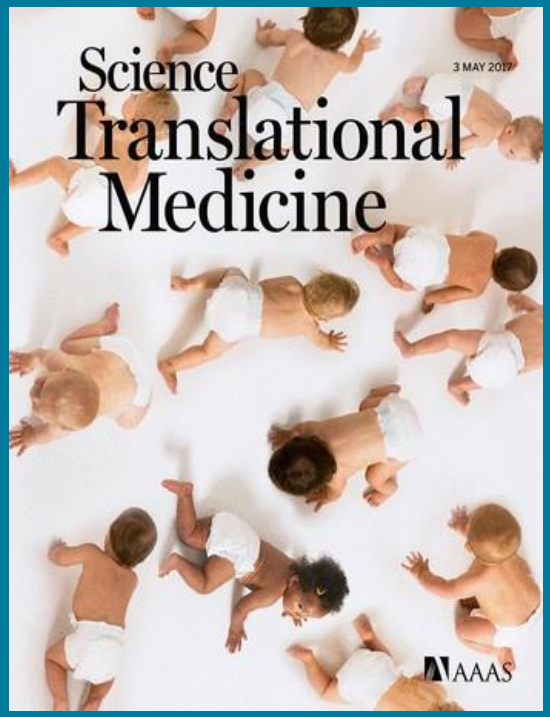
RSV Vaccine UPDATE 2023:

Not just for infants!



Janet A. Englund, M.D.
Professor of Pediatrics
Seattle Children's Hospital, University of Washington
Fred Hutchinson Cancer Center
Seattle, WA USA

.

ARVAC
June 8 and 15, 2023

Seattle Children's | UW Medicine

FINANCIAL DISCLOSURES AND CONFLICTS OF INTEREST

My institution has received research support for clinical studies from AstraZeneca, GSK, Merck, and Pfizer.

I serve as a consultant for Sanofi Pasteur, AstraZeneca, Moderna, and Meissa Vaccines

.

Seattle Children's

UW Medicine

MANY challenges for RSV Disease Prevention Over MANY Years: and finally PROGRESS!

RSV Celebration
Cake and Party
Nov. 2022
Seattle, WA

Acknowledgements:

H. Chu, MD, L. Eckert, MD, and A. Kachikis, MD, A. Waghmare, MD, and Peds ID Research Team - Seattle Children's Hospital/Univ. Washington

K. Edwards, MD, N. Halasa, MD- Vanderbilt University

F. Munoz, MD, P. Piedra, WP Glezen, MD - Baylor College of Medicine

M. Steinhoff, MD (deceased), J. Tielsch, PhD, J. Katz, PhD - G Washington U/Johns Hopkins)

Funding: NIAID, CDC, PATH, MedImmune, Thrasher, Novavax, Pfizer, Bill and Melinda Gates Fndn, Gates Ventures.

Seattle Children's

UW Medicine
SCHOOL OF MEDICINE

RSV Is An Important Pathogen For:

- **Infants/Children:**
  - Infants/toddlers 0-2 years
  - Young Children 2- 5 yrs;
  - School age children: ?spreaders

- **Immunocompromised patients:**

- **Older Adults**

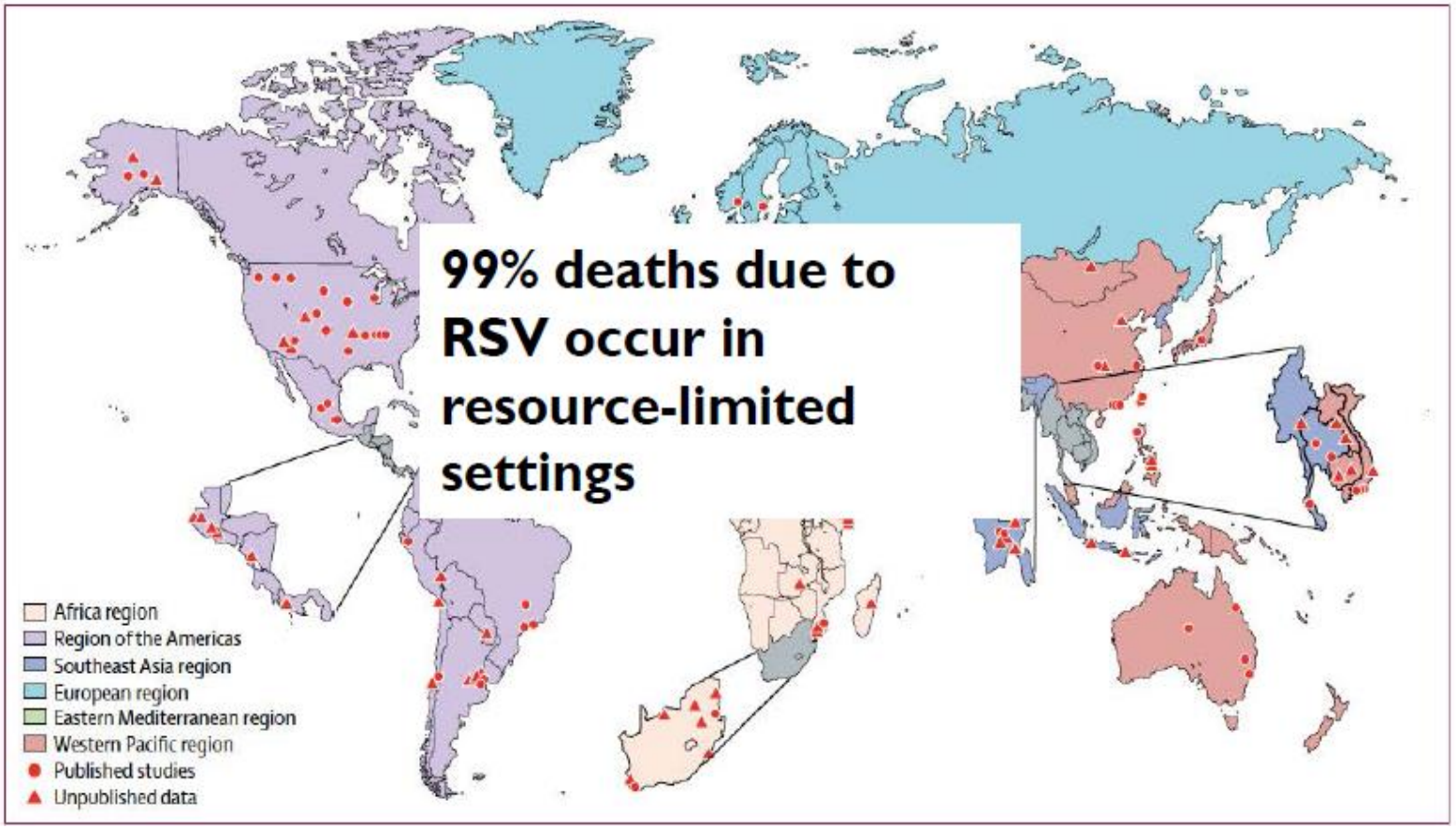
OBJECTIVES: RSV Vaccines Post-COVID

- Update on epidemiology, risk factors, and molecular virology for RSV
- Active immunization strategies
  - Older adults
  - High risk children, adolescents and younger adults
- Passive immunization strategies
  - Maternal Immunization
  - Monoclonal AB

NOTE: advances in RSV biology helped us move forward with COVID vaccines!

Global Burden of RSV Acute Lower Respiratory Tract Disease in Children: Meta-analysis Update

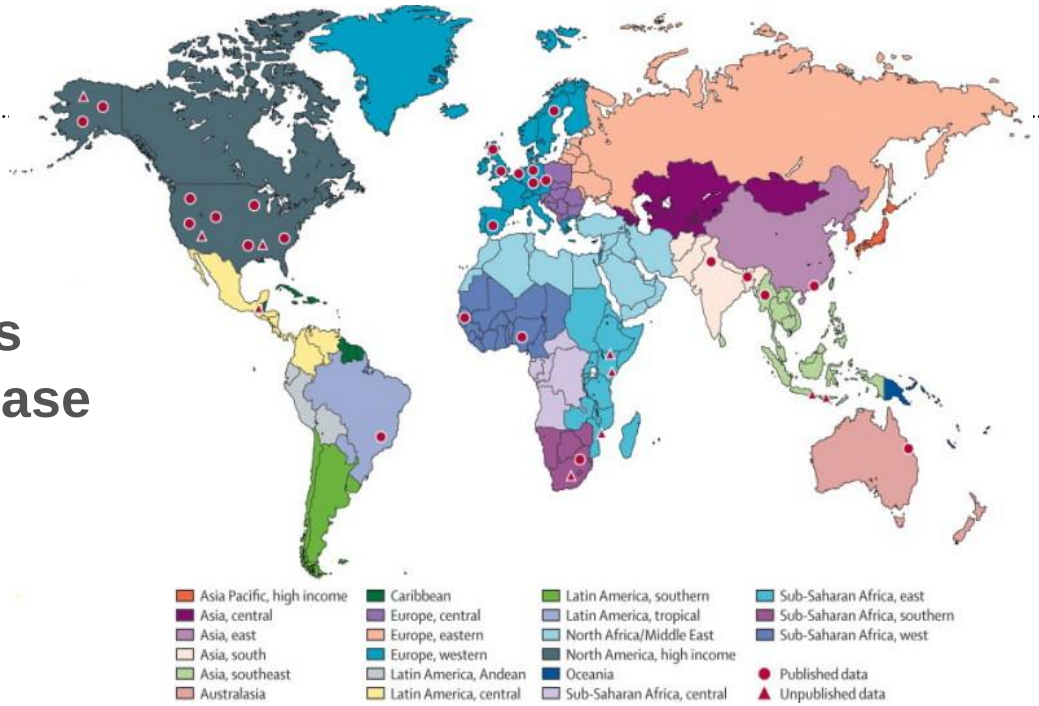
RSV associated with 28% of all ALRI and 13-22% all cause ALRI mortality in children.*



*Shi Lancet 2017

WHERE? Global burden of Acute LRI due to RSV in young children: Systematic Review (Nair, Lancet 2010;375:1545)

Location of 36 Study Sites for Global Burden of Disease



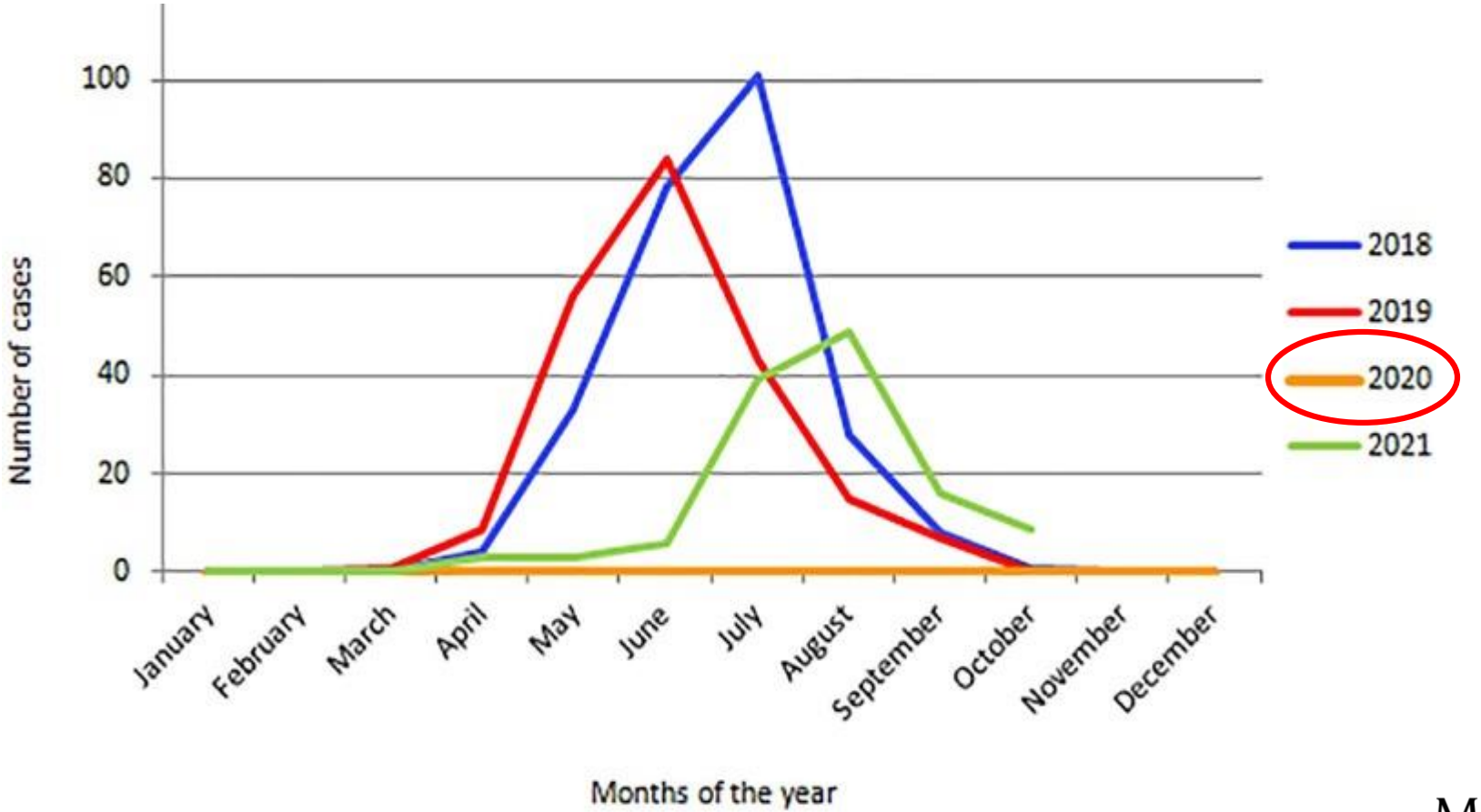
CONCLUSION:

- Estimated 33.8 (95% CI 19.3-46.2) million new episodes of RSV-associated ALRI occurred worldwide in children < 5 years (22% of ALRI episodes)
- At least 3.4 (2.8-4.3) million episodes severe RSV-associated ALRI hospital admits.
- Estimated 66 000-199 000 children <5 years died from RSV-associated ALRI with

RSV Epidemiology changed during pandemic…..

RSV reemergence in Argentina since the SARS-CoV-2 pandemic

Acuña Dolores [a,b], Goya Stephanie [a,1], Nabaes Jodar Mercedes S [a,1], Grandis Érica [a], Alicia S Mistchenko [a,c], Viegas Mariana [a,b,*]



Seattle Children's

UW Medicine
SCHOOL OF MEDICINE

RSV and Other Respiratory Viruses (except RHV) Went Away During the Pandemic: US Surveillance, 2016-2021*

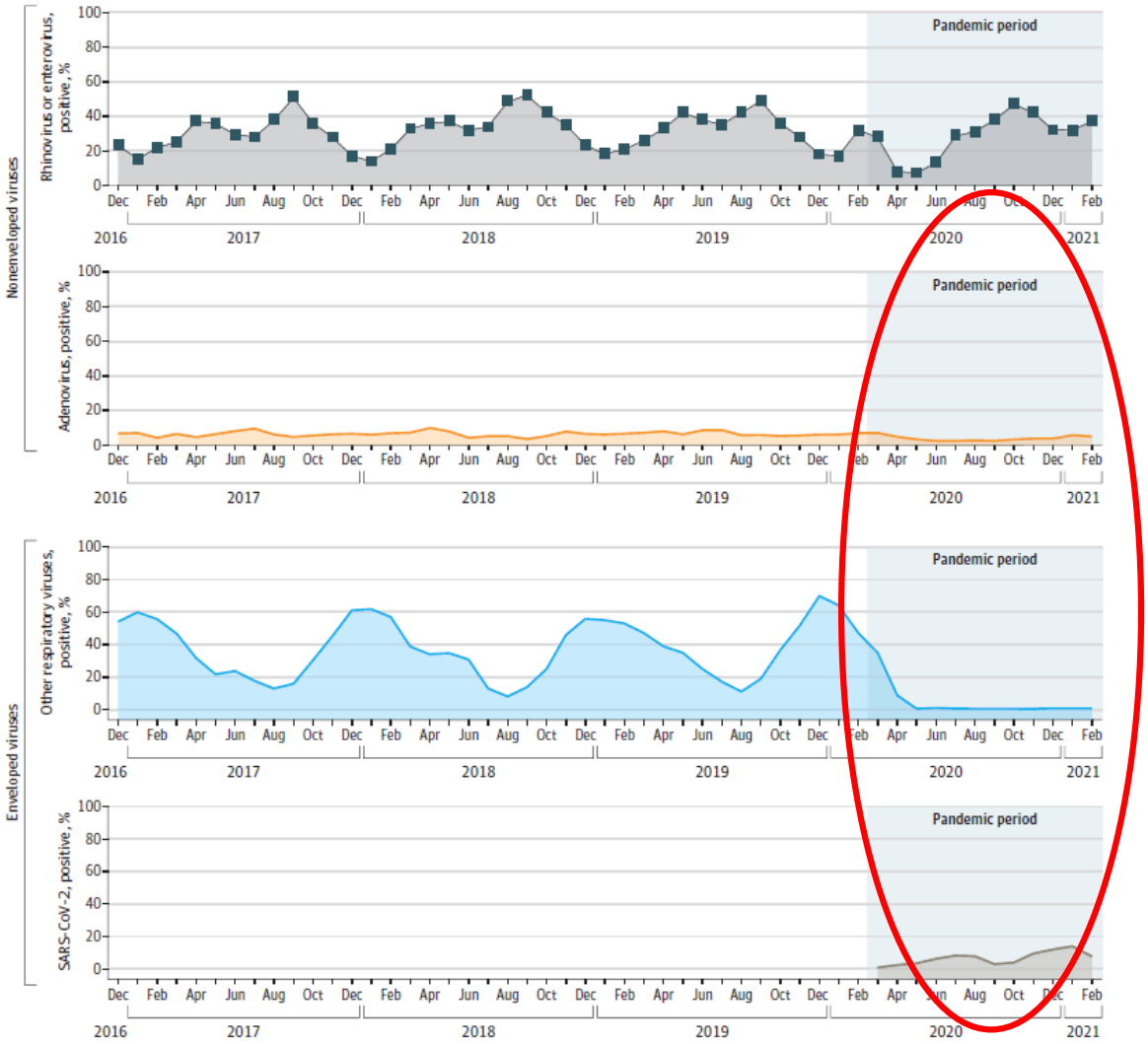
Rhinovirus (RHV)

Adenovirus

Other Resp. Viruses- Flu, RSV, HMPV, PIV1-4

SARS-CoV-2

Figure 1. Virus Circulation Among Children and Adolescents With Respiratory Virus Testing, From 2016 to 2021



Other respiratory viruses included influenza, parainfluenza types 1 to 4, respiratory syncytial virus, and human metapneumovirus.

Light blue = Pandemic Period

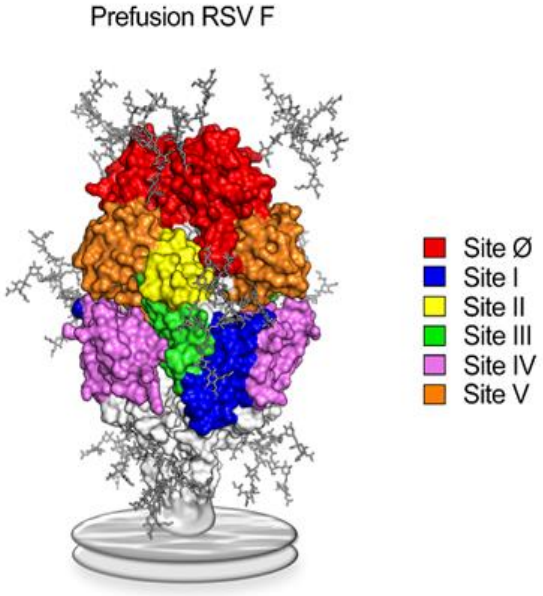
UW Medicine
SCHOOL OF MEDICINE

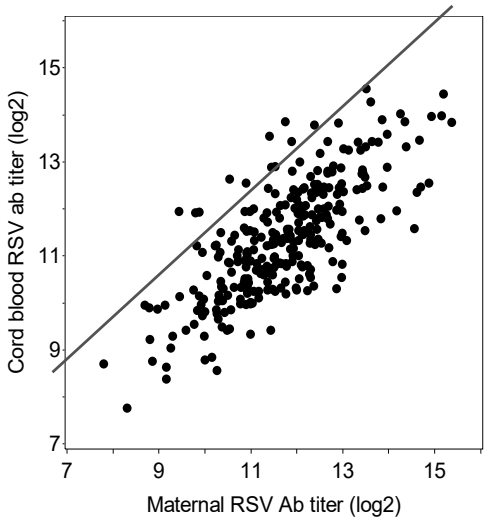
What are issues complicating RSV vaccine development?

- Enhanced pulmonary disease in young seronegative infants receiving formalin-inactivated RSV vaccine in the 1960's: unbalanced T cell response? formalin inactivation of RSV? Many researchers unwilling to do a protein RSV vaccine trial in young infants
- No perfect animal model
- Incomplete immunity to natural RSV infection in humans
- Primary target populations are difficult targets:
  - Young infants may have inadequate immune responses and/or maternal antibody still present
  - Pregnant women difficult to study
  - Older adults- dealing with immune senescence

Recent Advances in RSV Prevention

New findings about RSV pre-Fusion protein molecular structure and stabilization of F protein (McLellan et al Science 2013) leading to new vaccines and Mab's





Good transfer of maternal RSV neut AB across the placenta (>105%)- Glezen 1991, Chu 2014

Long-acting monoclonal Ab to pre-F protein

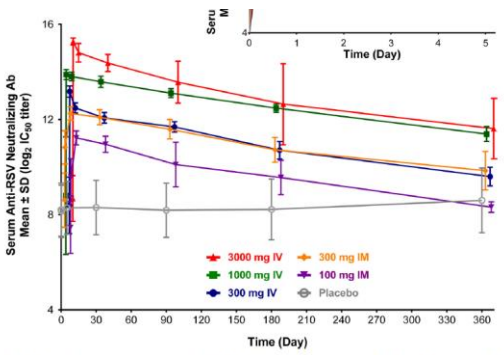


FIG 3 Anti-RSV neutralizing antibody titers after a single i.v. or i.m. dose of MEDI8897 or placebo. Data points represent the mean anti-RSV A2 neutralizing antibody titers on a $\log_2$ scale. Data have been jittered. Error bars represent the standard deviations. Ab, antibody.

RSV Pre- and Post-Fusion (F Protein) Structure

Review

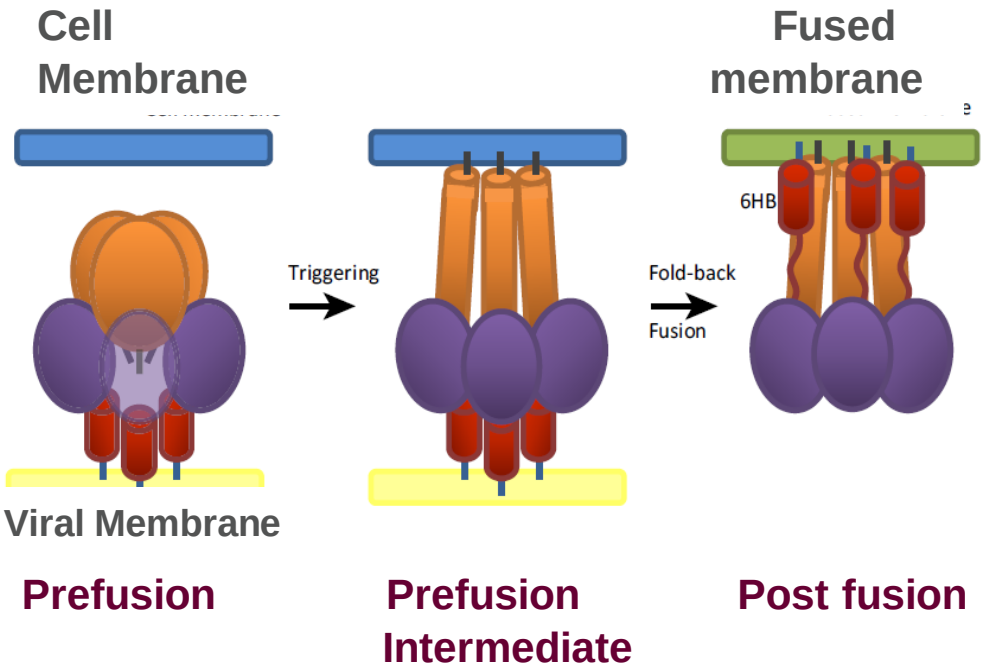
Clinical Potential of Prefusion RSV F-specific Antibodies

lebe Rossey,[1,2] Jason S. McLellan,[3] Xavier Saelens,[1,2,*] and Bert Schepens[1,2,*]

Trends in Microbiology, March 2018, Vol. 26, No. 3

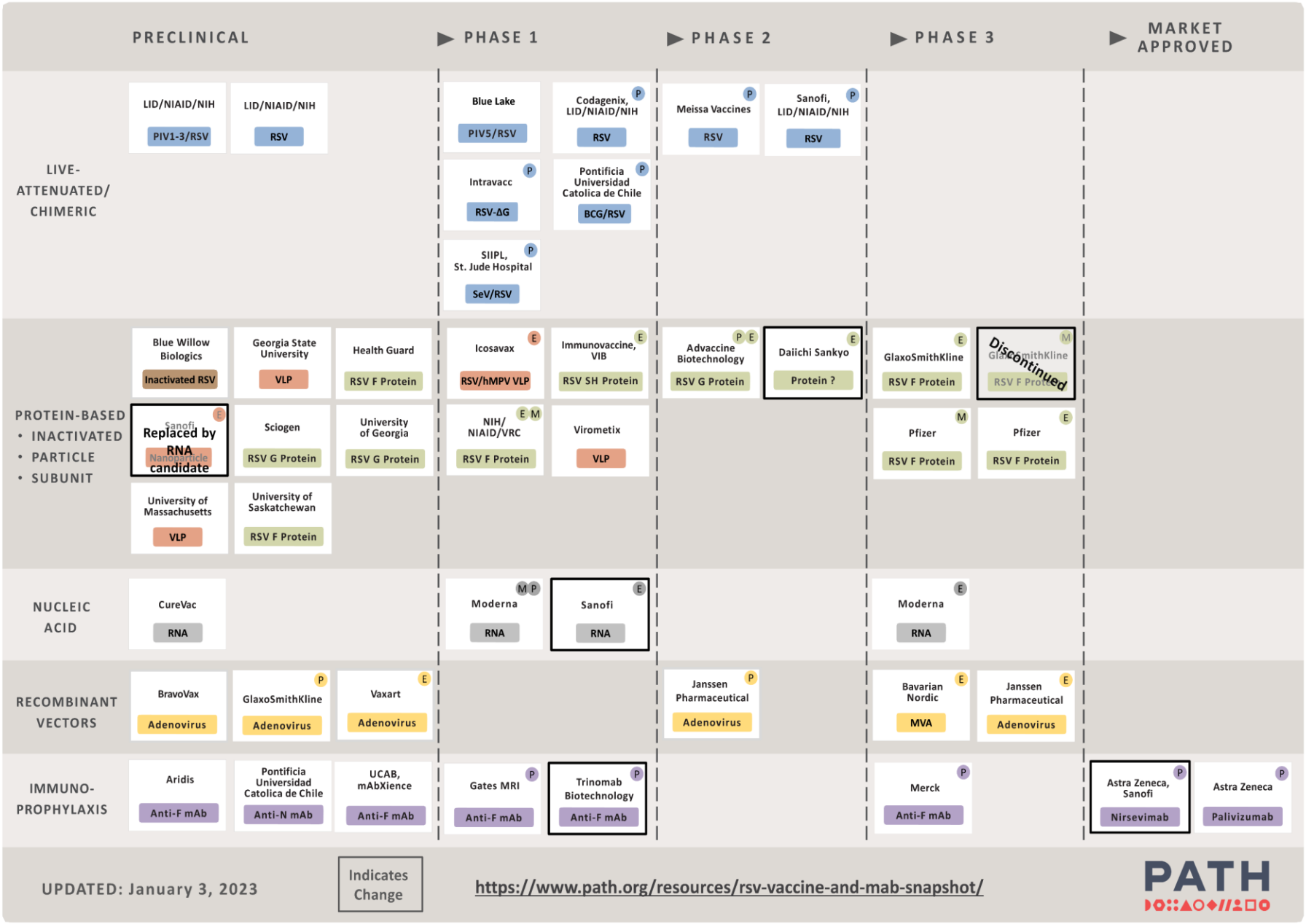
RSV F proteins: Potential candidates for immunization

- Rationale: Experience with MAb prophylaxis of infants with palivizumab (Synagis)
- Vaccine prefusion F protein candidates may increase AB response:
  - Immunogenic: induces high levels of protective neutralizing Ab in cotton rats, adult humans (already exposed)
  - Safe, non-reactogenic



RSV Vaccine and mAb Snapshot 2023

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



UPDATED: January 3, 2023

Indicates Change

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

PATH

APPROACHES TO THE PREVENTION OF RSV

Over 15 ongoing, or proposed RSV vaccine trials in Clintrials.gov:

ACTIVE IMMUNIZATION:

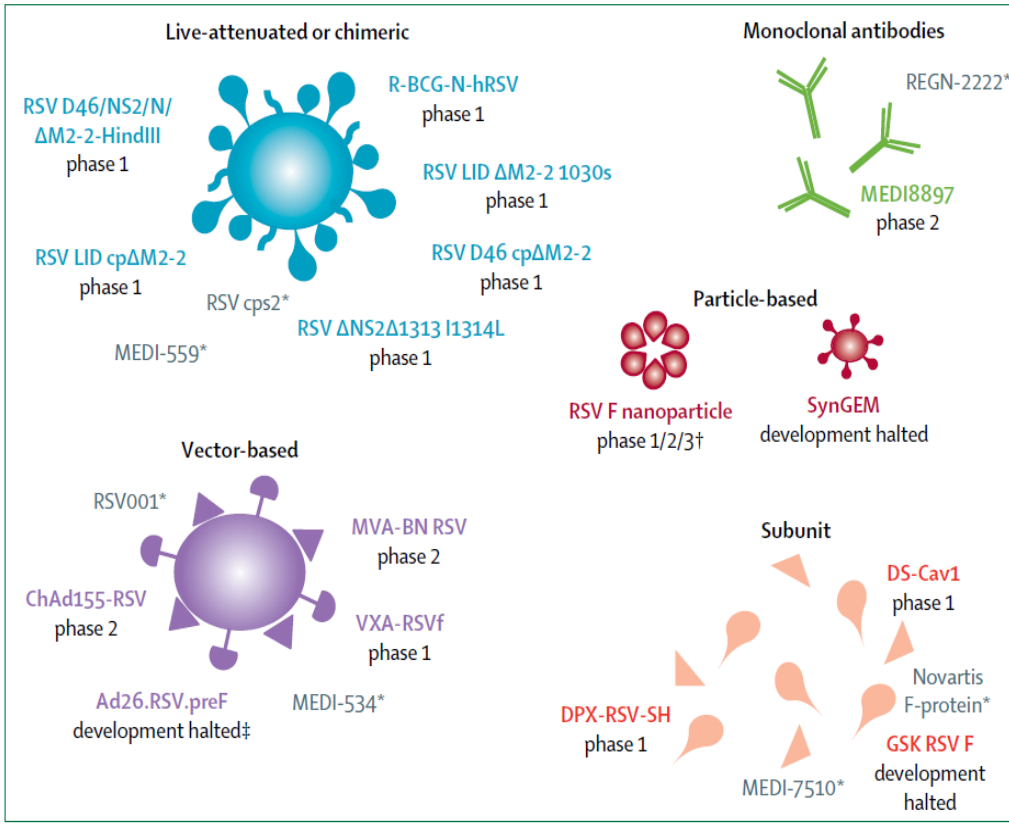
Vaccines

1. Live-attenuated
2. Vector-based vaccines
3. Nanoparticle vaccine
4. Protein subunit vaccines
5. mRNA vaccines and combination vaccines

PASSIVE IMMUNIZATON

1. Maternal immunization
2. Monoclonal Antibodies

Overview of Vaccine Candidates*



* Mazur N et al. Lancet 2018

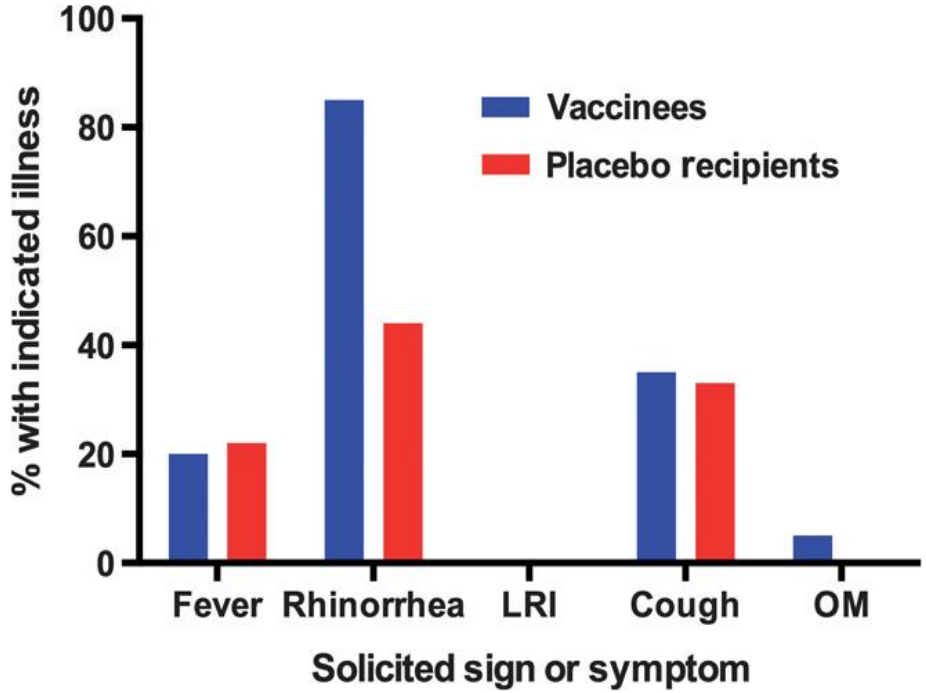
APPROACH #1. Live attenuated: RSV Δ M2-2 RSV vaccine Safety in RSV-seronegative vaccinees vs placebo recipients.

RESEARCH ARTICLE

INFECTIOUS DISEASE

A gene deletion that up-regulates viral gene expression yields an attenuated RSV vaccine with improved antibody responses in children

Ruth A. Karron,[1]* Cindy Luongo,[2] Bhagvanji Thumar,[1] Karen M. Loehr,[1] Janet A. Englund,[3] Peter L. Collins,[2] Ursula J. Buchholz[2]



Conclusion:

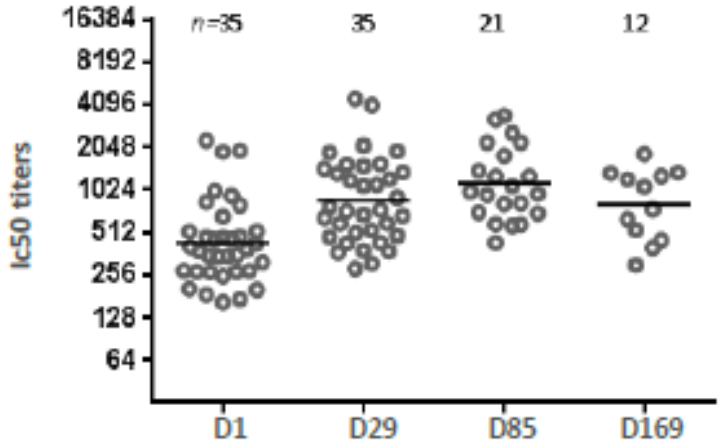
SAFE in RSV-seronegative infants

Ruth A. Karron et al., Sci Transl Med 215;7:312ra175

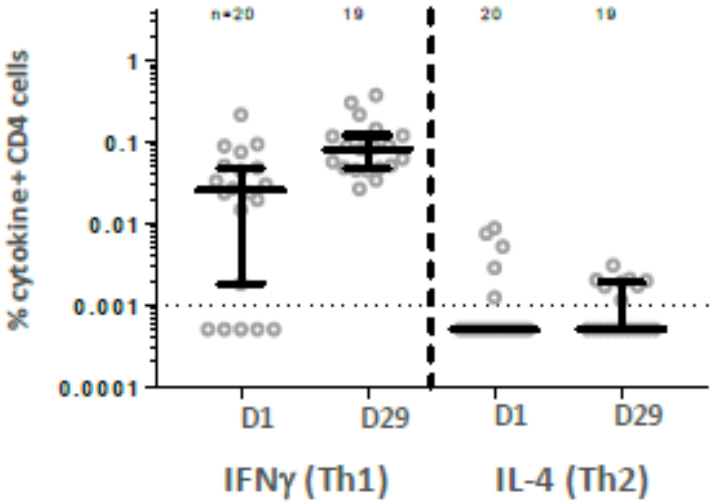
APPROACH # 2. AdV Vector vaccines: Immunogenicity in adults (presented at VRBPAC- FDA, 2017)

Immunogenicity of a single dose of Ad26.RSV.FA2 in healthy adults

RSV Neutralization Assay

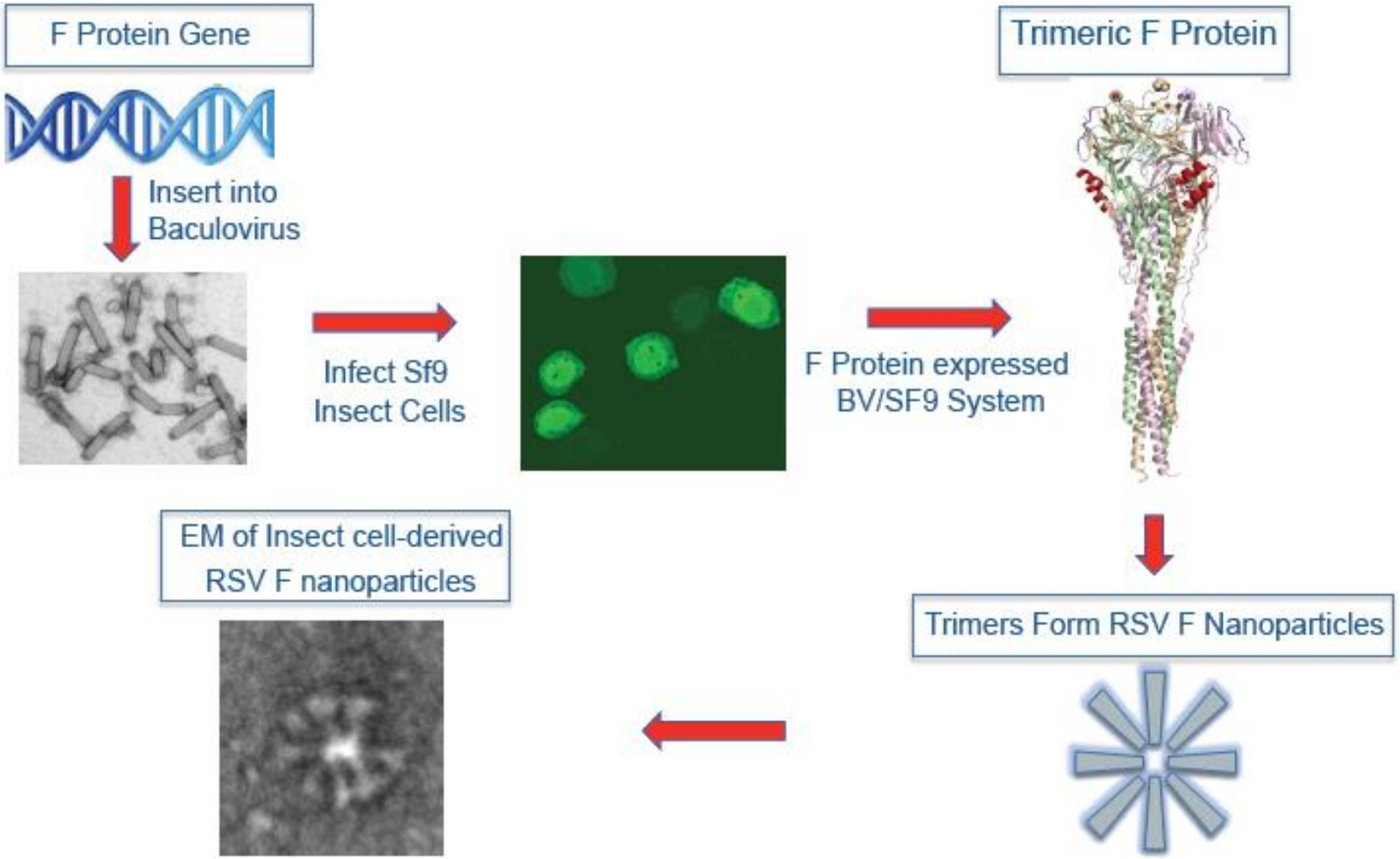


Intracellular Cytokine Staining



- Single immunization in RSV pre-exposed adults boosts humoral and cellular immune responses and maintains the Th1 predominance
- Durable humoral and cellular immune responses
- Preliminary data (D29) with Ad26.RSV.preF in older adults show comparable or higher immune responses

Approach #3. Recombinant Nanoparticle Vaccine – Novavax*



APPROACH #4. RSV Subunit Vaccines

Vaccine	Target Popula-tion	Target Ag	Immune response	Mucosal/ Systemic	Status
GSK- RSV stabilized pre-F protein + adj	Older Adults	Pre-F stabilized target	Pre-F specific neut Ab	Systemic	**Trial finished in adults; FDA Approved**
Pfizer RSV stabilized Pre-F protein	Older Adults, high risk children	Pre-F meta stabilized protein	Pre-F specific neut Ab	Systemic	**Trial finished; FDA approved**
GSK RSV pre F-stabilized protein	Pregnant Women	Pre-F stabilized target	B & T cell response	Systemic	WITHDRAWN
Pfizer RSV stabilized Pre-F protein	Pregnant women	Pre-F meta stabilized protein	Pre-F specific neut Ab	Systemic	**Trial finished; Submitted FDA**
DPX-RSV(VIB, (Dalhousie Univ, immunovaccine	Adults	Extra-cellular domain of SH with Depovax^{R} technology	B cell response specific to She Ag	Systemic	

RSV Vaccines for adults over 60 years old: Multiple Good Candidates

Per Dr. Barney Graham, formerly of NIH, all the new RSV vaccines "are going to work well enough to be approved, depending on the side effect profiles"

- **GSK:** NEJM 2023: RSV stabilized pre-F vaccine with adjuvant. N = 24,966 receiving vx or placebo at 1:1 ratio
  - Efficacy: 94% reduction in severe RSV disease and 83% reduction in symptomatic RSV disease in all age/risk groups including > 80 yrs.
  - Reactogenicity: pain at injection site, fatigue, headache, myalgia
- **J&J:** NEJM Feb 2023 Phase 2 trial; ADV vectored vaccine; N =
  - Efficacy:80% VE in adults: 80% protection from lower tract disease and 70% protection from milder disease
  - AE: 4.6% of vaccine participants and 4.7% of the placebo group
- **Pfizer** NEJM Apr 2023. RSV bivalent Pre-F stabilized protein vaccine; N = 34,000 total recipients receiving vx or placebo at 1:1 ratio
  - Efficacy: Reduction in severe RSV illness of 86%
  - Reactogenicity:
- **Moderna**: mRNA vaccine vaccine against F protein in same lipid nanoparticles as COVID-19 vaccine. Press release Jan. 17, 2023.
  - Efficacy against severe RSV LRTI was 83.7% effective

Phase III RSV Vaccine Efficacy Trials in Adults: as of Apr 2023

VACCINE Manu-facturer	Population	RSV Target	BLA Accepted by FDA	Presented at FDA VRBPAC
GSK	Older Adults	RSV Pre-F + ASo1e	22 Nov 22 ~80% VE	1 Mar 2023
Pfizer	Older Adults	RSV Pre-F A and B	7 Dec 2022 ~80% VE	28 Feb 2023
Pfizer	Pregnancy	RSV Pre-F A and B	21 Feb 23 70-80% VE	18 May 2023
Moderna	Older Adults	mRNA PreF	Phase 3 initiated Feb 2022	(not yet)
Janssen	Older Adults	Ad26+preF protein	Phase 2-3 pub-lished Feb 2023 NEJM: 70-80% VE	WITHDRAWN!

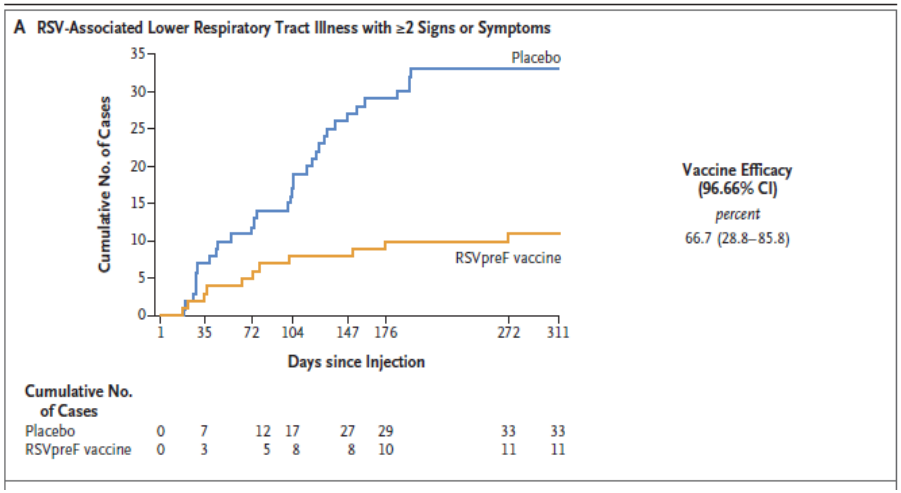
NEJM RSV VACCINES FOR "OLDER PERSONS" (>60 yrs): BOTH WORK WELL!

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, M. Rämet, Y. Fukushima, N. Hussen, L.J. Bont, J. Cardona, E. DeHaan, G. Castillo Villa, M. Ingilizova, D. Eiras, T. Mikati, R.N. Shah, K. Schneider, D. Cooper, K. Koury, M.-M. Lino, A.S. Anderson, K.U. Jansen, K.A. Swanson, A. Gurtman, W.C. Gruber, and B. Schmoele-Thoma, for the RENOIR Clinical Trial Group*



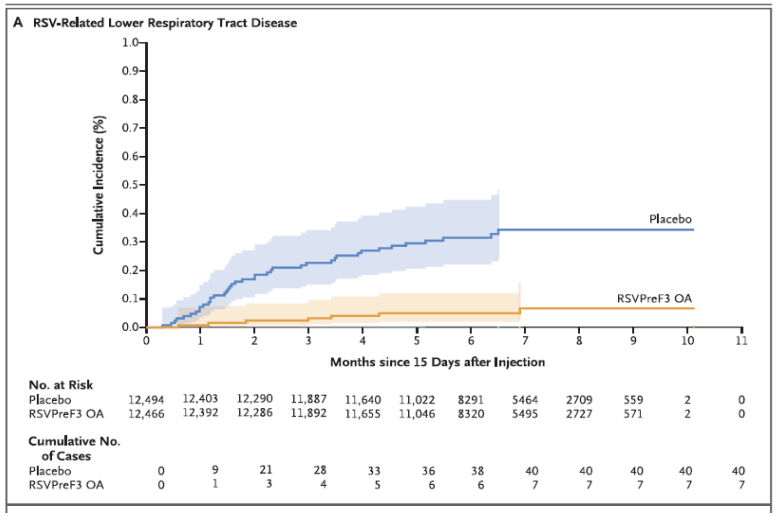
This article was published on April 5, 2023, at NEJM.org.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults

A. Papi, M.G. Ison, J.M. Langley, D.-G. Lee, I. Leroux-Roels, F. Martinon-Torres, T.F. Schwarz, R.N. van Zyl-Smit, L. Campora, N. Dezutter, N. de Schrevel, L. Fissette, M.-P. David, M. Van der Wielen, L. Kostanyan, and V. Hulstrøm, for the AReSVi-006 Study Group*



N Engl J Med 2023;388:595-608.

NEJM RSV VACCINES FOR "OLDER PERSONS" (>60 yrs): BOTH WORK WELL!

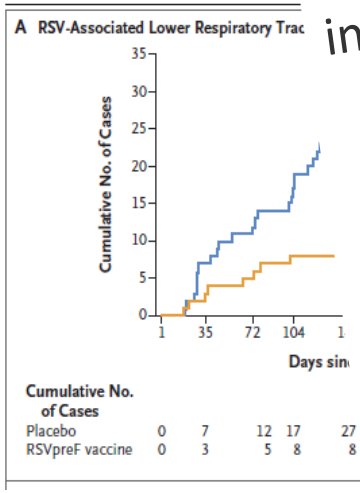
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

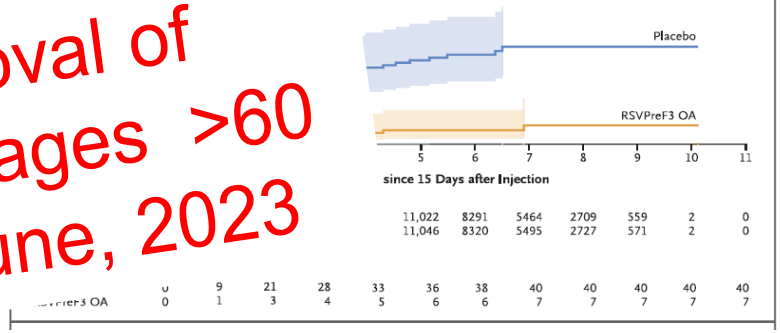
Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults

E.E. Walsh, G. Pérez Marc, A.M. Zareba, A.R. Falsey, Q. Jiang, M. Patton, F.P. Polack, C. Llapur, P.A. Doreski, K. Ilangovan, N. Hussen, L.J. Bont, J. Cardona, D. Eiras, T. Mikati, R.N. A.S. Anderson, K.U. Jar B. Schmoele-Th

RSV is the worst disease that nobody knows about," said co-investigator Ann Falsey, MD,



FDA and EU Approval of RSV vaccines for ages >60 yrs in May and June, 2023



This article was published 2023, at NEJM.org.

N Engl J Med 2023;388:595-608.

#5. mRNA Investigational RSV Vaccine*

Moderna mRNA 1345 vaccine:

- single mRNA sequence coding for a stabilized prefusion F glycoprotein
- Use same liquid nanoparticles as Moderna COVID-19 vx
- Prefusion F protein highly conserved across A and B

Five clinical trials underway:

- ConquerRSV pediatric trial: fully enrolled in phase 1 study
- Combination viral clinical trials
- FDA granted Moderna “breakthrough therapy designation” in Jan. 2023 for their RSV vaccine candidate

*https://investors.modernatx.com/news/news-details/2023/Moderna-Announces-mRNA-1345-an-Investigational-Respiratory-Syncytial-Virus-RSV-Vaccine-Has-Met-Primary-Efficacy-Endpoints-in-Phase-3-Trial-in-Older-Adults/default.aspx

mRNA RSV Pre-F Protein Vaccines : Phase 1 Trial

RESEARCH PAPER

Check for updates

HUMAN VACCINES & IMMUNOTHERAPEUTICS
2021, VOL. 17, NO. 5, 1248–1261
https://doi.org/10.1080/21645515.2020.1829899

A phase 1, randomized, placebo-controlled study to evaluate the safety and immunogenicity of an mRNA-based RSV prefusion F protein vaccine in healthy younger and older adults

Antonios O. Aliprantis[a], Christine A. Shaw[b], Paul Griffin[c,d,e], Nicholas Farinola[f], Radha A. Railkar[a], Xin Cao[a], Wen Liu[a], Jeffrey R. Sachs[a], Christine J. Swenson[b], Heather Lee[b], Kara S. Cox[a], Daniel S. Spellman[a], Colleen J. Winstead[a], Igor Smolenov[b], Eseng Lai[a], Tal Zaks[b], Amy S. Espeseth[a], and Lori Panther[b]

[a]Merck & Co., Inc., Kenilworth, NJ, USA; [b]Moderna, Inc., Cambridge, MA, USA; [c]QPharm, Herston, Australia; [d]The University of Queensland, Brisbane, Australia; [e]Mater Research Raymond Terrace, South Brisbane, Australia; [f]CMAX, Adelaide, Australia

- Demonstrated rapid design and scalabilty of a mRNA product.
- Phase 1 study dose ranging and safety study in younger 18-49 yrs (N = 79) and older healthy adults ages 60-79 yrs (N = 116).
- All dose levels 25 -300 ug safe and well tolerated
- Humoral immune response shown by:
  - Increase in serum RSV Neut activity
  - Increase in serum AB to preF
  - D25 competing Ab to preF peptides
  - CMI to pre-F peptides

Seattle Children's | UW Medicine

Phase 3 Clinical mRNA RSV Vaccine Candidate Trial

- ConquerRSV trial (Moderna): randomized, double-blind placebo-controlled study of 37,000 adults > 60 years in 22 countries (NCT05127434)
- Primary efficacy endpoint based on RSV–LRTD
- Interim analysis based on 64 cases (55 placebo, 9 vx group) resulting in VE of 83.7 % against RSV LRTD defined by two or more symptoms in older adults
- Another primary efficacy endpoint against RSV-LRTD defined by three or more symptoms also met: VE of 82.4% (96.36% CI: 34.8%, 95.3%; p=0.0078).
- Vaccine was well-tolerated with no safety concerns identified by the DSMB. Trial is ongoing

Other Potential Populations for RSV Vaccines:

Other high-risk populations to be considered for RSV vaccines:

- Children and adolescents-
  - Asthmatics
  - Underlying chronic lung disease including cystic fibrosis
  - Genetic predisposition to lung disease such as Down syndrome,
  - Restrictive lung disease such as muscular dystrophy
- Adults with chronic lung conditions, COPD, heart disease or even health care workers?

- COMBINATION VACCINES – For Children?
  - Vectored, live, or recombinant protein vaccines with RSV+PIV
  - mRNA vaccines - under investigation as either single or multicomponent vaccines in adults and children, and combined with human metapneumovirus or other viruses (Moderna)

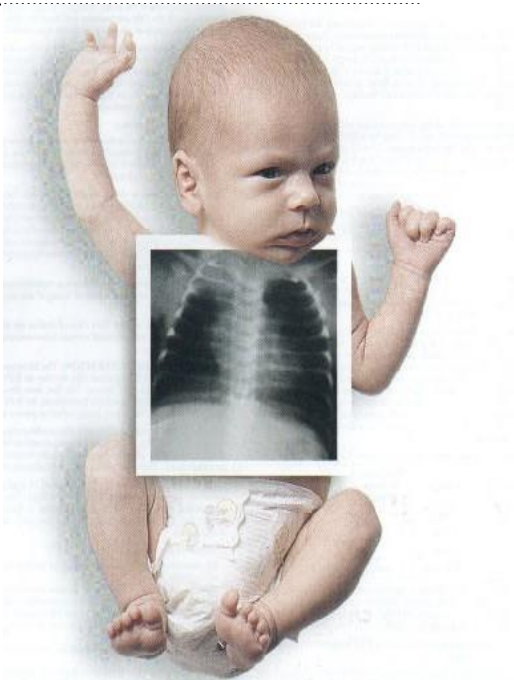
MATERNAL IMMUNIZATION

DEFINITION:

Giving a vaccine to a pregnant women to provide protection to the mother, fetus, and infant through active antibody production and transplacental antibody transfer

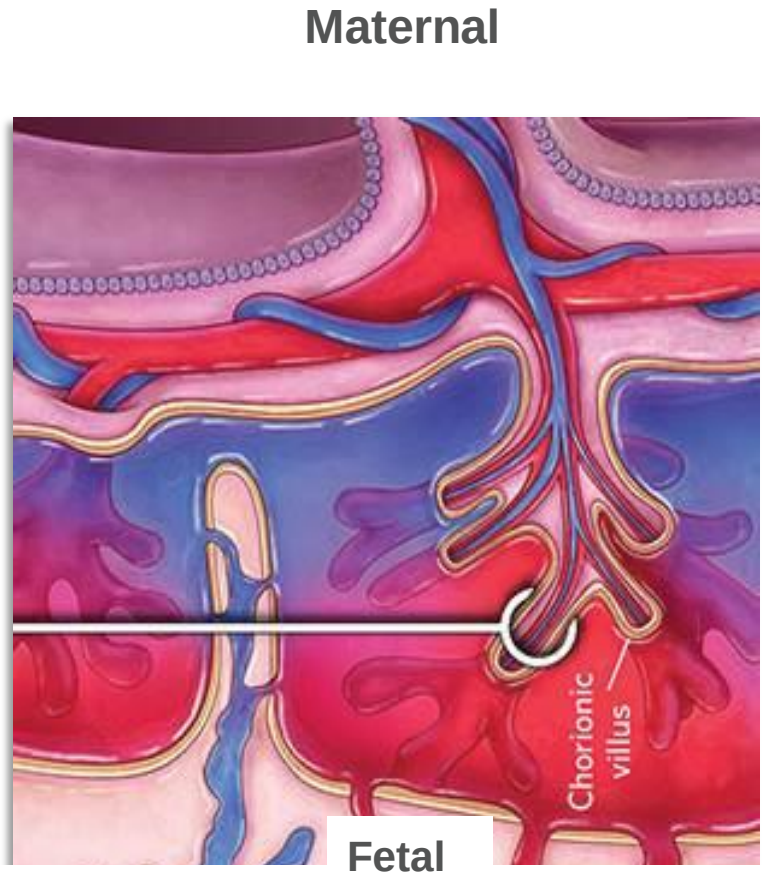
Maternal Immunization to Prevent Infant RSV Disease

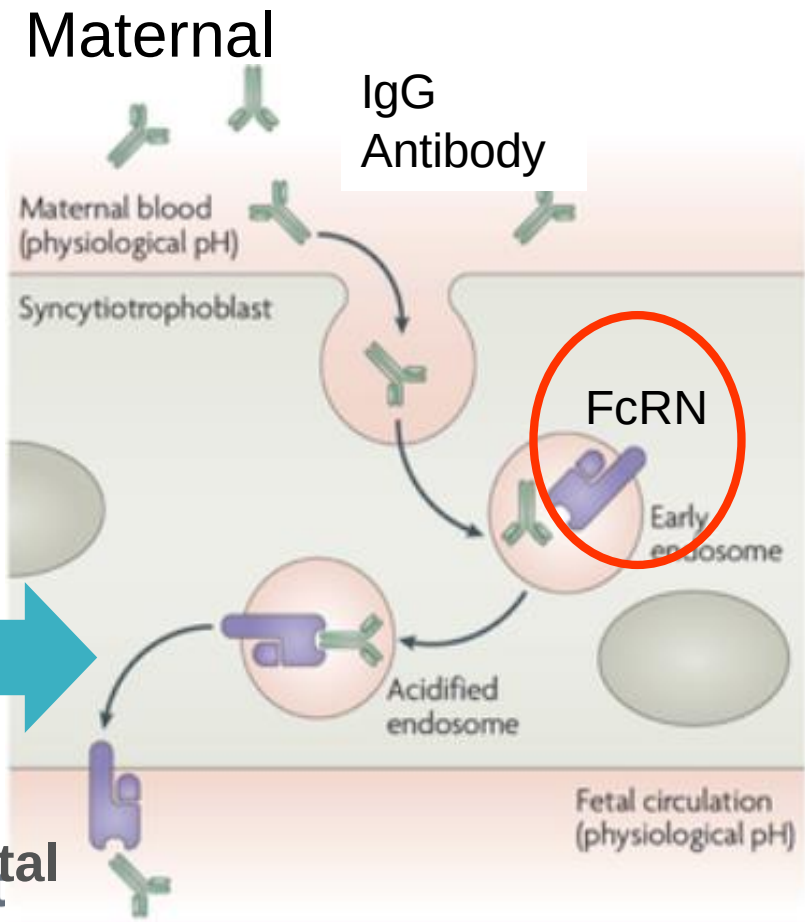
- Most urgent need for protection against RSV is during first few months of life; >75% of RSV disease hospitalization occurs in full term, healthy infants.
- Efficient RSV-specific IgG transfer from mothers to neonates.
- Newer RSV vaccines showing good safety and immunogenicity in adults pregnant women.
- US government regulation (FDA): No evidence teratogenicity in animal models (required prior to human trials).



Mechanisms of transplacental transport

- Maternal IgG is **actively** transferred across the placenta via FcRn receptors of of syncytiotrophoblast cells in the chorionic villi and released from endosomes into fetal circulation.





https://www.the-scientist.com/?articles.view/articleNo/43618/title/The-Prescient-Placenta/

CHALLENGES OF MATERNAL RSV IMMUNIZATION

1) Placental transfer of antibody: is this generalizable to all populations?
   a) Impact of HIV?
   b) Impact of maternal IgG?
2) Timing of vaccination
3) Safety – in both mother and baby
4) Efficacy-
   a) requiring large controlled clinical studies in geographical diverse and developing/developed countries
   b) Clinical and laboratory endpoints

RSV DISEASE IN PREGNANT WOMEN:
Not a serious problem generally in pregnant persons

Location of study	Sx criteria	Timing	Samples tested	Type of testing	Criteria	Prevalence
Nepal	Fever + resp sx	Year-round	Nasal swabs	RT-PCR	PCR	7/3693 (0.2%)
Mongolia	Influenza-like illness	Flu season	Nasal swabs	Antigen	PCR	4/1260 (0.3%)
South Africa	Resp illness +/- fever	Flu season	Nasal swabs	RT-PCR	PCR	HIV+:3/194 (2%) HIV-:18/2116 (1%)
Nepal	None	Year-round	2nd trim & birth sera	RSV neut ab	4-fold rise in ab titer	8/317 (3%)
Bangladesh (re-analysis)	None	Year-round	3rd trim & birth sera	RSV neut ab	4-fold rise in ab titer	3/149 (2%)
Houston, TX, US	Resp illness +/- fever	Oct-May	Nasal swabs	RT-PCR	PCR	8/81 (10%) of AR

RSV MAT AB IN NEPALESE WOMEN: No correlation between RSV AB transfer ratio and gestational age of infant*

Transplacental transfer of maternal respiratory syncytial virus (RSV) antibody and protection against RSV disease in infants in rural Nepal☆

Helen Y. Chu[a,*], James Tielsch[b], Joanne Katz[c], Amalia S. Magaret[d], Subarna Khatry[e], Stephen C. LeClerq[e], Laxman Shrestha[f], Jane Kuypers[d], Mark C. Steinhoff[g], Janet A. Englund[a,h]

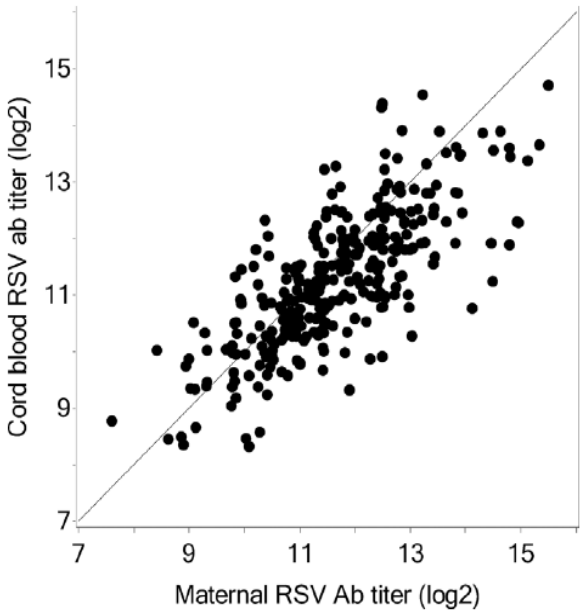


Fig. 1. Comparison of RSV antibody in maternal (x-axis) and infant cord blood (y-axis) at time of delivery in 310 mother-infant pairs (Pearson's correlation coefficient 0.77, $p < 0.0001$).

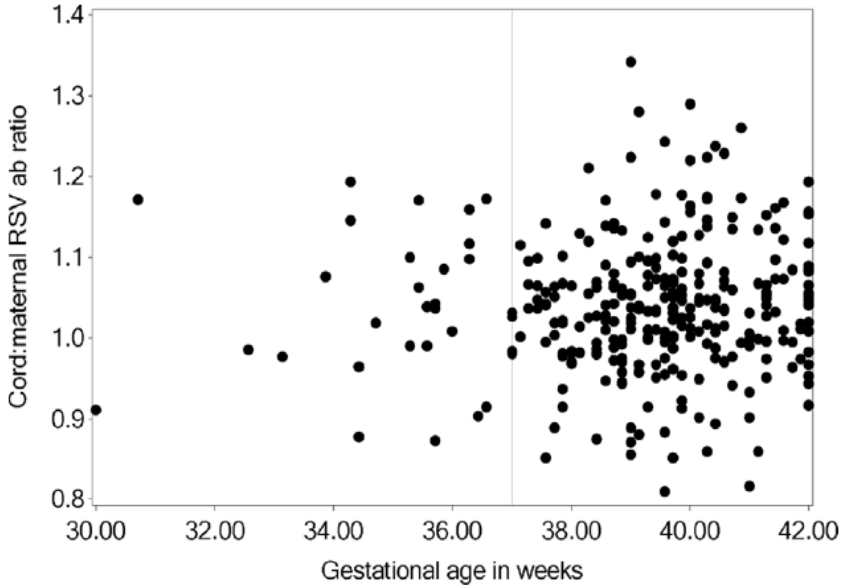


Fig. 2. Comparison of cord:maternal RSV antibody transfer ratio by gestational age at delivery. No significant correlation was found between RSV antibody ratio and gestational age in weeks at birth ($R = 0.05$; $P = 0.37$).

Journal of Clinical Virology 95 (2017) 90–95

Seattle Children's

UW Medicine
SCHOOL OF MEDICINE

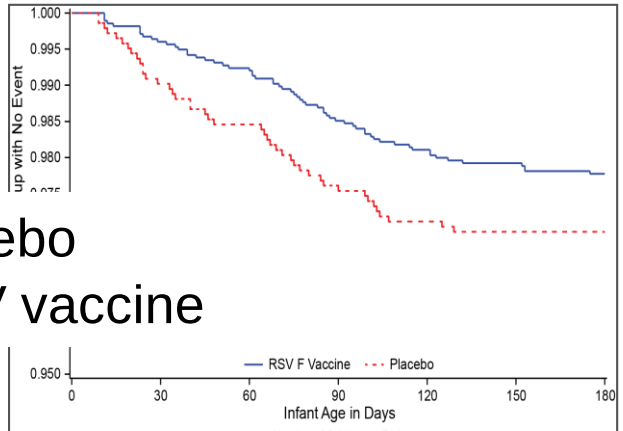
NOVAVAX RSV MATERNAL IMMUNIZATION TRIAL: A NOVEL STUDY (Madhi et al NEJM 2021)

- First study aimed at licensing an investigational vaccine in pregnant women with clinically relevant endpoints
- Important first clinical vx trial that demonstrated safety and efficacy against RSV LRTI in healthy infants, with other clinical studies ongoing

STUDY ISSUES:

- **Endpoints and efficacy goals**
- **Immunogenicity of vaccine**
- **Differences in results between sites (S. Africa vs USA)**

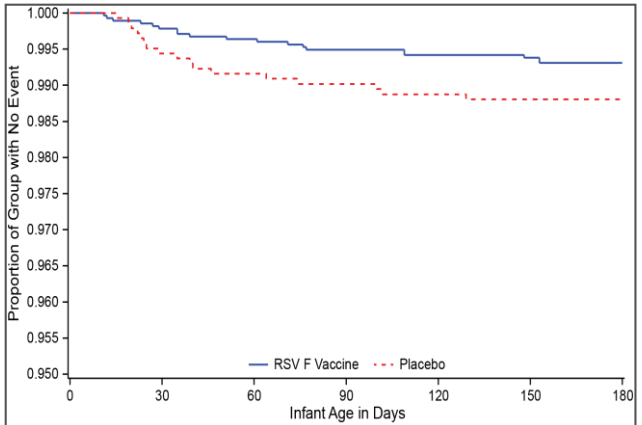
Medically-significant RSV LRTI



Red = placebo

Blue = RSV vaccine

RSV with severe hypoxemia



EXAMPLE #4: Prefusion Stabilized F Protein Vaccine in Pregnancy to Prevent RSV Disease in Infants

This article was published on April 5, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2216480

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

*Drs. Kampmann, Madhi, and Munjal contributed equally to this article.

Primary Endpoints	Criteria
Medically attended RSV LRTI	Medically attended visit **and ≥1**: •tachypnea (RR ≥60 (<2 m [60 days]) or ≥50 (≥2 to 12 m) •peripheral capillary oxygen saturation (SpO2) measured in room air <95% •chest wall indrawing
Medically attended severe RSV LRTI	Medically attended visit **and ≥1**: •tachypnea (RR ≥70 (<2 m [60 days]) or ≥60 (≥2 to 12 m) •SpO2 measured in room air <93% •high-flow nasal cannula or mechanical ventilation •ICU admission for >4 hours; unresponsive/unconscious

LRTI: Lower respiratory tract illness; SpO2: peripheral capillary oxygen saturation

https://clinicaltrials.gov/ct2/show/NCT04424316?term=C3671008&draw =2&rank=1

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

This article was published on April 5, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2216480

Placebo

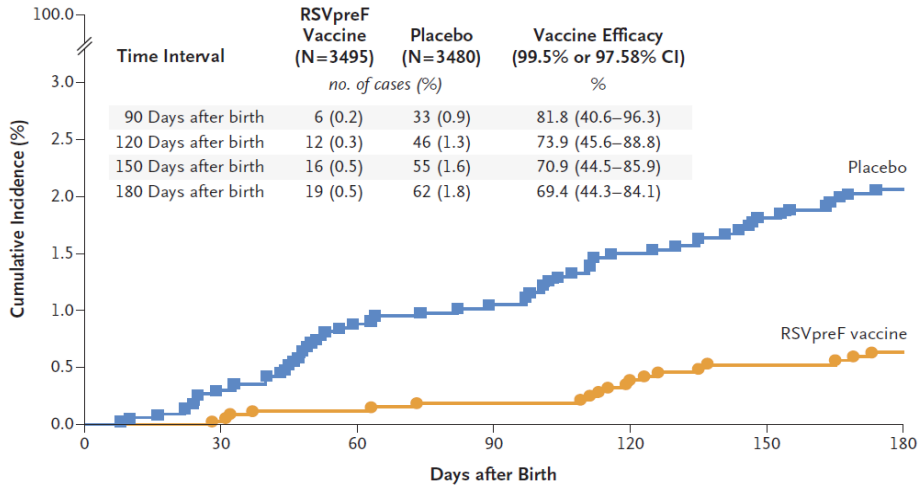
Vaccine

- **Panel A**: VE in infants with medically attended severe RSV LRTI within 180 days of birth
- **Panel B**: VE in infants with medically attended RSV LRTI within 180 days of birth

GOOD VACCINE EFFICACY AND GOOD SAFETY!

ally 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)

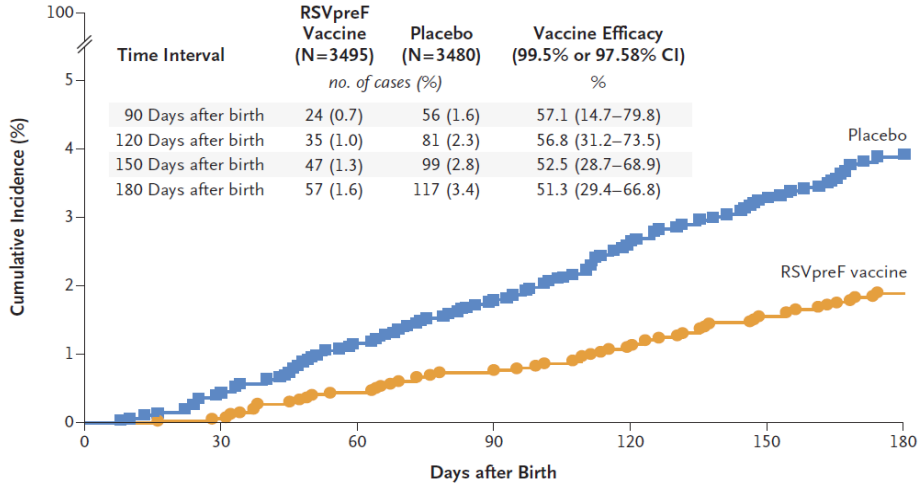


No. at Risk

Placebo	3480	3292	2973	2899	2833	2776	2749
RSVpreF vaccine	3495	3349	3042	2981	2916	2867	2820

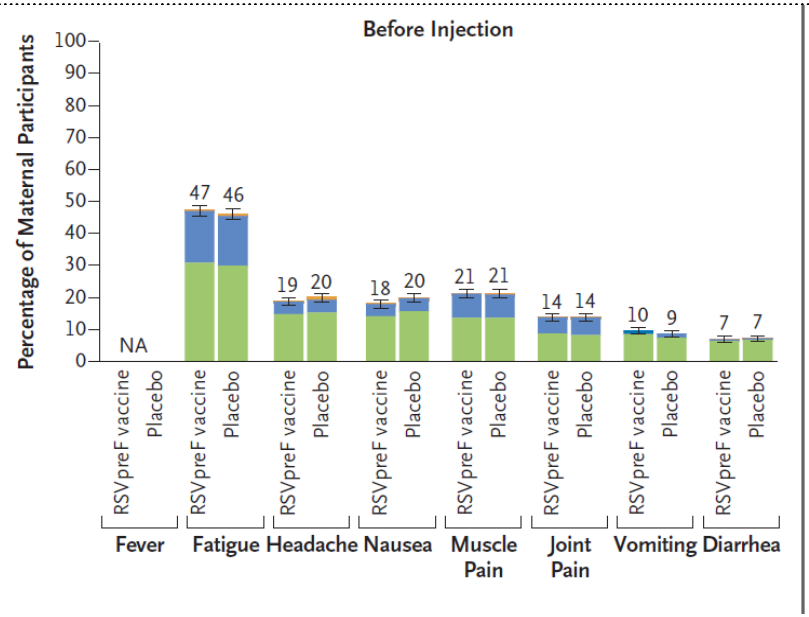
B Medically Attended RSV-Associated Lower Respiratory Tract Illness

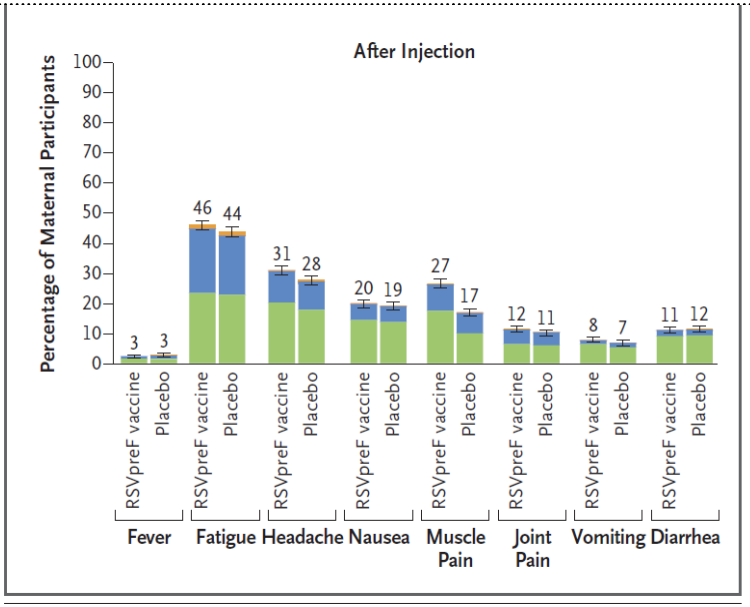
Time Interval	RSVpreF Vaccine (N=3495)	Placebo (N=3480)	Vaccine Efficacy (99.5% or 97.58% CI)
	no. of cases (%)		%
90 Days after birth	24 (0.7)	56 (1.6)	57.1 (14.7–79.8)
120 Days after birth	35 (1.0)	81 (2.3)	56.8 (31.2–73.5)
150 Days after birth	47 (1.3)	99 (2.8)	52.5 (28.7–68.9)
180 Days after birth	57 (1.6)	117 (3.4)	51.3 (29.4–66.8)



No. at Risk

SIMILAR REACTOGENICITY FOLLOWING RSV VACCINE AND PLACEBO IN MATERNAL PARTICIPANTS



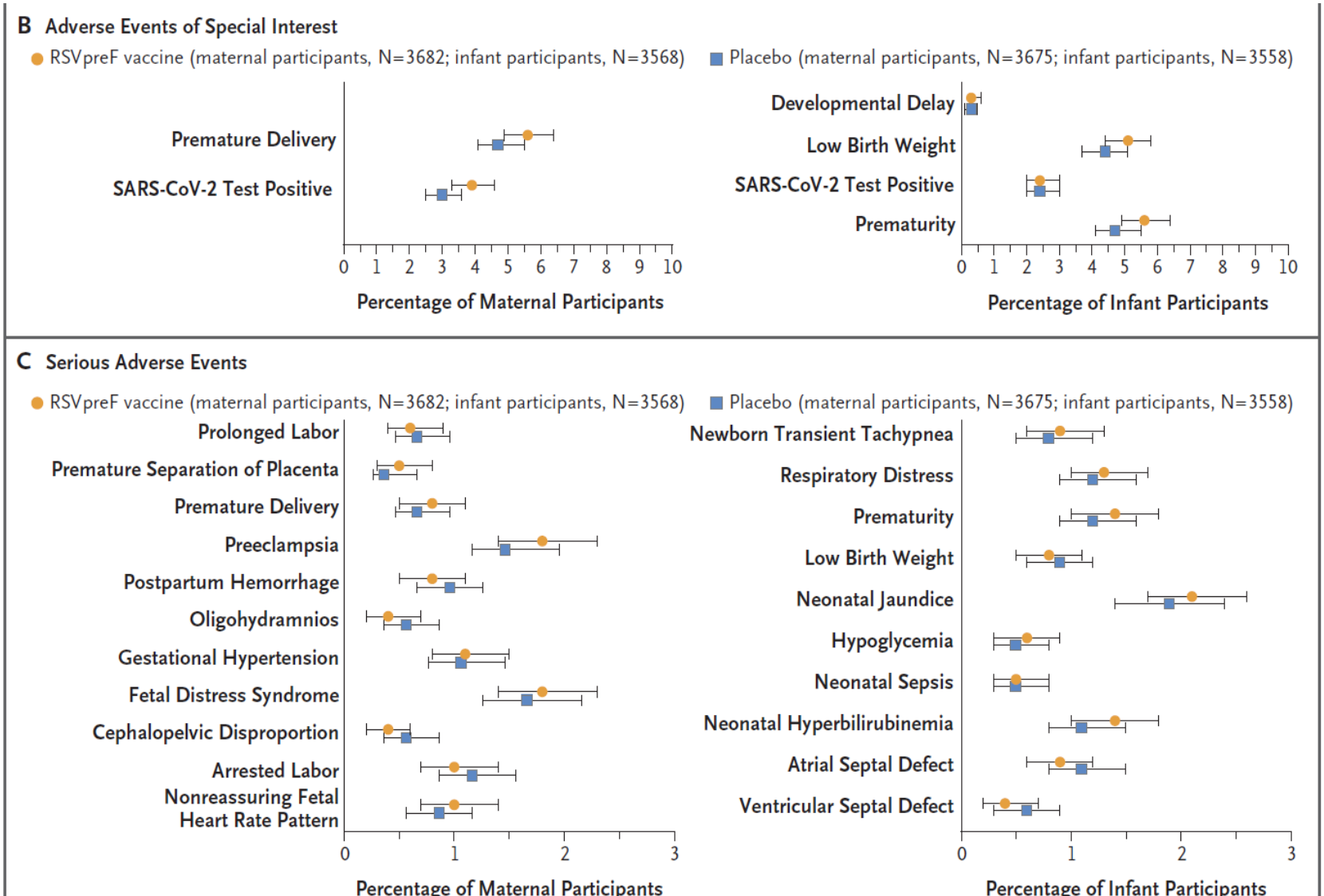


- Similar rates of reactions before and after injection
- Similar rates of reactions in vaccine vs placebo

Seattle Children's

UW Medicine
SCHOOL OF MEDICINE

ADVERSE EVENTS IN DELIVERY AND INFANTS FOLLOWING RSV VX IN PREGNANT PERSONS



CURRENTLY AVAILABLE HUMANIZED RSV MONOCLONAL ANTIBODY: Palivizumab

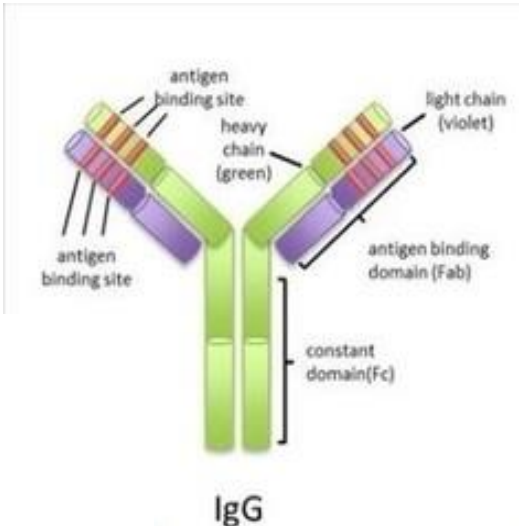
- RSV F-protein antibody protects high-risk infants from lower respiratory tract disease

FOR WHOM?

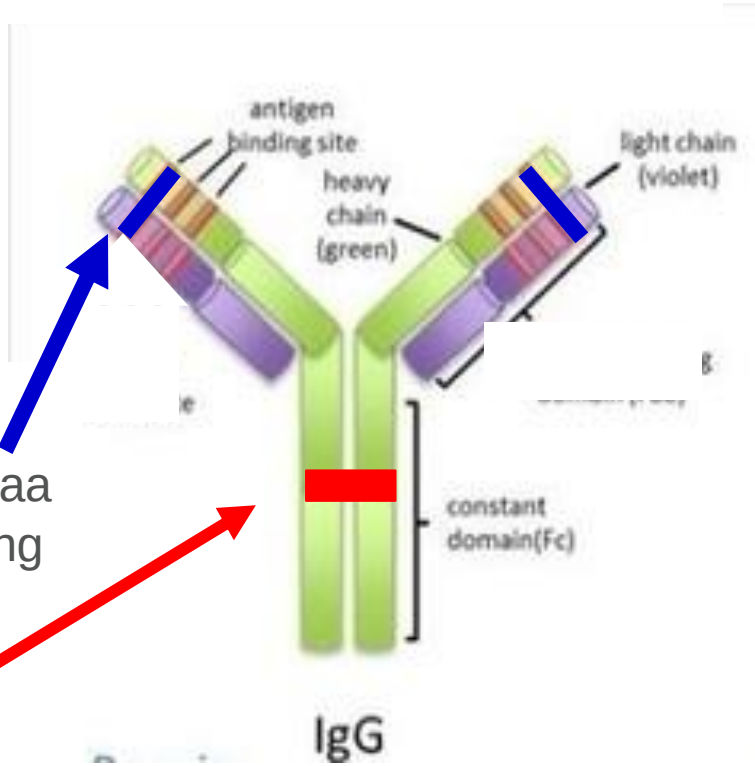
- Approved in USA and EU for use in infants and children <2 years of age with chronic lung disease and babies born at <28 weeks gestation:
  - Palivizumab (Synagis^{R}; AstraZeneca); given IM at 15 mg/kg monthly x 3-5 months
  - Very expensive and requires multiple doses
- **New RSV Mab Candidates under study**: Nirsevimab (AstraZeneca), Clesrovimab (Merck),

How to make an RSV-specific IgG Antibody last longer……

Typical IgG1 Antibody



Nirsevimab (MEDI8897) Antibody (simplified version)



What makes nirsevimab work?

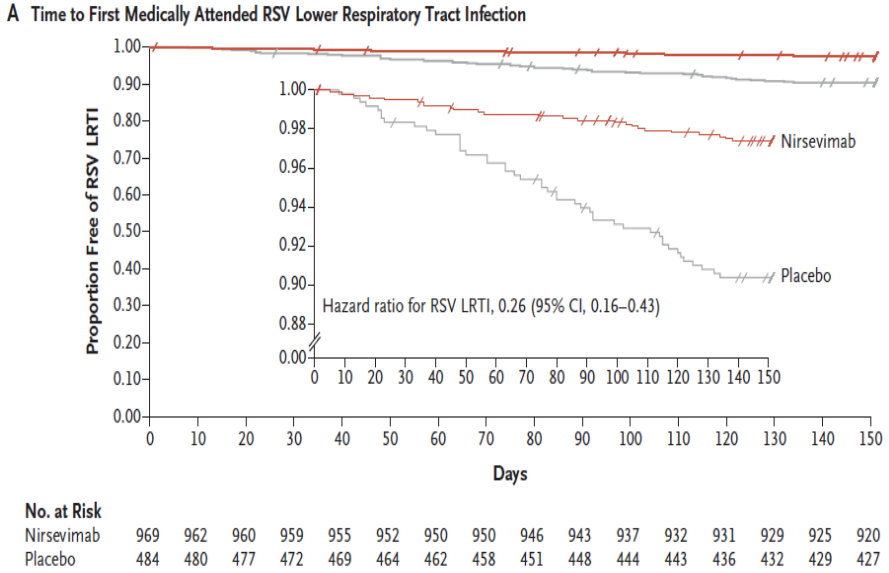
- 4-fold increase in neutralizing activity by 5 aa substitutions in complementarity-determining regions (Rossey et al, Trends Micro 2018)
- Ab half life increased 3-4x through 3 aa substitutions (YTE) in Fc, which enhances IgG1 binding in lysozyme preventing degradation & increasing recirculation of Ab to cell surface (Griffin et al, AAC 2017)

Nirsevimab: Monoclonal Ab strategy for RSV prevention in high risk and healthy infants with one shot

The NEW ENGLAND

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

2020 NEJM Griffin P et al



N Engl J Med 2020;383:415-25.
DOI: 10.1056/NEJMoa1913556

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

2022 NEJM Hammitt et al; 2023 Muller et al

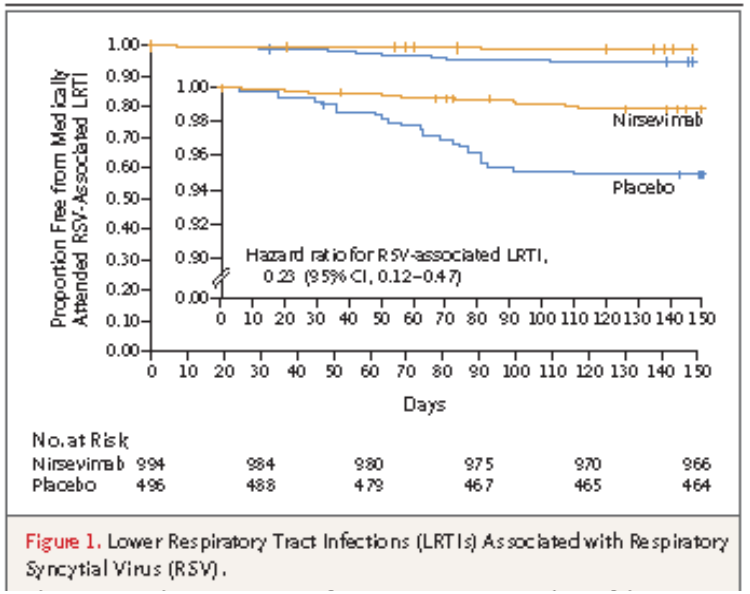


Figure 1. Lower Respiratory Tract Infections (LRTIs) Associated with Respiratory Syncytial Virus (RSV).

N Engl J Med 2022;386:837-46.
DOI: 10.1056/NEJMoa2110275

Efficacy shown in clinical trials of nirsevimab:

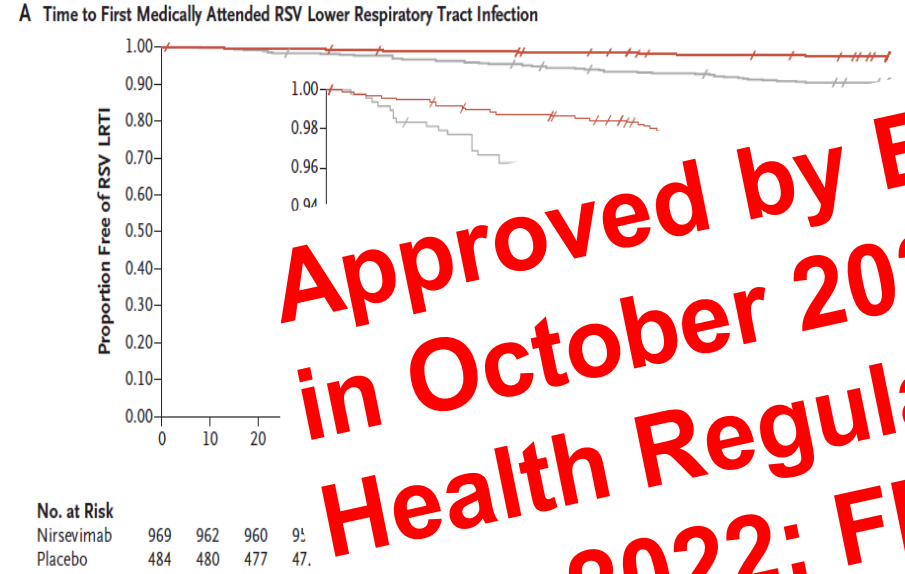
- Preterm at risk infants with heart/lung disease: nirsevimab vs palivizumab
- Healthy infants > 35 wks: nirsevimab vs placebo

Nirsevimab: Monoclonal Ab strategy for RSV prevention in high risk and healthy infants with one shot

The NEW ENGLAND

Single-Dose Nirsevimab for Prevention of RSV in Preterm Infants

2020 NEJM Griffin P et al



N Engl J Med 2020;383
DOI: 10.1056/NEJMoa1

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

2022 NEJM Hammitt ... Muller et al

N Engl J Med 2022;386:837-46.
DOI: 10.1056/NEJMoa2110275

Approved by European EMA in October 2022 and UK Health Regulatory Agency in Nov. 2022; FDA approval pending

Efficacy in clinical trials of nirsevimab:

- Preterm at risk infants with heart/lung disease: nirsevimab vs palivizumab
- Healthy infants > 35 wks: nirsevimab vs placebo

Bringing RSV Prevention to Infants in Low and Middle Income Countries: Challenges and Opportunities*

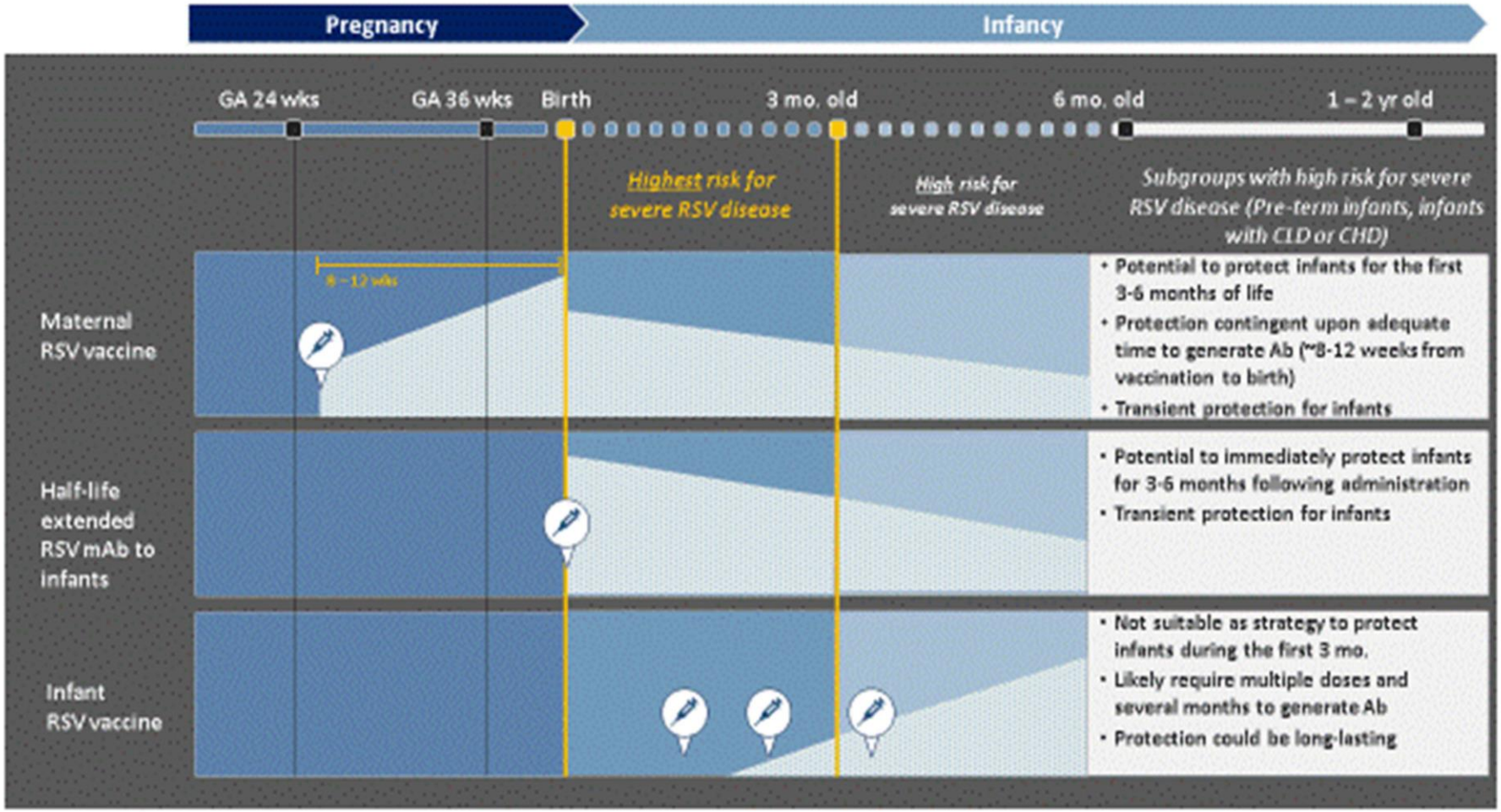
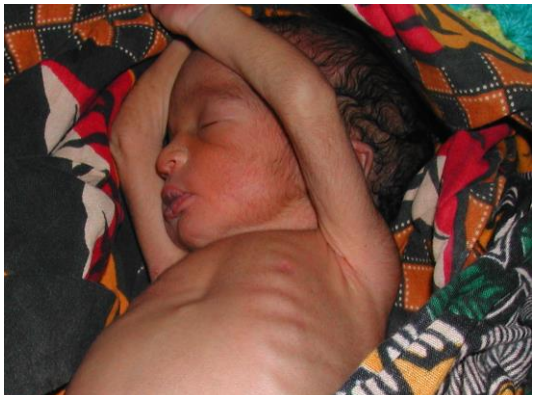


Figure. RSV prevention strategies for infants

* Anawaoranich and Heaton. Vaccines 2021

Conclusions: RSV Treatment and Prevention

- We now have a better understanding of the epidemiology and importance of RSV worldwide
- Unmet medical need for RSV prevention is more widely appreciated
- Improved understanding of molecular biology of RSV has helped the development of safe new vaccines and antibodies likely to be cost-effective
- Implementation and financing will be critical



Seattle Children's

UW Medicine