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Clinical Considerations of RSV in infants from birth through 6 months of age

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Conflicts of Interest Declaration

I served on advisory boards for Abbvie, Merck, and Pfizer, and have previously consulted for Ellume.

I have previously received research funding and in-kind support from Cepheid, Ellume, and Gates Ventures.

I have given CME lectures for Vindico, Clinical Care Options, Medscape, and Cataylst.

Outline

- Characteristics of Maternal and Infant RSV infection
  - Risk of infant hospitalization by age
  - Risk of infant primary and repeated infection
  - Burden of disease in pregnant persons
- Transplacental RSV antibody transfer and kinetics
  - Antibody half-life and duration of protection
  - Impact of gestational age and other factors
- Other considerations
  - Breast milk antibody
  - Use in conjunction with nirsevimab
  - Concomitant administration with Tdap

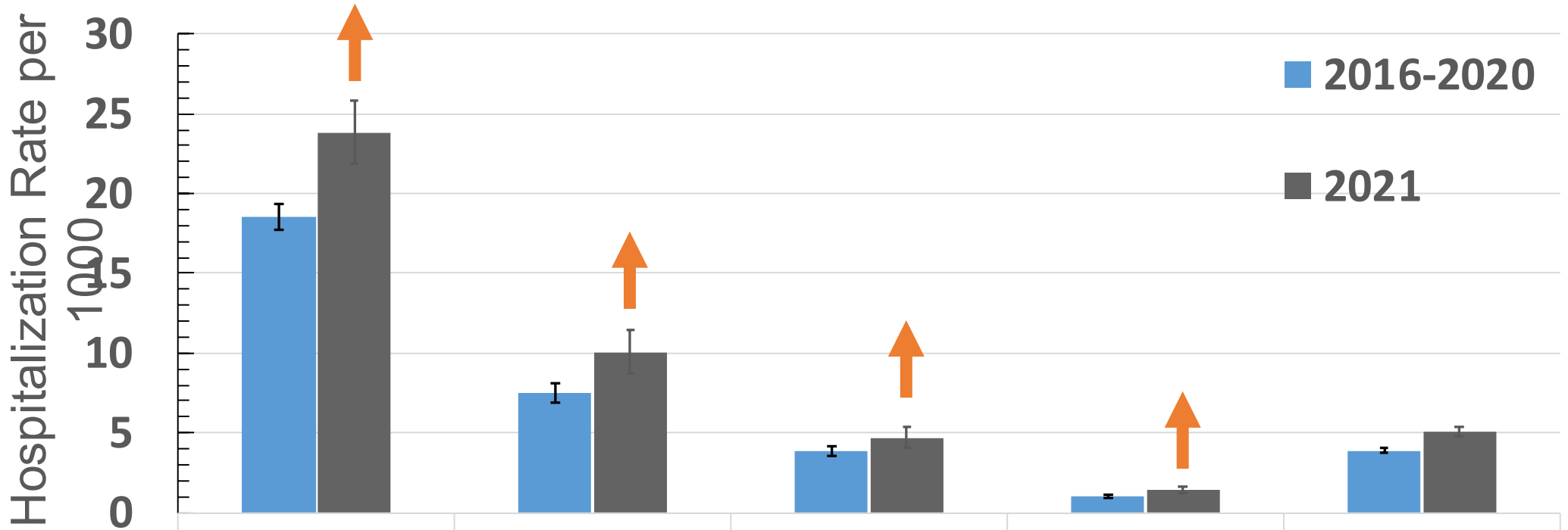
RSV causes bronchiolitis and pneumonia and is the #1 cause of hospitalization for infants in the US

- Nearly all children infected by 3 years of age, repeated infections through lifetime indicating lack of sterilizing immunity
- Impacts on school and work absenteeism is significant among children < age 3
  - Mean duration of illness: 13 days
  - Parents missed ≥1 day of work in 52% of cases; mean duration of 2.6 days
- Supportive treatment only, with no RSV-specific treatments licensed for use
- Palivizumab provides proof-of-concept for the protective effect of antibody directed against F protein

https://www.cdc.gov/rsv/high-risk/infants-young-children.html May 13, 2023

Suh, JID 2022, Heikkinen, JID 2017

Infant risk of RSV infection highest in < 6 months and decreases with age; however, risk of hospitalization still high in older ages



	0-5 months	6-11 months	12-23 months	24-59 months	0-59 months
2016-2020	18.5	7.5	3.9	1.0	3.9
2021	23.8	10.0	4.7	1.4	5.1

Slides courtesy of Meredith McMorrow

Risk of reinfection is high in a birth cohort of children followed over several years

Risk of Reinfection With Respiratory Syncytial Virus for Children Followed up From Birth*

Age, mo	No. With Prior Infection	No. (Rate/100 Child-Years) Reinfected	No. (Rate/100 Child-Years) With LRD
13-24	58	44 (75.9)	11 (19.0)
25-36	64	29 (45.3)	7 (10.9)
37-48	39	13 (33.3)	3 (7.7)
49-60	24	12 (50.0)	0 (0)
Total	185	98 (53.0)	21 (11.4)

*Among those followed for at least 36 months

Glezen, AJDC 1986;140:543-546

Higher cord blood RSV neutralizing antibody delays disease in infants

Higher levels of RSV neutralizing antibody are important in prevention of disease in young infants

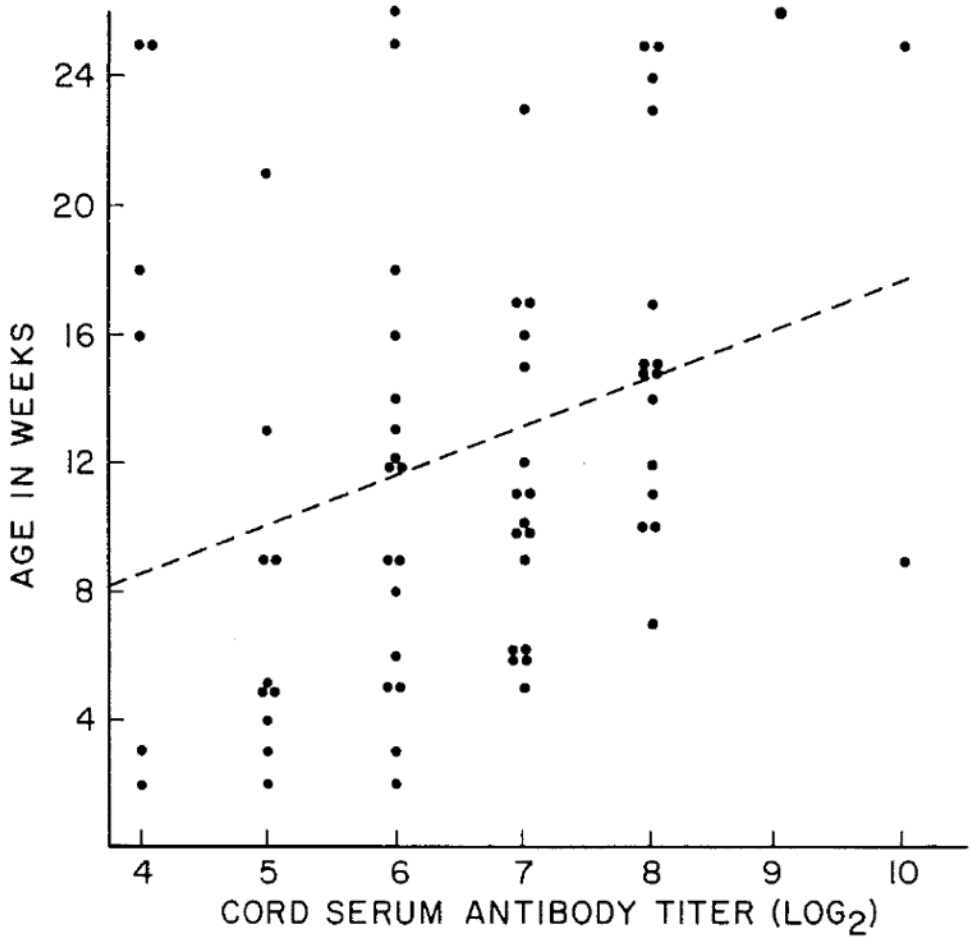


Fig. 2. Correlation between the level of maternal antibody at birth and age at the time of culture-proven infection with respiratory syncytial virus for infants less than 6 months of age ($r = 0.306$, $P < 0.05$).

Glezen J Pediatrics 1981

Higher levels of neutralizing antibody protective against repeated infection, in particular lower respiratory tract disease

Risk of Reinfection With Respiratory Syncytial Virus Related to Preexisting Neutralizing Antibody Titer*			
Log_2 RSV neut ab titer (Reciprocal)	No. of children	No. (Rate/100 Child-Years) Reinfected	No. (Rate/100 Child-Years) with LRD
≤ 8	46	38 (82.6)	10 (21.7)
16-64	60	32 (53.3)	6 (10.0)
≥ 128	17	2 (11.8)	0 (0)
Total	123	72 (58.5)	16 (13.0)

Glezen, AJDC 1986;140:543-546

RSV burden in pregnancy is low, across multiple populations

Study site	Symptom criteria	Timing	Type of testing	Prevalence
Nepal	Fever + resp symptoms in community	Year-round	RT-PCR	7/3693 (0.2%)
Mongolia	Influenza-like illness	Flu season	Antigen	4/1260 (0.3%)
South Africa	Resp illness +/- fever	Flu season	RT-PCR	HIV+:3/194 (2%) HIV-:18/2116 (1%)
Houston, TX	Resp illness +/- fever presenting for care	Oct-May	RT-PCR	8/81 (10%) of acute respiratory illness

Chu, PLoS ONE, 2016 ;Chaw, PLoS ONE, 2016 ;Nunes CID 2018; Hause, JID 2018

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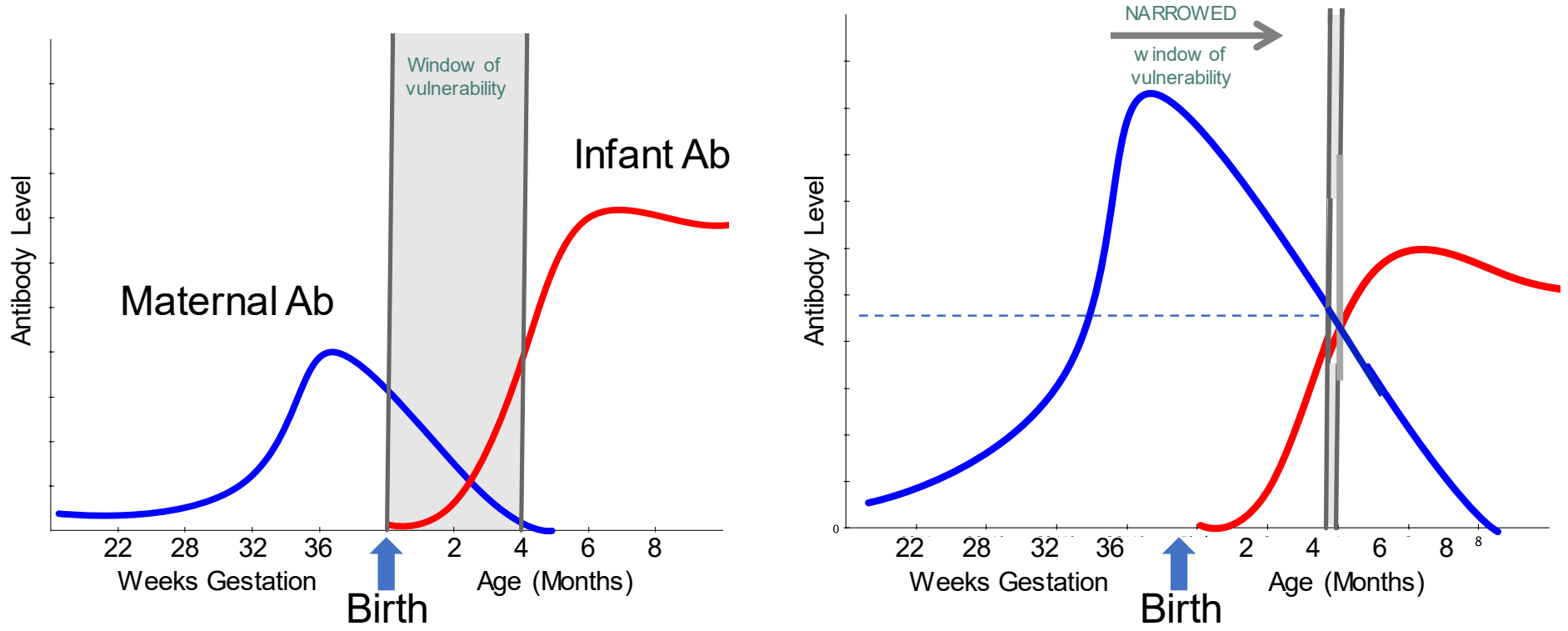
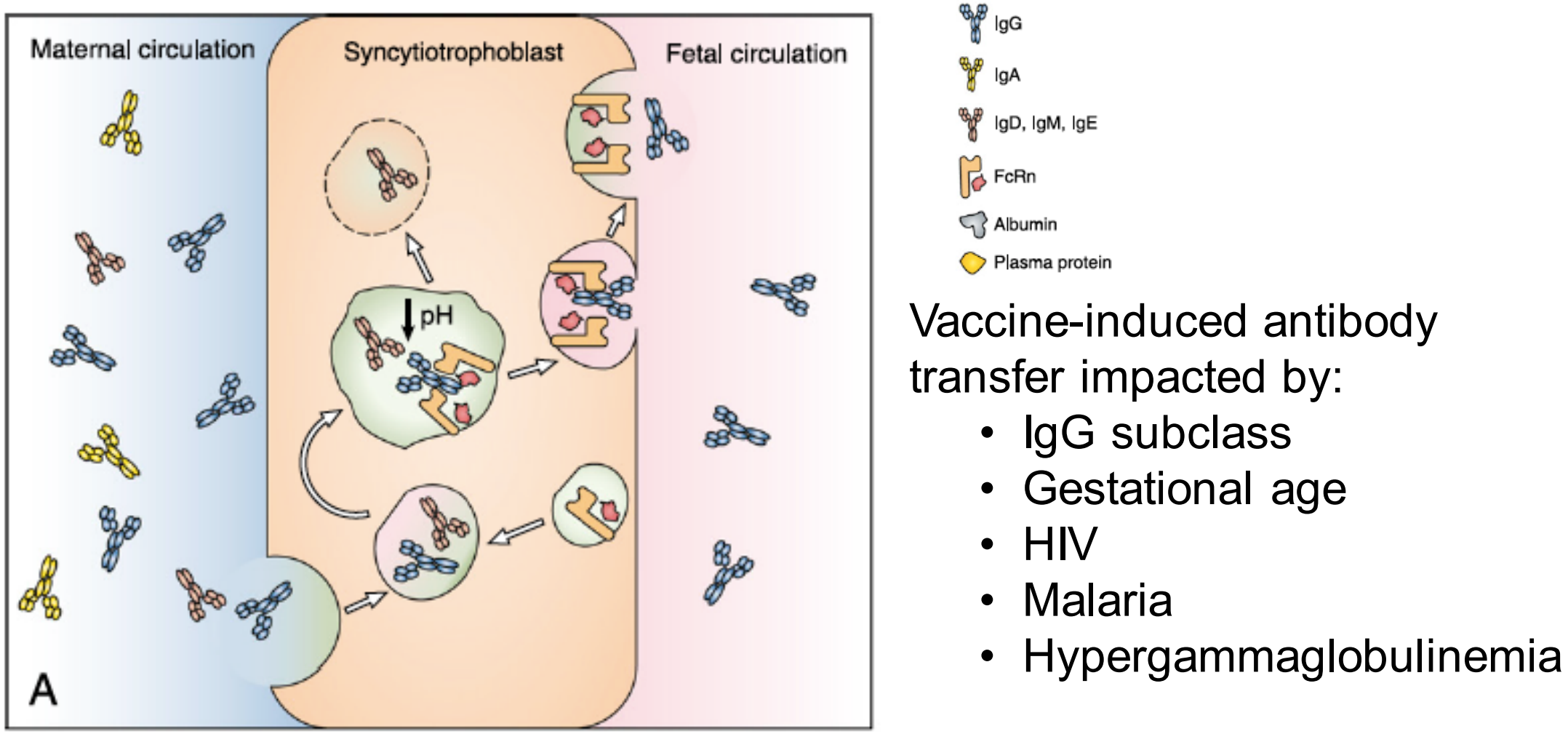
Vaccines given during pregnancy increase maternal antibody titers and lead to transplacental antibody transfer



Maternal vaccine → (2 weeks) → Maternal Antibody → Transplacental transfer

Courtesy of Linda Eckert

Multiple factors impact transplacental antibody transfer



Vaccine-induced antibody transfer impacted by:

- IgG subclass
- Gestational age
- HIV
- Malaria
- Hypergammaglobulinemia

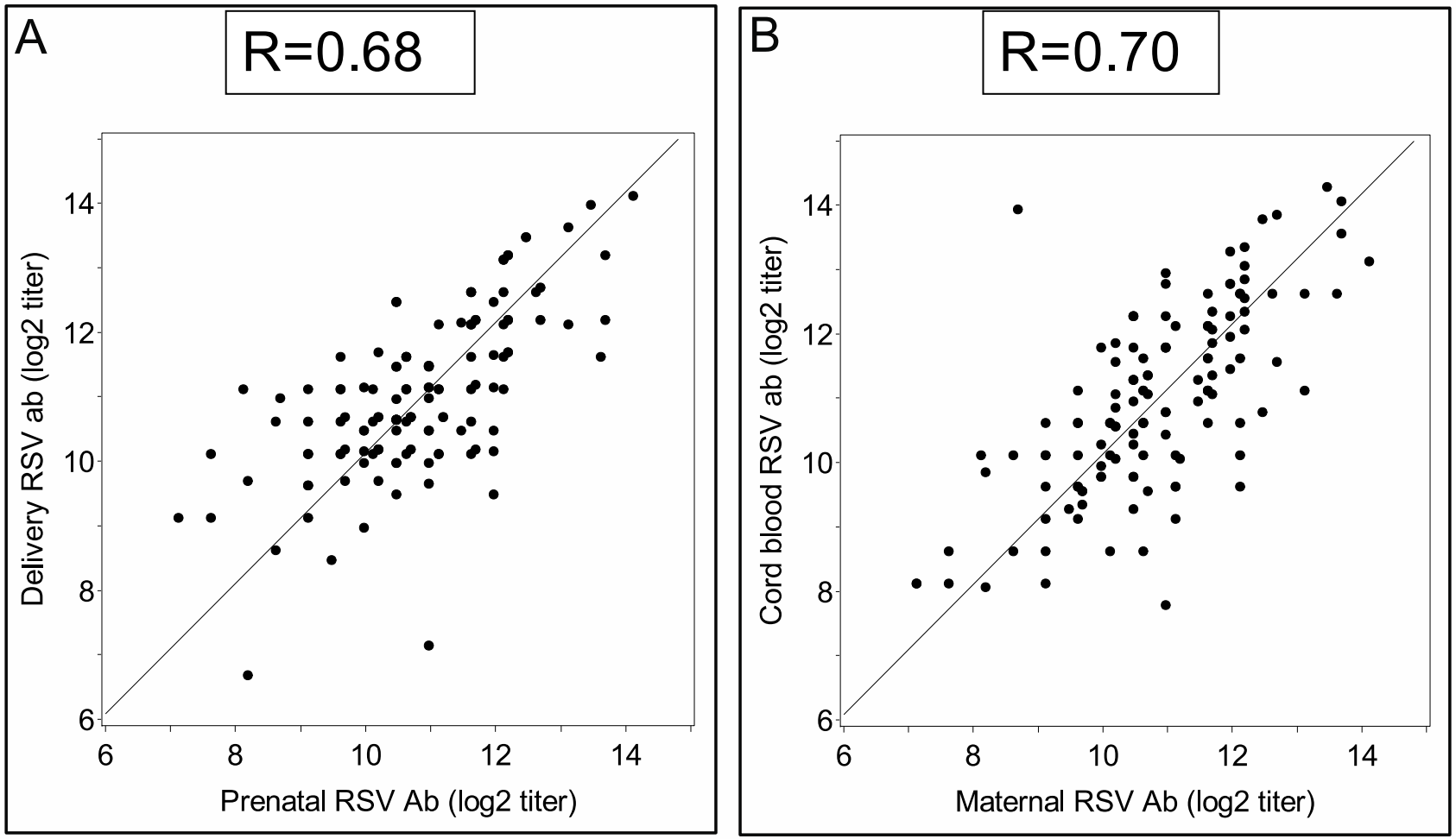
RSV transplacental antibody transfer in Bangladesh

- 149 mother-infant pairs
- Tested for RSV ab

- Maternal RSV Ab titers highly correlated with cord blood Ab titers
- Antibody half-life = 38 days
- ↑ Cord blood RSV Ab's → ↓ infant RSV infection
  ↑ infant RSV Ab level
  → Protective Threshold

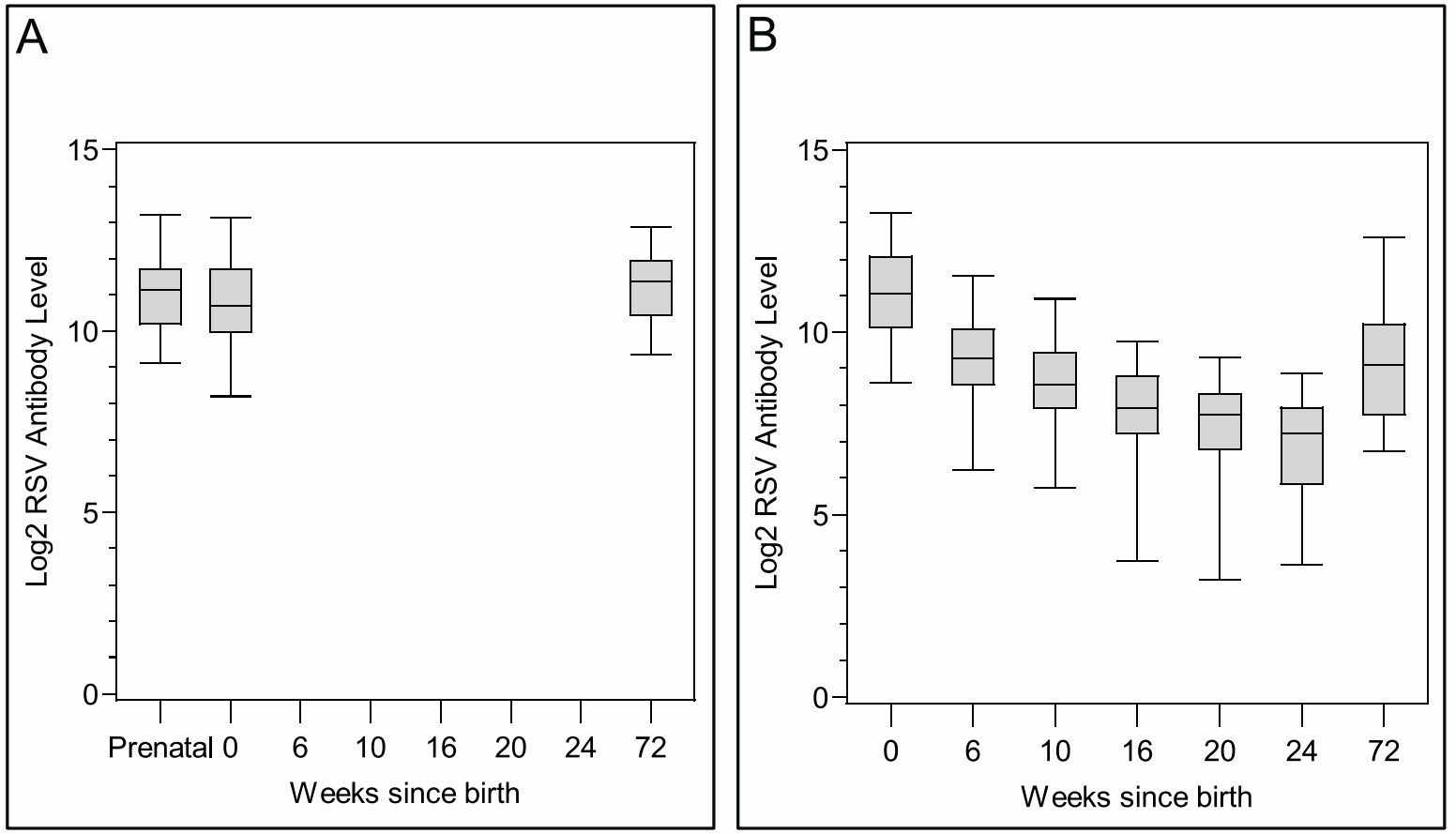
Chu et al. JID 2014.

Antibody titers are stable across pregnancy, and transfers efficiently at time of delivery



Chu, JID 2014

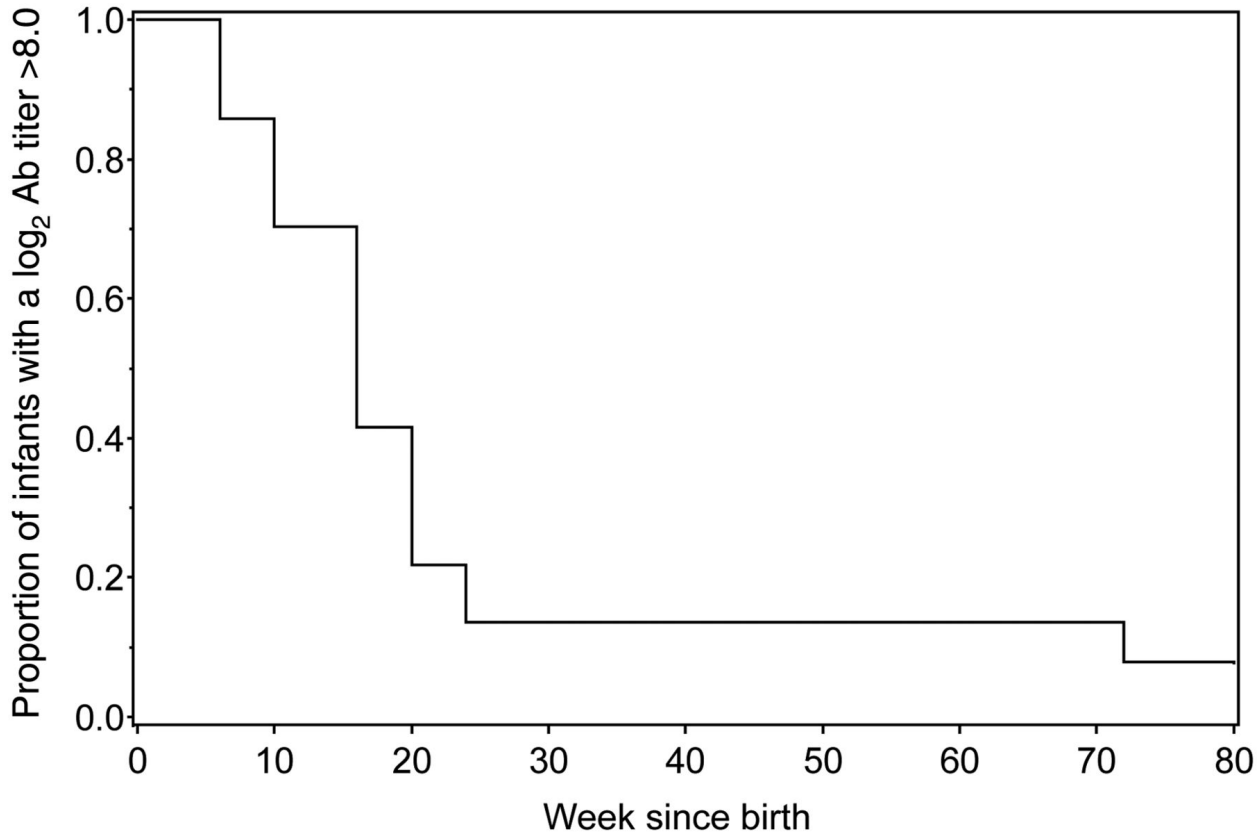
Antibody stays stable throughout pregnancy, and declines in infants in the first 4-6 months after birth



Maternal

Infant

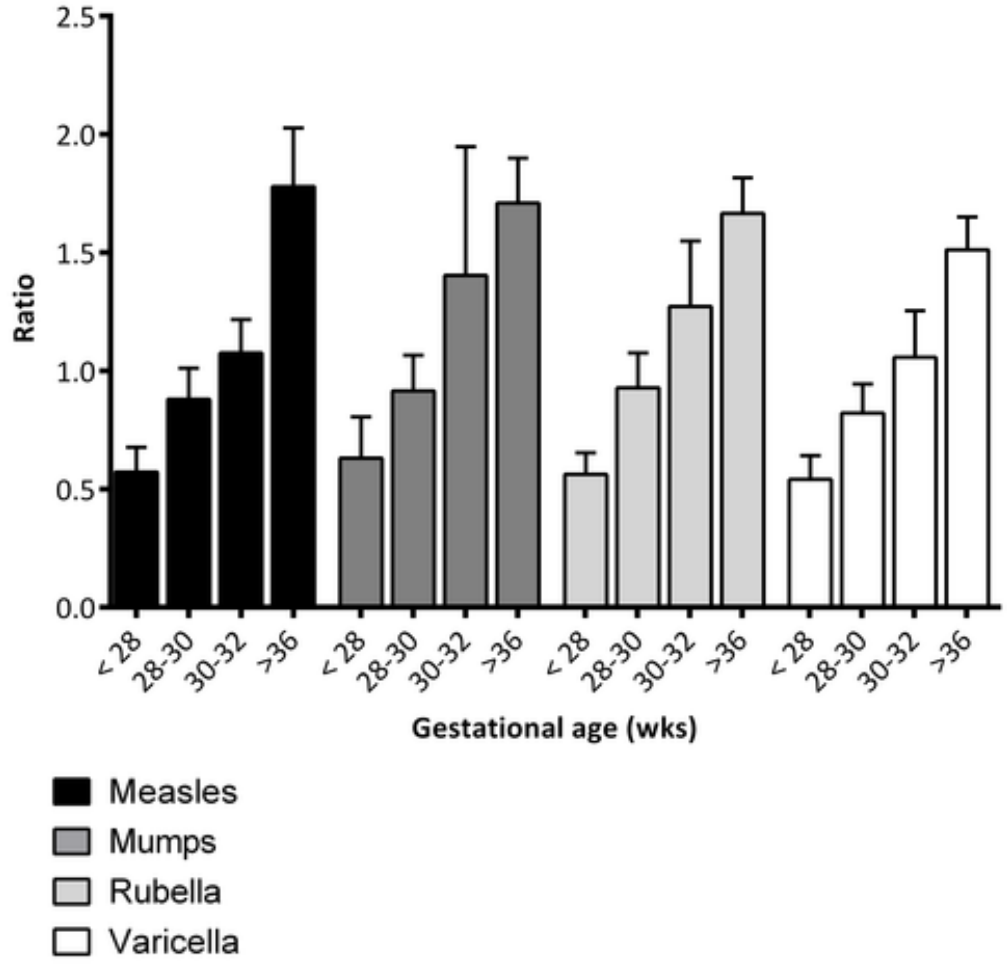
The median time for RSV antibody to drop below a potential protective titer of $\log_2$ 8.0 was 17 weeks (95% CI, 14–20 wks)



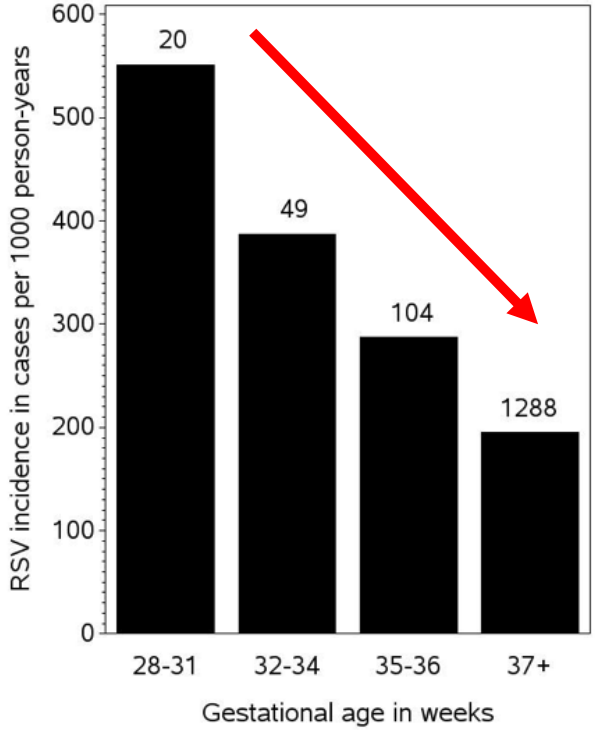
Chu, JID 2014

Transplacental antibody transfer increases with gestational age

Gestational age: 10% at beginning of 2nd trimester, 50% by end of 2nd trimester, & >100% by birth



Preterm infants at highest risk for severe RSV infection



van den Berg JP. PloS One 2014, Chu, J Infection, 2016

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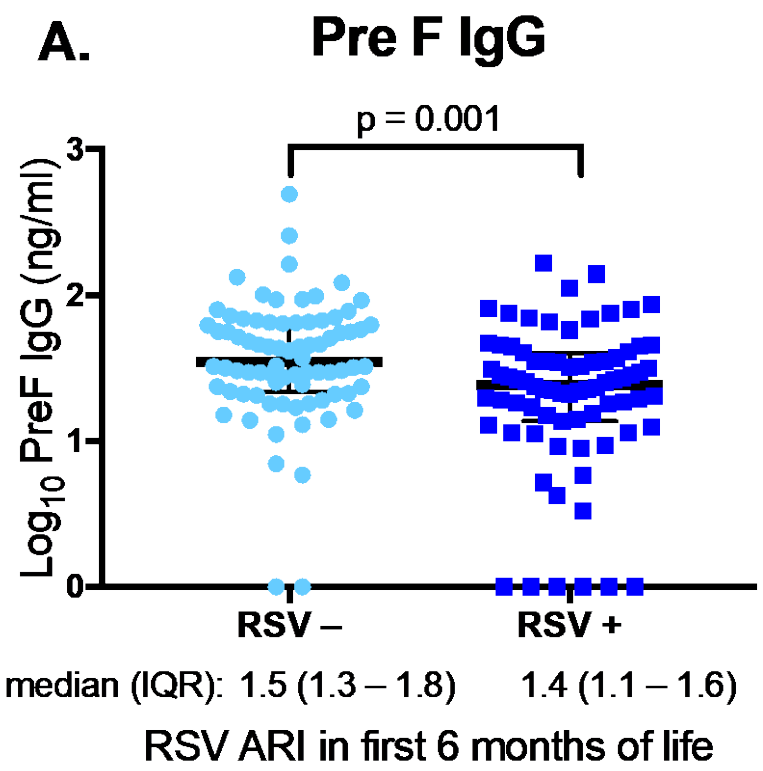
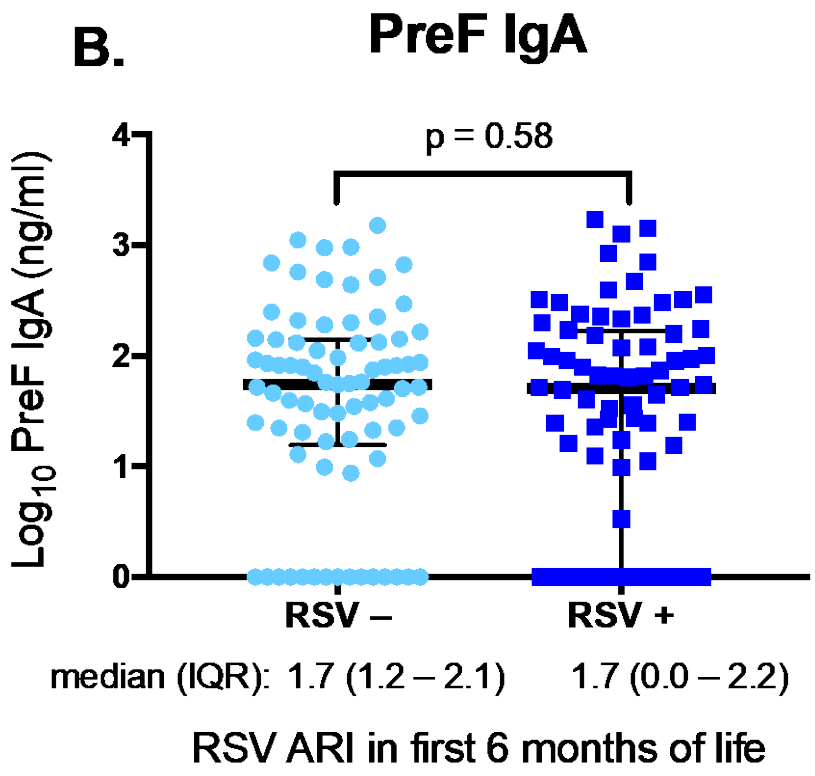
Higher levels of breast milk pre-fusion RSV antibody is associated with protection from RSV infection in infants





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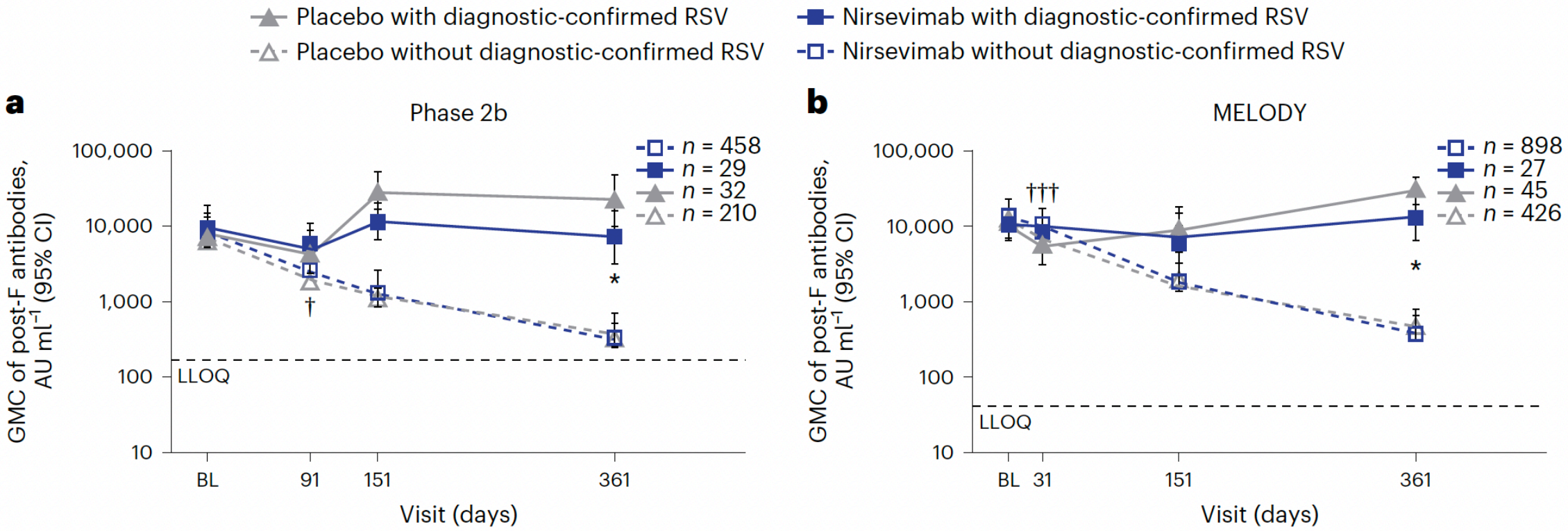
Laboratory of Translational Immunology

Mazur et al. JID 2018

Considerations with potential use in combination with birth dose monoclonal antibody

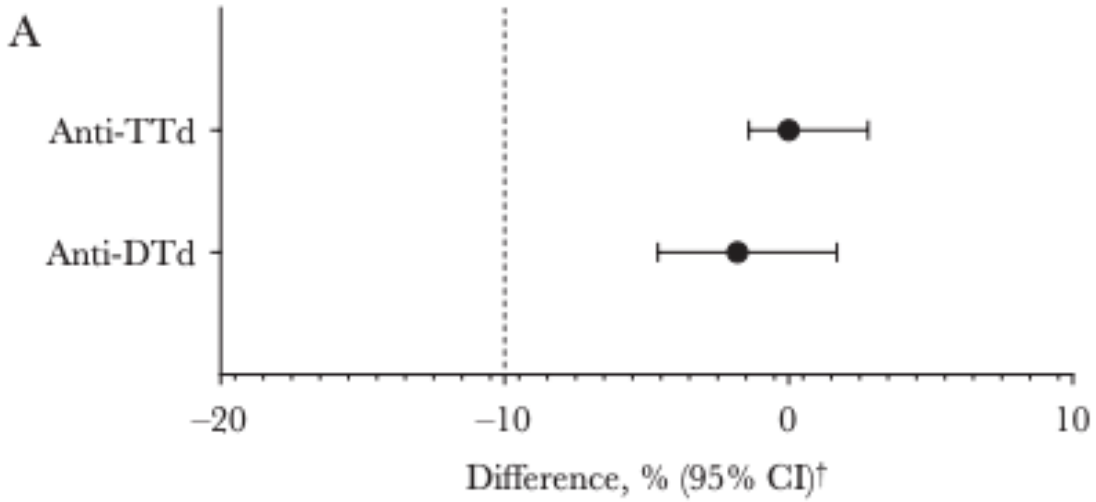
- Maternal antibody is estimated to last 3-4 months after birth
- Infants born preterm have lower levels of transplacentally-acquired antibody, and are more likely to benefit from a monoclonal antibody administered at birth
- No published data to show the effect of maternal RSV vaccine on birth dose monoclonal antibody titers, though would not expect interference from polyclonal response generated from vaccination

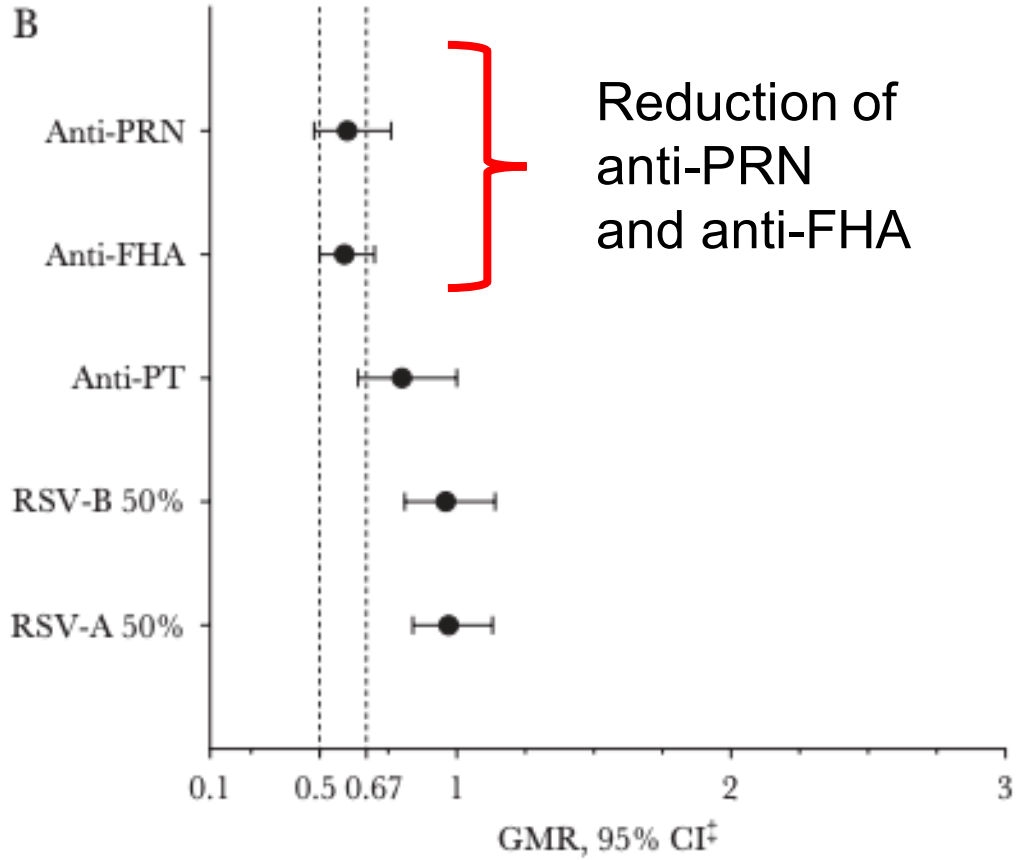
Infants are able to mount an antibody response to RSV infection in presence of nirsevimab



Wilkins, Nature Medicine 2023

Concomitant administration of RSV and Tdap vaccine demonstrates decreased immunogenicity of pertussis component of Tdap vaccine





Reduction of anti-PRN and anti-FHA

Peterson, JID 2022

Conclusions

- RSV causes severe disease in young infants, and repeated infections throughout childhood
- Serum RSV neutralizing antibody is protective against severe disease and repeated infections
- Maternal antibody transfers across the placenta, and is impacted by gestational age as well as other factors
- Durability of maternal antibody above potential protective threshold is estimated at 3-4 months
- Factors including concomitant administration with other maternal vaccines, as well as potential blunting of infant response to subsequent vaccines, need to be monitored over time

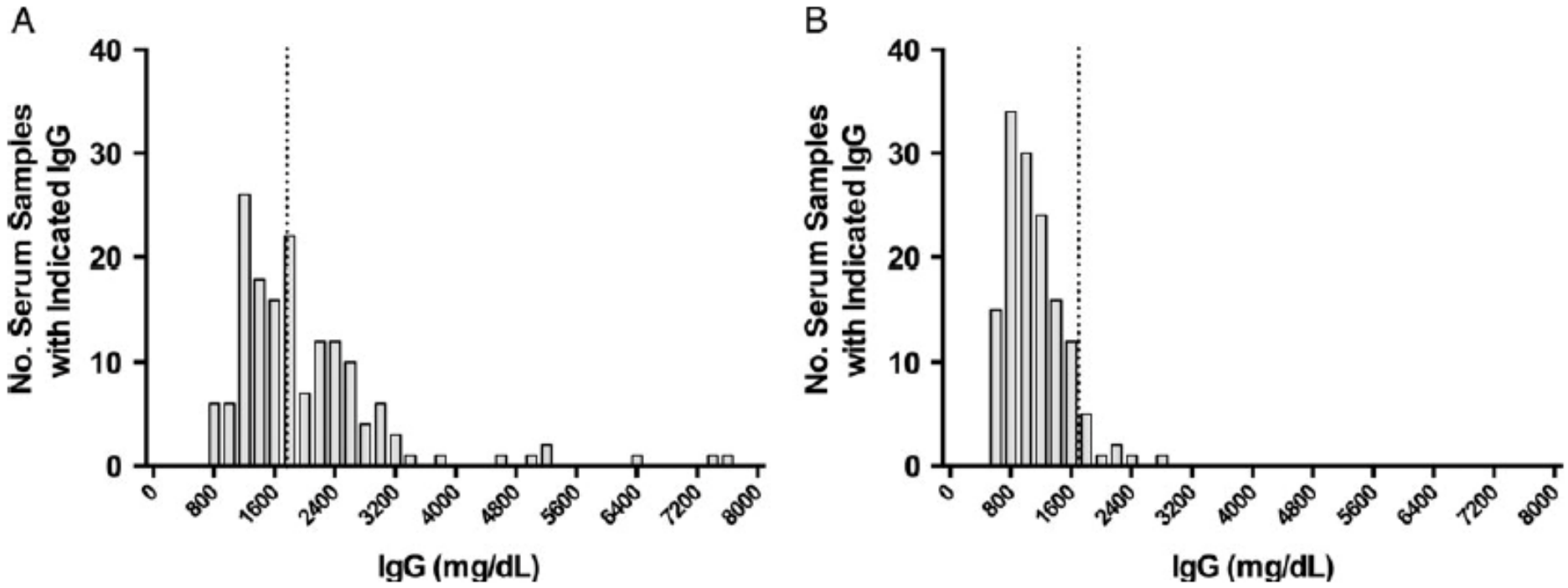
Interference with potential infant vaccine response seen with maternal vaccines

- Concerns regarding effect of maternal Tdap vaccine on interference of response to infant DTaP vaccine series
- RCT: Tdap immunization in pregnancy
  - At 7 mos (after 3 doses of DTaP), infants of mothers who were vaccinated with Tdap in pregnancy had:
  - Equivalent concentrations of antibodies to PRN
  - Lower concentrations to PT and FIM (32.8% and 40.6% lower, respectively, but not statistically significant)
  - Significantly lower concentrations to FHA (48.3% lower)
- At 13 months (after 4 doses of DTaP), differences resolved

- **<u>Currently no approved RSV vaccines in older infants</u>**

Munoz, JAMA 2014

Hypergammaglobulinemia impairs RSV antibody transfer



HYPERGAMMAGLOBULINEMIA ASSOCIATED WITH IMPAIRED RSV-SPECIFIC ANTIBODY TRANSFER

EFFECT GREATER IN THOSE WITH LOWER MATERNAL RSV ANTIBODY TITERS

Atwell, JID 2015

HIV-exposure in utero decreases transplacental antibody transfer

South Africa		
RSV cord:maternal ab ratio		P-value
HUU	0.82 (0.75-0.91)	0.112*
HEU	0.67 (0.61-0.72)	
Hypergam -	0.80 (0.74-0.86)	<0.001
Hypergam +	0.58 (0.52-0.65)	

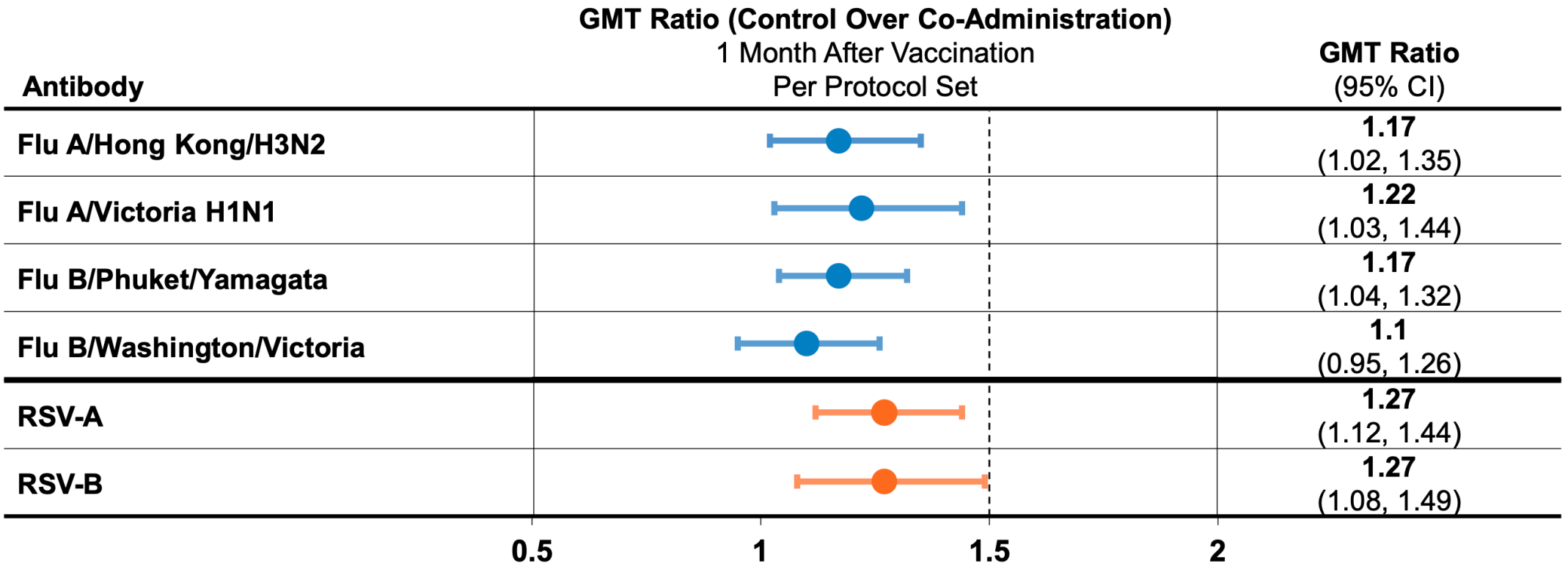
*Adjustment for hypergammaglobulinemia

Botswana		
RSV cord:maternal ab ratio		P-value
HUU	1.15 (1.03-1.27)	0.02
HEU	1.02 (0.93–1.12)	
HIV VL<400	1.06 (0.94–1.18)	0.01
HIV VL>400	0.55 (0.33–0.77)	
Birthweight >3000 g*	1.10 (0.97–1.23)	0.004
Birthweight <3000 g	0.94 (0.80–1.07)	

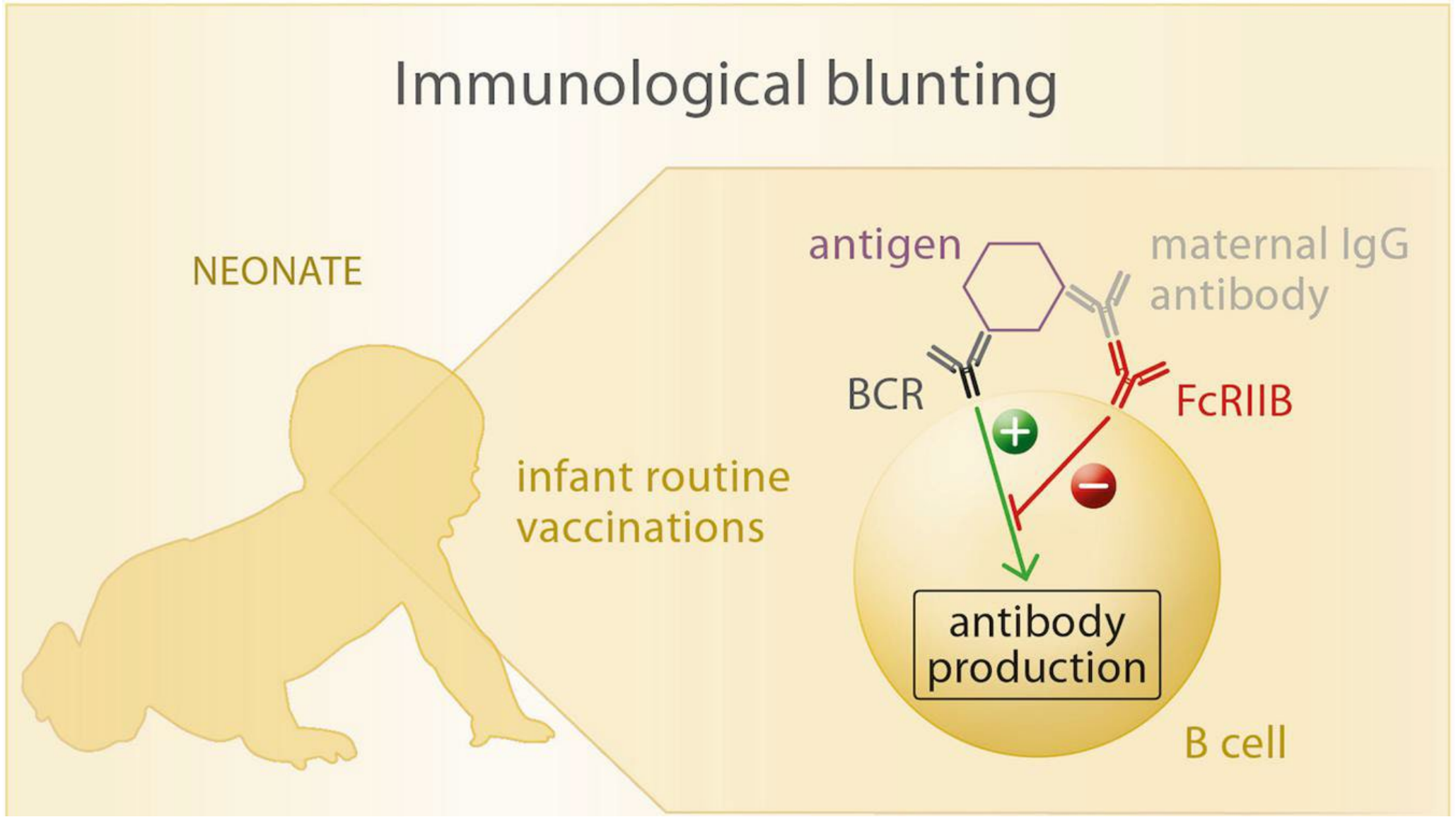
*As a proxy for gestational age, which was unavailable

Jallow, CID 2019; Patel, JPIDS 2020

Concomitant administration of flu and RSV vaccine shows non-inferiority to RSV vaccine alone in older adults



FDA Vaccines and Related Biologics Advisory Committee. RSVPreF3 vaccine for respiratory syncytial virus (RSV) in older adults. https://www.fda.gov/media/165649/download



Albrecht, Front Imm 2020