Optimizing the Timing of Maternal Influenza Vaccination

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Maternal Vaccination Policy (US)

- Advisory Committee on Immunization Practices (ACIP, CDC) recommends that pregnant women be vaccinated against:
  - Tetanus, Diphtheria, Pertussis (Tdap).
    - "Health-care personnel should administer a dose of Tdap during each pregnancy irrespective of the patient's prior history of receiving Tdap. To maximize the maternal antibody response and passive antibody transfer to the infant, **optimal timing for Tdap administration is between 27 and 36 weeks of gestation** although Tdap may be given at any time during pregnancy."
  - Influenza (TIV)
    - "Pregnant and postpartum women are at higher risk for severe illness and complications from influenza than women who are not pregnant because of changes in the immune system, heart, and lungs during pregnancy.... Influenza vaccination can be administered at **any time during pregnancy**, before and during the influenza season. Women who are or will be pregnant during influenza season should receive IIV. "
  - Risk-benefit approach is recommended for other vaccines, but without specific guidance for timing.

CDC, updated Aug 2016

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Why Vaccinate Mothers?

- Infants are typically vaccinated with TIV at 6 months of age. Until then, infants rely on transferred IgG from the mother via the placenta. There is evidence that IgG transfer depends on:
  - **maternal levels** of total IgG and specific antibodies: infant levels are approximately maternal levels (i.e. “transfer efficiency”)
  - **gestational age**: majority of transfer in the last 4 weeks of pregnancy
  - placental integrity
  - IgG subclass: IgG1 > IgG4 > IgG3 > IgG2
  - nature of the antigen; thymus-dependent > other
- Both maternal levels and gestational age are time-dependent, suggesting that “any time during pregnancy” (TIV) may not be optimal.
- Experience with Tdap suggests that timing matters.

Palmeira 2012

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Causal Chain and Key Questions

- vaccination leads to maternal antibodies
  - What are the kinetics of antibodies in the mother?
  - Can we leverage information about humoral immunity to gain greater insight with limited antibody data?
- maternal levels of antibodies and gestational age impact infant levels at birth
  - Is there peak in maternal antibody levels and when?
  - If pre-term infants have lower antibody levels, can we adjust maternal immunization timing to better protect this population?
- antibody levels wane in infants after birth
  - What are the kinetics of antibodies in the infants?
  - Can we leverage information about antibody kinetics to gain greater insight with limited antibody data?
- waning antibody levels convey protection in infants
  - Outside the scope of this presentation, but the ultimate goal of these efforts.

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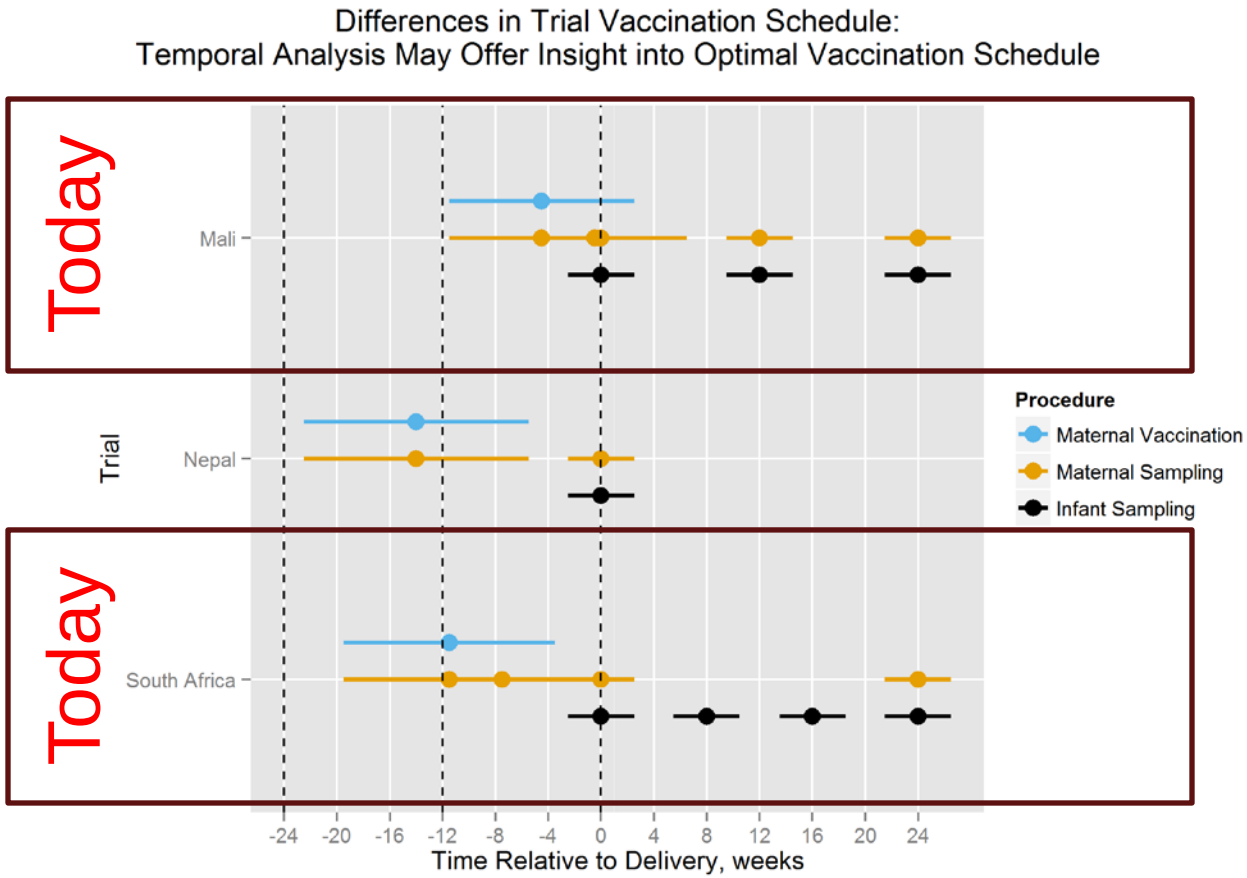
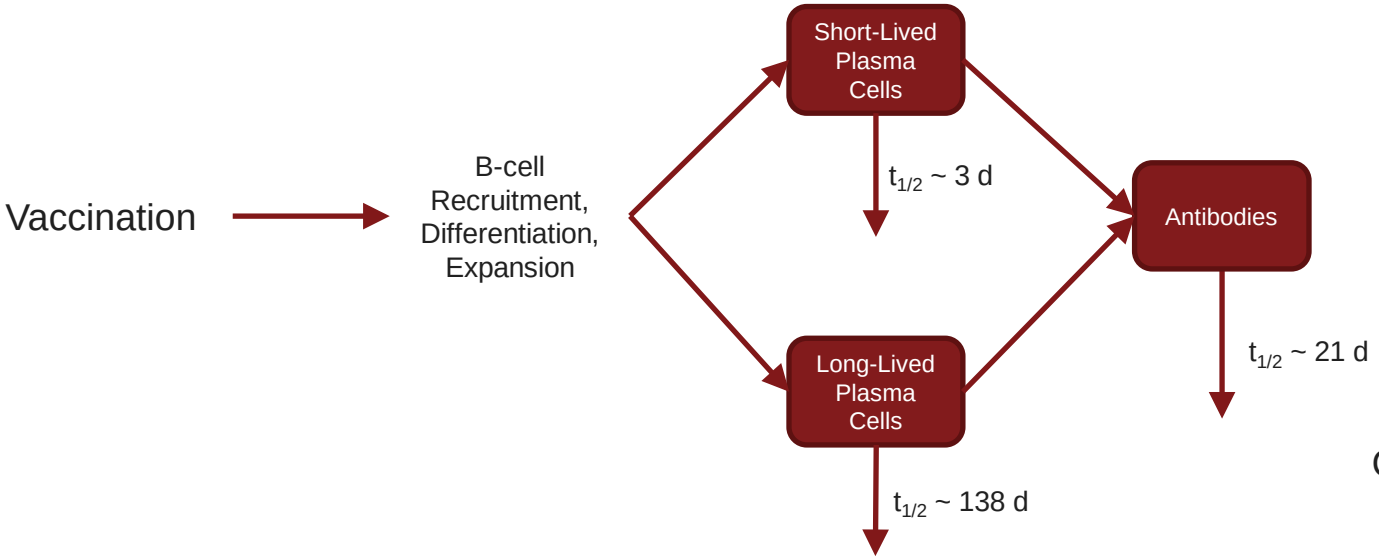
Maternal Influenza Immunization Working Group

- Each trial offers perturbation on vaccination time relative to delivery.
- **Can we leverage these data to determine optimal vaccination time?**



Maternal Antibody Generation after Vaccination

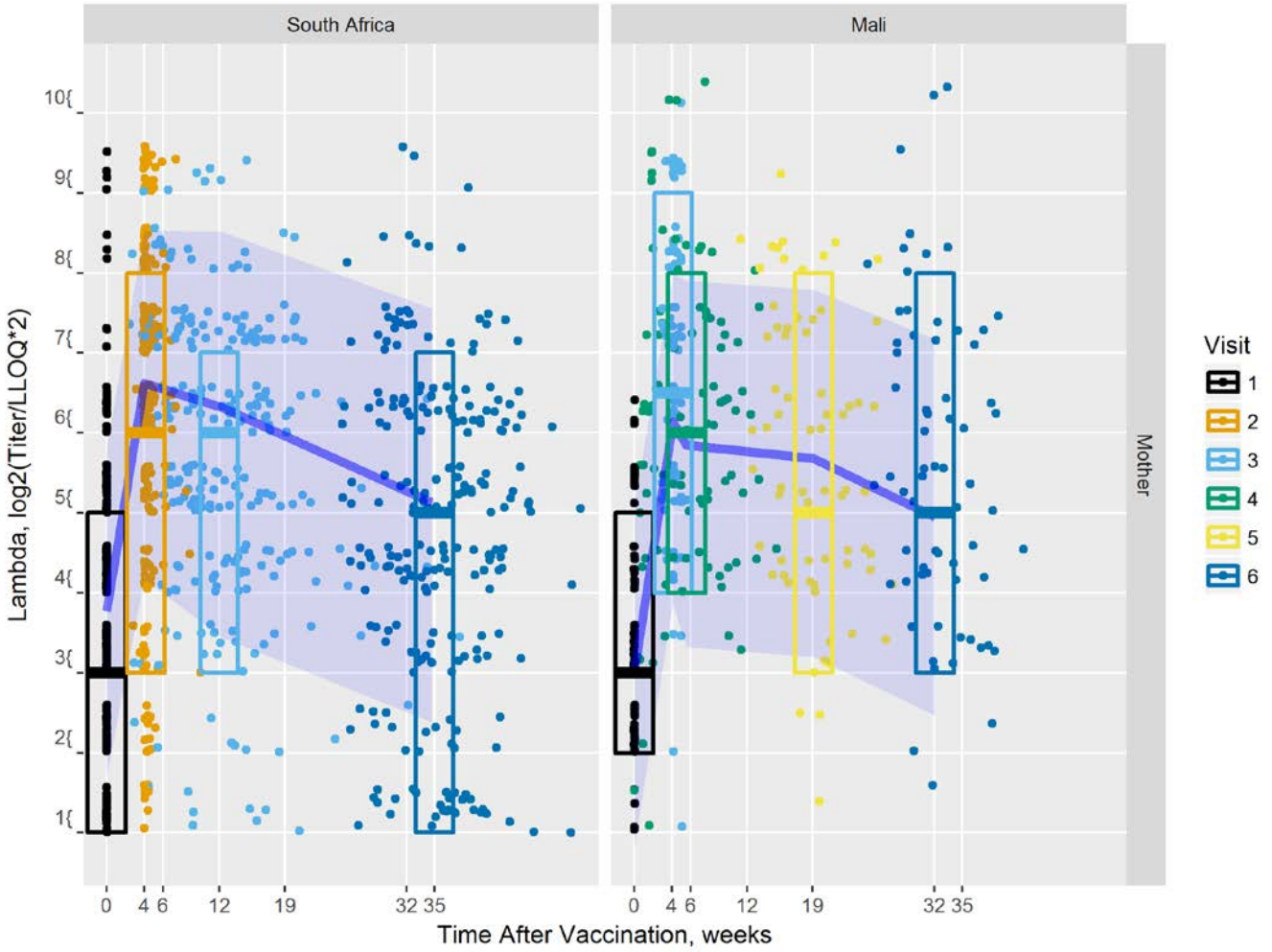
- Antibodies are produced by plasma cells
- Plasma cells require time for recruitment, differentiation, population expansion.
- Lumped, we have two populations of plasma cells:
  - short-lived: half-life of ca. 3 days.
  - long-lived: half-life of ca. 138 days. *Note*: *South Africa trial reported maternal antibody half-life at 90.8-142 days.*
- Once produced antibodies have a half-life of ca. 21 days (in adults).



Nunes 2015
Castiglione 2005
Slifka 1998
Davda 2014

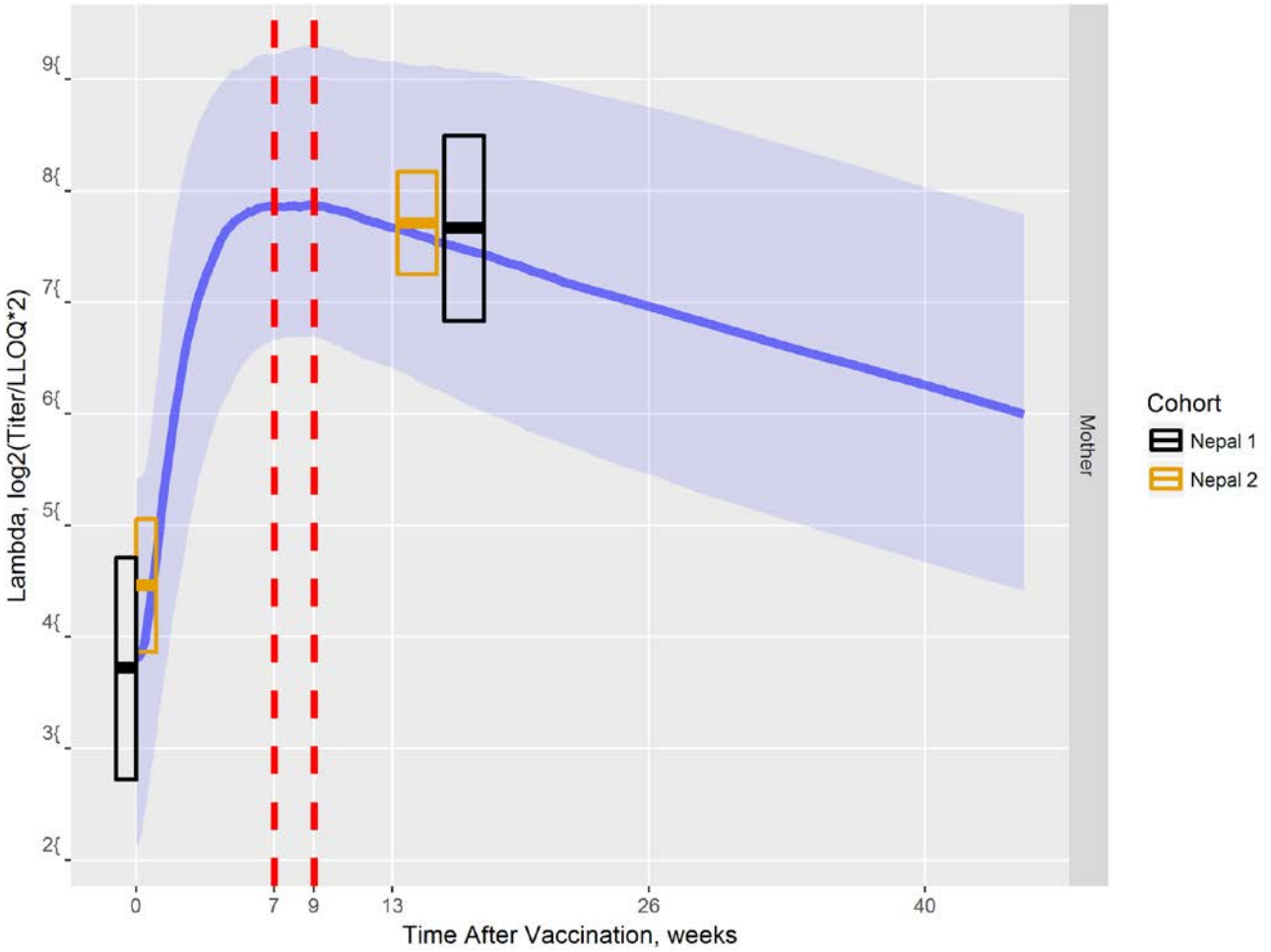
Fits to Maternal Antibody Data

- Model adequately captures baseline, rise and fall of maternal titer values.
- Mean transit time (MTT, “lag”) of plasma cell recruitment ~20 days.
- ~85% of the titer over one year is produced by the long-lived plasma cells.
- Covariate search ongoing



Time to Maximal Maternal Antibodies

- Simulation of maternal antibodies after vaccination
- Sharp rise after vaccination (plasma cells)
- Peaks around 8 weeks
- Slow decline after peak
- Comparison to the Nepal data set (reserved for model validation) appears reasonable



Comparison to Tdap Results

- ACIP recommends Tdap administration between 27 and 36 weeks of gestation
  - Eberhardt et.al. conducted a prospective study in 335 women immunized in second (n=122) or third trimester (n=213), and concluded that early second-trimester produced more infant titer
- Simulation of maternal TIV titers suggest the maximal titer is achieved 7-9 weeks (49-63 days) after vaccination, and closely matches the infant Tdap titer optimum reported by Eberhardt et.al.

Interval vaccination/delivery	Tdap Infant Anti-PT Titer		Tdap Infant Anti-FHV Titer		*TIV Maternal Titer*	
	Central	95% CI	Central	95% CI	*Central*	*90% CI*
<15 days	NR		NR		*4.7*	*(2.9-6.7)*
15-30 days	4.1	(2.8-5.9)	5.8	(4.2-8.0)	*7.0*	*(5.2-8.6)*
31-60 days	7.4	(4.7-1.8)	11.1	(7.3-16.7)	*7.8*	*(6.5-9.2)*
61-90 days	6.7	(4.2-10.5)	12.54	(8.4-18.8)	*7.8*	*(6.6-9.3)*
91-120 days	6.7	(4.5-9.8)	9.66	(6.8-13.7)	*7.6*	*(6.2-9.1)*
121-150 days	4.7	(2.9-7.6)	7.64	(5.0-11.7)	*7.3*	*(5.9-9.0)*
>151 days	6.0	(3.8-9.3)	8.15	(5.5-12.1)	*6.6*	*(5.0-8.4)*

Eberhardt 2016

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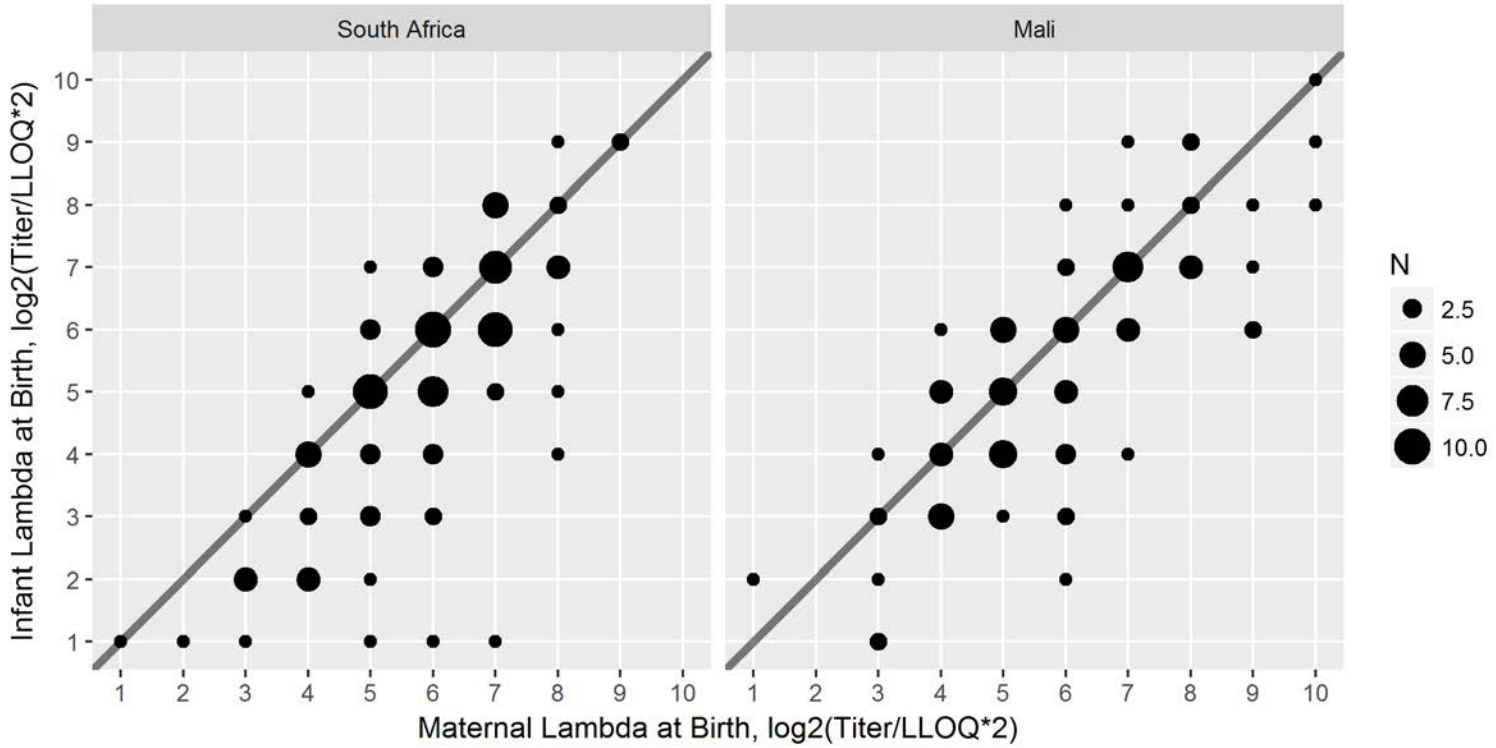
Infant:Maternal Antibody Ratios at Birth

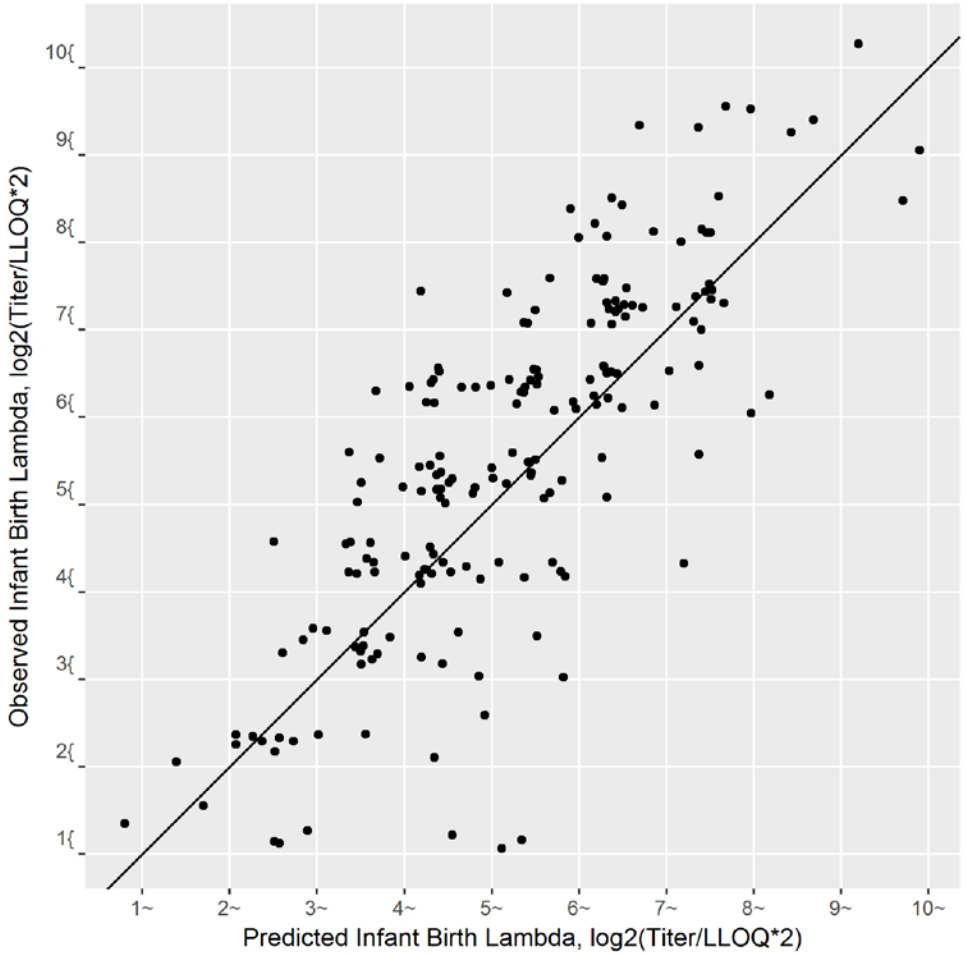
- Infant titer at birth correlated with maternal titer at birth (0.90-fold)
  - South Africa trial reported infant:mother ratio of 0.82 for HIV-uninfected cohort



Nunes 2015

Predicting Infant Antibodies at Birth

- Covariate search is ongoing, but preliminary results suggest that infant titer at birth correlated with
  - maternal titer at birth (0.90-fold)
    - South Africa trial reported infant:mother ratio of 0.82 for HIV-uninfected cohort
  - durability of maternal plasma cell response
  - amount of maternal short-lived plasma cell response



Infant Antibodies Wane After Birth

- popPK of palivizumab in adults and children were described by a 2-compartment model
- clearance in children was affected by:
  - body weight and gestational age + postnatal age (***novel***)
- For a full-term (40 wk) infant, CL **is 41.1% of expected CL based on body-weight alone**.
- popPK model from palivizumab adopted to describe waning antibodies in infants.

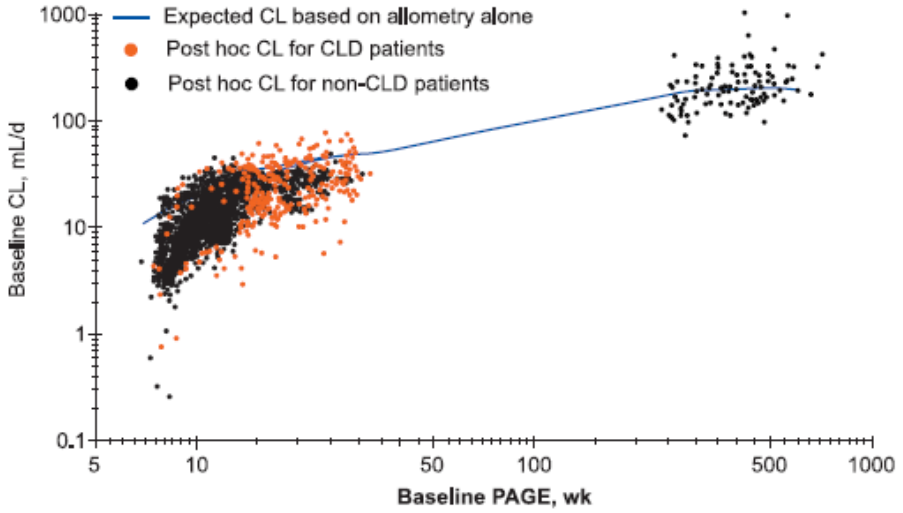
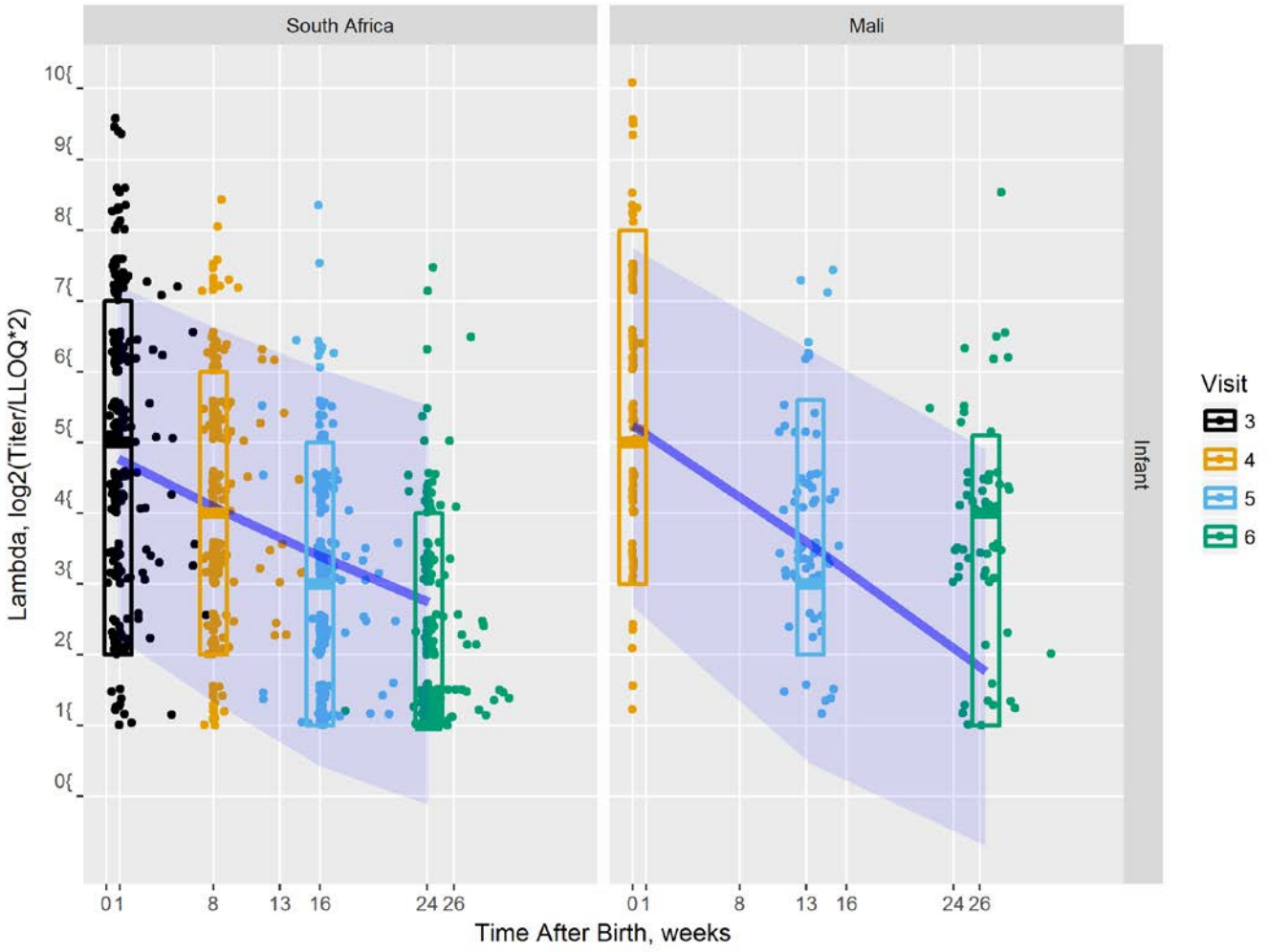


FIG 6 Comparison of *post hoc* clearance values in children compared with clearance values expected based on allometry alone.

Robbie 2012

Fits to Infant Antibody Data

- Without their own plasma cells, infant Ab kinetics follow first-order elimination, just as if we had injected a mAb at delivery.
- However, the half-life 40-50 days, not the ~21 days expected for an Ab (in an adult)
- Mali Week 26 data include infants with natural immunity (infection)



Nunes 2015
Davda 2014

Future Work – Linking Titer to Protection

- Collaborate with the Maternal Influenza Immunization Data Analysis Working Group to describe the relationship between titer and protection in infants.
- Model can be used to impute titer level in infants that had an influenza infection
- **Work backwards through the causal chain to understand how the timing of maternal immunization impact protection.**

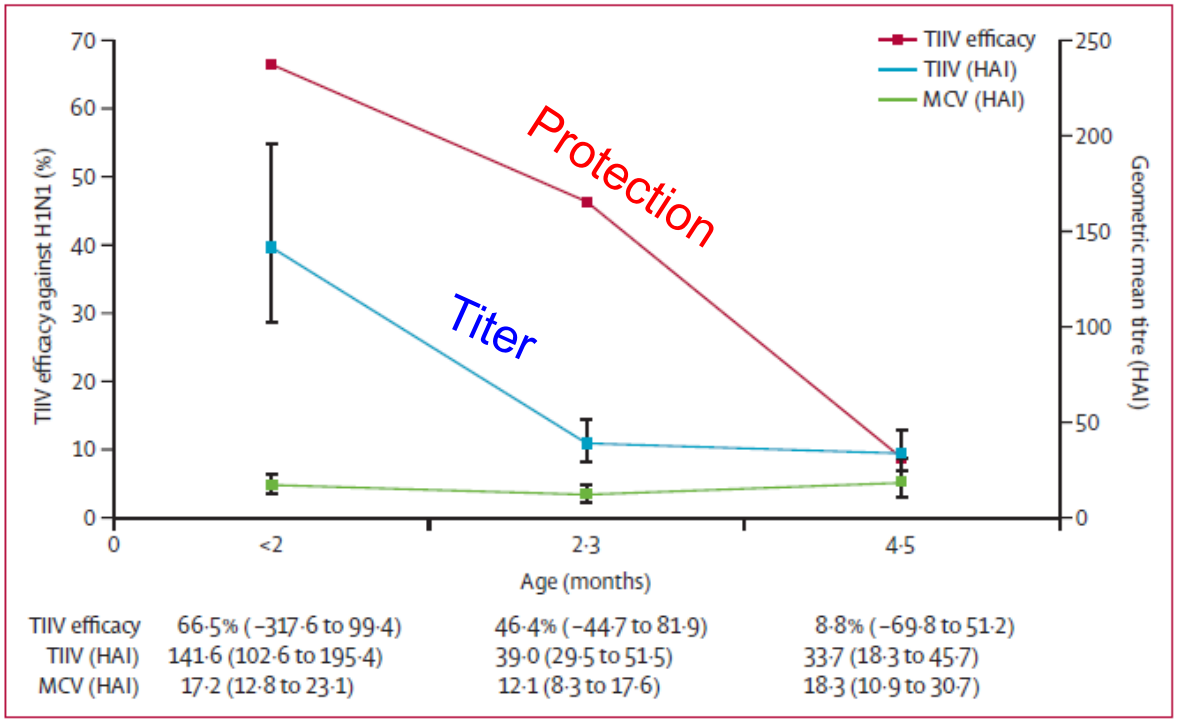


Figure 2: **Vaccine efficacy and HAI antibody geometric mean titres in infants, by age and maternal vaccine group**
Error bars and data in parentheses show 95% CIs.TIIV=trivalent inactivated influenza vaccine. MCV=quadrivalent meningococcal conjugate vaccine. HAI=hemagglutination inhibition antibodies.

Tapia 2016

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Summary of *Preliminary* Analysis

- Maternal IgG production follows from humoral immune response biology
  - Short- and long-lived plasma cells appear after a delay and generate an infusion of IgG
  - Maternal IgG kinetics are net of **+**) plasma cell production and **-**) IgG turn-over (common to IgG and mAbs)
- Infant levels at birth are highly associated with maternal levels
  - A deeper covariate search is required to elucidate effect of gestational age; we can't control gestational age at birth, but need to factor this in to our thinking.
- Infant levels wane after birth
  - Antibody kinetics similar to those observed for palivizumab, where increasing weight and post-natal+gestational age increase clearance.

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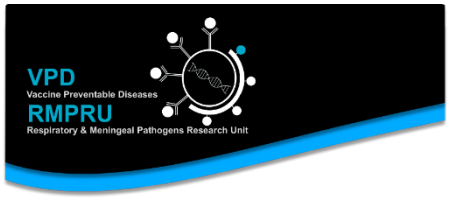

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