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“Challenge” Assessment of a Novel Rotavirus Vaccine

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Rationale for Non-replicating Rotavirus Vaccine (NRRV) Project

- Currently licensed oral live, attenuated rotavirus vaccines offer great benefit to populations in resource-limited countries but are costly and have reduced efficacy in those populations
- Subunit protein NRRV candidates:
  - May provide superior efficacy in target populations
  - Projected to be less expensive (<$1 per dose)
  - May be combined with EPI vaccines, facilitating delivery and reducing costs
  - Negligible risk of intussusception
- Parenteral vaccines can protect against enteric diseases (e.g., polio, cholera, typhoid, hepatitis A)
- Focus on vaccines capable of eliciting a rotavirus neutralizing antibody response as passive transfer of such antibodies can provide protection

Challenges to Assessment of Novel Rotavirus Vaccines

- No clear correlate
  - Data for IgA and neutralizing antibodies do not support as correlate without clinical endpoint
  - Commonly used IgA assay not relevant for many subunit vaccines
- Placebo-controlled efficacy trials increasingly difficult to justify
- Active comparator design dramatically increases necessary sample size

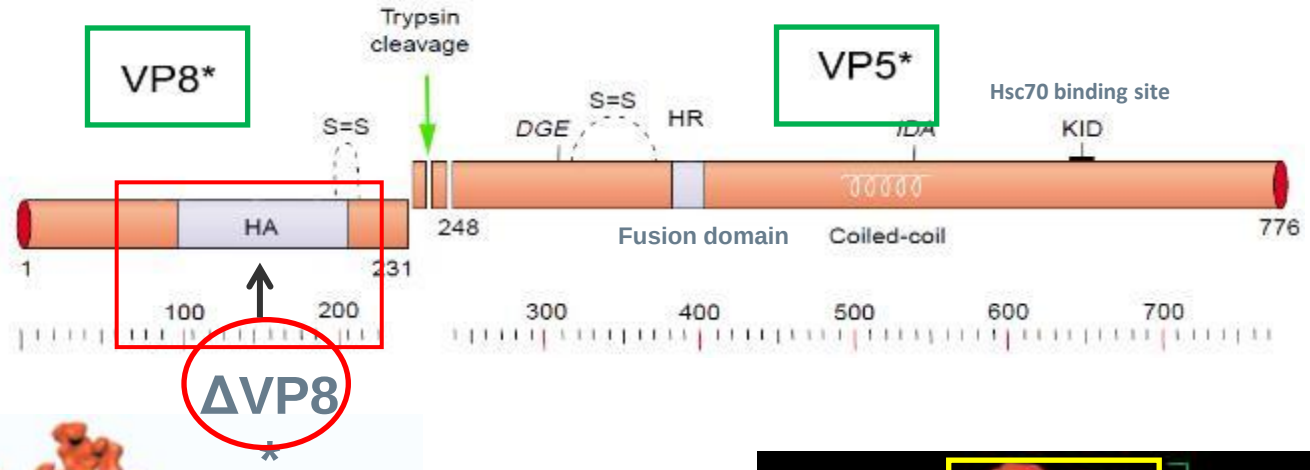
Assessment of New Oral Poliovirus Vaccines – Use of Licensed Vaccine as Challenge

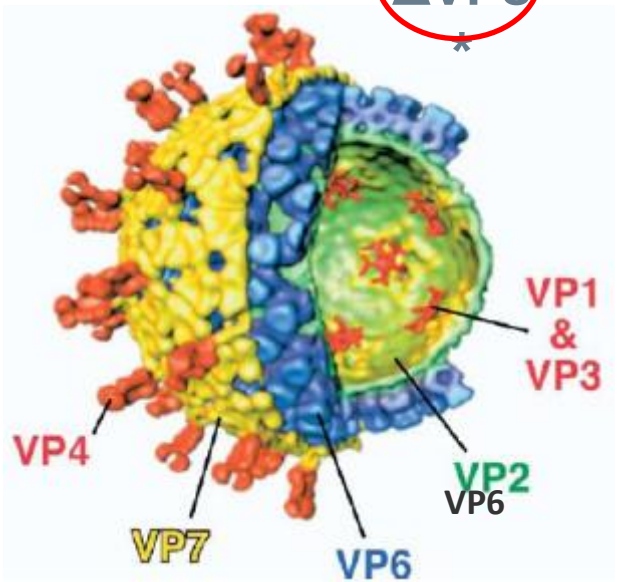
- "Induction of mucosal immunity by candidate and comparator vaccines may be determined by assessing virus excretion after administering a challenge dose of mOPV."

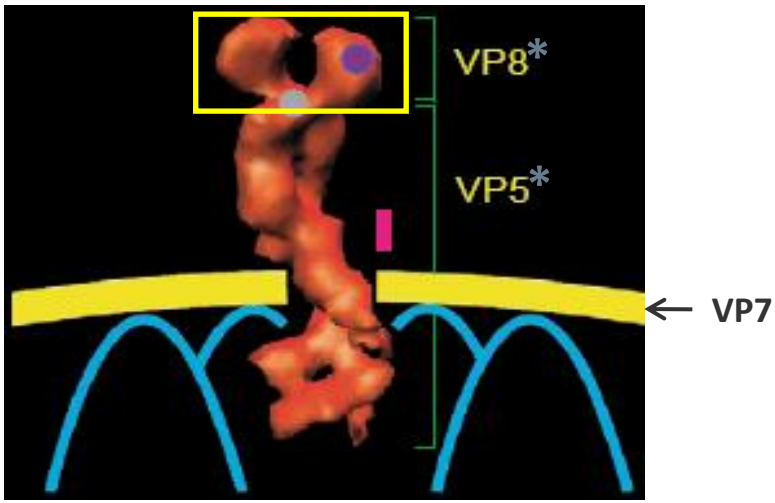
- "For evaluation of modified strains (intentionally containing additional mutations compared to Sabin strains) then studies of mucosal immunity may be required rather than being optional."

WHO 2014 Annex 2: Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (oral, live, attenuated)

Rotavirus VP4







López and Arias 2004 Trends Microbiol 2004

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Characteristics of Trivalent P2-VP8 Vaccine

- Initially developed at US NIH, led by Dr. Yasutaka Hoshino.
- Truncated VP8 subunits from RV strains expressing P[4](DS1)/P[6] (1076)/P[8] (Wa) serotypes, each fused to the tetanus toxin P2 CD4 epitope
- Approximately 21 kDal in molecular weight
  - Expressed in *E. coli* – synthesized protein is >95% soluble
  - Two step purification process using hydrophobic interaction and anion exchange liquid chromatography
  - Liquid formulation, adsorbed to aluminum hydroxide
- No unexpected toxicity when tested in formal toxicology study in rabbits at doses up to 180 µg total protein with 0.56 mg aluminum hydroxide
- Elicits antibodies that neutralize rotavirus strains expressing P[4], P[6] and P[8] strains of rotavirus in preclinical studies

Rationale for Vaccine Construct and Formulation

Preclinical Studies

- Inclusion of P2 T-cell epitope engendered higher neutralizing antibody (NAb) titers
- Addition of aluminum adjuvant promoted earlier rise in NAb and increased overall titer levels
- Immunization results in protection from rotavirus disease in neonatal piglets evidenced by delayed onset and shorter duration of diarrhea in addition to decreased shedding of challenge strain
- Trivalent vaccine elicited substantially higher NAb GMTs to P4[and P[6] than monovalent; P[8] response was comparable

First in Human Study of Monovalent P2-VP8 (P[8])
Adults – US

- Phase 1 trial in Baltimore, MD, USA – completed in 2013
- Healthy adults
- Dose-escalation: 10 => 30 => 60 µg
- Three IM doses, one month apart
- Well tolerated and no safety signals
- Promising immunogenicity
  - IgG
  - IgA
  - Neutralizing antibodies
  - Antibody in lymphocyte supernatant (ALS)

Fix, et. al., Vaccine, 2015. 33(31): 3766-72

VAC 013 – Soweto, South Africa

A Phase I/II descending age, double-blinded, randomized, placebo-controlled dose escalation study to examine the safety, tolerability and immunogenicity of the P2-VP8 subunit parenteral rotavirus vaccine in healthy South African toddlers and infants

Respiratory and Meningeal Pathogens Research Unit (RMPRU) at Chris Hani Baragwanath Academic Hospital

12 March 2014 to 28 October 2015

Groome, et. al., Lancet Infect Dis, 2017. 17(8): 843-853

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VAC 013 Objectives

Primary Objectives:

Safety:

- Evaluate the safety & tolerability of P2-VP8 subunit rotavirus vaccine at escalating dose levels in healthy South African toddlers and infants

Immunogenicity:

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

Secondary Objective:

"Efficacy:"

- ***Evaluate the impact of P2-VP8 subunit rotavirus vaccination on shedding of Rotarix subsequently administered in healthy South African infants as a test of concept***

Rotarix Shedding Estimates After First Dose

Location	Shedding ~7 days after first dose
US	60-100%
Finland	~60%
Singapore	~80%
Vietnam	65%
Columbia/Mexico/Peru	50%
Brazil/Mexico/Venezuela	~45%
Bangladesh	14-30%
South Africa	~35%

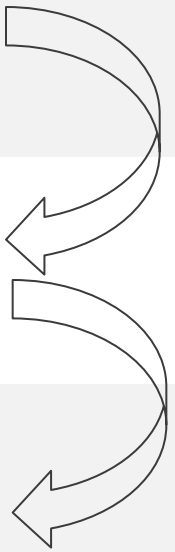
Infant Sample Size Calculation on Basis of Reduction in Rotarix Shedding

- Study sample size of 50 participants per group primarily driven by this secondary objective

- Assumptions
  - ≥30% shedding in placebo group
  - 10% dropout
  - 80% power to detect 80% reduction in shedding

Toddlers

Cohort	Dosing Groups	N
Cohort A 24-35 months	10 µg vaccine with $Al(OH)_3$	12
	Placebo	2
	30 µg vaccine with $Al(OH)_3$	12
	Placebo	2
	60 µg vaccine with $Al(OH)_3$	12
	Placebo	2
	Total	36 vaccine 6 placebo

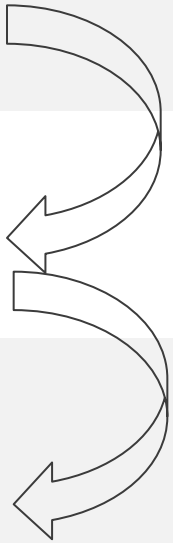


Vaccine Schedule: Day 0

Placebo – Sodium Chloride 0.9%

Infants – dose escalation

Cohort	Dosing Groups	N
Cohort B1 ≥6 and <8 weeks	10 µg vaccine with $Al(OH)_3$	12
	Placebo	4
	30 µg vaccine with $Al(OH)_3$	12
	Placebo	4
	60 µg vaccine with $Al(OH)_3$	12
	Placebo	4
	Total	36 vaccine 12 placebo



Vaccine Schedule: Days 0, 28 and 56

Infants – expanded cohort

Cohort	Dosing Groups	N
Cohort B2 ≥6 and <8 weeks	30 µg vaccine with $Al(OH)_3$	38
	60 µg vaccine with $Al(OH)_3$	38
	Placebo	38

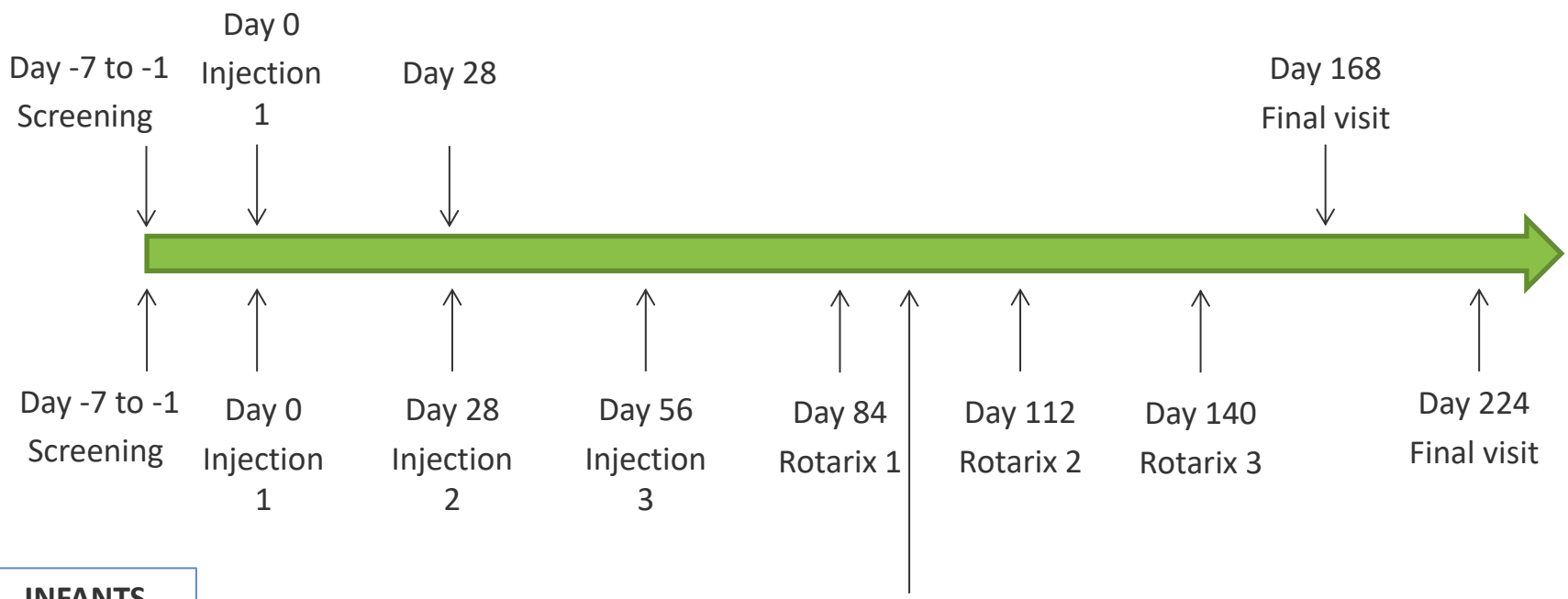
Concurrent randomization of all 3 groups

Vaccine Schedule: Days 0, 28 and 56

The highest and 2nd highest doses in expanded cohort (B2) determined from safety data of infant Cohort B1

Study visits

TODDLERS



INFANTS

Fecal shedding of Rotarix assessed during the week after the first dose – stool samples collected on day 5, 7 and 9.

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Anti-P2-VP8 P[8] IgA Responses - Infants

Dose	Pre-vaccination GMT (95% CI)	Post-vaccination GMT (95% CI)	GMT Fold-increase (95% CI)	Seroresponse Rate N (%) (95% CI)
Placebo	**7** (5–8)	**12** (8–17)	**1.9** (1.37 - 2.51)	9 **(20.0)** (10–35)
30µg	**6** (5–7)	**56** (39–82)	**10** (6.89 - 14.60)	38 **(80.9)** (67–91)
60µg	**6** (5 –7)	**38** (28–51)	**6.7** (4.85 - 9.34)	32 **(68.1)** (53–81)

Anti-P2-VP8 P[8] IgG Responses - Infants

Dose	Pre-vaccination GMT (95% CI)	Post-vaccination GMT Titer (95% CI)	GMT Fold-increase (95% CI)	Seroresponse Rate N (%) (95% CI)	
				Unadjusted	Adjusted*
Placebo	***95*** (60–151)	***32*** (22-46)	***1.4*** (1.0-1.8)	1 (2.2) (0.1-12)	4 ***(8.9)*** (2.5-21)
30 µg	***107*** (72–161)	***9,583*** (7,544-12,172)	***374*** (223 – 630)	46 (97.9) (89-100)	46 ***(97.9)*** (89-100)
60 µg	***166*** (116–237)	***9,576*** (8,131-11,278)	***243*** (159 – 371)	46 (97.9) (89-100)	47 ***(100)*** (92-100)

*Adjustment for decay in maternal antibodies

Neutralizing Antibody Responses – Infants
(Adjusted*, ≥4-fold increase 28 days after 3rd dose)

Strain	P type	Placebo % (CI)	30 µg % (CI)	60 µg % (CI)
Wa	8	**7** (1.4, 18)	**85** (72, 94)	**85** (72, 94)
89-12	8	**9** (2.5, 21)	**89** (77, 97)	**81** (67, 91)
DS1	4	**9** (2.5, 21)	**32** (19, 47)	**32** (19, 47)
1076	6	**9** (2.5, 21)	**23** (12, 38)	**23** (12, 38)

*Adjustment for decay in maternal antibodies

Rotarix Shedding by ELISA

	Day 5		Day 7		Day 9		Anytime		Percent Reduction (Anytime)
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	
Placebo	41	10 (24.4%)	40	11 (27.5%)	36	5 (13.9%)	44	17 (***38.6%***)	
30µg	38	3 (7.9%)	37	4 (10.8%)	40	5 (12.5%)	45	6 (***13.3%***)	**65%**
60µg	34	6 (17.6%)	40	6 (15.0%)	38	3 (7.9%)	46	9 (***19.6%***)	**49%**
30µg + 60µg	72	9 (12.5%)	77	10 (13.0%)	78	8 (10.3%)	91	15 (***16.5%***)	**57%**
Logistic regression for overall effect		p = 0.1683		p = 0.1488		p = 0.6993		***p = 0.0179***	
Pairwise comparisons for shedding at any time									
30µg versus placebo								***p = 0.0087***	
60µg versus placebo								***p = 0.0493***	
30µg+60µg versus placebo								***p = 0.0052***	
30µg versus 60µg								***p = 0.4255***	

Considerations for Expansion of Challenge

- Sufficient demonstration of breadth of “protection”
- Single strain vs. multiple strain exposure
- Need to demonstrate correlation of impact on shedding and clinical efficacy
- Restriction to licensed vaccines?

Shedding of Live, Oral Rotavirus Vaccines after 1st Dose

- RRV-TV >50%
  - Tetravalent, rhesus reassortant
- Rotarix ~50%
  - Single strain, human attenuated – G1P8
- RotaTeq ~10%
  - Pentavalent, bovine reassortant
- ROTAVAC 11-33%
  - Single strain, human neonatal – G9P11
- Rotavin ~50%
  - Single strain, human attenuated – G1P8
- Rotasiil – low
  - Pentavalent, bovine reassortant

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