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Profiles and influence of maternal and infant histo-blood group antigens (HBGA) on oral rotavirus vaccine (ROTARIX®) immunogenicity in Zambia

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14th International Rotavirus Symposium

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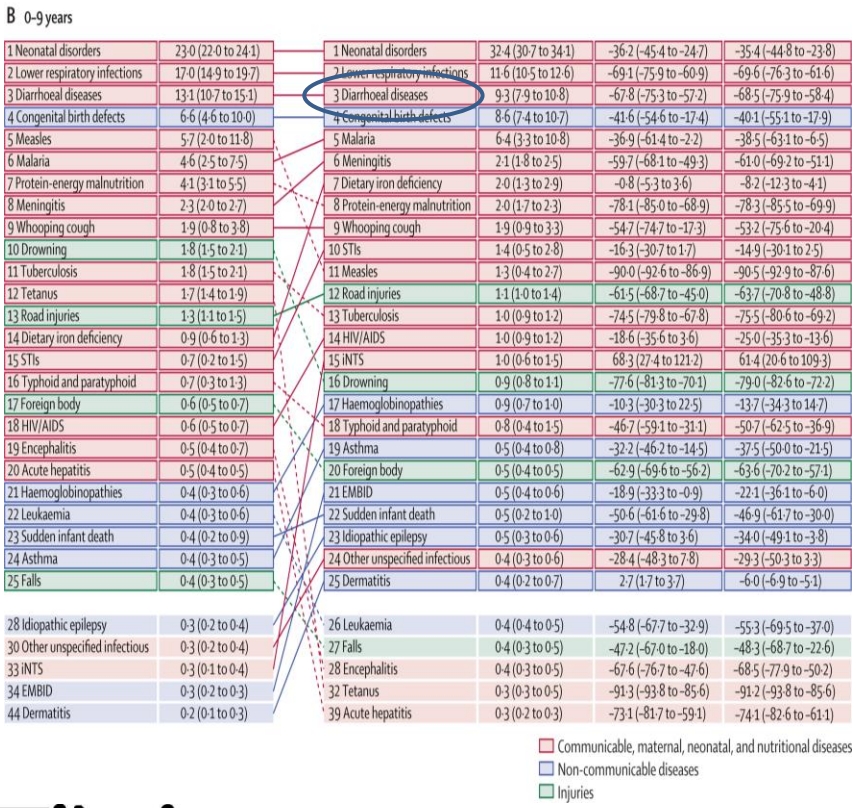
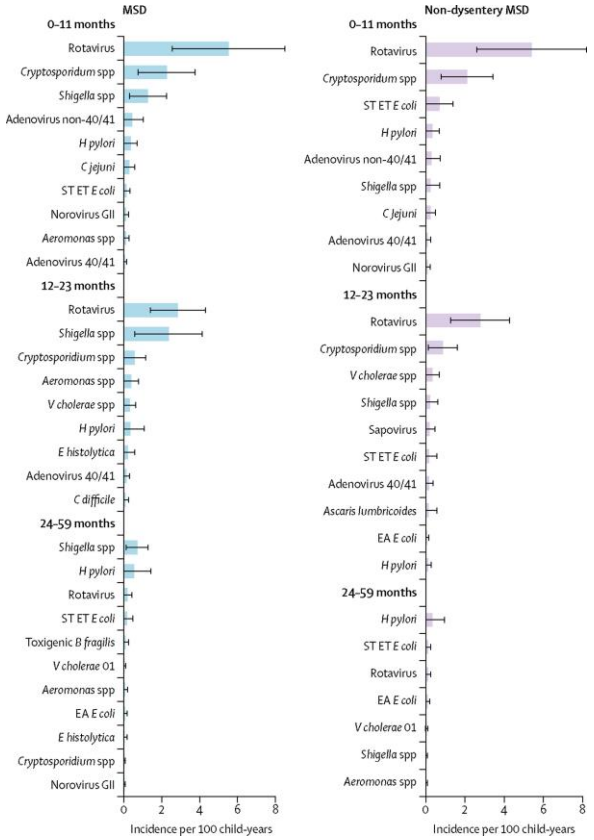
Background

Global Burden of Disease study (GBD 2019)



Global Enteric Multicenter study (GEMS 2019)



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Background Cont'd

- Oral live-attenuated RV vaccines (e.g. Rotarix™) are available life-saving tools but exhibit low immunogenicity in LMIC children.
  (Church et al., 2017)

- Variations in host genetic susceptibility to RV via histo-blood group antigens (HBGA) has been proposed as plausible explanation
  (Lee at el.,2018)

- FUT2 gene (secretor gene) regulates expression and ability to secrete these HBGA (e.g. on mucosal epithelial cells, in breast milk & saliva)
  (Cooling, 2015)

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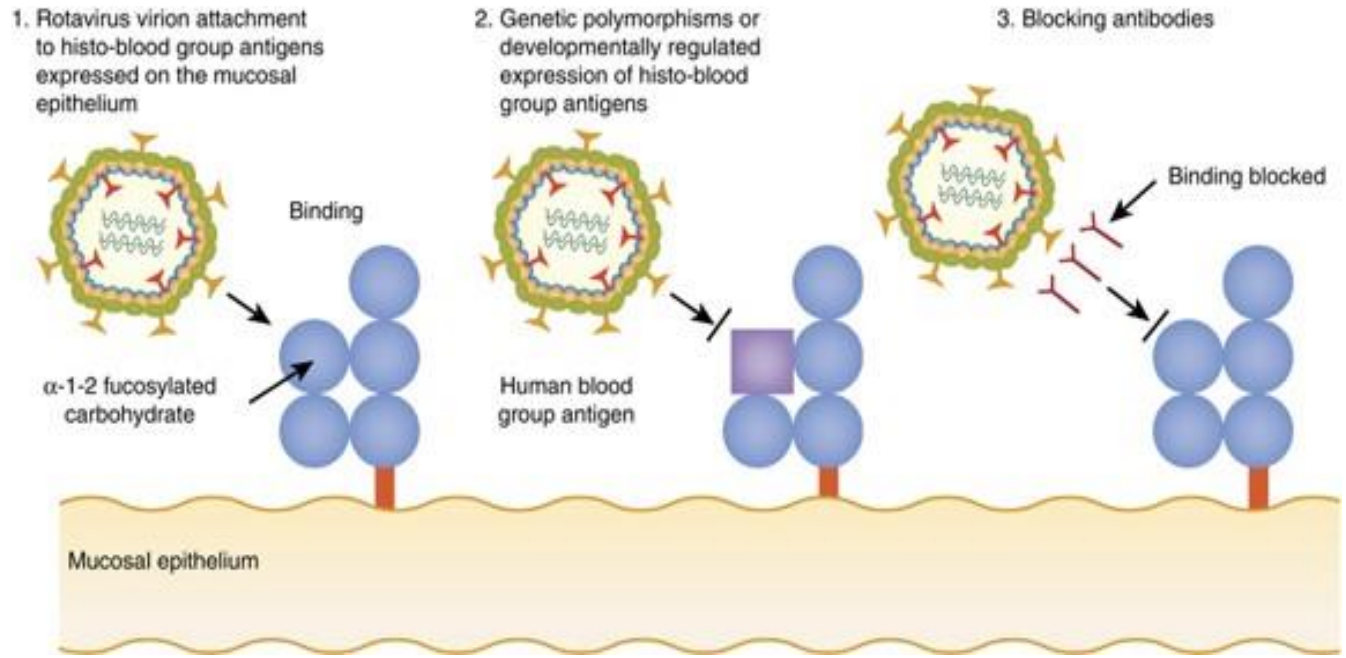
Rationale: Polymorphisms in HBGA gene and secretor status may influence susceptibility to RV infection and live oral RV vaccines



RV can use HBGA as receptors during infection

Figure 1. (Gozalbo-Rovira *et al.*, 2019; Huang et al., 2012)

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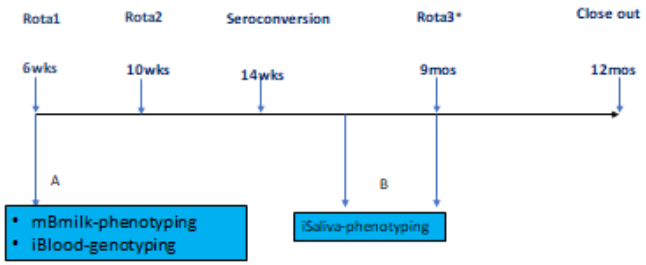
Aim: To profile HBGA genotypes and phenotypes in a mother-infant pair vaccination cohort and assess influence on Rotarix™ vaccine immunogenicity

Study sample collection



A.1. Profile of maternal HBGA and association with (i) RV-IgA titre (ii) seroconversion at 14 weeks
2. Profile of infant genotype and association with (i) RV-IgA tire (ii) seroconversion at 14 weeks

B. 1. Profile of infant HBGA phenotype and association with RV-IgA titre post dose 3 at 12 months

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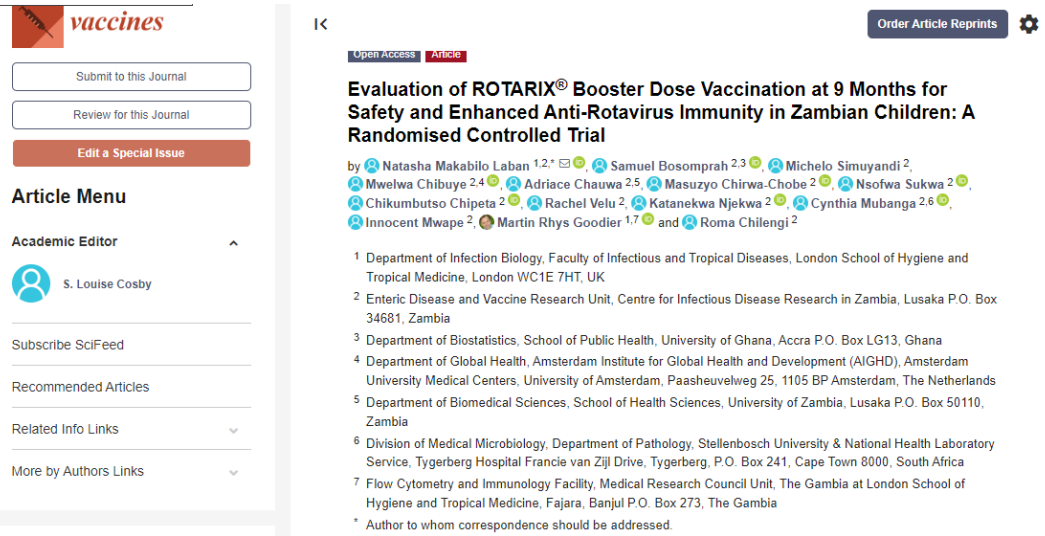
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Evaluation of ROTARIX® Booster Dose Vaccination at 9 Months for Safety and Enhanced Anti-Rotavirus Immunity in Zambian Children: A Randomised Controlled Trial

by Natasha Makabilo Laban [1,2,*], Samuel Bosomprah [2,3], Michelo Simuyandi [2], Mwelwa Chibuye [2,4], Adriace Chauwa [2,5], Masuzyo Chirwa-Chobe [2], Nsofwa Sukwa [2], Chikumbutso Chipeta [2], Rachel Velu [2], Katanekwa Njekwa [2], Cynthia Mubanga [2,6], Innocent Mwape [2], Martin Rhys Goodier [1,7] and Roma Chilengi [2]

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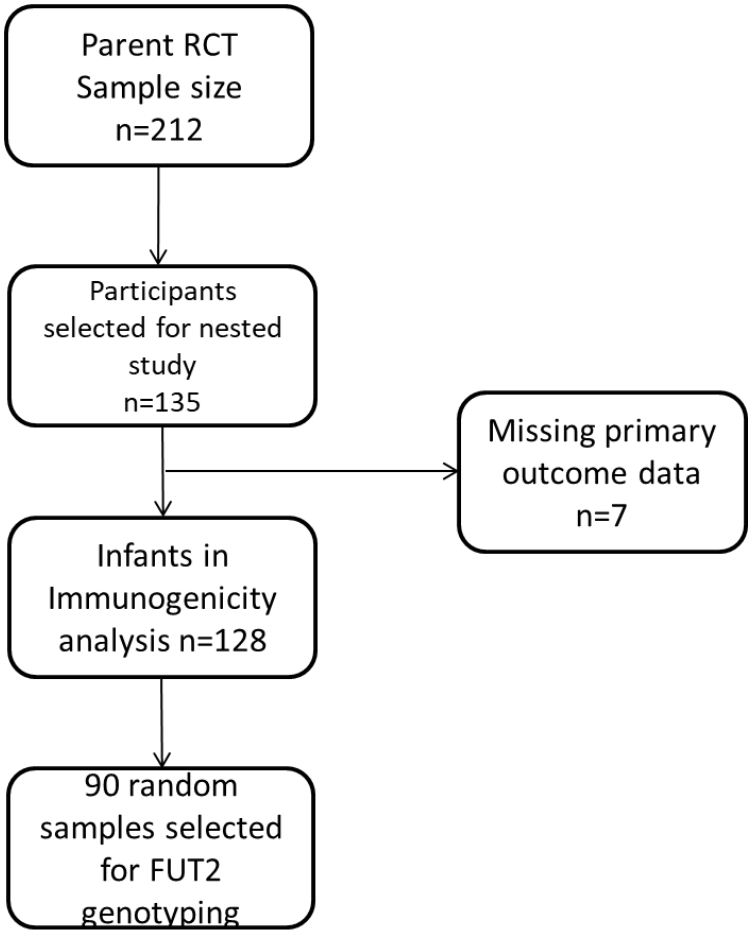
Figure 2. Analysis Flow Chart



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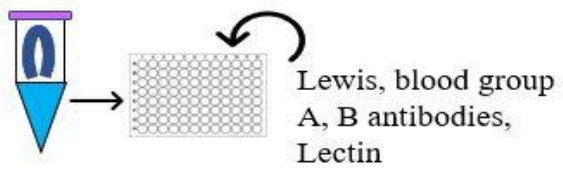
Laboratory Materials & Methods

Assays
HGBA Phenotyping
Lewis A, B antibodies (ELISA)
Blood Group A, B, H antibodies (ELISA)
Lectin (UEA-1) (ELISA)
FUT2 Genotyping
RFLP_PCR
Serology
Rotavirus-IgA antibody (ELISA)

HBGA Phenotyping using infant saliva and breastmilk using ELISA



~1ml saliva/breastmilk

HBGA genotyping on buffy coat using RFLP-PCR

~200ul buffy coat

DNA extraction

RFLP-PCR

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Table 1. Baseline Characteristics and Infant Seroconversion

	Total Population (N=128)	Seroconverted: No (n = 91, 71.1%)	Seroconverted: Yes (n = 37, 28.9%))	P-value
	n (%)	n (%)	n (%)	
Infant Characteristics				
Age (Weeks)				
Median (IQR)	6 (6-6)	6 (6-6)	6 (6-6)	0.442
Mean (Std.Dev)	6 (0.6)	6 (0.6)	5.9 (0.7)	
Sex				
Male	69 (53.9)	51 (73.9)	18 (26)	0.447
Female	59 (46.1)	40 (67.7)	19 (32.2)	
Treatment				
Control	57 (44.5)	41 (71.9)	16 (28)	0.852
Intervention	71 (55.5)	50 (70.4)	21 (29.5)	
Feeding				
Exclusive Breastfeeding	122 (95.3)	86 (70.4)	36 (29.5)	0.672
Mixed Feeding	6 (4.7)	5 (83.3)	1 (16.6)	
Birthwieght (kg)				
< 2.5	5 (3.9)	3 (60)	2 (40)	0.626
≥ 2.5	123 (96.1)	88 (71.5)	35 (28.4)	
HIV Exposure				
Not Exposed	89 (69.5)	62 (69.6)	27 (30.3)	0.590
Exposed	39 (30.5)	28 (73.6)	10 (26.3)	
Nutritional Status				
Malnourished				
No (WHZ ≥ -2)	126 (98.4)	89 (70.6)	37 (29.3)	1.000
Yes (WHZ < -2)	2 (1.6)	2 (100)	0 (0)	
Stunted				
No (HAZ ≥ -2)	107 (83.6)	78 (72.8)	29 (27.1)	0.310
Yes (HAZ < -2)	21 (16.4)	13 (61.9)	8 (38)	
Wasted				
No (WAZ ≥ -2)	119 (93.0)	86 (72.2)	33 (27.7)	0.281
Yes (WAZ < -2)	9 (7.0)	5 (55.5)	4 (44.4)	

		Seroconverted		
Mother's Characteristics				
Age				
<20	20 (15.6)	15 (75)	5 (25)	0.080
20-24	45 (35.2)	37 (82.2)	8 (17.7)	
25-29	34 (26.6)	19 (55.8)	15 (44.1)	
≥30	29 (22.7)	20 (68.9)	9 (31)	
Highest Education Level				
None	6 (4.7)	4 (66.7)	2 (33.3)	0.470
Primary	40 (31.3)	25 (62.5)	15 (37.5)	
Secondary	81 (63.3)	61 (75.3)	20 (24.6)	
Tertiary	1 (0.8)	1 (100)	0 (0)	
Water Source				
Piped into house/yard	45 (35.2)	33 (75)	12 (25)	0.882
Protected well	5 (3.9)	4 (80)	1 (20)	
Public borehole/tap and pipe	78 (60.9)	54 (80)	24 (20)	
Shared Toilet Facility				
No	24 (18.8)	17 (70.8)	7 (29.1)	0.975
Yes	104 (81.3)	74 (71.1)	30 (28.8)	
Type of Toilet Faciity				
Flushing toilet	26 (20.3)	17 (65.4)	9 (34.6)	0.476
Pit laterine	102 (79.7)	74 (72.6)	28 (27.5)	

Figure 3. Maternal and Infant HBGA Frequency Distribution

Figure 3(a). Maternal Lewis and Secretor profiles

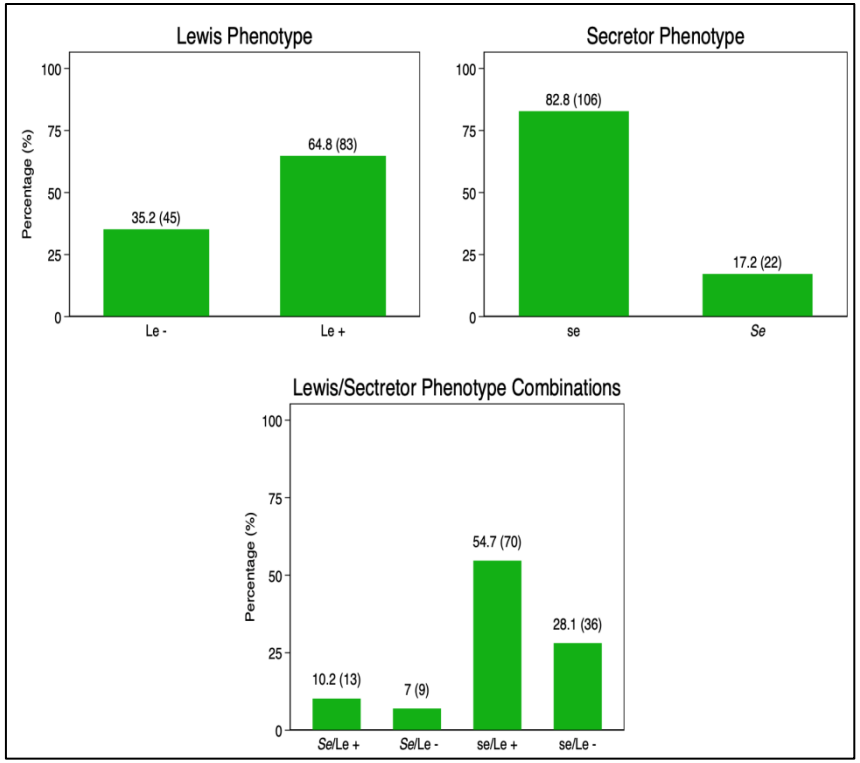

Figure 3(b). Infant ABO, Lewis and Secretor HBGA profiles

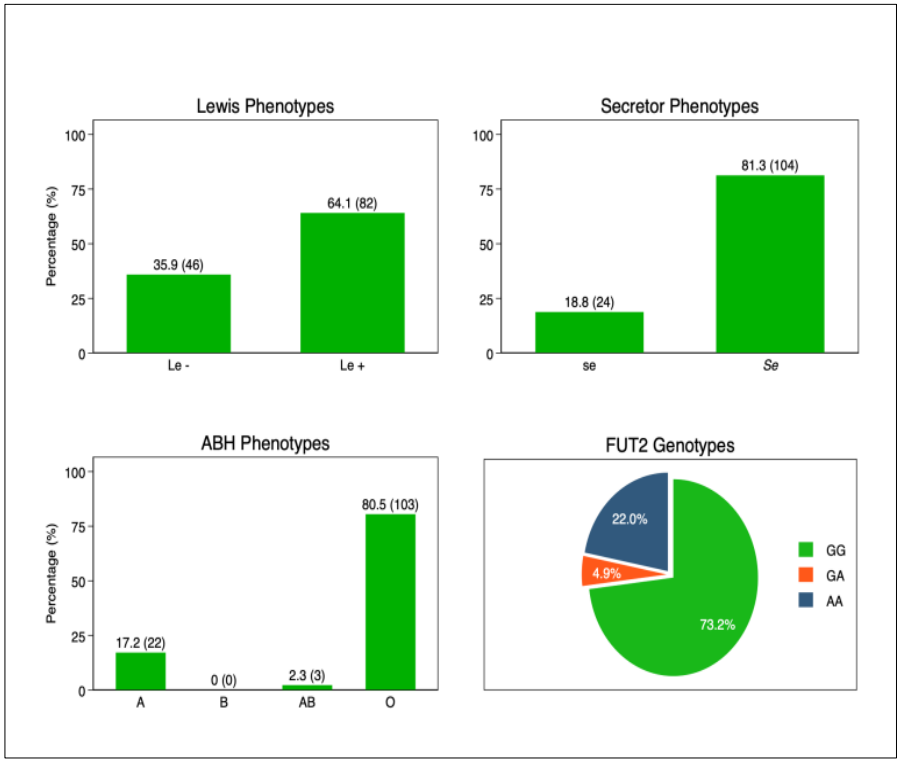

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Figure 4. Maternal and Infant HBGA Frequency Distribution

Figure 4(a). Two-sided t-test Trend plot for infant RV-IgA titre by infant ABO phenotype

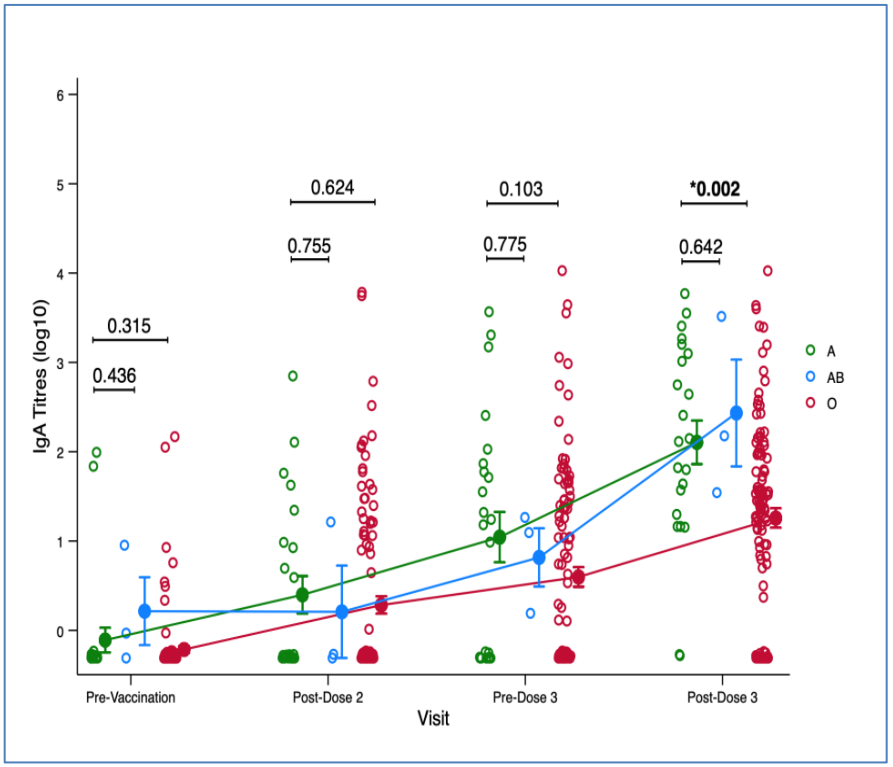

Figure 4(b). Two-sided t-test Trend plot for infant RV-IgA titre by Lewis phenotype

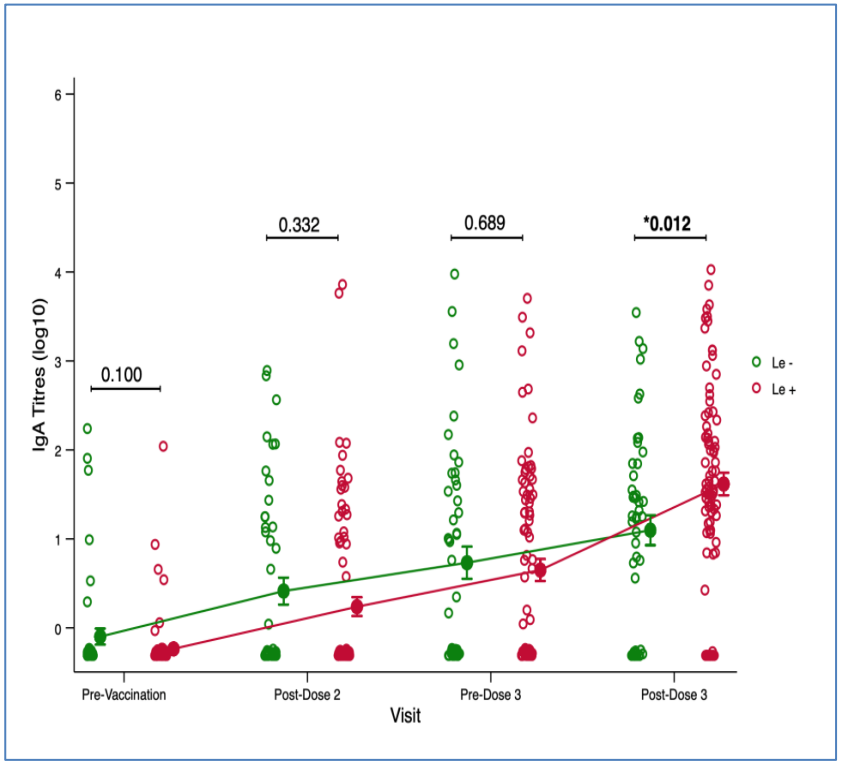

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Table 2. Maternal and infant HBGA profiles and anti-rotavirus IgA titres 1- month post ROTARIX® dose 2

(N = 128) (Overall)								
Characteristics	Number of mother-infant pairs (% of total)	GMTs GMT (95% CI)	ANOVA P-value	GMT Ratio GMR (95% CI)	ANOVA P-value	Seroconversion (n = 37, 28.9%) n (%)	Chi-Square P-value
Infant							
Infant HBGA Phenotype							
A	22 (17.2)	2.5 (0.9, 6.8)	0.874	ref		7 (31.8)	0.929
AB	3 (2.3)	1.6 (0, 270.6)		0.6 (0.1, 5.6)	0.690	1 (33.3)	
O	103 (80.5)	1.9 (1.2, 3)		0.8 (0.3, 2.2)	0.620	29 (28.2)	
Infant Lewis Phenotype							
Le- (Le a-b-)	46 (35.9)	2.6 (1.3, 5.2)	0.332	ref		14 (30.4)	0.775
Le+ (Le a+b-,Le a-b+, or Le a+b+)	82 (64.1)	1.7 (1.1, 2.8)		0.7 (0.3, 1.5)	0.341	23 (28.2)	
Secretor Phenotype							
Non-secretor (se)	24 (18.8)	1.3 (0.6, 2.8)	0.279	ref		5 (20.8)	0.24
Secretor Phenotype (Se)	104 (81.3)	2.2 (1.4, 3.5)		1.7 (0.7, 4.2)	0.213	32 (30.8)	
Infant FUT2 Genotype*							
Homozygous secretor (GG)	60 (46.9)	1.4 (0.8, 2.5)	0.093	ref		15 (25.0)	0.289
Heterozygous secretor (GA)	4 (3.1)	5.6 (0, 1426.5)		3.9 (0.2, 85.1)	0.385	2 (50.0)	
Non-secretor (AA)	18 (14.1)	4.9 (1.5, 16.3)		3.4 (1.0, 11.9)	0.050	7 (38.9)	
Missing	46 (35.9)	2 (1, 3.8)		1.4 (0.6, 3.2)	0.447	13 (28.3)	
Mother							
Lewis Phenotype							
Le- (Le a-b-)	45 (35.2)	1.6 (0.9, 2.8)	0.358	ref		13 (28.9)	0.997
Le+ (Le a+b-,Le a-b+, or Le a+b+)	83 (64.8)	2.3 (1.4, 3.9)		1.5 (0.7, 3.2)	0.330	24 (28.9)	
Secretor Phenotype							
Non-secretor (se)	106 (82.8)	2 (1.3, 3.1)	0.850	ref		32 (30.2)	0.336
Secretor Phenotype (Se)	22 (17.2)	1.8 (0.7, 5.2)		0.9 (0.3, 2.6)	0.852	5 (22.7)	

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Table 3. Maternal and infant HBGA profiles and seroconversion 1- month post ROTARIX® dose 2

Characteristics	Crude Odds Ratio (95% CI)	P-value
Infant HBGA Phenotype		
A	ref	
AB	1.1 (0.1, 13.9)	0.958
O	0.8 (0.3, 2.3)	0.731
Infant Lewis Phenotype		
Le- (Le a-b-)	ref	
Le+ (Le a+b-,Le a-b+, or Le a+b+)	0.9 (0.4, 2)	0.775
Infant Secretor Phenotype		
Non-secretor (se)	ref	
Secretor Phenotype (Se)	1.7 (0.6, 4.9)	0.337
Infant FUT2 Genotype		
Homozygous secretor (GG)	ref	
Heterozygous secretor (GA)	3 (0.4, 23.2)	0.292
Non-secretor (G428A)	1.9 (0.6, 5.8)	0.255
Mother Lewis Phenotype		
Le- (Le a-b-)	ref	
Le+ (Le a+b-,Le a-b+, or Le a+b+)	1.0 (0.4, 2.2)	0.997
Mother Secretor Phenotype		
Non-secretor (se)	ref	
Secretor Phenotype (Se)	0.7 (0.2, 2.0)	0.484
Treatment Arm		
Control (MR)	ref	
Intervention (ROTARIX® +MR)	1.1 (0.5, 2.3)	0.852

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Table 4. Maternal and Infant HBGA profiles and anti-rotavirus IgA titres at 12-months

Characteristics	V12 GMTs	ANOVA, P-value	GMT Ratio (95% CI)	P-value
	GMT (95% CI)			
Infant				
Infant ABO Phenotype				
A	5.02 (4.14, 6.07)	**0.002**	ref	
AB	5.28 (1.86, 15)		0.59 (0.10, 3.47)	0.560
O	3.7 (3.35, 4.08)		0.36 (0.09, 1.41)	0.140
Infant Lewis Phenotype				
Le- (Le a-b-)	3.57 (3.03, 4.22)	**0.015**	ref	
Le+ (Le a+b-,Le a-b+, or Le a+b+)	4.17 (3.75, 4.63)		0.83 (0.31, 2.23)	0.705
Secretor Phenotype				
Non-secretor (se)	2.89 (2.26, 3.71)	**< 0.001**	ref	
Secretor Phenotype (Se)	4.14 (3.78, 4.54)		1.94 (0.59, 6.4)	0.276
Infant FUT2 Genotype				
Secretor (GG)/(GA)	3.95 (3.45, 4.52)	0.063	ref	
Non-secretor (AA)	3.24 (2.44, 4.31)		1.66 (0.96, 2.83)	0.543
Mother				
Lewis Phenotype				
Le- (Le a-b-)	4.02 (3.52, 4.58)	0.521	ref	
Le+ (Le a+b-,Le a-b+, or Le a+b+)	3.95 (3.51, 4.44)		1.09 (0.41, 2.88)	0.863
Secretor Phenotype				
Non-secretor (se)	4.08 (3.72, 4.48)	0.368	ref	
Secretor Phenotype (Se)	3.45 (2.64, 4.51)		0.83 (0.25, 2.70)	0.751
Treatment Arm				
Control (MR)	4.08 (3.56, 4.67)	0.260	ref	
Intervention (ROTARIX®+MR)	3.88 (3.44, 4.37)		1.39 (0.55, 3.49)	0.479

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Discussion

- Infant ABO phenotypes showed a higher frequency of group O, followed by A, AB
- A higher frequency of secretors than non-secretor infants (both phenotype and FUT2 genotype)
- Infant Lewis profile showed higher frequency of Lewis(+) than Lewis-null phenotype
- Maternal HBGA profiles showed a higher frequency of non-secretors than secretors and more Lewis(+) than Lewis-null phenotype

Discussion Cont'd

- Infant blood group AB showed the highest increase in RV-IgA titres between 9 and 12-months
- Infant Lewis(+) phenotype also showed a significantly higher increase in RV-IgA titres at 12-months compared to Lewis-null phenotype
- Infant secretor phenotype also showed a statistically higher increase in GMTs at 12-months compared to non-secretors

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Conclusion

- Maternal and infant HBGAs were not associated with Rotarix® immunogenicity in early infant life.

- Infant HBGAs antigens seem to influence rotavirus-IgA antibody titres much later in infant life.
- *Increase in titres most likely as a result of natural infection*
- Further robust studies are needed to comprehensively establish reasons for low Rotarix® immunogenicity in early infant life

- Next study approaches to focus on alternative RV vaccines, OR improvements on currently existing oral, live-attenuated vaccines

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Thank You!