Safety and immunogenicity of a parenteral P2-VP8 subunit rotavirus vaccine

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12th African Rotavirus Symposium, Johannesburg, July 30-August 1 2019

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Rationale for non-replicating rotavirus vaccine (NRRV)

Oral rotavirus vaccines

- interference by high levels of transplacentally-acquired maternal rotavirus antibodies
- rotavirus antibodies in breast-milk
- co-administration of oral polio vaccine
- micronutrient deficiency
- enteric co-infections and microbiome
- concurrent diseases e.g. HIV infection
- host genetics

NRRVs

- bypass the need for intestinal replication
- may provide enhanced efficacy
- safety benefit - no increased risk of intussusception
- produced at low cost
- combination with other childhood vaccines
- safe in children with severe immunodeficiency

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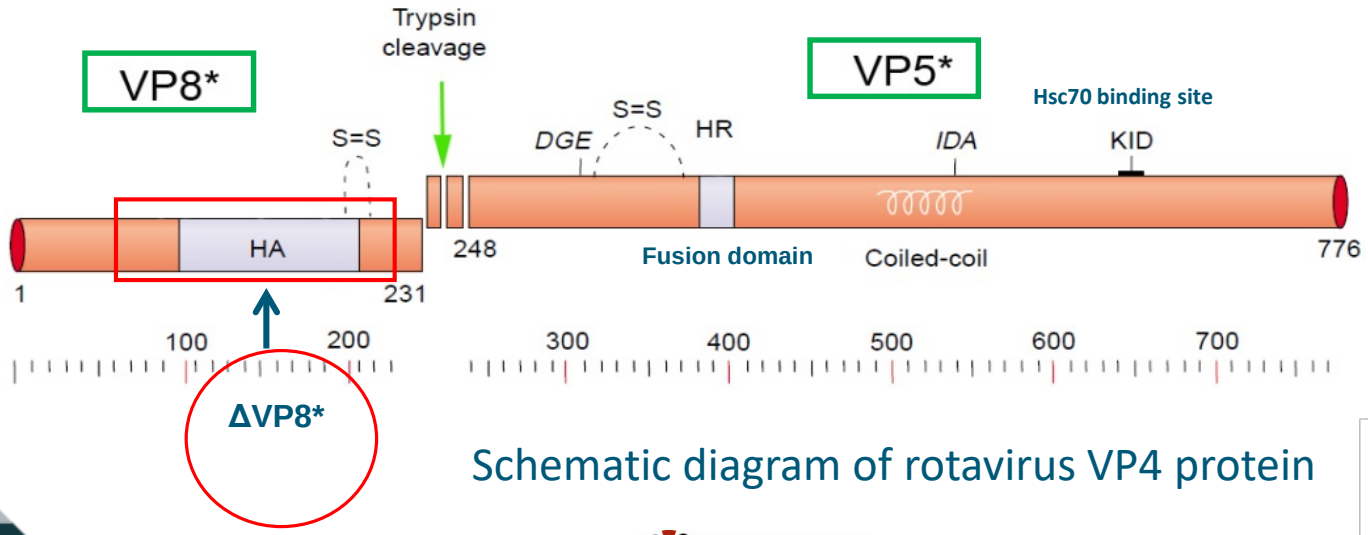
P2-VP8 rotavirus vaccine

- Developed at US NIH.
- Truncated VP8 subunit protein from human Wa strain (G1P[8]) fused to the tetanus toxin P2 epitope:
  - Expressed in E. coli
- Liquid formulation, adsorbed onto aluminum hydroxide adjuvant, administered intramuscularly.



Schematic diagram of rotavirus VP4 protein

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Vaccine development

Pre-clinical development

Clinical development

First in human
Adults 18–45 yrs
Baltimore
Dec 2012–Oct 2013

P2-VP8-P[8]

VAC 013
Phase I/II
Toddlers and infants
Soweto, South Africa
Mar 2014–Oct 2015

- Safe and well tolerated
- Robust neutralising Ab responses to homologous P[8] strains, modest to heterologous P[4] and P[6] strains.
- Reduced viral shedding following Rotarix

P2-VP8-P[4],P[6],P[8]

VAC 041
Phase I/II
Adults, toddlers and infants
3 sites, Soweto, South Africa
Feb 2016–Dec 2017

Fix, *Vaccine,* 2015; Groome, *Lancet ID*, 2017

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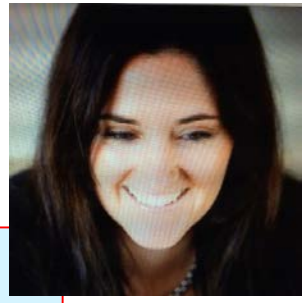
VAC 041 – trivalent P2-VP8 vaccine

- Trivalent vaccine, including P[4], P[6], and P[8] antigens (DS-1, 1076 and Wa).
- Dose 5µg to 30µg per serotype (15 to 90µg total antigen) - lack of a clear dose-response in previous study.
- Double-blind, randomized, placebo-controlled, descending-age, dose-escalation study to evaluate safety, tolerability and immunogenicity in adults, toddlers, and infants.
- Multi-centre study: March 2016–Jan 2018.

Respiratory and Meningeal Pathogens Research Unit (National PI/Site PI - Dr Michelle Groome)



Family Clinical Research Unit (FAM-CRU) (Site PI - Dr Julie Morrison)

Shandukani Research Centre (Site PI - Dr Lee Fairlie)

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Group		TV P2-VP8 Dose	N
A Adult	A1	30 µg	12
		Placebo	3
	A2	90 µg	12
		Placebo	3
A Total			**30**
B Toddler	B1	30 µg	12
		Placebo	3
	B2	90 µg	12
		Placebo	3
B Total			**30**
C Infant	C1	15 µg	12
		Placebo	4
	C2	30 µg	12
		Placebo	4
	C3	90 µg	12
		Placebo	4
C Total			**48**
D Infant		15 µg	138
		30 µg	138
		90 µg	138
		Placebo	138
D Total			**552**

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All sites

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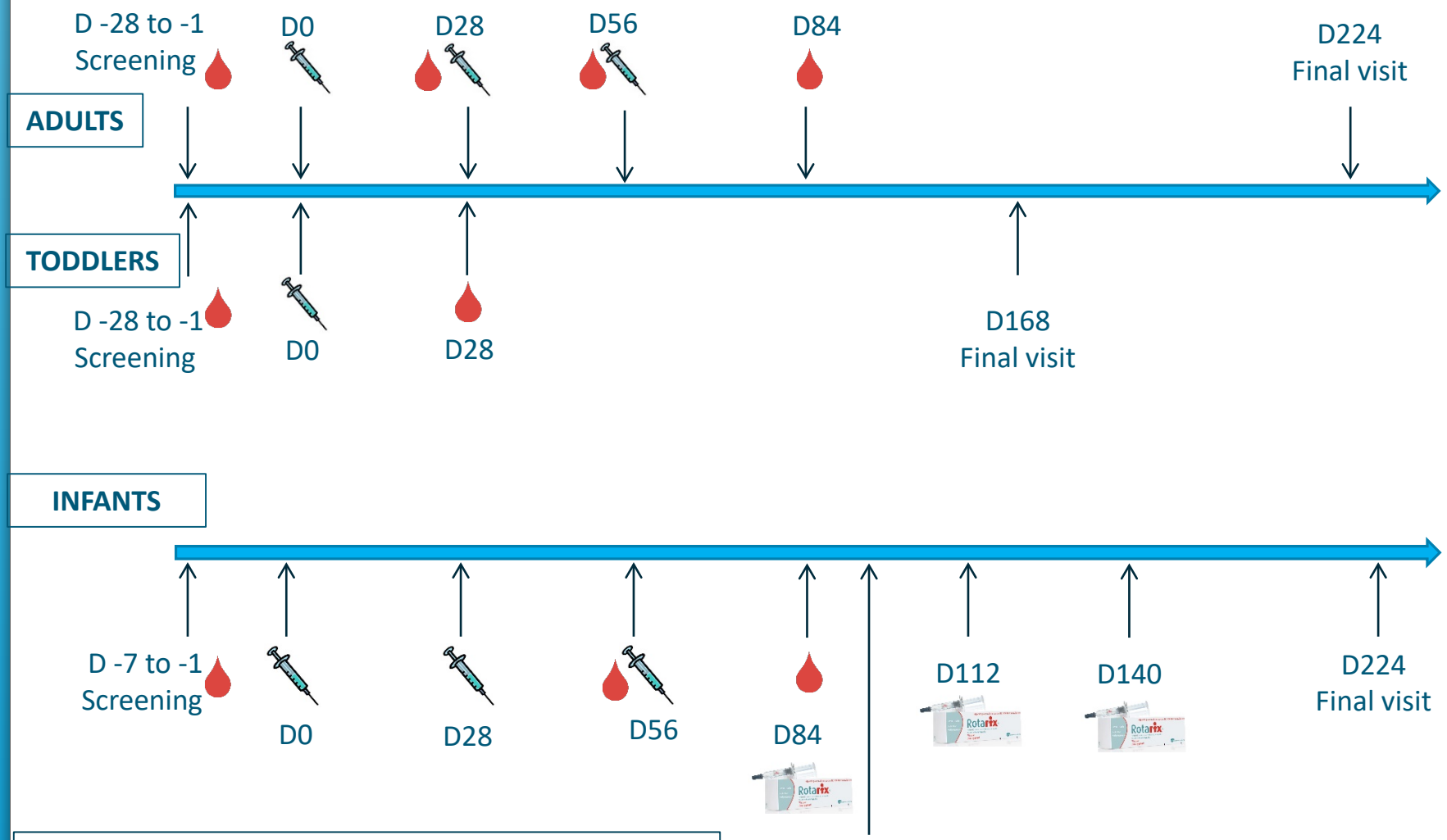

- Cohorts A, B, C – Day 7 safety bloods collected
- Safety visits on day 7 post vaccination for Cohort A and days 3 and 7 for Cohorts B, C, D

Faecal shedding of Rotarix assessed during the week after the first dose – stool samples collected on day 5, 7 and 9 – **subset at RMPRU only**.

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Objectives

» Primary Objectives:

> Safety

To evaluate the safety and tolerability of the trivalent P2-VP8 subunit rotavirus vaccine at escalating dose levels in healthy South African adults, toddlers and infants

> Immunogenicity

To evaluate the immunogenicity of the trivalent P2-VP8 subunit rotavirus vaccine at different dose levels in healthy South African infants

» Exploratory Objective:

> Efficacy

To evaluate the impact of the trivalent P2-VP8 subunit rotavirus vaccination on shedding of Rotarix subsequently administered in healthy South African infants (subset)

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Primary safety endpoints

- Number of adverse events and serious adverse events through 28 days after the last study injection
- Number of vaccine-induced reactions within 7 days after each injection
  - Local - injection site pain/tenderness, redness, swelling, itching, local lymphadenopathy
  - Systemic - fever, vomiting, nausea, fatigue, chills and myalgia for adults; fever, vomiting, irritability, decreased activity, and decreased appetite for toddlers and infants

Note:

- Progression from adults, toddlers to infants and for dose escalation: Safety Review Committee evaluated clinical and laboratory safety data through 7 days after the 1st injection.
- DSMB oversight.

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Primary immunogenicity endpoints

- IgG to P2-VP8 vaccine antigens
  - Three assays, one for each antigen – P[4], P[6] and P[8]
  - 4-fold rise in titer from baseline to 28 days after the 3rd vaccination
  - Results both unadjusted and adjusted for maternal antibody
- IgA to P2-VP8 vaccine antigens
  - Three assays, one for each antigen – P[4], P[6] and P[8]
  - 4-fold rise in titer from baseline to 28 days after the 3rd vaccination
- Neutralizing antibodies to the strains from which vaccine antigens derived
  - Assay strains – DS-1 (P[4]), 1076 (P[6]) and Wa (P[8])
  - 2.7-fold rise in titer from baseline to 28 days after the 3rd vaccination
  - Results both unadjusted and adjusted for maternal antibody

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Enrolment

- Cohort A: 30 adults (15 per cohort; safety analysis)
- Cohort B: 30 toddlers (15 per cohort; safety analysis)
- Cohort C and D:

	Placebo	15 µg	30 µg	90 µg	Total
Randomized	139	140	140	139	558
Vaccinated	139	139	140	139	557
Completed Day 84 visit	133 (96%)	134 (96%)	134 (96%)	135 (97%)	536 (96%)
Day 84 blood collected/analyzed	130 (94%)	133 (95%)	133 (95%)	134 (96%)	530 (95%)
PP immune population	130 (94%)	132 (94%)	132 (94%)	134 (96%)	528 (95%)

Safety

» No statistically significant differences observed between the treatment groups in the proportions of participants with local reactions, systemic reactions or unsolicited adverse events: all cohorts

Infants	Placebo n (%)	15µg n (%)	30µg n (%)	90µg n (%)
Any local reaction (Grade 2 or higher)	9 (6.5)	19 (13.7)	13 (9.3)	16 (11.5)
Any systemic reaction (Grade 2 or higher)	30 (21.6)	44 (31.7)	30 (21.4)	42 (30.2)
Any unsolicited AE (Grade 2 or higher)	19 (13.7)	24 (17.3)	18 (12.9)	20 (14.4)
Any SAE	8 (5.8)	13 (9.4)	6 (4.3)	8 (5.8)
Any AE related to product	3 (2.2)	2 (1.4)	3 (2.1)	2 (1.4)

Immunogenicity
(Per Protocol Population)

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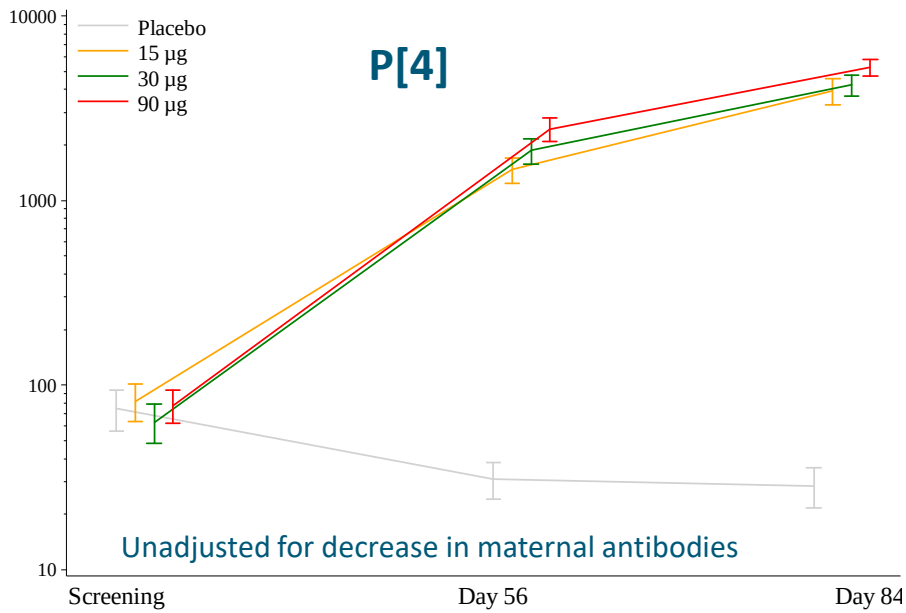
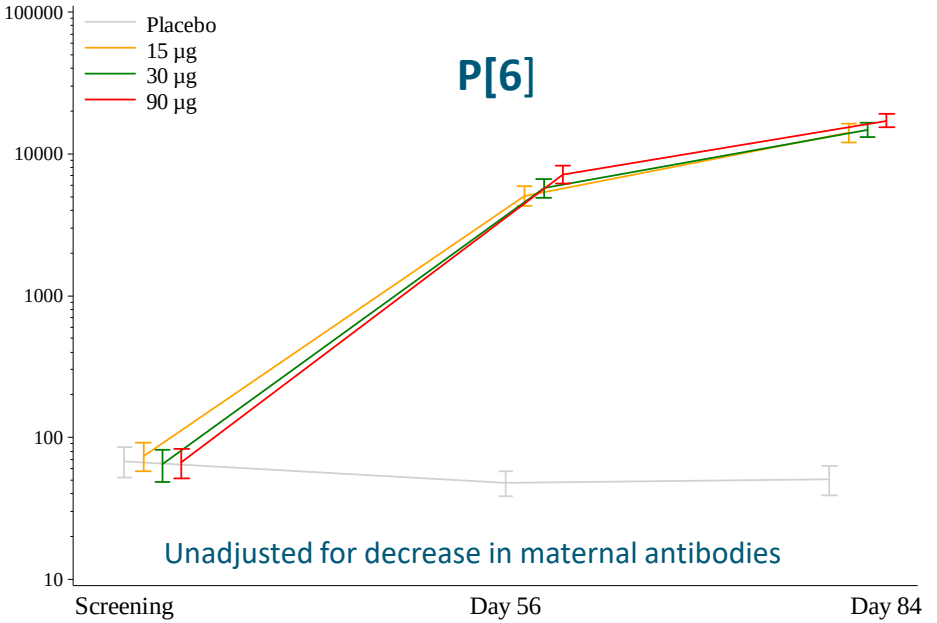
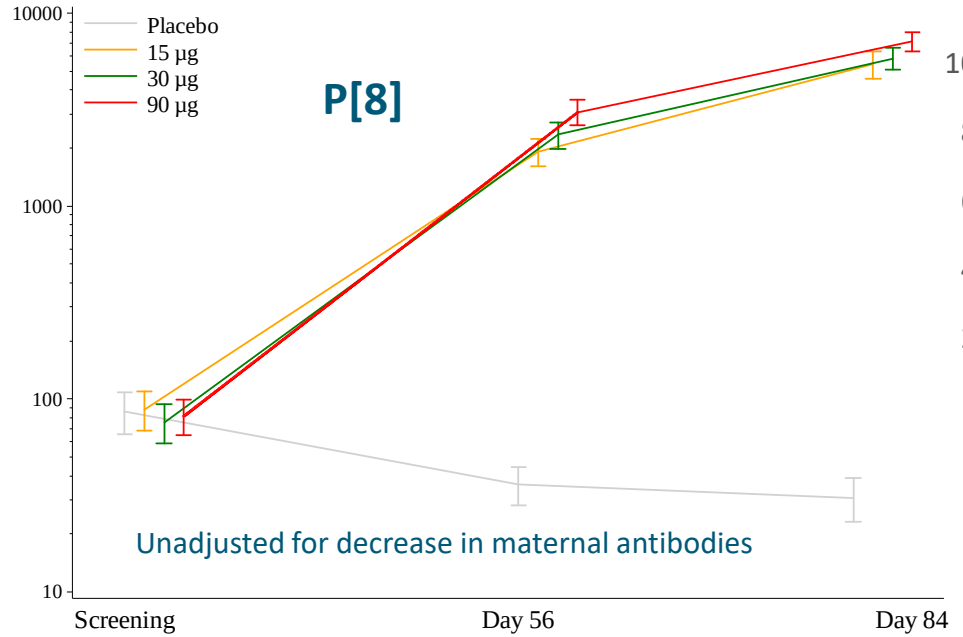
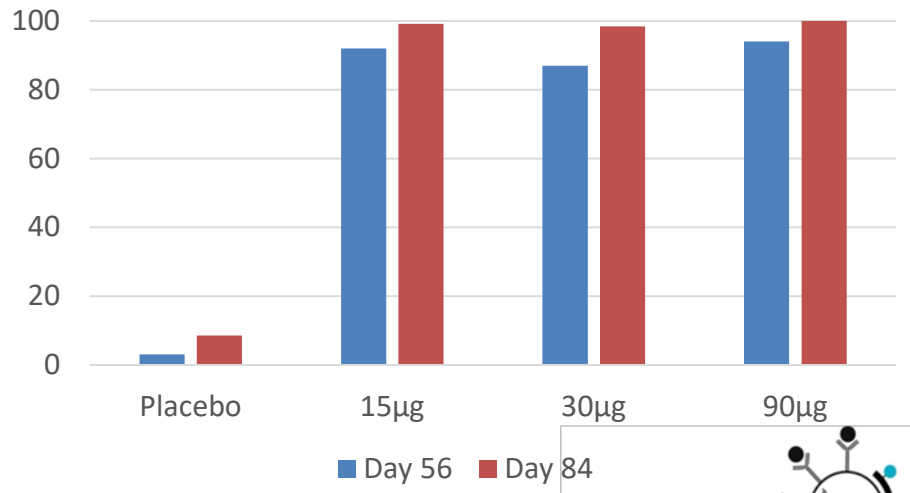
Anti-P2-VP8 IgG in infants









Seroresponses for all 3 antigens (adjusted for maternal antibodies)

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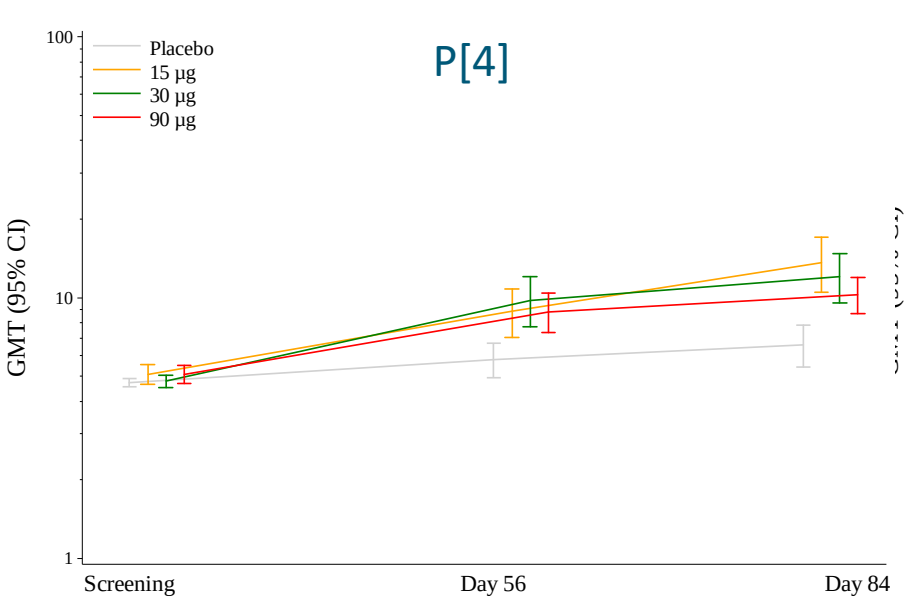
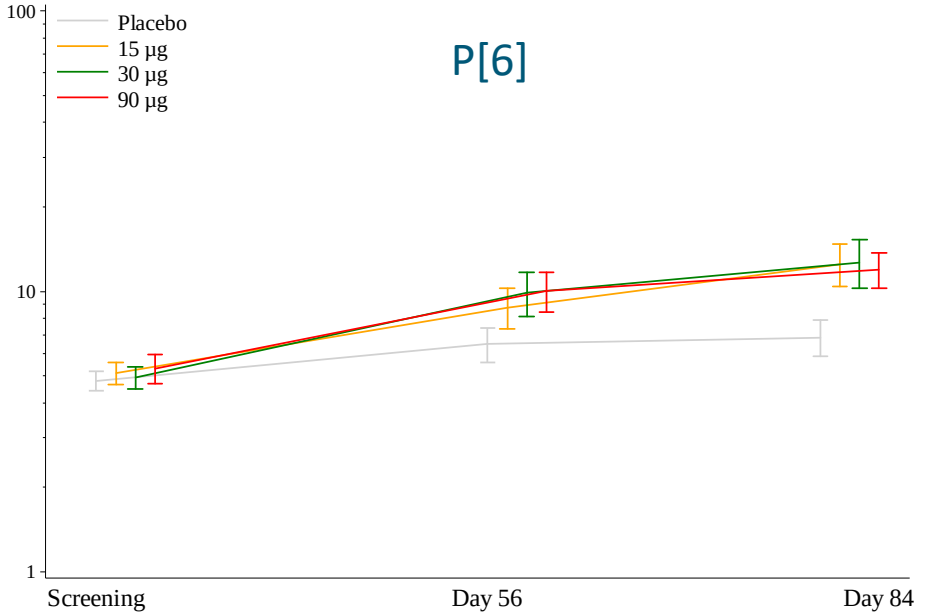
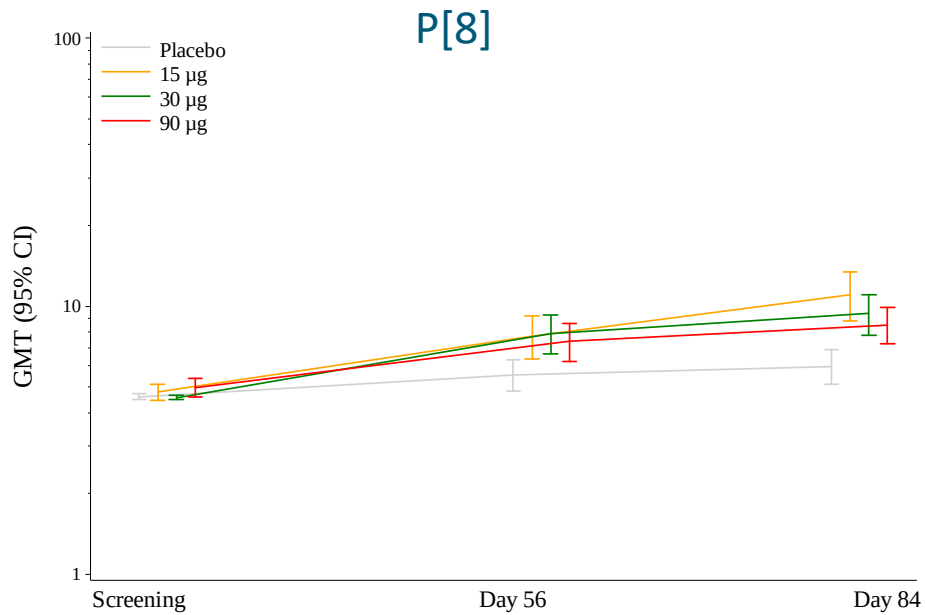
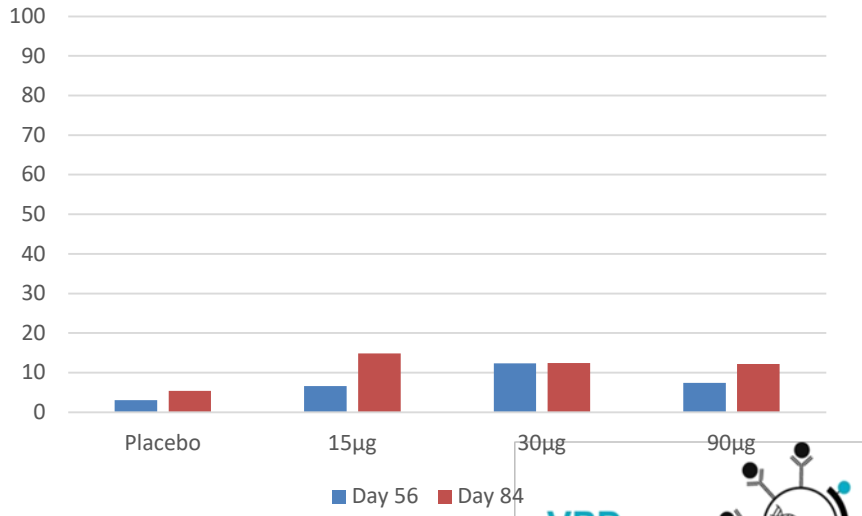
Anti-P2-VP8 IgA titers in infants









Seroresponses for all 3 antigens

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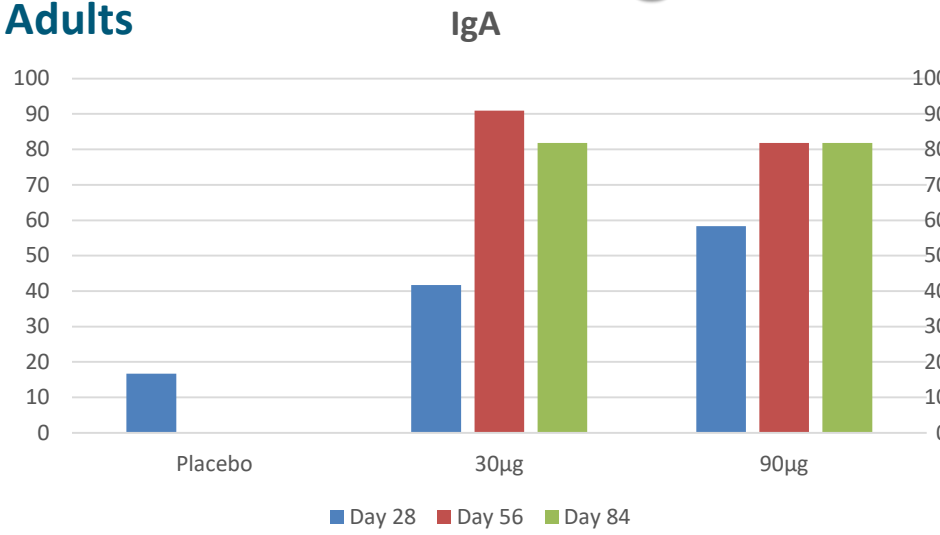
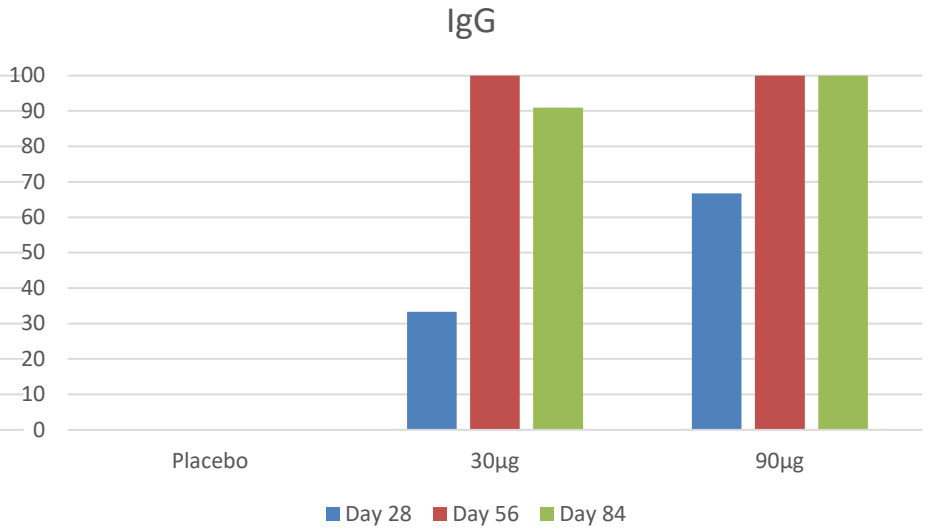
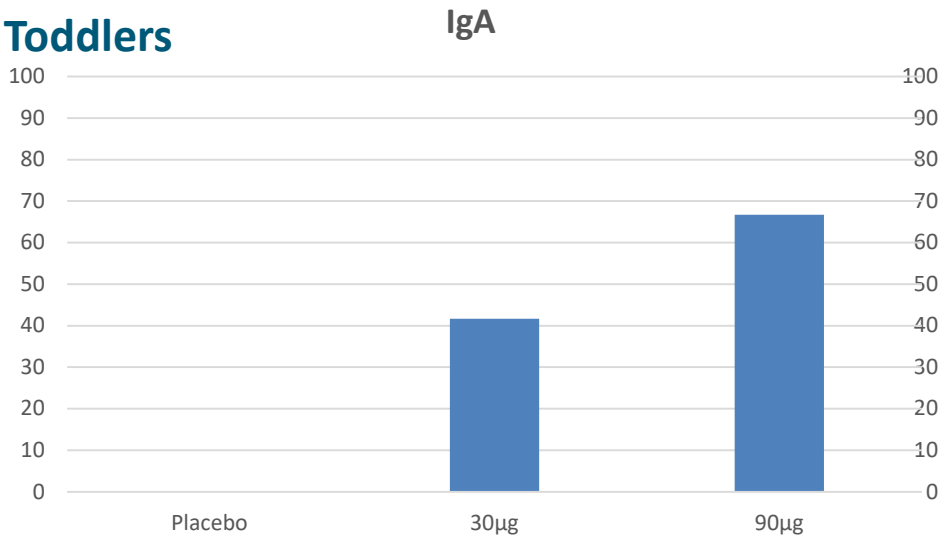
Serum anti-P2-VP8 IgA and IgG seroresponses for all 3 antigens in adults and toddlers

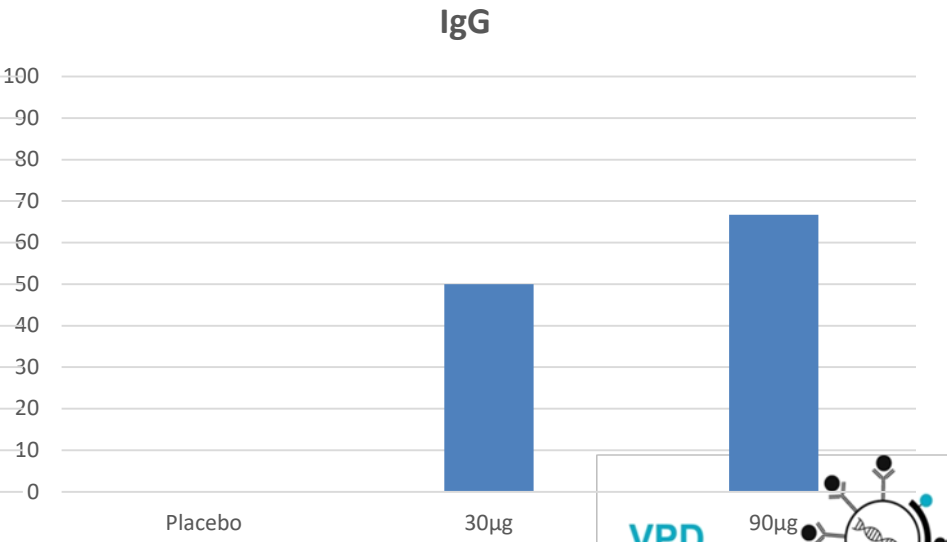
Adults





Toddlers





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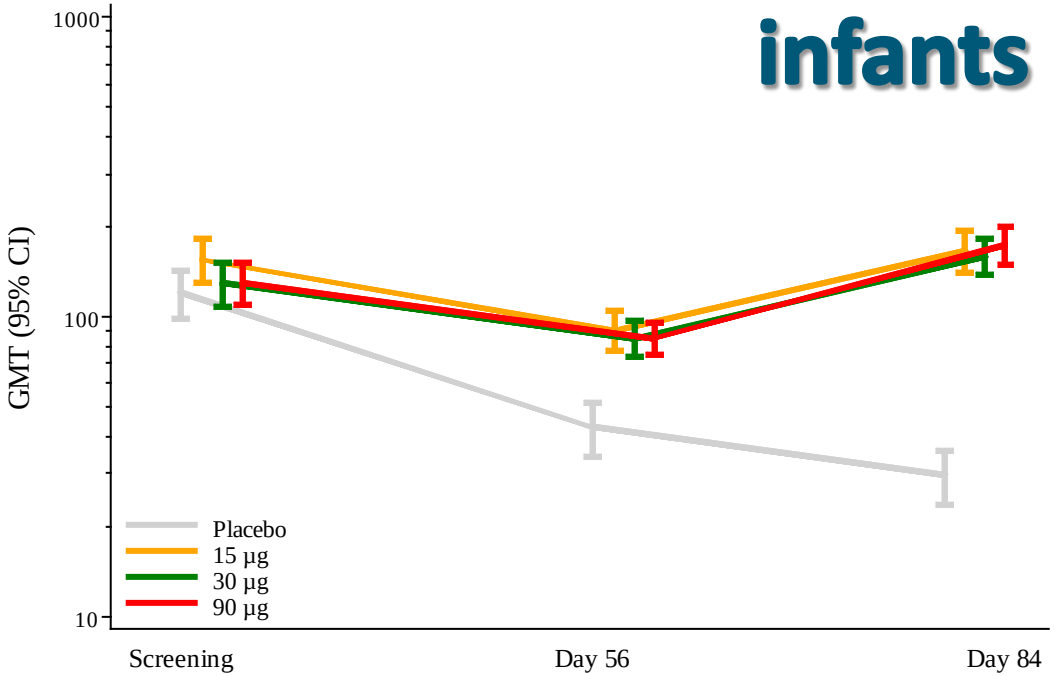
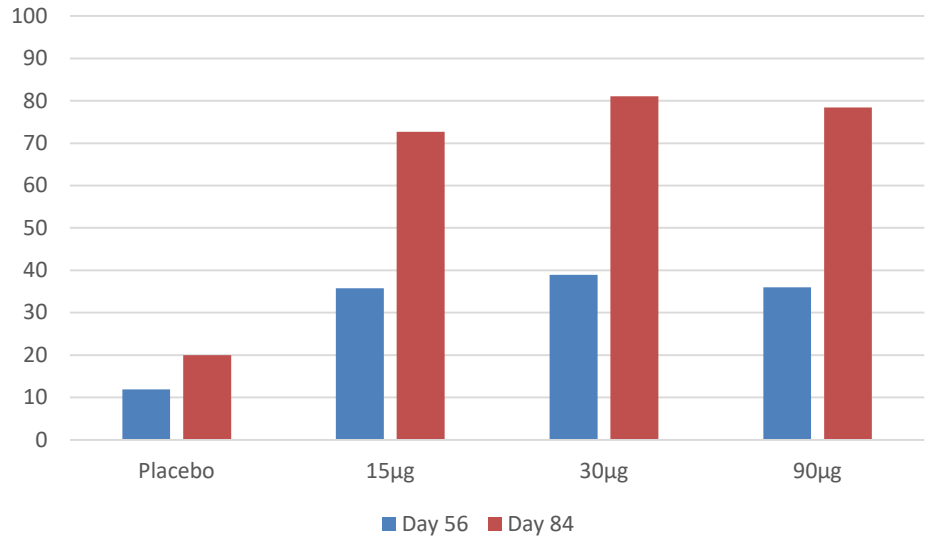
Serum Neutralizing Antibodies to Wa in infants



Neutralizing Antibodies to Wa in Infants - GMT and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies



Neutralizing antibody seroresponse against Rotavirus Strain Wa in Infants - Per-Protocol Population
Adjusted for decay in maternal antibodies

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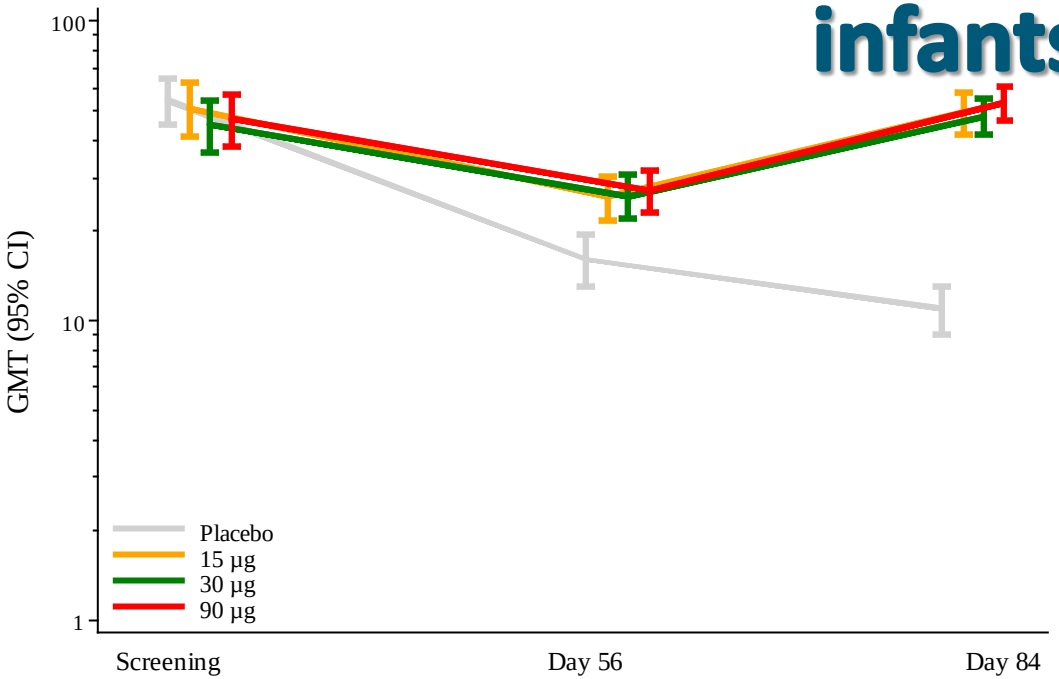
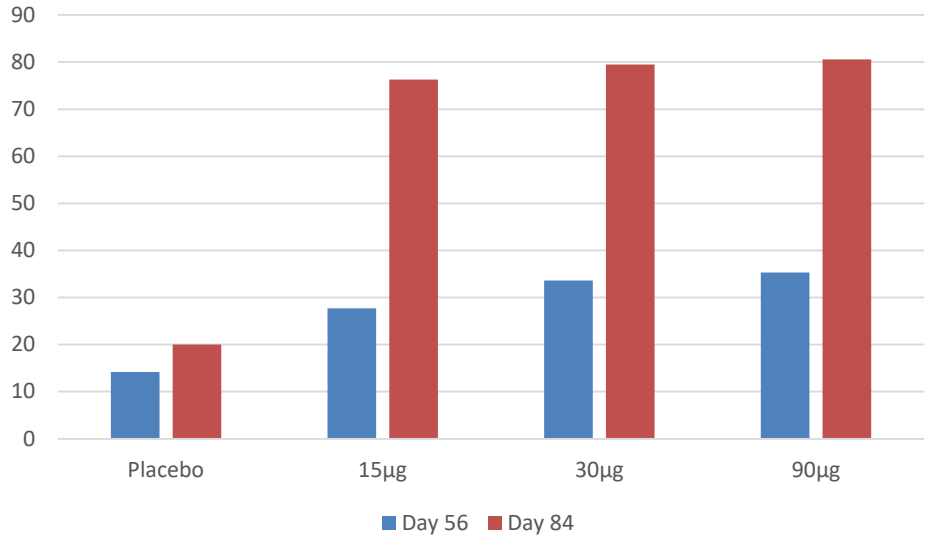
Serum Neutralizing Antibodies to DS-1 in infants



Neutralizing Antibodies to DS-1 in Infants - GMT) and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies



Neutralizing antibody seroresponse against Rotavirus Strain DS-1 in Infants - Per-Protocol Population
Adjusted for decay in maternal antibodies

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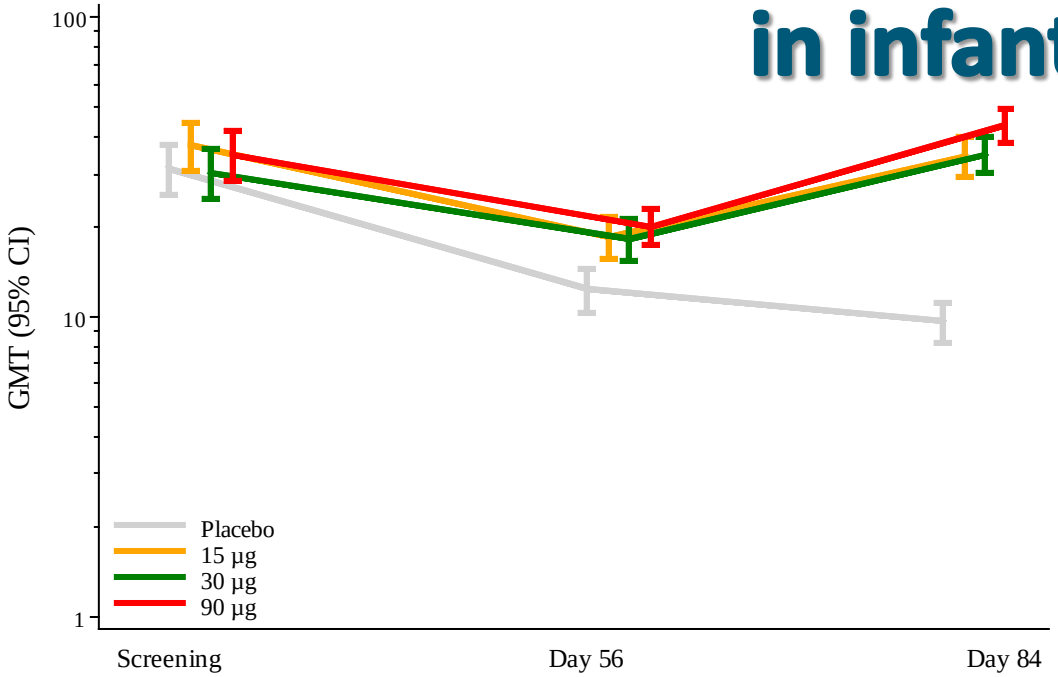
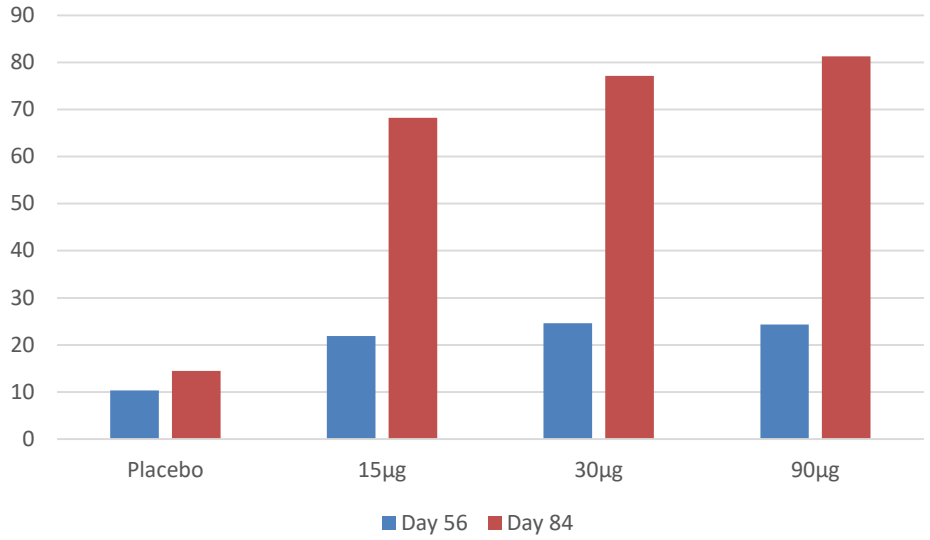
Serum Neutralizing Antibodies to 1076 in infants



Neutralizing Antibodies to 1076 in Infants - GMT) and 95% CI Per-Protocol Population, unadjusted for decrease in maternal antibodies



Neutralizing antibody seroresponse against Rotavirus Strain 1076 in Infants - Per-Protocol Population
Adjusted for decay in maternal antibodies

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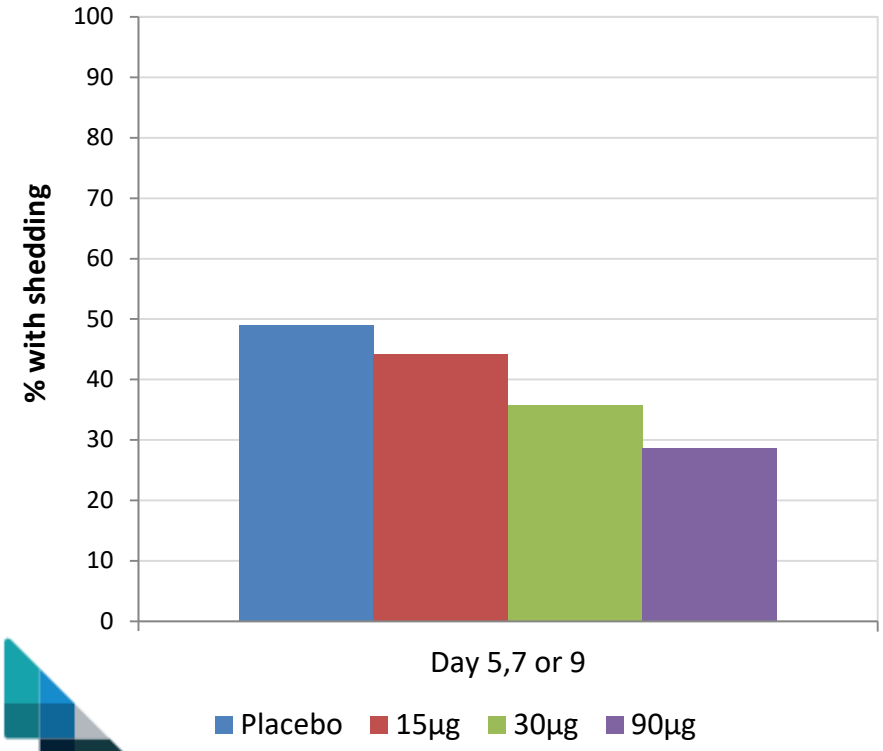
Rotavirus shedding post-Rotarix - infants

» Proportion of infants shedding rotavirus (ELISA) 5, 7 or 9 days after administration of the first dose of Rotarix® (4 weeks after the 3rd P2-VP8/placebo injection).

» Subset – infants at RMPRU:

Placebo	15 µg	30 µg	90 µg	Total
53	52	56	56	217



Reduction compared to placebo (any of the three days):

- 15µg: 10% (95% CI: -36-40)
- 30µg: 27% (-14-53)
- 90µg: 42% (4-65)

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Conclusions

- All dose-levels well tolerated and no safety signals.
- Excellent anti-P2-VP8 IgG across the three vaccine P-types.
- Very good neutralising antibody responses to Wa, DS-1 and 1076 strains.
- Broader anti-P2-VP8 IgG and neutralising antibody responses than demonstrated for the monovalent vaccine.
- Responses better after 3 doses compared to 2 doses.
- Anti-P2-VP8 IgA in infants lower than anticipated.
- Significantly fewer infants vaccinated with the 90µg dose shed rotavirus compared to placebo recipients.

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Considerations for Future Development Plans

- Assessment of efficacy of the stand-alone vaccine.
- Exploration of prime-boost regimens of live, oral RV vaccines and the P2-VP8 vaccine.
- Development of co-formulated vaccine, combining other EPI/UIP vaccines and P2VP8 in a single injection, including clinical assessment.
- Licensure and WHO prequalification of stand-alone and/or co-formulated vaccine for global availability.

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Assessment of Efficacy of the Standalone Vaccine

- **CVIA 061**
  A double-blind, randomized, active comparator-controlled, group-sequential, multinational trial to assess the safety and efficacy of a trivalent P2-VP8 subunit rotavirus vaccine in prevention of severe rotavirus gastroenteritis in healthy infants

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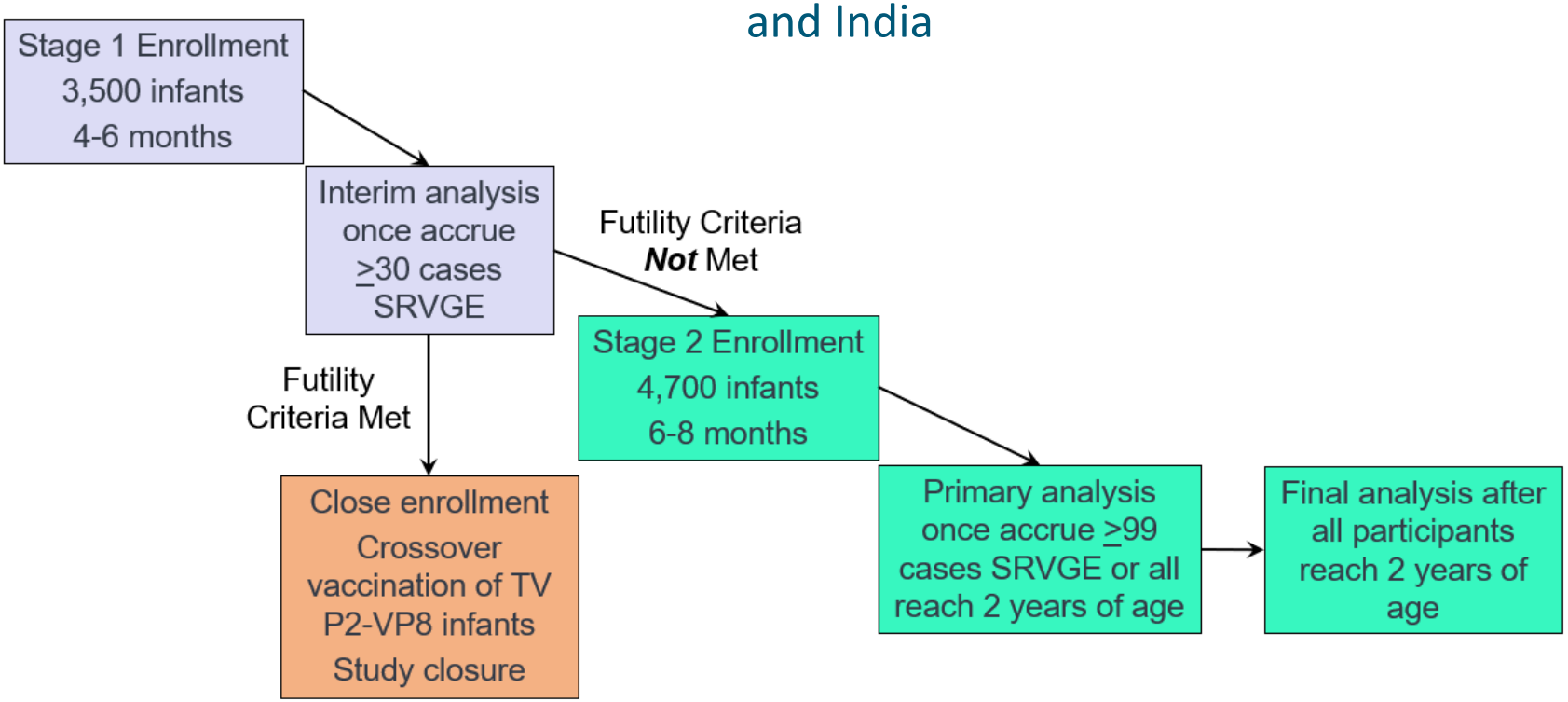
CVIA 061 Study Outline

- Multinational
  - Sites in Zambia, Malawi, Ghana and India



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Acknowledgements

RMPRU site
Anthonet Koen
Lisa Jose
Carol Taoushanis
Clinic team
Data team
Laboratory team

PATH
Alan Fix
Stanley Cryz
Maureen Power
Catherine Johnson
Margaret Wecker
Allison Stanfill
Jorge Flores

Shandukani site

FAM-CRU site

EMMES
Val Brown and team
Len Dally

Cincinnati Children's Hospital Medical Center
Monica McNeal
Nicole Meyer
Brandi Phillips

National Institute for Communicable Diseases, South Africa Dr Nicola Page
NIH – vaccine development

Funding from the Bill & Melinda Gates Foundation