

RSV infection during the COVID-19 pandemic: BC experience and future vaccination strategies

Bahaa Abu-Raya
MD, PhD



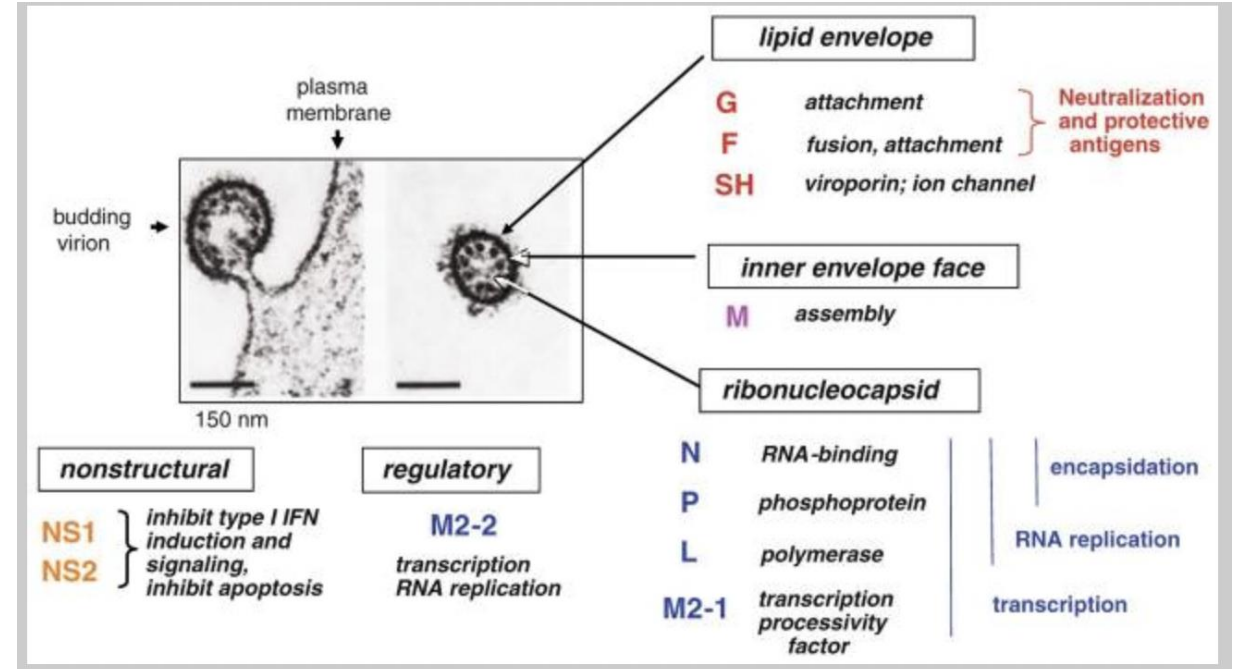
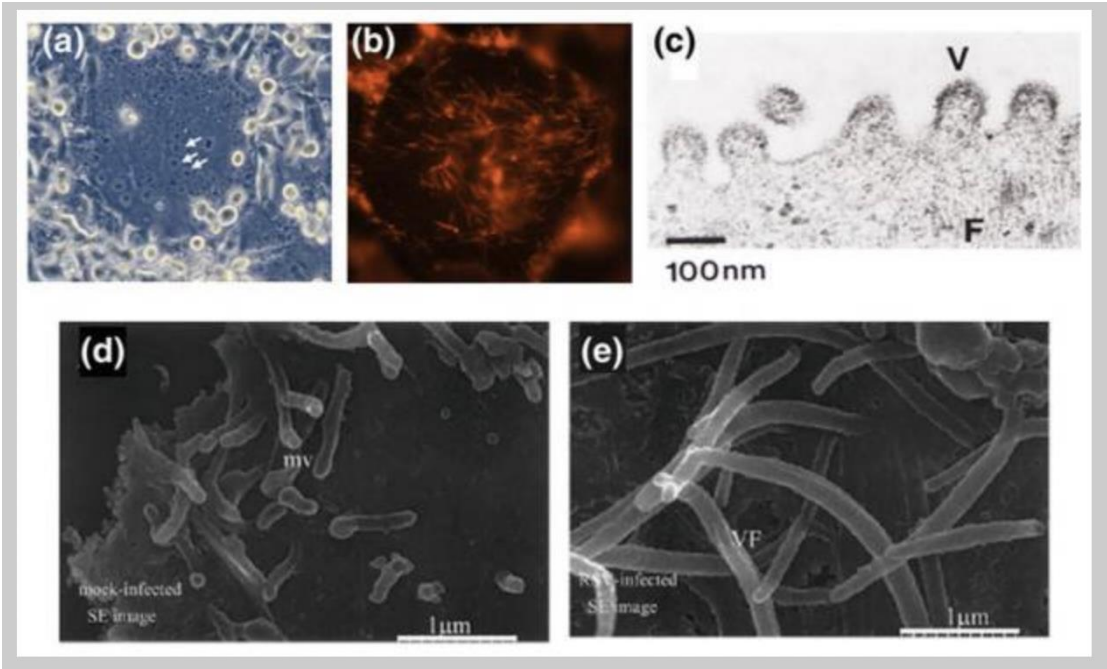
Disclosure:

- BA received honoraria for participation in live meetings from Sanofi Pasteur France and Canada related to pertussis and RSV.

Content

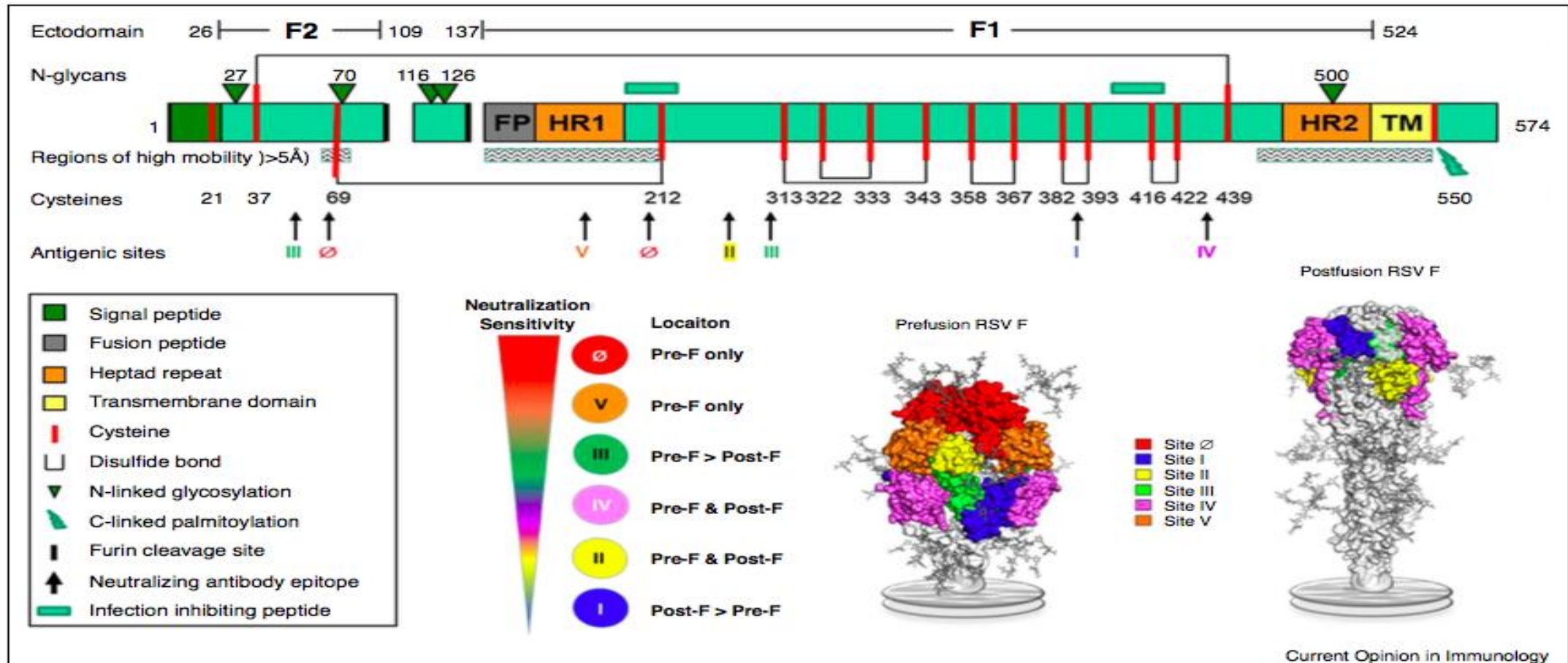
- Respiratory syncytial virus
- High risk groups for severe RSV infection
- RSV epidemiology and immunity during the COVID-19 pandemic – BC experience
- Passive and active immunization in the pipeline

Respiratory Syncytial Virus

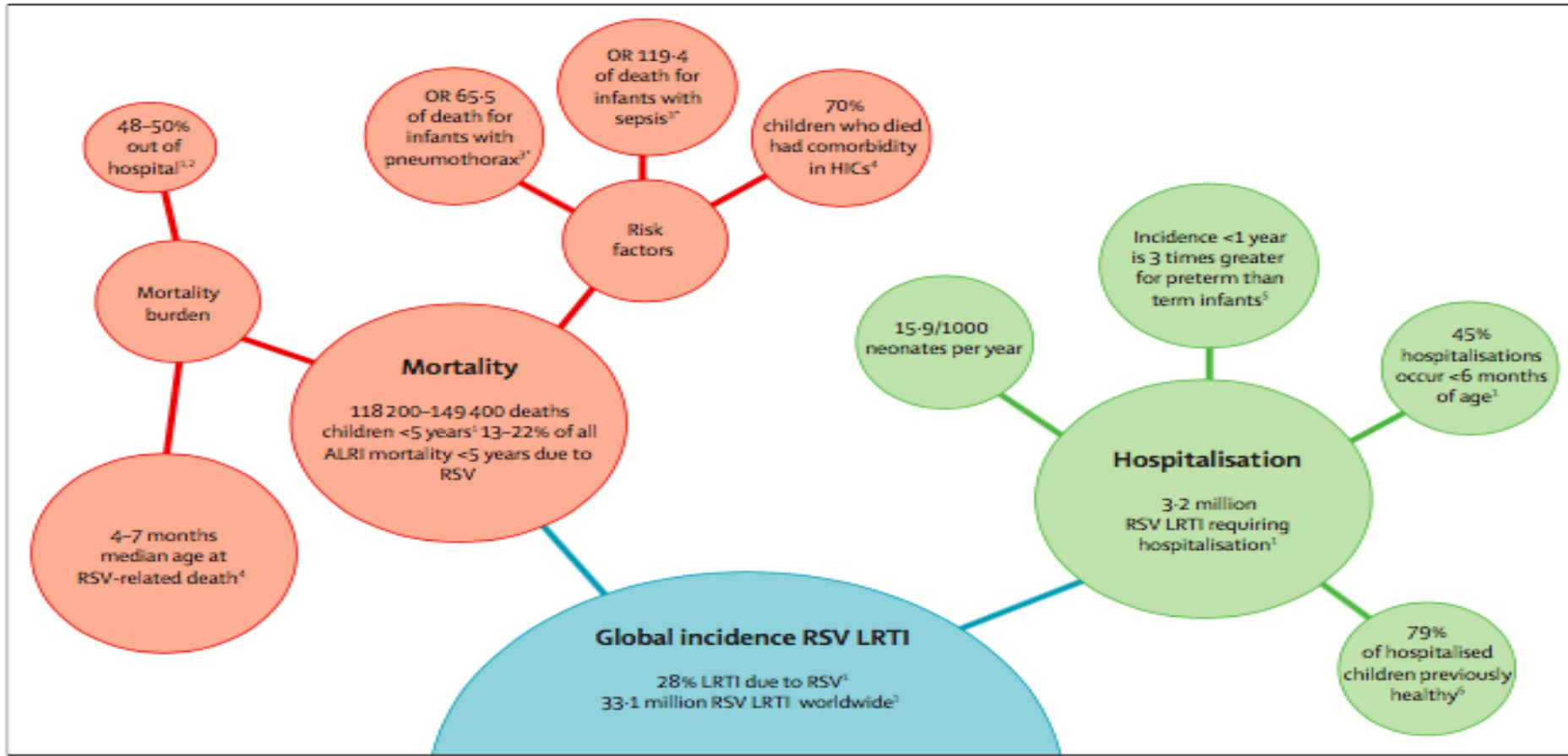


- Enveloped, non-segmented negative-strand RNA virus
 - Paramyxoviridae family

Pre-F conformation: more neutralization sites that post-F

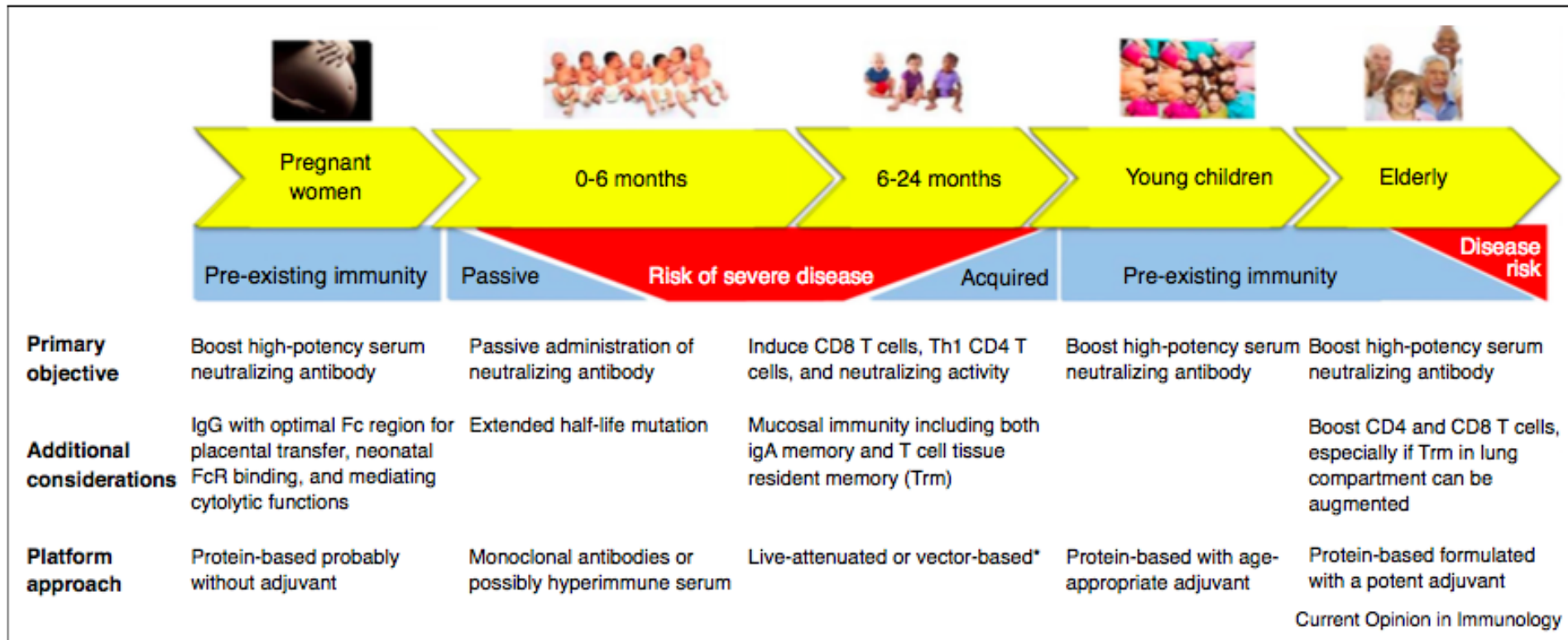


RSV burden and clinical manifestations



- **Manifestations**
- Runny nose
- Cough
- Sneezing
- Fever
- Wheezing
- Bronchiolitis
- Pneumonia

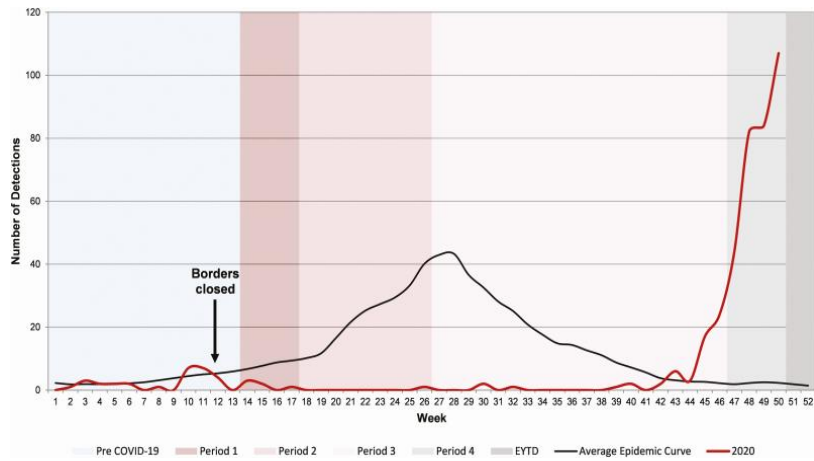
RSV severity across different age groups



Premature
CLD or CHD
Immunodeficiency
Neuromuscular dis

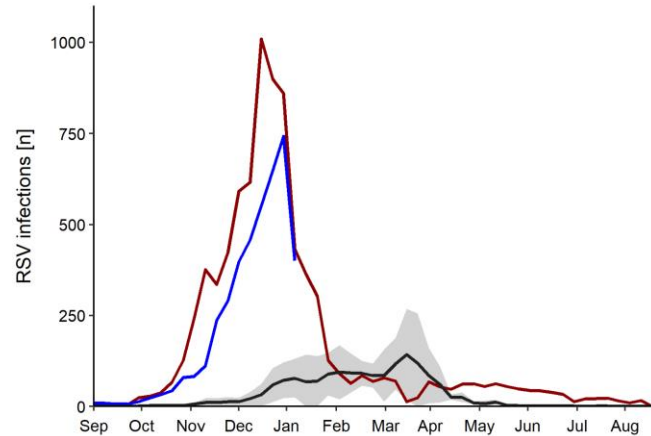
>65 years
CLD, heart disease
Immunocompromised

Atypical surge of RSV associated with the relaxation of the COVID-19 pandemic mitigation measures

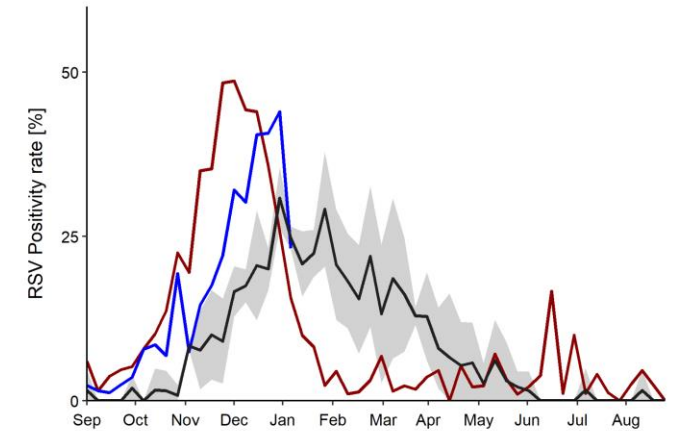
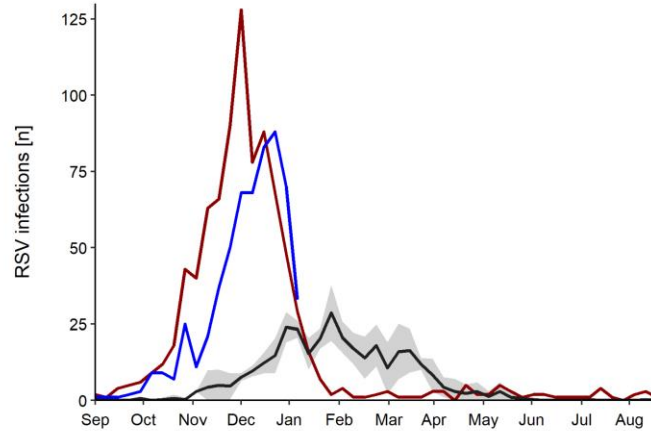
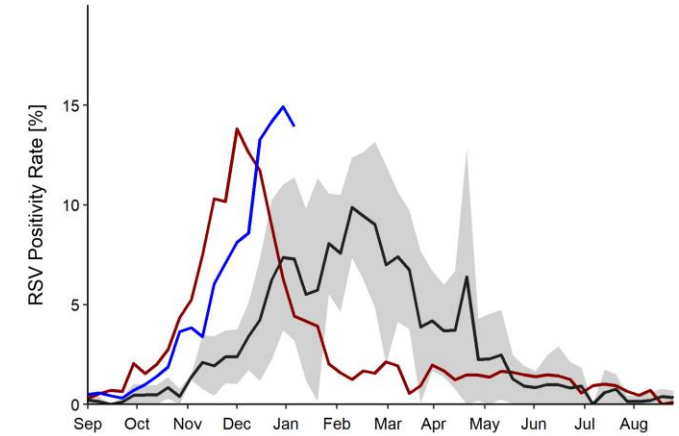


RSV detection, Western Australian.
Foley et al., CID, 2021

BC



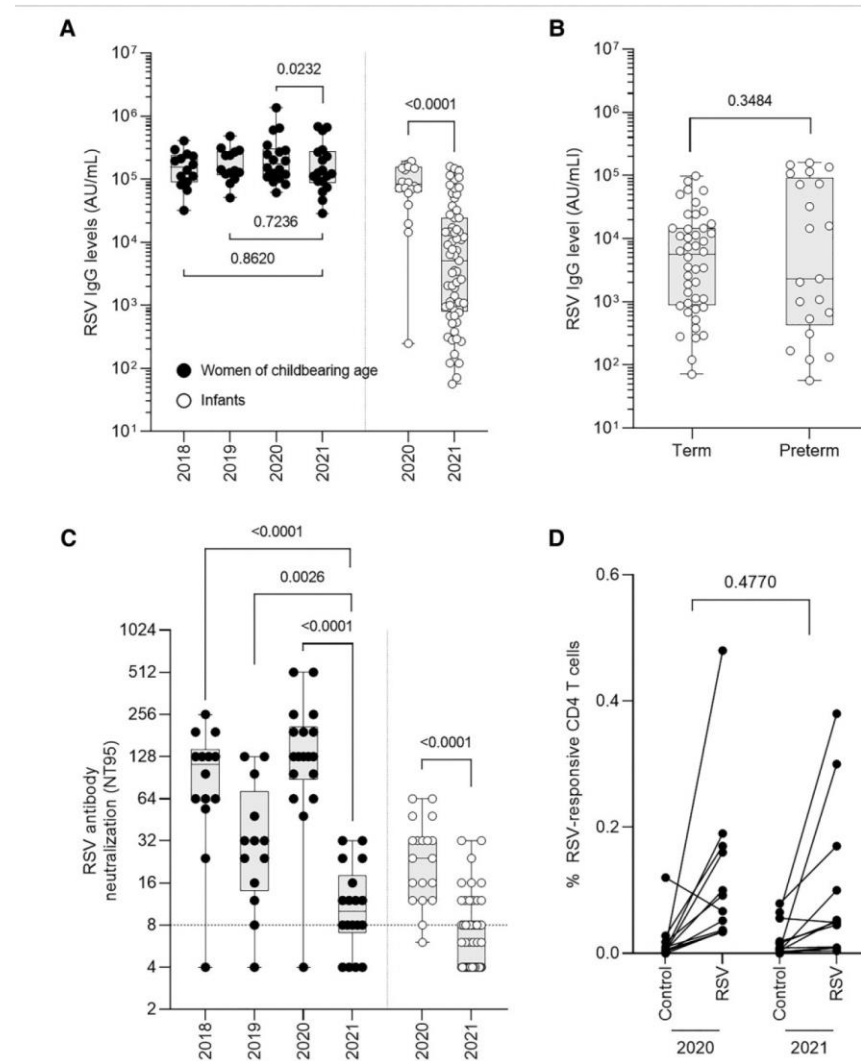
BCCH



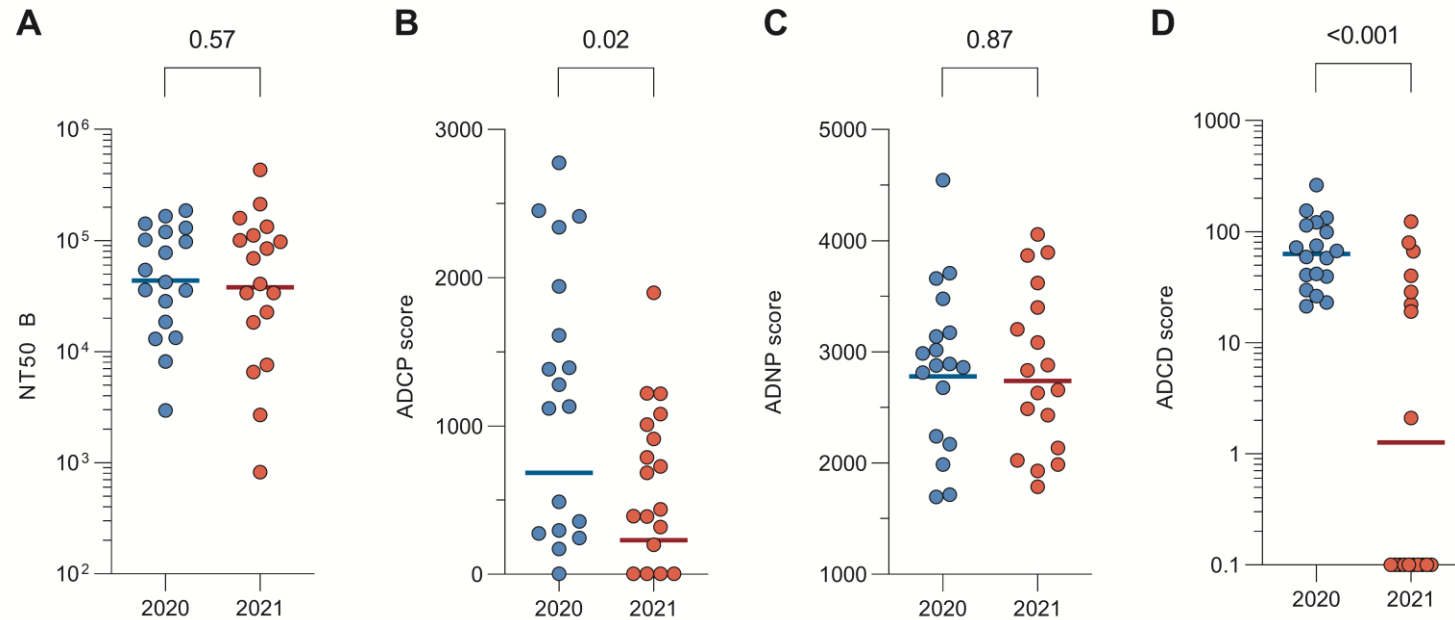
Vineta et al, Unpublished data

Black-2017-2020 aggregated
Red-2021-2022
Blue-2022-2023

Waning Immunity Against RSV During the Coronavirus Disease 2019 Pandemic

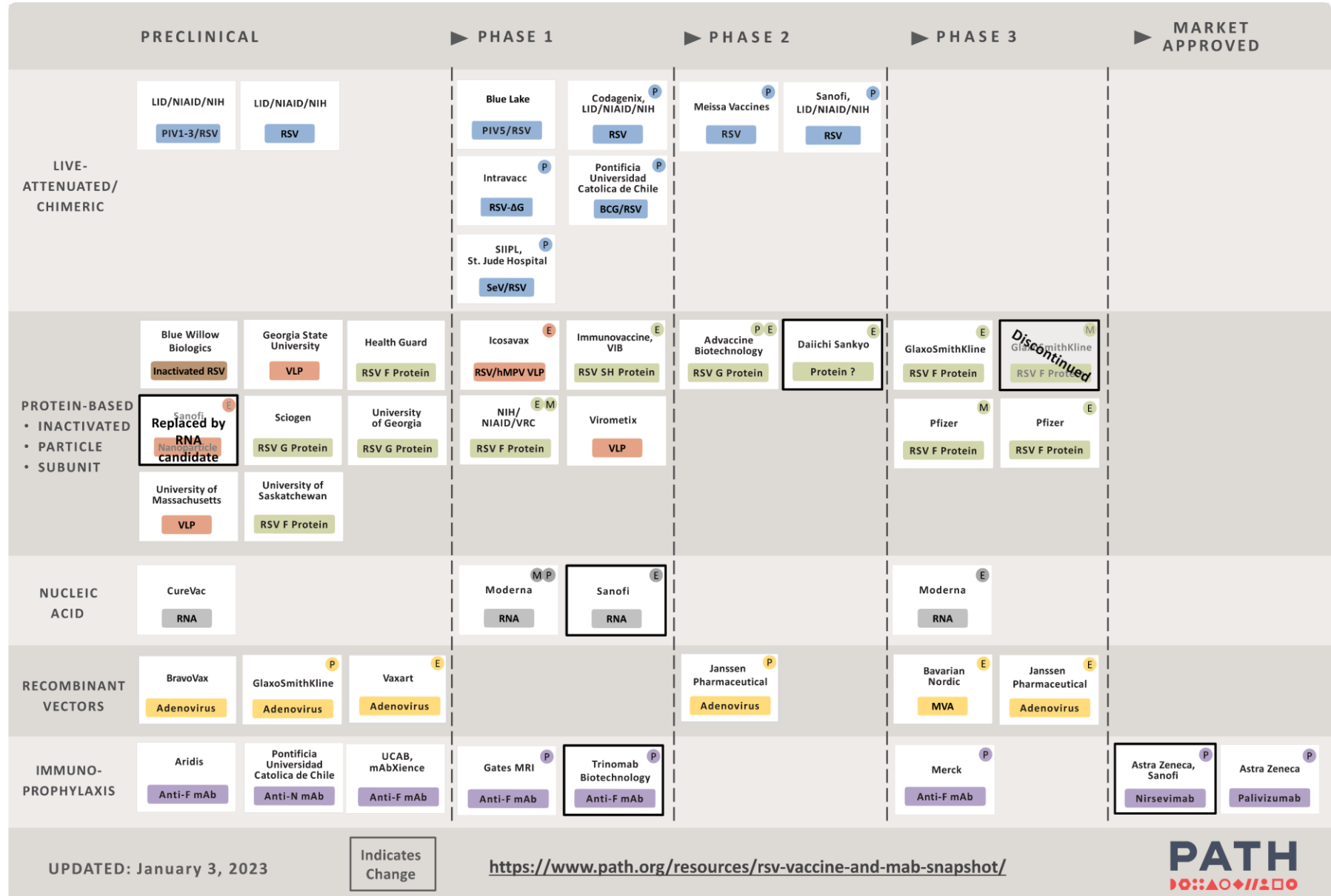


Selective loss of function of RSV antibodies associated with COVID-19 mitigation measures



RSV Vaccine and mAb Snapshot

TARGET INDICATION: P=PEDIATRIC M=MATERNAL E=ELDERLY



UPDATED: January 3, 2023

Indicates Change

<https://www.path.org/resources/rsv-vaccine-and-mab-snapshot/>

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

Phase 3 RCT; Adults 60 years or older

A single dose of AS01E-adjuvanted RSV prefusion F protein–based vaccine (RSVPreF3 OA GSK) or placebo before the RSV season.

Primary objective: VE against RSV-related LRTI, confirmed by RT-PCR, during one RSV season.

LRTI: at least two lower respiratory symptoms or signs (including at least one lower respiratory sign) or at least 3 lower respiratory symptoms lasting for at least 24 hours

Acute respiratory infection: at least 2 respiratory symptoms/signs or at least one respiratory and one systemic symptom/sign lasting for at least 24 hours.

Table 2. Vaccine Efficacy against First Occurrence of RSV-Related Lower Respiratory Tract Disease and RSV-Related Acute Respiratory Infection (Modified Exposed Population).*

End Point	RSVPreF3 OA Group				Placebo Group				Vaccine Efficacy (CI)†
	No. of Participants	No. of Events	Follow-up	Incidence Rate	No. of Participants	No. of Events	Follow-up	Incidence Rate	
			participant-yr	no. of events/1000 participant-yr			participant-yr	no. of events/1000 participant-yr	%
RSV-related lower respiratory tract disease									
Overall	12,466	7	6,865.9	1.0	12,494	40	6,857.3	5.8	82.6 (57.9 to 94.1)
Severe‡	12,466	1	6,867.9	0.1	12,494	17	6,867.7	2.5	94.1 (62.4 to 99.9)
According to RSV subtype§									
RSV A	12,466	2	6,867.4	0.3	12,494	13	6,868.9	1.9	84.6 (32.1 to 98.3)
RSV B	12,466	5	6,866.7	0.7	12,494	26	6,862.3	3.8	80.9 (49.4 to 94.3)

VE:

- RSV-related LRTI 82.6%
- Severe RSV-related LRTI 94.1%
- RSV related acute respiratory infection 71.7%

🕒 25 November 2022

GSK Canada submits respiratory syncytial virus (RSV) vaccine candidate for regulatory review

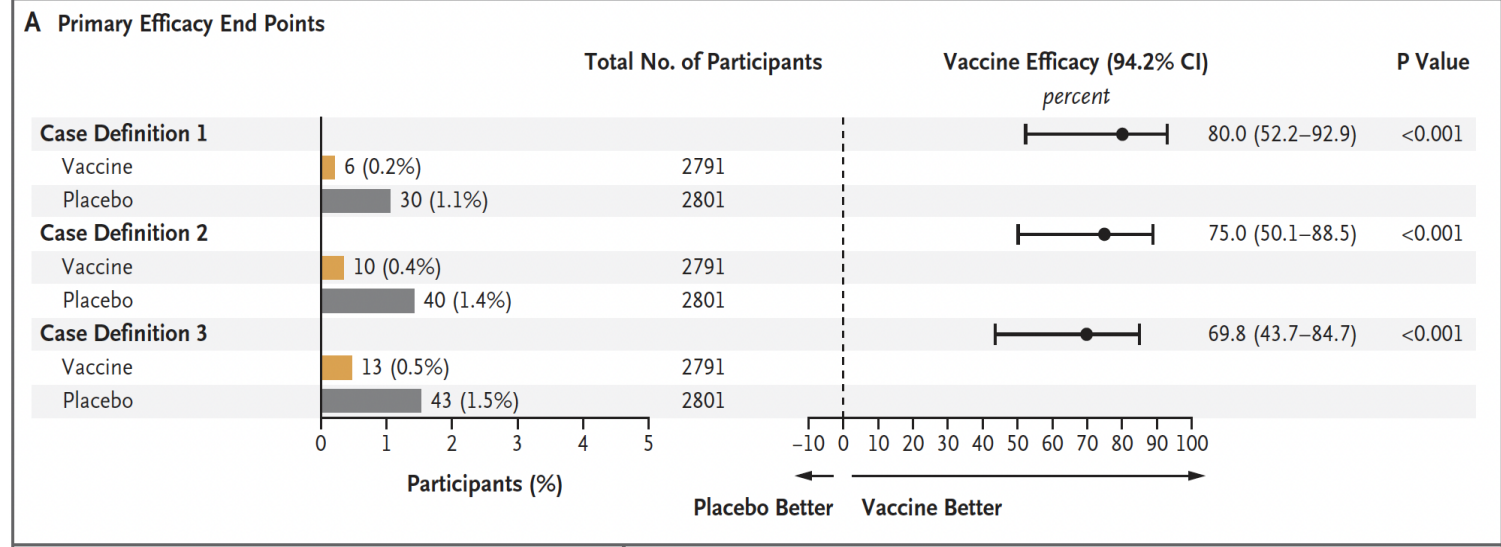
- Vaccine candidate has the potential to be the first available to help protect adults aged 60 years and older from lower respiratory tract disease caused by respiratory syncytial virus
- Application includes important pivotal phase III data evaluating the efficacy and safety of our vaccine candidate against respiratory syncytial virus-lower respiratory tract disease in adults aged 60 years and above
- Canadian regulatory submission follows regulatory submissions in the US, Europe and Japan

MISSISSAUGA, ON - GSK has filed a New Drug Submission (NDS) to Health Canada for its respiratory syncytial virus (RSV) older adult vaccine candidate. If approved, GSK's RSV older adult vaccine candidate has the potential to be the first vaccine available to help

Efficacy and Safety of an Ad26.RSV.preF–RSV preF Protein Vaccine in Older Adults

RCT phase 2b; Adults 65 years or older
Ad26 .RSV.preF–RSV preF protein vaccine
(Janssen Vaccines and Prevention) vs
placebo.

Primary end point: first occurrence of RSV-mediated LRTI that met one of 3 case definitions: three or more symptoms of LRTI (definition 1), two or more symptoms of LRTI (definition 2), and either two or more symptoms of LRTI or one or more symptoms of LRTI plus at least one systemic symptom (definition 3).



Safety: % of participants with solicited local and systemic adverse events were higher in the vaccine group than in the placebo group (local, 37.9% vs. 8.4%; systemic, 41.4% vs. 16.4%); most adverse events were mild to moderate in severity.

The frequency of serious adverse events was similar in the vaccine group and the placebo group (4.6% and 4.7%, respectively).

Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

Phase 3 RCT, adults older than 60 years

Unadjuvanted RSVpreF vaccine 120

µg (Pfizer, 60 µg of RSV A and RSV B) or placebo

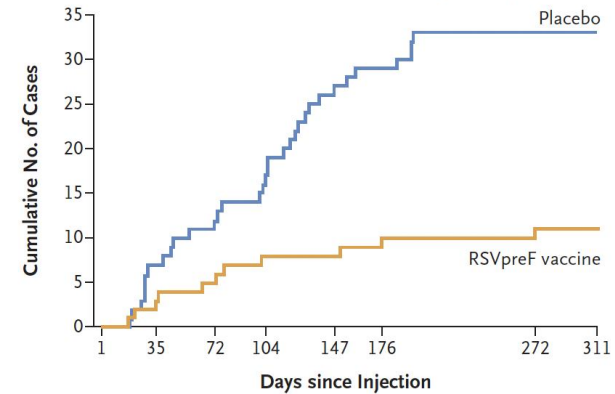
First primary end point: efficacy of RSVpreF vaccine in preventing lab-confirmed RSV-associated

LRTI (i.e., acute respiratory illness) with at least two signs or symptoms (i.e., cough, wheezing, sputum production, SOB, or tachypnea) lasting more than 1 day.

Second primary end point: efficacy of RSVpreF vaccine in preventing of lab-confirmed RSV-associated LRTI with at least 3 signs or symptoms lasting more than 1 day

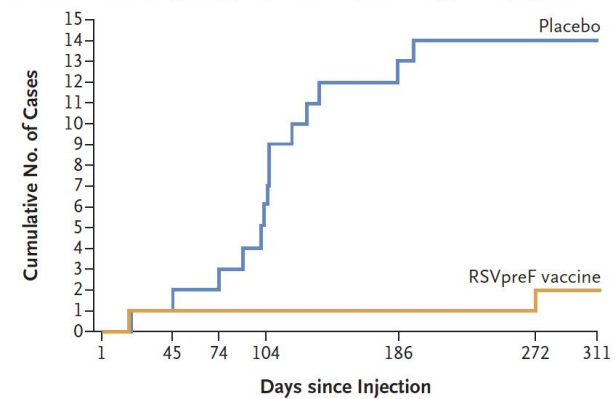
Statistical success criterion: lower boundary of the confidence interval >20%.

A RSV-Associated Lower Respiratory Tract Illness with ≥ 2 Signs or Symptoms



Vaccine Efficacy
(96.66% CI)
percent
66.7 (28.8–85.8)

B RSV-Associated Lower Respiratory Tract Illness with ≥ 3 Signs or Symptoms



Vaccine Efficacy
(96.66% CI)
percent
85.7 (32.0–98.7)

Interim analysis

MODERNA GRANTED FDA BREAKTHROUGH THERAPY DESIGNATION FOR MRNA-1345, AN INVESTIGATIONAL RESPIRATORY SYNCYTIAL VIRUS (RSV) VACCINE CANDIDATE

JANUARY, 30, 2023

 [DOWNLOAD](#)

Designation based on positive topline data from the ConquerRSV Phase 3 pivotal efficacy trial, which demonstrated vaccine efficacy of 83.7% against RSV lower respiratory tract disease, defined by 2 or more symptoms in older adults

CAMBRIDGE, MA / ACCESSWIRE / January 30, 2023 / Moderna, Inc. (NASDAQ:MRNA), a biotechnology company pioneering messenger RNA (mRNA) therapeutics and vaccines, today announced mRNA-1345, an investigational mRNA vaccine candidate for respiratory syncytial virus (RSV), has been granted Breakthrough Therapy Designation by the U.S. Food and Drug Administration (FDA) for the prevention of RSV-associated lower respiratory tract disease (RSV-LRTD) in adults aged 60 years or older. The designation was based on positive topline data from the ConquerRSV Phase 3 pivotal efficacy trial.

"The FDA's Breakthrough Designation for mRNA-1345 further emphasizes the significant health impact of RSV in older adults and the high unmet need," said Stéphane Bancel, Chief Executive Officer of Moderna. "With this designation, we look forward to productive conversations with the FDA in the hopes of bringing our RSV vaccine candidate for older adults to the market safely and quickly. Moderna's mRNA platform has now demonstrated two positive Phase 3 infectious disease trial results and we continue to advance a portfolio of respiratory mRNA vaccines targeting the most serious diseases. We are grateful to the FDA for this designation."

The FDA's Breakthrough Therapy Designation is granted to expedite the development and review of drugs that are intended to treat a serious condition, and when preliminary clinical evidence indicates the drug or vaccine may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).¹

mRNA-1345 was previously granted Fast Track designation by the FDA in August 2021. Moderna intends to submit a license application for regulatory approval in the first half of 2023.

The ConquerRSV study, a randomized, double-blind, placebo-controlled study evaluating the efficacy of mRNA-1345 against RSV-LRTD as defined by two or more symptoms. The study met its primary efficacy endpoints, including vaccine efficacy (VE) of 83.7% (95.88% CI: 66.1%, 92.2%; p<0.0001) against RSV-LRTD as defined by two or more symptoms and VE of 82.4% (96.36% CI: 34.8%, 95.3%; p=0.0078) in RSV-LRTD as defined by three or more symptoms.

PVZ: moderately effective in high risk infants

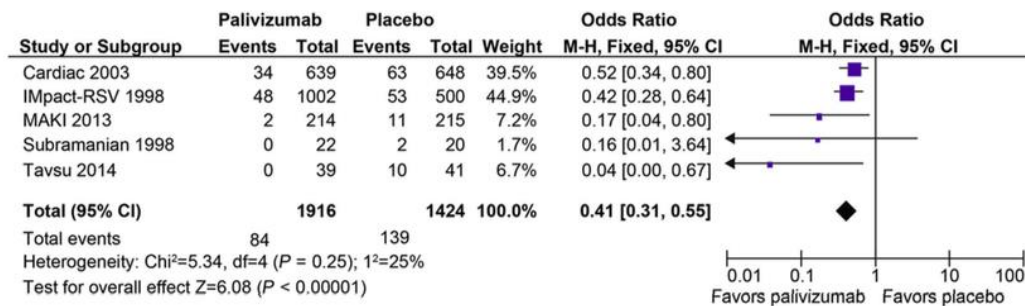
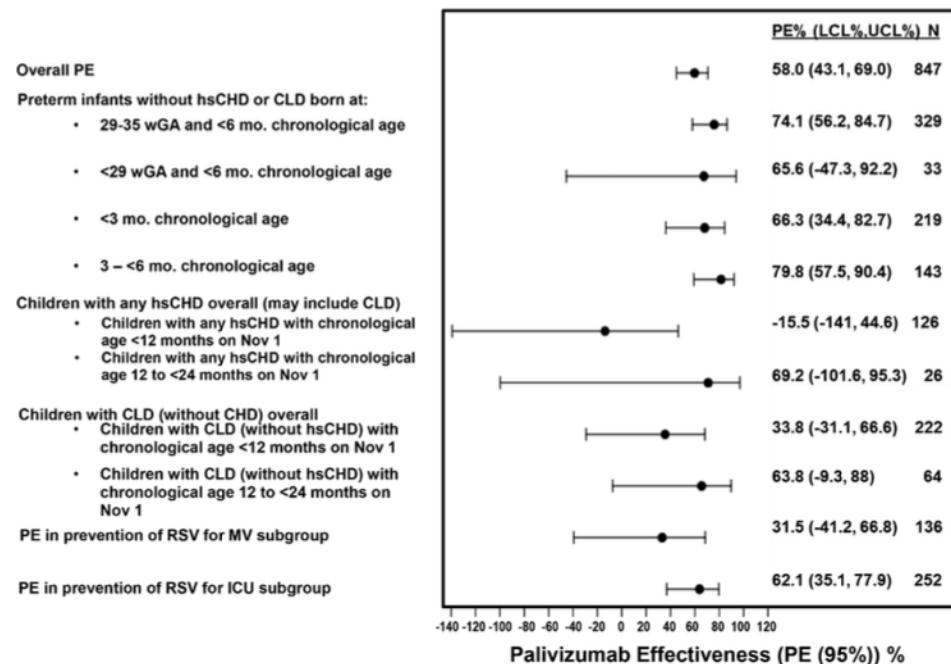


Fig. 3 Meta-analysis of RSV-related hospitalization in the randomized, placebo-controlled trials. *M-H* Mantel-Haenszel method, *RSV* respiratory syncytial virus

Wegzyn et al, Infect Dis Ther (2014) 3:133–158

Monthly injection
 Logistics
 Cost
 Partial effectiveness, short half life
 Limited to high risk infants



Anderson et al, PIDJ 2017 3:133–158

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

M. Pamela Griffin, M.D., Yuan Yuan, Ph.D., Therese Takas, B.S., Joseph B. Domachowske, M.D., Shabir A. Madhi, M.B., B.Ch., Ph.D., Paolo Manzoni, M.D., Ph.D., Eric A.F. Simões, M.D., Mark T. Esser, Ph.D., Anis A. Khan, Ph.D., Filip Dubovsky, M.D., Tonya Villafana, Ph.D., and John P. DeVincenzo, M.D., for the Nirsevimab Study Group*

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

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

Griffin et al, NEJM 2020

ORIGINAL ARTICLE

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

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

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

Hammitt et al, NEJM 2022

Study period: July 23 2019–October 27 2021

Hold between March 15 2020 –April 9 2021

Underpowered to show VE against hospitalization –
Termination due to COVID19

CORRESPONDENCE

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

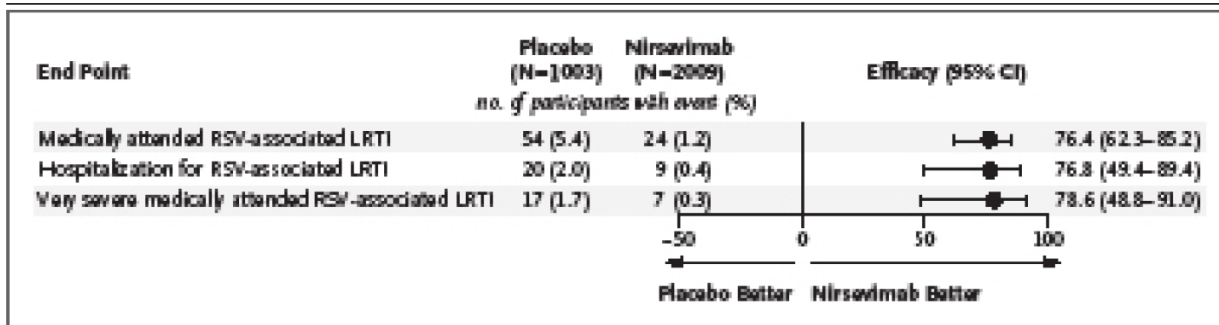


Figure 1. Incidence of Medically Attended Respiratory Syncytial Virus (RSV)–Associated Lower Respiratory Tract Infection (LRTI) through 150 Days after Injection and Efficacy of Nirsevimab as Compared with Placebo.

Very severe medically attended RSV-associated LRTI was defined as infection for which hospitalization and supplemental oxygen or intravenous fluids were warranted. Data are from the intention-to-treat population, which consisted of all infants who had undergone randomization.

Approved by European Medicines Agency

Approved by UK Medicines

US FDA accepted AstraZeneca’s Biologics License Application for review.

Health Canada (authorized, April 24th 2023)

Expanding indication to other high risk groups before RSV season?

Full study after resumption of enrollment

Muller et al, NEJM 2023

Prefusion F Protein–Based Respiratory Syncytial Virus Immunization in Pregnancy

- Phase 2b trial
- Bivalent RSV Pre-F protein-based vaccine
- 24-36 WG

Interim analysis

B Infant Participants at Birth

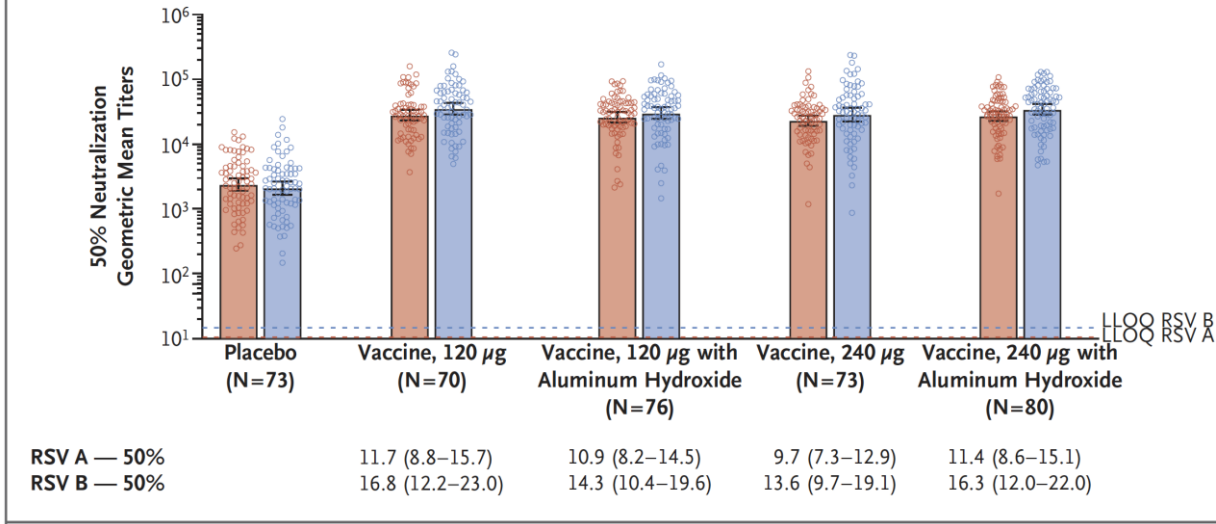


Table 2. Efficacy of Maternal Vaccination against RSV-Associated Lower Respiratory Tract Illness in the U.S. Cohort of 508 Infants.

Efficacy End Point	RSVpreF Vaccine (N = 405)	Placebo (N = 103)	Estimated Vaccine Efficacy (95% CI)
	number of infants with event		
Any medically attended RSV-associated lower respiratory tract illness*	3	5	84.7 (21.6 to 97.6)
Medically attended severe RSV-associated lower respiratory tract illness†	1	3‡	91.5 (–5.6 to 99.8)

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

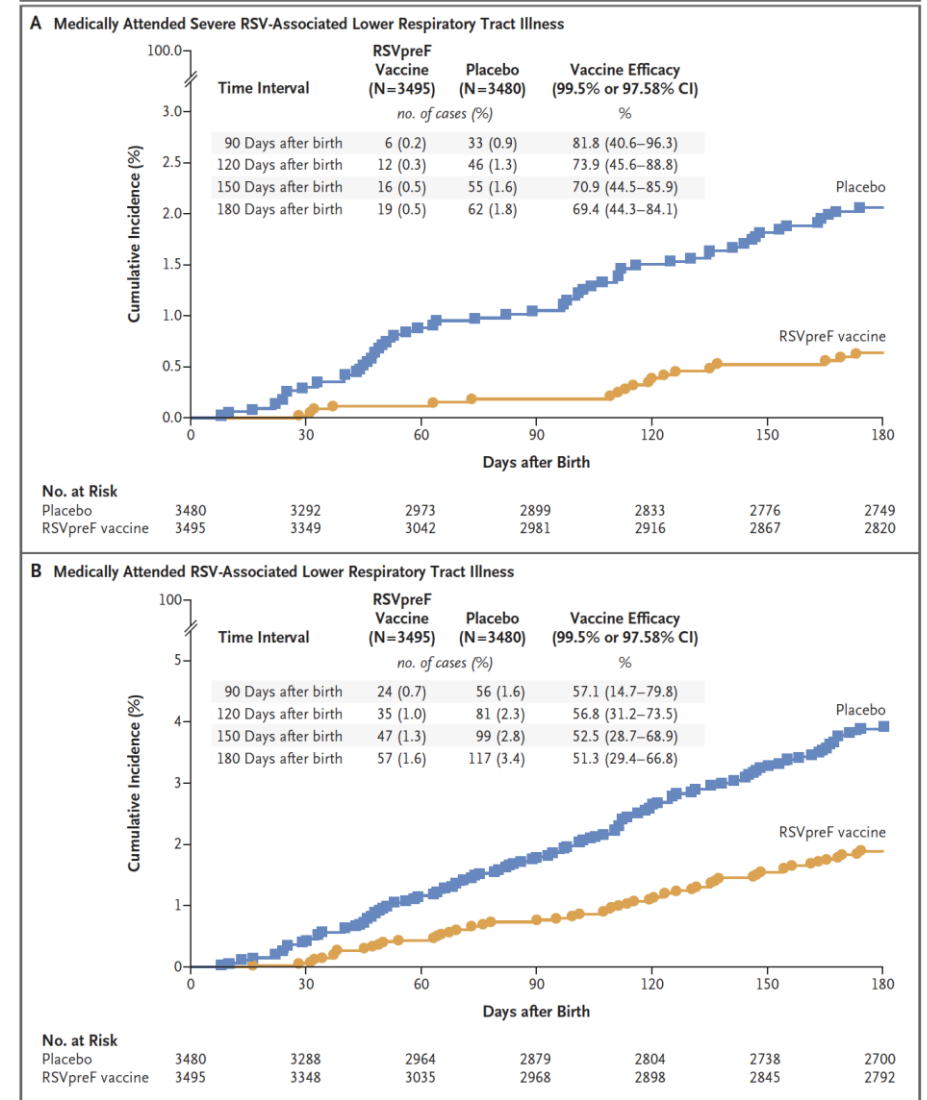
Phase 3 RCT (18 countries)

120 µg of a bivalent RSV prefusion F protein-based (RSVpreF) vaccine (Pfizer) (60 µg each of RSV A and RSV B antigens) or placebo at 24-36 WG

Two primary efficacy endpoints:

- Medically attended severe RSV-associated LRTI
- Medically attended RSV-associated LRTI in infants within 90, 120, 150, and 180 days after birth.

Statistical analysis: a lower boundary of the CI that was greater than 20% was considered to meet the success criterion for VE primary end points



Key points

- RSV more severe in young infants and old adults with comorbidities
- RSV circulation affected by COVID-19 pandemic
 - Early disappearance then resurgence?
 - Waning of RSV immunity early during COVID-19 could contribute
- RSV passive and active immunization in the pipeline (mAbs for infants, Pre-F vaccines for pregnant women and adults)

Thank you !