Impact of Maternal Antibodies and Microbiota Development on the Immunogenicity of Oral Rotavirus Vaccine in African, Indian, and European Infants: a Prospective Cohort Study

Edward P. K. Parker [1,*], **Christina Bronowski [2,*],** Kulandaipalayam Natarajan C. Sindhu [3,*], Sudhir Babji[3], Blossom Benny[3], Noelia Carmona-Vicente[2], Nedson Chasweka[4], End Chinyama[4], Nigel A. Cunliffe[2,5], Queen Dube[4], Sidhartha Giri[3], Nicholas C. Grassly [6], Annai Gunasekaran[3], Deborah Howarth[2], Sushil Immanuel[3], Khuzwayo C. Jere [2,4,7], Beate Kampmann [1], Jenna Lowe[2], Jonathan Mandolo[4], Ira Praharaj[3], Bakthavatsalam Sandya Rani[3], Sophia Silas[3], Vivek Kumar Srinivasan[3], Mark Turner [8], Srinivasan Venugopal[3], Valsan Philip Verghese[9], Alistair C. Darby[2,12], Gagandeep Kang[3,12] & Miren Iturriza-Gómara [2,10,12]

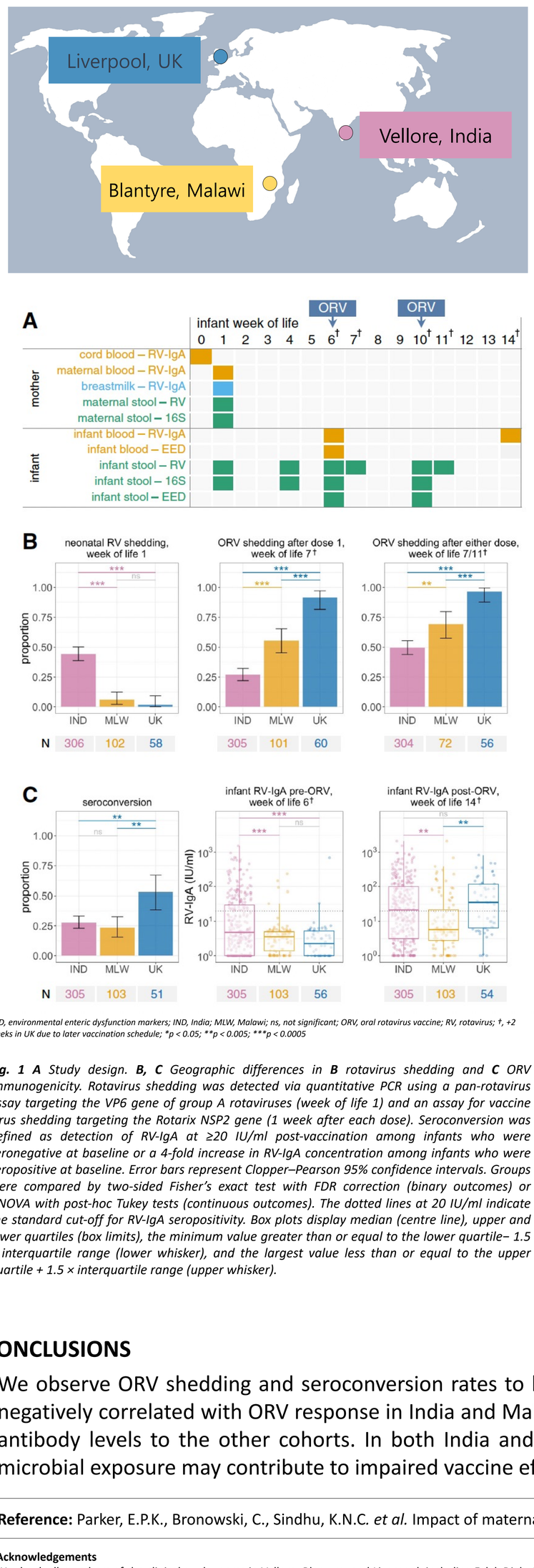
[1] The Vaccine Centre, Department of Clinical Research, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK. [2] Institute of Infection, Veterinary and Ecological Sciences, University of Liverpool, Liverpool L69 7BE, UK. [3] Division of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu 632004, India. [4] Malawi-Liverpool-Wellcome Trust Clinical Research Programme, University of Malawi, Blantyre PO Box, 30096, Malawi. [5] NIHR Health Protection Research Unit in Gastrointestinal Infections, University of Liverpool, Liverpool, UK. [6] Department of Infectious Disease Epidemiology, Imperial College London, London W2 1PG, UK. [7] Department of Medical Laboratory Sciences, College of Medicine, University of Malawi, Private Bag 360, Chichiri, Blantyre 3, Malawi. [8] Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool L8 7SS, UK. [9] Department of Child Health, Christian Medical College, Vellore, Tamil Nadu 632004, India. [10] Centre for Vaccine Innovation and Access, PATH, Geneva, Switzerland

BACKGROUND

The roll-out of oral rotavirus vaccine (ORV) —in parallel with advances in sanitation infrastructure and increased use of oral rehydration therapy—has led to substantial declines in global diarrhoeal mortality. Yet the potential impact of ORV is constrained by the impaired performance of current vaccines in low- and middle-income countries (LMICs). The 1-year protective efficacy of Rotarix against severe rotavirus-associated gastroenteritis is >95% in Europe but may fall below 50% in sub-Saharan Africa. Moreover, while a variety of interventions to boost ORV performance have been tested (e.g. temporary withholding of breastfeeding), these have generally proven either ineffective or of modest benefit, highlighting the need for new strategies informed by a deeper understanding of the mechanisms underlying the vaccine efficacy gap. Identifying risk factors for impaired oral rotavirus vaccine (ORV) efficacy in low-income countries may lead to improvements in vaccine design and delivery.

In this prospective cohort study, we measure **maternal rotavirus antibodies**, **environmental enteric dysfunction (EED)**, and **bacterial gut microbiota development** among infants receiving two doses of Rotarix in India (n = 307), Malawi (n = 119), and the UK (n = 60), using standardised methods across cohorts.

Experimental set up and Rotavirus vaccine response



*EED, environmental enteric dysfunction markers; IND, India; MLW, Malawi; ns, not significant; ORV, oral rotavirus vaccine; RV, rotavirus; †, +2 weeks in UK due to later vaccination schedule; *p < 0.05; **p < 0.005; ***p < 0.0005*

Fig. 1 *A Study design. **B, C** Geographic differences in **B** rotavirus shedding and **C** ORV immunogenicity. Rotavirus shedding was detected via quantitative PCR using a pan-rotavirus assay targeting the VP6 gene of group A rotaviruses (week of life 1) and an assay for vaccine virus shedding targeting the Rotarix NSP2 gene (1 week after each dose). Seroconversion was defined as detection of RV-IgA at ≥20 IU/ml post-vaccination among infants who were seronegative at baseline or a 4-fold increase in RV-IgA concentration among infants who were seropositive at baseline. Error bars represent Clopper–Pearson 95% confidence intervals. Groups were compared by two-sided Fisher's exact test with FDR correction (binary outcomes) or ANOVA with post-hoc Tukey tests (continuous outcomes). The dotted lines at 20 IU/ml indicate the standard cut-off for RV-IgA seropositivity. Box plots display median (centre line), upper and lower quartiles (box limits), the minimum value greater than or equal to the lower quartile− 1.5 × interquartile range (lower whisker), and the largest value less than or equal to the upper quartile + 1.5 × interquartile range (upper whisker).*

Association between maternal antibodies and oral rotavirus vaccine response

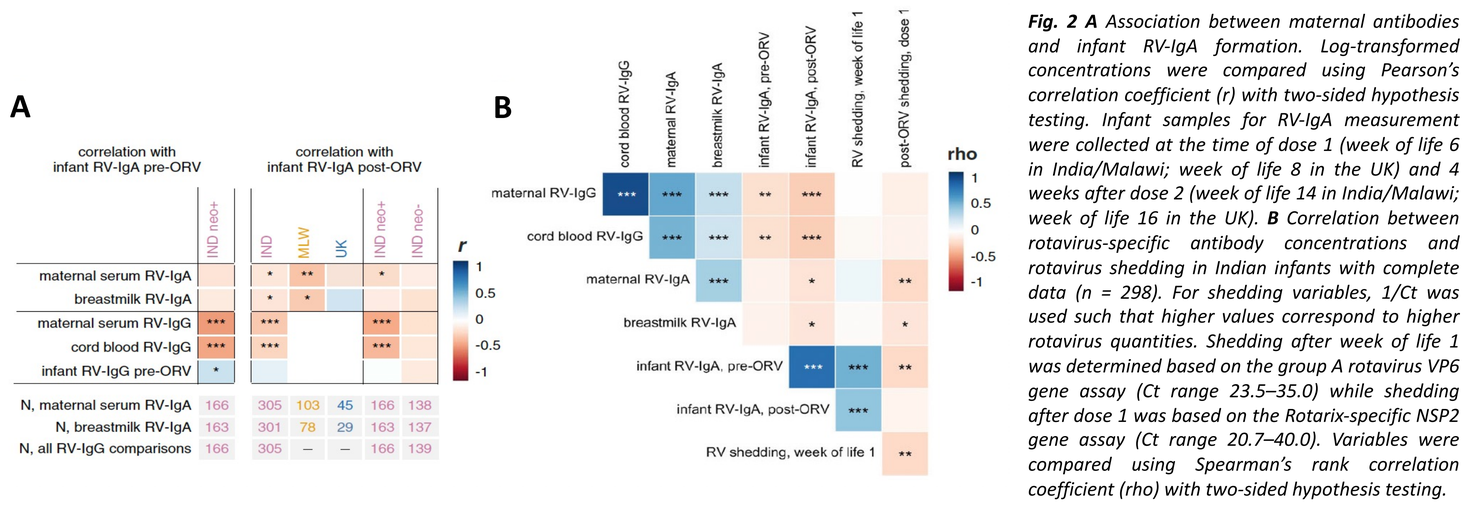
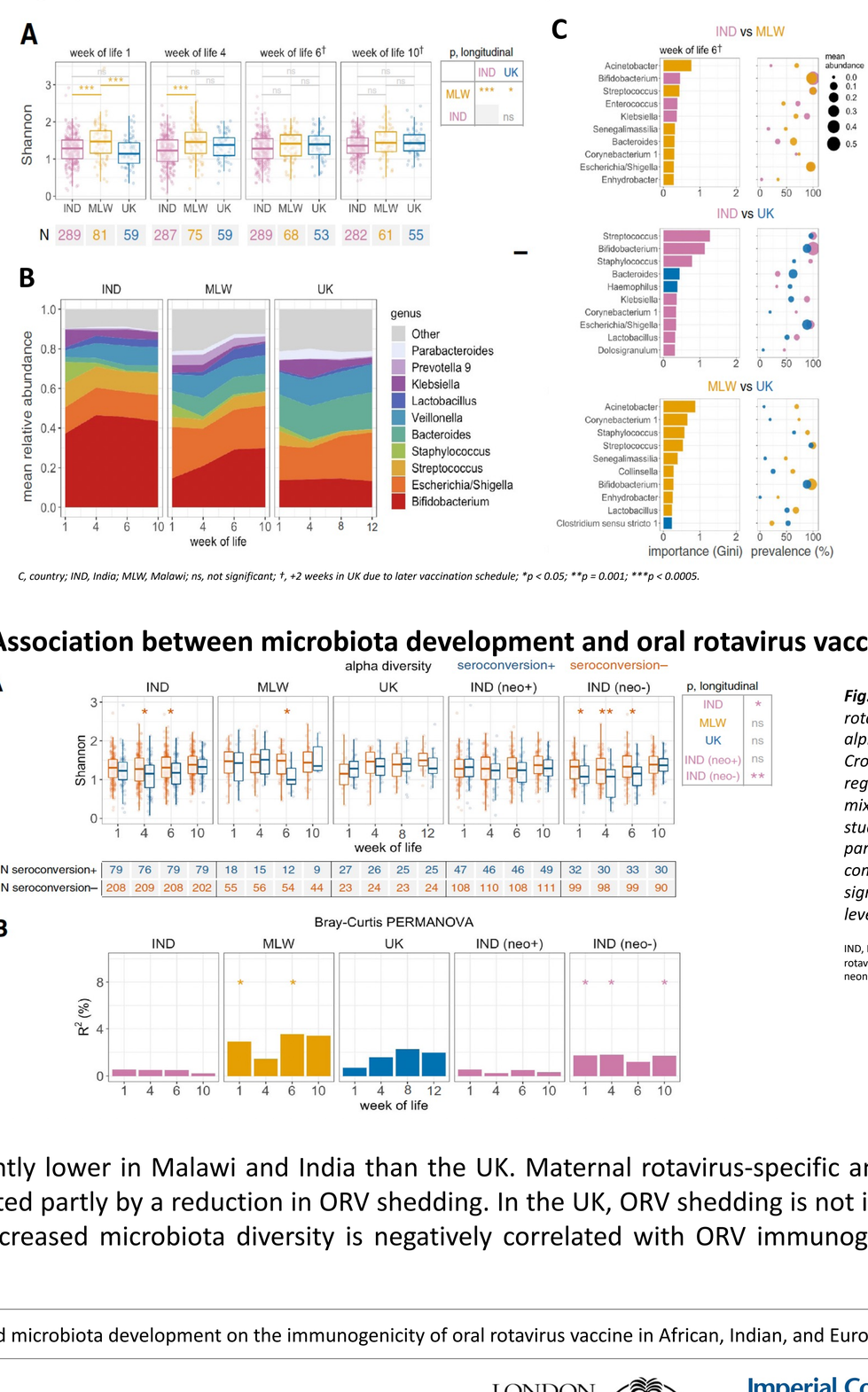


Fig. 2 *A Association between maternal antibodies and infant RV-IgA formation. Log-transformed concentrations were compared using Pearson's correlation coefficient (r) with two-sided hypothesis testing. Infant samples for RV-IgA measurement were collected at the time of dose 1 (week of life 6 in India/Malawi; week of life 8 in the UK) and 4 weeks after dose 2 (week of life 14 in India/Malawi; week of life 16 in the UK). **B** Correlation between rotavirus-specific antibody concentrations and rotavirus shedding in Indian infants with complete data (n = 298). For shedding variables, 1/Ct was used such that higher values correspond to higher rotavirus quantities. Shedding after week of life 1 was determined based on the group A rotavirus VP6 gene assay (Ct range 23.5–35.0) while shedding after dose 1 was based on the Rotarix-specific NSP2 gene assay (Ct range 20.7–40.0). Variables were compared using Spearman's rank correlation coefficient (rho) with two-sided hypothesis testing.*

*neo+, infected with rotavirus neonatally (defined by detection of rotavirus shedding in week of life 1 or baseline seropositivity); neo−, uninfected with rotavirus neonatally; ns, not significant; ORV, oral rotavirus vaccine; RV, rotavirus; *p < 0.05; **p < 0.005; ***p < 0.0005.*

Geographic differences in microbiota development



*C, country; IND, India; MLW, Malawi; ns, not significant; †, +2 weeks in UK due to later vaccination schedule; *p < 0.05; **p = 0.001; ***p < 0.0005.*

Association between microbiota development and oral rotavirus vaccine seroconversion

Fig. 4 *Association between microbiota development and oral rotavirus vaccine seroconversion. **A** Longitudinal analysis of alpha diversity. Shannon index was calculated at genus level. Cross-sectional comparisons were performed using logistic regression. Longitudinal comparisons were performed using mixed effects models including week of life as a covariate and study ID as a random effect. See Fig. 1 legend for box plot parameters. **B** Proportion of variation in microbiota composition associated with seroconversion. R2 and statistical significance were determined by PERMANOVA using genus-level unweighted Bray–Curtis distances.*

IND, India; MLW, Malawi; neo+, infected with rotavirus neonatally (defined by detection of rotavirus shedding in week of life 1 or baseline seropositivity); neo−, uninfected with rotavirus neonatally; ns, not significant *p < 0.05; **p < 0.005; ***p < 0.0005.

CONCLUSIONS

We observe ORV shedding and seroconversion rates to be significantly lower in Malawi and India than the UK. Maternal rotavirus-specific antibodies in serum and breastmilk are negatively correlated with ORV response in India and Malawi, mediated partly by a reduction in ORV shedding. In the UK, ORV shedding is not inhibited despite comparable maternal antibody levels to the other cohorts. In both India and Malawi, increased microbiota diversity is negatively correlated with ORV immunogenicity, suggesting that high early-life microbial exposure may contribute to impaired vaccine efficacy.

Reference: Parker, E.P.K., Bronowski, C., Sindhu, K.N.C. *et al.* Impact of maternal antibodies and microbiota development on the immunogenicity of oral rotavirus vaccine in African, Indian, and European infants. Nat Commun 12, 7288 (2021)

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