Effect of non-secretor/Lewis Phenotype on rotavirus-specific IgA response, vaccine take and clinical protection following monovalent rotavirus vaccination in Malawian infants

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Background

Rotavirus (RV) vaccine efficacy is lower in Malawi and other high-burden, low-income settings than in lower-burden, higher-income settings. Several explanations for this have been proposed, but supportive data are limited. Histo-blood-group-antigen(HBGA) phenotypes are associated with genotype-specific susceptibility to rotavirus infection. Evidence suggests non-secretor/Lewis negative infants may be resistant to G1P[8] infection. Since current vaccines are based on P[8] strains, this could limit vaccine efficacy. We tested the hypothesis that non-secretor/Lewis negative phenotype leads to reduced vaccine virus replication, IgA response and clinical protection following monovalent G1P[8] rotavirus (RV1) vaccination in Malawian infants.

Methods

Population

Vaccine virus replication and immunogenicity were determined by a cohort study of infants receiving 2 doses of RV1 at 6 and 10 weeks of age. Clinical protection was determined by a cross-sectional case:control study comparing vaccinated infants <12 months with severe rotavirus gastroenteritis (RVGE) to age-matched, vaccinated, asymptomatic community controls.

Laboratory methods

Stool was collected on alternate days from days 4-10 post vaccine. Vaccine virus faecal shedding was determined by NSP2 RT-PCR with confirmatory VP6 qRT-PCR. Shedding was defined as detectable RV1 from ≥2 post vaccine samples. Post-vaccine plasma rotavirus(RV)-specific IgA was determined by ELISA. Seroconversion defined as RV-specific IgA>20 U/L with ≥fourfold rise in concentration among infants seropositive at baseline. HBGA phenotype was determined by salivary ELISA. RVGE cases were confirmed by VP6 qRT-PCR. Genotype was determined by RT-PCR.

Statistical methods

Log-binomial regression, logistic regression and conditional logistic regression were used to compare outcomes by HBGA phenotype in the cohort, genotype analysis and matched case:control studies respectively.

Results: Cohort Study

293 infants were recruited to the cohort study between May 2015 and August 2016, of whom 202 completed follow-up and were included in the analysis. **HBGA phenotype and vaccine virus faecal shedding** The likelihood of vaccine virus faecal shedding (vaccine take) did not differ between infants with secretor compared to non-secretor phenotype, or between infants with Lewis positive compared to Lewis negative phenotype (**Table 1**).

Table 1

HBGA phenotype	Proportion of infants with vaccine virus faecal shedding n, % (95%CI)	Likelihood of vaccine virus faecal shedding RR (95%CI), p value
Secretor vs Non-secretor	86/157, 55 (47-62%) vs 18/45, 40 (26-55%)	1.4 (0.9-2.0) vs 0.73 (0.5-1.1) p=0.11
Lewis positive vs Lewis negative	84/159, 53 (45-61%) vs 20/43, 47 (32-62%)	1.1 (0.8-1.6) vs 0.88 (0.6-1.3) p=0.48

HBGA phenotype and RV-specific IgA response

In 196 cohort infants with paired serology, the likelihood of seroconversion did not differ between infants with secretor compared to non-secretor phenotype, or between infants with Lewis positive compared to Lewis negative phenotype (**Table 2**).

Table 2

HBGA phenotype	Proportion of infants with RV-specific IgA seroconversion n, % (95%CI)	Likelihood of RV-specific IgA seroconversion RR (95%CI), p value ^b
Secretor vs Non-secretor	27/151, 27 (21-35%) vs 6/45, 13 (6-27%)	2.0 (0.9-4.5) vs 0.5 (0.2-1.1) p=0.08
Lewis positive vs Lewis negative	35/149, 24 (17-31%) vs 12/47, 26 (15-40%)	0.9 (0.5-1.6) vs 1.1 (0.6-1.9) p=0.77

Results: Case-Control Study

5990 GE cases were screened and 319 RVGE cases identified between January 2015 February 2017. 123 eligible RVGE cases <12 months old were recruited, 119 with HBGA phenotype data. **HBGA phenotype and genotype-specific susceptibility to RVGE** Genotype data was available for 114 rotavirus cases, 28 asymptomatic rotavirus infections, and 43 rotavirus-negative community controls. Secretor phenotype was associated with increased risk of P[8] and P[4] RVGE. Lewis negative phenotype was associated with increased risk of P[6] RVGE (**Table 3**).

Table 3

	Secretor n=148 OR (95% CI)	Lewis negative n=39 OR (95% CI)
P[8] RVGE n=47	n=45 7.8 (1.8-33.7) p=0.006	n=4 0.28 (0.09-0.83) p=0.022
P[4] RVGE n=38	n=36 5.8 (1.3-25.2) p=0.019	n=36 0.17 (0.04-0.73) p=0.017
P[6] RVGE n=34	n=27 0.99 (0.39-2.5) p=0.98	n=13 3.0 (1.3-6.7) p=0.008

HBGA phenotype and clinical protection

119 RV GE cases (vaccine failures) were compared to 119 age-matched community controls .The prevalence of non-secretor phenotype in community controls was 28%(20-37%) and Lewis negative phenotype 26%(19-35%). Non-secretor phenotype was associated with reduced risk of clinical vaccine failure (**Table 4**).

Table 4

HBGA phenotype	Prevalence in RV GE cases n, % (95%CI)	Odds of rotavirus vaccine failure OR (95%CI)
Non-secretor	14/119, 12 (7-19%)	0.39 (0.20-0.75) p=0.005
Lewis negative	24/119, 20 (14-28%)	0.70 (0.37-1.3) p=0.265

Conclusions

We found no evidence that HBGA phenotype determines vaccine virus shedding or seroconversion. The lower vaccine failure in non-secretors is due to the relative protection this phenotype confers against the common P[8] and P[4] rotavirus strains. HBGA phenotype distribution is unlikely to contribute significantly to reduced rotavirus vaccine effectiveness in Malawi.