2023: the year of RSV

Ruth Karron
GVIRF 2023

Declaration of interests

Research funding from:

- US National Institutes of Health and Sanofi for evaluation of live-attenuated RSV vaccines for older infants and toddlers
- Bill and Melinda Gates Foundation for pre-implementation research related to maternal immunization

Respiratory syncytial virus (RSV)

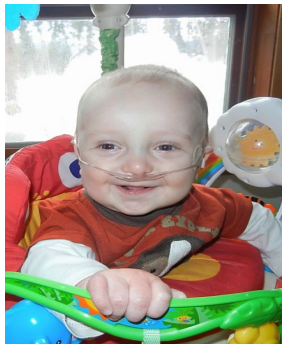
- Leading global cause of pneumonia in young children
  - 33 million cases of LRTI [1]
  - 3.6 million hospital admissions [1]
  - >100,000 deaths [1]
  - >95% deaths occur in LMICs [1]
- Important cause of LRTI in older individuals
  - 60,000-160,000 RSV hospitalizations and 6-10,000 deaths annually in older US adults[2]
  - Data from LMIC are less robust; global estimates 336,000 hospitalizations; 14,000 in-hospital deaths[3]

1. Li Y et al. Lancet. 2022 May 28;399(10340):2047-2064.
2. https://www.cdc.gov/rsv/research/index.html
3. Shi T et al. J Infect Dis 2020 Oct 7;222(Suppl 7):S577-S583.

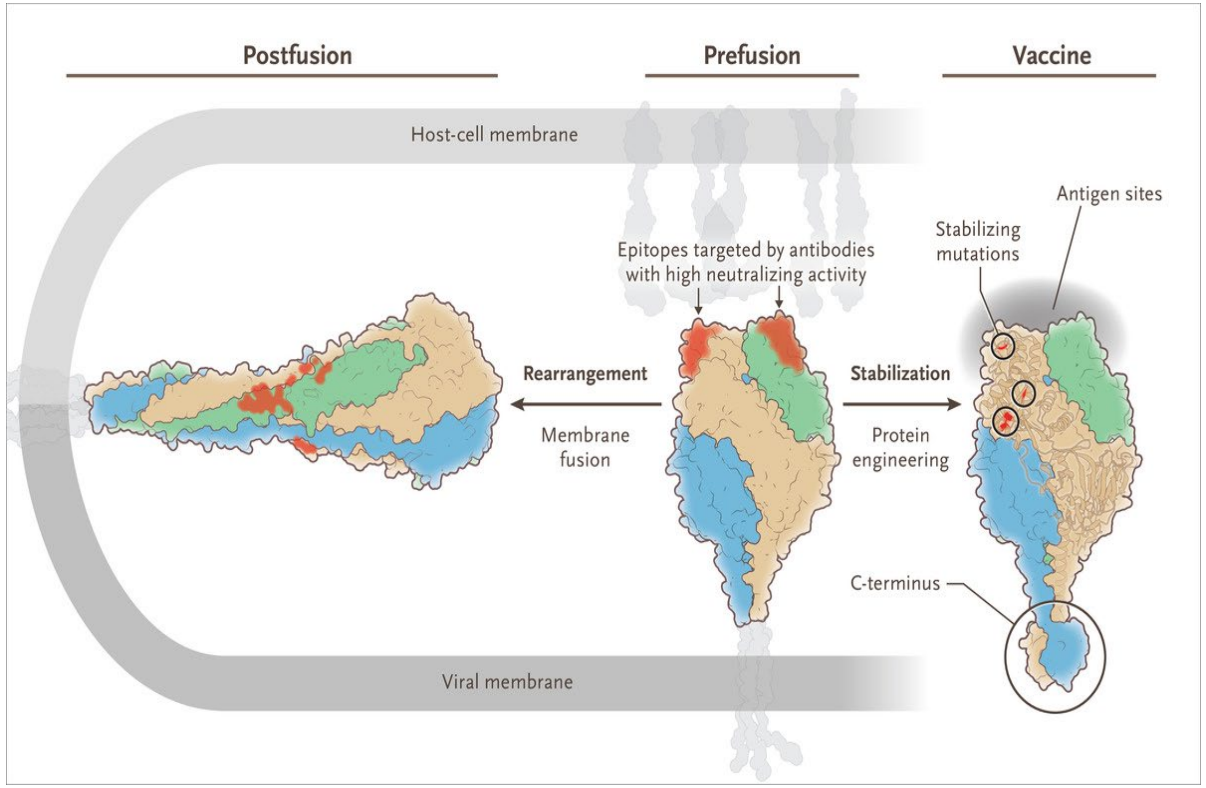
Strategies for prevention of RSV LRTI

- Passive immunization of young infants
  - Maternal immunization with RSV fusion (F) protein in prefusion conformation
    OR
  - Infant immunization with long-acting ‘vaccine-like’ mAb

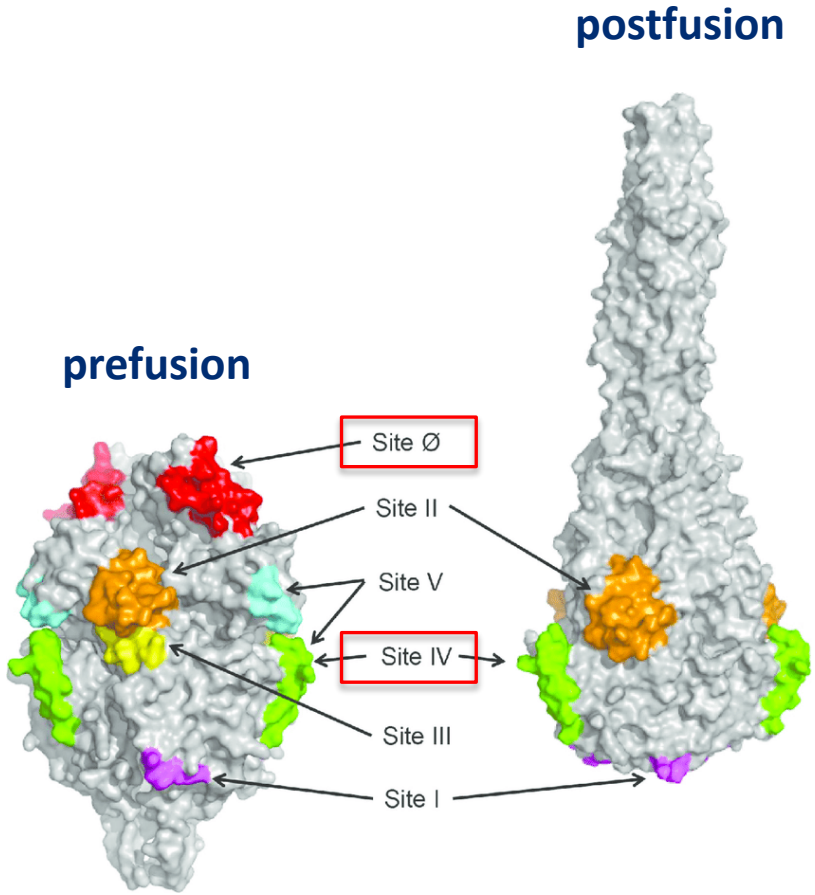
- Active immunization of older infants, toddlers, older adults
  - Live-attenuated vaccines in development for children
  - RSV F subunit and vectored vaccines for older adults



The Effect of Respiratory Syncytial Virus (RSV) Fusion Glycoprotein (F) Structure on Antigenicity



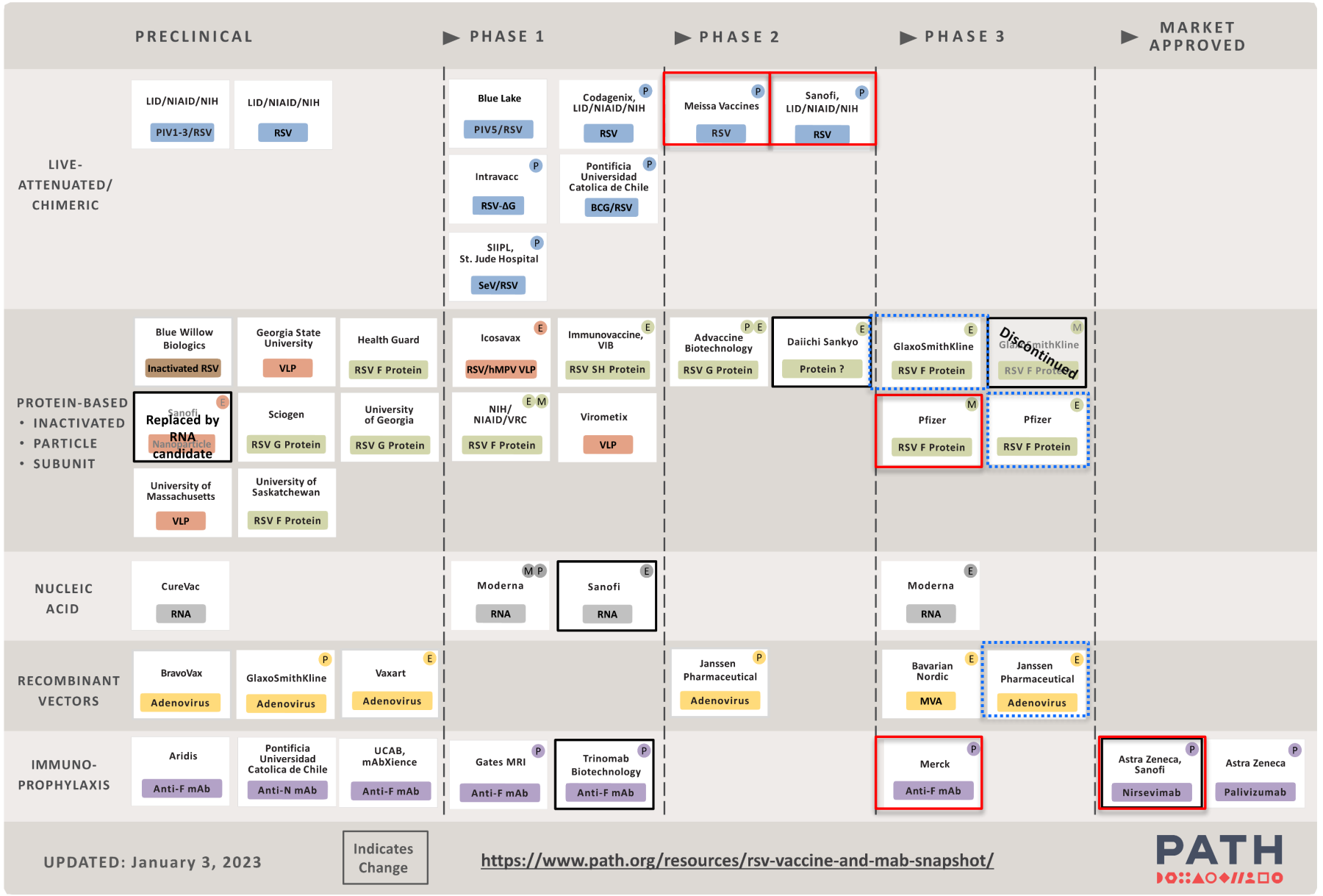
BS Graham. N Engl J Med 2023;388:579-581.



Flynn JA PLoS ONE 11(10):e0164789

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/

PATH

Three RSV F vaccines show substantial efficacy in older adults

- **Ad26.RSV.preF–RSV preF protein vaccine (Janssen)**
  - 5782 participants; VE against RSV illness 69.8-80% depending upon case definition[1]
- **AS01$_E$-adjuvanted RSV prefusion F protein (GSK)**
  - 24,966 participants; VE against any RSV ARI 71.7%; RSV LRTI 82.6%; severe RSV LRTI 94.5%[2]
- **RSV prefusion F protein (Pfizer)**
  - 35,971 participants; VE against any RSV LRTI with ≥2 sx 66.7%; with ≥3 sx 85.7%[3]

1. Falsey AR et al. N Engl Med 2023 Feb 16;388(7):609-620.
2. Papi A et al. N Engl J Med2023 Feb 16;388(7):595-608.
3. https://www.fda.gov/media/165625/download

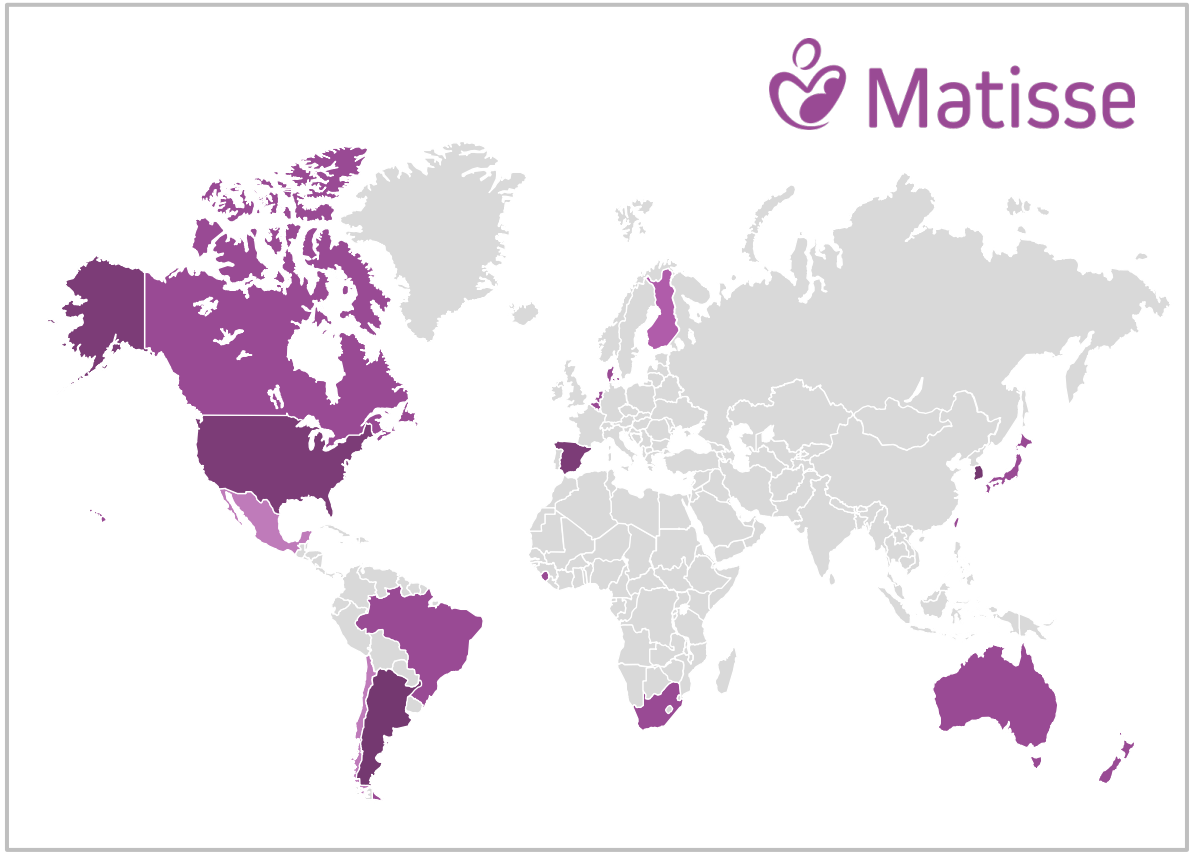
Maternal RSVpreF vaccine

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

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

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

7,128 Infants enrolled



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

Phase 3 Efficacy Endpoints Defined

Weekly active surveillance for ARI symptoms
Symptoms trigger nasal swab and possibly a visit

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

Positive validated RT-PCR in central laboratory

Medically attended visit: Infant participant taken to or seen by a healthcare provider (e.g. outpatient or inpatient visit, emergency room, urgent care, or home visit)

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

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

Primary Endpoints:

Vaccine Efficacy by Cumulative Days after Birth for Two Primary Endpoints

	Maternal Vaccine Group (as Randomized)		
RSV-Positive Severe MA-LRTI	RSVpreF 120 µg (N[a]=3495)	Placebo (N[a]=3480)	
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI*)**
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)
RSV-Positive MA-LRTI			
Time Interval	**Number of Cases (%)**	**Number of Cases (%)**	**Vaccine Efficacy[b] (%) (CI*)**
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)

*99.5% CI for 90 days, 97.58% CI for 120/150/180 days. CI LB >20% for all time points.

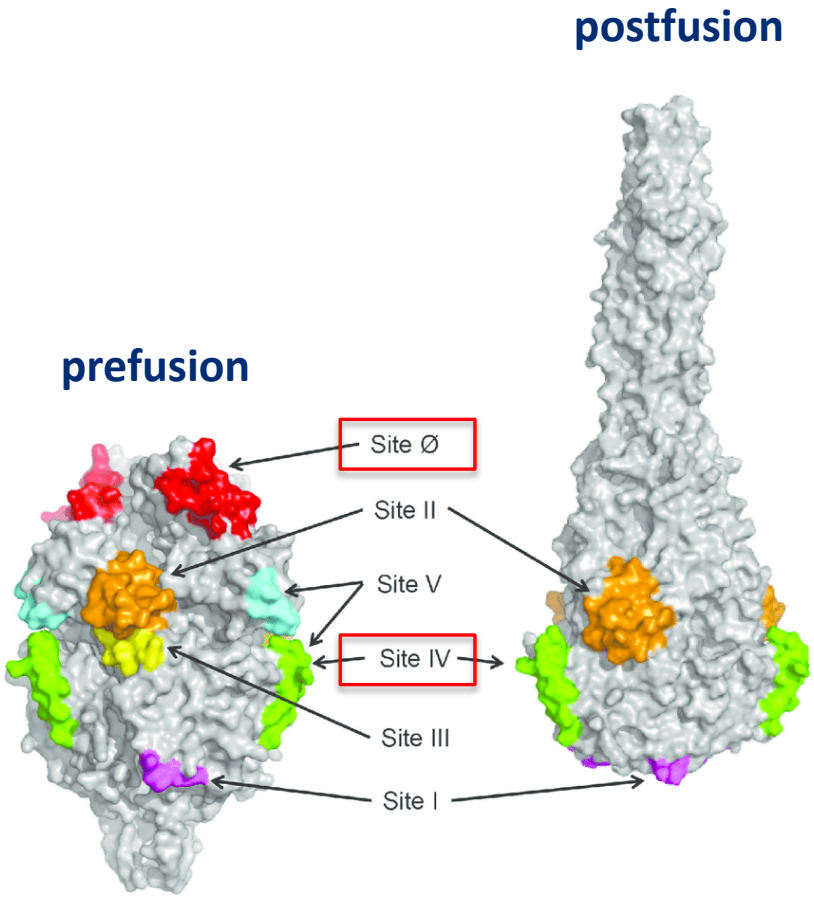
Abbreviations: RSV = respiratory syncytial virus. a. N = number of participants (at risk) in the specified group. These values are used as the denominators for the percentage calculations. b. Vaccine efficacy was calculated as 1-(P/[1-P]), where P is the number of cases in the RSVpreF group divided by the total number of cases. The confidence interval was adjusted using Bonferroni procedure and accounting for the primary endpoints results.

Status of maternal RSVpreF vaccine

- Submission of dossier/BLA to regulatory authorities (FDA and EMA); review expected by Q3 2023; other submissions in progress

- Multidose vials for use in LMICs being prepared with support from BMGF

Long-acting ‘vaccine-like’ RSV mAbs



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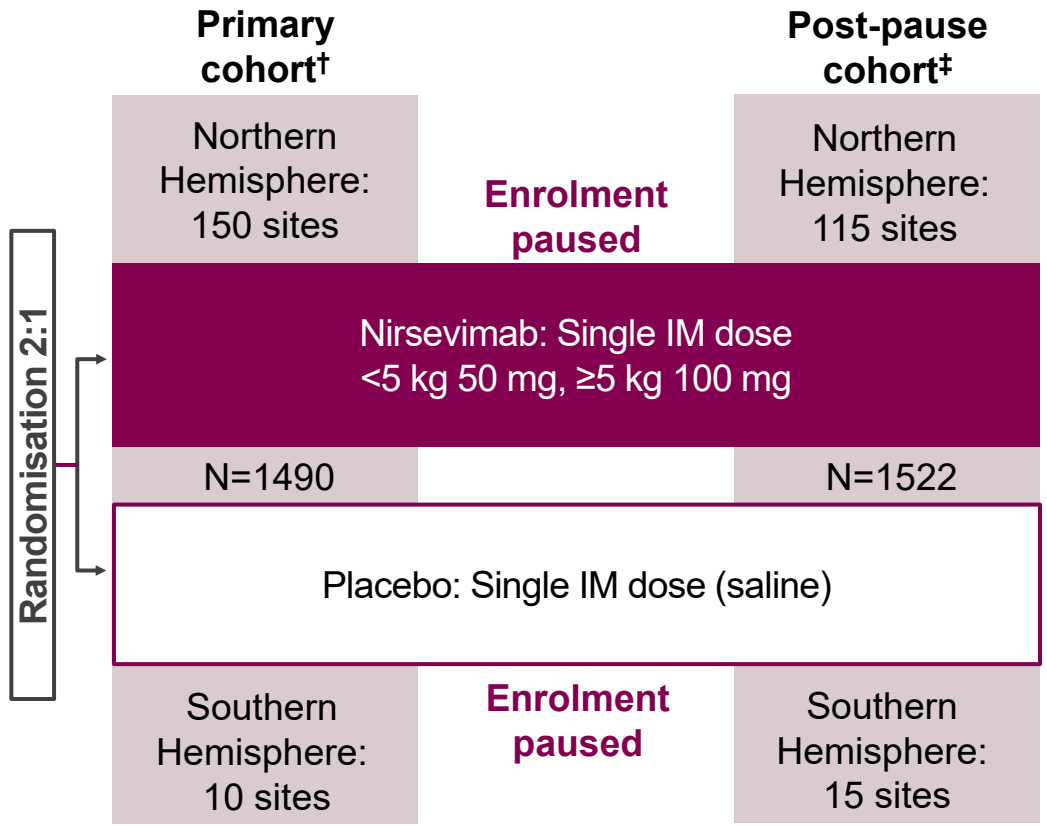
- Site Ø: nirsevimab (AstraZeneca and Sanofi)
- Site 4: clesrovimab (Merck)
- Both have mutations in Fc to delay clearance, with $t_{1/2}$ ~ 6 weeks
- Single dose to protect throughout RSV season

MELODY: A Phase 3, randomised, placebo-controlled trial in healthy late-preterm and term infants from 31 countries

- **Endpoints assessed over 150 days post-dose**
- **Primary: MA RSV LRTI**
  - PCR-confirmed RSV
  - PLUS signs indicative of lower respiratory tract disease
  - PLUS ≥1 clinical signs of disease severity*
- **Secondary: Hospitalisation for RSV LRTI**
  MA RSV LRTI requiring admittance to hospital
- **Exploratory: Very severe RSV LRTI**
  Hospitalisation requiring supplemental O_2 or IV fluids

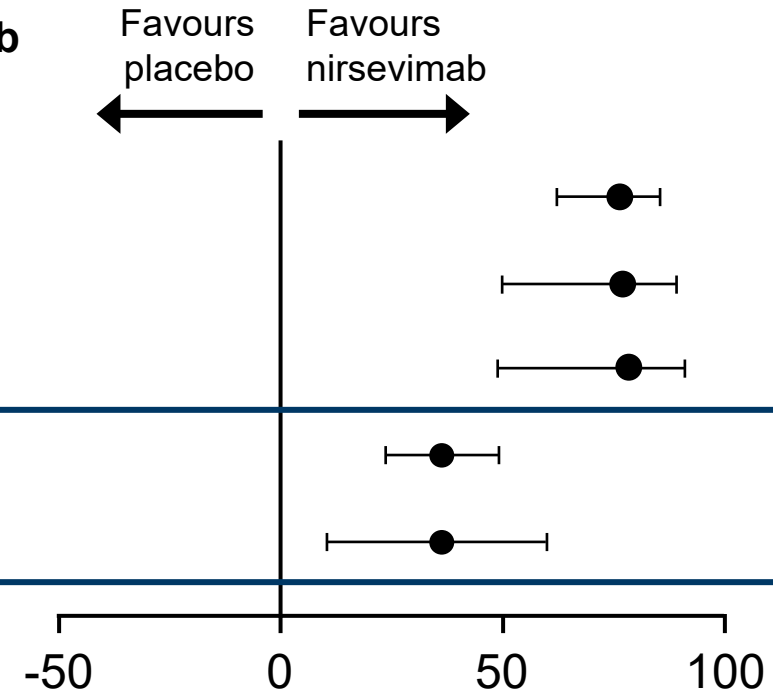


*Increased respiratory rate, hypoxemia, acute hypoxic or ventilatory failure, new onset apnoea, nasal flaring, retractions, grunting, dehydration.

 †Primary cohort includes those infants enrolled prior to the pause due to COVID-19. ‡Post-pause cohort includes infants enrolled after the pause due to COVID-19. IM, intramuscular; IV intravenous.

Nirsevimab efficacy against all-cause LRTI during 150 days of follow-up in the full analysis

	Placebo (n=1003)	Nirsevimab (n=2009)	Efficacy RRR (95% CI)
MA RSV LRTI	54 (5.4)	24 (1.2)	**76.4** (62.3, 85.2)
MA RSV LRTI with hospitalisation	20 (2.0)	9 (0.4)	**76.8** (49.4, 89.4)
MA RSV LRTI (very severe)	17 (1.7)	7 (0.3)	**78.6** (48.8, 91.0)
All-cause LRTI	139 (13.9)	171 (8.5)	**38.2** (23.7, 50.0)
All-cause LRTI with hospitalisation	37 (3.7)	45 (2.2)	**38.9** (6.3, 60.2)



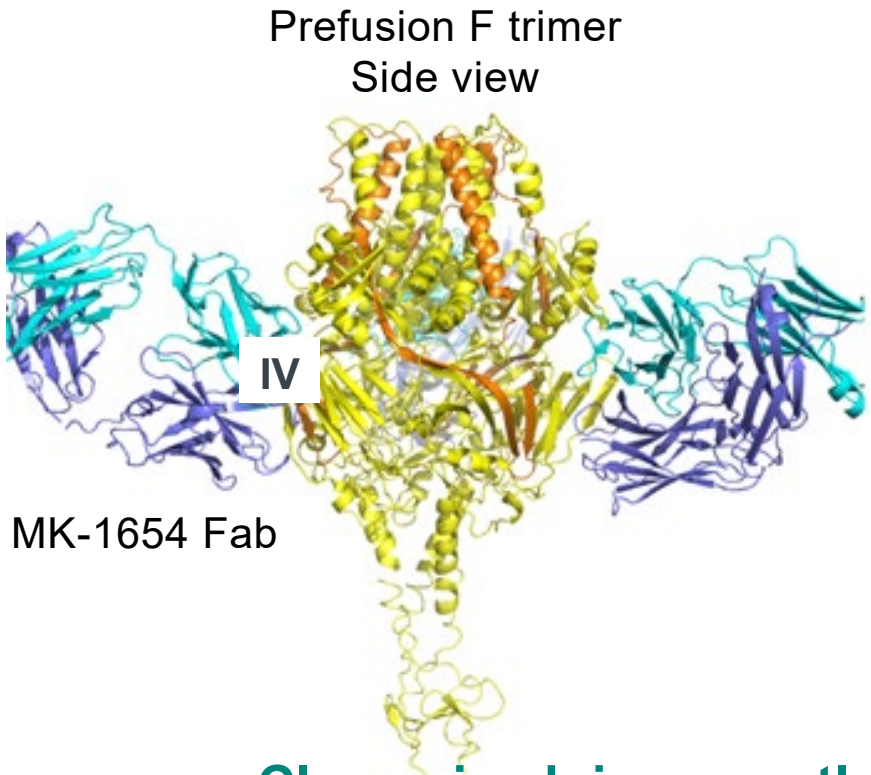
- NNT to prevent one all-cause MA LRTI hospitalisation: 53
- 57 days of hospitalisation averted for every 1000 infants treated

 NNT, number needed to treat

Status of nirsevimab (Beyfortus)

- Approved by the European Commission in October 2022 and by UK Medicines and Healthcare products Regulatory Agency (MHRA) in November 2022
- Submission to US FDA with review expected in 2023
- Submission to other regulatory authorities in progress
- Use anticipated Q3-Q4 2023

Clesrovimab (MK-1654) RSV-neutralizing monoclonal antibody



- Binds with high affinity to antigenic **Site IV** of RSV fusion protein[1]
  - Epitope is highly conserved, with **99.9% identity** among >3,000 reported RSV-A and RSV-B sequences[1]
- High potency in vitro against a range of clinical isolates[1]
  - Equipotent against RSV-A and RSV-B
- The Fc region is engineered with 3 mutations for half-life extension: YTE (M252Y/S254T/T256E)

Clesrovimab is currently in Phase 3 for the prevention of RSV-associated disease in infants

100 mg dose for all infants

[1]Tang A, et al. *Nat Commun*. 2019;10(1):4153.

Observed efficacy for RSV-associated MALRI Days 1 to 150 postdose from Phase 1b/2a study

	Clesrovimab		Placebo		
	Participants in Full Analysis Set	**Number of RSV-Associated MALRI cases**	**Participants in Full Analysis Set**	**Number of RSV-Associated MALRI cases**	**Observed Efficacy % (95% CI)**
Combined clesrovimab dose groups vs. Placebo	N=143	3	N=38	3	74.2 (-92.9, 96.5)
Clesrovimab 100 mg vs. placebo	N=64	1	N=38	3	80.6 (-141.2, 99.6)

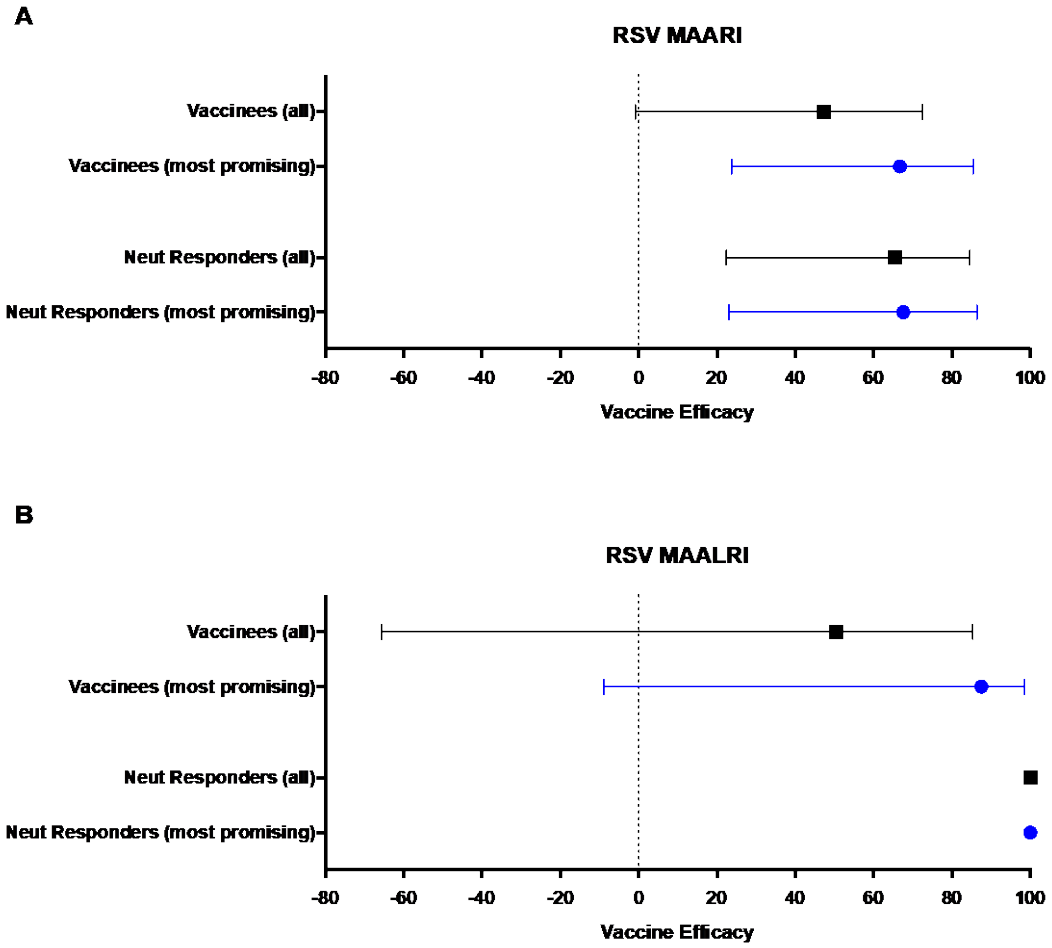
95% CI Estimated based on exact binomial method proposed by Chan and Bohidar.

Live-attenuated RSV vaccines for older infants and toddlers

- Meissa
  - Live-attenuated vaccine with multiple mutations in F,G, SH, NS1 and NS2 genes
  - Ongoing phase 1 evaluation in infants and toddlers

- Sanofi has a CRADA with the LID, NIH for development of live-attenuated intranasal vaccine candidates, to be administered to children 6 – 24 months
  - A phase 1/2 study with the lead live-attenuated candidate is wrapping up (last visits expected in April). Interim results will be presented at ESPID in May and final results expected late 2023.
  - Decision about a phase 3 study will be based on these results and ongoing parallel studies.

Preliminary efficacy of LAIN* vaccines against RSV-MAARI and RSV-MAALRI: Pooled data from 7 phase I trials in RSV-naïve infants and children



Total n=239 (160 V, 79 P)

Illness in placebo recipients

RSV-MAARI= 19%

RSV-MAALRI=7%

No child with ≥4 fold RSV neut Ab rise had RSV-MAALRI

Karron RA et al. Am J Respir Crit Care Med. 2021 Mar 1;203(5):594-603.

LAIN= live-attenuated intranasal vaccines developed at LID, NIAID, NIH

MAARI= medically attended acute respiratory illness. MAALRI= medically attended acute lower respiratory illness. "Most promising": ≥80% vaccinees with RSV neutralizing antibody response

2023: the year of RSV

- Products to protect older adults and the youngest infants likely to be approved this year (or have already been approved)

- Substantial work remains to ensure implementation and uptake of products to protect young infants in LMIC, the group at greatest risk of severe RSV disease and death

Acknowledgements

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