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Review of Investigational RSV (mRNA-1345) and RSV/hMPV (mRNA-1365) Vaccines in Infants and Children < 2 Years

Moderna, Inc.

December 12, 2024

Vaccines and Related Biological Products Advisory Committee

Introduction

Christine Shaw, PhD

Vice President, Portfolio Head, Infectious Disease Vaccines

Moderna, Inc.

Background for Today's Presentation

- **Moderna's RSV vaccine (mRESVIA) is licensed for use in adults ≥60 years of age**
  - Safety and efficacy demonstrated in global study of >36,000 adults; RSV hospitalizations only in placebo recipients[1]
- **Pediatric program pursued to address significant unmet medical need**
  - Conservative, step-wise approach to age de-escalation
  - Developed in consultation with regulatory agencies and following established guidance
- **Recent Phase 1 trial identified potential imbalance of severe/hospitalized RSV in RSV-naïve infants 5-7 months of age**
  - Occurred more frequently in vaccine vs placebo recipients
- **Dosing in this study paused in July 2024 based on predefined protocol criteria**
  - No subsequent enrollment or dosing; surveillance continues
  - No plan to continue RSV vaccine program in children under 2 years

Goal: Share available data to help inform pediatric RSV vaccine development and guidance

1. ACIP Feb 2024

Agenda

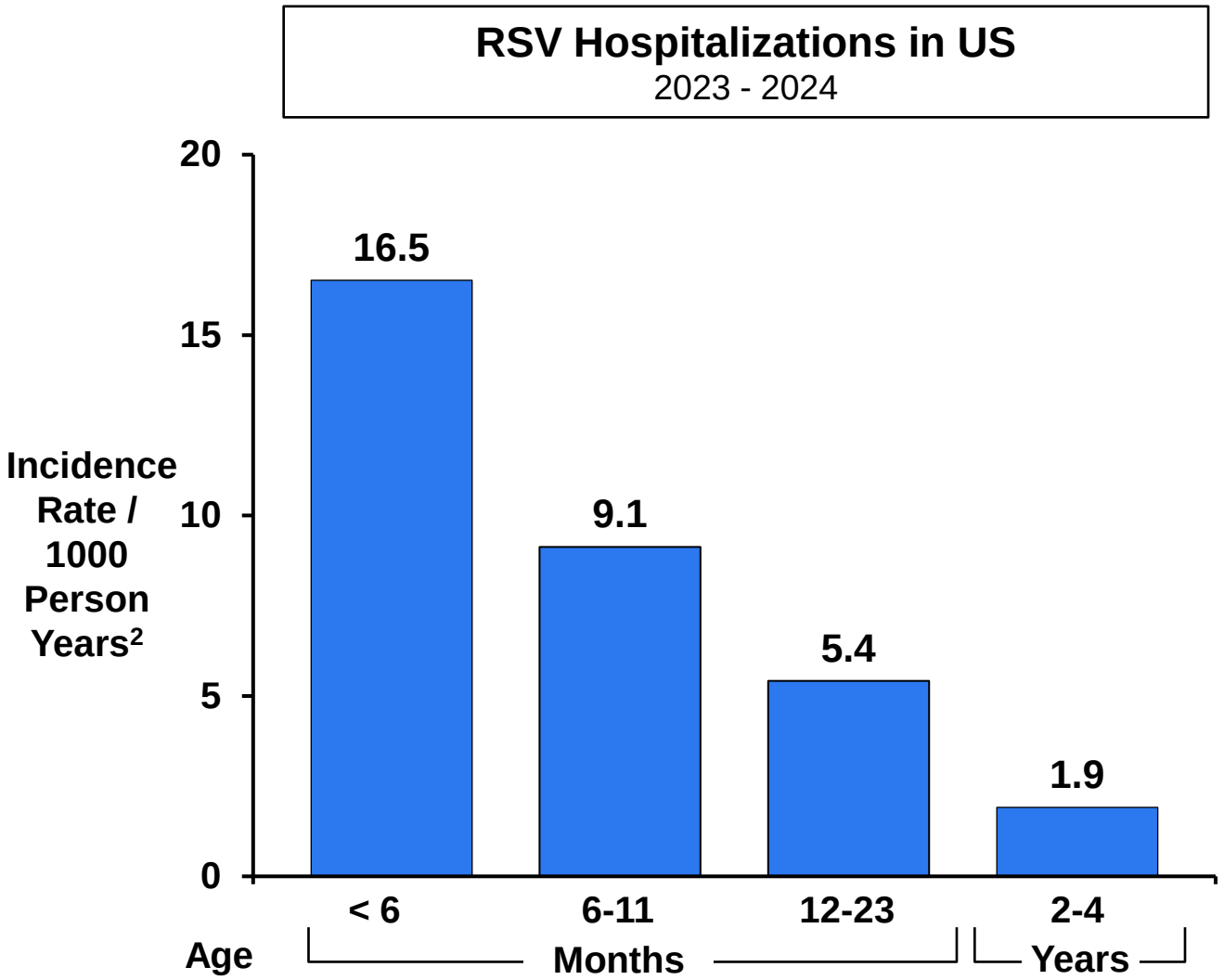
- Introduction/Background
- Nonclinical Data

Christine Shaw, PhD
VP Portfolio Head, Infectious Disease Vaccines
Moderna

- Clinical Data
- Summary

Matthew Snape, MBBS MD
VP, Pediatric and Maternal Vaccines
Moderna

Respiratory Syncytial Virus (RSV) Remains a Key Unmet Medical Need in Young Children in the United States

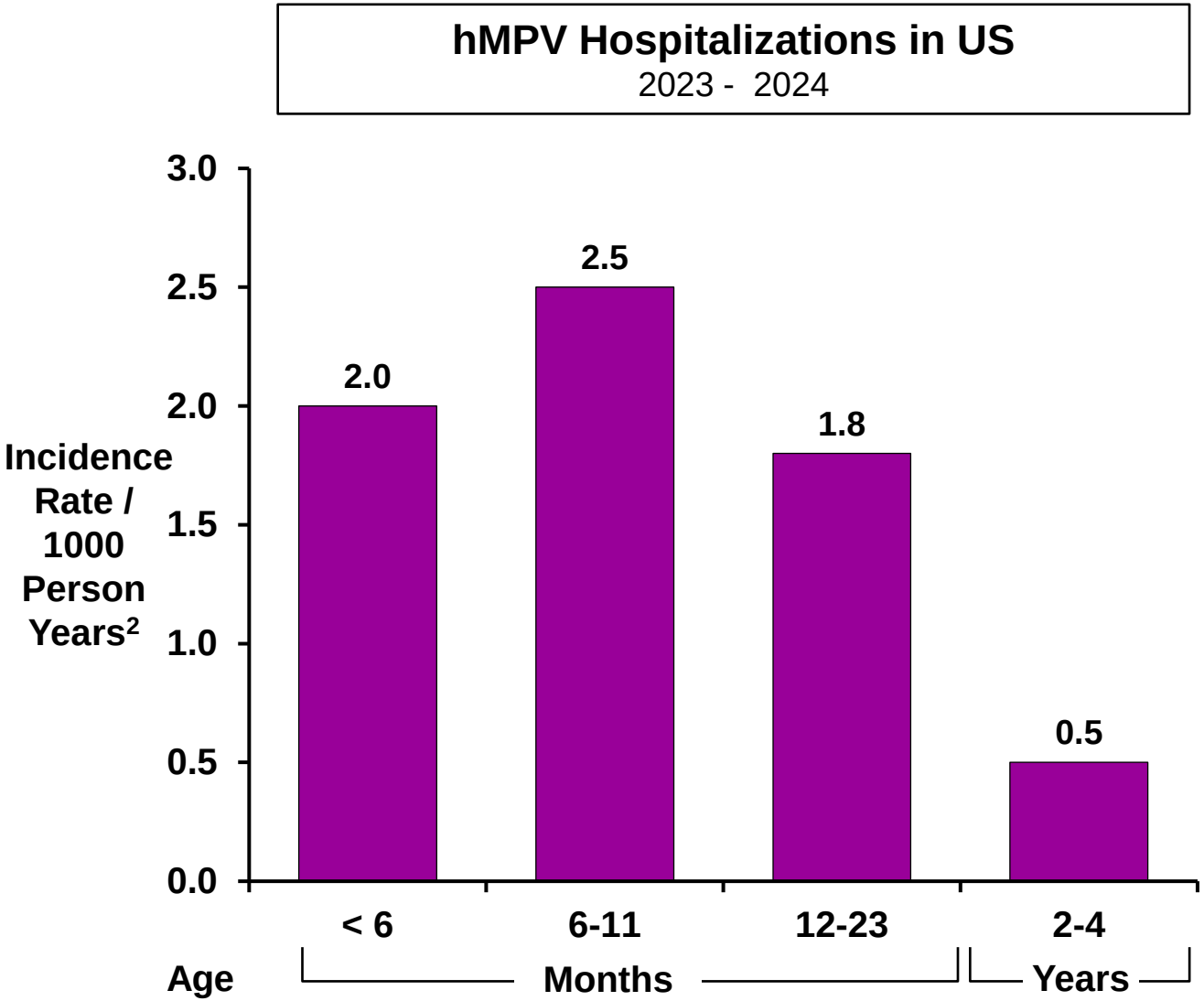


Children <5 Years

- **The leading cause of infant hospitalization**
  - ~300 deaths[1]
  - ~80,000 hospitalizations[2]
  - ~2.1 million outpatient visits[2]
- **Nearly every child infected by age 2**[3]
- **Vaccination remains important tool in preventing RSV in children**[4]
  - Maternal RSV vaccination
  - RSV monoclonal Ab for infants
- **Medical need remains for RSV prevention through active immunization**[5]

1. Hansen, CL et al, 2022; 2. CDC RSV Research & Surveillance; 3. www.cdc.gov/rsv/infants-young-children/index.html;
4. Immunizations to Protect Infants, CDC; 5. Mejias A, et al, 2024

Human Metapneumovirus (hMPV), Related to RSV, is Another Key Unmet Medical Need in the United States



Children <5 Years

- **Significant respiratory disease burden[1]:**
  - ~ 20,000 hospitalizations
  - > 260,000 ED visits
  - ~ 1 million outpatient visits
- **hMPV circulation overlaps with RSV, but begins later (winter through spring)[4]**
- **3rd most common cause of community-acquired pneumonia[3,4]**
- **Most children infected by age 5[5]**
- **No specific antiviral therapy or vaccine available[6]**

1. Edwards, KM et al, 2013; 2. Davis, CR et al, JPIDS, 2015; 3. Yun, KW et al, PIDJ, 2022; 4. Jain et al, 2015; 5. Kahn, JS 2006; 6. About Human Metapneumovirus, CDC

History of Enhanced Respiratory Disease (ERD) in Pediatric RSV Vaccine Development

FI-RSV Associated ERD

- Formalin-Inactivated RSV (FI-RSV) vaccine studied in 1960s resulted in ERD in RSV-naive infants after subsequent natural RSV infection
  - 80% hospitalized, 2 died[1]
- Contributing humoral and cellular factors likely included[2]:
  - Low neutralizing antibody levels; Induction of non-neutralizing, binding antibody and immune complex-mediated complement activation in airways
  - High Th2 cytokine response resulting in airway inflammation

Risk of ERD Based on Prior RSV Exposure

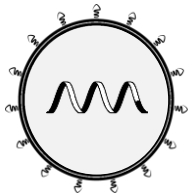
- RSV-experienced children and adults are not considered at risk:
  - Repeat RSV infection does not cause ERD
  - **No vaccine-associated ERD reported in RSV-experienced persons**
- RSV-naïve infant risk is dependent on vaccine type:
  - Live-attenuated virus and **mRNA vaccines** were considered **low risk** because of similarities with the virus

1. Kim et al, *Am J Epidem*, 1969; 2. Acosta et al, *Clin Vaccine Immunol*, 2015

Investigational Pediatric RSV (mRNA-1345) and RSV/hMPV (mRNA-1365) Vaccines

RSV Vaccine
mRNA-1345
mRESVIA

=



mRNA-encoding
RSV-F in LNPs

RSV/ hMPV Vaccine
mRNA-1365

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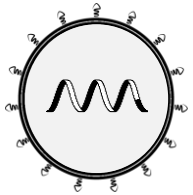
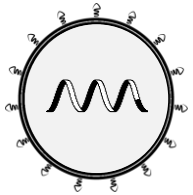


mRNA-encoding
RSV-F in LNPs

+
(1:1)



mRNA-encoding
hMPV-F in LNPs

RSV F mRNA: Encodes the membrane-anchored RSV fusion (F) protein stabilized in the prefusion conformation

hMPV F mRNA: Encodes the membrane-anchored native hMPV F protein

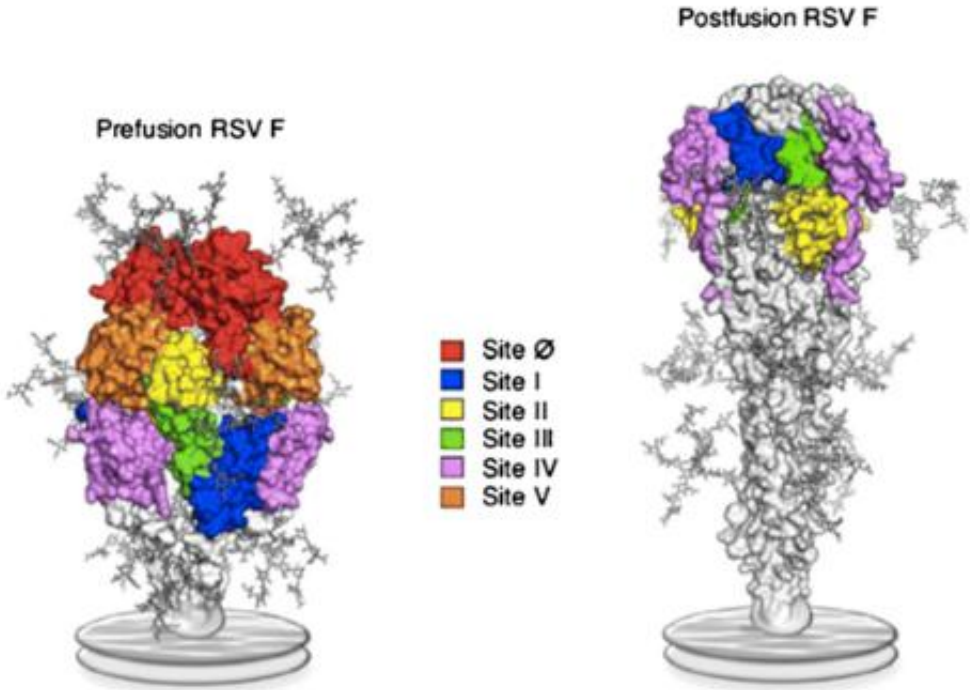
- mRESVIA is licensed for prevention of RSV in persons ≥60 years; no ERD
- Same mRNA platform authorized or licensed for prevention of COVID-19 in persons ≥ 6 months; no ERD
  - >1 million doses have been administered to children <5 years (as of Oct 2023)

LNP = Liquid Nanoparticle; ERD: enhanced respiratory disease

mRNA RSV and RSV/hMPV Vaccines Encode the RSV F Protein Stabilized in the Prefusion Conformation

- RSV F protein is conserved across RSV-A and RSV-B subtypes
- F protein exists in 2 primary conformational states: prefusion (preF) and postfusion (postF)
- PreF is the primary target of neutralizing antibody response following RSV exposure
- PreF displays all the epitopes known to elicit neutralizing antibody

FI-RSV displays only postF; inactivating process of heat and formalin destroys preF epitopes



Taleb, SA et al, 2018

	Sites	Neutralizing Potency
PreF	Ø, V, III	high
PreF	II, IV	moderate
PostF	I	low/none

Killikelly, AM et al, 2016; FI-RSV: Formalin-Inactivated RSV

Moderna's Pediatric RSV (hMPV) Vaccine Development Program Followed Conservative, Stepwise Approach

WHO, FDA, and EMA[1-3]

RSV Vaccine Development Guidance

- ✓ **Developed to Ensure Safety**
  Driven by ERD in RSV-naïve infants administered FI-RSV vaccine
- ✓ **Nonclinical Data Requirements**
  Discriminate properties of vaccine candidate from FI-RSV
- ✓ **Stepwise Clinical Approach**
  Adults and RSV-experienced children before RSV-naïve infants

- RSV pediatric vaccine development aligned with established guidelines[1-3]
  - Strict compliance with safety and efficacy standards
- No hMPV-specific vaccine guidance
  - No clinical precedent of ERD
  - Moderna applied same conservative approach to hMPV pediatric vaccine development

1. EMA: Guideline on respiratory syncytial virus (RSV)
2. FDA: Respiratory Syncytial Virus Infection: Developing Antiviral Drugs for Prophylaxis and Treatment Guidance for Industry | FDA3,
3. WHO: Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines, Annex 2, TRS No 1024

Nonclinical Data

Nonclinical Testing Requirements for RSV Candidate Vaccines Prior to Evaluation in RSV-naïve Infants[1]

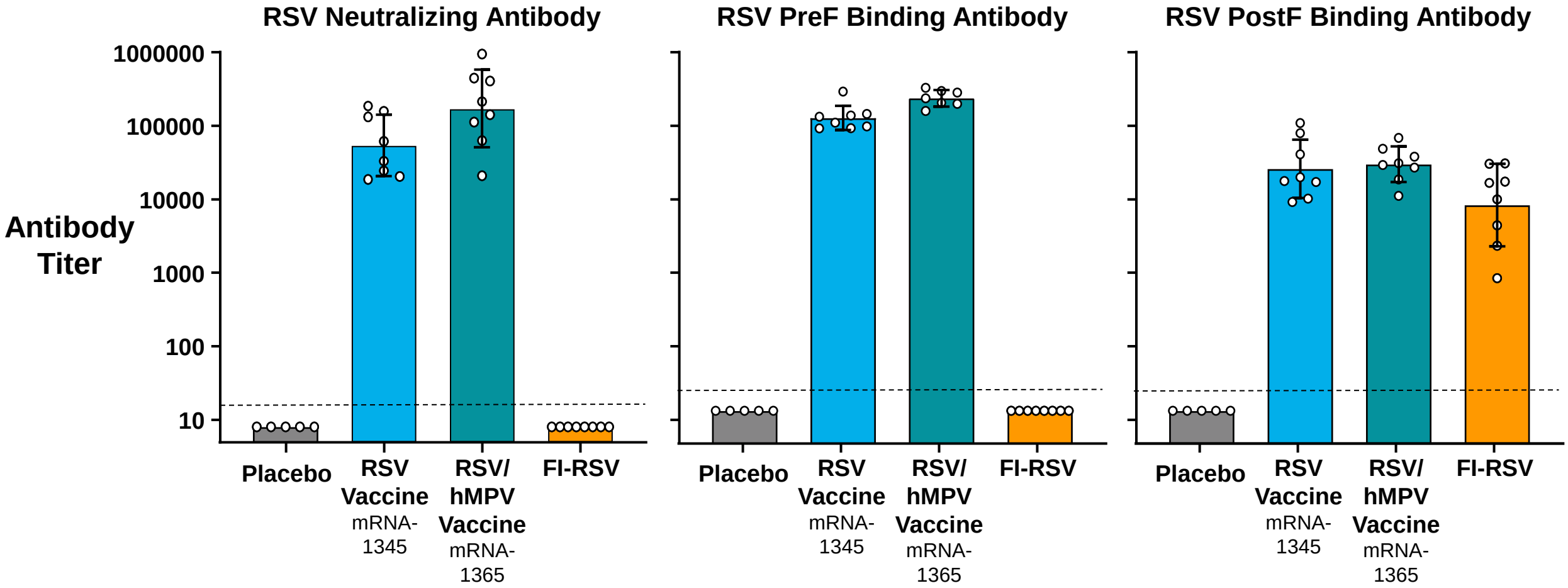
- ✓ Evaluate candidate vaccine in ≥1 nonclinical animal model
- ✓ Induce RSV neutralizing antibodies
- ✓ Avoid induction of excess non-neutralizing antibodies
- ✓ Avoid Th2-biased response
- ✓ Induce CD8 T cells
- ✓ Avoid lung inflammation (alveolitis) after a live RSV challenge

- This profile will ensure aspects of the FI-RSV immune response that may have led to ERD in RSV-naïve infants are not present in new candidate RSV vaccine

[1] **WHO: Guidelines on the quality, safety and efficacy of respiratory syncytial virus vaccines https://www.who.int/publications/m/item/respiratory-syncytial-virus-vaccines-annex-2-trs-no-1024**

RSV and RSV/hMPV mRNA Vaccines Induce RSV Neutralizing Antibody without Excess Non-neutralizing Antibody in Mice

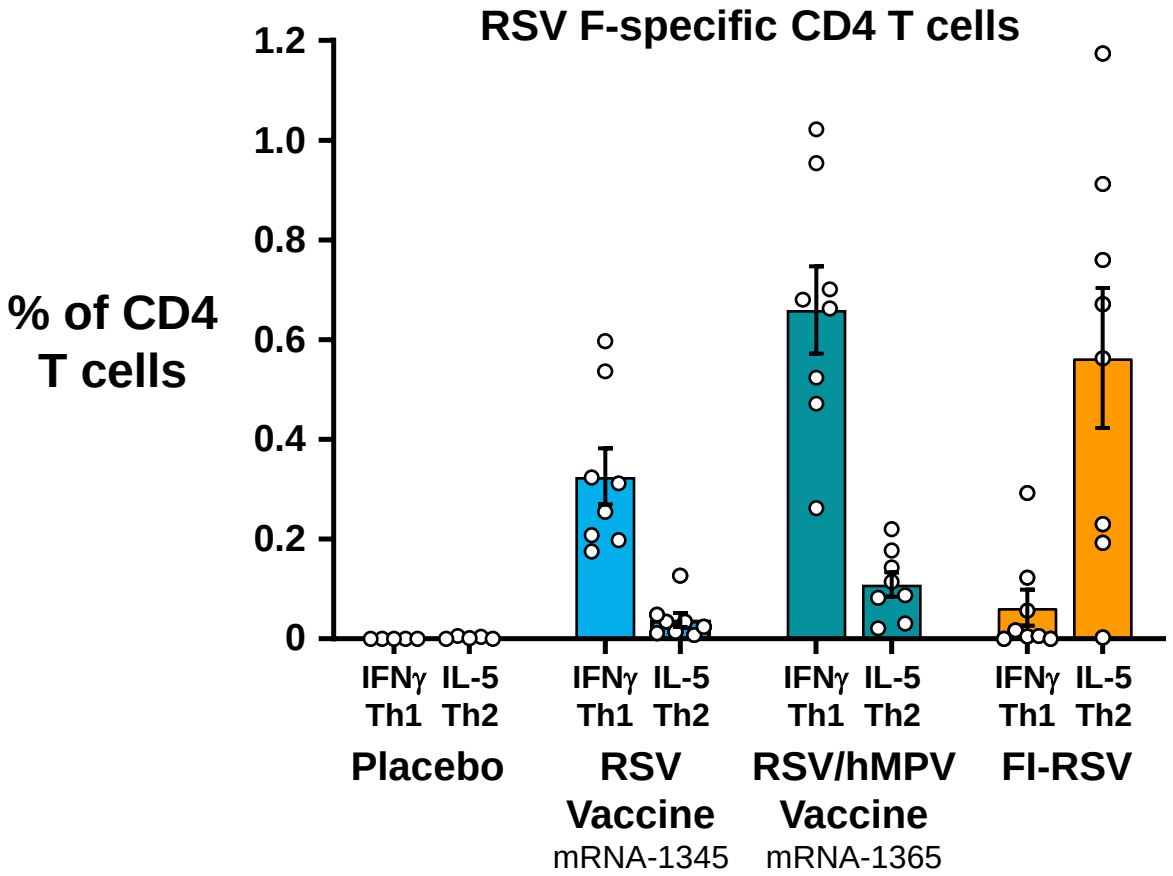
3-Dose Regimen

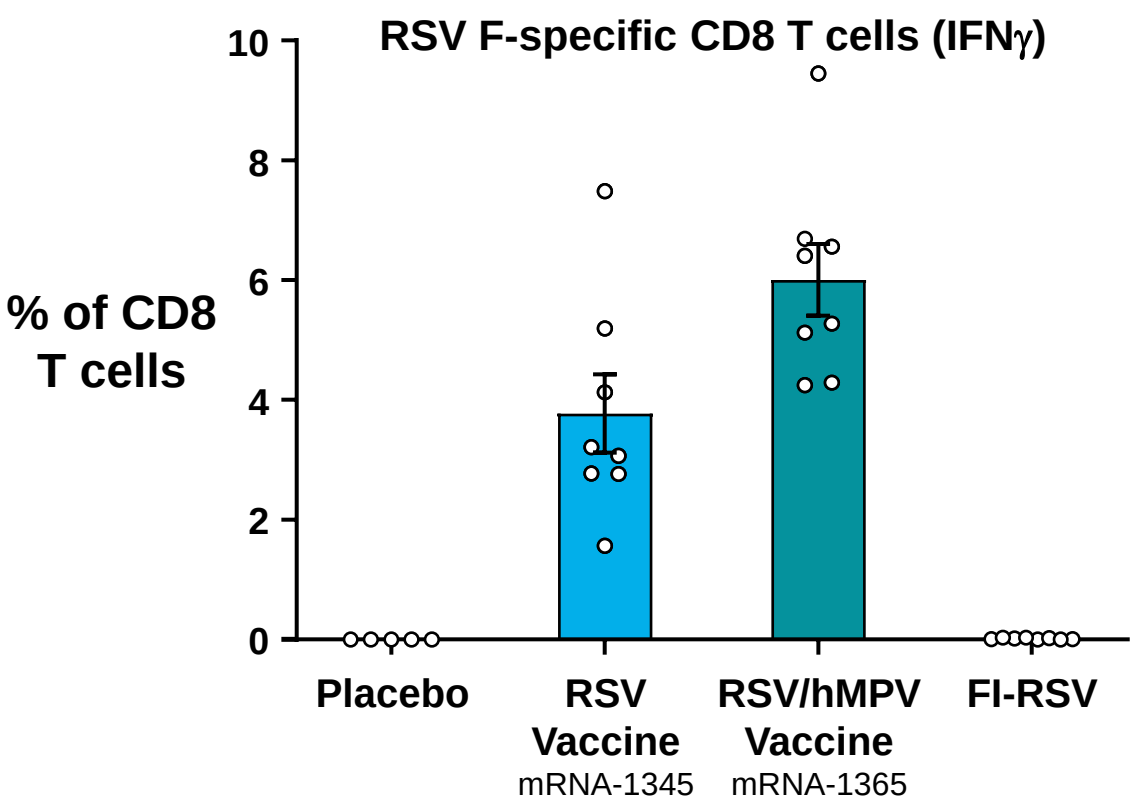


- RSV and RSV/hMPV mRNA vaccines induce RSV neutralizing and binding antibody
- FI-RSV induces non-neutralizing antibody against postF only

RSV and RSV/hMPV mRNA Vaccines Induce Th1 CD4 and CD8 T Cell Responses Against RSV in Mice

3-Dose Regimen





- RSV and RSV/hMPV mRNA vaccines induce Th1-biased (IFNγ > IL-5) CD4 and CD8 T cell responses
- FI-RSV induces a Th2-biased (IL5 > IFNγ) CD4 T cell response; no CD8 T cell response

RSV mRNA Vaccine Evaluated in Cotton Rat RSV Challenge Model Following WHO Guidance[1]

Suboptimal dose/regimen that induces a weak immune response and provides only partial protection

0.003 ng – 30 µg — RSV Vaccine (mRNA-1345) — RSV Vaccine (mRNA-1345)

0.3 µg — RSV Vaccine (mRNA-1345)

ERD Positive Control
FI-RSV predisposed to ERD in humans — FI-RSV — FI-RSV

ERD Negative Control [a]
Previous RSV infection does not predispose to ERD in humans — RSV i.n.

RSV i.n. challenge

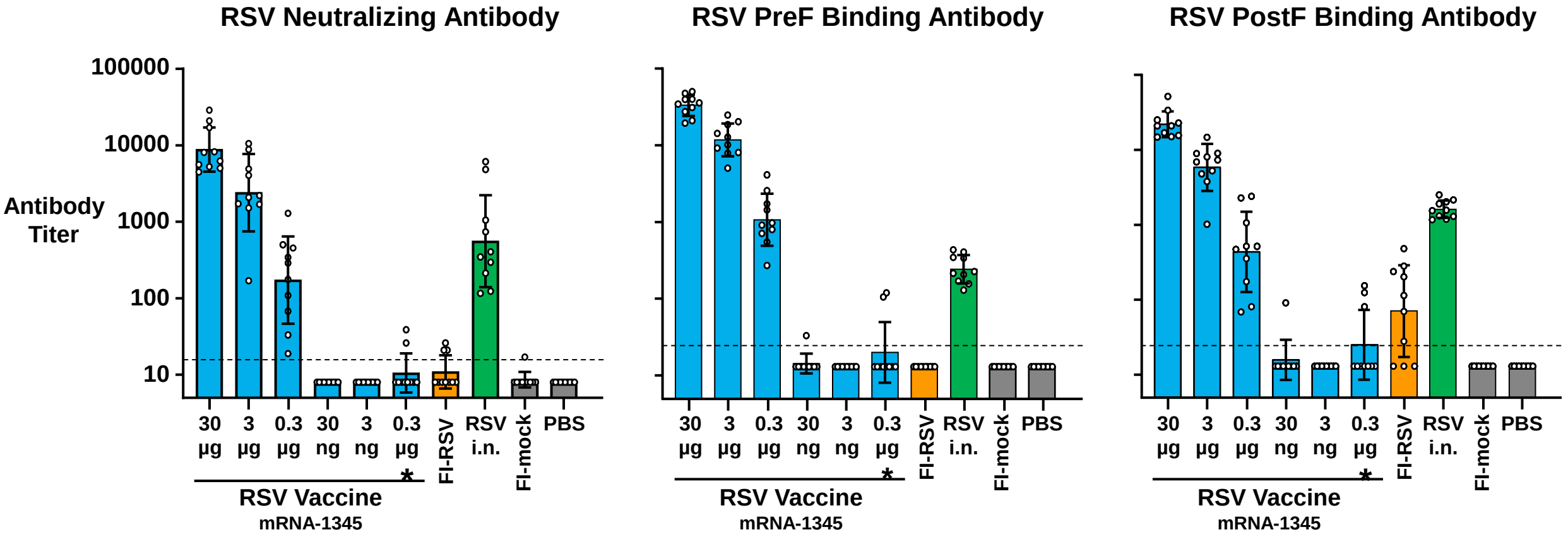
Day 0 — 28 — 56 — 61

Antibody assessment

Lung viral load
Lung cytokines
Lung pathology

a. Additional negative controls included PBS (phosphate buffered saline) and formalin-inactivated mock (FI-mock) to assess roll of cell culture antigen; each were dosed on Days 0 and 28; i.n. – intranasal; all other doses intramuscular 1. https://pubmed.ncbi.nlm.nih.gov/4305198/

RSV Vaccine Induces RSV Neutralizing and PreF-biased Antibody without Excess Non-neutralizing Antibody in Cotton Rats

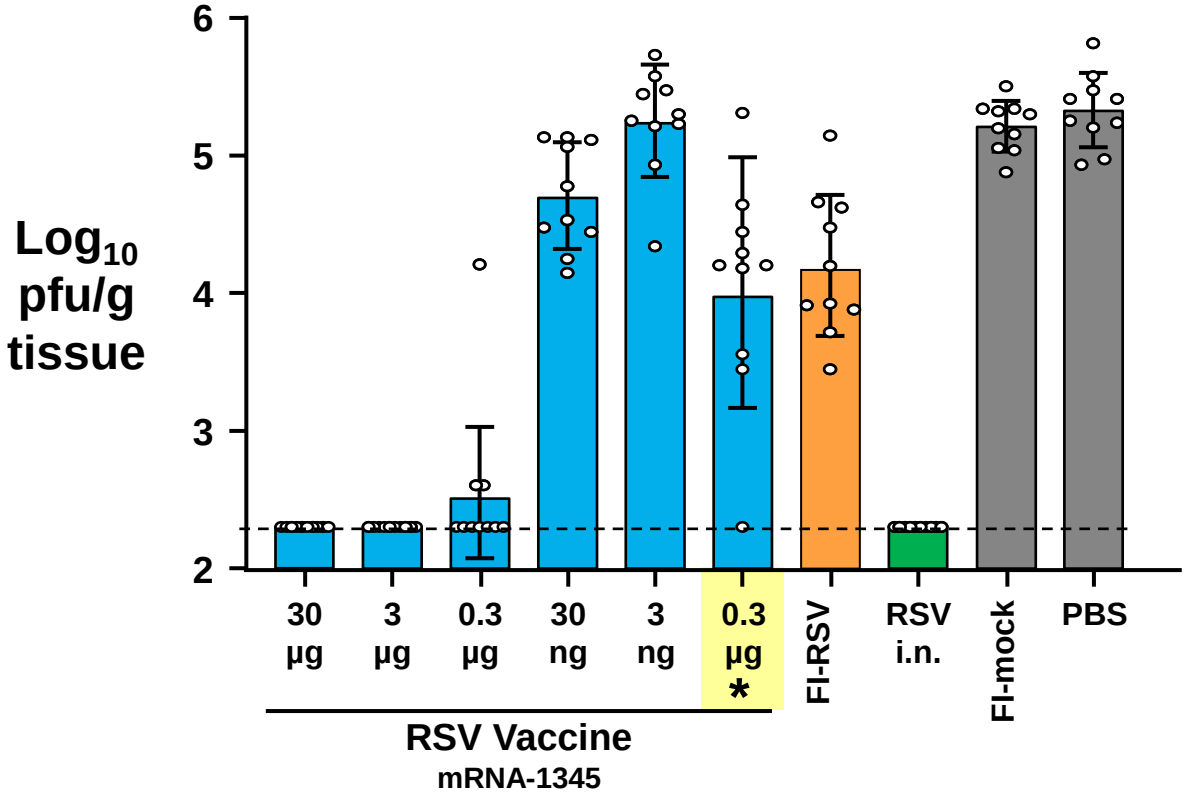


- RSV mRNA vaccine induces dose-dependent RSV neutralizing and preF antibody response
- FI-RSV induces antibody to postF only; weak/no neutralizing activity

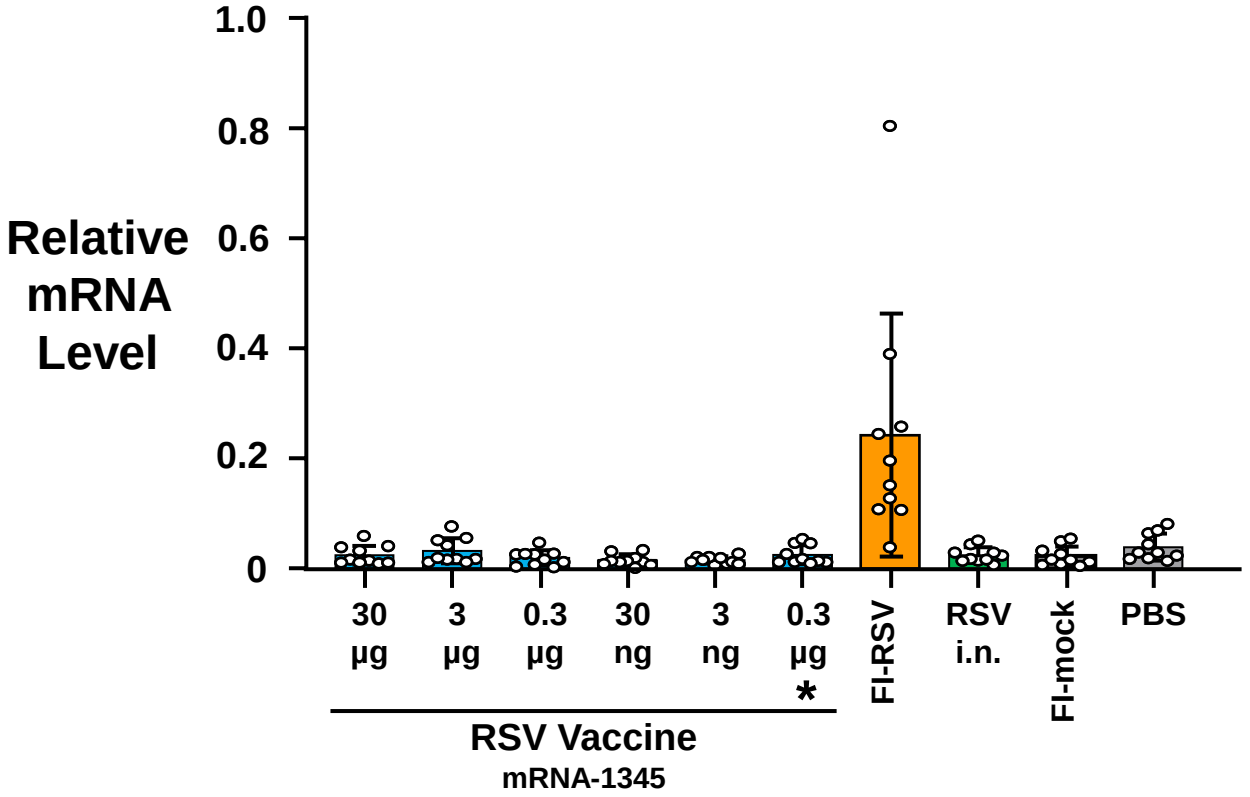
* Single RSV vaccine (mRNA-1345) injection

RSV mRNA Vaccine Protects Cotton Rats from RSV Challenge without Induction of Th2 Response

Lung Viral Load After RSV Challenge



Lung IL-4 After RSV Challenge

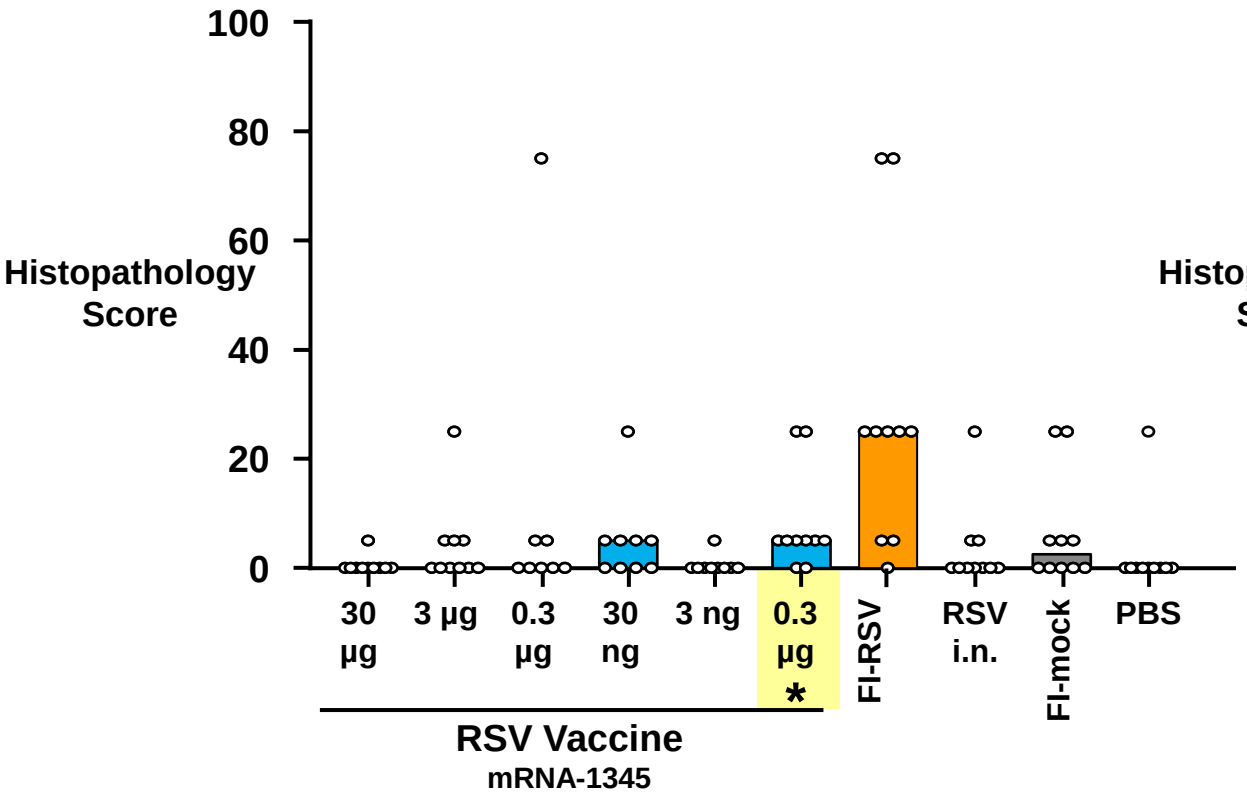


- RSV mRNA vaccine provides dose-dependent protection from RSV challenge without lung IL-4
- FI-RSV provides partial protection from RSV challenge with associated lung IL-4

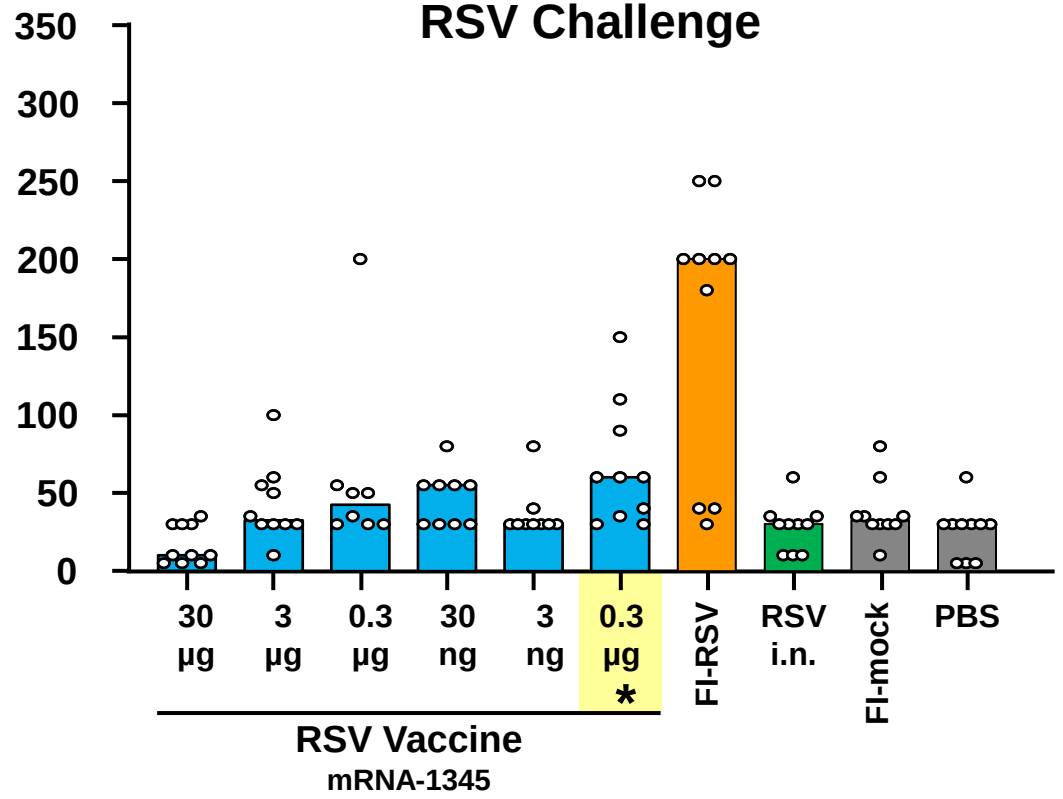
* Single RSV vaccine (mRNA-1345) injection

RSV mRNA Vaccine Does Not Induce ERD in Cotton Rat RSV Challenge Model

Lung Alveolitis After RSV Challenge



Cumulative Lung Inflammation After RSV Challenge



- RSV mRNA vaccine does not promote enhanced lung inflammation after RSV challenge – no ERD
- FI-RSV promotes enhanced lung inflammation after RSV challenge – ERD

*** Single RSV vaccine (mRNA-1345) injection**

Cumulative lung inflammation equals sum of individual alveolitis, interstitial pneumonia, peribronchiolitis, and perivasculitis histopathology scores

Summary – RSV mRNA Vaccines Induce Protective Immune Response Without RSV ERD in Nonclinical Animal Models

Mice and Cotton Rat Models

FI-RSV	RSV mRNA	
☒	☑	Induces neutralizing antibodies
☒	☑	Avoids induction of excess non-neutralizing antibodies
☒	☑	Avoids Th2-biased response
☒	☑	Induces CD8 T cells
☒	☑	Avoids lung inflammation (alveolitis) after virus challenge

- mRNA vaccine profile is distinct from FI-RSV profile
- Supported clinical evaluation of the mRNA vaccines in RSV-naïve infants

Summary – RSV and hMPV mRNA Vaccines Induce Protective Immune Response Without RSV or hMPV ERD in Nonclinical Animal Models

Mice and Cotton Rat Models

FI-RSV; FI-hMPV	RSV mRNA	hMPV mRNA	
☒	☑	☑	Induces neutralizing antibodies
☒	☑	☑	Avoids induction of excess non-neutralizing antibodies
☒	☑	☑	Avoids Th2-biased response
☒	☑	☑	Induces CD8 T cells
☒	☑	☑	Avoids lung inflammation (alveolitis) after virus challenge

- mRNA vaccine profile is distinct from FI-RSV and FI-hMPV profile
- Supported clinical evaluation of the mRNA vaccines in RSV- and hMPV-naive infants

Clinical Data

Matthew Snape, MBBS MD

Vice President, Pediatric and Maternal Vaccines

Moderna, Inc.

Positive Results in Adults and Seropositive Children Allowed Further Age De-escalation Per Regulatory Guidelines

Vaccine	Age	Serostatus	Neutralizing Antibody Induced	No Safety Concerns Including ERD
RSV (mRNA-1345)	**Adults and 1 - 4 years**	**RSV Seropositive[1]**	✓ RSV	✓
hMPV/PIV3 (mRNA-1653)	**Adults and 1 - 4 years**	**hMPV/PIV3 Seropositive[2]**	✓ hMPV	✓

1. Snape et al ESPID 2023; 2. Schnyder Ghamloush et al *Pediatrics* 2024

Study Design and Methods

Study 101

Age De-Escalation Study in Infants and Children, 5-23 Months, Developed in Consultation with Regulatory Agencies

Part A (8-23 Months)

Cohort 1 RSV Vaccine 30 µg : Placebo (2:1)
Cohort 2 RSV/hMPV Vaccine 30 µg : Placebo (2:1)

DSMB Review

Part B (5-7 Months)

Cohort 3 RSV Vaccine 15 µg : Placebo (2:1)
Cohort 4 RSV/hMPV Vaccine 15 µg : Placebo (2:1)

DSMB Review

Cohort 5 RSV Vaccine 30 µg : Placebo (2:1)
Cohort 6 RSV/hMPV Vaccine 30 µg : Placebo (2:1)

Part C (8-11 Months)

Cohort 7 *exposed to Nirsevimab* RSV Vaccine 30 µg
Cohort 8 *not exposed to Nirsevimab* RSV Vaccine 30 µg

- Healthy participants with gestational age ≥37 weeks and birthweight > 2.5 kg
- **3-dose intramuscular regimen** - Day 1, Month 2, Month 4 with 24-month follow-up

DSMB – Data Safety Monitoring Board

Key Primary and Secondary Study Objectives

Primary Objectives

- Evaluate the safety & reactogenicity of study injections

Secondary Objectives

Safety

- Evaluate the occurrence of clinical RSV or hMPV infections

Immunogenicity

- Evaluate the antibody response
- Characterize cellular immunogenicity in a subset of participants

Extensive Active RSV and hMPV Surveillance Over Study Duration

E-Diary used by parents to report

- **New occurrence OR worsening** of RTI symptoms (cough, runny nose, blocked nose)
- During RSV & hMPV seasons, parents received weekly prompts to complete e-Diary

If parent reported RTI symptoms

- Site followed up within 1 working day and scheduled assessment visit **within 5 days of RTI symptom onset**
- RT-PCR nasal swab collected for local and central laboratory testing

- Dosing pause rule to be triggered if ≥2 severe RSV or hMPV LRTI cases reported

Protocol Definitions of RSV or hMPV-related Respiratory Tract Illness/Lower Respiratory Tract Illness (RTI/LRTI)

Confirmed RSV or hMPV Infection

RTI	LRTI	Severe LRTI	Very Severe LRTI	Hospitalization
		Meeting Case Definition of LRTI		
AND Runny nose or blocked nose or cough	*AND* Cough or difficulty breathing *AND* SpO2 <95%, or RR increase	*AND* SpO2 <93% OR Lower chest wall in-drawing	*AND* SpO2 <90% OR inability to feed OR failure to respond / unconscious	*AND* Hospitalized for acute medical condition

Severe/hospitalized RSV or hMPV Disease subsequently defined as a combination of any per-protocol severe LRTI, very severe RSV LRTI, or RSV hospitalization

SpO2 – Oxygen saturation; RR – respiratory rate

Study Overseen by Independent Data Safety Monitoring Board (DSMB)

Unblinded Data Review at Prespecified Intervals				
Oversight of Study	Reactogenicity and Safety Data	Serious Adverse Events (SAEs)	Incidence of Severe RSV/hMPV Cases	*Ad hoc M*eetings in Case of Safety Events
✓	✓	✓	✓	✓

- **Independent group of RSV experts**
- **Prespecified Intervals for Data Review**
  - Initiation of age de-escalation
  - Initiation of dose escalation
  - Monthly review of data after initiation of 5-7-month-old cohort

Determination of Baseline RSV Serostatus

Study 101

Determination of Serostatus for RSV Naïve vs RSV Experienced Based on PostF IgG Binding Assay

	Part A (8-23 Months) & **Part C** (8-11 Months)		**Part B** 5-7 Months	
	RSV-Naïve	**RSV-Experienced**	**RSV-Naïve**	**RSV-Experienced**
PostF IgG Baseline Cutoff (AU/mL)	**< 200**	**≥ 200**	**< 1800**	**≥ 1800**

- PostF binding antibody at baseline chosen to determine RSV experienced vs naïve
  - Minimal impact by Nirsevimab presence, therefore applicable to Part C
- Presence of maternal antibody in youngest children required higher antibody cutoff

Study Results

Study 101, Part A (8-23 Months of Age)

Part A: 8-23 Months – Enrollment and RSV Status

Part A (8-23 Months)

Cohort 1 **RSV Vaccine 30 µg** **:** **Placebo** (2:1)
Cohort 2 **RSV/hMPV Vaccine 30 µg** **:** **Placebo** (2:1)

85 of 90 received all 3 Doses

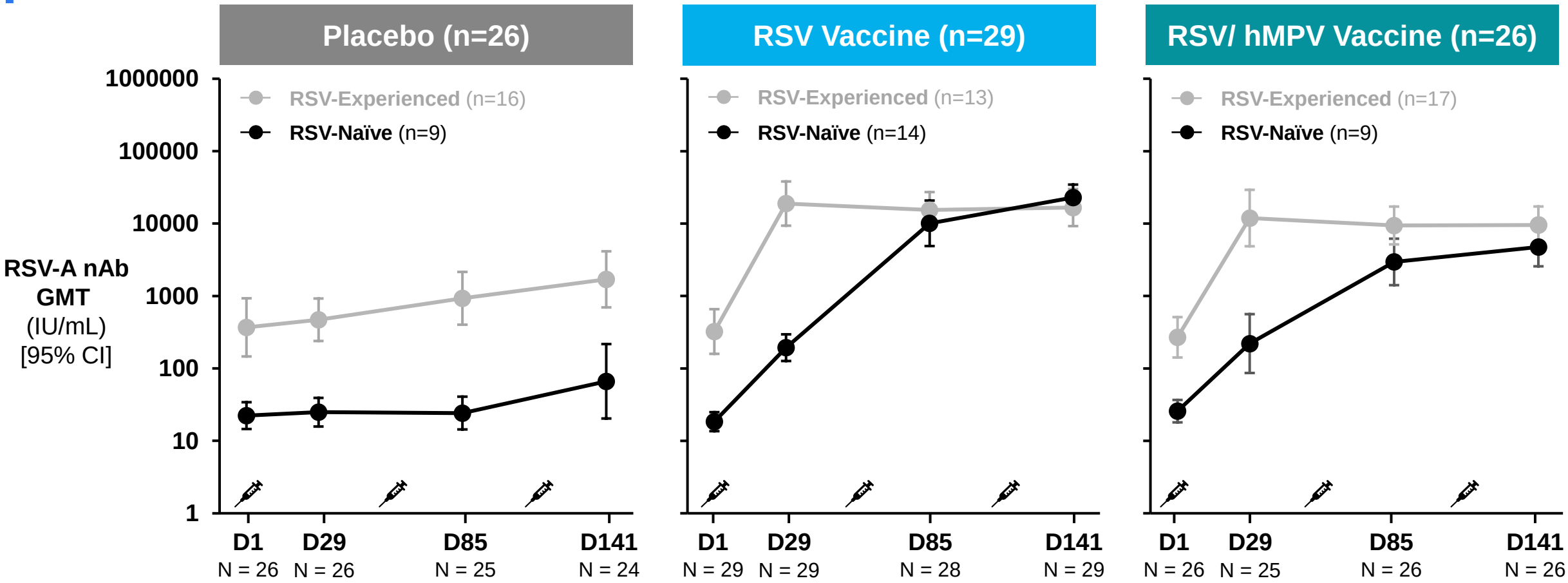
RSV Serostatus	
Total Participants	**90**
RSV Naïve	36/85 (42.4%)
RSV Experienced	49/85 (57.6%)
Unknown	5

Panama
N = 65

USA
N = 25

RSV Neutralizing Antibody (nAb) Responses Demonstrated in Both RSV Naïve and Experienced 8-23 Month Olds

Part A



- Day 1 vaccination elicited RSV nAb in RSV experienced participants
- nAb titers further increased after Dose 2 in RSV naive participants

RSV-Experienced = PostF IgG ≥ 200 AU/ml at baseline. RSV-Naïve = PostF IgG < 200 AU/ml at baseline

PreF Biased Binding IgG Response, Especially in RSV Naïve Infants

Part A, 8-23 Months

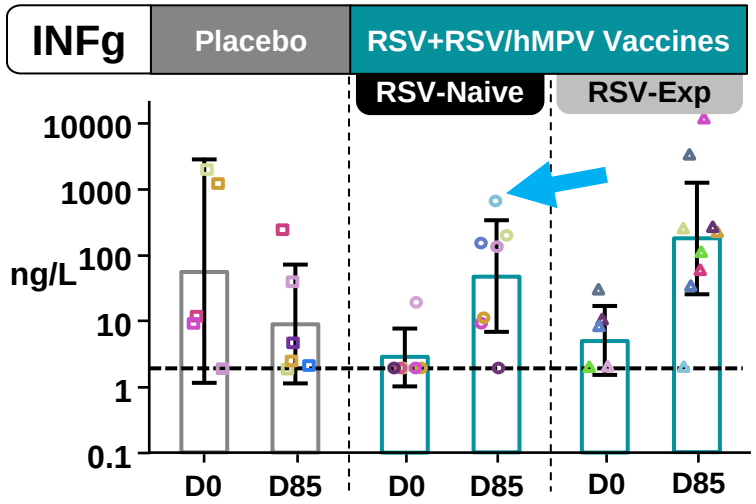
PreF/PostF Ratio (Day 141)	Placebo	RSV Vaccine	RSV/hMPV Vaccine
RSV-Naïve	0.8	22.6	16.6
RSV-Experienced	1.7	2.1	2.0

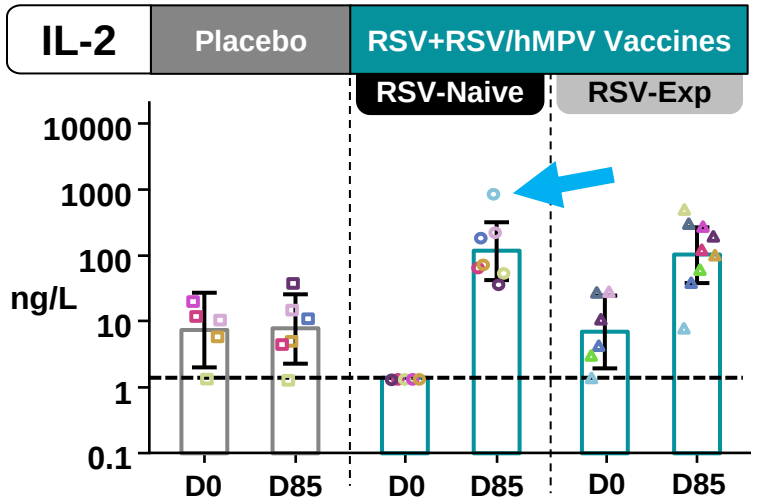
RSV-Experienced = PostF IgG ≥ 200 AU/ml at baseline. RSV-Naïve = PostF IgG < 200 AU/ml at baseline

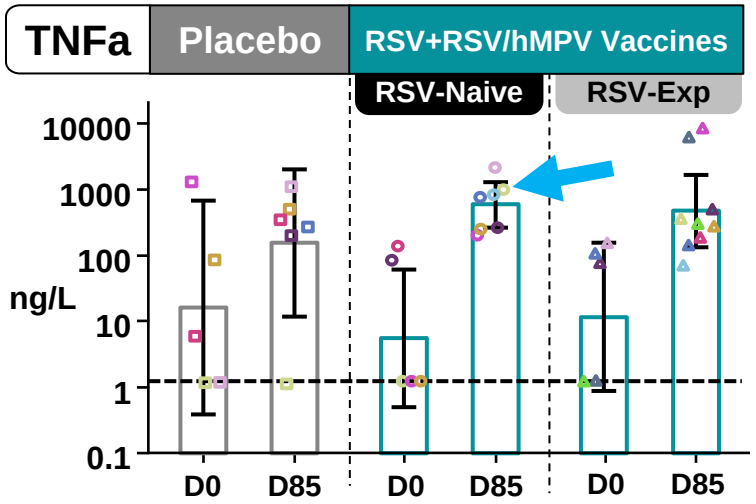
Th1 Biased RSV-F Specific Cellular Response in 12-23 Month Olds (Part A Subset)

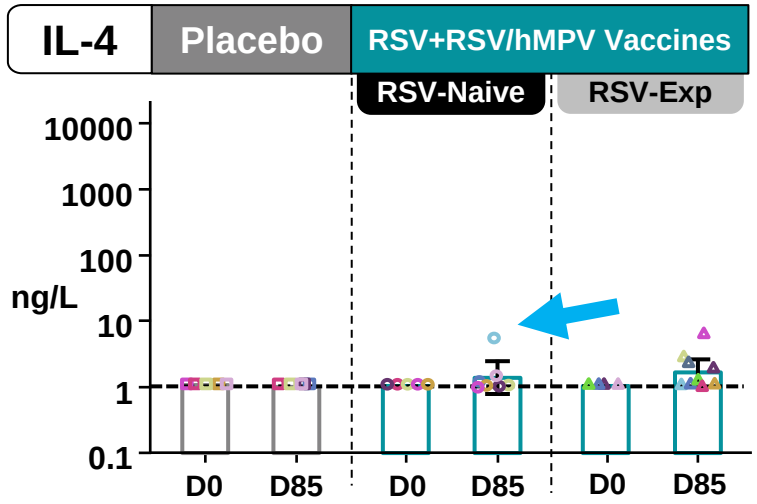
Th1

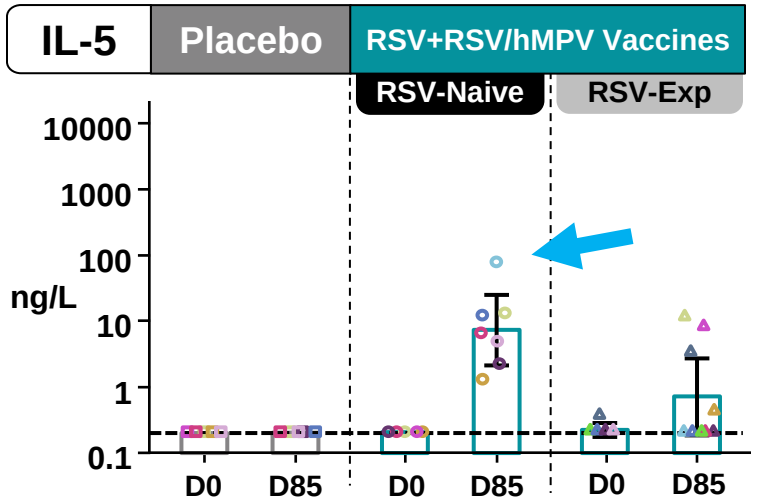
Th2

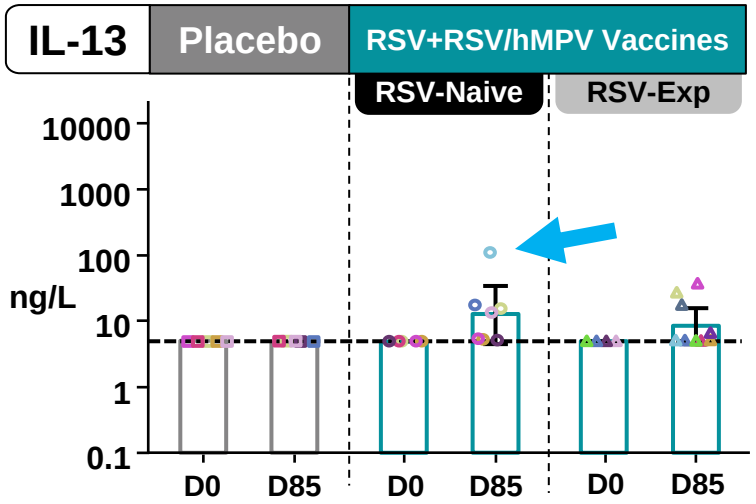












No Severe/Hospitalized RSV Cases in 8-23 Month Olds After First RSV Season (DSMB Review, March 2024)

Part A (3 doses, 30 µg)

	RSV Vaccine	RSV/ hMPV Vaccine	Combined	Placebo
Total Participants	**29**	**30**	**59**	**31**
Symptomatic RSV	**5 (17.2%)**	**4 (13.3%)**	**9 (15.3%)**	**8 (25.8%)**
Severe/Hospitalized RSV	*0*	*0*	*0*	*0*

Safety and Immunogenicity Data from 8-23 Month Olds Supported Further Age De-escalation

Part A

Study Results

- ☑ No safety concerns identified during entire RSV 2023/2024 season
- ☑ No severe / hospitalized RSV cases up to March 2024
- ☑ Robust neutralizing antibody responses against RSV-A & RSV-B
- ☑ Binding antibody response preferentially directed against RSV PreF
- ☑ Cell-mediated immunity induced (primarily Th1)

- Clinical results similar to nonclinical data in which no evidence of ERD was found
- Support age de-escalation according to WHO guidelines

After Careful Review of Data, DSMB Supported Age De-escalation to 5-7 Month Olds on March 28, 2024

Data Reviewed on 8-23 Month Olds Prior to Enrollment of 5-7 Month Olds		
Safety data after complete RSV season in Panama & US	Unblinded review of RSV and hMPV infections	Immunogenicity data
✓	✓	✓

Ongoing Surveillance (up to October 15, 2024)

Study 101, Part A (8-23 Months of Age)

Only One Case of Severe/Hospitalized RSV Disease in RSV Naïve 8-23 Month Olds

Cohorts 1 & 2 (3 doses, 30 µg)

		RSV Vaccine	RSV/ hMPV Vaccine	Combined	Placebo
	Total Participants	29	30	59	31
RSV-Naïve (N = 36)	**RSV-Naïve Participants**	14	9	23	13
	Symptomatic RSV	6 (42.9%)	6 (66.7%)	12 (52.2%)	8 (61.5%)
	Severe/Hospitalized RSV	*0*	*1 (11.1%)*[1]	***1 (4.3%)***[1]	***0***
RSV-Experienced (N = 49)	**RSV-Experienced Participants**	13	19	32	17
	Symptomatic RSV	5 (38.5%)	7 (36.8%)	12 (37.5%)	6 (35.3%)
	Severe/Hospitalized RSV	*0*	*0*	*0*	*0*

- Single case of hospitalized RSV LRTI, occurring in vaccine recipient in August 2024, after decision to age de-escalate to 5 – 7-month-old infants
- No severe/hospitalized cases in RSV experienced 8 to 23 months old children

RSV-Experienced = PostF IgG ≥ 200 AU/ml at baseline. RSV-Naïve = PostF IgG < 200 AU/ml at baseline. 1. Co-infection with Human Rhinovirus/ Enterovirus. Data cut-off 15 October 2024. Five participants did not have baseline postF values therefore the baseline serostatus is unknown. None of these participants had a symptomatic RSV infection.

Study Results

Study 101, Part B (5-7 Months of Age)

Part B: 5-7 Months - Enrollment and Dosing

Part A (8-23 Months): Panama N= 65, US N= 25

Cohort 1 RSV Vaccine 30 µg : Placebo (2:1)
Cohort 2 RSV/hMPV Vaccine 30 µg : Placebo (2:1)

Received All 3 Doses

DSMB Review

Part B (5-7 Months)

Cohort 3 RSV Vaccine 15 µg : Placebo (2:1)
Cohort 4 RSV/hMPV Vaccine 15 µg : Placebo (2:1)

59 children received 2 Doses

DSMB Review

Cohort 5 RSV Vaccine 30 µg : Placebo (2:1)
Cohort 6 RSV/hMPV Vaccine 30 µg : Placebo (2:1)

21 children received 1 Dose

Panama
N = 80

UK
N = 1

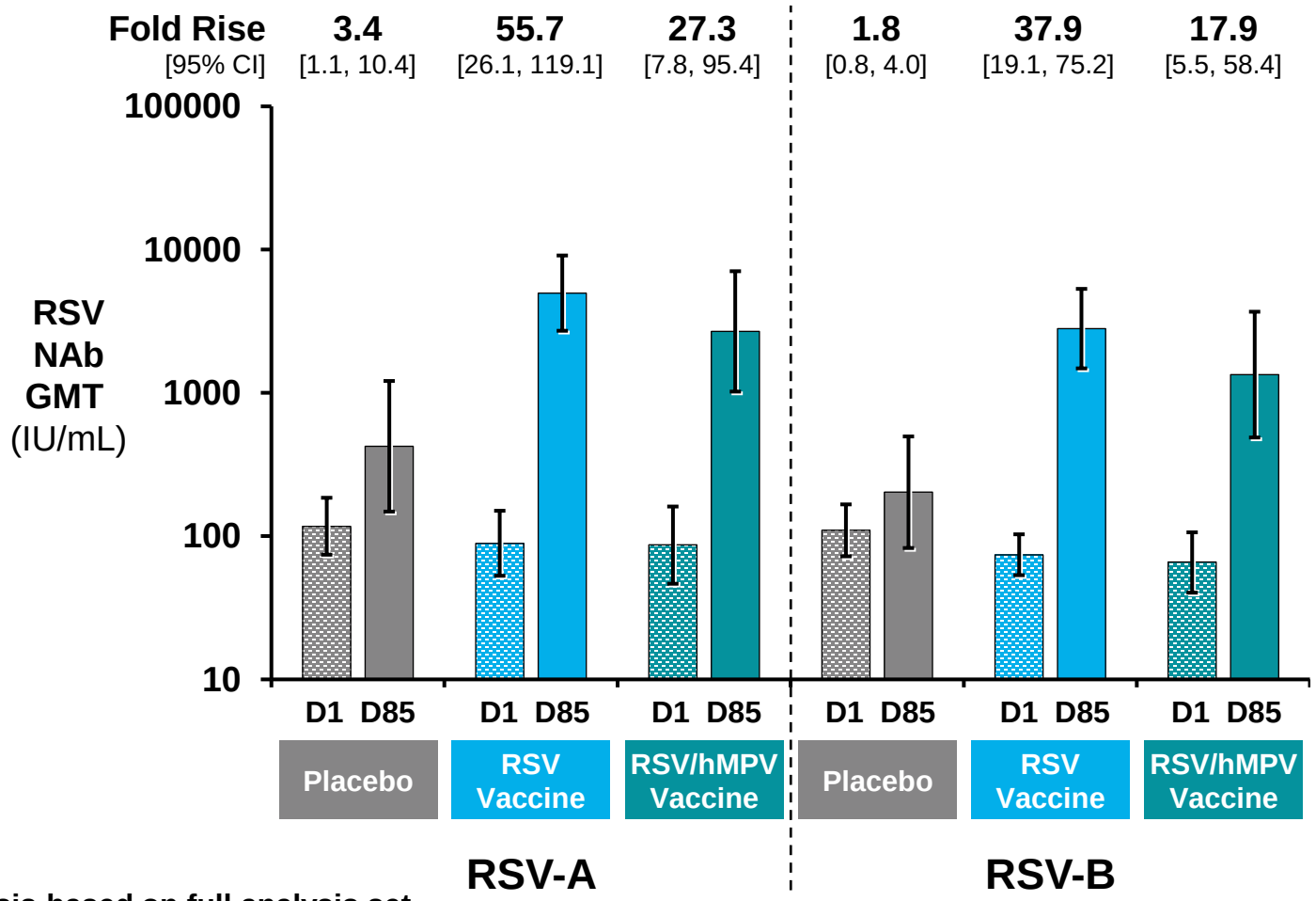
- Participants born end 2023 RSV season and enrolled before 2024 RSV season
- Dosing pause followed report of 2 RSV severe LRTI cases in Part B

Immunogenicity Evaluation

Part B (5-7 Months of Age)

Two Doses of RSV or RSV/hMPV Vaccine Induced RSV Neutralizing Antibody (nAb) in 5-7 Month Olds

Cohorts 3 & 4 (2 doses, 15 µg)*

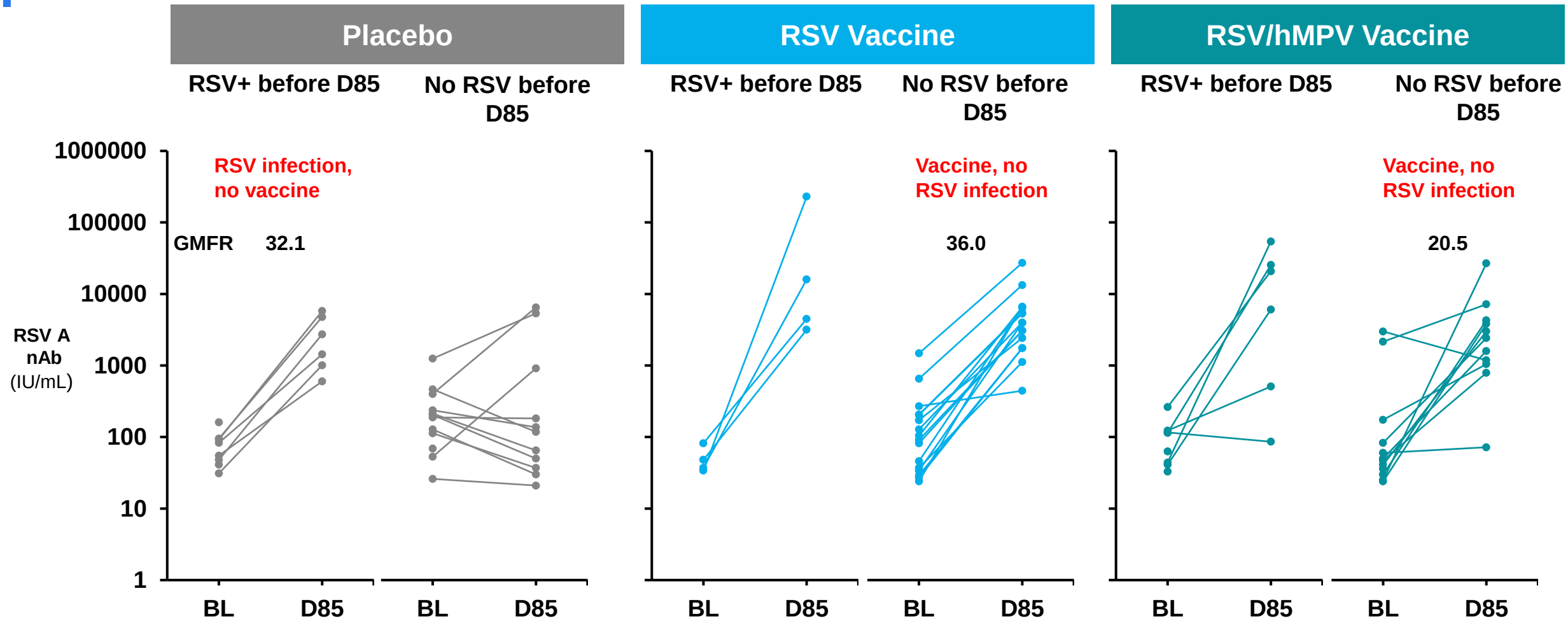


RSV Status of Participants	
Total Participants	**60**
RSV Naive	53 (88.3%)
RSV Experienced	7 (11.7%)

Analysis based on full analysis set
RSV-Experienced = PostF IgG ≥ 1800 AU/ml at baseline
RSV-Naïve = PostF IgG < 1800 AU/ml at baseline
* immunogenicity data for cohorts 5 & 6 (1 x 30 µg) not available; 15 ug for RSV vaccine; 7.5 ug of each component in RSV/hMPV vaccine

RSV A Neutralizing Antibody Rise Following RSV Vaccine Comparable to Natural Infection

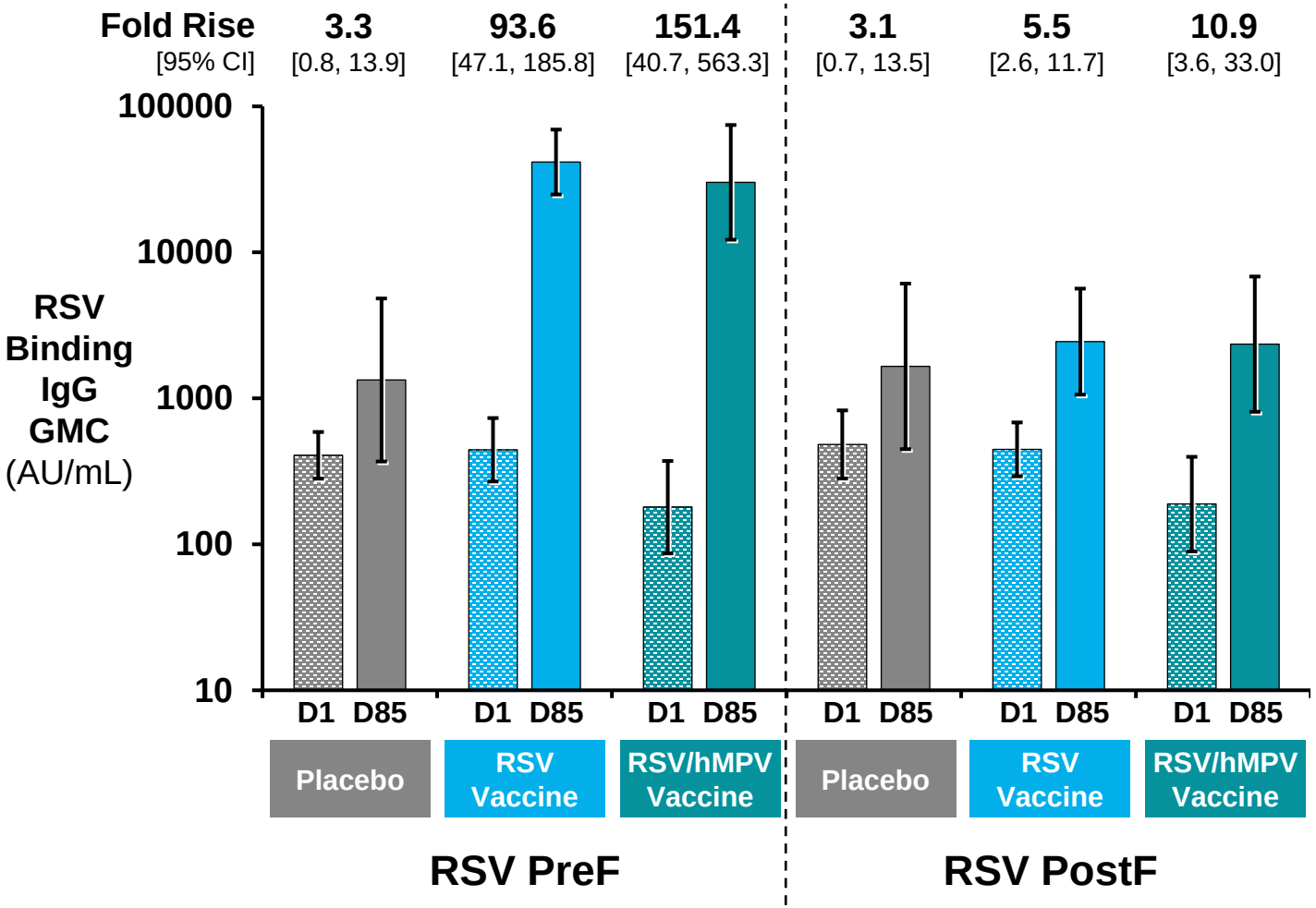
Cohorts 3 & 4 (2 doses, 15 µg)



- Increase in RSV A neutralizing antibody seen for almost all vaccinated participants
- Induced by vaccines, independent of infection

Two Doses of RSV or RSV/hMPV Vaccines Increased RSV F Binding IgG with a PreF Bias in 5-7 Month Olds

Cohorts 3 & 4 (2 doses, 15 µg)



	Placebo	RSV Vaccine	RSV/ hMPV Vaccine
Day 85 Pre/PostF Ratio (95% CI)	**0.8** (0.5, 1.2)	**17.0** (9.6, 30.2)	**12.8** (8.0, 20.7)

Respiratory Infection Surveillance

Study 101, Part B (5-7 Months of Age)

Multiple Activities After Dosing Pause Initiated July 17, 2024 Following 2 Severe RSV-LRTI in 5-7 Month Olds

JUL 17 – Pause Role Invoked by Moderna

- FDA and DSMB notified
- All enrollment and vaccination stopped

JUL | AUG | SEP | OCT

Updates to IRB/ Ethics & Regulatory Agencies

Participants' Parents and Investigators Notified

Ongoing Engagement with DSMB

More Severe/Hospitalized RSV Cases Seen in RSV Naïve Vaccine Recipients 5-7 Months Old

Cohorts 3 & 4 (2 doses, 15 µg)

		RSV vaccine	RSV/ hMPV vaccine	Combined	Placebo
	Total Participants	20	20	40	20
RSV-Naïve (N=53)	**RSV-Naïve Participants**	18	17	35	18
	Symptomatic RSV	8 (44%)	8 (47%)	**16 (46%)**	**12 (67%)**
	Severe/Hospitalized RSV	2 (11%)	3 (18%)[1]	**5 (14%)[1]**	**1 (6%)[2]**
RSV-Experienced (N=7)	**RSV-Experienced Participants**	2	3	5	2
	Symptomatic RSV	0	1 (33%)	1 (20%)	0
	Severe/Hospitalized RSV	0	0	0	0

- Trend towards lower symptomatic RSV infections in vaccine vs placebo recipients
- More severe/hospitalized RSV cases among vaccine recipients than placebo recipients
- Severe/clinically significant cases only observed in RSV naive participants

RSV-Experienced = PostF IgG ≥ 1800 AU/ml at baseline. RSV-Naïve = PostF IgG < 1800 AU/ml at baseline.
1. One participants with SARS-CoV-2 co-infection 2. One participant with hMPV Co-infection. Data cut-off 15 October 2024.

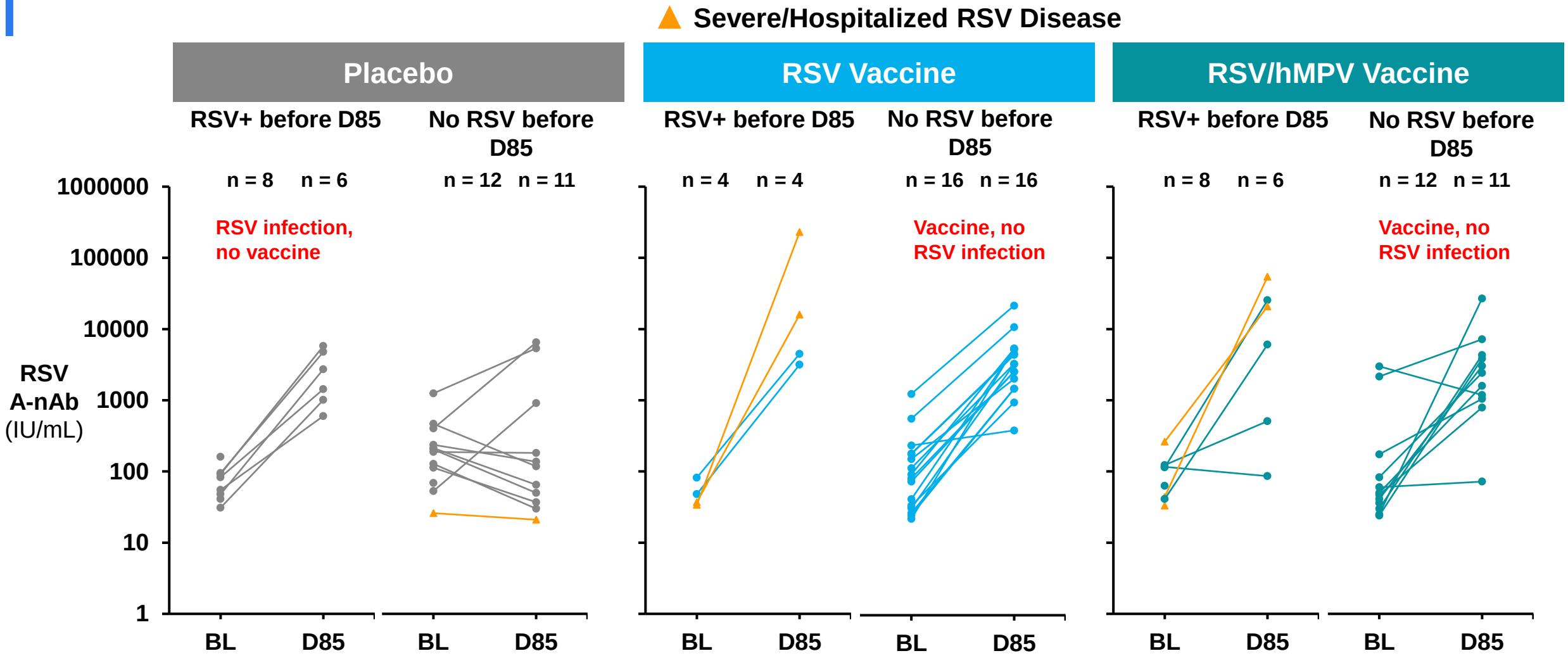
Characteristics of 6 Severe/Hospitalized RSV Cases Among Vaccine/Placebo Recipients 5-7 Months Old

Cohorts 3 & 4 (2 doses, 15 µg)

Vaccine /Placebo	Onset	Site of Care	Care	Coinfection(s)	Resolution
RSV/hMPV	10 Days Post Dose 2	Hospitalized 16 days, 10 in ICU	Mechanical Ventilation (7 days)	None	Arterial Hypertension Persists
RSV/hMPV	26 Days Post Dose 2	Hospitalized 4 days, non-ICU	O_2	SARS-CoV2	Resolved
RSV/hMPV	23 Days Post Dose 1	Hospitalized 4 days, non ICU	O_2	None	Resolved
RSV	14 Days Post Dose 2	Hospitalized 4 days, non-ICU	None	None	Resolved
RSV	3 Days Post Dose 2	ER	O_2	None	Resolved
Placebo	37 Days Post Dose 2	Hospitalized 5 days, non-ICU	O_2	hMPV	Resolved

O_2: oxygen

High Neutralizing Antibody Titers In Participants Who Received 2 Doses and Developed Severe/Hospitalized RSV



No Severe/Hospitalized RSV Disease in 5-7 Month Olds after One 30 µg Dose

Cohorts 5 & 6 (1 dose, 30 µg)

	RSV Vaccine	RSV/ hMPV Vaccine	Combined	Placebo
Total Participants	7	7	14	7
Symptomatic RSV	4 (57.1%)	1 (14.3%)	5 (35.7%)	4 (57.1%)
Severe/Hospitalized RSV	0	0	0	0

Data cut-off 15 October 2024

hMPV Infections

Several Severe/Hospitalized hMPV Infections in 5-7 Month Olds Following RSV/hMPV Vaccine

Cohort 4 (2 doses, 15 µg) and Cohort 6 (1 dose, 30 µg) (Total N=27)

Clinical Data	▪ 3 children in Panama hospitalized with hMPV infection, Sept-Dec 2024
	  ▪ 2 received two 15 µg doses; 1 received one 30 µg dose
	  ▪ Onset:
	  ▪ 69 & 100 days after dose 2
	  ▪ 161 days after dose 1
	  ▪ 1 on CPAP for 48 hours
	  ▪ 2 managed with supplemental oxygen alone
	  ▪ Discharged days 4-9 after admission
	  ▪ Investigation of these events is ongoing

Immunogenicity Data	▪ Pending for 5-7-month-olds

CPAP – continuous positive airway pressure

RSV Vaccination Following Nirsevimab

Study 101, Part C (8-11 Months of Age)

Passive Immunity with Nirsevimab vs Active RSV Vaccine

- Nirsevimab is standard of care for passive protection against RSV[1]
  - Recommended for US infants <8 months of age born during or entering first RSV season
- Important to understand how nirsevimab might impact response to active immunization with RSV vaccine
- Non-clinical data suggest inhibition of RSV vaccine antibody response by prior administration of monoclonal antibody
  - Able to be overcome by subsequent vaccine doses

1. CDC MMWR 2023, https://www.cdc.gov/vaccines/vpd/rsv/hcp/child.html

Enrollment and Dosing in 8-11 Month Olds Exposed/Not Exposed to Nirsevimab

Part C

Part A (8-23 Months): Panama N= 65, US N= 25

DSMB Review

Part B (5-7 Months): Panama N=80; UK N=1

USA
N = 15
9 Nirsevimab exposed
6 Nirsevimab not exposed

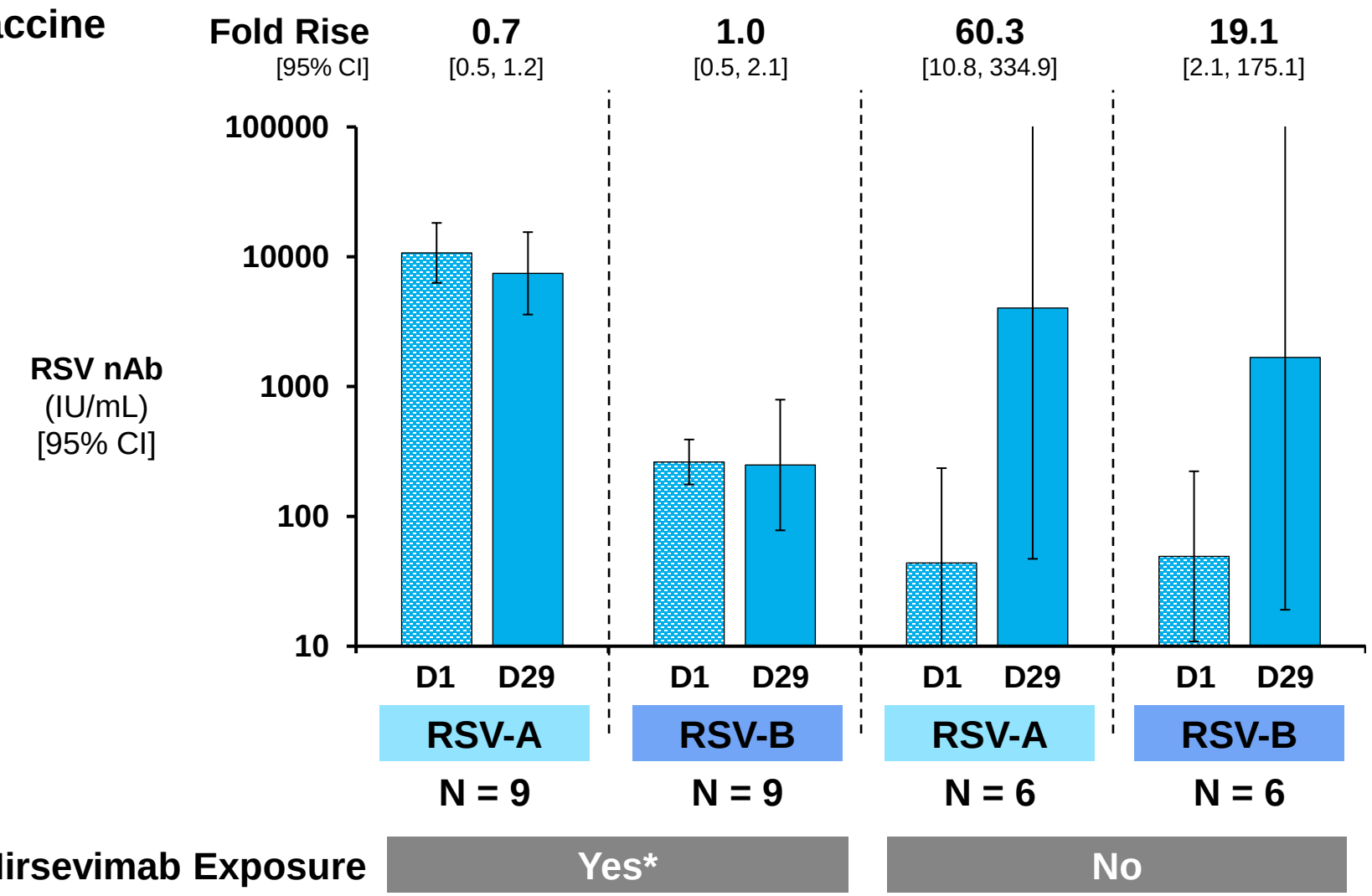
Part C (8-11 Months)

Cohort 7 (N ~50) *exposed to Nirsevimab* **RSV Vaccine 30 µg**
Cohort 8 (N ~50) *not exposed to Nirsevimab* **RSV Vaccine 30 µg**

Intent to administer 3 doses of RSV vaccine, 30 µg

- 15 received single dose prior to dosing pause
- No symptomatic RSV cases reported

No Increase in RSV Neutralizing Antibody in 8-11 Month Olds Following 1 Dose of RSV Vaccine After Nirsevimab



* Nirsevimab administered 6- 9 months prior to vaccine, mean 7.4 months

Summary: 5-7 Month Olds Receiving mRNA RSV Vaccine After Nirsevimab

- Based on small number of infants receiving prior nirsevimab:
  - No increase observed in neutralizing antibody after 1 dose of RSV vaccine
  - Suggests potential inhibition by pre-existing monoclonal antibody
  - Potential to overcome this with subsequent doses could not be evaluated given dosing pause

Summary

SUMMARY – Vaccination of Children & Infants with mRNA RSV and RSV/hMPV Vaccines *(1 of 2)*

RSV Vaccine Development in Children	▪ Active vaccination against RSV for children remains an urgent unmet need to provide protection beyond infancy
	▪ Moderna pursued a pediatric development plan with its mRNA RSV vaccines based on proven efficacy of its mRNA vaccines to prevent:
	  ▪ RSV disease in older adults
	  ▪ SARS-CoV-2 disease in children and adults
	▪ Pediatric RSV development program progressed to RSV-naïve infants in accordance with regulatory guidelines

Immunogenicity	▪ RSV naïve infants showed robust neutralizing antibodies with Pre-F bias ▪ No increase in RSV antibody following initial dose of mRNA RSV vaccine in infants that had previously received nirsevimab

SUMMARY – Vaccination of Children & Infants with mRNA RSV Vaccines *(2 of 2)*

Safety	▪ No safety concerns identified in RSV experienced children ▪ Pause rule triggered in <2-year-old pediatric study ▪ Enrollment and vaccination in all studies in this age stopped ▪ Suggestion of higher rate of severe/ hospitalized RSV illness in RSV naïve 5–7-month-old vaccine vs placebo recipients ▪ Ongoing surveillance for RSV and hMPV continues ▪ Neither nonclinical studies nor clinical studies in children ≥8 months predicted the imbalance of severe/ hospitalized RSV disease
Path Forward	▪ Safety and immunogenicity surveillance will continue for children in this study ▪ Our understanding of clinical and immunological picture continues to evolve as we gather more data

THANK YOU

- All investigators
- Study site personnel
- The children and families who participated in these trials