Live-attenuated RSV vaccines for older infants and toddlers

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ESWI 2024

Declaration of interests

Research funding from:

- US National Institutes of Health and Sanofi for evaluation of live-attenuated RSV vaccines

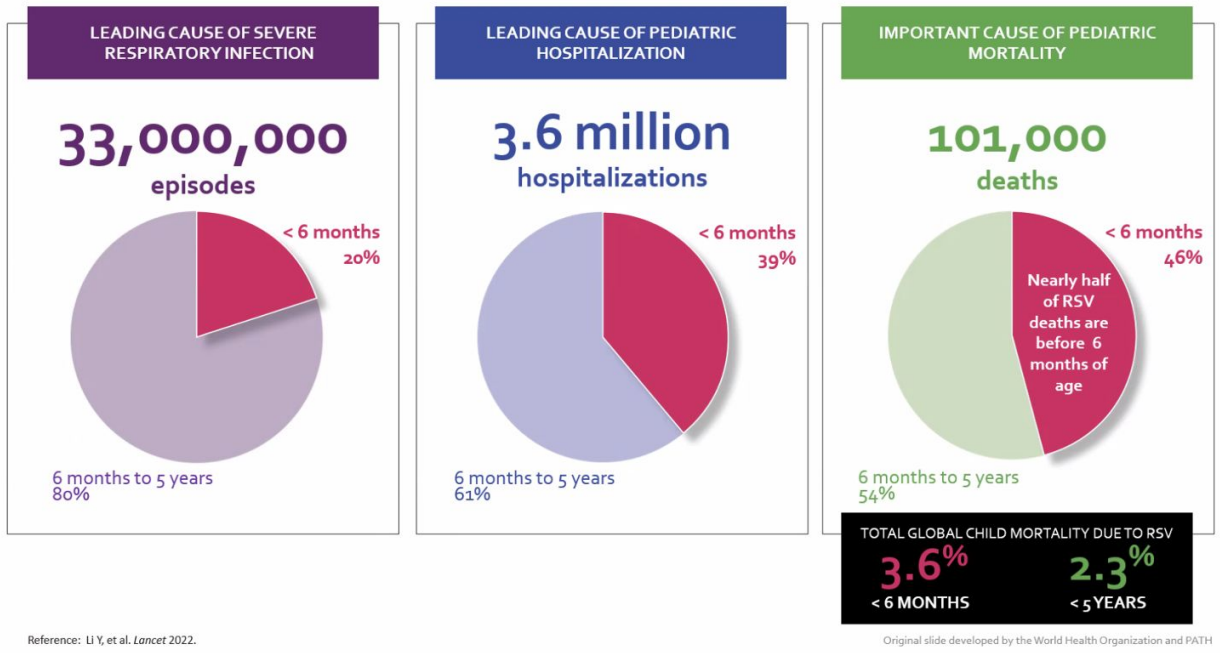
but the views presented are my own….

Victims of FI-RSV vaccine development

Ross Otto Hambrick 1965-1966
Victor King 1965-1966

https://undark.org/2023/10/09/rsv-vaccine-children-trials

The case for RSV vaccination of older infants and toddlers



Substantial annual inpatient and outpatient burden

- ~33.1 million cases of RSV-ALRI

~80% ≥ 6 months

- ~3.6 million hospitalizations

~60% ≥ 6 months

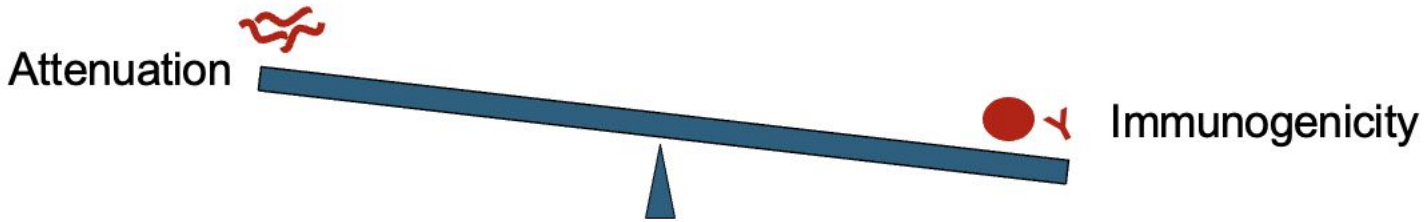
- ~101,000 deaths

~54 % ≥6 months

Shi T. et al, Lancet 390:946–958, 2 September 2017

The case for live-attenuated RSV vaccines for older infants and toddlers

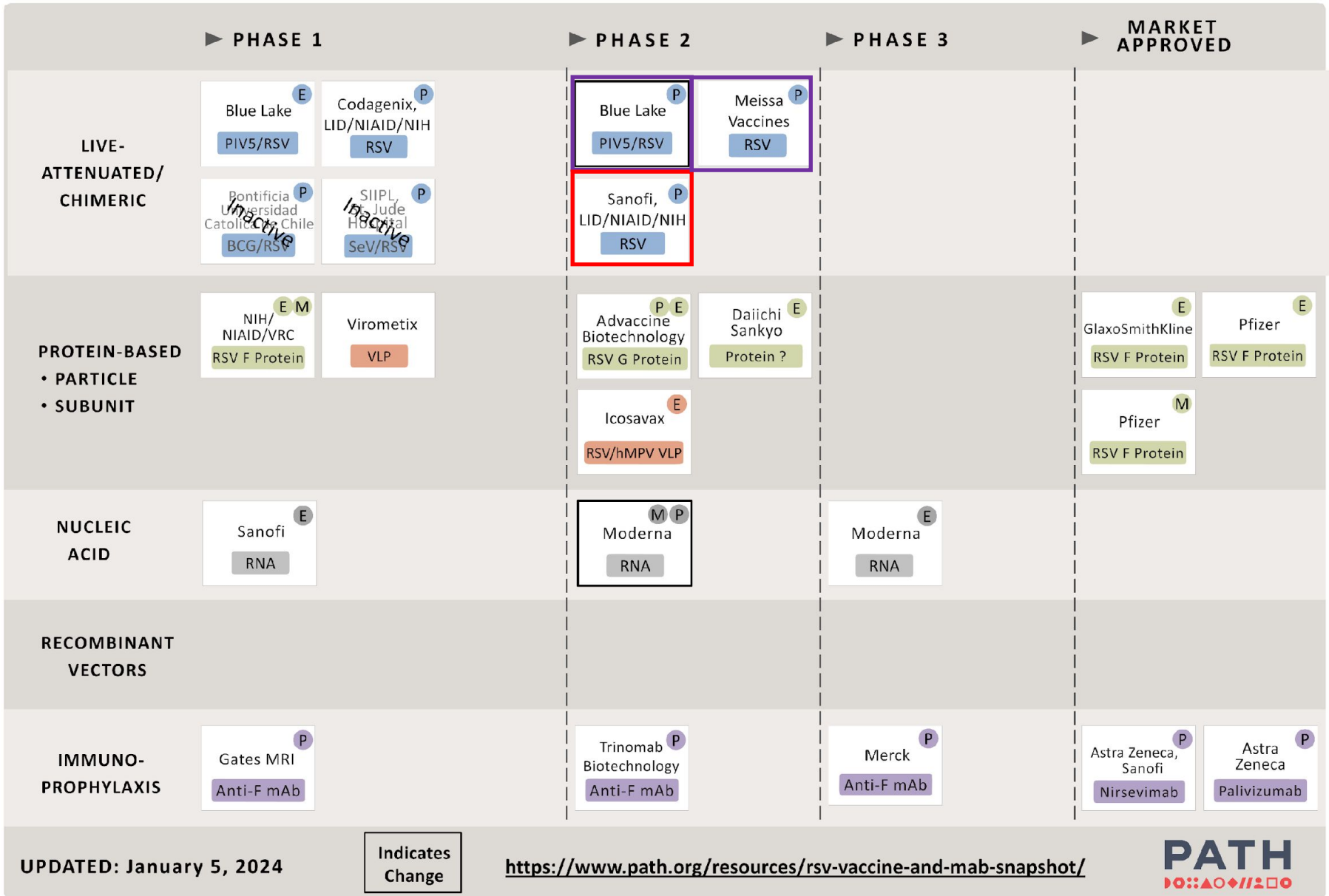
- Induction of long-lasting immunity with potent memory responses
- Administered intranasally ; infectious in the presence of passively acquired antibody
- Balanced humoral, cellular, mucosal immune responses, without markers of enhanced RSV disease in animal models
- Multiple strategies to shift the balance: enhance immunogenicity while maintaining or augmenting attenuation



Murphy et al J, Clin Micro, 1986
Connors et al, J Virol, 1992
Polack, Pediatr Res, 2007
Delgado et al, Nat Med, 2009
Acosta et al., CVI. 2015
Schneider-Ohrum et al., J. Virol. 2017

RSV Vaccine and mAb Snapshot

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



UPDATED: January 5, 2024

Indicates Change

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

PATH

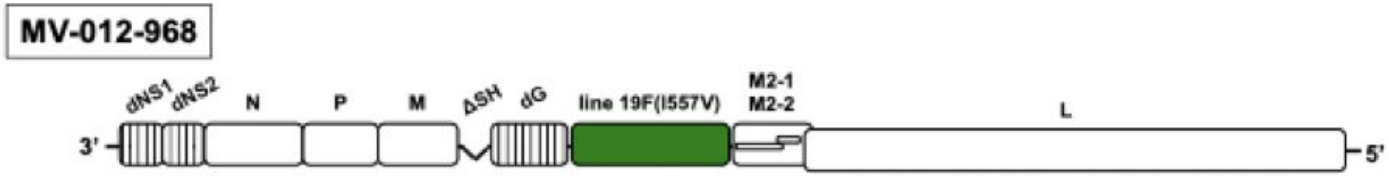
BLB-201, PIV-5 vectored RSV F (Blue Lake Biotechnology)

- PIV-5 is the etiologic agent of kennel cough; some humans have PIV-5 antibodies but human PIV-5 illness has not been reported
- Phase 1 trial of BLB-201[1]
  - $10^{7.5}$ pfu administered by nasal spray to adults aged 33 to 75 years
  - Mild rhinorrhea reported; 17% of participants shed vaccine virus
  - Neutralizing antibodies increased 1.5-fold, nasal IgA and T cell responses detected
- Phase 1/2a study of 10^6 and 10^7 pfu in children 18-59 months and 6-24 months of age is ongoing (NCT05655182)

1. Sci Adv. 2023 Oct 27;9(43):eadj7611.

Meissa MV-012-968 live-attenuated nasal spray RSV vaccine

- Contains codon-deoptimized genes (NS1, NS2) and a gene deletion
- Phase 1 dose-ranging study (n=79) in RSV-seronegative infants and toddlers showed that the vaccine was well-tolerated and immunogenic (NCT04909021)
- Phase 2/3 development anticipated



Symbol	Modification
dNS1 / dNS2	Codon-deoptimized NS1 and NS2 for human expression
ΔSH	Deletion of SH protein
dG	Codon-deoptimization of G for human expression
Line19 F	Chimeric expression of line19 F

Live-attenuated RSV vaccines developed at LID, NIH using reverse genetics

A panel of rationally-designed candidates with precise attenuating mutations:

- **"Stabilized" attenuating point mutations**
  - mutations in L gene refractory to de-attenuation
- **Deletion of non-essential accessory proteins**
  - **ΔM2-2:** Up-regulation of transcription and antigen expression to increase immunogenicity
  - **ΔNS1, ΔNS2:** Reduced viral suppression of host interferon and apoptosis responses; ΔNS2 diminishes epithelial shedding and airway obstruction
- **Other approaches**
  - **Gene order rearrangements**: moving F and G to promoter proximal positions to enhance transcription and translation

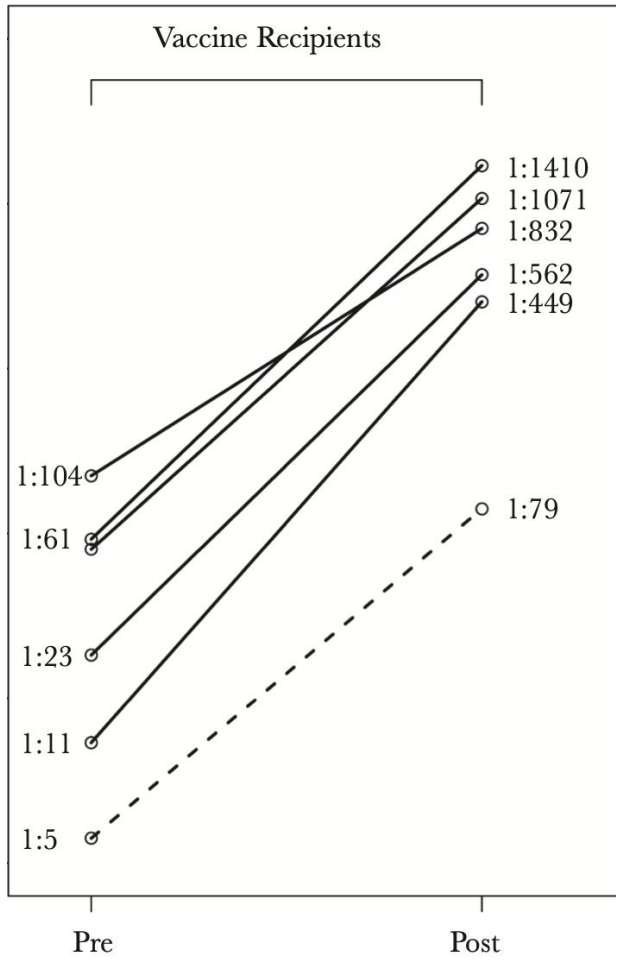
Attenuation
Enhanced immunogenicity
Attenuation and enhanced immunogenicity

→ **RSV ΔNS2/Δ1313/I1314L**

Luongo et al., J. Virol. 2012, 2013
Biacchesi et al., 2004 (HMPV)
Le Nouen et al., PNAS 2014, 2017, 2021
Liesman R Clin Investm2014 May;124(5):2219-33

Recalibrating expectations:
RSV antibody levels achieved with live-attenuated RSV vaccines

- Priming with live-attenuated RSV results in modest primary RSV neut Ab responses (although comparable to primary wt RSV infection)
- Subsequent natural infection with wt RSV yields potent memory responses in the absence of medically-attended RSV illness



RSV Infection and memory response in the absence of MARI

McFarland E et al. J Infect Dis. 2020 Feb 3;221(4):534-543

Preliminary suggestion of vaccine efficacy with live-attenuated vaccines

Post-hoc analysis: vaccines grouped by frequency of immune response:

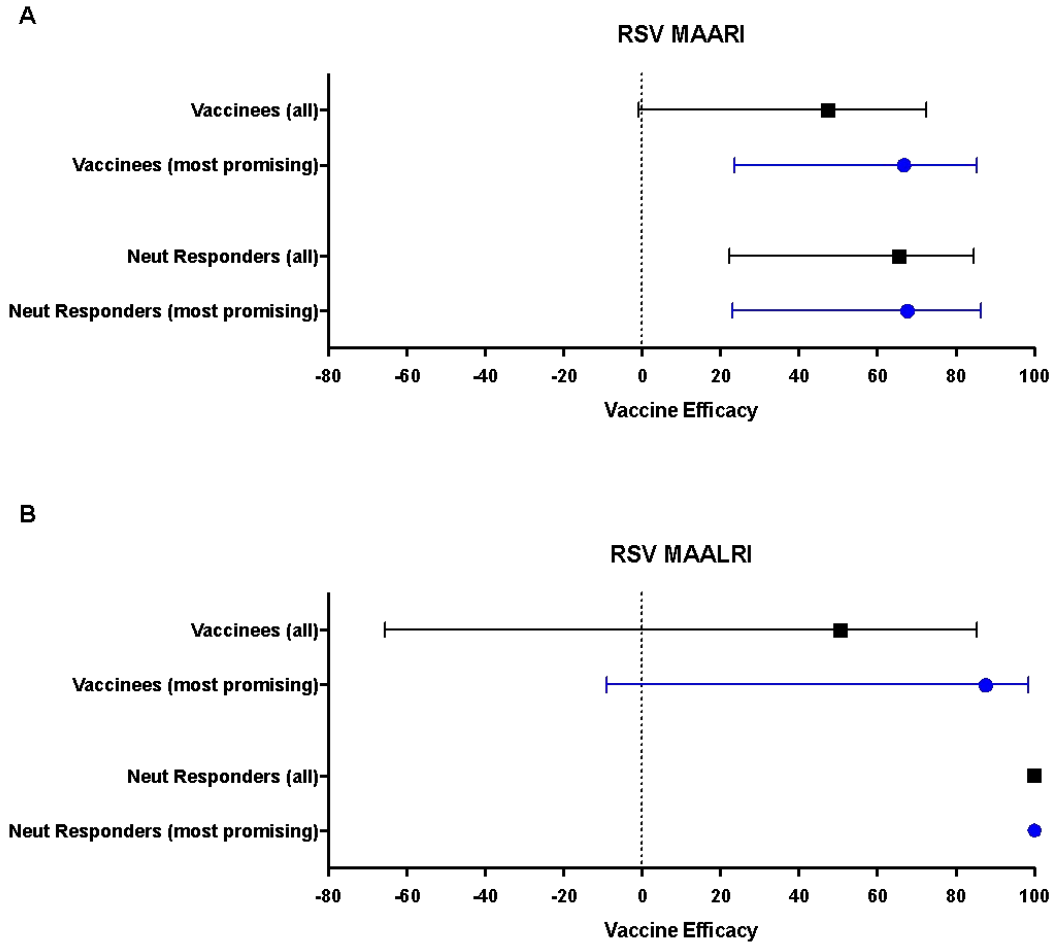
Vaccine	
MEDIΔM2-2	95%
LIDΔM2-2	90%
ΔNS2/Δ1313/I1314L(10^6 dose)	80%
LIDΔM2-2/1030s	85%
D46/NS2/N/ΔM2-2-HindIII	95%
RSVcps2	59%
ΔNS2/Δ1313/I1314L(10^5 dose)	47%
LID/cp/ΔM2-2	45%

5 “most promising” vaccine candidates

Total n= 239 (160 vaccinees, 79 placebo recipients)

Karron et al., AJRCCM 2021

Proof of concept:
efficacy against RSV-MAARI and RSV-MAALRI from pooled analysis



Total n=239 (160 V, 79 P)

<u>Illness in placebo recipients</u>

RSV-MAARI= 19%

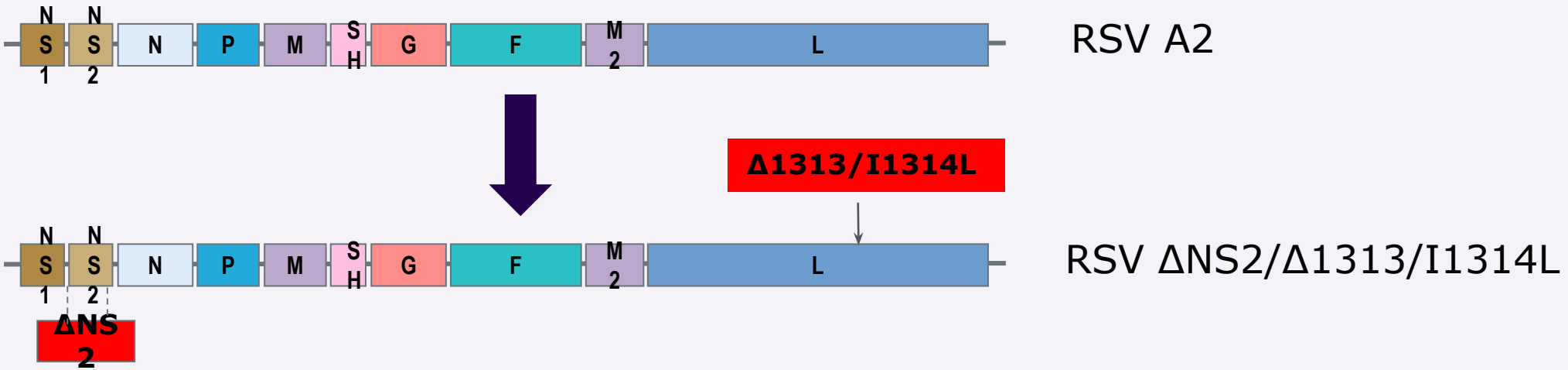
RSV-MAALRI=7%

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

4-fold rise in RSV neut Ab titer, rather than absolute titer, predicted protection

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

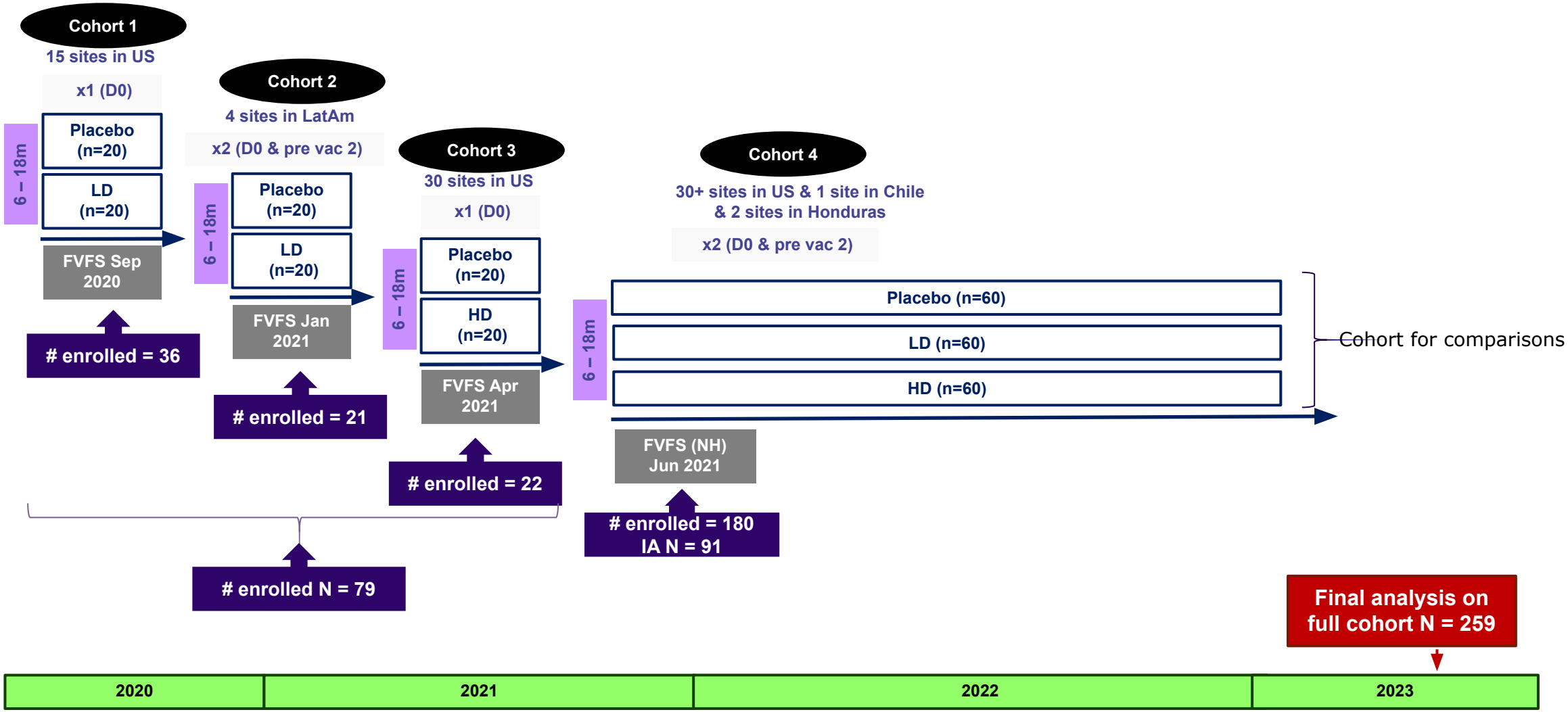
RSVt vaccine in clinical trials: Sanofi/NIH co-development



- **ΔNS2:**
  - attenuates virus and removes the risk of NS2 mediated epithelial sloughing/airway obstruction
  - may improve immunogenicity leading to effective viral clearance
- **Δ1313/I1314L:**
  - deletion of 1313 confers moderate temperature-sensitive phenotype; I1314L stabilizes this deletion
- **RSV ΔNS2/Δ1313/I1314L:**
  - well-tolerated and immunogenic in phase I/II trials in infants and children ages 4-24 months[1,2]

1. Karron RA J Infect Dis. 2020 Jun 16;222(1):82-91.
2. Cunningham CK J Infect Dis. 2022 Dec 13;226(12):2069-2078.

Study design: Phase 1b/2 trial of RSVt vaccine



ClinicalTrials.gov Identifier: NCT04491877

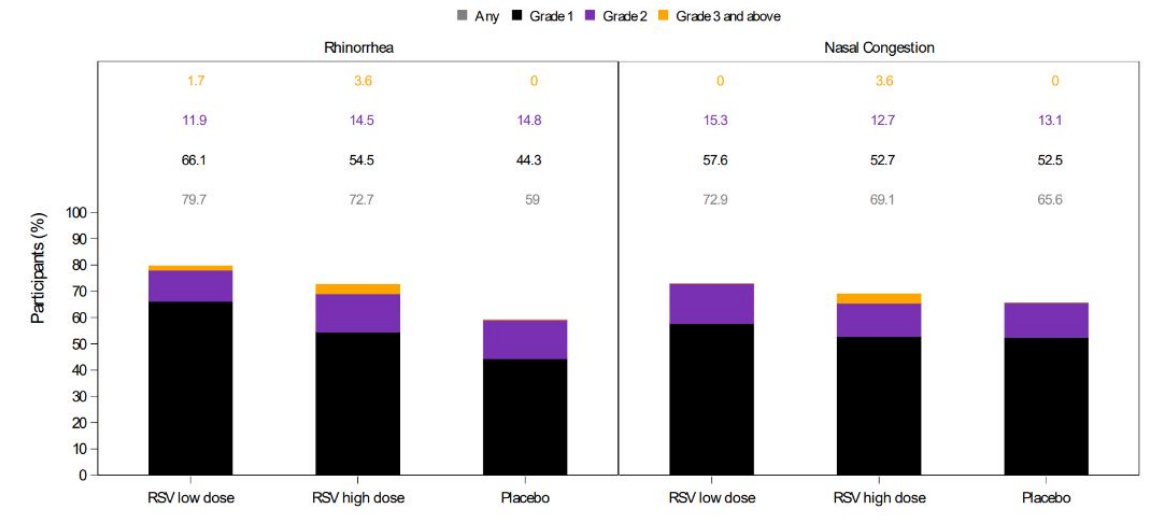
FVFS, first visit, first subject; PFU, plaque forming unit; IA, interim analysis; LD, low dose; HD, high dose; vac, vaccination

Favorable safety profile; Transient rhinorrhoea and nasal congestion were common administration site reactions

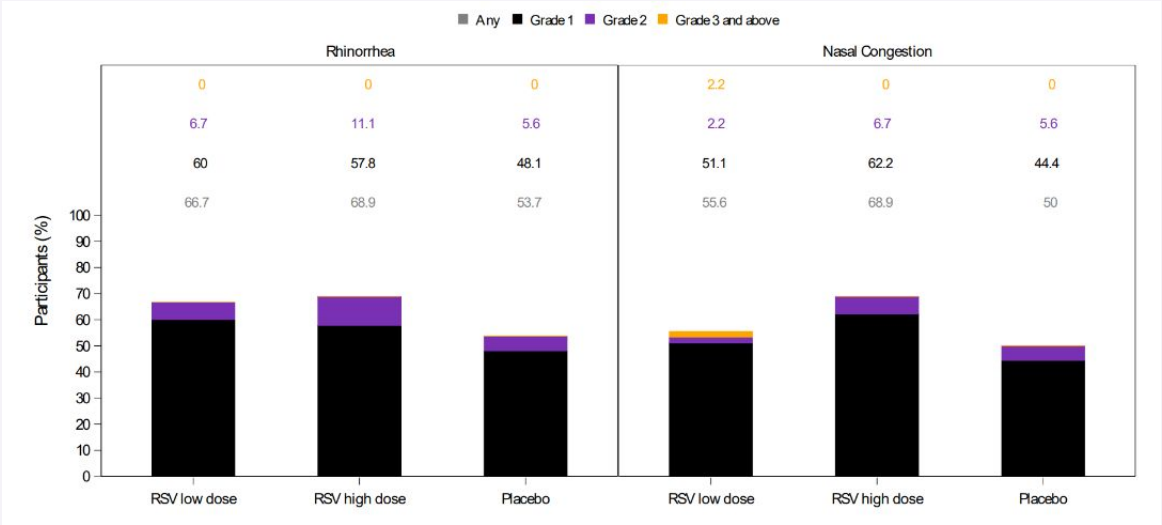
Rhinorrhoea and nasal congestion occurred with similar frequency between the 2 dose levels;

Rhinorrhoea was slightly less common in placebo recipients following vaccination 1

Vaccination 1

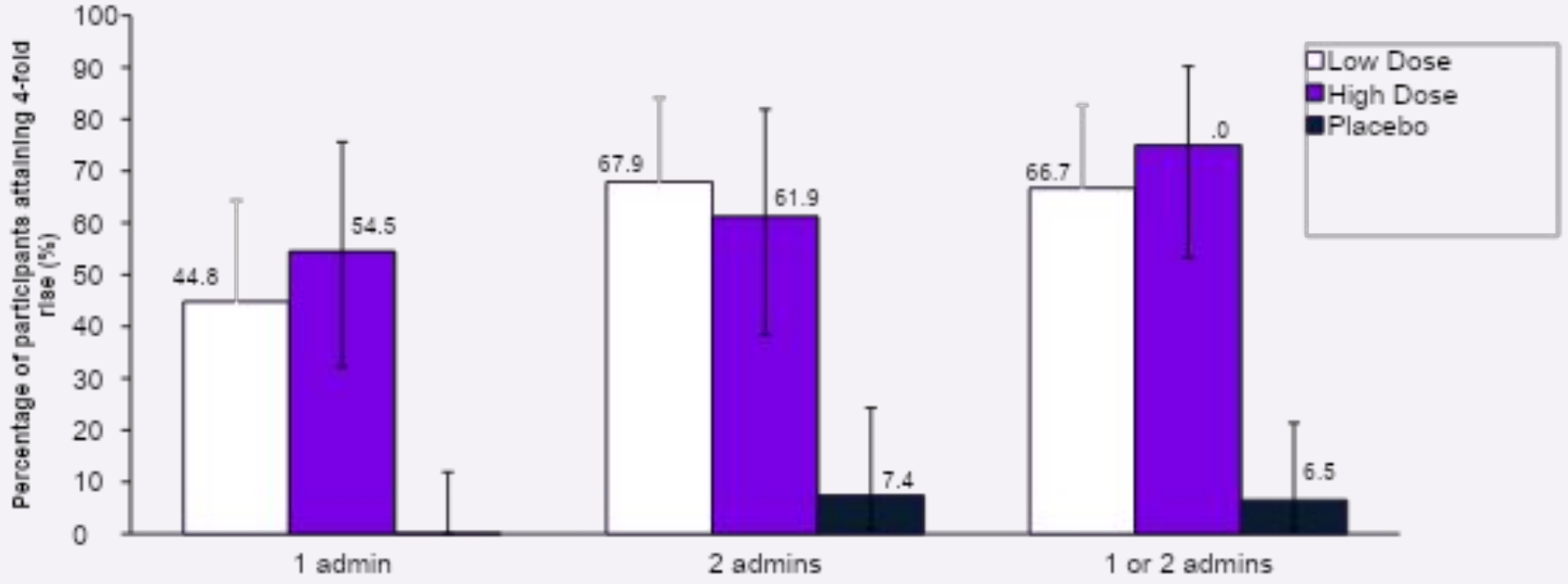


Vaccination 2



Safety Analysis Set. (all participants receiving at least one vaccine dose; cohort 4).
Summary of participants with solicitated administration site reactions during the solicited period by grade. For vaccination 1, N=61 for RSV low dose, N=57 for RSV high dose, and N=61 for placebo. For vaccination 2, N=48 for RSV low dose, N=48 for RSV high dose, and N=54 for placebo.
Maximum intensity during solicited period shown

4-fold rise in neutralizing antibody titres after 2 vaccinations



RSV naive participants; cohort 4

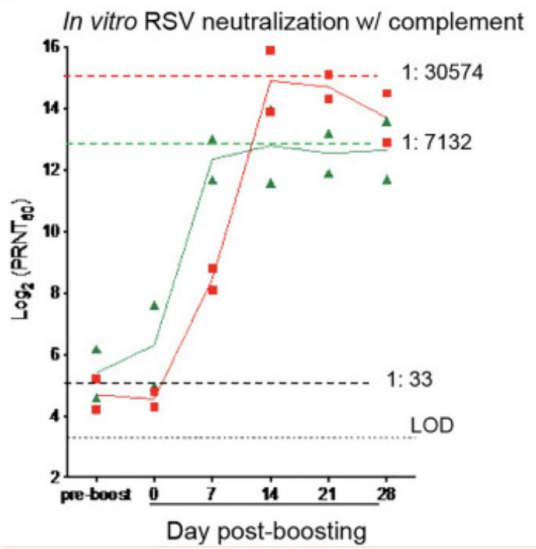
RSVt Phase III (PEARL) study initiated February 2024: anticipated global footprint

NCT06252285

An alternative approach: bovine/human parainfluenza virus RSV preF

BPIV3 N, P, M, L proteins: host range restriction in primates

- B/HPIV3 expressing RSV preF (DS-Cav1 or DS-Cav1-CT) as a dual HPIV3/RSV vaccine
- Potential advantages:
  - Protection against 2 important pediatric respiratory pathogens
  - May be particularly useful after a primary infection or in the presence of RSV Ab
  - In NHP studies:
    - not inhibited by preexisting RSV immunity
    - boosting with rB/HPIV3-RSV-pre-F yields significantly higher titers of RSV neut Ab compared to live-attenuated native RSV in preimmune animals
- Potential disadvantage: contains a single RSV protein
- Clinical evaluation of rB/HPIV3-RSV-pre-F anticipated in 2024



Liang et al., J Virol 2020

Some final thoughts

- Substantial burden of pediatric RSV disease exists beyond early infancy
- Live RSV vaccines currently in clinical development fall into 2 broad categories:
  - Native RSV attenuated by gene deletions, point mutations, codon deoptimization (NIH/Sanofi, Meissa)
  - Vectored RSV F with heterologous backbones (PIV-5 [Blue Lake Biotechnology]; B/HPIV3 [NIH])
- As with LAIV, products may be efficacious without a detectable CoP
  - Passive immunity cannot be used as a benchmark—priming is important!
  - Mechanisms of protection may differ between native RSV vaccines and vectored vaccines
- The next 3-5 years will be critical for live-attenuated RSV vaccine development

With thanks to:

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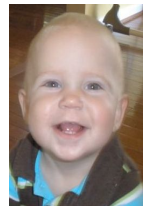
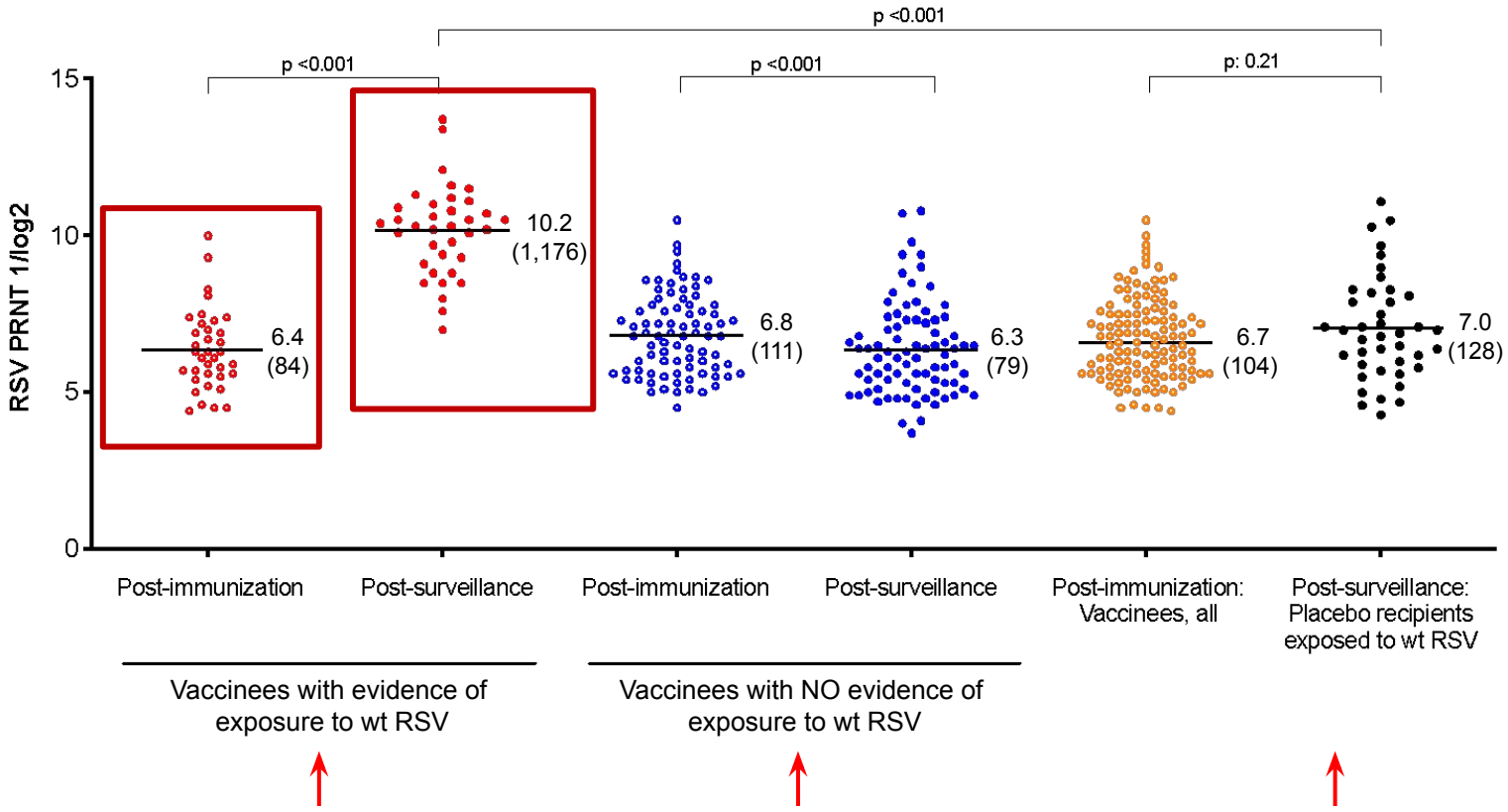
The children and parents who participated in these studies



Extra slide

Combined RSV serum neutralizing antibody data from 7 LID vaccine studies

Comparison of RSV serum antibodies on day 56 after immunization with live-attenuated RSV vs serum antibodies after the following RSV surveillance season



Karron et al., AJRCCM 2021

Live-attenuated RSV vaccines prime for strong anamnestic responses to wt RSV.

Antibody responses are stable over time.

Antibody titers to vaccines are comparable to those induced by primary RSV infection.

→ Can we boost primary RSV serum antibody titers to levels similar to anamnestic responses?