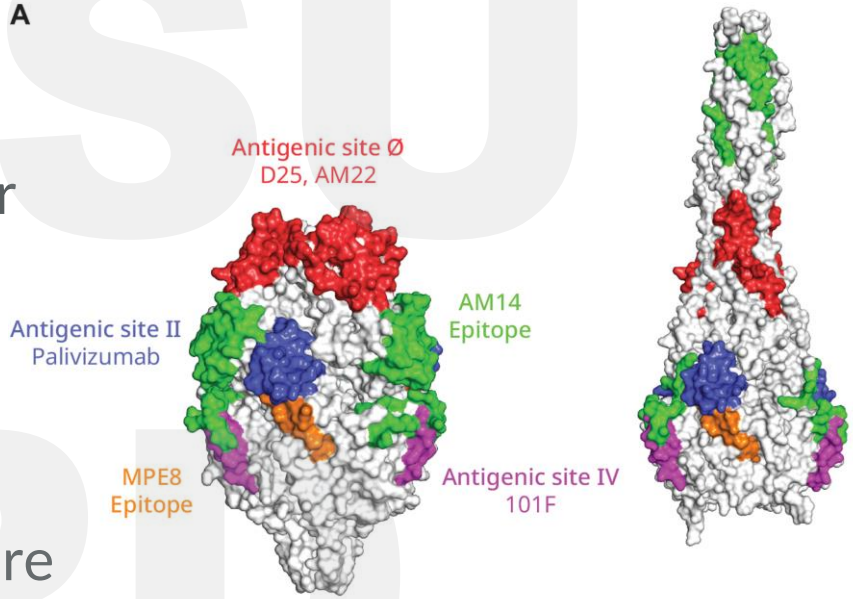
Vaccination with formaldehyde inactivated virus

T- and B-lymphocytes recognize and respond to inactivated virus

Wild-type virus is recognized, but not neutralized

RSV F-protein

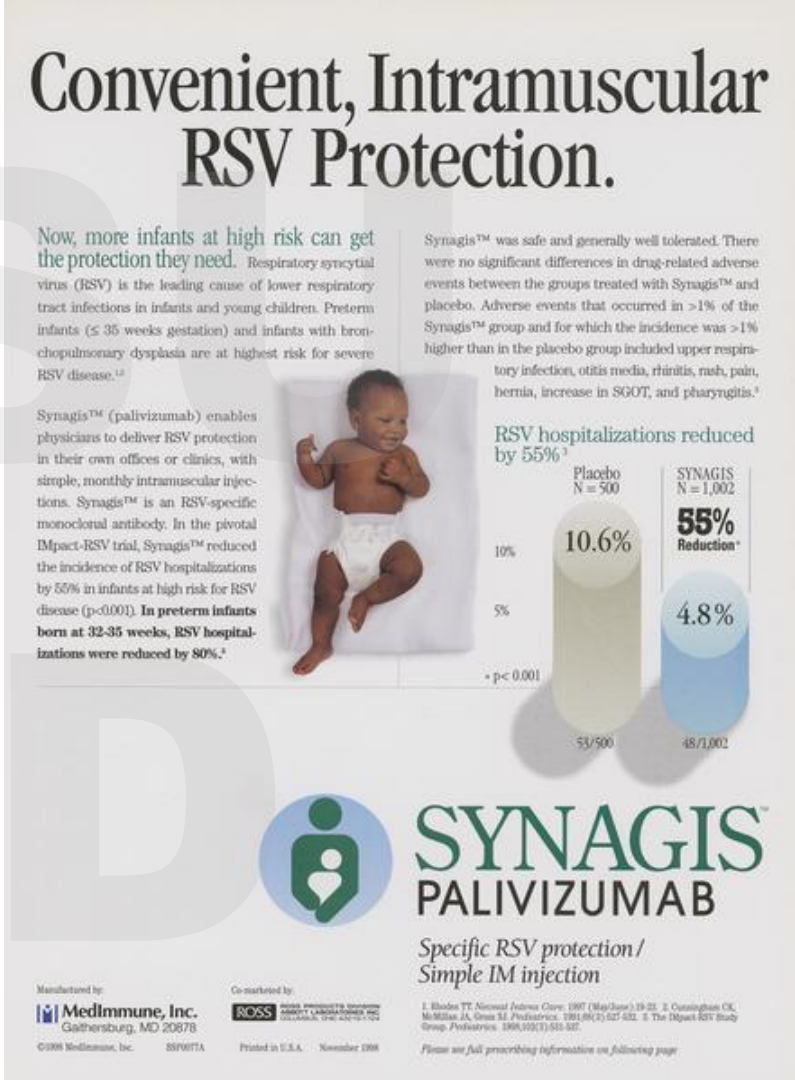
- Fusion protein responsible for cell entry
- Major target for antibody neutralization
- Different conformations before and after fusion



Sci Transl Med. 2023 Apr 26;15(693):eade6422.

Palivizumab (Synagis)

- Monthly IM injections
- Not cost-effective for universal use
- Recommended for high-risk sub-groups over the first and second RSV seasons



Wang et al. Health Technol Assess. 2011 Jan;15(5):iii-iv, 1-124.
https://search.library.wisc.edu/digital/A4GQ63WM3KPIP48T/pages

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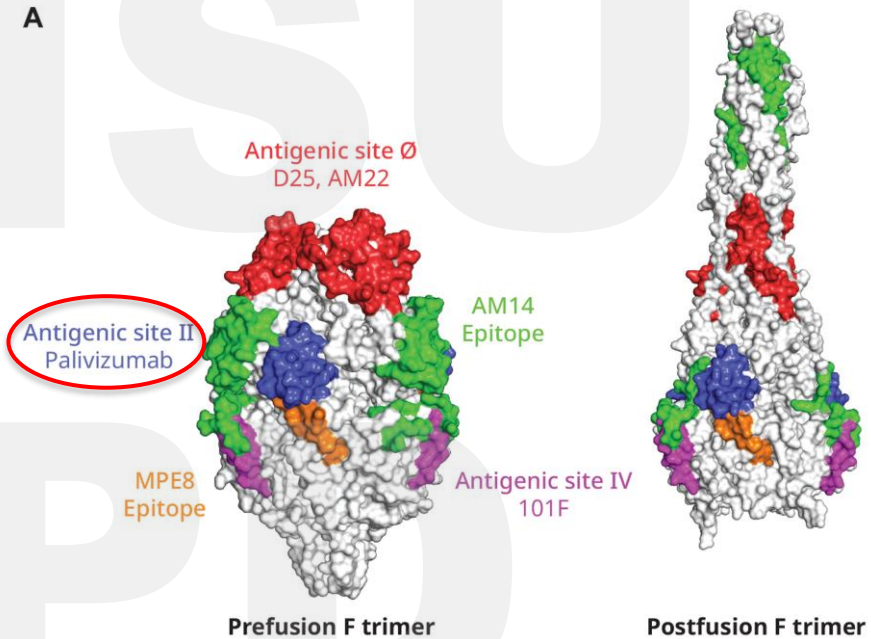

Wang et al. Health Technol Assess. 2011 Jan;15(5):iii-iv, 1-124.
Sci Transl Med. 2023 Apr 26;15(693):eade6422.

Part 2: New RSV-prevention tools

RSV prevention strategies

- Goal: functional antibodies in the first year of life

RSV maternal (parental) antibody

- Antibodies cross the placenta

Long-lasting passive antibody

- Antibodies directly injected

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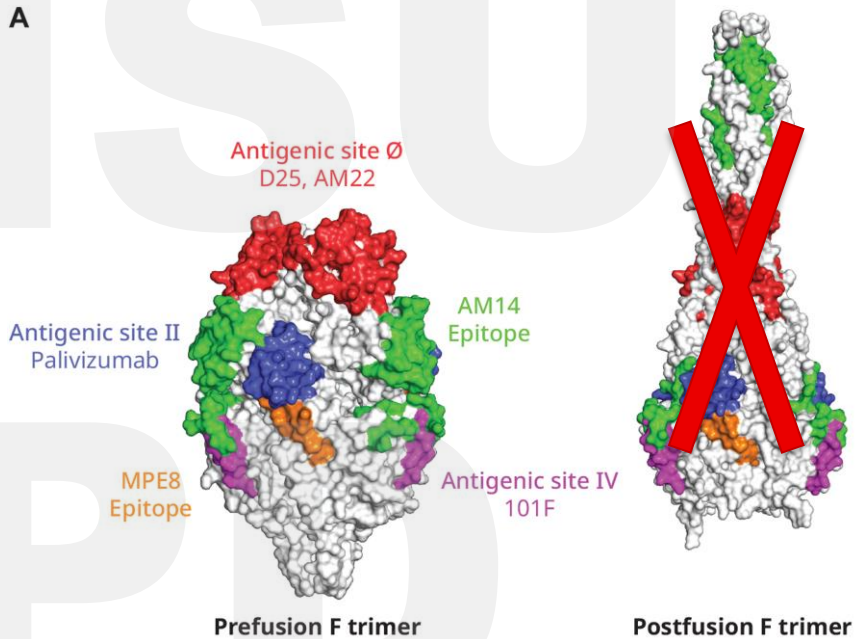
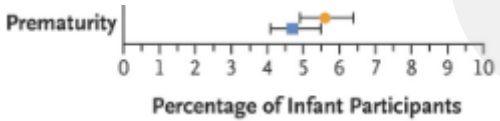
RSV preF RSV vaccine (Abrysvo)

- Recombinant protein vaccine against RSV Fusion protein
- Pregnant people (and adults ≥ 60 years)
- Single dose (IM injection)
- Given September-January between 32-36 weeks of pregnancy



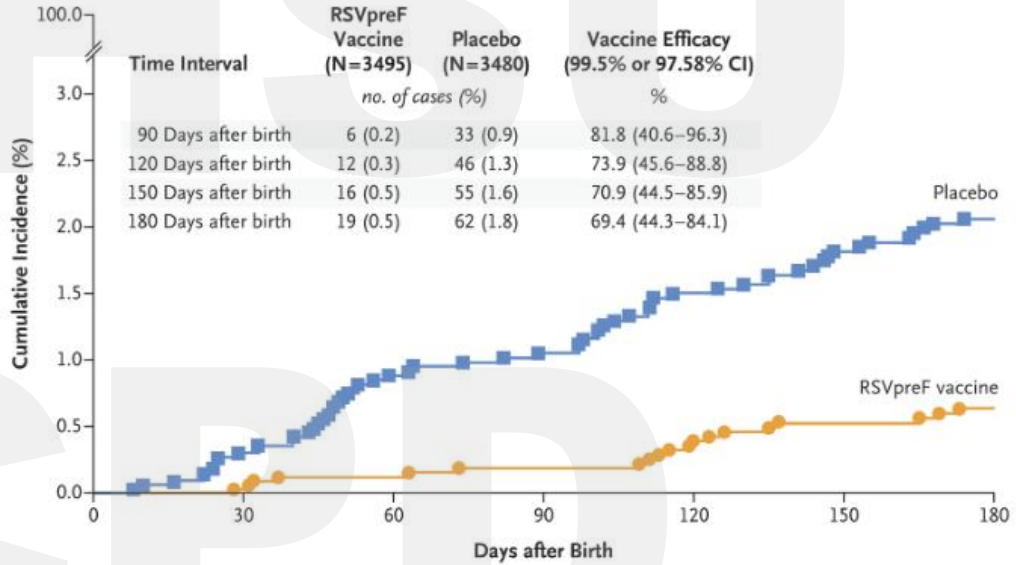
RSV preF RSV vaccine (Abrysvo)

- 7392 pregnant people
  - Randomized
    1:1 vaccine : placebo
- 7128 infants followed after delivery
- Non-significant trend towards increased prematurity with vaccine



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

Kampmann et al. N Engl J Med. 2023 Apr 20;388(16):1451-1464.

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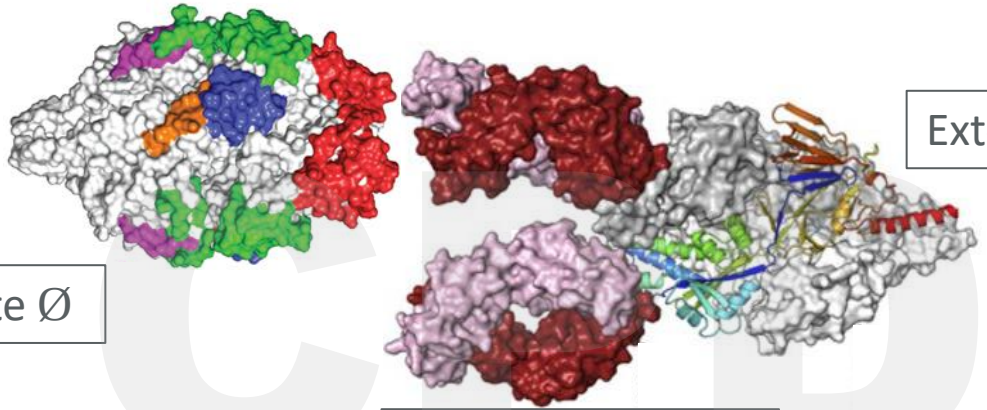
Nirsevimab (Beyfortus)

- Engineered antibody against RSV Fusion protein
- Fc region modified to enhance half-life



Zhu et al. Sci Transl Med . 2017 May 3;9(388):eaaj1928.

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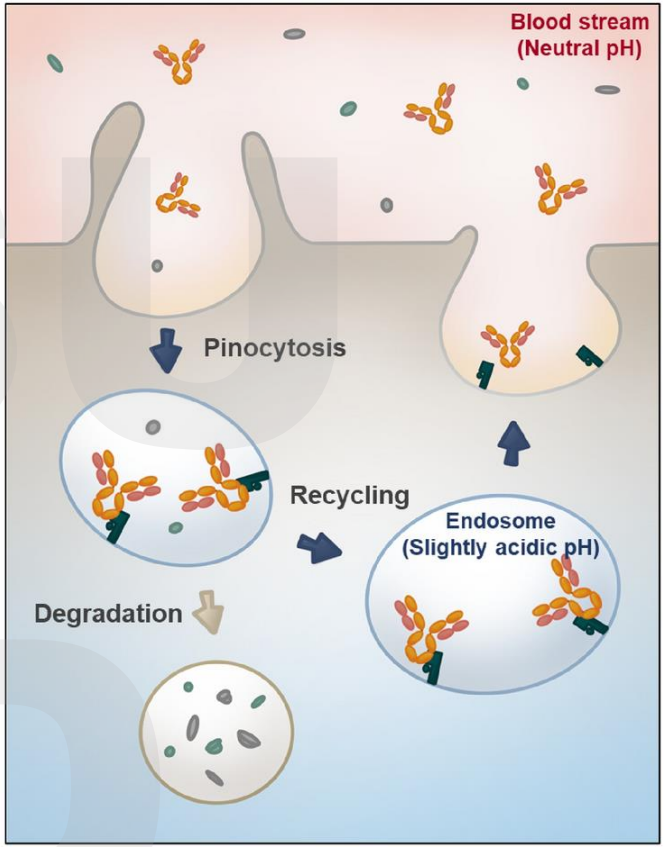
IgG Recycling

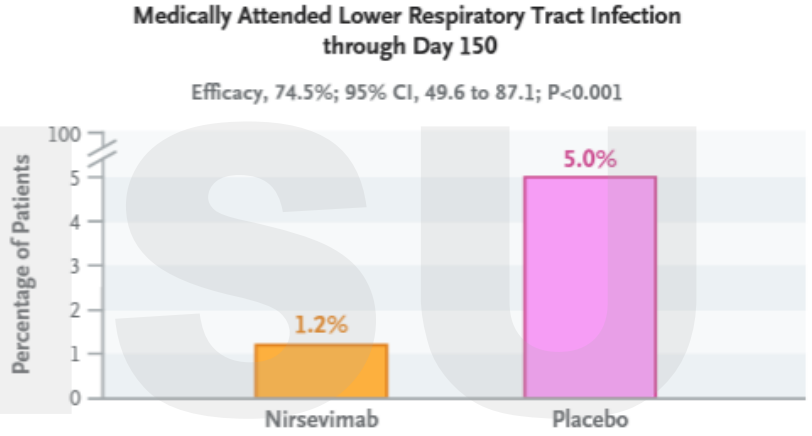
- IgG proteins are recycled through acidified endosomes
- Engineered Fc region enhances binding to Fc receptor
- $t_{1/2}$ palivizumab: 20 days
- $t_{1/2}$ nirsevimab: **up to 6 months**

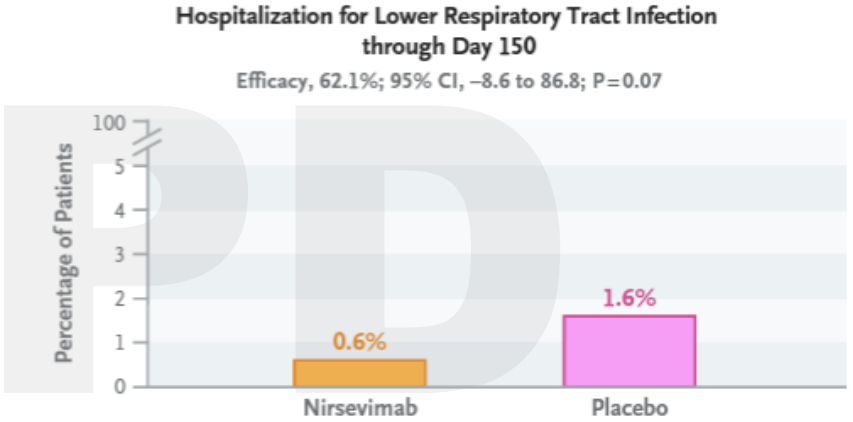


Ko S, et al. BioDrugs. 2021 Mar;35(2):147-157.

The NEW ENGLAND JOURNAL of MEDICINE

- 1490 infants in 1st RSV season
  - Randomized 2:1 vaccine : placebo
- 37 medically-attended LRTI
- 14 hospitalizations for LRTI
- No important safety signal





Hammitt et al. N Engl J Med 2022; 386:837-846.

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ACIP Evidence Summary

Efficacy	Nirsevimab	RSVpreF
RSV-related attended LRTI	79.0% [68.5–86.1]	57.3% [29.8–74.7]
RSV-related hospitalization	80.6% [62.3–90.1]	76.5% [41.3–92.1]
RSV-related ICU hospitalization	90.0% [16.4–98.8]	--------
Cost per QALY	$102,811	$167,280

Recommendation: universal use of RSVpreF **OR** nirsevimab for infants < 8 months of age during their 1st RSV season

Jones et al. MMWR Morb Mortal Wkly Rep. 2023 Aug 25;72(34):920-925.
Fleming-Dutra KE et al. MMWR Morb Mortal Wkly Rep. 2023 Oct 13;72(41):1115-1122.

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Part 3: The first year of RSV prevention

2023-2024 experience

- Was RSV prevention effective?
- Were these products acceptable to parents?
- Was this approach cost-effective?

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Nirsevimab in the real world

Setting	N (vaccinees)	Estimated efficacy	
		Hospitalization	ICU Care
France	690	83%	70%
US (NVSN)	407	90%	---

No evidence of enhanced disease in the 2nd RSV season

Assad Z, et al. N Engl J Med. 2024 Jul 11;391(2):144-154.
Moline HL, et al. MMWR Morb Mortal Wkly Rep. 2024 Mar 7;73(9):209-214.
Dagan R, et al. J Pediatric Infect Dis Soc. 2024 Feb 26;13(2):144-147.

RSV pre-F in the real world

Uptake of RSV protection

High demand for nirsevimab leads to supply glitches

News brief | October 19, 2023

Lisa Schnirring

Topics: Respiratory Syncytial Virus (RSV)

Razzaghi H, et al. MMWR Morb Mortal Wkly Rep. 2024 Sep 26;73(38):837-843.
https://www.cidrap.umn.edu/respiratory-syncytial-virus-rsv/high-demand-nirsevimab-leads-supply-glitches

Uptake of RSV protection

- 678 pregnant people eligible for RSV vaccination
  - **32.6%** report receipt of RSV pre-F vaccine
- 866 infants eligible for nirsevimab
  - **44.6%** report receipt of nirsevimab
- **55.8%** report one or more RSV protection product

Razzaghi H, et al. MMWR Morb Mortal Wkly Rep. 2024 Sep 26;73(38):837-843.
https://www.cidrap.umn.edu/respiratory-syncytial-virus-rsv/high-demand-nirsevimab-leads-supply-glitches

PERSPECTIVES

Nirsevimab: The Hidden Costs

Samantha Neumann, DO, Brian Alverson, MD

- More expensive than any universally-recommended vaccine
  - $495 list price
  - $395 VFC
- Protection is short-lived

TABLE 1 Number Needed to Immunize per Event and Cost per Health Event Averted[9]

Event	Number of Infants Needed to Immunize to Prevent 1 Event	Cost per Health Event Averted (at $445/Dose)
Outpatient visit	17	$2662
Emergency department visit	48	$7473
Inpatient day	24	$3687
Inpatient stay	128	$19 909
ICU day	194	$30 165
ICU stay	581	$90 464

Neumann S, et al. Hosp Pediatr. 2024 May 9;14(6):e2024007739.

PERSPECTIVES

Nirsevimab: The Hidden Costs

Samantha Neumann, DO, Brian Alverson, MD

- More expensive than any universally-recommended vaccine
  - $495 list price
  - $395 VFC
- Protection is short-lived

Vaccine	$/QALY
Nirsevimab	$102,811
MenB	$3.7 – 9.4 million
HPV	$3,000 – $45,000
PCV-13	$20,200
Influenza (older adult)	$612

Neumann S, et al. Hosp Pediatr. 2024 May 9;14(6):e2024007739.

Patterns in nirsevimab uptake

Practices administering nirsevimab		Infants receiving nirsevimab	
Factor	**Relative Risk**	**Factor**	**Relative Risk**
Large practice	**2.12** [1.16-3.90]	Medical complexity	**1.24** [1.11-1.38]
Medium practice	**2.12** [1.15-3.92]	Non-English speaking	**1.10** [1.01-1.19]
Publicly insured patients	*0.97* [0.95-0.98]	Public insurance	*0.76* [0.69-0.84]
Lowest-income ZIP codes	*0.86* [0.84–0.88]	Lowest-income ZIP codes	*0.90* [0.81-0.99]
52/79 practices (65.8%) of practices administered nirsevimab			
Individual Uptake: 47.3% of eligible infants at practices administering nirsevimab			

Abraham C, et al. Pediatrics. 2024 Jul 1;154(1):e2023065425.

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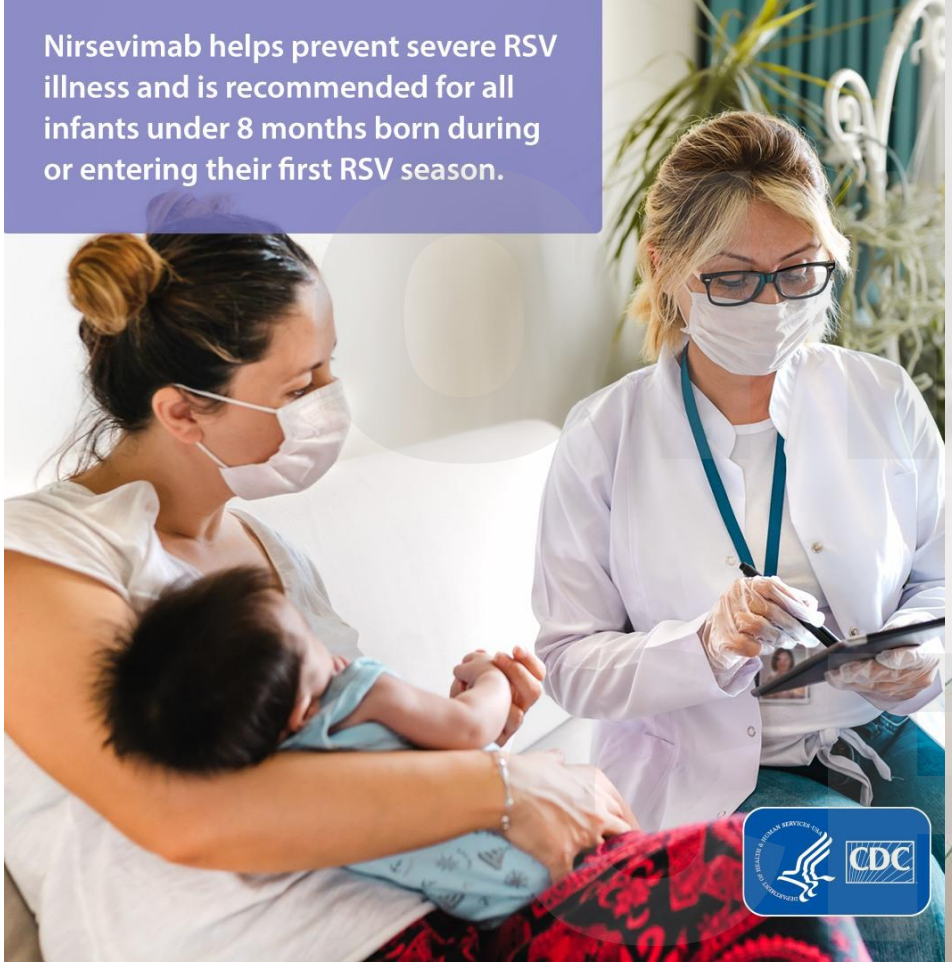
Part 4: Current Recommendations



https://www.instagram.com/acog_org/p/Cx6IfsEsPAH/
https://www.facebook.com/cdc/photos/cdc-recommends-use-of-nirsevimab-to-protect-all-infants-younger-than-8-months-an/683549590473149/

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RSV preF recommendations

- All pregnant people 32 0/7 – 36 6/7 weeks gestation
- Eligible season: Sept 1 – Jan 31
- Pfizer product (Abrysvo) only
- Repeat vaccination with subsequent pregnancies not recommended at this time

Nirsevimab recommendations

- All infants < 8 months of age during their first RSV season
- Eligible season: Oct 1 – Mar 31
- Not indicated if pregnant parent received RSV preF vaccination > 14 days before delivery
- High risk infants 8-19 months in their 2nd season

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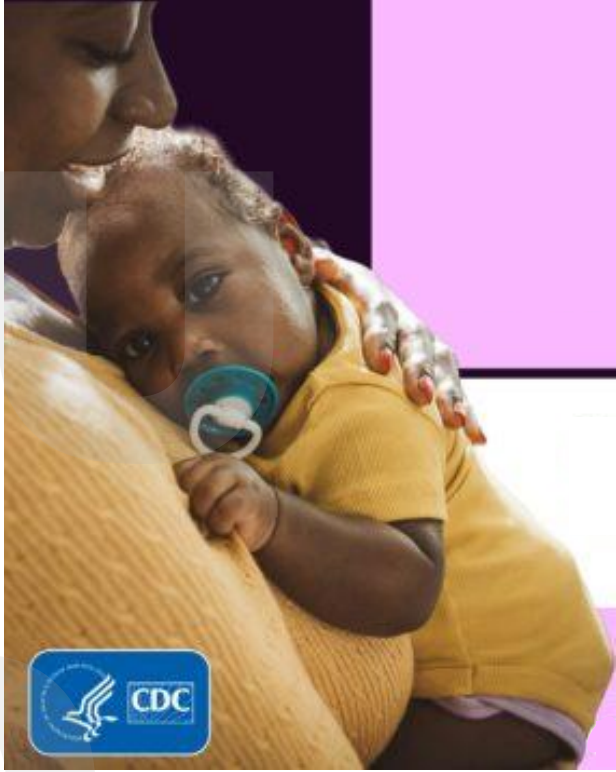
High risk groups

- CLD of prematurity requiring medical support in the last 6 months
- Severe immunocompromise
- Cystic fibrosis with severe lung disease, CXR abnormalities or growth failure
- American Indian and Alaska Native children



https://www.cdc.gov/mmwr/volumes/73/wr/mm7309a4.htm

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Loss of RSV preF antibodies

- Nirsevimab indicated despite RSV preF vaccination:
  - Vaccination < 14 days before delivery
  - Immunocompromised pregnant parent
  - ECMO or cardiopulmonary bypass
  - Substantially increased risk of severe RSV (e.g. severe CHD requiring supplemental O_2 at discharge)

https://www.aap.org/en/patient-care/respiratory-syncytial-virus-rsv-prevention/nirsevimab-frequently-asked-questions/

RSV preF

- Pregnancy vaccines well-established practice
- Relies on maternal immune system and placental transfer

Nirsevimab

- Novel approach
- Fewer intermediaries
- Can be given in newborn nursery
  - Risk of non-follow-up

The most effective vaccine is the one that is given!

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Open questions

- What is the real-world efficacy of RSV preF vaccination?
- What disparities can we anticipate in uptake of RSV protection, and how can they be mitigated?
- Will RSV evolve to escape immunity?
- Will non-lasting immunity have downstream effects?

Thank You