Early B cell responses following rotavirus vaccination and infection in Indian children

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Background

- The mechanism of immunological protection induced by infection or vaccination with Group A rotaviruses is not understood
- There is no defined correlate of protection at the level of the individual- serum rotavirus IgA is used as surrogate
- B cells are absolutely necessary for development of immunity
- This study describes the early B cell response in children following rotavirus vaccination or symptomatic infection in Indian children

Aim and Objectives of the study

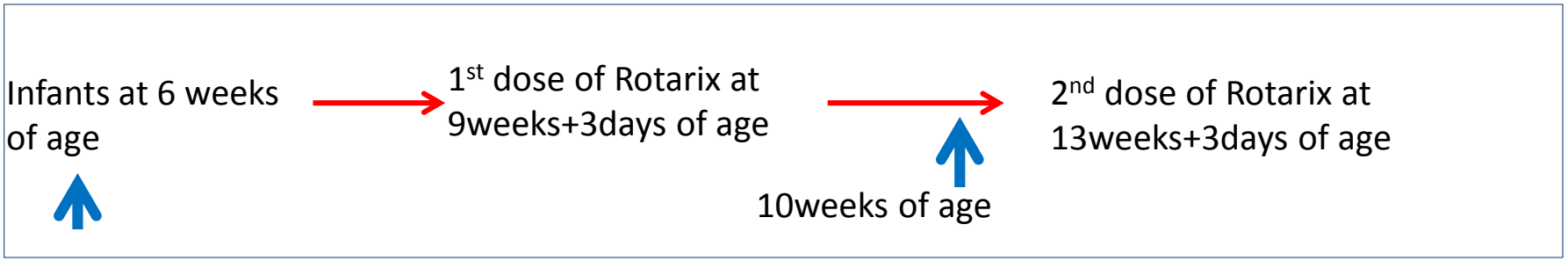
To study the antibody secreting cells (ASCs) and plasmablast response in infants following rotavirus vaccination or infection

- Define the early B cell responses post vaccination or infection
- To determine the effect of pre existing rotavirus exposure on this episode
    a. Defined by pre existing rotavirus IgA in the infection group
    b. Defined by rotavirus specific ASCs/pre existing rotavirus IgA pre vaccination in the vaccination cohort or post 2nd dose of vaccine

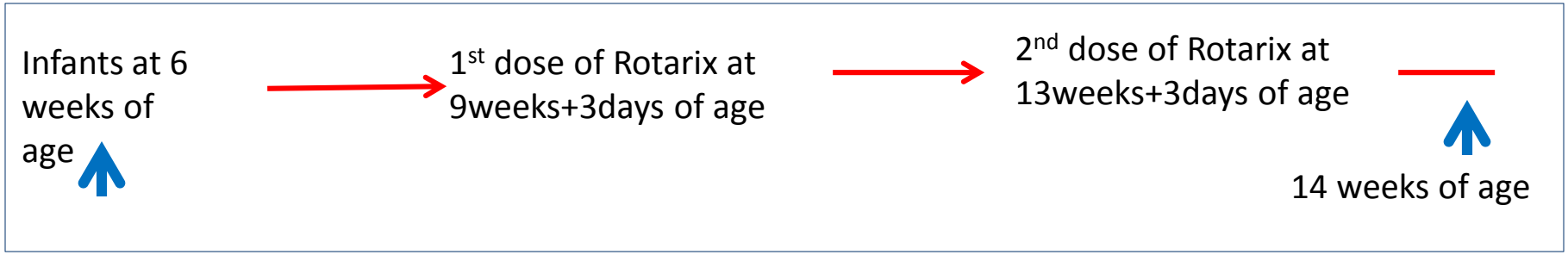
Study design

Vaccination Cohort

Primary response to vaccination n= 30



Secondary response to vaccination n= 30



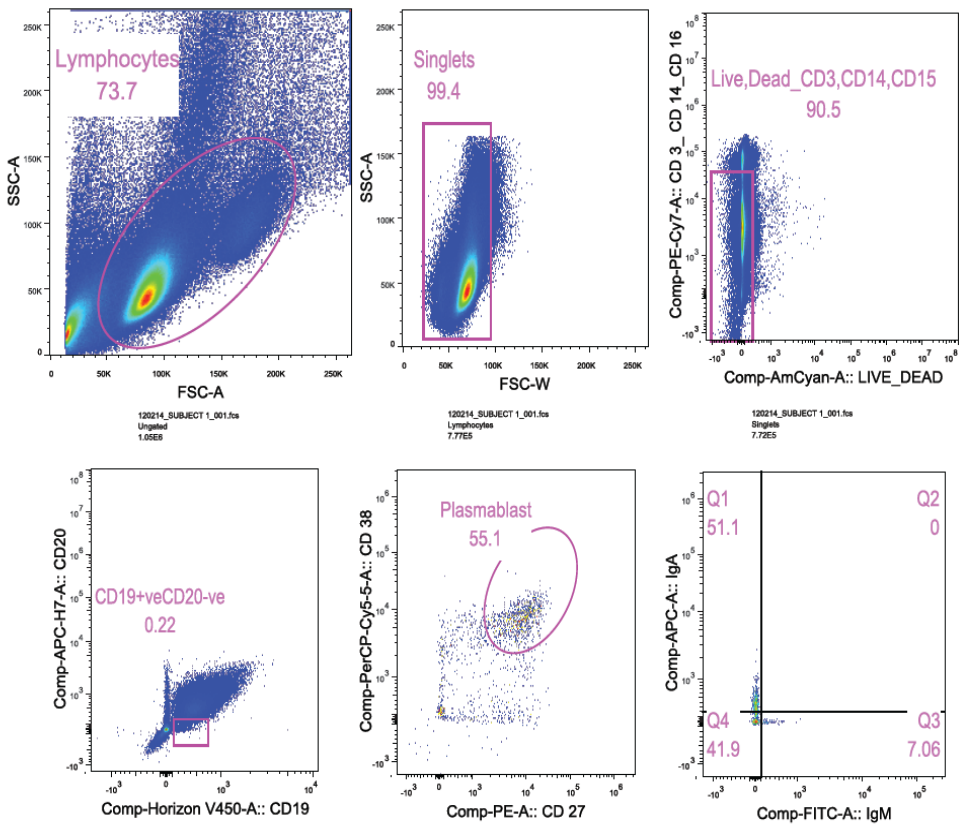
Infection Cohort

Infants hospitalized with rotavirus gastroenteritis n= 10

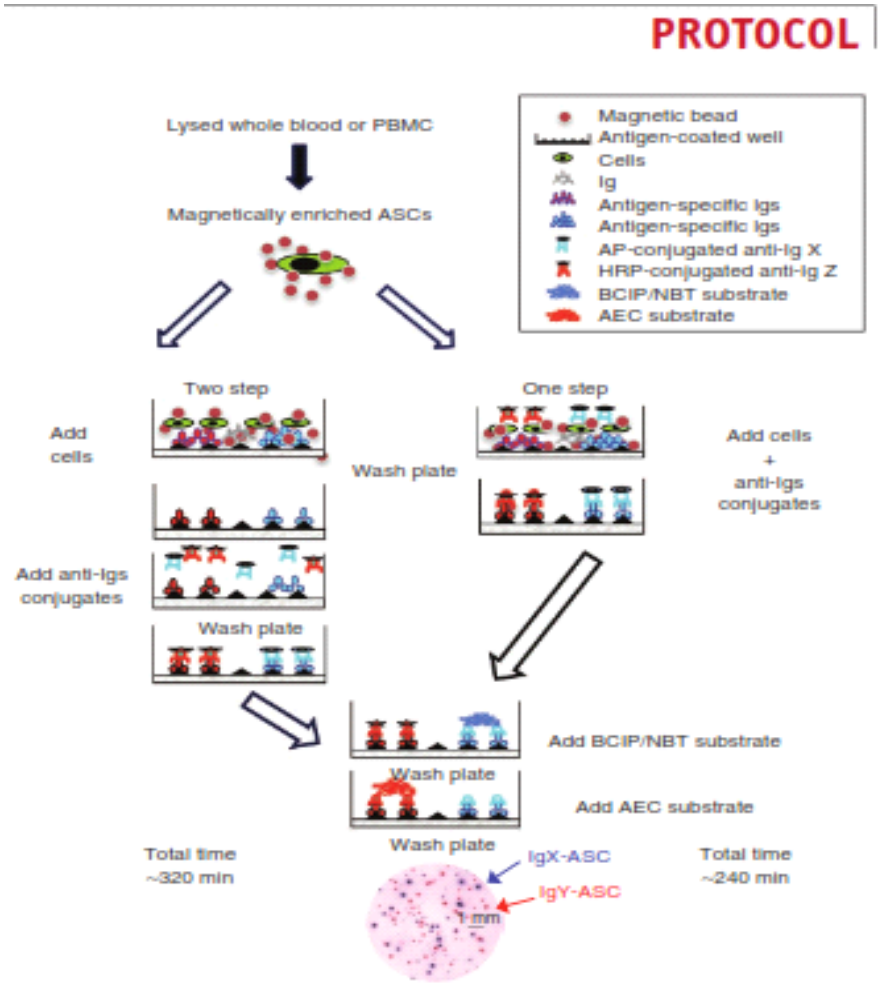
Indicates blood draw

Methods used

- Peripheral blood mononuclear cells isolated by the Ficoll-Hypaque method from 4 ml of blood
- Total plasmablasts enumerated by flow cytometry using a panel of fluorescent tagged antibodies
- Elispot assay to enumerate total and rotavirus specific IgA and IgG ASCs
- Serum rotavirus IgA by ELISA



Plasmablasts identified based on live, single cell gating and the CD3/14/16- CD19+ CD20lo/- CD27hi CD38hi surface phenotype. Surface expression of IgA and IgM facilitated detection of isotype-specific plasmablast frequencies



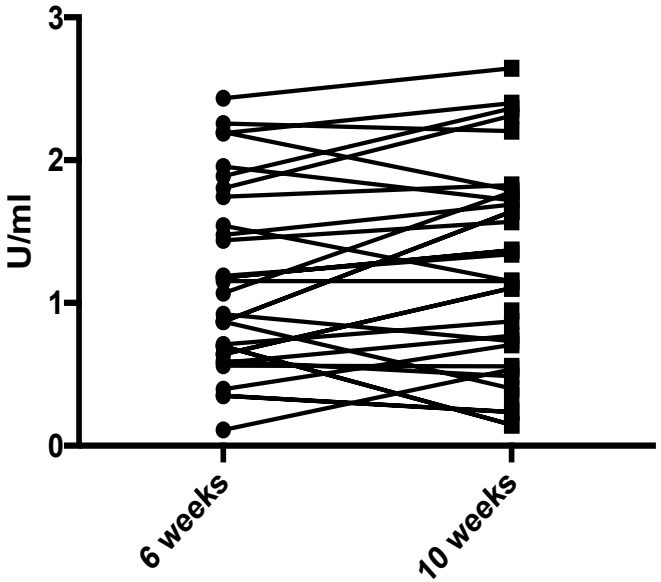
Elispot protocol- Modified from *Saletti et al Nature Methods 2013*

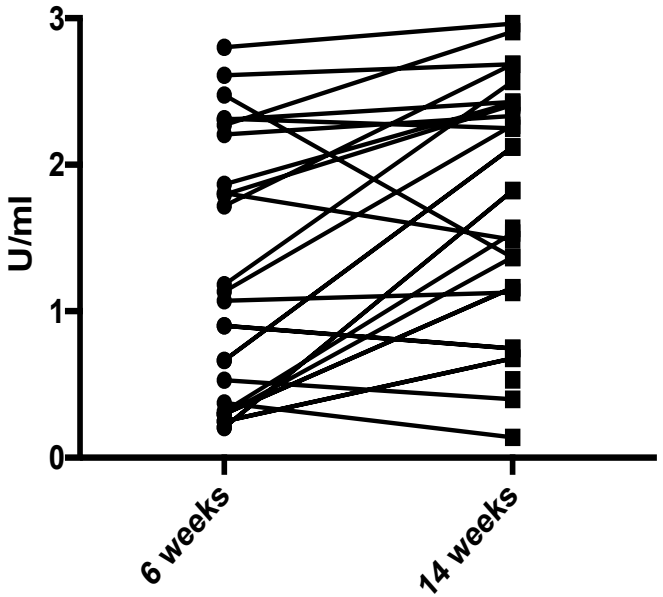
Results

- **Vaccination cohort**
  - A total of 59 infants finished the study in the vaccination cohort
  - 22/59 (42%) of the infants had rotavirus specific IgA at 6 weeks of age in the vaccination cohort [GMT(95%CI)-112.20(76.71,164.20)]
  - 14/30(47%) and 20/29(69%) infants had a rotavirus specific ASC response post 1st dose and post 2nd dose of vaccine respectively

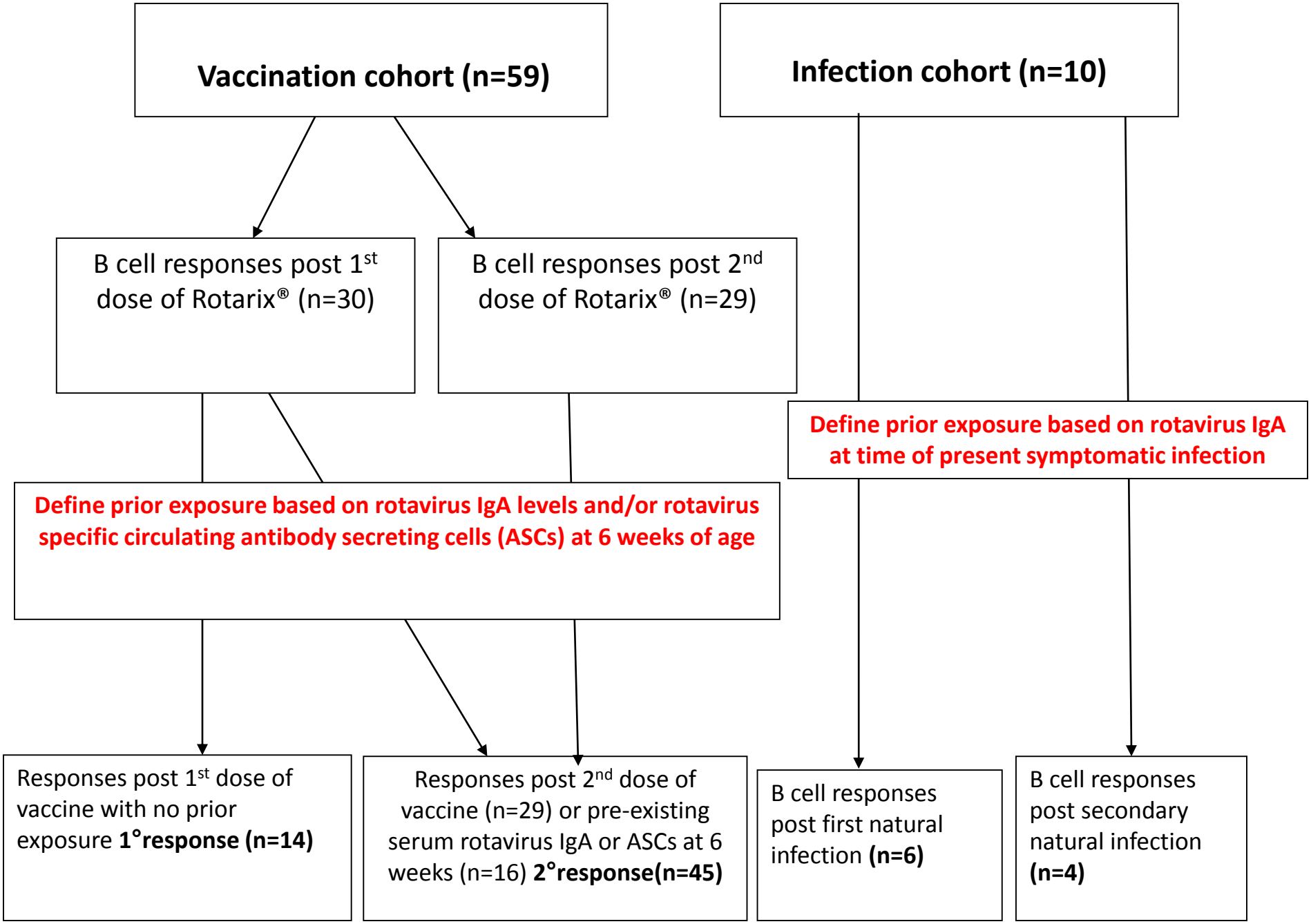
- **Infection group**
  - Ten infants were recruited in the infection cohort. Median age at recruitment was 12 months(IQR-8.5-20.5). Median day of recruitment after onset of symptoms was 2 days
  - G1P[8] was the most commonly isolated genotype
  - 4/10 (40%) of the infants admitted with rotavirus gastroenteritis had rotavirus specific IgA. GMT(95%CI)-71.10(11.41,443)]
  - 7/10(70%) infants had a rotavirus specific ASC response

Rotavirus Serum IgA (log transformed)

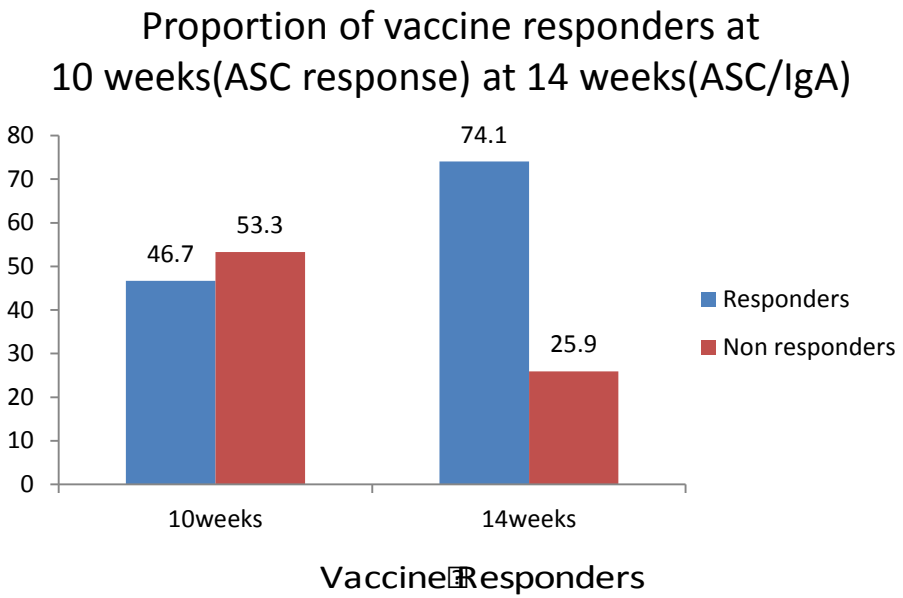


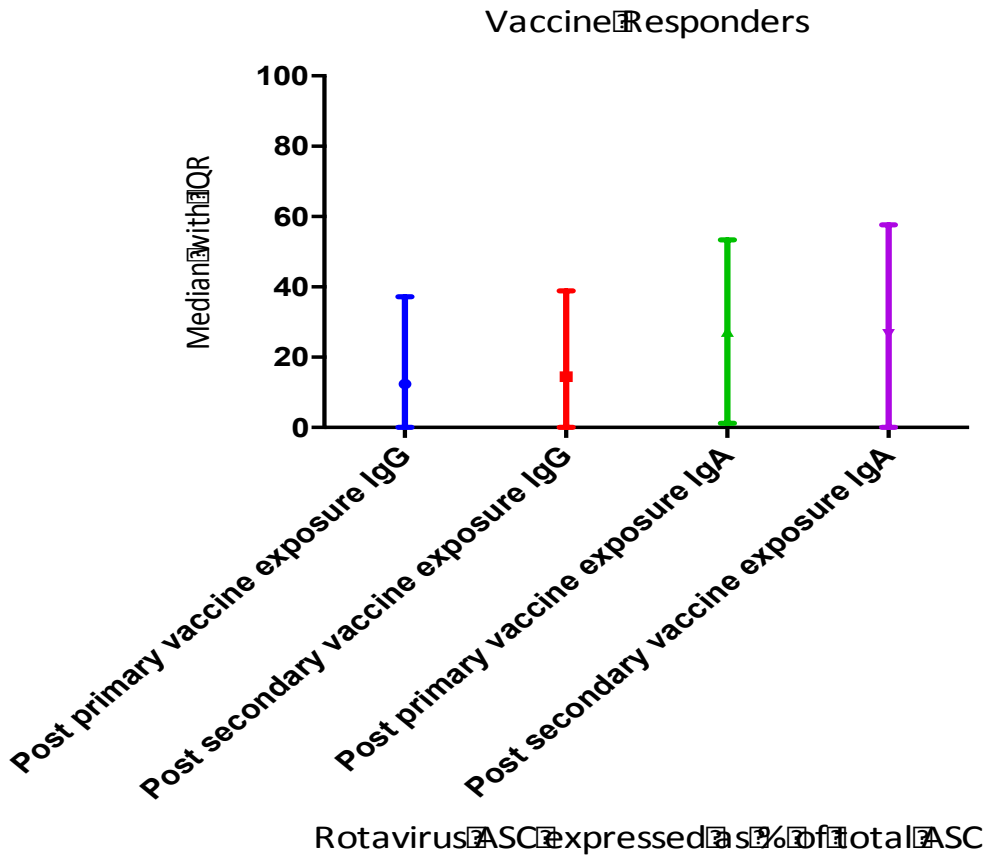


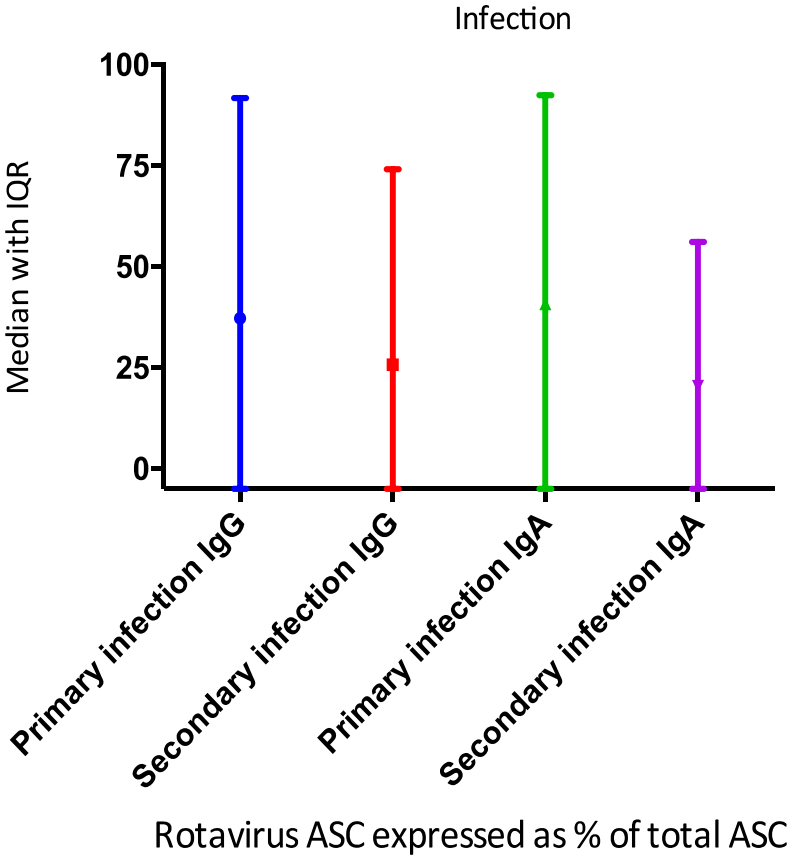
Rotavirus IgA		10 weeks(n=30)		14 weeks(n=29)	
		<20U/ml	>20U/ml	<20U/ml	>20U/ml
6 weeks	<20 U/ml	15	4	11	7
	>20 U/ml	1	10	0	11


Vaccination cohort (n=59)
Infection cohort (n=10)
B cell responses post 1st dose of Rotarix® (n=30)
B cell responses post 2nd dose of Rotarix® (n=29)
Define prior exposure based on rotavirus IgA at time of present symptomatic infection
Define prior exposure based on rotavirus IgA levels and/or rotavirus specific circulating antibody secreting cells (ASCs) at 6 weeks of age
Responses post 1st dose of vaccine with no prior exposure 1°response (n=14)
Responses post 2nd dose of vaccine (n=29) or pre-existing serum rotavirus IgA or ASCs at 6 weeks (n=16) 2°response(n=45)
B cell responses post first natural infection (n=6)
B cell responses post secondary natural infection (n=4)

ASC response







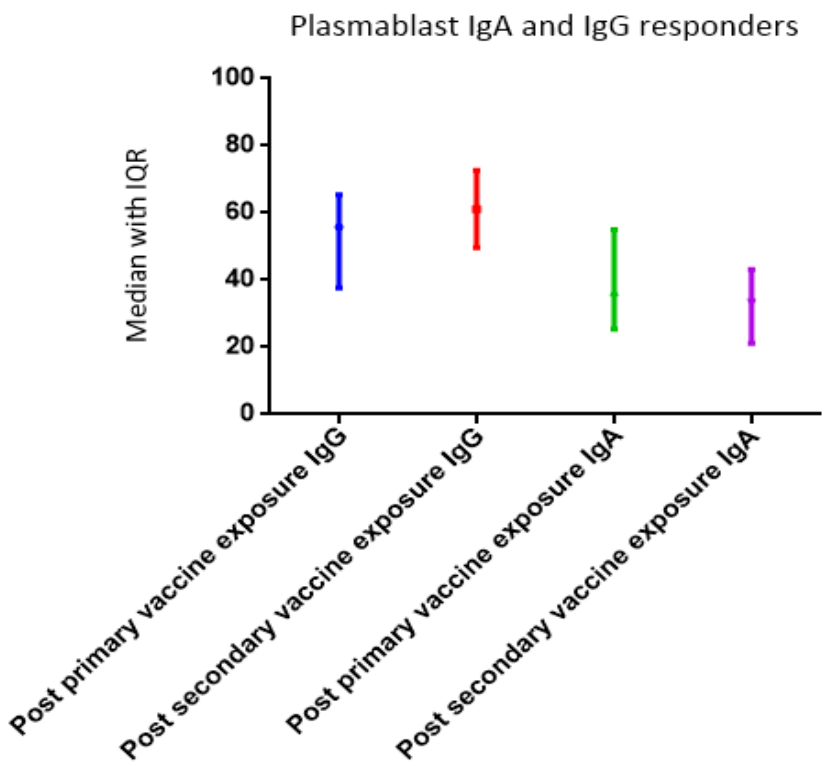
Does prior rotavirus exposure affect the ASC response?

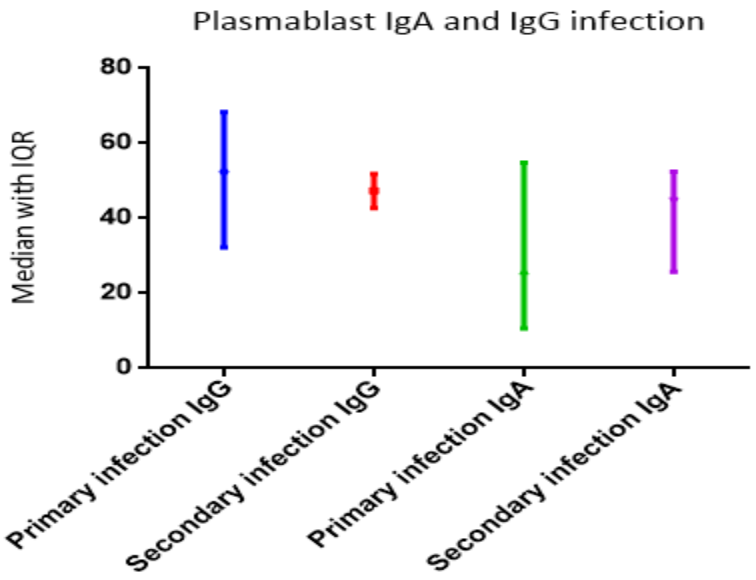
- Infants with prior rotavirus exposure did not have a significantly different ASC response compared to unexposed infants

Does infection produce a more robust ASC response compared to vaccination?

- 57% of infants in the vaccination cohort and 70% of infants in the infection cohort showed an ASC response but the number of ASCs between the two groups was not significantly different

Total plasmablast response





•Plasmablast response in infants infected with rotavirus for the first time was more than infants exposed to vaccine for the first time [Median 81.20 vs 42.15 (p value 0.008)]

•Infants in the vaccination group developed a stronger IgG plasmablast response compared to IgA post second dose of vaccine [Median 61.10 vs 33.60 (p value <0.001)]

Conclusion

- Very early exposure to rotavirus in this cohort
- The rotavirus specific ASC (total) and isotype response(IgA/IgG) did not differ significantly between the vaccination and the naturally infected groups

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