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Journal

Vaccine, 32(6)

ISSN

0264-410X

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Publication Date

2014-02-01

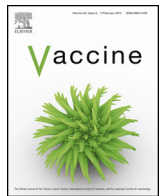
DOI

10.1016/j.vaccine.2013.12.017

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Transplacental rotavirus IgG interferes with immune response to live oral rotavirus vaccine ORV-116E in Indian infants[☆]



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ARTICLE INFO

Article history:

Received 1 July 2013

Received in revised form 15 October 2013

Accepted 10 December 2013

Available online 25 December 2013

Keywords:

Maternal antibody

Dose

Seroconversion

IgA

Rotavirus

Vaccine

ABSTRACT

The lower immune response and efficacy of live oral rotavirus (RV) vaccines tested in developing countries may be due in part to high levels of pre-existing RV antibodies transferred to the infant from mother via the placenta. The candidate RV vaccine strain 116E was isolated from a newborn indicating that it might grow well even in the presence of this transplacental rotavirus antibody. Since the immune response to this vaccine among infants in the Indian subcontinent has been greater than that of the commercially licensed vaccines, we questioned whether this might be due to the ability of RV 116E to grow well in infants despite the presence of maternal RV antibody. To this end, we tested pre-immunization sera from Indian infants enrolled in a phase Ia/Ib trial of candidate RV vaccine ORV-116E for transplacental RV IgG to see whether it affected the immune responses and seroconversion to the vaccine. We found that the high titers of transplacental RV IgG diminished the immune responses of infants to ORV-116E vaccine. However, the vaccine was able to overcome the inhibitory effect of this RV IgG in a dose-dependent manner. This report clearly demonstrates the interference of maternal antibody on RV vaccine immunogenicity in infants in a field study as well as the ability of ORV-116E to overcome this interference when used at a higher dose.

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1. Introduction

Rotavirus (RV) is the leading cause of severe gastroenteritis (GE) in children <5 years of age and is estimated to cause ~125 million clinical cases of GE worldwide and ~275,000–450,000 deaths every year, ~85% of which occur in low income countries [1,2]. Two vaccines, Rotarix[®] and Rotateq[®], are currently licensed internationally [3]. The efficacy of these vaccines against severe rotavirus gastroenteritis (SRGE) was 85–98% in developed countries, but only ~51% efficacy in low income settings of Africa and Asia [3–8]. Several factors have been hypothesized to explain this failure, including

the RV antibodies in breast milk and the high levels of circulating pre-existing maternal RV antibody in the infant that could inhibit replication of these live oral vaccines [3,9–13].

In the late 1980's, a RV isolate, now known as strain 116E, was identified in neonates at a hospital in New Delhi. Further characterization of this strain established it to be a natural human-bovine reassortant [14,15]. Strain 116E was found to have 10 gene segments from a human RV, but a single gene encoding the surface VP4 protein from a bovine strain. VP4 is a hemagglutinin critical for virus attachment and entry and a target for neutralizing antibodies [10]. The bovine origin of this gene was speculated to allow this virus to replicate well in newborns despite the presence of high titers of transplacental RV antibodies [16,17]. In fact, newborns naturally infected with this strain were asymptomatic and shed virus in their stool, mounted high levels of RV-specific IgA following the infection, and were subsequently found to be protected against SRGE [18,19]. A candidate vaccine, ORV-116E, was developed from this strain and phase I and II trials in infants in India demonstrated high

[☆] Clinical trials registration: NCT00439660 and ISRCTN57452882.

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rates of seroconversion [16,17,20]. Unlike other RV vaccines tested in developing countries including India, ORV-116E induced ~90% seroconversion in Indian infants when administered as three doses of 10^5 FFU titrated vaccine [4,21,22].

Although not proven conclusively, some studies indicate a protective role of RV IgA [23,24]. Nevertheless, RV IgA responses are considered true indicators of seroconversion to the vaccine [23]. In order to establish if transplacental RV IgG antibody affected the immunogenicity of ORV-116E in neonates, we determined the pre-immunization titer of RV IgG (hereafter referred to as maternal IgG) in serum collected from vaccinees in the recently concluded phase Ia/IIb trial in India [21] and compared this to their IgA response to the vaccine. Interestingly, our analyses demonstrated that the IgA responses to ORV-116E were inversely related to the levels of RV IgG prior to immunization. We also observed that ORV-116E administered at a higher titer could overcome the interference from maternal antibody in a dose-dependent manner. These data highlight the critical importance of administering multiple doses of vaccine in order to enhance immune responses and seroconversion.

2. Materials and methods

2.1. Clinical trial details

The phase Ia/IIb trial of the ORV-116E, a randomized, double-blinded, placebo-controlled study (Clinical trials registration: NCT00439660 and ISRCTN57452882) to determine the dose-escalation safety and immunogenicity of the vaccine in infants recruited at 6 weeks of age, has been previously described [21]. Briefly, two doses of vaccine containing 10^4 FFU and 10^5 FFU of RV 116E were tested. ORV-116E or placebo was administered at 8, 12, and 16 weeks of age. About 90 infants were enrolled for each dose of the test article. Blood samples were collected from all infants before the first administration of the test article and from one-third (30 vaccine recipients and 30 placebo recipients) of infants 28 days after the first, second and third administration. The pre- and post-vaccination serum RV IgA concentrations in the study participants were determined by an ELISA as arbitrary units (AU)/ml [21]. The minimum detection limit of the ELISA was 4 AU/ml. If IgA concentrations were below the detection limit, a concentration of 2 AU/ml (50% of the lower detection limit) was assigned. Seroconversion was defined as a ≥ 4 -fold increase in IgA (FI-IgA) concentration following vaccination, measured one month after the first, second, or third administration. Infants having RV IgA in their pre-vaccination serum at a titer of ≥ 8 AU/ml, that suggested an early neonatal RV infection, were excluded from analyses. Similarly, participants diagnosed with non-vaccine RV in their stool samples during the trial were excluded, irrespective of their serum pre-immunization IgA concentrations.

2.2. Quantitation of transplacental RV IgG in the infant

Once infants with an elevated IgA titer at 8 weeks were excluded from analyses, it was assumed that the RV IgG in their serum drawn at the time of the first dosing was a measure of the RV IgG that they had received from the mother in utero. The RV IgG concentrations were determined using an ELISA. Briefly, microtiter plates coated with Vero cell-cultured RV-116E antigen, or culture supernatant from Vero cells, were incubated with appropriately diluted serum samples and the RV IgG was detected using anti-human IgG-HRP conjugate (Dako, Denmark) and o-phenylenediamine substrate. The optical density (OD) for the serum sample obtained on antigen negative well was subtracted from that on the antigen positive well. The subtracted OD was used to extrapolate the IgG concentration from a standard curve that was generated using a

RV hyperimmune serum containing an arbitrarily defined RV IgG concentration.

2.3. Statistical analyses

Statistical analyses were carried out using SAS® Software, version 9.3 (SAS Institute Inc., USA). As the variables being analysed were non-normally distributed, non-parametric methods were applied. The maternal immunity (RV IgG) and immune responses to the administered test article (FI-IgA) were plotted in a scatter-gram and the relationship between the two was examined by linear regression analysis followed by the test for statistical significance using the Spearman correlation test. When comparing more than two groups, if the Kruskal–Wallis test suggested significant difference, the statistical difference was further established between groups using the Wilcoxon rank-sum test. An alpha level of 0.05 ($p < 0.05$) was considered significant for all tests.

3. Results

3.1. Study population and RV immunity

Of the 369 clinically healthy infants enrolled in the phase Ia/IIb trial, 187 received the 10^4 FFU dose and 182 received the higher dose of 10^5 FFU [21]. Following the exclusion criteria described in the methods, data from 124 infants in the 10^4 FFU dose group and 152 infants in the 10^5 FFU dose group were considered for analyses. Overall, 62 infants (17%) were excluded from the analyses because of high titers of pre-existing IgA and 24 (6.5%) had a non-vaccine RV infection during the study (Table 1).

Seroepidemiological studies across different geographical regions suggested that infants in the first semester of life in developed countries possess low levels (range: 800–6400) of RV antibodies, whereas those in the developing and low-income countries possess a wide range (range: 160–80,000) of these antibodies [25–29]. Infants included in the present study had a wide range of RV IgG (894–85,360) at the time the first dose of the test article was administered (Table 2). The distribution of RV IgG titers between the placebo recipients from 10^4 FFU and 10^5 FFU dose groups was similar. However, between the vaccine-treated groups, IgG titers were significantly higher in the 10^4 FFU dose group ($p = 0.0057$).

3.2. Transplacental RV antibody inhibits the IgA responses to ORV-116E

RV IgG levels at immunization had a clear inhibitory effect on the IgA response (Table 2). After exclusions, 22% of the placebo recipients ($n = 14$ for 10^4 FFU, and $n = 17$ for 10^5 FFU groups) and 73–76% of the vaccinees ($n = 45$ for 10^4 FFU, and $n = 55$ for 10^5 FFU groups) had a four-fold or greater rise of IgA. While levels of maternal IgG did not affect the seroconversion in placebo recipients who became infected with RV during the course of the study, vaccinees that seroconverted had significantly lower median IgG titers than those who failed to seroconvert. Interestingly, the difference in the FI-IgA was significant between the seroconverted participants in the 10^4 FFU and 10^5 FFU placebo-treated groups ($p = 0.0048$), perhaps reflecting a different RV season when they were enrolled in the study: the 10^4 FFU dose participants were studied during November 2006–July 2007 and the 10^5 FFU dose participants were studied during September 2007–March in 2008 [21].

Demonstration of ≥ 4 -fold increase in RV IgA concentration and absence of RV in stool samples of the placebo recipients during the study period suggest that these participants were indeed infected with the natural RV strains, which induced strong anti-RV immune responses, and that these RV strains failed to replicate sufficiently in the gut of these participants to cause clinical illness. As no severe

Table 1

Number of participants included in the analysis. Exclusion criteria for the analyses included (1) study participants who had pre-immunization serum RV IgA concentrations ≥ 8 AU/ml and (2) those who had RV antigen in their stool samples.

Formulation	No. of participants recruited	No. of participants excluded and the criteria			No. of participants considered for the analysis
		Pre RV-IgA ≥ 8 AU/ml	Non-vaccine RV infection	Both criteria	
10 ⁴ FFU Placebo	92	19	10	2	65
10 ⁴ FFU Vaccine	86	24	4	1	59
10 ⁵ FFU Placebo	90	9	4	0	77
10 ⁵ FFU Vaccine	91	10	6	0	75

Table 2

Levels of RV IgG and FI-IgA in different study groups. Median pre-IgG and the median FI-IgA for the total number of participants (pool) and for those who seroconverted (yes) and those who did not seroconvert (no) within each immunization group were calculated. Chi-Square test was applied to calculate the significance of difference (*p* value) in pre-IgG concentrations between the groups.

Formulation	Seroconversion status (n)	Median pre-IgG AU/ml [range]	<i>p</i> value	Median FI-IgA AU/ml [range]
10 ⁴ FFU Placebo	Pool (65)	9620 [906–45136]	–	1 [0.29–379.7]
	No (51)	9784 [906–45136]	0.72	1 [0.29–3.9]
	Yes (14)	9562 [1864–31692]		7.1 [4.1–379.7]
10 ⁵ FFU Placebo	Pool (77)	10080 [894–49820]	–	1 [0.28–3398]
	No (60)	10128 [894–49820]	0.79	1 [0.28–3.6]
	Yes (17)	8010 [2386–45886]		166.2 [4.4–3398]
10 ⁴ FFU Vaccine	Pool (59)	14962 [1394–50788]	–	16.8 [0.48–878.1]
	No (14)	20437 [6390–48294]	0.016	1 [0.48–2.7]
	Yes (45)	13148 [1394–50788]		27.1 [4.1–878.1]
10 ⁵ FFU Vaccine	Pool (75)	9140 [1122–85360]	–	13 [1–711.9]
	No (20)	15243 [5742–85360]	0.0008	1 [1–3.9]
	Yes (55)	7278 [1122–48532]		34 [4.2–711.9]

RV gastroenteritis was reported from any of these participants it would appear that the pre-existing RV antibodies, while providing protection, did not interfere in seroconversion caused by natural RV infection.

We further examined the relation between an infant's RV IgG titer at the beginning of the study and their seroconversion (as FI-IgA to the vaccine) (Fig. 1). For both vaccine dose groups, we found a significant inverse relationship between RV IgG titer and the IgA response, indicating RV IgG interference (Fig. 1B and D). However, no such relationship was seen in the placebo-treated participants in either dose groups (Fig. 1A and C). Consistent with this, in both vaccine dose groups, the difference in median RV IgG between participants who seroconverted and those who did not was statistically significant, whereas this difference in the placebo-treated groups was not significant (Table 2).

3.3. ORV-116E can overcome maternal antibody interference in a dose-dependent manner

We next examined whether the magnitude of the immune response to ORV-116E (FI-IgA) was affected by pre-existing RV IgG and, as speculated, whether a higher titer of the ORV-116E vaccine could overcome this interference (Fig. 2). Infants in each dose group were stratified into four subgroups in ascending order of their RV IgA seroresponses. Again, we hypothesized that if IgG levels affected an infant's IgA response to the vaccine, then the median RV IgG across the four IgA subgroups should differ significantly.

For both doses of the vaccine, we observed a trend in which infants having the greatest IgA responses to the vaccine (e.g., >64 fold) had titers of RV IgG that were one-third to one-quarter lower than those who had no response (i.e., <4 fold). While we could not determine the threshold of RV IgG titer that would allow an adequate vaccine response, it was clear that infants with the lowest IgG titers did have the most vigorous immune response to vaccine. For the 10⁴ FFU dose of the vaccine, the median RV IgG titers between the adjacent subgroups did not differ significantly except for those between the 16– <64 and >64 FI-IgA subgroups, indicating that RV IgG indeed affected the IgA response and significantly

lower RV IgG titers were required for the vigorous RV IgA response (>64 FI-IgA). For the 10⁵ FFU dose group, however, there was no significant difference between the adjacent FI-IgA groups indicating that the magnitude of RV IgG had no bearing on the extent of RV IgA response. These data indicate that the higher dose of vaccine had the ability to overcome the interference of the maternal RV antibodies.

The analysis presented thus far was based on the composite data on seroconversions in all infants regardless of whether their sera was tested after the first, second or third dose of the vaccine. Having seen an inhibitory effect of maternal IgG to dampen the immune response to the vaccine, we went on to determine if this effect was more pronounced after the first administration of vaccine or if waning of this maternal IgG over time might have yielded higher rates of seroconversion in those infants whose blood was sampled later, after the third administration (Fig. 3). Maternal immunity imposed a strong and sustained inhibitory effect on the immunogenicity of both high and low doses of ORV-116E after the first and second administration. After the third administration of the vaccine, the inhibitory effect was again seen for both doses of the vaccine, but the inverse relationship between RV IgG and the IgA response was not significant for the higher dose. Of note, after the first administration of vaccine, only 1 of 8 infants in the low dose group and 0 of 10 in the high dose group had IgG titer 10,000 AU/ml or less and failed to seroconvert. This suggests a natural threshold for this inhibition.

4. Discussion

Our results demonstrate a clear inverse relationship between the levels of pre-existing RV IgG and the immune response to ORV-116E vaccine, establishing clearly that maternal antibody interfered with an infant's immune response to rotavirus vaccine. Infants who seroconverted to the vaccine had significantly lower median RV IgG titers than those who failed to seroconvert. Additionally, infants with lower RV IgG titers showed the highest level of seroconversion. These observations were true for both the lower as well as the higher dose of ORV-116E. Importantly, the higher

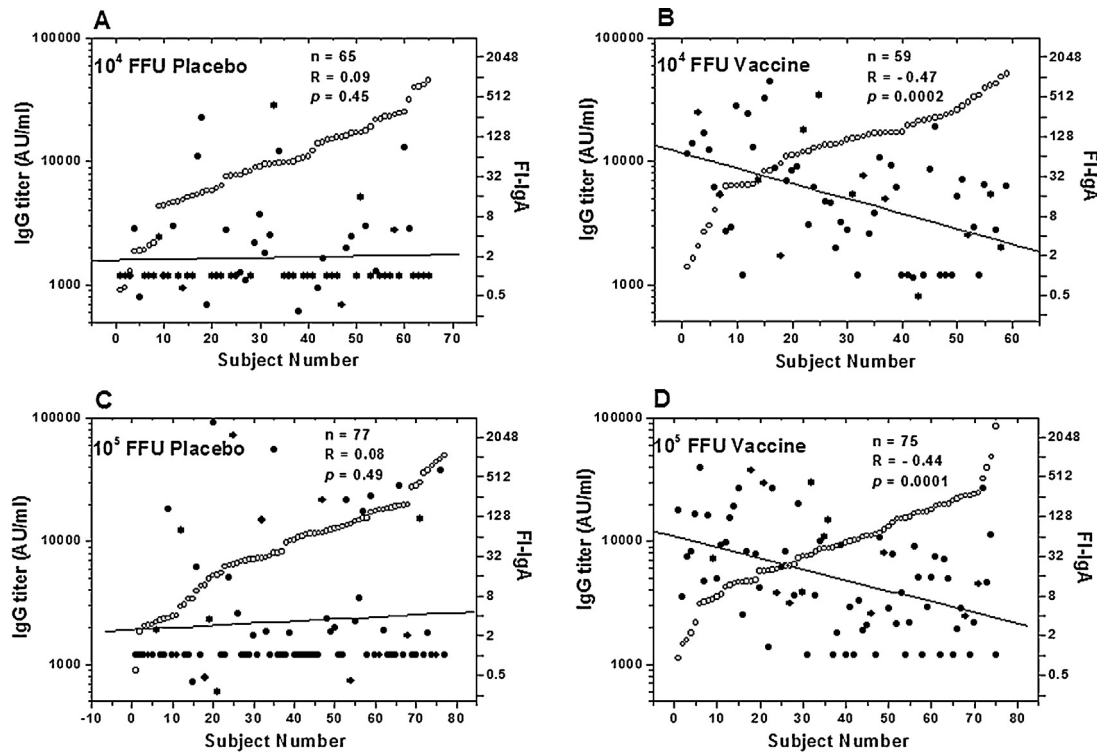


Fig. 1. Transplacental RV IgG and immune response to ORV-116E. Study participants are arranged in order of their ascending RV IgG concentrations (open circles) and matched with corresponding fold-increases in their post-immunization RV-IgA concentrations (FI-IgA) (closed circles). The Spearman coefficients calculated for the non-normally distributed data points indicate a significant inverse relationship between RV-IgG and FI-IgA in the case of participants receiving the vaccine. However, this relationship in the case of participants receiving the placebo was not significant. Linear fit applied on the data points depicts the relation between RV-IgG and FI-IgA.

dose of vaccine administered on a 3 dose schedule demonstrated the ability to overcome interference by maternal antibody.

Our study focused on the role of transplacental RV IgG on vaccine immunogenicity. As the infants enrolled in the study were 8-weeks-old, contribution of RV antibodies present in the breast milk cannot be ruled out.

Our observations on maternal antibody interference are similar to those reported in the case of polio and measles vaccine [30,31]. Despite much speculation, no data have been published to date indicating the interference of transplacental maternal antibodies on the immune response to currently licensed RV vaccine in infants [3,13]. However, recent studies in gnotobiotic piglets have shown that high titers of maternal RV antibodies imposed

strong suppressive effect on RV vaccine take [12,32]. Additionally, dose-dependency of immune responses in the presence of maternal immunity has been reported for other vaccines and some of the studies with RV vaccines have also alluded to similar interference [11,33–38]. The most relevant observations consistent with our findings are those of Steele and co-workers who conducted a study in South Africa in which several different vaccine schedules were examined in an attempt to improve the immune response to the monovalent RV vaccine, Rotarix [39]. The schedule recommended by the manufacturer was to administer two doses at 6 and 10 weeks of age. In the African trial, a three dose schedule (6, 10, and 14 weeks) and a two dose schedule (10 and 14 weeks) did much better than the 6 and 10 week schedule and the 6-week dose did not

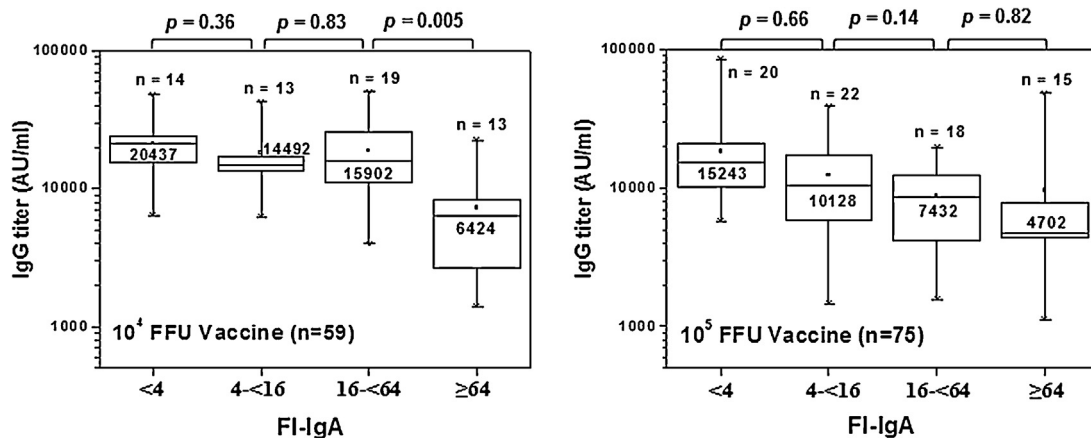


Fig. 2. Levels of RV IgG in different FI-IgA subgroups. Box-and-Whisker plots depict the range (and median) of the RV IgG among vaccinees that were grouped based on the FI-IgA levels. The significance of variance in median RV IgG across different FI-IgA groups was calculated using Kruskal–Wallis test followed by Wilcoxon rank-sum test. p-values indicate the significance of variance between the adjacent FI-IgA groups.

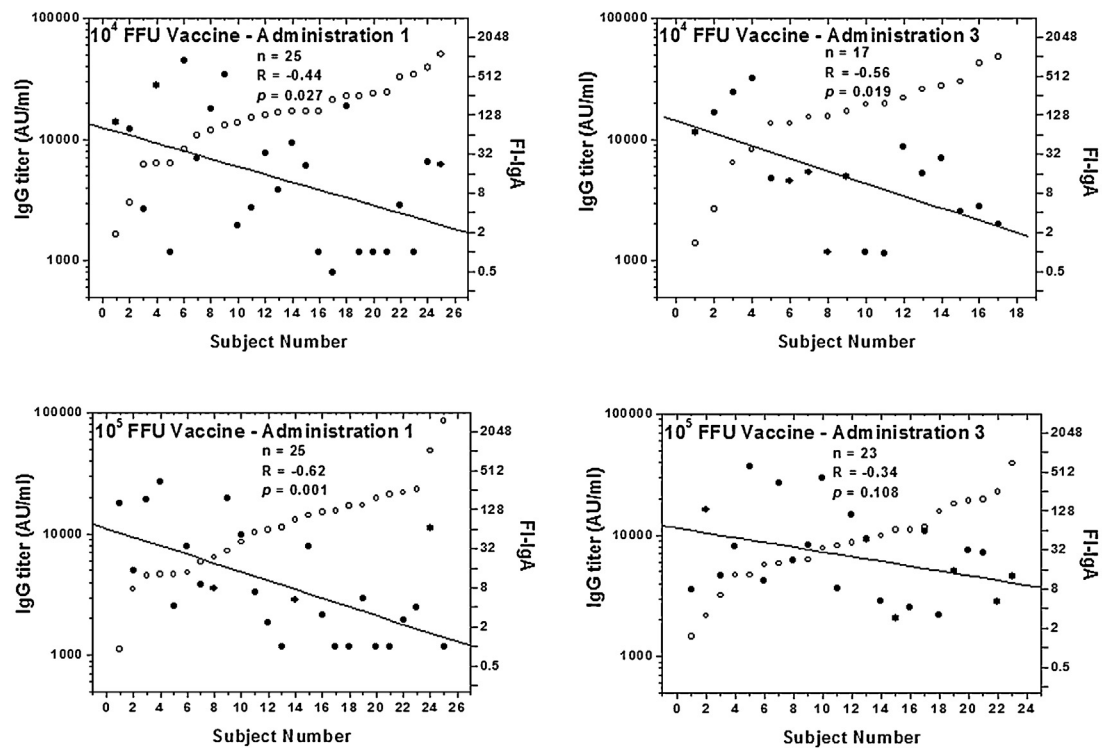


Fig. 3. Transplacental RV IgG and immune response to ORV-116E after the first and third dose. Study participants are arranged in ascending order of their RV IgG titers (open circles) and matched with corresponding immune responses represented as FI-IgA (closed circles). The Spearman coefficients and the *p* values are presented. The linear fit applied on the data points indicates a significant inverse relationship between the two in all cases except for administration 3 of the 10⁵ FFU dose of the vaccine.

contribute to vaccine take. Since transplacental RV IgG wanes with a half-life of 3–4 weeks, the later the vaccine is administered, the lower will be the inhibitory effect and the better will be the chance of a successful take. Consequently, in their pivotal efficacy trial, they administered the vaccine using the delayed two dose schedule (i.e., 10 and 14 weeks) and the alternative three dose schedule (i.e., 6, 10, and 14 weeks) to improve the immune response and achieve greater efficacy [4]. Although this study was not powered to detect such differences, there was a slight but non-significant trend toward higher seroconversion rates and vaccine efficacy with the three-dose schedule.

The inhibitory effect of maternal antibody could represent one possible reason why other live oral RV vaccines have been less immunogenic and effective in low income settings, particularly South Asia [3–6]. The higher dose ORV-116E given in a three-dose schedule was more immunogenic in infants with high titers of RV IgG, an observation that has important implications for its licensure and application in India and other countries where infants receive high titer RV IgG transplacentally from their mothers. In newborns and young infants, RV IgG comes primarily from the mother and only marginally from natural RV infections in the first month or two of life. RV-116E was isolated from asymptomatic newborns who acquired infection in the hospital in the few days following delivery. The fact that the strain grew well in newborns, and the observation that the outbreak was widespread in the newborn unit, suggested that the strain could grow in the presence of maternal RV IgG. We attributed this ability exclusively to the presence of a single bovine-VP4, the hemagglutinin spike protein responsible for cell attachment which might be less inhibited by RV IgG acquired from the mother. This study, however, demonstrated that the pre-existing RV IgG did inhibit the vaccine strain but the vaccine was still able to overcome the interference in a dose-dependent manner, replicate in the infant's intestine, and induce a robust immune response.

Our data provide new evidence that levels of RV IgG present at the time of immunization of an infant with a live oral RV vaccine can inhibit the immune response to the vaccine, even one derived from a newborn strain that grew well during natural infection in newborns having higher titers of maternal antibody. Nonetheless, we were able to establish that despite this inhibitory effect, the dose and schedule chosen should diminish this problem and allow the infants to mount a robust immune response to the vaccine. The proof of these observations remains in the outcome of the on-going phase III clinical trial. Our observations should encourage other vaccine developers to examine more carefully any suboptimal immune response to their live oral RV vaccines in the developing countries and assess the extent to which pre-existing RV IgG is inhibitory to a good take of their vaccine. Several strategies have been proposed to improve rotavirus vaccine immunogenicity [3,33,34,40]. Based on the results of this study, use of higher dose of vaccine virus and/or the addition of multiple administrations could improve the immune response to the vaccine and, hopefully, the efficacy of live oral RV vaccines for infants in these challenging low income settings.

Acknowledgments

We thank Duncan Steele and John Clemens for critical reading of the manuscript and valuable comments. This work was supported by the core grant provided by the Department of Biotechnology, Govt. of India to the National Institute of Immunology and the Translational Health Science and Technology Institute.

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