

Arrinconando al VRS

Octavio Ramilo



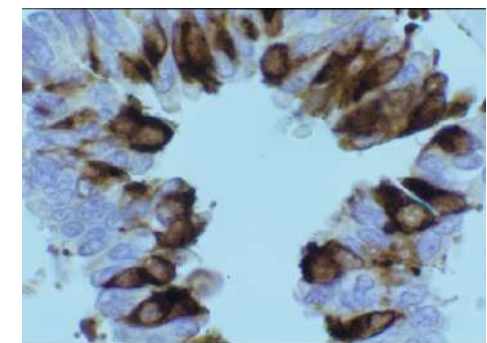
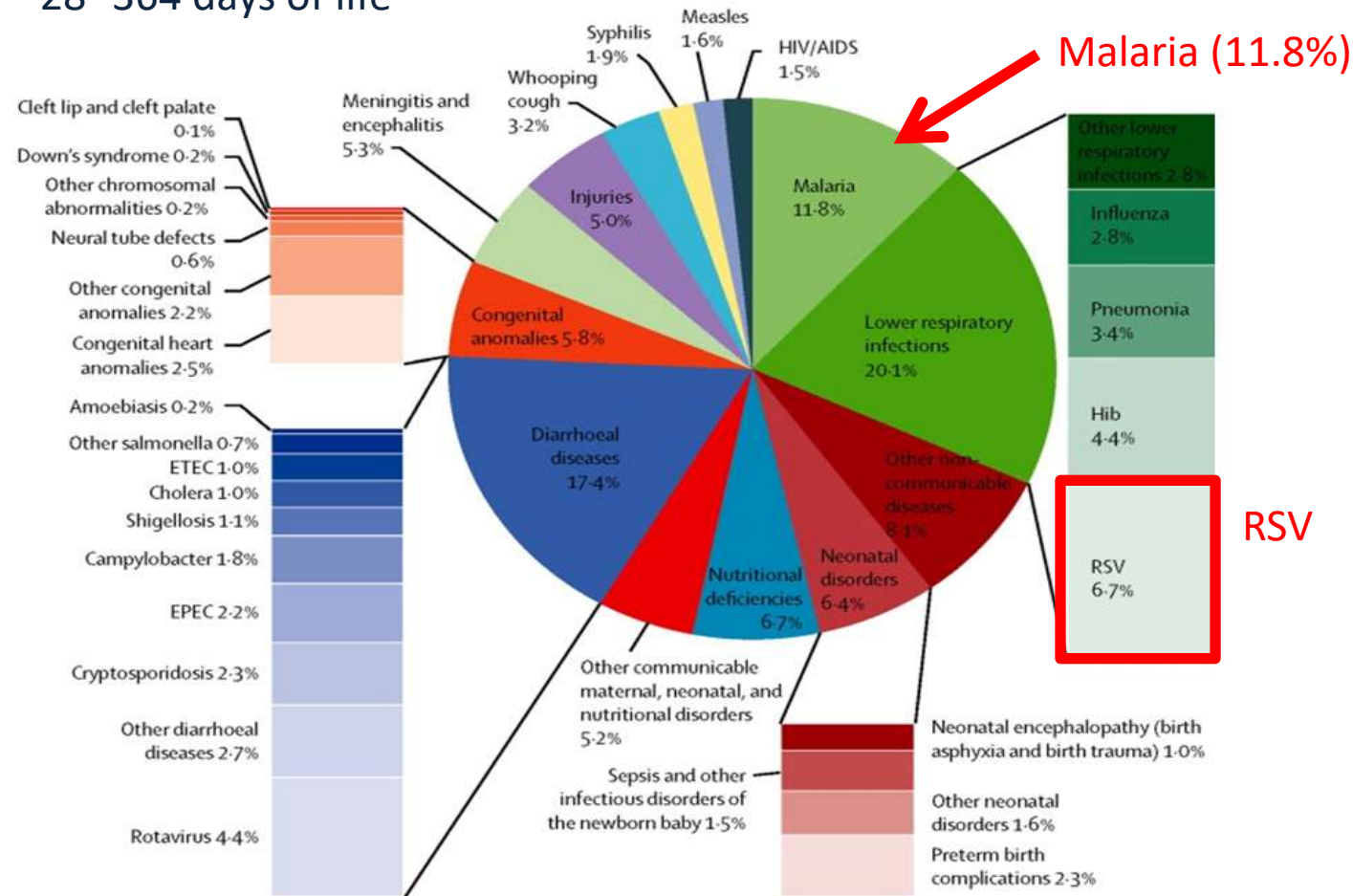
Indice

1. Impacto global del virus respiratorio sincitial
2. Variabilidad en la presentacion clinica
3. Importancia de anticuerpos maternos
4. Inmunidad innata en la infeccion por VRS
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6. Nuevos anticuerpos monoclonales

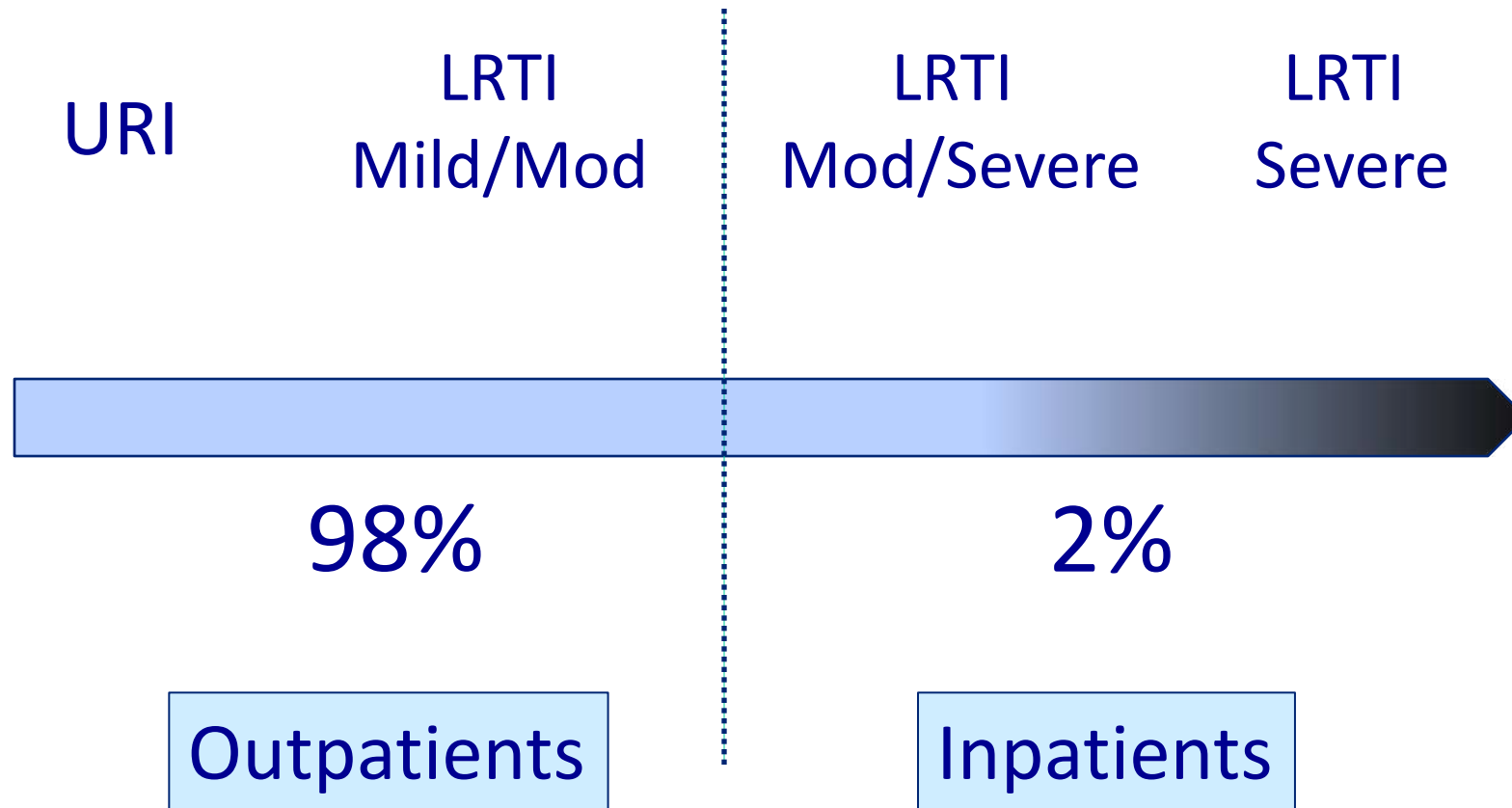
Global RSV disease burden

RSV kills more children aged <1 year than any other single pathogen except malaria

28–364 days of life

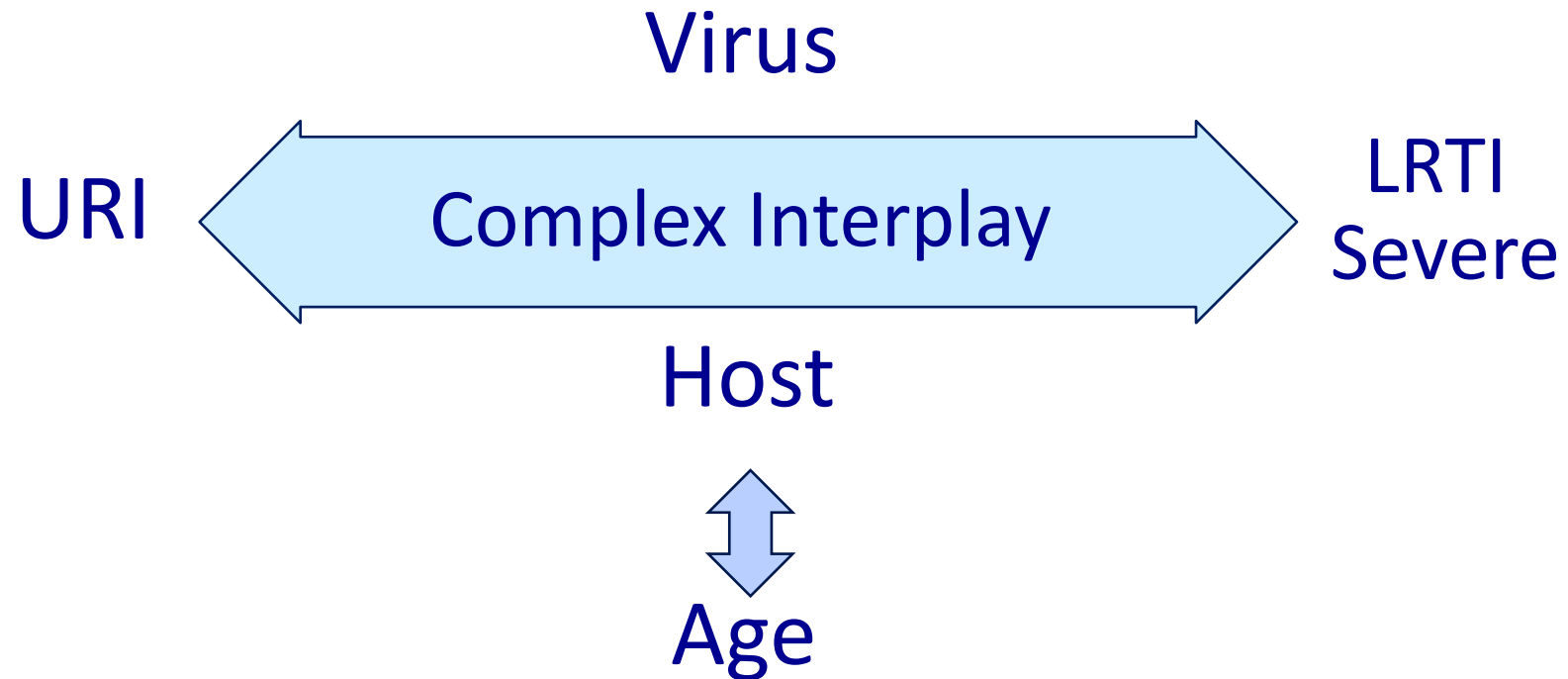


Variability in clinical presentation of RSV infections



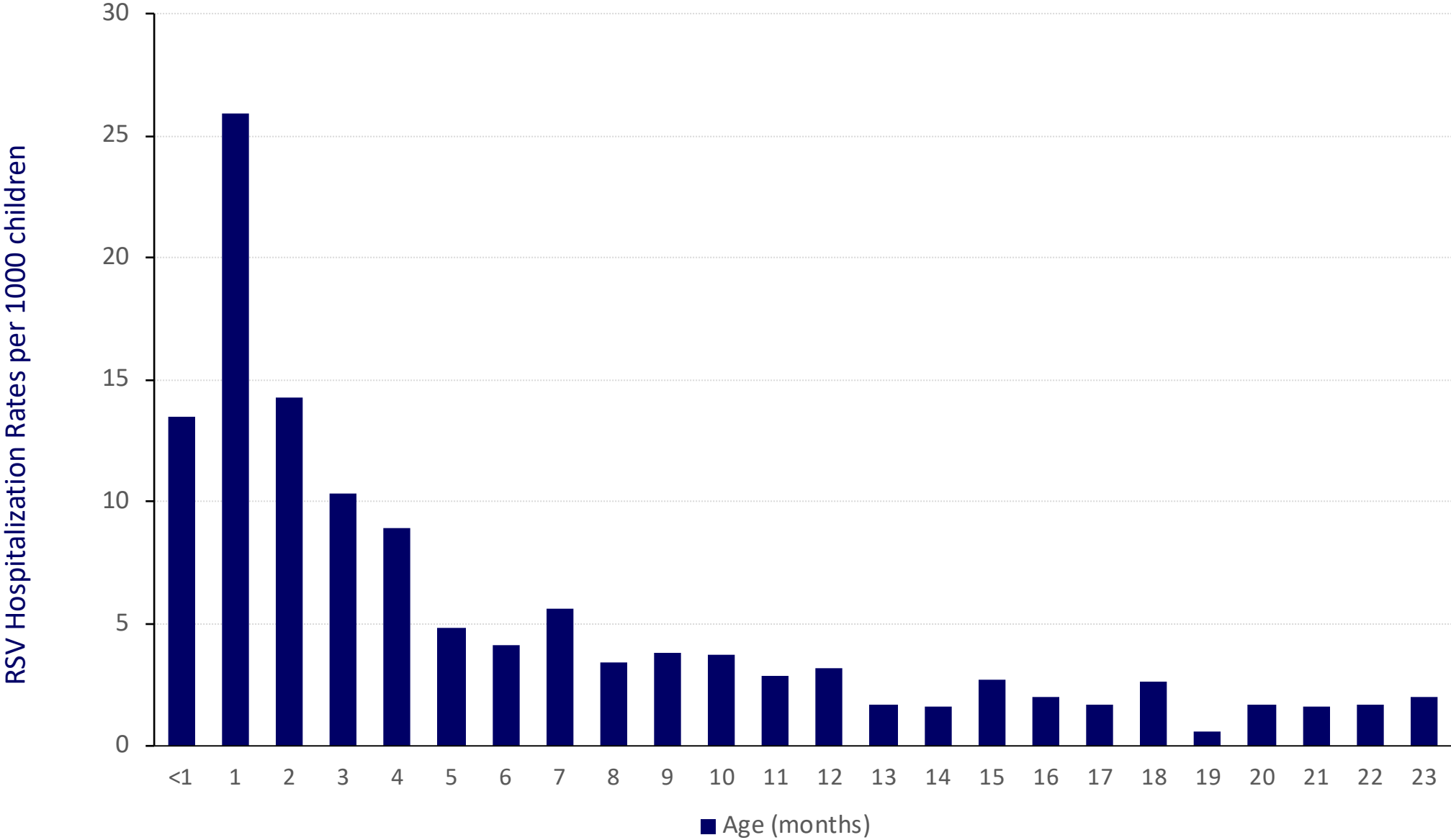
LRTI, lower respiratory tract infection; URI, upper respiratory infection

How do we explain the variability in clinical presentations?



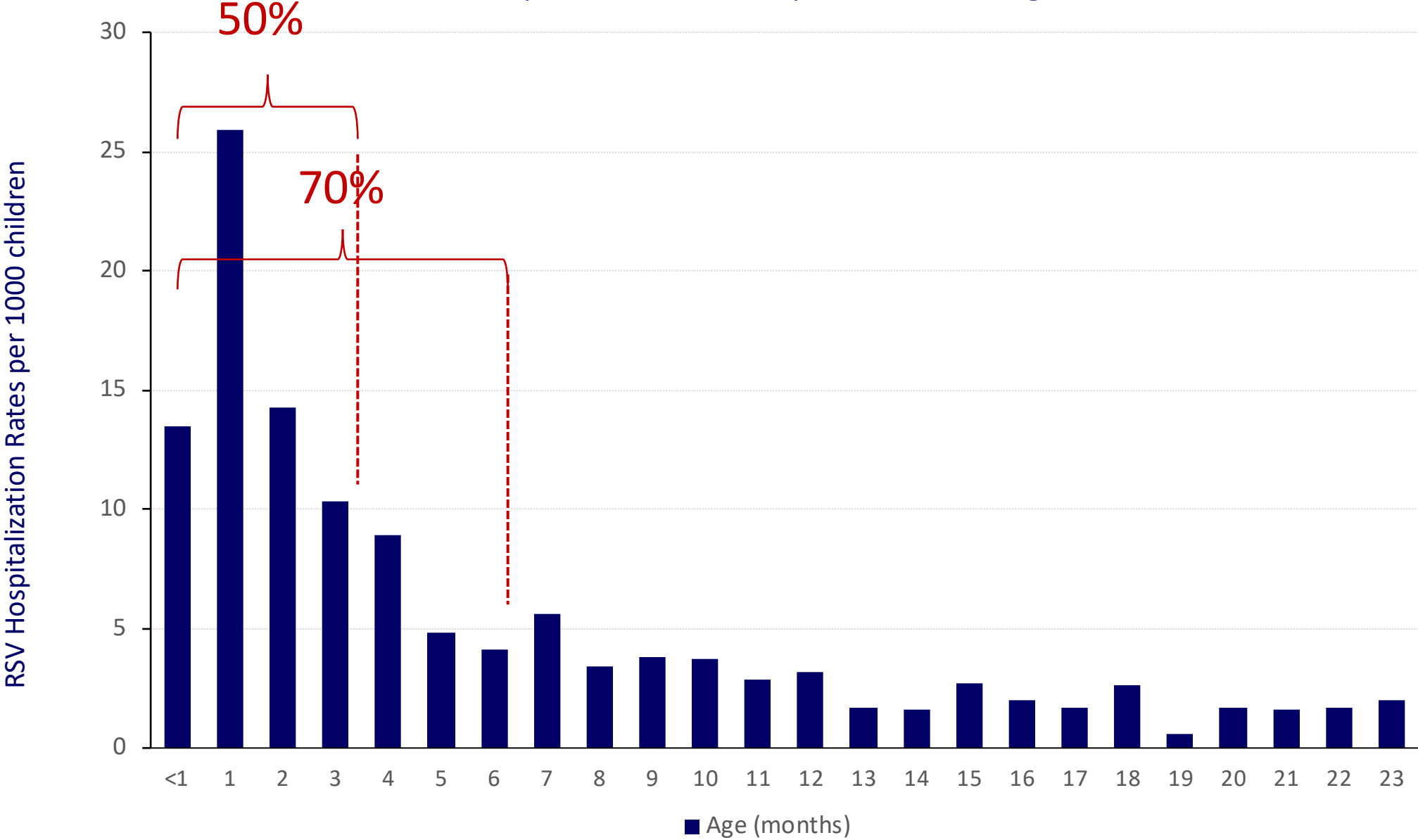
Age and Disease Severity

Hospitalization Rates per Month of Age



Hall CB, et al. Pediatrics. 2013;132:e34–e348.

Hospitalization Rates per Month of Age

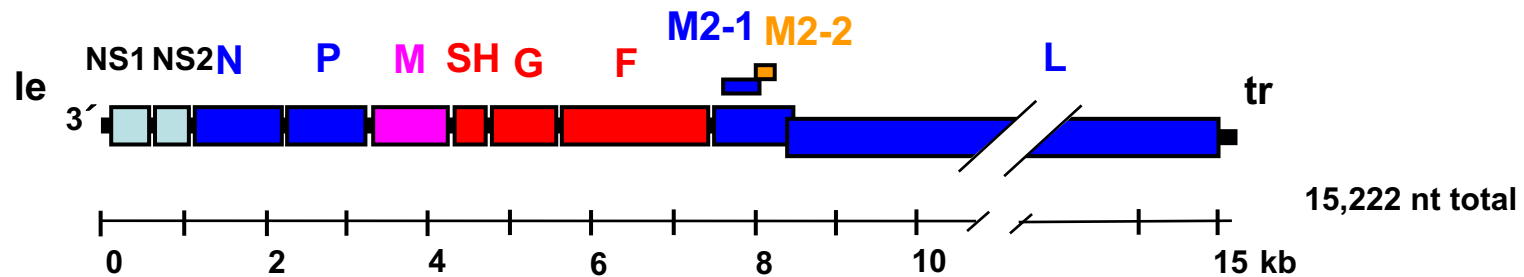
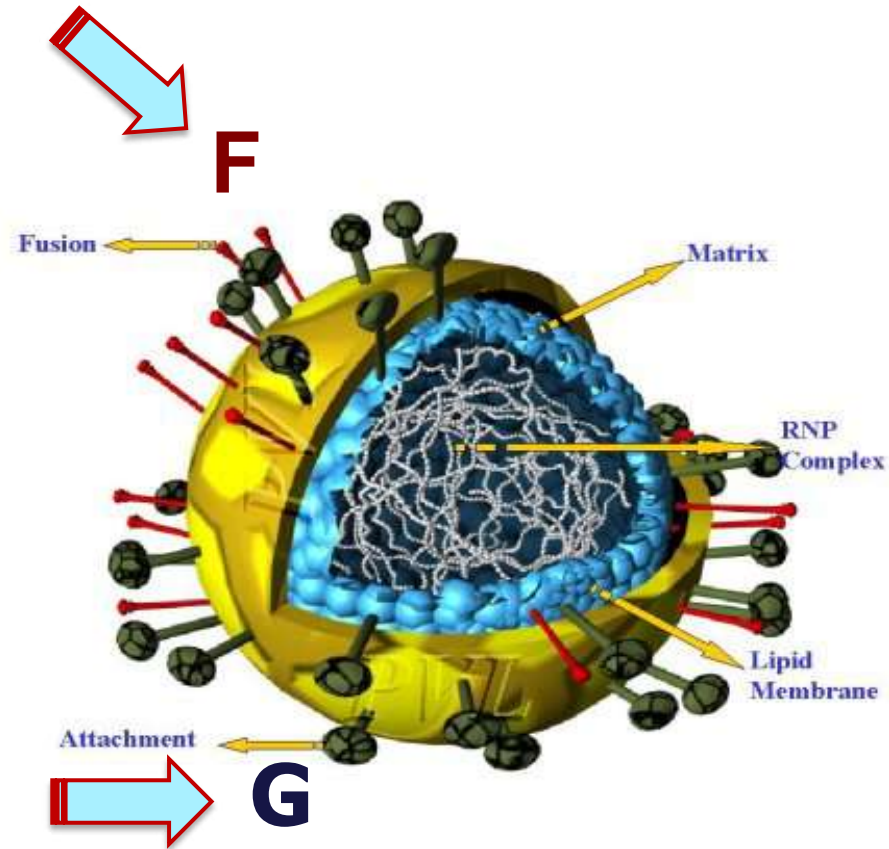


Hall CB, et al. Pediatrics. 2013;132:e34–e348.

Do maternal antibodies influence disease severity?

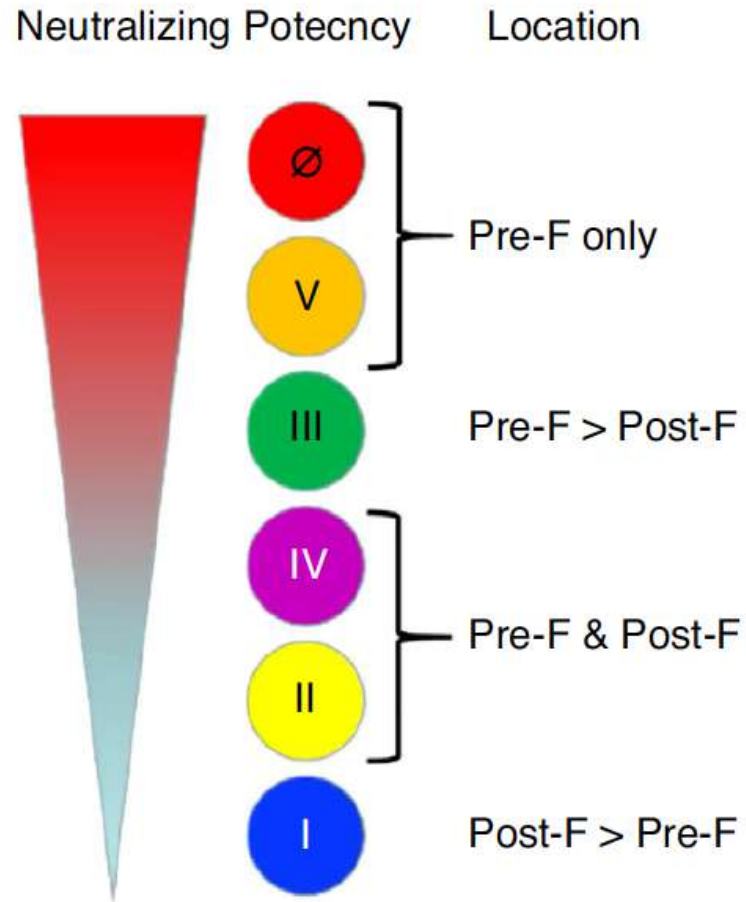
If so, which specific antibodies are more relevant?

RSV: The Virus

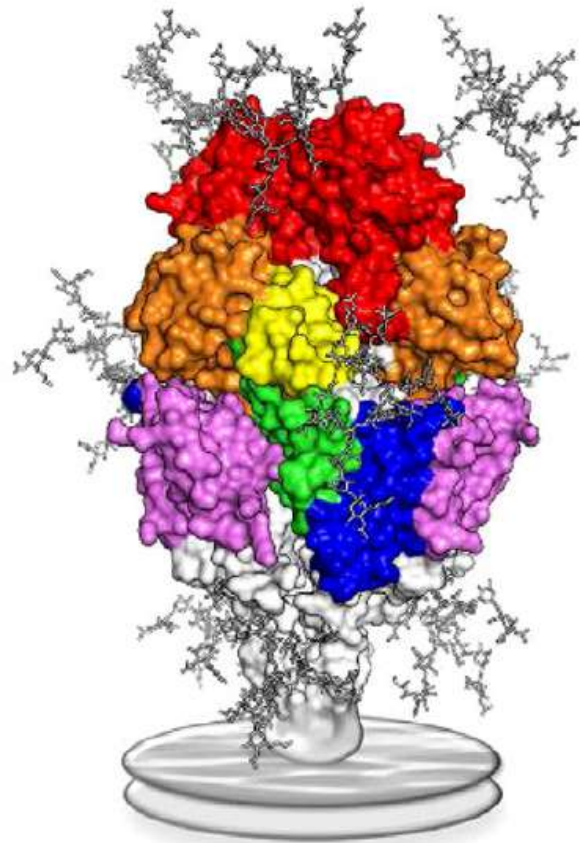








Modified from Park JW and Barnett DW. South Med J. 2002;95:353-7; Collins PL, et al. Curr Top Microbiol Immunol. 2013;372:3-38; McLellan JS, et al. Curr Top Microbiol Immunol. 2013;372:83-104.

RSV PreF and PostF Antigenic Sites

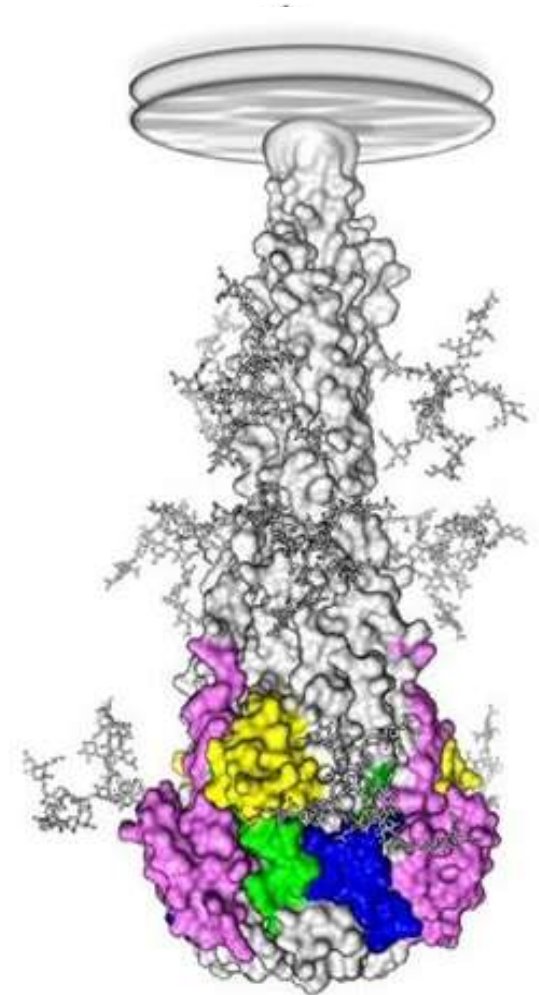


Prefusion RSV F



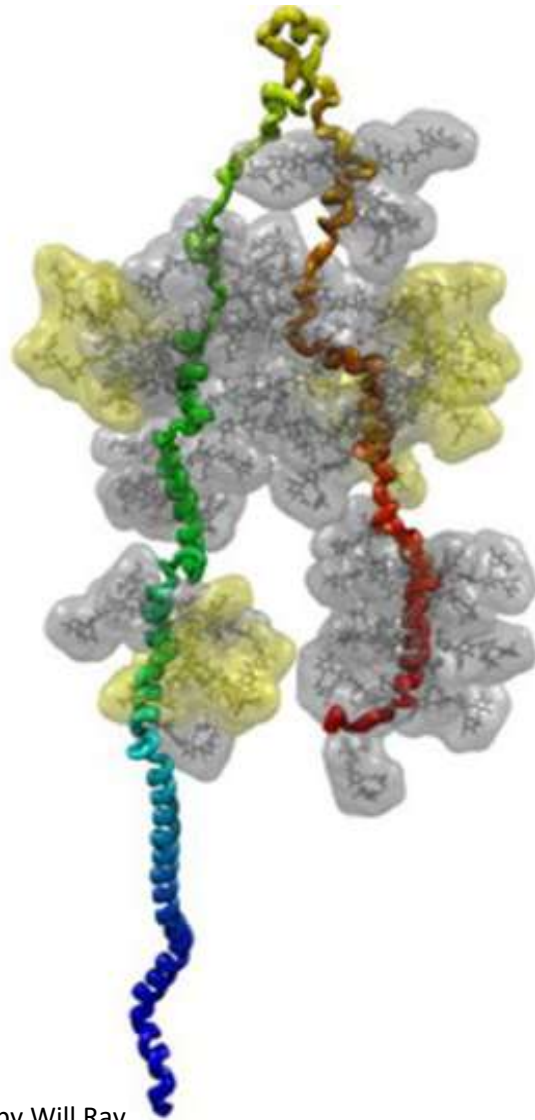
-  Site Ø
-  Site I
-  Site II
-  Site III
-  Site IV
-  Site V

Postfusion RSV F

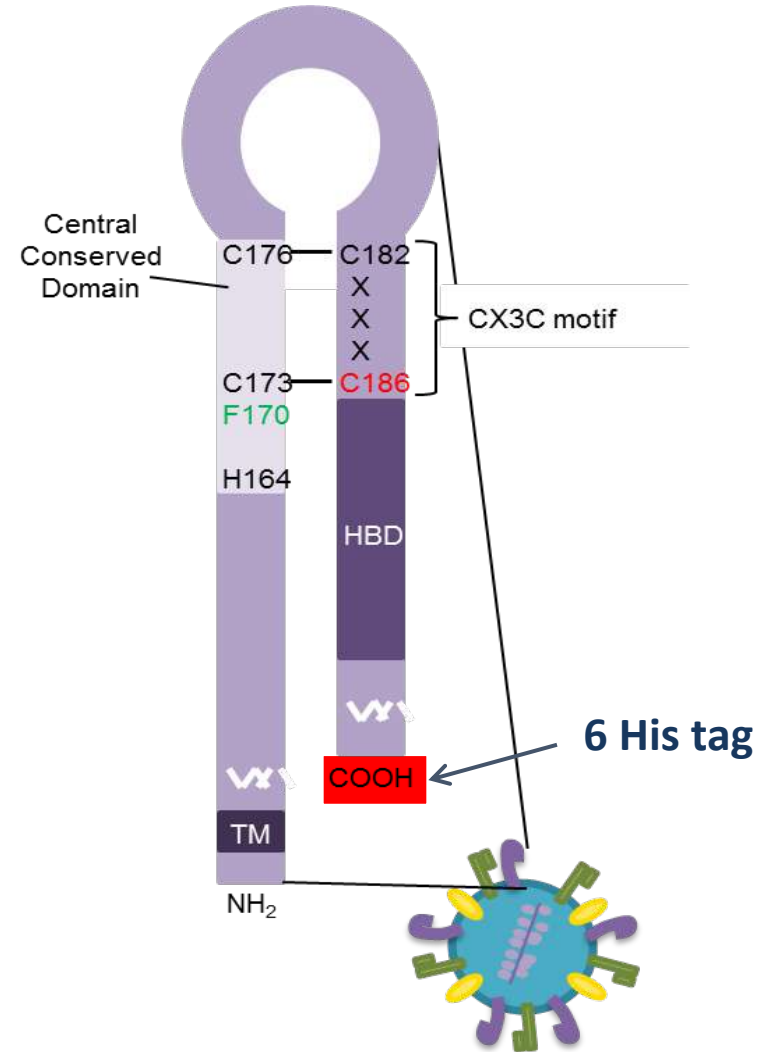


PreF, prefusion RSV F; PostF, postfusion RSV F
 Adapted from Graham B. *Curr Opin Virol.* 2017;23:107–12.

RSV G Induces Neutralizing Antibodies



Approximation by Will Ray



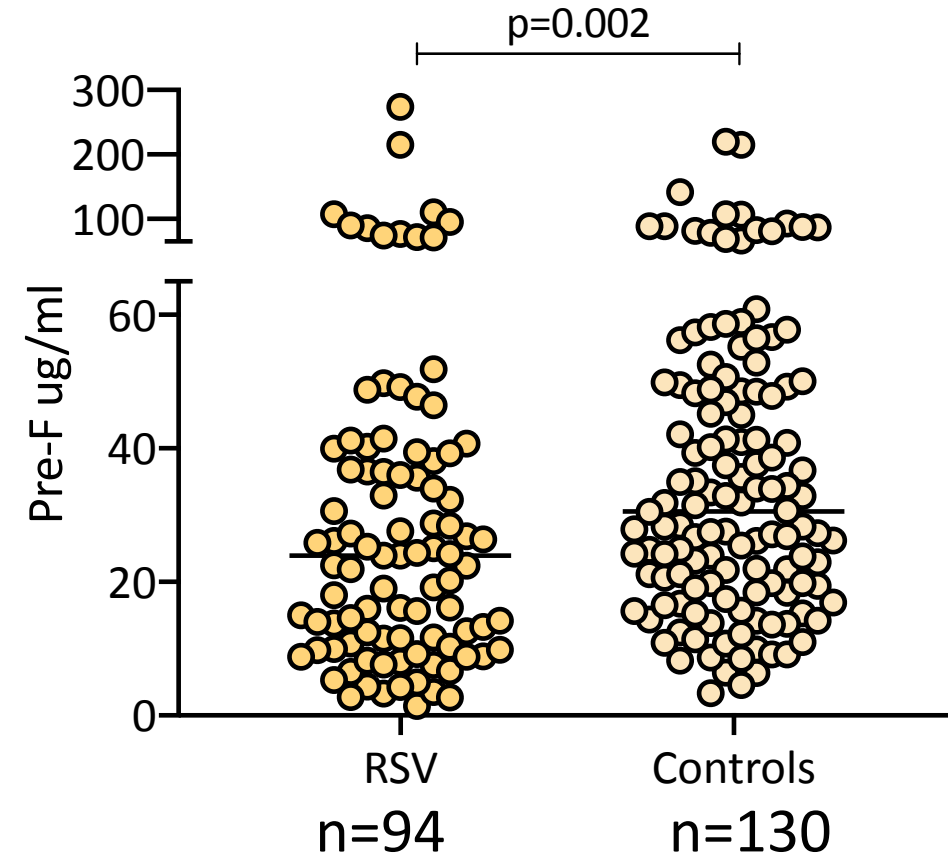
Courtesy of Mark Peebles

Higher maternal PreF antibodies and lower risk of severe RSV disease in infants

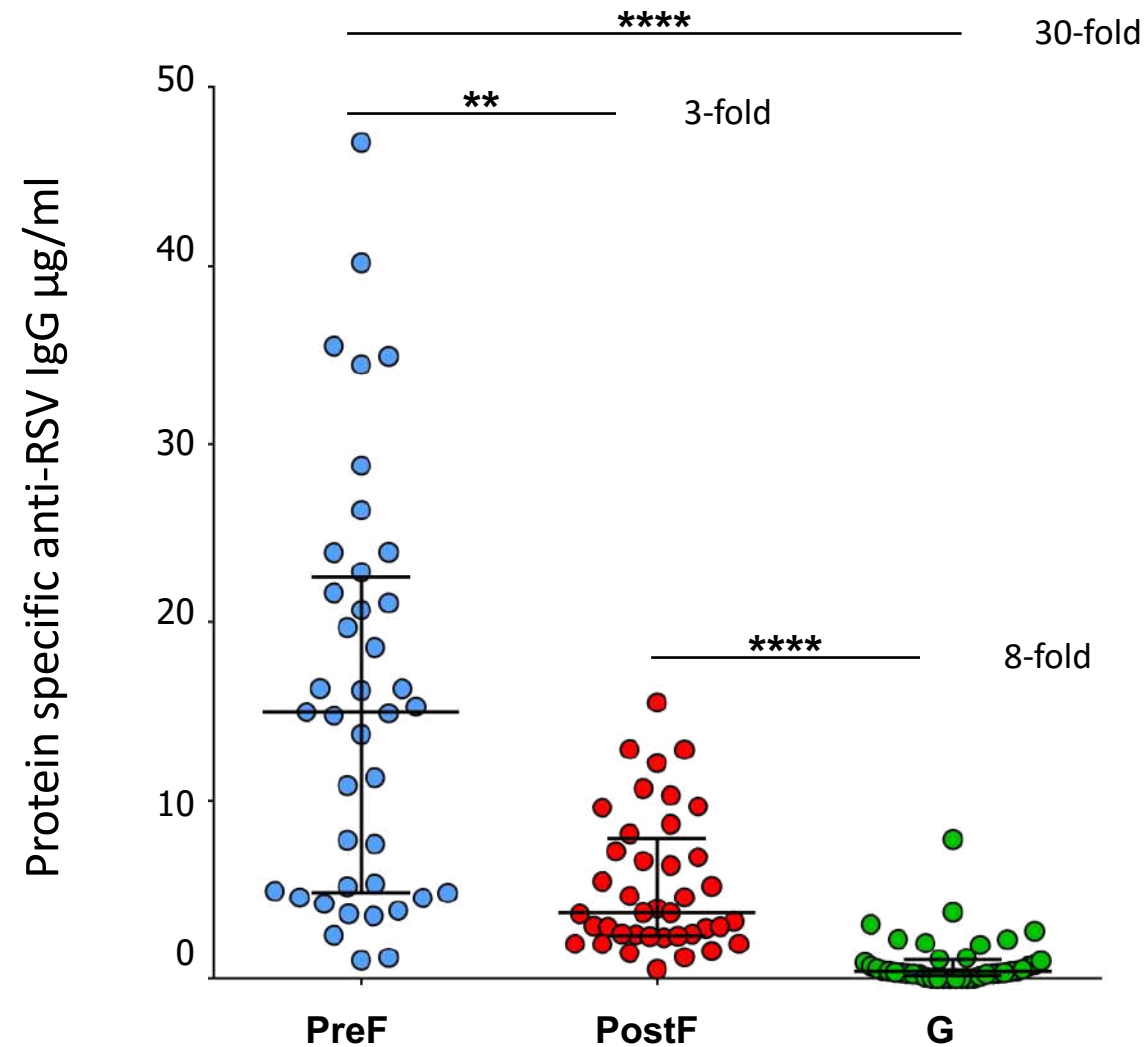
Serum maternal antibodies
(1st trimester [9-12 weeks of gestation])



Risk of hospitalization for severe RSV
Infection in first 3 months of age



PreF are the most abundant antibodies in infants with acute Infection



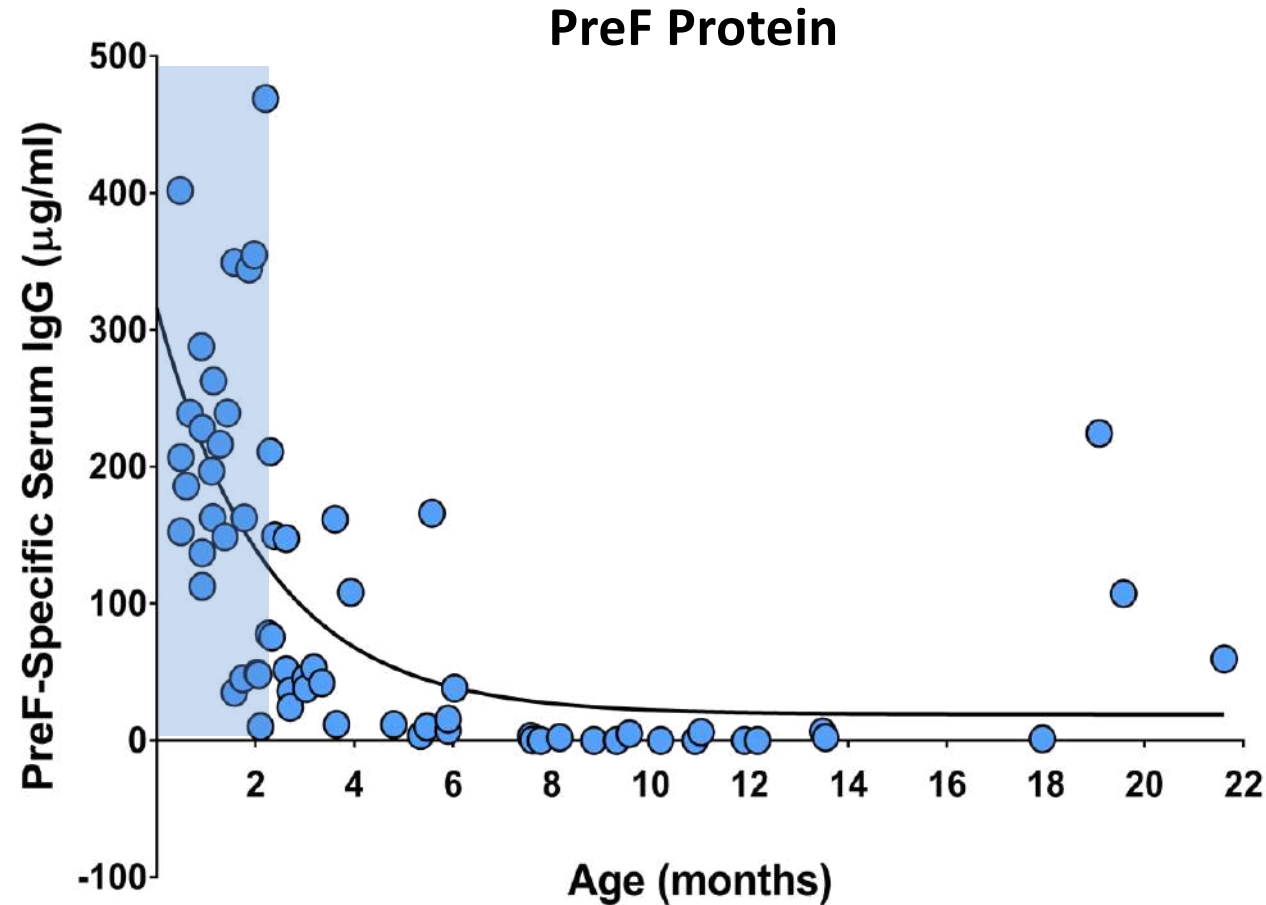
Patients ≤ 4 months of age

n = 44; 40 Acute patients (circles)

Statistics: Kruskal-Wallis followed by Dunn's Test to adjust for multiple comparisons

Capella C, et al. J Infect Dis. 2017;216(11):1398–1406.

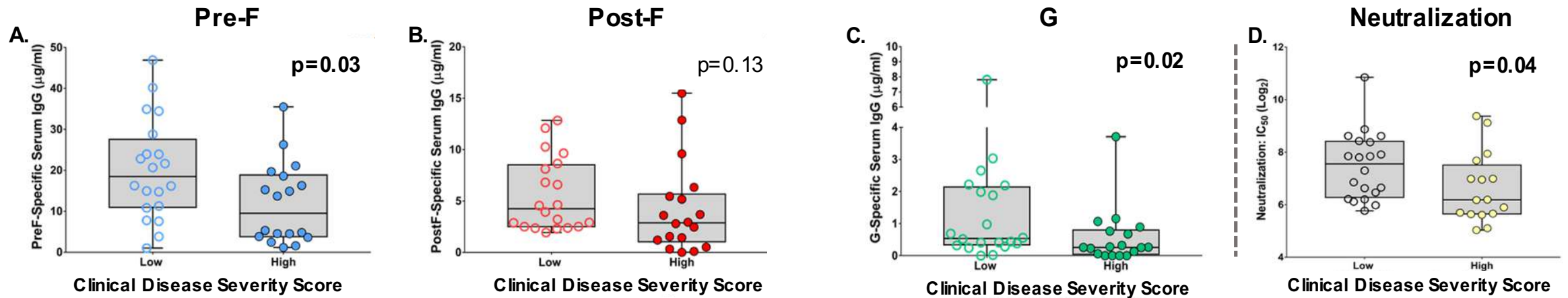
Serum IgG antibodies against RSV glycoproteins inversely correlate with age



$p < 0.0001$
 $r = -0.73$

n = 65; 45 hospitalized patients and 20 outpatients
Spearman (r) correlation is indicated
Non-linear regression, one phase decay (shaded values)
IgG, immunoglobulin G
Capella C, et al. J Infect Dis. 2017;216(11):1398–1406.

Patients with low severity scores had higher PreF- and G-specific antibodies



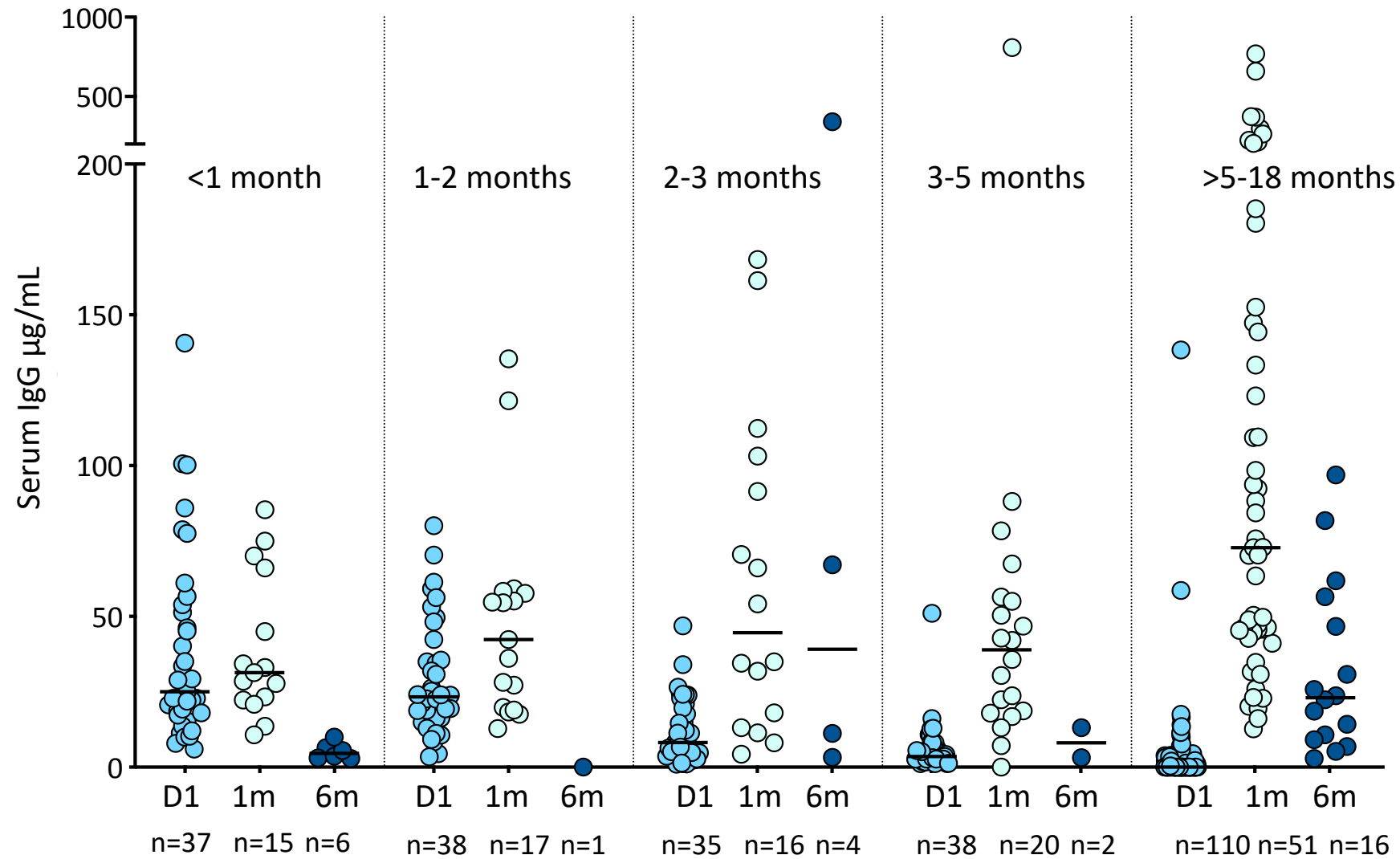
Patients ≤ 6 months of age
n = 38 hospitalized patients

Statistics: Mann-Whitney, median with (IQR)

Capella C, et al. J Infect Dis. 2017;216(11):1398–1406.

Are young infants capable of
generating an effective antibody response to RSV?

Pre-F Ab concentrations acute, 1 month and 6 months follow-up

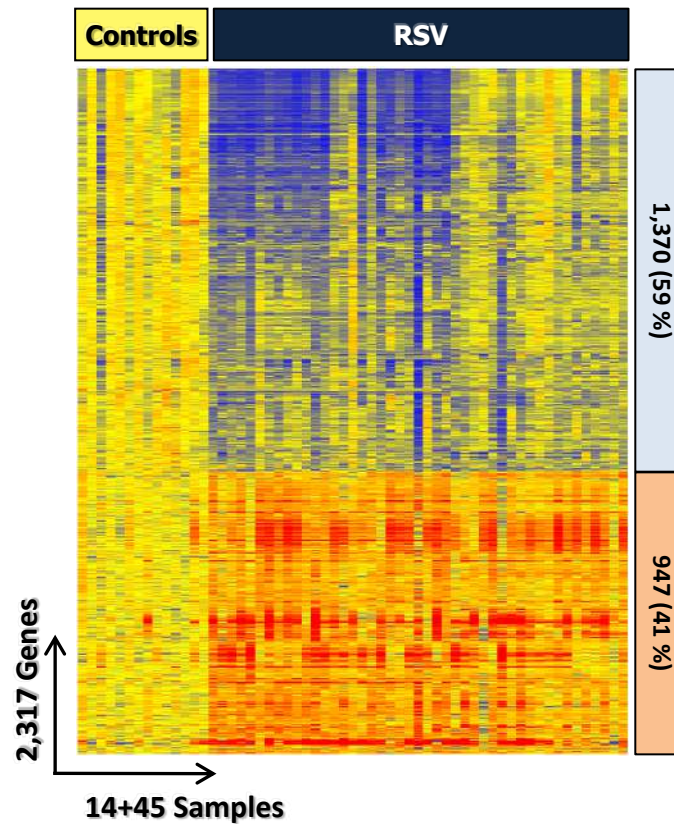


RSV and the innate the immune system

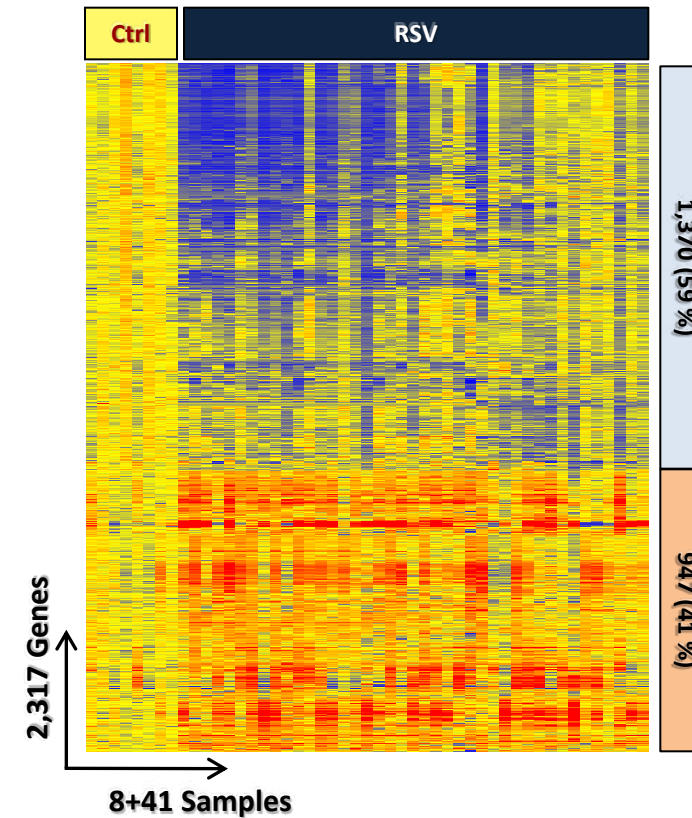


Transcriptional profiles in children with RSV bronchiolitis

Training Set
Dallas, TX (n=59)



Test Set
Dallas, TX (n=49)



Mann-Whitney <0.01 , Benjamini MTC x1.25-fold change

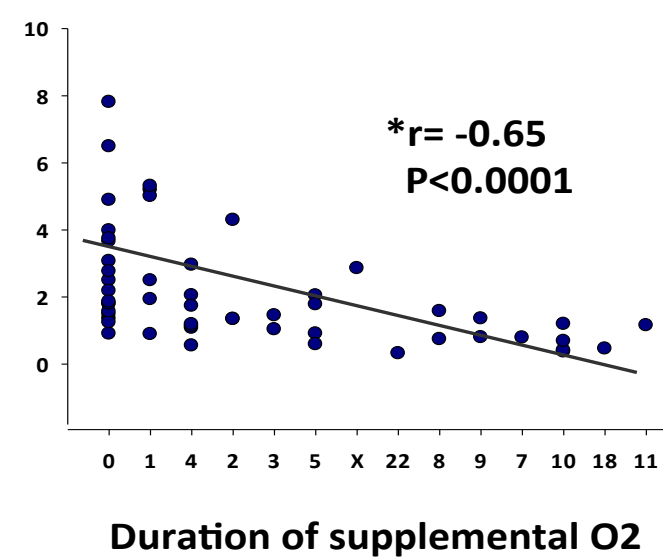
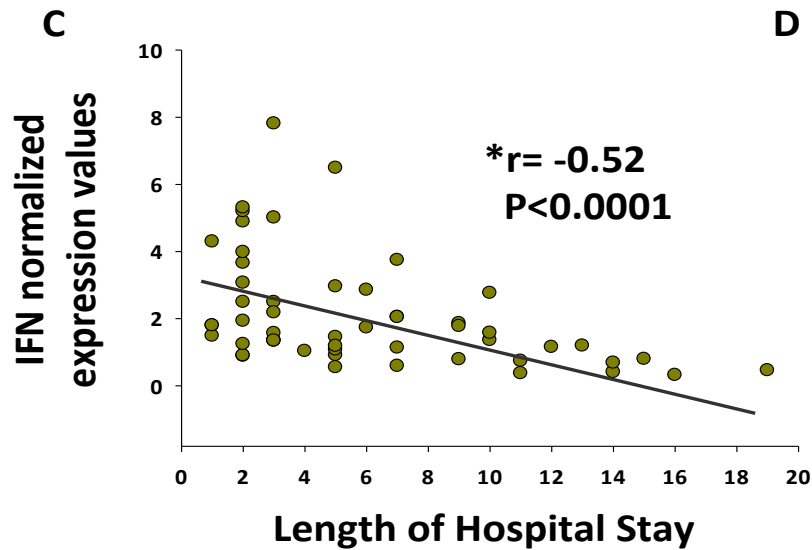
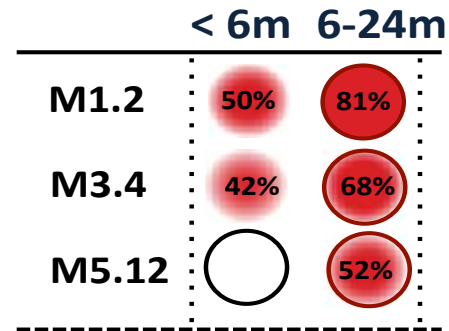
Mejias A, et al. PLoS Medicine. 2013;10(11):e1001549.

And.... what about age?

RSV-induced immune profiles by age group



Interferon modules

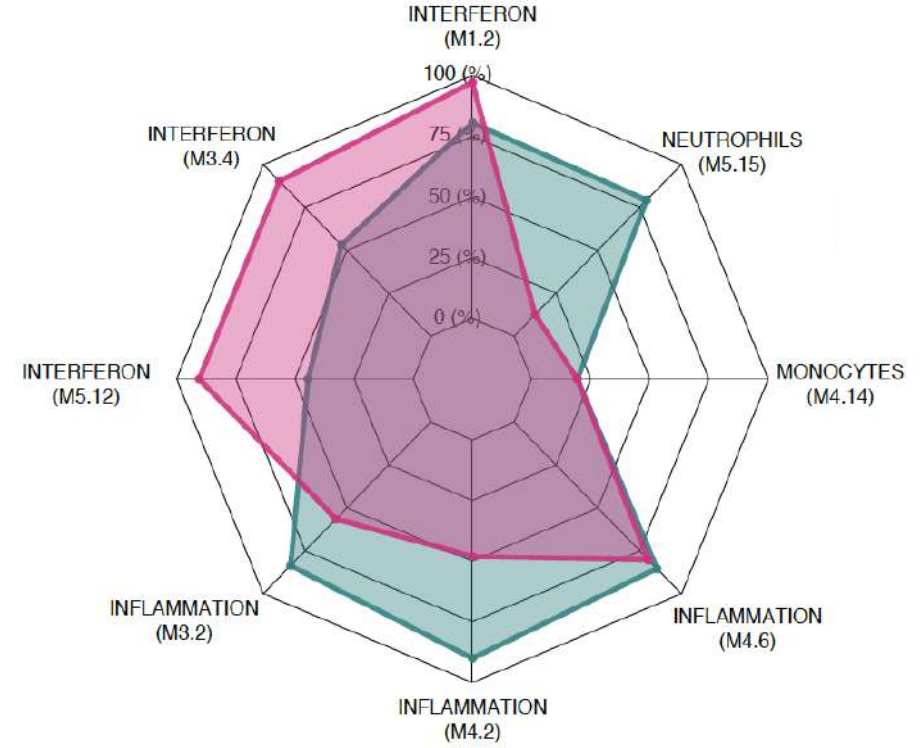
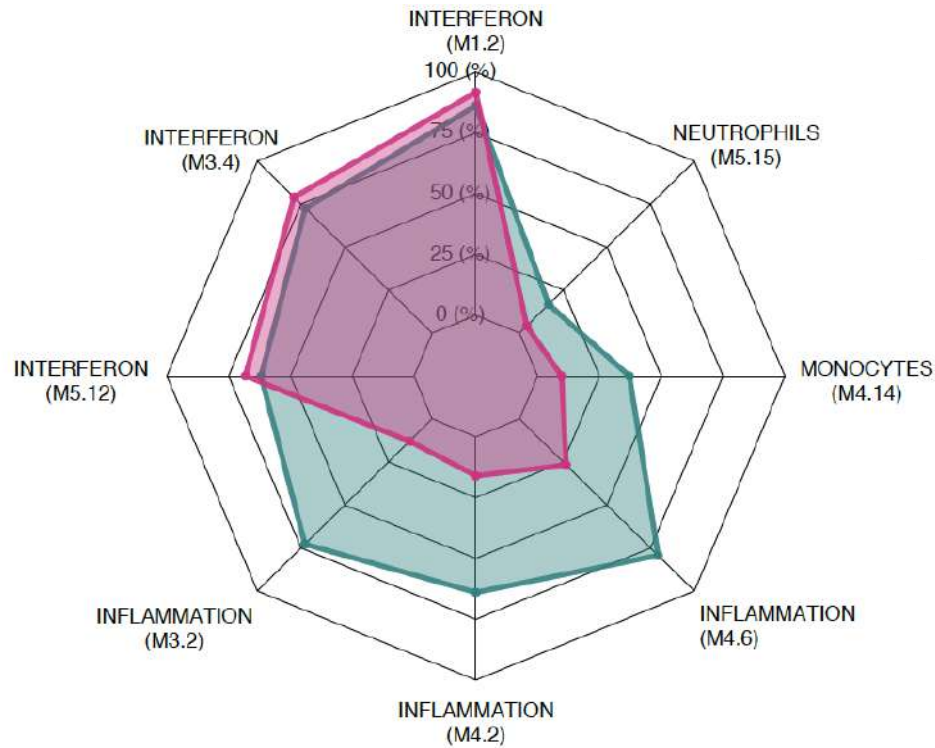


RSV Immune responses: Age and disease severity

0–6 months

● Inpatients ● Outpatients

6–24 months

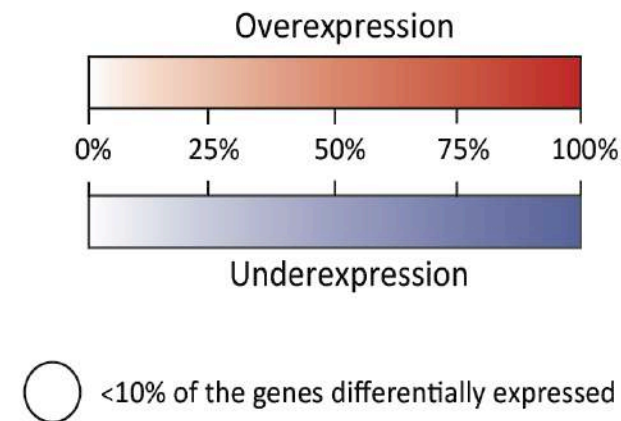
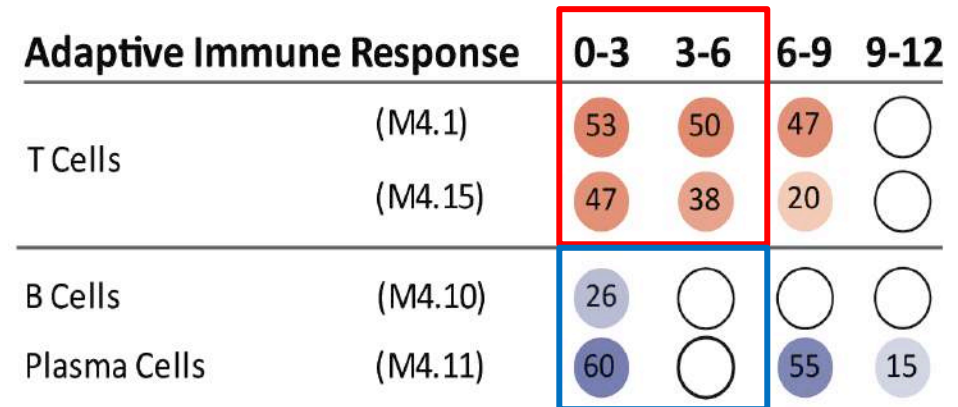
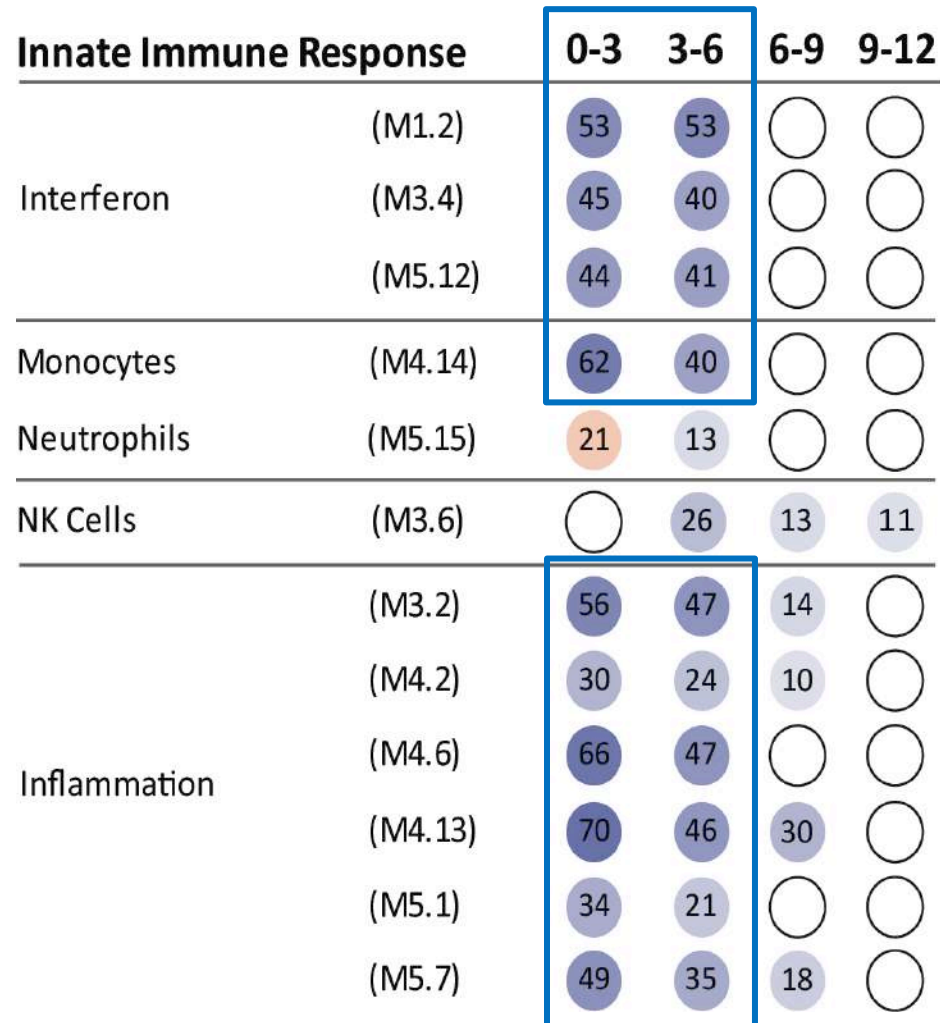


	Inpatients (n=10)	Outpatients (n=12)
Age (months)	3.0 (2.0–4.9)	4.5 (2.3–5.6)
Males	60%	67%

	Inpatients (n=14)	Outpatients (n=12)
Age (months)	9.0 (7.1–11.0)	8.6 (7.7–12.0)
Males	60%	67%

Is this relevant for healthy infants?

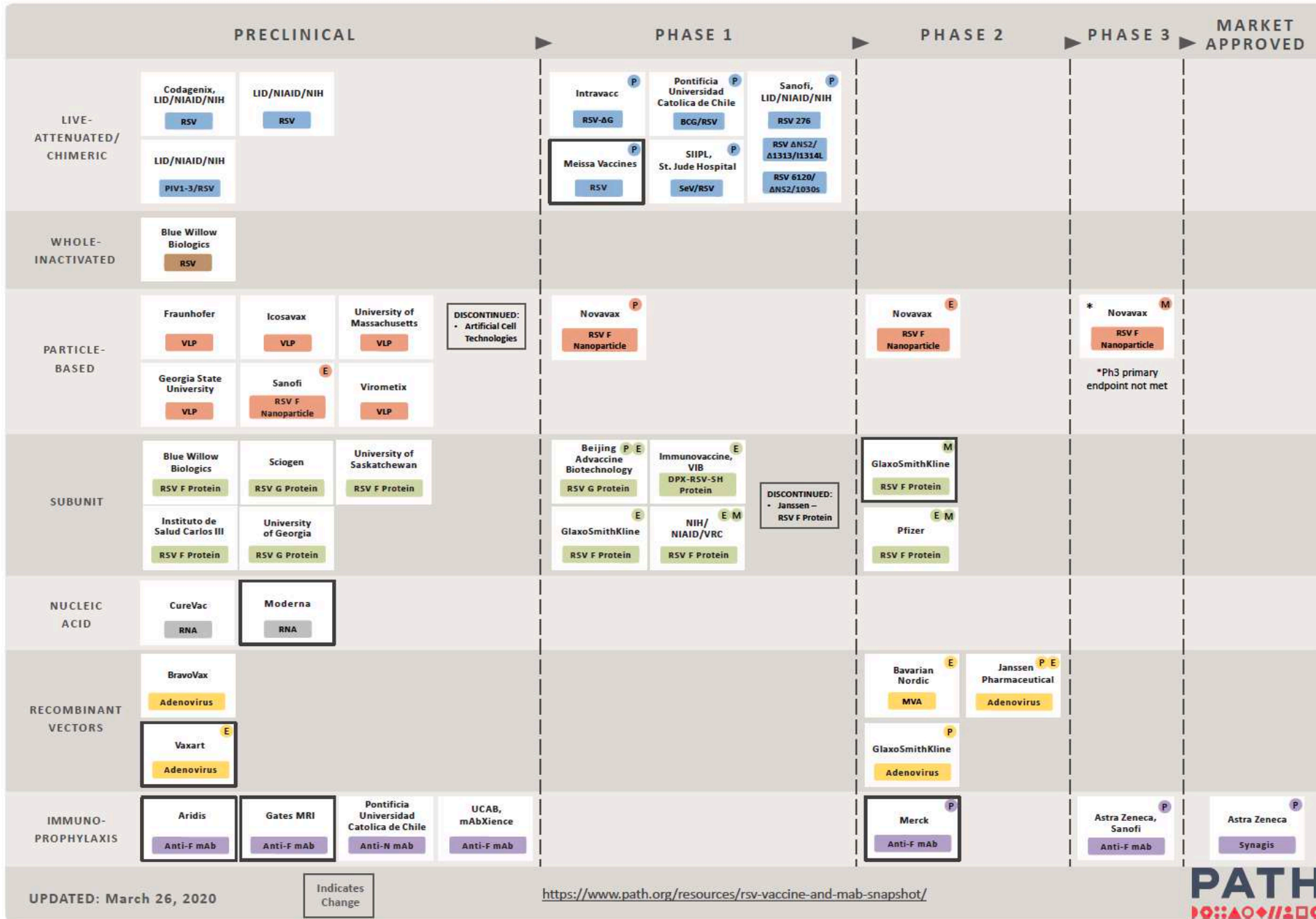
Infants aged <6 months show underexpression of interferon, inflammation and B cell genes, but overexpression of T cell genes



Preventing RSV

RSV Vaccine and mAb Snapshot

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

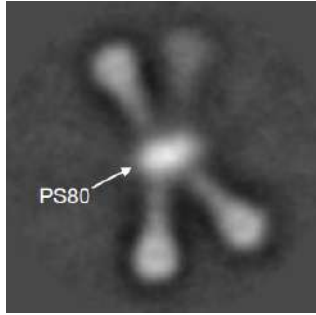


UPDATED: March 26, 2020

Indicates Change

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

Maternal Vaccination



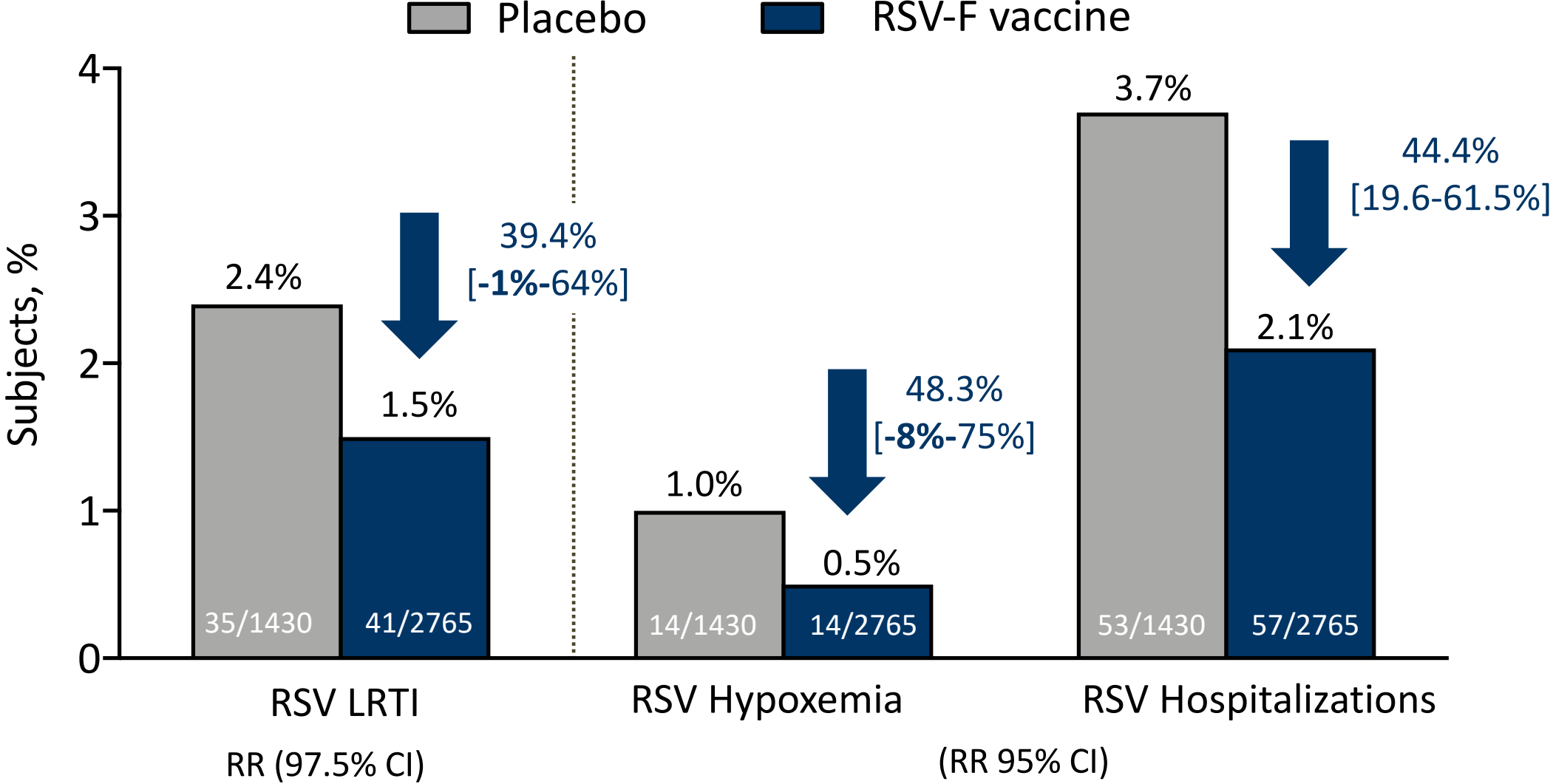
Prefusogenic F particle

Phase 3 and beyond: The RSV F nanoparticle vaccine for infants via maternal immunization

- Healthy pregnant women, at 28- 36 weeks gestation
- Randomized 2:1 IM of RSV F nanoparticle vaccine or placebo
- Primary endpoint: 90 days
- Infants followed 364 days (safety)

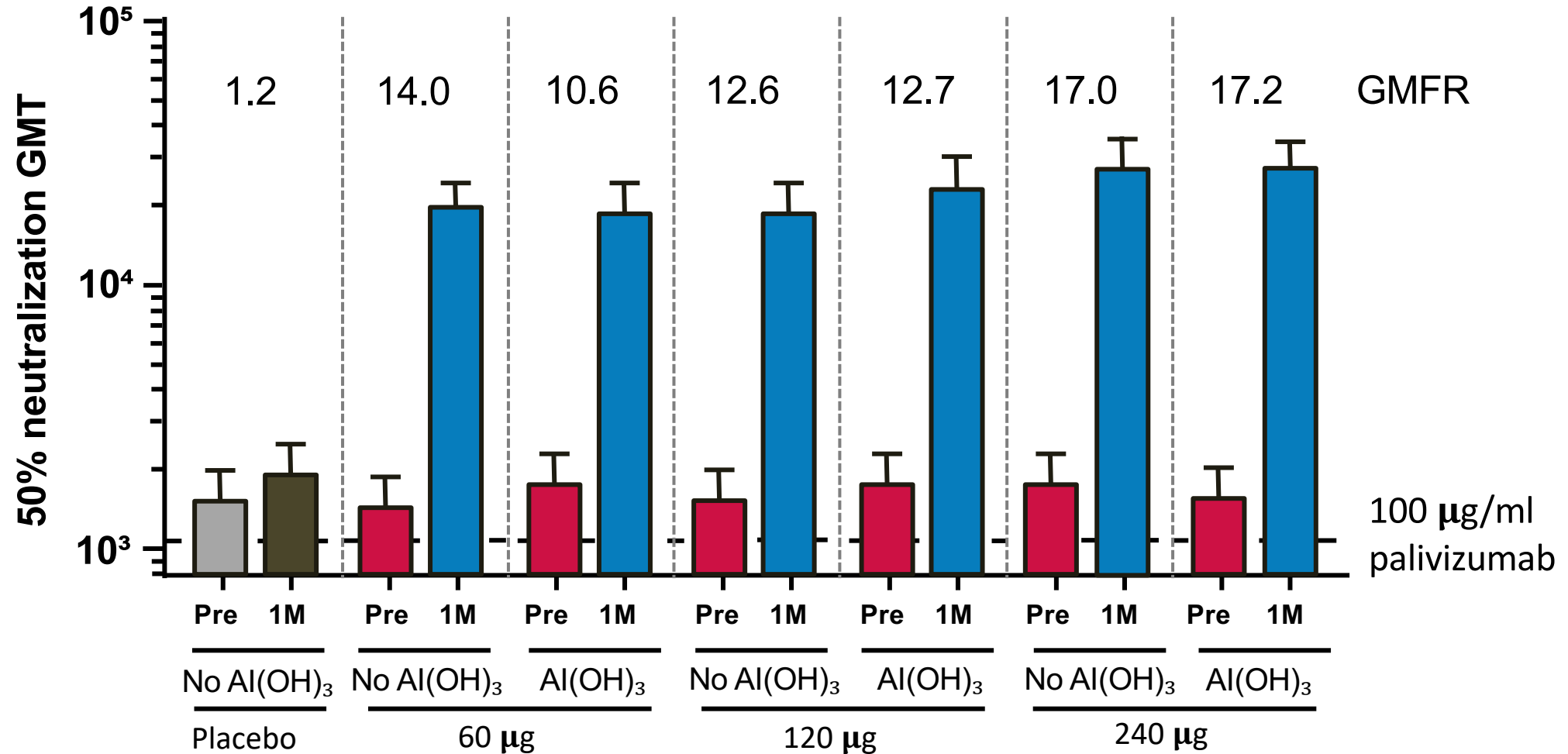
RSV vaccination during pregnancy and effects in infants

n=4636



PreF subunit vaccine

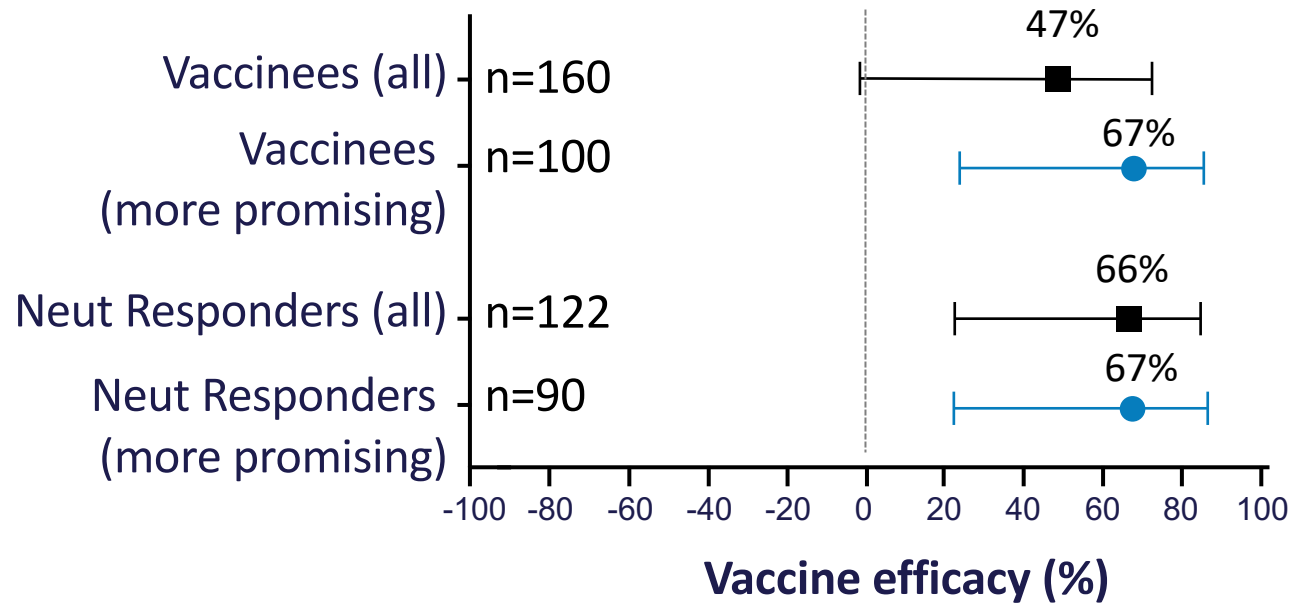
RSV 50% neutralization GMTs and GMFRs



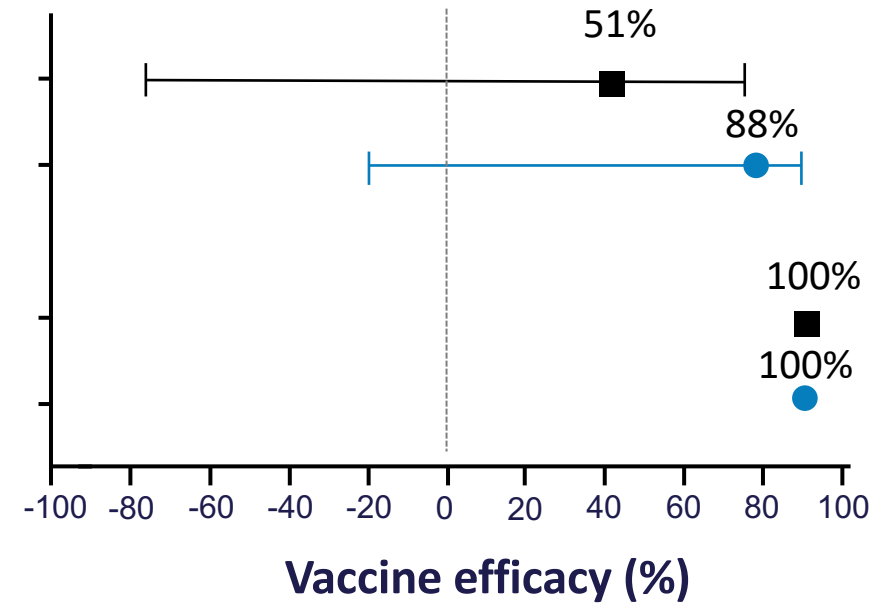
Active Immunization for children > 6 months of age

Efficacy of RSV live attenuated vaccines

A. RSV-MAARI



B. RSV-MAALRI

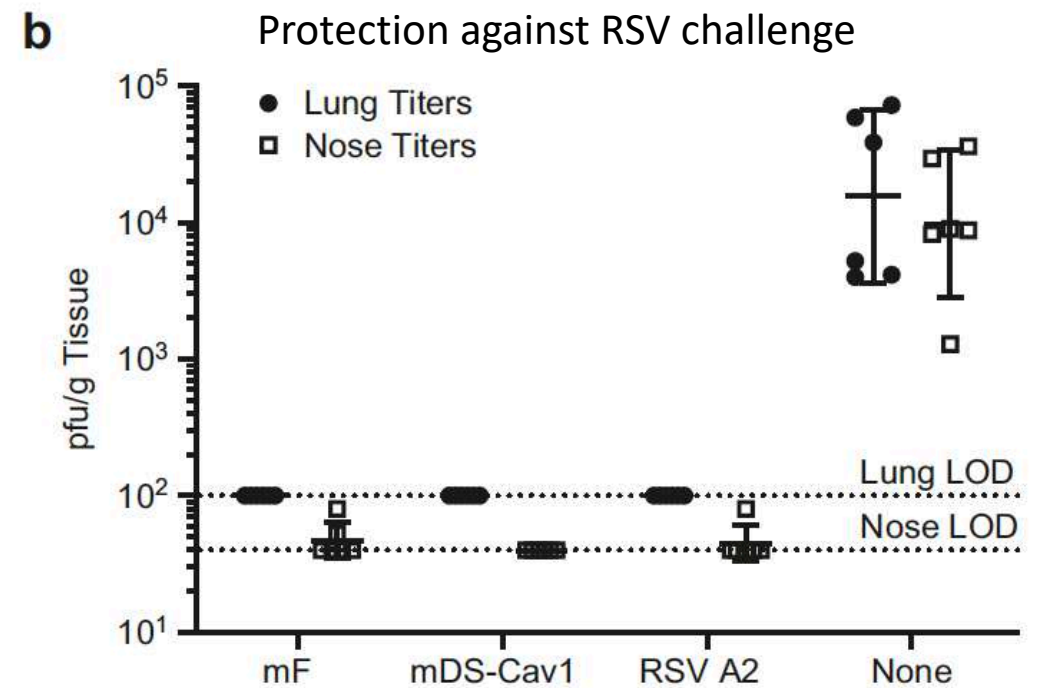
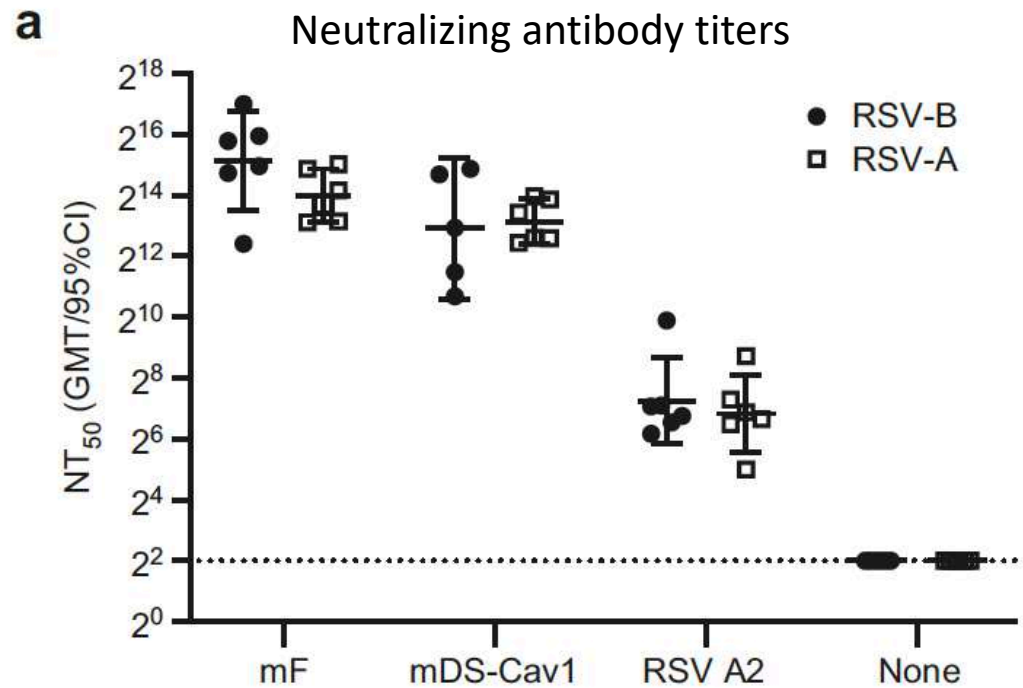


Point estimates and 95% CI*

Karron et al AJRCCM September 2020

mRNA/lipid nanoparticle vaccine expressing RSV F variants

Cotton rat experimental model



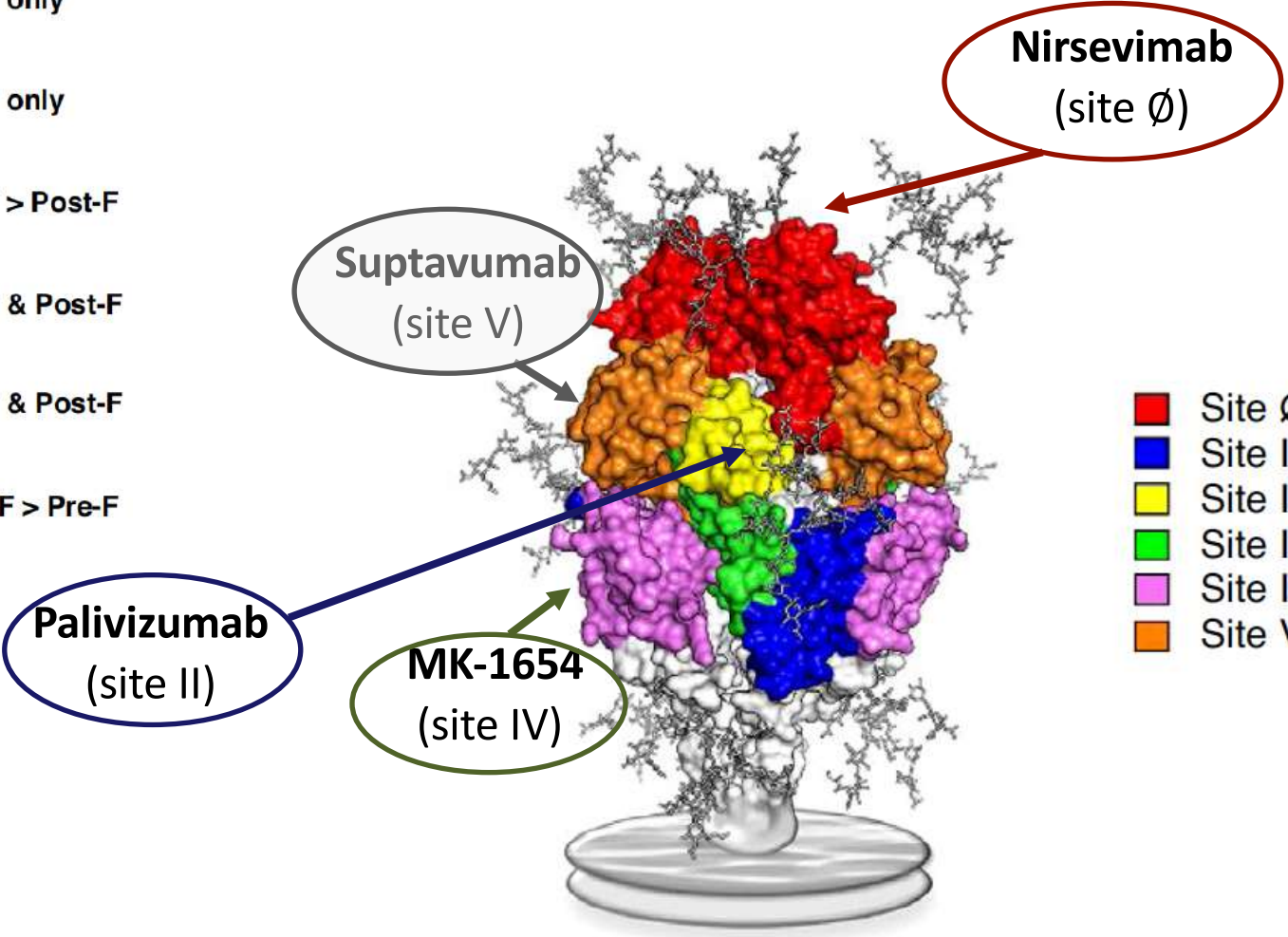
RSV PreF monoclonal antibodies

Neutralization Sensitivity

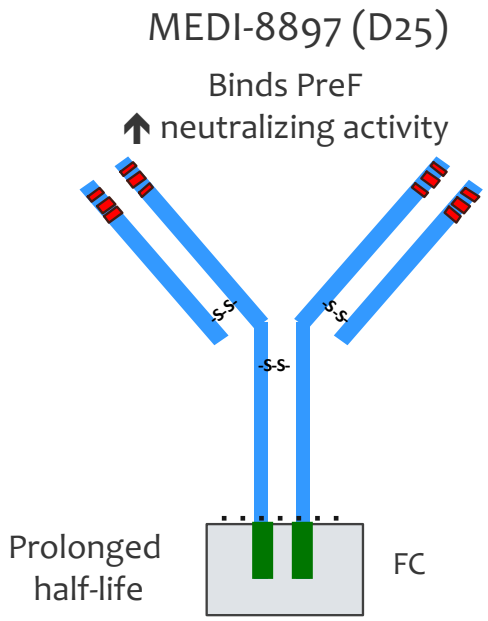
Location



- \emptyset Pre-F only
- V Pre-F only
- III Pre-F > Post-F
- IV Pre-F & Post-F
- II Pre-F & Post-F
- I Post-F > Pre-F

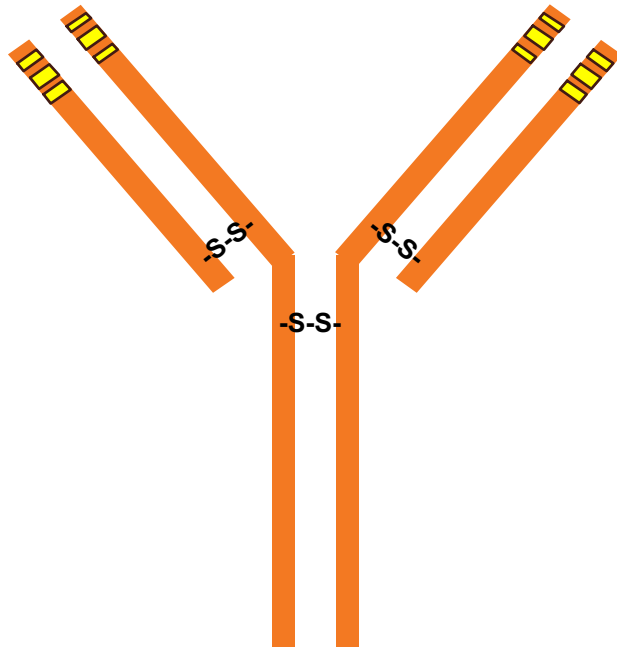


- Site \emptyset
- Site I
- Site II
- Site III
- Site IV
- Site V

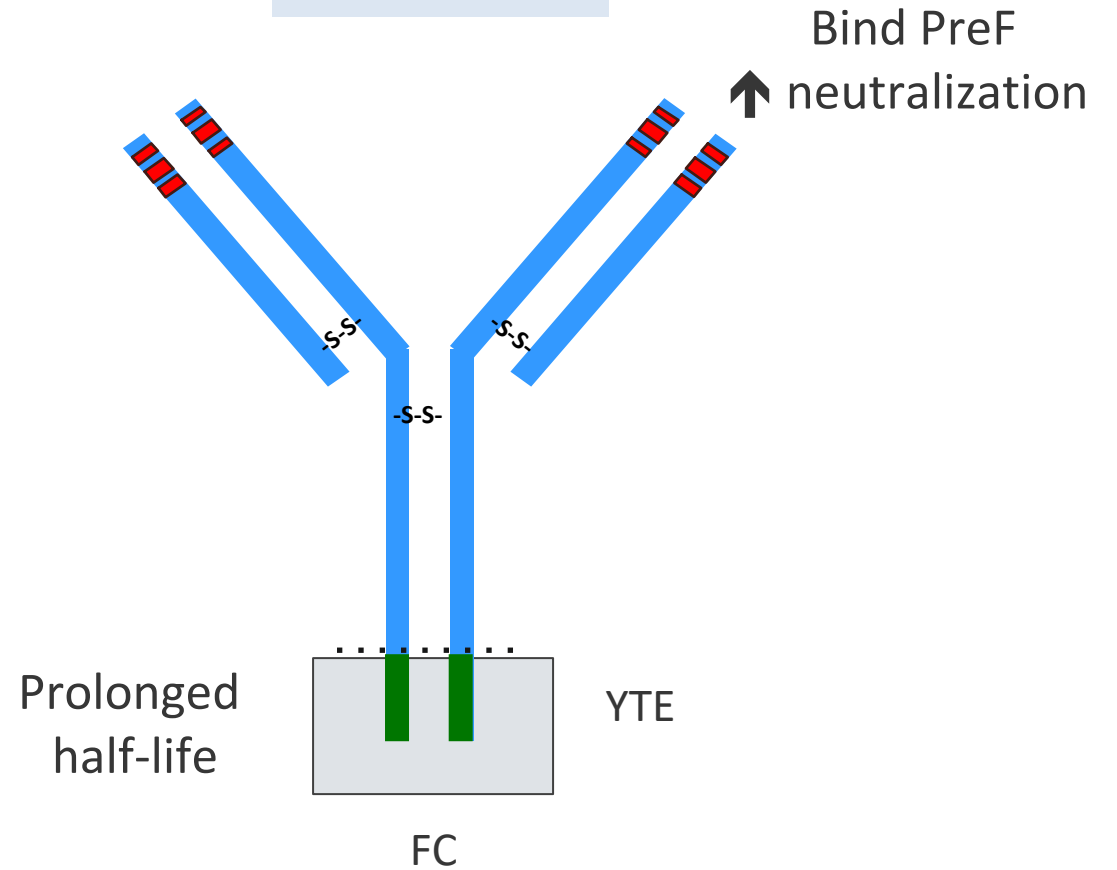


Anti-RSV neutralizing mAbs

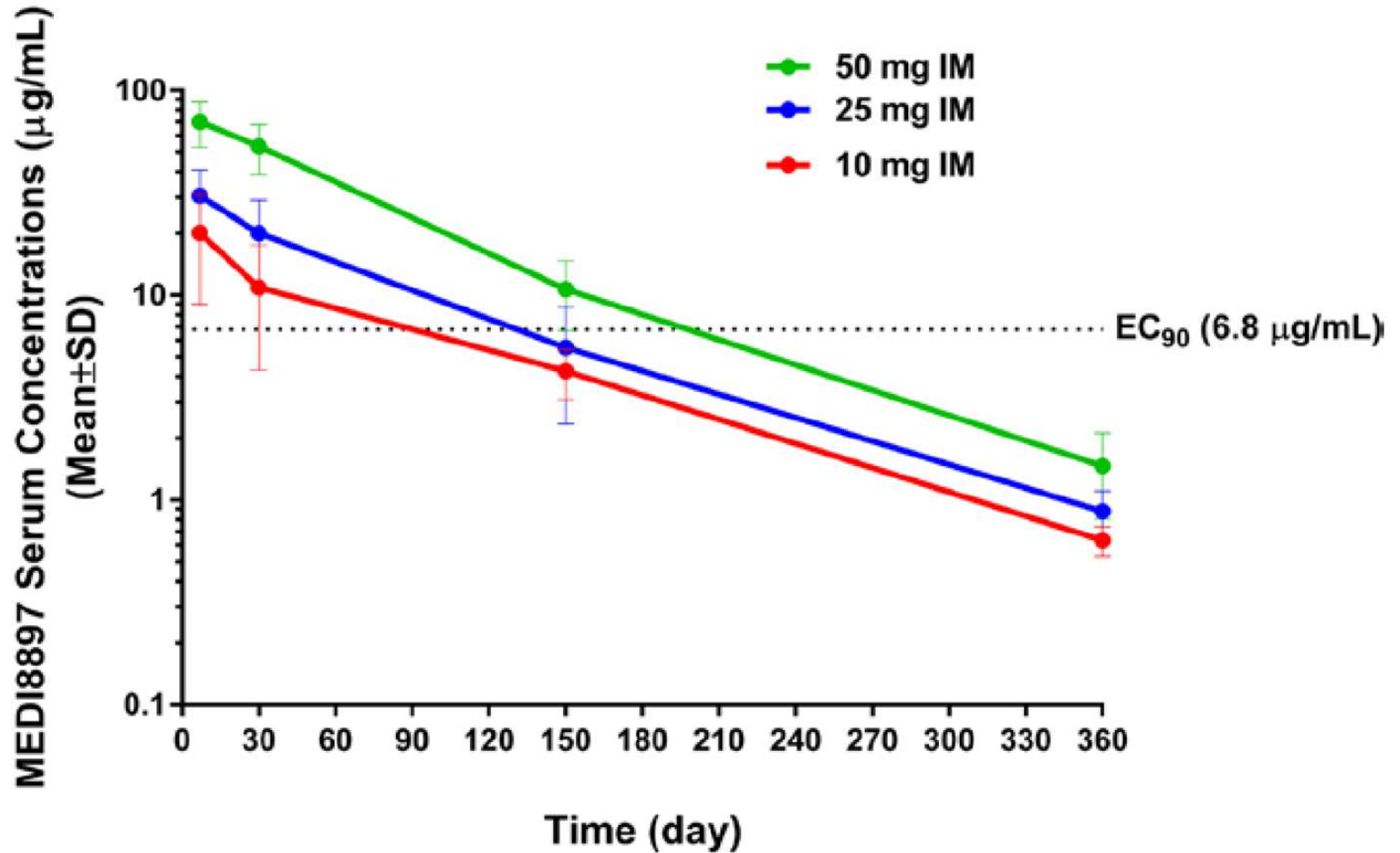
Palivizumab



Nirsevimab
MK-1645

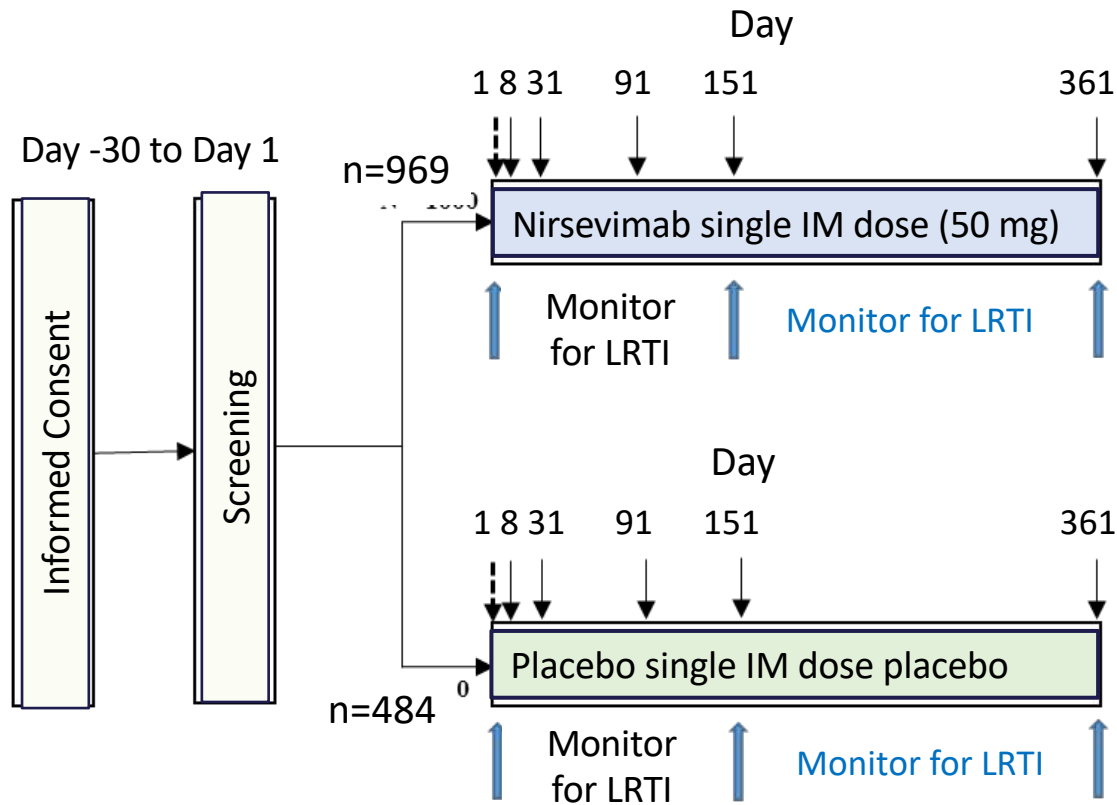


Nirsevimab serum concentrations time-profiles



Single dose Nirsevimab for Prevention of RSV in Preterm Infants

- Randomized, Phase-2b double-blind, placebo-controlled study to evaluate the safety and efficacy of Nirsevimab in **1453 preterm infants** 29 – 35 weeks GA (Synagis-ineligible)



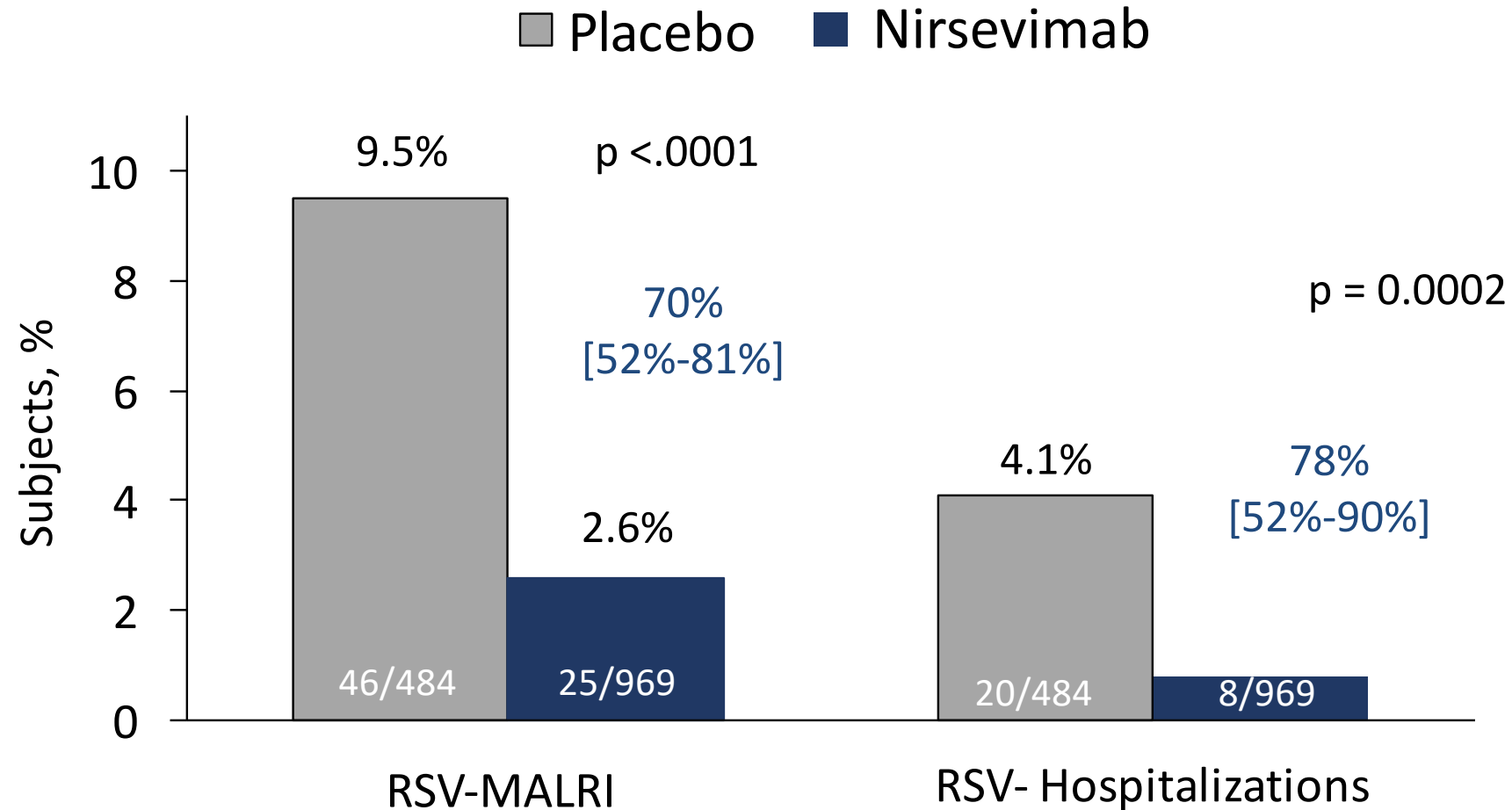
- **Primary endpoint**

- Incidence of **medically attended LRTI** (inpatient and outpatient) caused by PCR confirmed RSV for 150 days after dosing

- **Secondary and exploratory endpoints**

- Incidence of **hospitalizations** due to PCR-confirmed RSV for 150 days after dosing
- Safety, PK, and ADA
- Healthcare utilization and caregiver burden

Nirsevimab for prevention of RSV in preterm infants

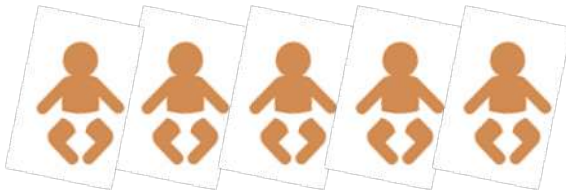
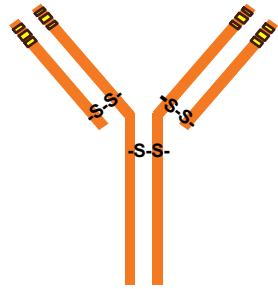


Relative risk reduction; 95% CI

Griffin P, N Engl J Med 2020

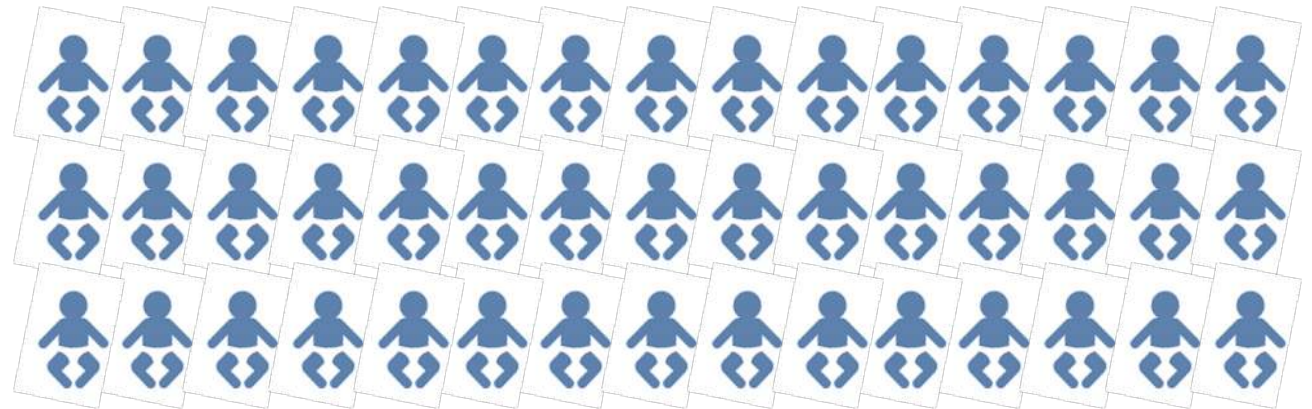
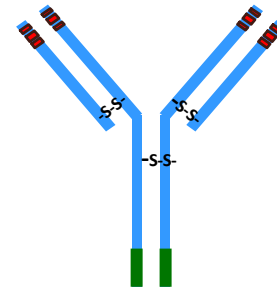
Reinventing the role of mAbs for prevention of RSV

Palivizumab



MEDI8897

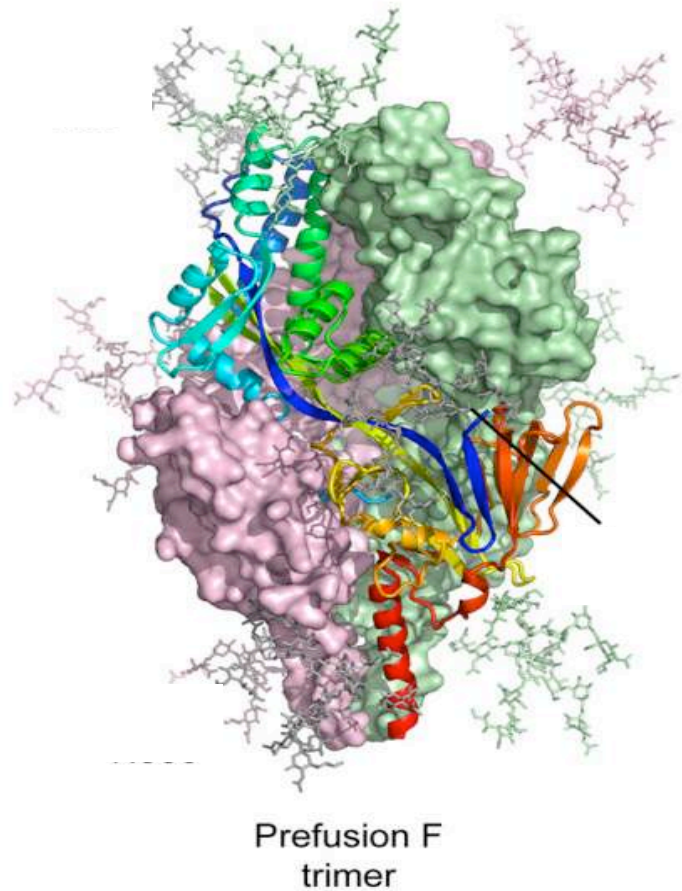
MK-1645



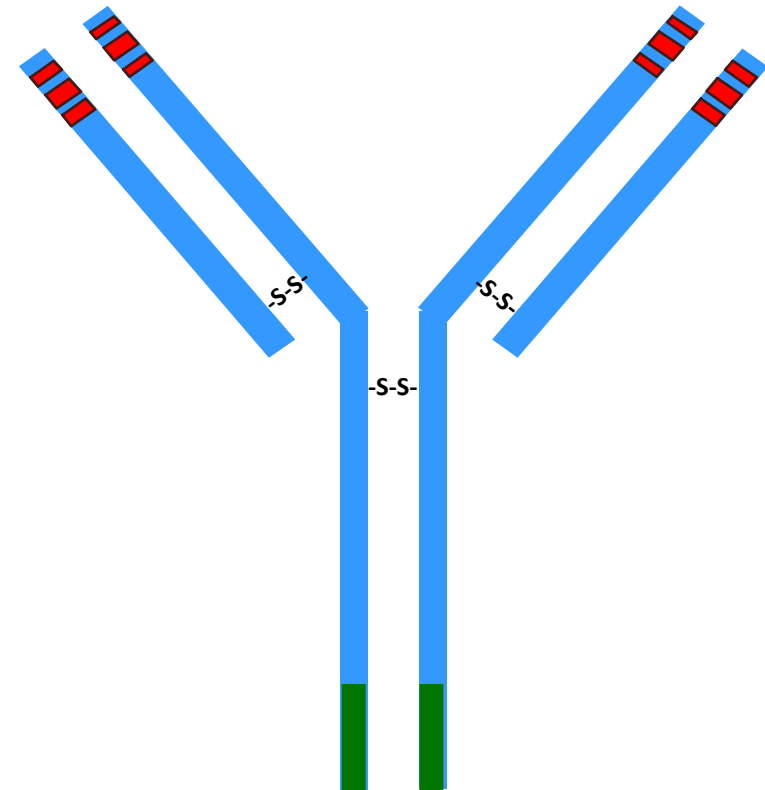
Summary

1. Young infants are at increased risk for severe RSV disease
2. Age and host response play major role in disease severity
3. RSV pre-F and G antibodies modulate disease severity
4. Infants demonstrate limited antibody responses to RSV
5. Interferon responses are inadequate in early life
6. Passive immunization best approach to prevent severe RSV infection

Two major strategies for passive immunization against RSV



and



Maternal vaccines (PreF)

Extended half-life mAbs

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