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Head-to-head comparison of the immunogenicity of RotaTeq and Rotarix rotavirus vaccines and factors associated with seroresponse in infants in Bangladesh: a randomised, controlled, open-label, parallel, phase 4 trial

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Summary

Background A head-to-head comparison of the most widely used oral rotavirus vaccines has not previously been done, particularly in a high child mortality setting. We therefore aimed to compare the immunogenicity of RotaTeq (Merck, Kenilworth, NJ, USA) and Rotarix (GlaxoSmithKline, Rixensart, Belgium) rotavirus vaccines in the same population and examined risk factors for low seroresponse.

Methods We did a randomised, controlled, open-label, parallel, phase 4 trial in urban slums within Mirpur and Mohakahli (Dhaka, Bangladesh). We enrolled eligible participants who were healthy infants aged 6 weeks and full-term (ie, >37 weeks' gestation). We randomly assigned participants (1:1), using block randomisation via a computer-generated electronic allocation with block sizes of 8, 16, 24, and 32, to receive either three RotaTeq vaccine doses at ages 6, 10, and 14 weeks or two Rotarix doses at ages 6 and 10 weeks without oral poliovirus vaccine. Coprimary outcomes were the rotavirus-specific IgA seroconversion in both vaccines, and the comparison of the rotavirus IgA seroconversion by salivary secretor phenotype in each vaccine arm. Seroconversion at age 18 weeks in the RotaTeq arm and age of 14 weeks in the Rotarix arm was used to compare the complete series of each vaccine. Seroconversion at age 14 weeks was used to compare two RotaTeq doses versus two Rotarix doses. Seroconversion at age 22 weeks was used to compare the immunogenicity at the same age after receiving the full vaccine series. Safety was assessed for the duration of study participation. This study is registered with ClinicalTrials.gov, NCT02847026.

Findings Between Sept 1 and Dec 8, 2016, a total of 1144 infants were randomly assigned to either the RotaTeq arm (n=571) or Rotarix arm (n=573); 1080 infants (531 in the RotaTeq arm and 549 in the Rotarix arm) completed the study. Rotavirus IgA seroconversion 4 weeks after the full series occurred in 390 (73%) of 531 infants age 18 weeks in the RotaTeq arm and 354 (64%) of 549 infants age 14 weeks in the Rotarix arm (p=0·01). At age 14 weeks, 4 weeks after two doses, RotaTeq recipients had lower seroconversion than Rotarix recipients (268 [50%] of 531 *vs* 354 [64%] of 549; p<0·0001). However, at age 22 weeks, RotaTeq recipients had higher seroconversion than Rotarix recipients (394 [74%] of 531 *vs* 278 [51%] of 549; p<0·0001). Among RotaTeq recipients, seroconversion 4 weeks after the third dose was higher than after the second dose (390 [73%] of 531 *vs* 268 [50%] of 531; p<0·0001]. In the RotaTeq arm, rotavirus IgA seroconversion was lower in non-secretors than in secretors at ages 14 weeks (p=0·08), 18 weeks (p=0·01), and 22 weeks (p=0·02). Similarly, in the Rotarix arm, rotavirus IgA seroconversion was lower in non-secretors than in secretors at ages 14 weeks (p=0·02) and 22 weeks (p=0·01). 65 (11%) of 571 infants had adverse events in the RotaTeq arm compared with 63 (11%) of 573 infants in the Rotarix arm; no adverse events were attributed to the use of either vaccine. One death due to aspiration occurred in the RotaTeq arm, which was not related to the vaccine.

Interpretation RotaTeq induced a higher magnitude and longer duration of rotavirus IgA response than Rotarix in this high child mortality setting. Additional vaccination strategies should be evaluated to overcome the suboptimal performance of current oral rotavirus vaccines in these settings.

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Introduction

Globally, rotavirus infections were responsible for an estimated 151 514 deaths in children younger than 5 years in 2019, along with millions of cases and hospitalisations,[1] with the highest burden in sub-Saharan Africa, southeast Asia, and south Asia. The live multivalent human–bovine reassortant rotavirus vaccine (RotaTeq; Merck & Co, USA) and the monovalent human attenuated oral rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals, Belgium) have successfully reduced the incidence of severe

Research in context

Evidence before this study

Live attenuated orally administered rotavirus vaccines have been introduced in more than 112 countries' national or subnational immunisation programme. However, the oral rotavirus vaccines that have undergone efficacy trials or effectiveness evaluations following the introduction in different socioeconomic settings have shown lower levels and perhaps shorter protection against moderate or severe rotavirus gastroenteritis in high child mortality settings compared with low child mortality settings. We therefore searched PubMed on May 3, 2022, for studies comparing the immunogenicity of different rotavirus vaccines in infants using the following search terms: "immunogenicity" AND "rotavirus vaccines" AND "clinical trial" [publication type]. The search was unrestricted by language or publication date. Notably, no randomised controlled trials assessed the immunogenicity of full doses of the most widely used oral rotavirus vaccines, RotaTeq and Rotarix, with a head-to-head study design.

Added value of this study

Our study is the first randomised controlled trial to make a head-to-head comparison of the immunogenicity of the three-dose RotaTeq series and two-dose Rotarix series. Results indicate that at age 14 weeks, after two vaccine doses, infants who received RotaTeq had lower rotavirus IgA seroresponse than infants who had received Rotarix. However, after full dose series, at age 22 weeks, the seroresponse waned among Rotarix recipients. Additionally, we identified an inhibitory effect of maternally derived antibodies on the immunogenicity of both rotavirus vaccines and that non-secretors (ie, infants who did not express the carbohydrate synthesised by FUT2 enzyme in their saliva) had lower rates of seroconversion than secretors. This study capitalised on a large and well characterised cohort of Bangladeshi infants; and we evaluated an extensive panel of risk factors around the time of oral vaccine administration associated with vaccine immunogenicity.

Implications of all the available evidence

Although evidence exists that rotavirus IgA correlates well with clinical protection at the individual and population level, we cannot determine whether higher rotavirus IgA levels result in a more sustained duration of vaccine-induced immunogenicity up to age 1 or 2 years. After the full dose series, at age 22 weeks, a faster waning of immunogenicity was observed in Rotarix recipients than in RotaTeq recipients. Existing oral rotavirus vaccines given at their current schedules beginning at age 6 weeks without a late infancy booster are only moderately effective in reducing morbidity and mortality from rotavirus among children in high child mortality settings. Therefore, the global research community should also strongly consider new and innovative ways to address this efficacy gap, including a decreased reliance on oral vaccines, to reduce the global burden of rotavirus disease. One strategy to address some of these challenges is the development of parenterally administered non-replicating rotavirus vaccines, which bypass the intestine and can potentially lead to enhanced efficacy.

rotavirus gastroenteritis worldwide. A meta-analysis of 20 randomised controlled trials and 38 case-control studies showed that RotaTeq reduced rotavirus gastroenteritis in children younger than 5 years by 65% and Rotarix by 68%.[2] However, evidence exists showing that the efficacies of RotaTeq and Rotarix are lower and wane more rapidly in high child mortality settings than in low child mortality settings.[3] A meta-analysis estimated that each of these vaccines had vaccine effectiveness of 86% against rotavirus disease among infants in countries with low child mortality compared with 63–66% in countries with high child mortality.[4]

A variety of risk factors have been linked with reduced oral rotavirus vaccine performance in high child mortality settings, including a higher incidence of interference from the transplacental maternal anti-rotavirus antibody, a higher incidence of rotavirus infection in early life, malnutrition, and coadministration of the oral poliovirus vaccine.[5] Host genetics have an important role in susceptibility to rotavirus infection and might also affect vaccine response. Histo-blood group antigens are a family of complex carbohydrates found in intestinal and other mucosae.[6] Polymorphisms in the genes that encode alpha 1,2 fructosyltransferase 2 (secretor enzyme) and Lewis enzyme, and glycosyltransferases A and B contribute to the differences in the innate susceptibility to rotavirus. Rotaviruses are designated by genes encoding the VP7 (termed G genotype) and VP4 (termed P genotype) proteins. VP4 is cleaved to VP8*, which appears to bind to particular histo-blood group antigens in a P-genotype-specific manner, with secretors more susceptible to P[8] and P[4] infections than non-secretors. Both RotaTeq and Rotarix contain rotavirus strains of genotype P[8], with RotaTeq also having P[5] genotype specificity.

None of the previous randomised controlled trials directly compared RotaTeq and Rotarix. In this study, we therefore aimed to assess the immunogenicity of RotaTeq and Rotarix in a head-to-head comparison given with the inactivated poliovirus vaccine (IPV) in the absence of OPV in Bangladeshi infants.[7] We also assessed whether histo-blood group antigens are associated with immunogenicity to rotavirus vaccines. Moreover, we aimed to identify risk factors that predict low seroresponse of both vaccines.

Methods

Study design and participants

We did a randomised, controlled, open-label, parallel, phase 4 trial in urban slums within Mirpur and Mohakahli in Dhaka, Bangladesh. This study was designed to assess the immunogenicity of full and

fractional doses of IPV. A rotavirus component was included to assess the immunogenicity of three doses of RotaTeq and two doses of Rotarix. Results of the IPV component have previously been reported;[7] in this current Article, we focused and reported on the rotavirus vaccine component.

Expectant mothers within assigned communities were identified by the study staff as eligible participants, and interested parents were invited to participate. Infants aged 6 weeks were eligible if they were full-term (ie, >37 weeks) singleton births and would remain in the area during the complete study. Infants were excluded if they received any rotavirus vaccine before enrolment; had any known allergies or sensitivity to rotavirus vaccines or their contents; had a history of intussusception, abdominal surgery, intestinal malformation, or a chronic medical condition identified by a study medical officer (not including stunting or wasting); a severe illness that required hospital admission; or vomiting or intolerance to liquids 24 h before enrolment. Study staff withdrew participants if a rotavirus vaccine was received outside the study, if they identified a medical condition in which participation posed a risk (eg, (a diagnosis or suspicion of bleeding disorder that would contraindicate collection of blood by venipuncture), if participants were given immunosuppressive medications, or if study staff could not obtain blood during the first visit. Parents could withdraw the consent for participation at any time.

The study protocol number PR-15105 was approved by the Institutional Review Board and Centre Director of the International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b). The protocol was shared with the US Centers for Disease Control and Prevention (CDC) but deferred to the icddr,b's Institutional Review Board. CDC staff had no interaction with participants nor any access to personally identifiable information. Written informed consent was obtained from the parents of all participants.

Randomisation and masking

We randomly assigned participants (1:1), using block randomisation via a computer-generated electronic allocation with block sizes of 8, 16, 24, and 32, to receive either three oral doses of the RotaTeq vaccine at ages 6, 10, and 14 weeks; or two oral doses of the Rotarix vaccine at ages 6 and 10 weeks (appendix p 2). In addition to stratification by rotavirus vaccines, randomisation was further stratified by four IPV groups. Briefly, group A received IPV at age 14 weeks and IPV booster at age 22 weeks, group B received IPV at age 14 weeks and a fractional IPV (fIPV) booster at age 22 weeks, group C received IPV at age 6 weeks and fIPV booster at age 22 weeks, and group D received fIPV at age 6 weeks and 14 weeks and fIPV booster at age 22 weeks (appendix p 2). At each study clinic, investigators with no participant engagement generated the randomisation sequence by use of R (version 3.2.1) and concealed randomisation assignment in sequentially numbered, sealed, opaque envelopes. Study clinic staff had no previous knowledge of the randomisation scheme; group assignment was unmasked to parents and study clinic staff when envelopes were opened.

Procedures

Upon enrolment, staff obtained the infant's clinical history (ie, breastfeeding, previous vaccinations, and health status), did a physical examination (including body temperature, bodyweight, and length), collected a sample of blood by venipuncture, administered RotaTeq or Rotarix, administered IPV (in group C only) or fIPV (in group D only; appendix p 2), and monitored infants for 30 min for any adverse events. Participants returned for study clinic visits at ages 10, 14, 18, and 22 weeks for assessments related to the rotavirus vaccine (appendix p 2). Staff collected a blood sample at age 14, 18, and 22 weeks for the RotaTeq arm and age 14 and 22 weeks for the Rotarix arm, collected a saliva sample at age 18 weeks for both study arms and monitored for adverse events. Infant anthropometry (ie, weight, length) was measured at every visit.

Blood samples were processed as previously described.[7] Saliva was collected from infants using the SalivaBio Infant's Swab (Salimetrics; State College, PA, USA). Infants did not feed or drink for 30 min or more before saliva collection. All serum and saliva samples were stored at –20°C at the study clinic and transported at the end of each day to the icddr,b laboratory to be stored at –20°C. Samples were shipped to the US CDC (Atlanta, USA) for testing. Serum rotavirus IgA and IgG were detected by enzyme-linked immunosorbent assay (EIA) using either RotaTeq G1 or Rotarix antigen, according to the vaccine arm (appendix p 3). Secretor, Lewis, and salivary ABO blood group phenotypes were determined as positive or negative using a saliva-based EIA (appendix p 3). For samples that were negative for secretor and Lewis status by EIA (phenotyping analysis), secretor genotyping was done (appendix p 3).

Outcomes

The coprimary outcome was the assessment of the rotavirus IgA seroresponse to RotaTeq and Rotarix. Rotavirus IgA seroresponse was measured in two ways: rotavirus IgA seroconversion and rotavirus IgA titres or geometric mean titres. Rotavirus IgA seropositivity was defined as a titre of 40 or more. Rotavirus IgA seroconversion was defined as IgA seropositivity (titre ≥40) in the subsequent sample if seronegative (titre <40) at age 6 weeks or a four-fold or greater increase in rotavirus IgA titre in the subsequent sample if rotavirus IgA seropositive (titre ≥40) at age 6 weeks. The geometric mean titres (GMT) were defined as the exponential of mean logarithmic transformation of the rotavirus IgA titres and IgG titres. Rotavirus IgA seroresponse was measured at three timepoints for the RotaTeq arm at ages

See Online for appendix

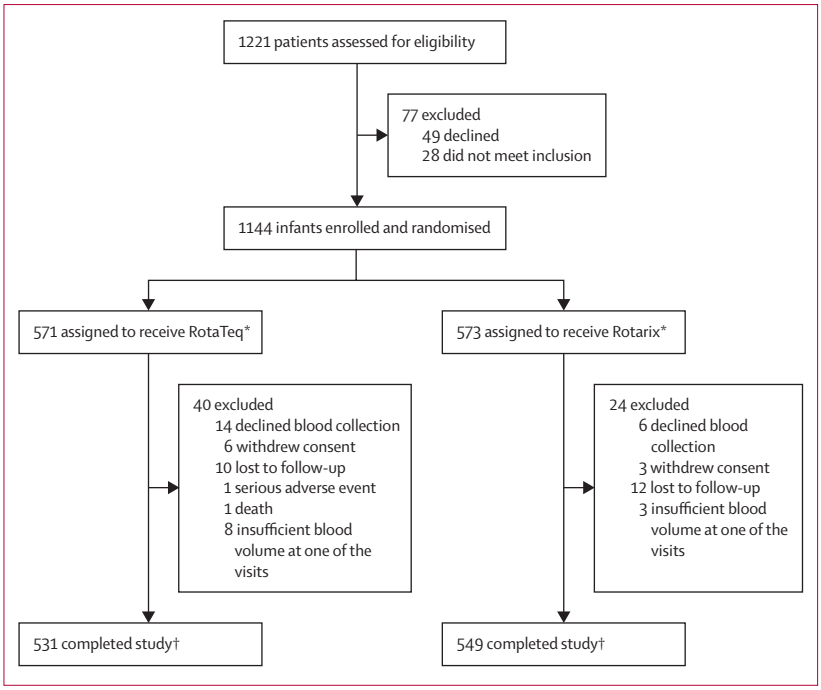

Figure: **Trial profile**
*Included in safety analysis. †Included in modified intention-to-treat analysis.

	RotaTeq arm (n=531)	Rotarix arm (n=549)
Age at first dose (days)	44 (43–46)	44 (43–46)
Sex		
Male	262 (49%)	284 (52%)
Female	269 (51%)	265 (48%)
IPV group		
A + B*	265 (50%)	276 (50%)
C	134 (25%)	134 (24%)
D	132 (25%)	139 (25%)
Mother's education		
No formal school	85 (16%)	102 (19%)
Primary school	201 (38%)	210 (38%)
Middle school	132 (25%)	133 (24%)
High school	90 (17%)	75 (14%)
University	23 (4%)	29 (5%)
Feeding practices at age 6 weeks		
Partial breastfeeding	393 (74%)	402 (73%)
Exclusive breastfeeding	138 (26%)	147 (27%)
Weight for length score	−0·3 (1·1)	−0·3 (1·1)
Length for age score	−0·8 (1·1)	−0·7 (1·1)

Data are n (%), median (IQR), or mean (SD). Length for age and weight for length were compared with the SD of an international reference population recommended by WHO. fIPV=fractional inactivated poliovirus vaccine. IPV=inactivated poliovirus vaccine. *For analysis purposes, IPV groups A and B were combined because both had the same rotavirus vaccine and IPV or fIPV schedules through age 18 weeks.

Table 1: **Baseline characteristics of the modified-intention-to-treat-population**

14, 18, and 22 weeks; and at two timepoints for the Rotarix arm at ages 14 and 22 weeks.

Rotavirus IgA seroconversion at age 18 weeks in the RotaTeq arm (4 weeks after third dose) and age 14 weeks in the Rotarix arm (4 weeks after second dose) was used to compare the immunogenicity of the complete series of each vaccine. Rotavirus IgA seroconversion at age 14 weeks (4 weeks after second dose) was used to compare the immunogenicity of two doses of RotaTeq versus two doses of Rotarix. Rotavirus IgA seroconversion at age 22 weeks was used to compare the immunogenicity at the same age after receiving the full vaccine series (age 22 weeks was 8 weeks after completion of RotaTeq series and 12 weeks after completion of Rotarix series). The IPV protocol determined the age for this post-series sample (ie, at age 22 weeks). In the RotaTeq arm, rotavirus IgA seroresponses at ages 14 and 18 weeks were used to compare the immunogenicity of two RotaTeq doses versus three RotaTeq doses.

Within each vaccine arm, rotavirus IgA seroresponses measured at the previously described timepoints were used to compare the immunogenicity of the vaccines by the infants' histo-blood group antigens phenotype (coprimary outcome): secretor status (and among secretors, by salivary ABO blood group) and Lewis antigen status, from the testing of the saliva sample. Serum rotavirus IgG was measured at age 6 weeks in the subset of rotavirus IgA seronegative infants at that timepoint (ie, in infants this age who had not been infected with wild-type rotavirus, rotavirus IgG titres are assumed to represent transplacental maternal antibodies).

Secondary outcomes were comparison of rotavirus IgA seroresponses by IPV group and, at the individual participant level, examination of change in rotavirus IgA titres. This latter outcome included examination of the change of rotavirus IgA titres between ages 14 and 18 weeks (ie, includes the response to the third dose given at age 14 weeks) and between ages 18 and 22 weeks in RotaTeq recipients (after no additional doses), and between ages 14 and 22 weeks in Rotarix recipients (after no additional doses). The participant's rotavirus IgA titre change between the timepoints was classified as consistent with waning, boosting, or no change (appendix p 4). Systemic adverse events were monitored during the study in the intention-to-treat population. Adverse events were defined as any illness occurring in infants during the study period. Serious adverse events were defined as death, admission to hospital, paralysis, severe disability, or an anaphylactic reaction after vaccine administration, as previously described.[7]

Statistical analysis

Using the enrolment target of 1144 participants to address the IPV component of the trial,[7] we determined that 572 participants per rotavirus vaccine arm would

	RotaTeq arm (n=531)	Rotarix arm (n=549)	p value
Rotavirus IgA positivity			
Age 6 weeks (before first dose)	67 (13%)	75 (14%)	0·65
Age 14 weeks (4 weeks after second dose)	303 (57%)	382 (70%)	<0·0001
Age 18 weeks (4 weeks after third dose)	414 (78%)	..	..
Age 22 weeks (8 weeks after third dose [RotaTeq]; 12 weeks after second dose [Rotarix])	412 (78%)	307 (56%)	<0·0001
Rotavirus IgA seroconversion			
Age 14 weeks (4 weeks after second dose)	268 (50%)	354 (64%)	<0·0001
Age 18 weeks (4 weeks after third dose)	390 (73%)	..	..
Age 22 weeks (8 weeks after third dose [RotaTeq]; 12 weeks after second dose [Rotarix])	394 (74%)	278 (51%)	<0·0001
Age 14 weeks (4 weeks after second dose [RotaTeq]) *vs* age 18 weeks (4 weeks after third dose [RotaTeq])	..	..	<0·0001
Age 22 weeks (8 weeks after third dose [RotaTeq]) *vs* age 18 weeks (4 weeks after third dose [RotaTeq])	..	..	0·83
Age 14 weeks (4 weeks after second dose [Rotarix]) *vs* age 22 weeks (12 weeks after second dose [Rotarix])	..	..	<0·0001
Age 14 weeks (4 weeks after second dose [Rotarix]) *vs* age 18 weeks (4 weeks after third dose [RotaTeq])	..	..	0·01
Rotavirus IgA titre			
Age 6 weeks (before first dose)	4 (3–4)	3 (2–3)	..
Age 14 weeks (4 weeks after second dose)	54 (43–67)	84 (68–104)	..
Age 18 weeks (4 weeks after third dose)	198 (161–244)	..	..
Age 22 weeks (8 weeks after third dose [RotaTeq]; 12 weeks after second dose [Rotarix])	218 (176–270)	36 (28–46)	..
Age 14 weeks (4 weeks after second dose [RotaTeq]) *vs* age 18 weeks (4 weeks after third dose [RotaTeq])	..	..	<0·0001
Age 22 weeks (8 weeks after third dose [RotaTeq]) *vs* age 18 weeks (4 weeks after third dose [RotaTeq])	..	..	0·52
Age 22 weeks (12 weeks after second dose [Rotarix]) *vs* age 14 weeks (4 weeks after second dose [Rotarix])	..	..	<0·0001
Rotavirus IgG titre*			
6 age weeks (before first dose)	2339 (2159–2533)	2483 (2280–2703)	0·32

Data are n (%) or GMT (95% CIs), unless otherwise specified. GMT=geometrical mean titres. *In infant's rotavirus IgA seronegative at age 6 weeks (n=938).

Table 2: **Serum rotavirus IgA responses**

have greater than 80% power to detect a difference of 8% in rotavirus IgA seroconversion between RotaTeq and Rotarix, assuming a baseline seroconversion of 70% in one of the arms. Sample size calculations were based on an assumption of 10% attrition. For analysis purposes, IPV groups A and B were combined because both had the same rotavirus vaccine and IPV and fIPV schedules through age 18 weeks. The log-transformed antibody titres were compared between the RotaTeq and Rotarix arms at individual timepoints using one-way ANOVA and for time courses (ie, comparison between two *vs* three RotaTeq doses) using two-way ANOVA, both with Dunnett's multiple comparison correction. All proportions were compared between groups using Fisher's exact test. A two-sided α and significance level of 0·05 was used for all statistical tests. Descriptive analyses (percentages and medians) were done for baseline characteristics and adverse events.

We did post-hoc analyses to examine potential causes for low seroresponse, among infants who were rotavirus-IgA seronegative at age 6 weeks using multivariable log-binomial regression models. We evaluated health and demographic variables for their potential association with rotavirus IgA seroconversion and post-vaccination rotavirus IgA titres, including maternally derived rotavirus IgG titres at age 6 weeks, exposure to season of high wild-type rotavirus circulation, and breastfeeding (appendix p 4). Results were analysed in the modified-intention-to-treat population.

Data were analysed in SPSS (version 21) or R (version 3.3.3). This study is registered with ClinicalTrials.gov, number NCT02847026.

Role of the funding source

The funder of the study participated in study design, protocol development, data collection, data analysis, data interpretation, and manuscript development.

Results

Between Sept 1 and Dec 8, 2016, a total of 1144 infants were enrolled at 6 weeks of age; 571 in the RotaTeq arm and 573 in the Rotarix arm (figure). Upon completing the study, 1080 infants (531 in the RotaTeq arm and 549 in the Rotarix arm) had provided testable serum samples for each timepoint of interest. These participants were included in the modified intention-to-treat analysis for rotavirus vaccine immune response. At enrolment at age 6 weeks, the participants in both arms had similar baseline characteristics (table 1). The proportion of infants who were rotavirus IgA positive at age 6 weeks, indicative of previous rotavirus infection, was similar in both vaccine arms: 67 (13%) of 531 in the RotaTeq arm versus 75 (14%) of 549 in the Rotarix arm (table 2).

	Rotavirus IgA positivity at age 6 weeks	RR (95% CI)	p value	Rotavirus IgA seroconversion at age 14 weeks	RR (95% CI)	p value	Rotavirus IgA seroconversion at age 18 weeks	RR (95% CI)	p value	Rotavirus IgA seroconversion at age 22 weeks	RR (95% CI)	p value
RotaTeq arm												
Secretor phenotype												
Non-secretor	20/170 (12%)	..	..	76/170 (45%)	..	..	113/170 (66%)	..	..	115/170 (68%)	..	..
Secretor	47/356 (13%)	1·02 (0·95–1·09)	0·68	190/356 (53%)	1·19 (1·00–1·41)	0·08	274/356 (77%)	1·46 (1·10–1·93)	0·01	276/356 (78%)	1·44 (1·08–1·93)	0·02
Salivary ABO blood group among secretors												
Blood group O	..	..	..	..	..	..	91/122 (75%)	..	..	..	..	..
Blood group A	..	..	..	..	..	..	64/78 (82%)	..	..	..	..	..
Blood group B	..	..	..	..	..	..	97/128 (76%)	..	..	..	..	..
Blood group AB	..	..	..	..	..	..	22/28 (79%)	..	0·86	..	..	..
Lewis phenotype												
Negative	1/15 (7%)	..	..	11/15 (73%)	..	..	11/15 (73%)	..	..	10/15 (67%)	..	..
Positive	66/516 (13%)	1·07 (0·93–1·23)	0·71	257/516 (50%)	0·53 (0·23–1·24)	0·11	379/516 (73%)	1·00 (0·43–2·35)	0·99	384/516 (74%)	1·30 (0·63–2·71)	0·55
Rotarix arm												
Secretor phenotype												
Non-secretor	21/156 (13%)	..	..	88/156 (56%)	..	..	NA	NA		59/156 (38%)	..	..
Secretor	53/382 (14%)	1·00 (0·93–1·08)	1·00	258/382 (68%)	1·34 (1·07–1·69)	0·02	NA	NA		213/382 (56%)	1·41 (1·19–1·66)	0·01
Salivary ABO blood group among secretors												
Blood group O	..	..	..	99/153 (65%)	..	..	NA	NA		..	..	..
Blood group A	..	..	..	62/84 (74%)	..	..	NA	NA		..	..	..
Blood group B	..	..	..	84/128 (66%)	..	..	NA	NA		..	..	..
Blood group AB	..	..	..	13/17 (76%)	..	0·49	NA	NA		..	..	..
Lewis phenotype												
Negative	3/27 (11%)	..	..	20/27 (74%)	..	..	NA	NA		15/27 (56%)	..	..
Positive	72/522 (14%)	1·03 (0·90–1·18)	1·00	334/522 (64%)	0·72 (0·38–1·38)	0·31	NA	NA		263/522 (50%)	0·90 (0·58–1·38)	0·69

Data are n/N (%), unless otherwise specified. Five (1%) of 531 saliva samples in the RotaTeq arm and 11 (2%) of 549 in the Rotarix arm were not successfully phenotyped for histoblood group antigens by enzyme-linked immunosorbent assay. RR=relative risk. NA=not applicable.

***Table 3*: Rotavirus IgA titres by secretor phenotype, salivary ABO blood group (among secretors), and Lewis antigen status**

4 weeks after the three-dose vaccine series completion, recipients of RotaTeq had rotavirus IgA seroconversion in 390 (73%) of 531 infants and a rotavirus IgA geometric mean titre of 198 (95% CI 161–244) at 18 weeks of age. 4 weeks after the two-dose series completion, recipients of Rotarix had rotavirus IgA seroconversion in 354 (64%) of 549 infants and a rotavirus IgA geometric mean titre of 84 (95% CI 68–104) at 14 weeks of age (table 2). Rotavirus IgA seroconversion after full series in the RotaTeq arm was significantly higher than in the Rotarix arm (390 [73%] of 531 *vs* 354 [64%] of 549; p=0·01]). At age 14 weeks, 4 weeks after two vaccine doses, RotaTeq participants had significantly lower rotavirus IgA seroconversion than those who received Rotarix (268 [50%] of 531 *vs* 354 [64%] of 549; p<0·0001). However, at age 22 weeks, participants in the RotaTeq arm had significantly higher rotavirus IgA seroconversion than those in the Rotarix arm (394 [74%] of 531 *vs* 278 [51%] of 549; p<0·0001). An increased seroresponse was shown after the third dose of RotaTeq given at age 14 weeks with seroconversion at age 18 weeks compared with after the second dose of RotaTeq (390 [73%] of 531 *vs* 268 [50%] of 531 p<0·0001). A similar pattern was found in the rotavirus IgA geometric mean titres of infants who were seropositive at the indicated timepoint in both vaccine arms (appendix p 5).

526 (99%) of 531 saliva samples from participants in the RotaTeq arm and 538 (98%) of 549 samples from those in the Rotarix arm were successfully phenotyped for histo-blood group antigens by EIA (appendix p 5). 16 samples (five from RotaTeq arm and 11 from Rotarix arm) were negative in all phenotyping assays and were assessed with secretor genotyping. By genotyping, these 16 were found to be secretor-positive. These 16 were excluded from the analysis because of this discordance. The proportion of infants in the RotaTeq arm that were secretors (356 [68%] of 526) was similar to that in the Rotarix arm (382 [71%] of 538; appendix p 5). The proportion of infants that were Lewis positive was also similar in both arms; 516 (97%) of 531 in the RotaTeq arm and 522 (95%) of 549 in the Rotarix arm.

In the RotaTeq arm, rotavirus IgA seroconversion was higher in secretors than in non-secretors at ages 14 weeks

	Rotavirus IgA seroconversion at age 14 weeks				Rotavirus IgA seroconversion at age 18 weeks				Rotavirus IgA seroconversion at age 22 weeks			
	n/N (%)	Univariable p value	Multivariable RR (95% CI)	Multivariable p value	n/N (%)	Univariable p value	Multivariable RR (95% CI)	Multivariable p value	n/N (%)	Univariable p value	Multivariable RR (95% CI)	Multivariable p value
Sex												
Female (ref)	..	..	..	..	173/244 (71%)	..	..	..	..	..	..	..
Male	..	..	..	..	180/220 (82%)	0·01	1·7 (1·1–2·7)	0·03	..	..	..	..
Rotavirus IgG titres at age 6 weeks (tertiles)												
80–1280 (ref)	108/169 (64%)	..	..	..	141/169 (83%)	..	..	..	147/169 (87%)	..	..	..
2560	87/158 (55%)	0·10	0·6 (0·4–1·0)	0·06	126/158 (80%)	0·39	0·7 (0·4–1·3)	0·26	117/158 (74%)	0·01	0·4 (0·2–0·7)	0·01
5120–10 240	52/133 (39%)	<0·0001	0·3 (0·2–0·5)	<0·0001	84/133 (63%)	0·0001	0·3 (0·2–0·6)	0·0001	86/133 (65%)	<0·0001	0·3 (0·1–0·5)	<0·0001
Secretor phenotype												
Non-secretor (ref)	..	..	..	..	102/150 (68%)	..	..	..	..	..	..	..
Secretor	..	..	..	..	248/309 (80%)	0·01	1·9 (1·2–3·1)	0·01	..	..	..	..
Rotavirus season exposure between ages 6 and 14 weeks												
Low (October to November 2016; ref)	58/135 (43%)	..	..	..	..	..	..	..	..	..	..	..
Moderate (December 2016)	93/179 (52%)	0·11	1·5 (1·0–2·4)	0·08	..	..	..	..	..	..	..	..
High (January to February 2017)	97/150 (65%)	0·0003	2·8 (1·7–4·7)	<0·0001	..	..	..	..	..	..	..	..
Feeding practices												
Partial breastfeeding at time of ≥1 dose (ref)	192/345 (56%)	..	..	..	290/358 (81%)	..	..	..	284/358 (79%)	..	..	..
Exclusive breastfeeding at time of each dose	56/119 (47%)	0·11	0·6 (0·4–0·9)	0·03	63/106 (59%)	<0·0001	0·4 (0·2–0·6)	<0·0001	68/106 (64%)	0·01	0·5 (0·3–0·8)	0·01

Rotavirus IgA seroconversion at ages 14, 18, and 22 weeks served as the dependent variable. Variables with a p value of less than 0·05 during multivariable analyses are shown. Univariable regression results of not retained variables are provided in the appendix (pp 12–14). Four (1%) of 464 serum samples were missing for the Rotavirus IgG titres at age 6 weeks variable. Five (1%) of 464 saliva samples were missing for the secretor phenotype variable. This analysis was done among all individuals who were rotavirus IgA seronegative at age 6 weeks (n=464). RR=relative risk. ref=reference.

Table 4: **Multivariable regression for rotavirus IgA seroconversion at ages 14, 18, and 22 weeks in infants who were rotavirus IgA seronegative at age 6 weeks in the RotaTeq arm**

(190 [53%] of 356 *vs* 76 [45%] of 170; relative risk [RR] 1·19 [95% CI 1·00–1·41]; p=0·08), 18 weeks (274 [77%] of 356 *vs* 113 [66%] of 170; 1·46 [1·10–1·93]; p=0·01), and 22 weeks (276 [78%] of 356 vs 115 [68%] of 170; 1·44 [1·08–1·93]; p=0·02; table 3). Additionally, secretors had significantly higher rotavirus IgA geometric mean titres than non-secretors (appendix p 6). Similarly, in the Rotarix arm, rotavirus IgA seroconversion was higher in secretors than in non-secretors at ages 14 weeks (258 [68%] of 382 *vs* 88 [56%] of 156; RR 1·34 [95% CI 1·07–1·69]; p=0·2) and 22 weeks (213 [56%] of 382 *vs* 59 [38%] of 156; 1·41 [1·19–1·66]; p=0·01; table 3). Additionally, secretors had significantly higher rotavirus IgA geometric mean titres than non-secretors (appendix p 6) No significant differences were observed in rotavirus IgA seroconversion post-series completion by salivary blood group in each vaccine arm among the secretors. In each vaccine arm, the seroconversion at all timepoints were not different by Lewis status. In the RotaTeq arm, among infants who were rotavirus IgA seropositive at ages 14, 18, and 22 weeks, secretors had significantly higher rotavirus IgA geometric mean titres than non-secretors (appendix p 7). Similarly, in the Rotarix arm, among infants who were rotavirus IgA seropositive at ages 14 and 22 weeks, secretors had significantly higher rotavirus IgA geometric mean titres than non-secretors.

Overall, at the individual participant level, 241 (45%) of 531 participants in the RotaTeq arm had boosting of rotavirus IgA titres from 14 weeks to 18 weeks following the third vaccine dose given at age 14 weeks (appendix p 8). Changes in rotavirus IgA titres were also observed in infants during periods when no additional vaccine doses were administered. In the RotaTeq arm, comparing the 18-week sample with the 22-week

	Rotavirus IgA seroconversion at age 14 weeks				Rotavirus IgA seroconversion at age 22 weeks			
	n/N (%)	Univariable p value	Multivariable RR (95% CI)	Multivariable p value	n/N (%)	Univariable p value	Multivariable RR (95% CI)	Multivariable p value
Rotavirus IgG titres at age 6 weeks (tertiles)								
80–1280 (ref)	129/173 (75%)	..	..	..	102/173 (59%)	..	..	..
2560	89/132 (67%)	0·17	0·6 (0·4–1·1)	0·09	74/132 (56%)	0·61	0·9 (0·5–1·4)	0·65
5120–10 240	99/169 (59%)	0·01	0·4 (0·2–0·6)	0·01	73/169 (43%)	0·01	0·5 (0·3–0·8)	0·01
Secretor phenotype								
Non-secretor (ref)	80/135 (59%)	..	..	..	55/135 (41%)	..	..	..
Secretor	230/329 (70%)	0·03	1·8 (1·2–2·8)	0·01	189/329 (57%)	0·01	2·2 (1·4–3·3)	0·01
Rotavirus season exposure between ages 6 and 14 weeks								
Low (October to November 2016; ref)	77/133 (58%)	..	..	..	..	..	..	..
Moderate (December 2016)	123/182 (68%)	0·08	2·0 (1·2–3·3)	0·01	..	..	..	..
High (January to February 2017)	117/159 (74%)	0·01	2·4 (1·4–4·0)	0·01	..	..	..	..

Rotavirus IgA seroconversion at ages 14 and 22 weeks served as the dependent variable. Variables with a p value of less than 0·05 during multivariable analyses are shown. Univariable regression results of not retained variables are provided in the appendix (pp 19–20). Ten (2%) of 474 saliva samples were missing for the secretor phenotype variable. This analysis was done among all individuals who were rotavirus IgA seronegative at age 6 weeks (n=474). RR=relative risk. ref=reference.

Table 5: **Multivariable regression for rotavirus IgA seroconversion at ages 14 and 22 weeks in infants who were rotavirus IgA seronegative at age 6 weeks in the Rotarix arm**

	RotaTeq arm (n=571)	Rotarix arm (n=573)
Infants with serious adverse events	9 (2%)	12 (2%)
Infants with any adverse events*	65 (11%)	63 (11%)
Respiratory infections	33 (6%)	35 (6%)
Diarrhoea	17 (3%)	11 (2%)†
Dermatological conditions‡	10 (2%)	7 (1%)
Other illnesses§	5 (1%)	10 (2%)

Data are n (%). *No cases of intussusception occurred. †One infant in the Rotarix arm had diarrhoea twice. ‡Cellulitis, chicken pox, scabies, and tinea capitis. §Conjunctivitis, oral thrush, respiratory and gastrointestinal coinfection, measles, and meningitis.

Table 6: **Adverse events in the intention-to-treat-population**

sample, 107 (20%) of 531 infants showed waning of rotavirus IgA titres and 122 (23%) of 531 had boosting of rotavirus IgA titres. In the Rotarix arm, comparing the 14-week sample with the 22-week sample, 222 (40%) of 549 infants showed waning of rotavirus IgA titres and 91 (17%) of 549 had boosting of rotavirus IgA titres. In both rotavirus vaccine arms, no significant differences were observed in rotavirus IgA seroconversion by IPV groups (appendix p 9).

To describe the contribution of different risk factors in determining the vaccine responses, we used the data from rotavirus IgA seronegative infants at age 6 weeks (464 for the RotaTeq arm and 474 for the Rotarix arm) in the log-binomial and linear regression models (tables 4, 5; appendix pp 10–22). Rotavirus IgG titres at age 6 weeks were similar in both rotavirus vaccine arms (table 2). For both vaccines, the upper tertile titres of rotavirus IgG antibodies at age 6 weeks were significantly negatively associated with rotavirus IgA seroconversion, and geometric mean titres, at all timepoints (tables 4, 5; appendix pp 10–11, 18). Positive secretor status was associated with an increased likelihood of rotavirus IgA seroconversion and higher geometric mean titres, except at age 14 weeks in the RotaTeq arm which did not have significant differences (tables 4, 5; appendix pp 10–12, 14, 18). Infants with high exposure to a rotavirus season by age 14 weeks had an increased likelihood of rotavirus IgA seroconversion and higher geometric mean titres at age 14 weeks than in infants with low exposure (tables 4, 5; appendix pp 10, 18). Additionally, infants who were exclusively breastfed at the age they received each of the two or three RotaTeq doses had significantly lower rotavirus IgA seroresponse than in infants who were partially breastfed at the time of at least one dose (table 4; appendix pp 10–11). The same trend was observed in the Rotarix arm based on samples collected at age 22 weeks but without significant differences (appendix pp 19–22).

65 (11%) of 571 infants had adverse events in the RotaTeq arm compared with 63 (11%) of 573 infants in the Rotarix arm (table 6). Serious adverse events occurred in nine (2%) of 571 infants in the RotaTeq arm and 12 (2%) of 573 in the Rotarix arm. None was attributed to the use of either vaccine. No cases of intussusception were reported. One death at about 23 weeks of age due to aspiration occurred in the RotaTeq arm, which was not related to the vaccine.

Discussion

This is the first head-to-head randomised controlled trial to compare antibody responses in infants who received a

complete series of RotaTeq or Rotarix in the same time frame and geographical location with IPV administration in the absence of OPV administration. Our study in Dhaka, Bangladesh, showed that a complete series of RotaTeq yielded a rotavirus IgA seroconversion of 73%. This finding was similar to another study in Bangladesh that showed a rotavirus IgA seroconversion of 78% for a complete RotaTeq series with concomitant OPV administration.[8] In that study, however, RotaTeq doses were given at slightly older ages (about ages 8, 13, and 17 weeks) than in our study. Our result was also similar to that from other countries with high child mortality, where RotaTeq with concomitant OPV administration elicited rotavirus IgA seroconversions of 61% in India, 74% in Kenya, 79% in Ghana, and 83% in Mali.[9–11] In our study, a complete series of Rotarix yielded a rotavirus IgA seroconversion of 64%. This finding was similar to a previous Rotarix study in Bangladesh that reported rotavirus IgA seroconversion of 67% in the non-OPV concomitant group and 57% in their OPV-concomitant group.[12] However, the Rotarix doses were given at older ages of 12 and 16 weeks than in our study. The rotavirus IgA seroconversion after Rotarix in our study was higher than that reported in three other studies in Bangladesh for a complete two-dose Rotarix series that was given with concomitant OPV: 27%, 42%, and 56%.[13] Our seroconversion results after Rotarix were also higher than that reported from other countries that have high child mortality where Rotarix was administered with concomitant OPV, yielding seroconversions of 58% in India, 44%, 57%, and 61% in South Africa (three studies), and 47% in Malawi.[14–17] Notably, in our study, the seroconversion at age 14 weeks after two vaccine doses was 14% higher in the Rotarix arm than in the RotaTeq arm. Administration of a third dose of RotaTeq increased the rotavirus IgA seroconversion by 23% from that of the second dose, demonstrating the importance of the third immunisation. In addition, Rotarix immunogenicity was lower or waned more rapidly when measured at age 22 weeks than that of RotaTeq (51% *vs* 74% rotavirus IgA seroconversion).

At the individual participant level, a lower proportion of infants in the RotaTeq arm had a waning of the rotavirus IgA response between the sample collected 4 weeks after the series completion and the sample collected at age 22 weeks, compared with the proportion of infants in the Rotarix arm with waning, possibly due to their third dose of RotaTeq. A previous study in Bangladesh showed that among vaccinated infants negative for week 24 seroconversion, eight (15%) of 52 had seroconverted at week 18 but subsequently seroreverted, indicating a fast waning in rotavirus IgA immunity.[18]

A recent sensitivity analysis of randomised controlled trials found that in countries with high child mortality from Asia and Africa, pooled vaccine efficacy of RotaTeq was 57% within the first year following vaccination and 44% through the second year; for Rotarix, the pooled vaccine efficacy was 57% in the first year and 29% through the second year.[19] A previous review of clinical trials (mostly immunogenicity) in high child mortality settings from Asia and Africa showed no significant benefit of giving additional Rotarix vaccine (three to five doses *vs* one to three doses) up until age 22 weeks.[5] However, the studies typically compared a schedule of Rotarix given at 6, 10, and 14 weeks of age versus a schedule given at 10 and 14 weeks of age (rather than the standard schedule given at 6 and 10 weeks of age), which might explain the absence of benefit observed. A mixed schedule of one Rotarix dose followed by two RotaTeq doses in the USA had significantly greater immunogenicity than the two Rotarix dose schedules.[20] A RotaTeq immunogenicity trial done in Mali has shown that an additional dose administered at age 9 months increased rotavirus IgA seroconversion by 30% from 45% to 75%.[21] An immunogenicity Rotarix trial in Bangladesh showed that an additional dose at age 9 months increased rotavirus IgA seroconversion by 17% from 53% to 70%. Also, an immunogenicity Rotarix trial in Australian indigenous infants showed that an additional dose at ages 6–11 months increased rotavirus IgA seroconversion by 16% from 69% to 85%. Taken together, these results suggest that an additional Rotarix dose after age 6 months is likely to increase rotavirus IgA seroconversion rates in high child mortality settings, where the majority of rotavirus gastroenteritis cases still occur during the first year of life.

Our study shows lower rotavirus IgA seroconversion and geometric mean titre among infants who were non-secretors compared with those who were secretors after three doses of RotaTeq or two doses of Rotarix. Among infants in each arm that were rotavirus IgA seropositive, non-secretors had lower rotavirus IgA geometric mean titres than secretors. The number of infants with Lewis-negative phenotype was too small to make a reliable interpretation of the effect, if any, of Lewis status on seroconversion. RotaTeq and Rotarix contain the predominant P[8] VP4 genotype. Thus, as for wild-type P[8] VP4 infections, we hypothesised that infants who were non-secretors would be more resistant to infection with and replication of the live-vaccine virus strains and therefore have a lower rotavirus IgA response from RotaTeq or Rotarix. Most studies examining Rotarix in Nicaragua, Pakistan and Ghana, and Malawi have reported a significantly lower proportion of seroconversion in non-secretors than in secretors.[6] However, no such differences were found in one previous study in Dhaka, Bangladesh.[22] Possible factors contributing to the absence of association in the previous Bangladesh study include their delayed Rotarix schedule, the time when seroconversion was measured, which might represent only the response to the first dose, and the relatively small sample size. Authors of the previous Bangladesh study[22] did find that

infants of non-secretor mothers were more likely to seroconvert than infants of secretor mothers. Furthermore, this association was independent of infant secretor status. A RotaTeq study in Nicaragua reported that non-secretor and Lewis-positive infants had lower seroconversion compared with secretors and Lewis-positive infants, and with Lewis-negative infants.[23] A few previous studies in highly vaccinated populations have shown that non-secretors had a reduced risk of rotavirus gastroenteritis because of resistance to naturally occurring genotypes,[24] thus suggesting that, even if non-secretors have lower vaccine response, their natural resistance to wild-type infections potentially counterbalances this finding.

Our study shows that high titres of maternal rotavirus IgG interfere with rotavirus IgA generation following vaccination in infants with RotaTeq and Rotarix. This passively acquired serum rotavirus IgG has also been linked with a reduction in the immunogenicity of Rotavac.[5] This finding also aligns with an increase in seroconversion rates by up to 25% observed following administration of Rotarix at ages 10 and 14 weeks instead of the standard schedule of 6 and 10 weeks when maternal antibodies will have had less time to wane.[5] The mechanism for increased immunogenicity when the administration of the rotavirus vaccine is delayed is possibly a combination of reduced interference from maternal antibodies[25] and infant immune system maturation. In our study, infants who were exclusively breastfed at the age they received each rotavirus vaccine dose had lower rotavirus IgA seroconversion than infants who were partially breastfed at the time of at least one dose; this effect was found at each endpoint in the RotaTeq arm and at 22 weeks of age in the Rotarix arm. Previously in Bangladesh, exclusive breastfeeding was associated with a lower likelihood of rotavirus infection in the first 6 months of life.[26] Hence, in this Bangladeshi population, full breastfeeding might protect the infants from natural rotavirus infection more than partially breastfeeding, and our observed lower rotavirus IgA seroconversion in breastfed infants might be a reflection of this effect. Previously, formula-fed infants in Mexico achieved higher rotavirus IgA titres after Rotarix than breast-fed infants, even though rotavirus IgA geometric mean titres in breast-fed infants was still quite robust.[5]

The strengths of this trial are its randomised design, strictly adhered administration schedule of vaccines, careful timing of sample collection allowing valid comparisons across groups, sample size powered for the primary outcome, low prevalence of loss to follow-up, and use of a vaccine antigen-matched EIA to assess the primary outcome. However, our study had limitations. First, comparison of two vaccines with different dose schedules is challenging, so the age at series completion is different. At the study endpoint at age 22 weeks, all the infants had the same lifetime of exposure to wild-type rotavirus. However, at age 22 weeks, in the Rotarix arm, 8 weeks had passed since the last vaccination compared with 4 weeks in the RotaTeq arm, which is possibly an important time difference when assessing waning immunity. Second, although evidence exists that rotavirus IgA correlates well with clinical protection at the individual and population level,[27,28] we cannot determine whether higher rotavirus IgA titres result in a more sustained duration of vaccine-induced antibodies, including rotavirus IgG and neutralising activity up to age 1 or 2 years because rotavirus IgA usually has a short life and might be a suboptimal correlate of protection. Third, although both the RotaTeq and Rotarix arms should have been equally affected due to our randomisation, we cannot separate wild-type rotavirus exposure from vaccine response.

In conclusion, this study is the first head-to-head comparison of the three-dose RotaTeq series with the two-dose Rotarix series. At age 14 weeks, after two vaccine doses, infants who received Rotarix had higher rotavirus IgA seroresponse than infants who had received RotaTeq. However, at age 22 weeks, we observed a faster waning of the seroresponse among infants who received Rotarix, the most widely used rotavirus vaccine in high child mortality, resource-poor settings. We confirmed the inhibitory effect of maternal antibodies on rotavirus vaccine immunogenicity in high child mortality countries. Moreover, non-secretors had lower rates of rotavirus IgA seroconversion than secretors. As part of a comprehensive effort to reduce morbidity and mortality from diarrhoeal illnesses in young children, in addition to safe drinking water and sanitation, our analysis suggests that future efforts should improve the immune response to rotavirus vaccination with higher vaccine effectiveness in challenging settings. An additional dose after the age of 6 months might increase protection in these settings with current oral vaccines. Circumventing the previously described reasons for the suboptimal immunogenicity of oral rotavirus vaccines, parenteral immunisation with non-replicating vaccines might lead to a higher and more durable immune response.[29] One potential strategy is to administer parenteral rotavirus vaccines to boost intestinal immunity in infants who receive live oral vaccines, as shown by sustained protection from an IPV booster dose among children who receive OPV in India.[30]

Contributors

DEV-P did the laboratory testing, statistical data analysis, data interpretation, and manuscript drafting and editing. XW and ZS did the laboratory testing. KZ contributed to the study design, verification of underlying data, and managed the study implementation in Bangladesh. MY contributed to the study design and managed the study implementation in Bangladesh. MMC, CJS, AA, and UP contributed to the study design, data interpretation, and manuscript editing. BJ contributed to laboratory supervision, verification of underlying data, and manuscript editing. VPC did the laboratory testing and manuscript editing. HMS and TBH contributed to manuscript editing. ABA and WH supervised the study implementation in Bangladesh. All authors read and approved the final version of the manuscript.

Declaration of interests
We declare no competing interests.

Data sharing
The study is registered with ClinicalTrials.gov, number NCT02847026, and aggregated data from table 2 will be added to the registration with publication. In accordance with the protocol, investigators of the International Centre for Diarrhoeal Disease Research, Bangladesh will have access to participant data with identifiers. External investigators will have access to de-identified participant data. De-identified data can be shared with national and international vaccine manufacturers and regulatory authorities upon request, and no participant level data will be shared further after publication. Requests for data should be directed to the corresponding author Baoming Jiang (bxj4@cdc.gov).

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