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Short communication

Histo-blood group antigen profile of Australian Aboriginal children and seropositivity following oral rotavirus vaccination

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ABSTRACT

Background: Histo-blood group antigens (HBGAs) may influence immune responses to rotavirus vaccination.
Methods: HBGA phenotyping was determined by detection of antigens A, B, H and Lewis a and b in saliva using enzyme-linked immunosorbent assay. Secretor status was confirmed by lectin antigen assay if A, B and H antigens were negative or borderline (OD ± 0.1 of threshold of detection). PCR-RFLP analysis was used to identify the *FUT2* 'G428A' mutation in a subset. Rotavirus seropositivity was defined as serum anti-rotavirus IgA $\geq$ 20 AU/mL.
Results: Of 156 children, 119 (76 %) were secretors, 129 (83 %) were Lewis antigen positive, and 105 (67 %) were rotavirus IgA seropositive. Eighty-seven of 119 (73 %) secretors were rotavirus seropositive, versus 4/9 (44 %) weak secretors and 13/27 (48 %) non-secretors.
Conclusions: Most Australian Aboriginal children were secretor and Lewis antigen positive. Non-secretor children were less likely to be seropositive to rotavirus antibodies following vaccination, but this phenotype was less common. HBGA status is unlikely to fully explain underperformance of rotavirus vaccines among Australian Aboriginal children.

1. Introduction

Rotavirus remains a leading cause of dehydrating diarrhoeal disease in young children [1]. The introduction of oral rotavirus vaccines into childhood immunization programmes has resulted in a significant reduction in the global burden of rotavirus disease, however vaccine effectiveness has varied across settings [2]. A systematic review of the performance of four oral rotavirus vaccines in high child mortality settings in Asia and Africa reported that vaccine efficacy was 48 to 57 % in the first year following vaccination, and 29 % to 54 % in the second year [3]. Reduced protection from oral rotavirus vaccines has also been reported among rural and remote Australian Aboriginal and Torres Strait Islander children [4].

The suboptimal protection from oral rotavirus vaccines observed in these settings has been variously attributed to high

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levels of maternally derived vaccine-neutralising anti-rotavirus antibodies transferred to infants via the placenta and breastmilk, poor infant nutrition, environmental enteropathy and intestinal dysbiosis, comorbid infection, and a high diversity of circulating rotavirus strains [2]. Histo-blood group antigens (HBGAs) appear to be an important determinant of host-susceptibility to rotavirus infection and may affect the immune response to oral rotavirus vaccines [5].

HBGAs are carbohydrates expressed on the surface of gut epithelium and in soluble forms in saliva and breast milk. Synthesis of secretor and Lewis HBGAs is catalysed by glycosyltransferase enzymes encoded by the *FUT2* and *FUT3* genes, respectively. Mutations in these genes can give rise to non-functional enzymes, and subsequently non-secretor and Lewis negative phenotypes. Differences in the prevalence of polymorphisms in the *FUT2* and *FUT3* genes gives rise to differential expression of secretor and Lewis status between populations [6].

The increasing evidence for the role that HBGA phenotype plays in susceptibility to rotavirus infection has stimulated interest in the possible role that HBGA may play in the immune response to oral rotavirus vaccines. All licensed rotavirus vaccines comprise live attenuated virus strains so it is plausible that factors which affect wild-type rotavirus infection may also apply to rotavirus vaccine strains, as vaccine virus replication within intestinal epithelial cells is required to induce local gut immunity and subsequent vaccine effects [7]. For the first time, this study reports the relationship between the HBGA status of Australian Aboriginal children and their seropositivity to rotavirus following receipt of a standard two-dose schedule of oral Rotarix rotavirus vaccine.

2. Methods

2.1. Study design & setting

The study was nested in ORVAC, a double-blind randomised, placebo-controlled clinical trial evaluating the immunological and clinical effect of administering an additional (booster) dose of oral Rotarix rotavirus vaccine to Australian Aboriginal and Torres Strait Islander children aged 6 to <12 months old. The ORVAC protocol has been published elsewhere [8]. In brief, children were eligible for enrolment if they were 6 to <12 months old, identified as Aboriginal and/ or Torres Strait Islander, and had been previously been vaccinated with at least one dose of oral Rotarix vaccine (scheduled at age 6 weeks and 4 months old). In ORVAC Stage 1, serum was collected at enrolment to determine IgA seropositivity to rotavirus (at age 6 to <12 months old) and consent was also sought from a subset of participants to collect a sample of the child's saliva at enrolment. Approvals were obtained from the Northern Territory Department of Health and Menzies School of Health Research Ethics Committee (2020-3759). The ORVAC protocol is registered on ClinicalTrials.gov (NCT02941107).

2.2. Blood samples

At enrolment, a blood sample of 1.2 mL was collected to measure anti-rotavirus serum IgA levels. As detailed previously [8], specific rotavirus IgA antibodies were measured by enzyme linked immuno-assay using rabbit anti-rotavirus polyclonal antisera as the coating antibody to capture a rotavirus lysate (G1P8) strain. Concentrations of rotavirus-specific IgA were measured in patient serum samples using a reference standard having been assigned a concentration of 1000 arbitrary units (AU/mL). Seropositivity was defined as anti-rotavirus IgA $\geq$ 20 AU/mL.

2.3. Saliva samples

At enrolment, 1 mL saliva sample was collected in the GeneFix-Saliva DNA Collection tube (Isolhelix, UK) containing 1 mL of stabilisation buffer. The samples were mixed then divided into two. Aliquot One (1 mL Saliva/Buffer) was used for HBGA phenotyping by enzyme-linked immunosorbent assay (ELISA), In brief, HBGA phenotyping was determined by detection of antigens A, B, H and Lewis a and b in saliva by enzyme-linked immunosorbent assay ELISA, using specific monoclonal antibodies, detected by peroxidase conjugated anti-mouse IgM as previously described [9]. Infants with detectable salivary A, B, or H antigen, were classified as "secretors" based on a threshold for the mean optical density (OD) of four times the level observed in the negative and blank controls for each HBGA ELISA (A, B, H and Lewis a, Lewis b and lectin). Samples with an OD within ±0.1 of this threshold were classified as borderline and the analysis was repeated. Where detection of A, B and H antigens was classified as negative or borderline, secretor status was confirmed by ELISA to detect lectin antigen (using Ulex Europaeus peroxidase conjugate Sigma-Alrich, St Louis, MO). Infants who were positive for either Lewis a or Lewis b antigen were classified as Lewis positive, and those negative for both Lewis a and b antigens were classified as Lewis negative [9]. Participants were classified as a non-secretor if negative on HBGA ELISA for A, B, H and lectin antigen.

Aliquot Two (1 mL Saliva/Buffer) was used to extract DNA from a subset of samples with either non-secretor or indeterminate phenotype results using the GeneFix Saliva DNA Mini Kit (Isohelix, UK). *FUT2* was amplified by polymerase chain reaction (PCR) and restriction fragment length polymorphism was used to identify the *FUT2* 'G428A' mutation (saliva DNA + *FUT2* PCR (195 bp amplicon) + AvaII restriction enzyme) [9], with results interpreted in Table 2. Participants who were positive for at least one of A, B or H, weak positive for lectin were classified as weak secretors. Samples that gave indeterminate results on repeated analysis were classified as indeterminate [9].

2.4. Statistics

Frequencies of anti-rotavirus IgA seropositivity at enrolment by Lewis, secretor and combined Lewis and secretor status were expressed as proportions and percentages, with the average concentration expressed as the geometric mean concentration (GMC). A non-informative beta conjugate prior to the binomial likelihood was used to estimate posterior distributions by phenotype classification and to derive relative risk ratios.

3. Results

There were 253 children enrolled into ORVAC Stage 1 between March 2018 and August 2020. Of these, 156 children had saliva collected for HBGA analysis. Baseline demographic characteristics were comparable to the total ORVAC Stage 1 cohort (Appendix 1) and almost all children (96 %) had received a complete two-dose course of oral Rotarix vaccine (Table 1).

Of the 156 participants, 119 (76 %) were secretors and 129 (83 %) were Lewis antigen positive (Table 2). Seven participants were classified as 'Lewis status untypeable' and one participant was "Lewis and secretor untypeable" as repeat of the HBGA ELISA the samples still yielded OD values within ±0.1 of the assay threshold. Only one of the 14 non-secretors assessed by the *FUT2* "G428A' PCR assay was homozygous for this mutation.

Of the 156 participants, 105 (67 %) were anti-rotavirus seropositive at baseline; 87 of 119 (73 %) secretors versus 4/9 (44 %) weak secretors and 13/27 (48 %) non-secretors were seropositive, and 89

Table 1
Baseline demographic characteristics including prior vaccine doses.

Characteristic	Participants (n = 156)
Sex	
- Female	77 (49 %)
Age, median (IQR), weeks	36.3 (29.9, 43.5)
Indigenous status	
- Aboriginal	148 (95 %)
- Torres Strait Islander	6 (4 %)
- Aboriginal and Torres Strait Islander	2 (1 %)
Breastfed	
- Exclusively	14 (9 %)
- Partially	108 (69 %)
Weight, median (IQR), kg	8.5 (7.7, 9.1)
MUAC*, median (IQR), mm	145 (139–154)
Vaccination status	
- Rotarix Dose 1	156 (100 %)
- Rotarix Dose 2	149 (96 %)

*MUAC = mid-upper arm circumference.

of 129 (69 %) Lewis antigen positive versus 10/ 19 (53 %) Lewis antigen negative were seropositive (Table 2). Crude (unadjusted) analyses, suggested that weak secretors and non-secretors were less likely to have evidence of IgA seropositivity compared to secretors, RR 0.62 (95%CrI, 0.25–1.02) and RR 0.66 (95%CrI, 0.41–0.93) respectively. Lewis negative participants were less likely to be seropositive than Lewis positive children, though evidence was weak RR 0.66 (95%CrI, 0.47–1.10).

4. Discussion

The ORVAC clinical trial undertaken in Australian Aboriginal children provided an opportunity to examine for the first time the association between HBGA status and immune response to oral rotavirus vaccine in this high-risk population.

We found that a higher proportion of children with the secretor phenotype, compared with those with weak or non-secretor phenotype, were seropositive for anti-rotavirus antibodies following administration of their routine Rotarix vaccine schedule (73 % vs. 44 % and 48%, respectively). Higher rates of rotavirus vaccine IgA seroconversion and/or vaccine strain shedding (a marker of vaccine "take") have been observed previously among secretors compared to non-secretors, in studies among children in Nicaragua, Pakistan, Ghana and Malawi [5]. With the exception of a study in Nicaragua, which observed a lower proportion of seroconversion among Lewis-positive non-secretors after 1 dose of either Rotarix or RotaTeq [5], previous studies have not identified an effect of Lewis antigen status on vaccine response. We found no evidence of reduced seropositivity for this group, and instead observed reduced seropositivity for Lewis-negative non-secretors, though numbers were small (n = 6).

While IgA seroconversion tends to broadly reflect oral rotavirus vaccine performance at the population level, individual level protection against rotavirus infection is mediated by both humoral and cellular components of the immune system [10]. A study of 238 vaccinated children in Malawi found that the prevalence of non-secretor phenotype was significantly lower among children with vaccine failure (12 %) compared to community controls with no diarrhoea (28 %) [9]. The authors proposed that although non-secretor children might be resistant to live rotavirus vaccine strains, their resistance to naturally circulating wild-type rotaviruses might, on balance, nonetheless protect them from rotavirus disease. Similarly, a trial among children in Bangladesh observed that Rotarix provides similar protection to children with secretor and non- secretor phenotype, and that Lewis phenotype did not impact vaccine effectiveness [11].

Globally, the rotavirus P-genotypes P[4], P[6] and P[8] predominate in children [10]. The secretor phenotype has been associated with increased susceptibility to P[4] and P[8] rotavirus infections, while Lewis negative phenotype individuals have been shown to be preferentially infected by the P[6] genotype independent of secretor status [5]. It is proposed that variation in the distribution of HBGA phenotype between populations and ethnic groups may account for some of the geographical variation in circulating rotavirus strains. For example, the high prevalence of Lewis negative phenotype in sub-Saharan Africa may explain why strains containing a VP4 P[6] are endemic there. [5] P[6] strains are infrequently detected in Australian children and the dominant genotypes circulating during the trial (2018–2020) were G2P[4] and G3P[8 12,13,14]. A higher diversity of circulating strains has been observed in the Northern Territory, compared to neighbouring jurisdictions, with increased proportion of G9P[8] and G3P[8] strains in particular, underscoring the importance of determining the HBGA phenotype and its potential influence on vaccine take in this population [15].

Maternal HBGA status may play a role in rotavirus vaccine seroconversion among breast-feeding children. A recent study in Bangladesh reported rotavirus-specific IgA seroconversion rates were higher among breast-fed children of non-secretor mothers than

Table 2
Rotavirus IgA seropositivity by Lewis and secretor status.

HBGA Phenotype	Participants Proportion (%)	IgA Seropositive ≥20 AU/mL (n/%)	RR (95%CrI)	IgA GMC AU/mL**
Secretor Phenotype				
Secretor	119/156 (76 %)	87/119 (73 %) (1)*	Reference	68.8
Weak Secretor	9/156 (6 %)	4/9 (44 %)	0.62 (0.25, 1.02)	42.6
Non-Secretor	27/156 (17 %)	13/27 (48 %) (2)*	0.66 (0.41, 0.93)	24.6
Untypeable	1/156 (1 %)	1/1 (100 %)	–	–
Lewis Phenotype				
Positive	129/156 (83 %)	89/129 (69 %)	Reference	56.2
Negative	19/156 (12 %)	10 (53 %)	0.79 (0.47, 1.10)	56.4
Untypeable	8/156 (5 %)	6/8 (75 %)	–	–
Combined Phenotype				
Lewis Positive Secretors	99/156 (63 %)	73/99 (74 %)	–	64.7
Lewis Positive Weak Secretors	9/156 (6 %)	4/9 (44 %)	–	52.6
Lewis Positive Non-Secretors	21/156 (13 %)	12/21 (67 %)	–	30.3
Lewis Negative Secretors	13/156 (8 %)	9/13 (69 %)	–	116.4
Lewis Negative Non-Secretors	6/156 (4 %)	1/6 (20 %)	–	9.2
Untypeable/ Secretor	7/156 (4 %)	5/7 (71 %)	–	–
Untypeable	1/156 (1 %)	1/1 (100 %)	–	–

*Extra numeric indicates number of missing IgA values.
**Geometric means are based on complete cases.

among children whose mothers were secretors (39 % vs 23 % respectively) [16]. Although many children in our study were fully or partially breastfed at the time of enrolment, we are unable to ascertain maternal HBGA status or exposure to breastmilk at the time of prior oral rotavirus vaccine administration.

There were several limitations. In this cohort, most children were secretor positive (76 %) and only a small proportion were Lewis negative (12 %). While these data are consistent with the prevalence observed in European, North American and some Asian populations, and among non-Indigenous Australian children [5,7], they contrast with earlier studies of Australian Aboriginal adults where 97 % of participants were reported to be secretor positive and the Lewis negative phenotype was reported to be as high as 58 % [17,18]. However, differences in the methodology, era of sample collection and the participant population (including age, region, tribal identity, potential for mixed ancestry) between these studies that may, at least in part, explain these observed differences. It is also relevant to note that HBGA expression is developmentally regulated and so fucosyltransferase enzymes may not have yet reached normal activity levels in infancy [19], and some young children express HBGA weakly. While the G428A is the most common *FUT2* mutation resulting in a non-secretor phenotype among Caucasians and Africans, a mutation at position 385 more commonly results in non-secretor phenotype among Asian people [20]. The PCR-RFLP analysis does not detect mutations other than at the 428 position in the *FUT2* gene and we were unable to confirm Lewis status by sequencing the *FUT3* gene. Finally, the ORVAC study design meant that there was a delay between rotavirus vaccine administration (routine schedule 6 weeks and 4 months) and collection of serum samples for rotavirus antibody testing at age 6 to <12 months old. We assume that seroconversion was largely driven by rotavirus vaccination, although it is likely that some children also had prior natural infection with circulating virus. Prior to introduction of rotavirus vaccination, approximately one quarter of rotavirus notifications were for infants <6 months old [21].

5. Conclusion

Most Australian Aboriginal children were secretor and Lewis HBGA positive. Those with weak secretor and non-secretor phenotypes were less likely to be IgA seropositive after a routine schedule of oral rotavirus vaccine but the prevalence of these two phenotypes was low in this cohort. Thus, the influence of HBGA status is unlikely to fully explain the underperformance of rotavirus vaccine at a population level among Australian Aboriginal children. Exploration of the influence maternal anti-rotavirus IgG, breast-milk anti-rotavirus IgA and gut microbiota/ microbiome on vaccine take and vaccine effectiveness, may be warranted in this population.

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Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: NC is affiliated to the NIHR Health Protection Research Unit in Gastrointestinal Infections at the University of Liverpool, a partnership with the UK Health Security Agency in collaboration with the University of Warwick. The views expressed are those of the author(s) and not necessarily those of the NIHR, the Department of Health and Social Care or the UK Health Security Agency. NC declares that he has participated on a Data Safety Monitoring Board and/ or Advisory Board for GlaxoSmith Kline and Sanofi Pasteur who manufacture rotavirus vaccines. CD declares she has been a member of a GSK expert advisory board and received a travel award to attend a meeting in 2022. JEB, CD, CK, NBD, AH and KB are/have been employed by MCRI; MCRI holds the license for the RV3-BB rotavirus vaccine. JEB declares that she has been a member of a Data Safety Monitoring Board for GmbH Germany. The authors declare no other competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.05.007.

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