

Safety, immunogenicity, and protective efficacy of two doses of RIX4414 live attenuated human rotavirus vaccine in healthy Brazilian infants

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Abstract

Objective: To determine the safety, immunogenicity and efficacy of two doses of rotavirus vaccine in healthy Brazilian infants.

Methods: A randomized, multicenter, double-blind, placebo-controlled trial was conducted in Brazil, Mexico and Venezuela. Infants received two oral doses of vaccine or placebo at 2 and 4 months of age, concurrently with routine immunizations, except for oral poliomyelitis vaccine (OPV). This paper reports results from Belém, Brazil, where the number of subjects per group and the viral vaccine titers were: 194 ($10^{4.7}$ focus forming units – FFU), 196 ($10^{5.2}$ FFU), 194 ($10^{5.8}$ FFU) and 194 (placebo). Anti-rotavirus (anti-RV) antibody response was assessed in 307 subjects. Clinical severity of gastroenteritis episodes was measured using a 20-point scoring system with a score of ≥ 11 defined as severe GE.

Results: The rates of solicited general symptoms were similar in vaccine and placebo recipients. At 2 months after the second dose, a serum IgA response to RV occurred in 54.7 to 74.4% of vaccinees. No interference was seen in the immunogenicity of routine vaccines. Vaccine efficacy against any rotavirus gastroenteritis (RVGE) was 63.5% (95%CI 20.8-84.4) for the highest concentration ($10^{5.8}$ FFU). Efficacy was 81.5% (95%CI 44.5-95.4) against severe RVGE. At its highest concentration ($10^{5.8}$ FFU), RIX4414 provided 79.8% (95%CI 26.4-96.3) protection against severe RVGE by G9 strain.

Conclusions: RIX4414 was highly immunogenic with a low reactogenicity profile and did not interfere with seroresponse to diphtheria, tetanus, pertussis, hepatitis B and Hib antigens. Two doses of RIX4414 provided significant protection against severe GE caused by RV.

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Introduction

Rotavirus (RV) is the major cause of severe dehydrating gastroenteritis (GE) in early childhood and it is annually estimated to account for 25 million clinic visits, 2 million hospitalizations and > 600,000 deaths among children aged less than 5 years.¹ Similar incidence rates of RV disease in both developed and developing countries sustain the concept that a vaccine, rather than improvements in hygiene and sanitation, is likely to be effective in controlling rotavirus gastroenteritis (RVGE).²

Several studies conducted in Latin America indicate that RV constitutes a major cause of diarrhea-related morbidity and mortality during infancy and childhood, accounting for an estimated 75,000 hospitalizations and 15,000 deaths each year.³ At least 36 surveys carried out across Brazil have demonstrated that RV accounts for 4.5-46% of cases of acute diarrhea among inpatients and/or outpatients.⁴ Preliminary estimates indicate that at least 2,000 RV-related deaths occur annually in Brazil among children aged less than 5 years.⁵ Numerous studies conducted in Brazil have shown the diversity of circulating RV strains. Although RV belonging to the G1 serotype seems to be predominant, uncommon strains such as G5 and the globally emerging G9 serotypes have also been detected.^{2,6,7}

Earlier studies conducted in Brazil included the evaluation of a low titer (4×10^4 plaque forming units – PFU/dose) tetravalent rhesus-human reassortant RV vaccine (RRV-TV). This vaccine provided only partial protection against any and moderate/severe GE, respectively.² A 10-fold higher formulation of RRV-TV (designated Rotashield™, Wyeth-Laboratories, Inc., Marietta, PA, USA), proved highly effective (80%-100%) against severe RV disease and hospitalization.² In August 1998, Rotashield™ was licensed and subsequently recommended for universal vaccination in the USA, but was later withdrawn due to an increased risk of intussusception during 3-14 days following the first and second vaccine doses.^{2,8}

There are currently two newly developed RV vaccines which have undergone large phase III trials. One is a pentavalent bovine-human reassortant vaccine (Rotateq™) developed by Merck (USA). The other one, which has been studied extensively in both developed and developing countries, is Rotarix™ (RIX4414), developed by GlaxoSmith-Kline Biologicals, Belgium.

RIX4414 is a live attenuated human rotavirus G1P[8] strain. It has been derived from the parent strain 89-12 following cell-culture passage and cloning. This strain yielded promising results in U.S. efficacy studies with a mild reactogenicity profile.⁹ Following dose-ranging studies involving Finnish infants¹⁰ and phase II trials conducted in

Finland, Latin America (Brazil, Mexico and Venezuela) and Singapore, RIX4414 was shown to be highly efficacious against severe RVGE.^{11,12}

This paper deals with the safety, immunogenicity and efficacy of two doses of RIX4414 in healthy infants in Belém, Brazil, where the heterologous (G9) RV strain was predominant.

Method

The study protocol, amendments and written informed consent were approved by the Institutional Ethics Review Board and the National Ethics Review Committee. The study was conducted in accordance with the October 1996 version of the Helsinki Declaration and the Good Clinical Practices guidelines.

This phase IIb multicenter study (444563/006) involved 2,155 healthy infants, as follows: Brazil (n = 778), Mexico (n = 405) and Venezuela (n = 972).

Written informed consent was obtained from parents or legal guardians prior to enrollment in Belém of the 778 infants, who received the first vaccine dose between May 2001 and April 2002. Most of these subjects were from low-income families living in the outskirts of Belém; they were in general well-nourished infants with only a few mild malnutrition cases being noted. A pediatrician performed physical examination of infants when inclusion/exclusion criteria and possible contraindications were checked. Eligible subjects, healthy full term infants between 6 and 12 weeks of age who weighed > 2,000 g at birth, were randomly assigned to one of four groups corresponding to three vaccine concentrations and placebo. This distribution followed a 1:1:1:1 allocation ratio as based on a computer-generated randomization list.

The vaccine was supplied lyophilized and kept at 2-8 °C until administered. The vaccine was reconstituted with a diluent containing calcium carbonate as buffer. Each dose contained either $10^{4.7}$ focus forming units (FFU), $10^{5.2}$ FFU, or $10^{5.8}$ FFU of RIX4414. The placebo was identical to RIX4414 without the viral content. Each infant was given 1 mL of either the reconstituted vaccine or placebo orally at approximately 2 and 4 months of age. Immunization was rescheduled for infants who had fever (axillary temperature ≥ 37.5 °C) or GE within the preceding 7 days. Feeding was allowed before and after administration of the vaccine.

Infants received routine immunizations including Tritanrix™ (diphtheria and tetanus toxoid, whole-cell pertussis, DPTw, and hepatitis B), Hiberix™ [*Haemophilus influenzae* type B (Hib)], and oral polio vaccine. The latter vaccine was given at an interval of at least 14 days before or after administration of the study vaccine.

Parents/guardians were instructed to record the occurrence of solicited symptoms in diary cards for 15 days after each dose. Weekly home visits were made by field workers to check whether diary cards were being properly completed. Unsolicited clinical symptoms were also recorded within the 43 days following each vaccination. A thorough surveillance of serious adverse events was conducted throughout the whole study period. An independent safety monitoring committee periodically reviewed all serious adverse events.

Pre-immunization blood samples were taken from all infants at their first visit to assess previous RV infections. Subsequent venous blood aliquots were obtained from a cohort of 307 infants, 2 months after the first and second doses. Blood samples were also obtained from all infants at the follow-up visit when they were aged 1 year. Anti-RV IgA was measured by ELISA, as previously described.⁹ Serum samples from the immunogenicity subset ($n = 307$) were also tested for antibodies to routine vaccine antigens (diphtheria, tetanus, pertussis, hepatitis B, Hib and the three poliovirus serotypes). Stool specimens were obtained after each dose from the first 200 enrolled subjects, to assess RV antigen excretion. In a first step, the samples were tested by ELISA.⁹ RV-positive samples were further subjected to reverse transcription polymerase chain reaction (RT-PCR) to determine the G serotype.¹³ A subsequent oligonucleotide sequence analysis was performed with all RV G1 strains to distinguish between wild- and vaccine-derived G1 RV serotypes.

When the first vaccine dose was administered and until one year of age, each child was visited weekly at home by trained field workers, to detect acute GE episodes (defined as three or more liquid or semiliquid stools in a 24-hour period). An episode was considered to be terminated when the infant, during five days or more, passed less than three looser-than-normal stools in each 24-hour period. Instructions were stressed to parents/guardians to make a telephone call to the study staff whenever they considered that their child had developed diarrhea. During diarrheal episodes symptoms were recorded by parents/guardians in appropriate diary cards and checked for completion by field workers. The severity of RVGE was graded by a 20-point scoring system.¹⁴ Cases of RVGE with scores of 0 to 6, 7 to 10 and ≥ 11 were defined as mild, moderate and severe, respectively.

Stool specimens were obtained as soon as possible following detection of an episode of diarrhea, but no later than 7 days after the onset of symptoms. All samples were primarily assayed for RV antigen using a commercially available ELISA (Premier Rotaclone™, Meridian Diagnostics, Inc., Cincinnati, Ohio, USA), being further confirmed using a different ELISA.⁹ Typing of RV strains was performed using a

reverse transcriptase polymerase chain reaction (RT-PCR), as described before.¹³ RV of G1 serotype was further analyzed to differentiate between vaccine and wild-type RV strain.

Overall analysis of the data was done at GSK Biologicals, using SAS software (version 8.2) and Proc StatXact-5 on Windows NT 4.0 and has been fully described elsewhere.¹⁵ Sample size for the whole multinational (Brazil, Mexico and Venezuela) trial was calculated based on an anticipated RV incidence rate of 12% for placebo recipients during the study period and a vaccine efficacy of 70%.¹⁵ An original overall sample size of 2,076 infants was estimated (planned similar numbers for each country), to yield 89% power to evaluate efficacy against any RVGE. For Belém, the overall assumed RV incidence rate of 12% for the placebo group is comparable to that reported in a previous, local longitudinal study.⁵

Results

A total of 778 infants participated in the study, of whom 194 were allocated in the $10^{4.7}$ group, 196 in the $10^{5.2}$ group, 194 in the $10^{5.8}$ group, and 194 in the placebo group. Demographic characteristics of these groups were comparable with regard to age, gender, height, weight and race. A full, two-dose vaccination schedule was given to 95.8% ($n = 745$) of the subjects between July 2001 and July 2002. There were 33 dropouts caused by: serious adverse event ($n = 1$); non-serious adverse event ($n = 1$); withdrawal of consent ($n = 13$); migration from the study area ($n = 17$); and loss to follow-up ($n = 1$). 778 subjects (total vaccinated cohort) were considered for the safety analysis. A total of 745 infants were included in the according-to-protocol (ATP) efficacy assessment and 268 were included in the ATP immunogenicity assessment.

Table 1 shows that RIX4414 was well-tolerated. The rates of solicited symptoms (fever, cough, diarrhea, vomiting, irritability and loss of appetite) during a 15-day follow-up period after the first and second doses did not differ significantly for vaccine and placebo recipients.

The frequency of infants with at least one unsolicited adverse event occurring within 43 days after any vaccination was similar between the study groups: 78.9% (95%CI 72.4-84.4) in the $10^{4.7}$ FFU group, 78.6% (95%CI 72.2-84.1) in the $10^{5.2}$ FFU group, 75.3% (95%CI 68.6-81.2) in the $10^{5.8}$ FFU group and 78.9% (95%CI 72.4-84.4) in the placebo group. Non-serious adverse events related to the respiratory system were found to predominate, mainly bronchitis and coughing. No cases of intussusception were reported.

Results of the ELISA IgA seroconversions are summarized in Figure 1. Post-dose 1 anti-RV antibody responses were similar for the 3 vaccine concentrations, ranging from 36.8% to 39.1%. Increased IgA antibody seroconversion rates were

Table 1 - Percentage of subjects reporting solicited signs and symptoms within the 15-day follow-up period after administration of each dose of RIX4414 vaccine (total vaccinated cohort)

Signs and symptoms	Dose of RIX4414 vaccine							
	10 ^{4.7} FFU		10 ^{5.2} FFU		10 ^{5.8} FFU		Placebo	
	Dose 1 (95%CI) (n = 194)	Dose 2 (95%CI) (n = 187)	Dose 1 (95%CI) (n = 196)	Dose 2 (95%CI) (n = 183)	Dose 1 (95%CI) (n = 194)	Dose 2 (95%CI) (n = 192)	Dose 1 (95%CI) (n = 194)	Dose 2 (95%CI) (n = 191)
Fever	76.3 (69.7-82.1)	60.4 (53.0-67.5)	73.5 (66.7-79.5)	48.6 (41.2-56.1)	72.2 (65.3-78.3)	60.4 (53.1-67.4)	73.7 (66.9-79.8)	52.9 (45.5-60.1)
Cough	64.4 (57.3-71.2)	66.8 (59.6-73.5)	66.8 (59.8-73.4)	72.7 (65.6-79.0)	61.3 (54.1-68.2)	67.2 (60.1-73.8)	68.6 (61.5-75.0)	72.3 (65.3-78.5)
Diarrhea	11.3 (7.2-16.7)	16.6 (11.6-22.7)	12.2 (8.0-17.7)	15.3 (10.4-21.3)	14.9 (10.2-20.8)	14.6 (9.9-20.4)	14.4 (9.8-20.2)	14.7 (10.0-20.5)
Vomiting	23.7 (17.9-30.3)	17.6 (12.5-23.9)	27.0 (21.0-33.8)	19.7 (14.2-26.2)	24.2 (18.4-30.9)	17.7 (12.6-23.9)	25.3 (19.3-32.0)	13.6 (9.1-19.3)
Irritability	84.5 (78.7-89.3)	64.2 (56.8-71.0)	81.6 (75.5-86.8)	66.1 (58.8-72.9)	86.1 (80.4-90.6)	64.1 (56.8-70.8)	87.6 (82.2-91.9)	56.5 (49.2-63.7)
Loss of appetite	27.8 (21.7-34.7)	29.9 (23.5-37.1)	29.1 (22.8-36.0)	24.6 (18.5-31.5)	29.9 (23.5-36.9)	24.5 (18.6-31.2)	34.0 (27.4-41.2)	24.1 (18.2-30.8)

95%CI = 95% confidence interval; FFU = focus forming units; n = number of subjects having received the considered dose.

noted 2 months after the second vaccine dose, ranging from 54.7% to 74.4% across the three vaccine groups.

RV antigen shedding on the 7th day after the first dose was highest in the 10^{5.2} FFU vaccine group. The percentages of vaccinees with virus antigen shedding 7 days after the second dose tended to be lower than those for the first dose, ranging from 10.7% to 24.0% across the three tested vaccine concentrations. None of the infants assigned to the placebo group excreted RV vaccine strains (data not shown).

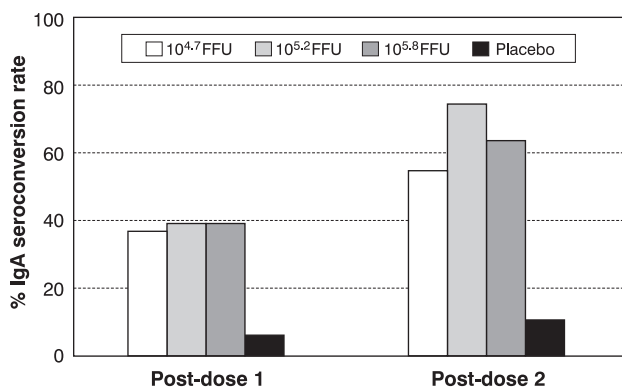


Figure 1 - Anti-RV IgA seroconversion rates in subjects vaccinated with RIX4414 vaccine vs. placebo group (ATP cohort for immunogenicity)
FFU = focus forming units.
Seroconversion = IgA concentration above the cutoff value (20 U/mL).

Table 2 shows that RIX4414 vaccine, given simultaneously with routine vaccinations, did not interfere with the

immune response to diphtheria, tetanus, pertussis, hepatitis B and Hib antigens. Similar seropositivity or seroprotection rates were seen 2 months after the second dose (at 6 months of age) if vaccine and placebo groups are compared. There were also no significant differences in seroresponses to the three poliovirus strains, which were administered 2 weeks apart from the RV vaccine, between vaccine and placebo groups. Similar levels of antibodies persisted up to 4 months after dose 3 (at 1 year of age) of routine vaccinations in the vaccine and placebo recipients.

Altogether, 69 episodes of RVGE were detected during the follow-up efficacy period, from 15 days after dose 2 until the infant reached the age of 1 year. Fourteen (20.3%) episodes were mild, 14 (20.3%) were moderate and 41 (59.4%) were graded as severe. Of these 69 RV isolates, 67 (97.1%) were serotyped. G9 and wild-type G1 RV serotypes were predominant, accounting for 62.7% and 32.8% of isolates, respectively. However, G3 and an isolation including G4 and G9 serotypes were also identified. An RV strain of canine origin was identified in one case.

Table 3 presents the protective efficacy of RIX4414 against RVGE for each vaccine group vs. placebo, according to clinical severity. The vaccine virus titers of 10^{5.2} FFU or higher yielded protection rates as high as 81.5% (95%CI 44.5-95.4) and 93.0% (95%CI 54.3-99.8) for severe RVGE and hospitalizations, respectively. The highest viral concentration of the vaccine (10^{5.8} FFU) provided 63.5% (95%CI 20.8-84.4) protection against any RVGE.

The highest viral (10^{5.8} FFU) concentration of RIX4414 vaccine provided 79.8% (95%CI 26.4-96.3) protection

against severe RVGE caused by G9 strain. Protection against severe RVGE by the homologous G1 strain was 78% among infants who received this formulation of RIX4414 vaccine, although with a wide confidence interval because of the small number of cases (data not shown in the table).

Discussion

The present study demonstrated that RIX4414 vaccine was well tolerated in healthy infants at the doses tested. When comparing the vaccine groups with placebo there were no significant differences in the frequencies of solicited symptoms. The high rates of fever observed were likely due to the concurrent administration of whole-cell pertussis component of routine DTPw-HBV and Hib as they were seen across both vaccine and placebo groups. It should be pointed out that DTPw-HB is not used routinely in Brazil; in fact Brazilian children are given DTPw-Hib concurrently with OPV. Tolerability data of this trial in Belém confirm the previously characterized low reactogenicity of RIX4414 among Finnish infants.^{10,12} As stated before, the Brazilian cohort was part of a multinational phase II study. In this context, local reactogenicity findings were similar to those from the whole

study, but a comparison between children from Brazil, Mexico and Venezuela cannot be currently made because specific data per country are yet to be published.^{11,15}

No serious vaccine-related adverse experiences were reported in Belém and elsewhere. Although the number of children in the present study was not sufficient to assess the risk of intussusception, data from a large Phase III trial with RIX4414 in 11 Latin American countries and Finland, involving more than 63,000 subjects, clearly ruled out such a risk.¹⁶

Overall, a two-dose regimen was found to be immunogenic in previously seronegative infants and there was a trend of increased seroconversion with increased vaccine viral concentrations. It is also noticeable that a second vaccine dose significantly increased the seropositivity rates.

For the highest vaccine titer ($10^{5.8}$ FFU), responses detected by IgA ELISA occurred in over 60% of Brazilian infants after the second dose (Figure 1). These rates were lower than those found in Singapore ($10^{6.1}$ FFU), the United States ($10^{5.0}$ FFU) and Finland ($10^{4.7}$ FFU), where the

Table 2 - Seropositivity rates to antigens in routine infant vaccine schedules (ATP cohort for immunogenicity)

Antibodies	Two months after dose 2 of routine vaccines				Six months after dose 3 of routine vaccines			
	Pooled vaccine groups		Placebo group		Pooled vaccine groups		Placebo group	
	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Anti-diphtheria*	146	43.8 (35.6-52.3)	47	53.2 (38.1-67.9)	185	68.6 (61.4-75.3)	61	65.6 (52.3-77.3)
Anti-tetanus*	146	99.3 (96.2-100)	47	97.9 (88.7-99.9)	186	98.9 (96.2-99.9)	61	100 (94.1-100)
Anti-BPT [†]	146	78.8 (71.2-85.1)	47	74.5 (59.7-86.1)	187	82.4 (76.1-87.5)	61	73.8 (60.9-84.2)
Anti-HBs [‡]	146	99.3 (96.2-100)	47	97.9 (88.7-99.9)	185	97.3 (93.8-99.1)	61	96.7 (88.7-99.6)
Anti-PRP [§]	144	100 (97.5-100)	47	97.9 (88.7-99.9)	185	99.5 (97.0-100)	61	100 (94.1-100)
Anti-poliovirus type 1	146	97.9 (94.1-99.6)	46	100 (92.3-100)	160	100 (97.7-100)	51	100 (93.0-100)
Anti-poliovirus type 2	146	98.6 (95.1-99.8)	46	100 (92.3-100)	182	99.5 (97.0-100)	61	98.4 (91.2-100)
Anti-poliovirus type 3	146	76.7 (69.0-83.3)	46	69.6 (54.2-82.3)	182	87.4 (81.6-91.8)	61	85.2 (73.8-93.0)

% = percentage of infants with antibody titer above the assay cutoff; 95%CI = 95% confidence interval; n = number of subjects included in each group.* Antibody levels determined by ELISA (cutoff value, 0.1 IU/mL).

[†] Antibody levels determined by ELISA (cutoff value, 15 EL.U/mL).

[‡] Antibody levels determined by Australia antigen (AUSAB; Abbott Laboratories, cutoff value, 10 mil/mL).

[§] Antibody levels determined by ELISA (cutoff value, 0.15 µg/mL).

^{||} Antibody levels determined by means of a virus neutralization test (cutoff value, ≥ 8).

Table 3 - Protective efficacy of two doses of RIX4414 vaccine against RVGE, according to clinical severity (ATP cohort for efficacy)

Vaccine and placebo groups	N	RVGE					
		Any		Severe*		Hospitalization	
		n	% Efficacy (95%CI)	n	% Efficacy (95%CI)	n	% Efficacy (95%CI)
Pooled vaccine groups	486	44	43.8 (3.4-66.6)	22	64.5 (30.7-81.7)	9	80.3 (51.1-92.5)
RIX4414, 10 ^{4.7} FFU	163	16	39.1 (-19.6-9.7)	9	56.7 (-0.4-82.7)	5	67.4 (4.1-90.8)
RIX4414, 10 ^{5.2} FFU	153	18	27.0 (-40.4-62.7)	9	53.9 (-7.0-81.6)	1	93.0 (54.3-99.8)
RIX4414, 10 ^{5.8} FFU	170	10	63.5 (20.8-84.4)	4	81.5 (44.5-95.4)	3	81.2 (32.7-96.5)
Placebo	149	24	-	19	-	14	-

95%CI = 95% confidence interval; FFU = focus forming units; n = number of subjects reporting at least one RV-related GE episode; N = number of subjects included in each group.

* Clinical severity as graded by the Ruuska and Vesikari scoring system.

percentage of infants who seroconverted in general exceeded 80%.^{10,15} Although vaccine virus titers and age at first dose were different between these studies, other reasons for local reduced immunogenicity should be taken into account. As described for other developing settings, factors such as a suppressive effect of maternal antibodies transferred in breast milk or transplacentally, or competition from other enteric viruses seem to play a role.²

A significant proportion (> 30%) of RIX4414 recipients given either of the two higher vaccine concentrations (10^{5.2} FFU or 10^{5.8} FFU) had vaccine virus antigens in stools on day 7 post-vaccination, with antigen excretion declining onwards. Of note, the rates of viral antigen excretion in Belém were similar to those reported for a multicenter phase II trial in Latin America.¹⁵

Of major importance for implementation of future RV vaccine programs in developing countries was the demonstration in Belém and elsewhere that no interference occurs when RIX4414 was co-administered with routine immunizations against diphtheria, tetanus, pertussis and hepatitis B.^{11,15}

With regard to OPV administered 2 weeks apart from RIX4414, recent studies in South Africa, where both vaccines were administered concomitantly, showed that two doses of RIX4414 did not impact on the seroprotection rates induced by any of the three poliovirus serotypes.¹⁷

In Belém, over 60% of RVGE episodes during the first efficacy follow-up period were caused by G9, a globally emerging type which was recently associated with more

severe disease in Latin America.^{18,19} The large predominance of G9 serotype makes the study in Belém unique when compared to other trials with RIX4414, where most of isolates were G1.^{10-12,15}

The canine RV strain obtained from the stools of an infant assigned to the placebo group may represent a reassortant between human and animal virus strains, but also raises the hypothesis of an interspecies transmission.²⁰

Most episodes of RVGE in Belém were caused by G9 serotype and thus provided an opportunity to assess the performance of the vaccine in a setting where a heterologous RV strain was predominant. It was therefore possible to show a significant protection (~80%; 95%CI 26.4-96.3) against severe GE caused by this serotype. Although vaccinees also showed a reduction as high as 78% in severe GE by G1, this was not statistically significant owing to the low number of isolates. The expected significant protection conferred by RIX4414 vaccine against severe disease caused by the homologous G1 serotype has, however, been largely demonstrated in several other studies,^{12,15} even during a large phase III trial recently completed in Latin America, including Belém.¹⁶ The present study provides an indication that RIX4414 is highly efficacious (81%; 95%CI 32.7-96.5) against severe infections caused by non-G1 RV serotypes. These findings are of major importance, since they represent a clinical proof that this G1P[8] rotavirus vaccine provided cross-protection in a country where a complex diversity of circulating strains has been largely recognized.^{2,5,6} Of note, RV strains bearing the G2-type specificity were not identified throughout the entire study period in Belém.

The results of this Brazilian subset of phase IIb trial strengthen previous observations that RIX4414 vaccine performs satisfactorily, especially as the local study population reflected the low socio-economic conditions and high diarrheal disease incidence typical of many developing countries. Importantly, a large phase III trial has recently been completed in 11 Latin American countries confirming both the overall safety profile, and the significant efficacy of RIX4414 vaccine during the first year of follow-up.¹⁶ Analysis is currently under way to assess efficacy of RIX4414 during the second year of follow-up in Latin American settings. In fact, extended duration of vaccine-induced protection is needed, since previous studies have shown that a significant proportion of RV episodes occur during the second year of life.² An additional challenge is to evaluate the performance of RIX4414, and other new RV vaccines, through the development of clinical trials in poor populations of Asia and Africa, where the burden of RV disease is greatest.

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Conflict of interest

AC Linhares was the principal investigator during the trial with RIX4414 in Belém, Brazil. His institution, Instituto Evandro Chagas, Secretaria de Vigilância em Saúde, Ministério da Saúde, under an agreement with GSK and a local foundation, received research funding solely destined to pay for external personnel, supplies, services and equipment.

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