Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study

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Summary

Background Peak incidence of rotavirus gastroenteritis is seen in infants between 6 and 24 months of age. We therefore aimed to assess the 2-year efficacy and safety of an oral live attenuated human rotavirus vaccine for prevention of severe gastroenteritis in infants.

Methods 15 183 healthy infants aged 6–13 weeks from ten Latin American countries randomly assigned in a 1 to 1 ratio to receive two oral doses of RIX4414 or placebo at about 2 and 4 months of age in a double-blind, placebo-controlled phase III study were followed up until about 2 years of age. Primary endpoint was vaccine efficacy from 2 weeks after dose two until 1 year of age. Treatment allocation was concealed from investigators and parents of participating infants. Efficacy follow-up for gastroenteritis episodes was undertaken from 2 weeks after dose two until about 2 years of age. Analysis was according to protocol. This study is registered with ClinicalTrials.gov, number NCT00140673 (eTrack444563–023).

Findings 897 infants were excluded from the according-to-protocol analysis. Fewer cases ($p<0·0001$) of severe rotavirus gastroenteritis were recorded for the combined 2-year period in the RIX4414 group (32 [0·4%] of 7205; 95% CI 0·3–0·6) than in the placebo group (161 [2·3%] of 7081; 1·9–2·6), resulting in a vaccine efficacy of 80·5% (71·3–87·1) to 82·1% (64·6–91·9) against wild-type G1, 77·5% (64·7–86·2) against pooled non-G1 strains, and 80·5% (67·9–88·8) against pooled non-G1 P[8] strains. Vaccine efficacy for hospital admission for rotavirus gastroenteritis was 83·0% (73·1–89·7) and for admission for diarrhoea of any cause was 39·3% (29·1–48·1). No cases of intussusception were reported during the second year of follow-up.

Interpretation Two doses of RIX4414 were effective against severe rotavirus gastroenteritis during the first 2 years of life in a Latin American setting. Inclusion of RIX4414 in routine paediatric immunisations should reduce the burden of rotavirus gastroenteritis worldwide.

Funding GlaxoSmithKline.

Introduction

Rotavirus is the leading recognised cause of severe gastroenteritis in infants and young children worldwide.[1–3] Estimates suggest that it accounts for more than a third of all diarrhoea-related hospital admissions and causes about 527 000 deaths per year in children aged less than 5 years, with most deaths occurring in developing countries.[1,2] Vaccination is thought to be the most effective approach to reduce the worldwide burden associated with rotavirus gastroenteritis, and the development of a safe and effective vaccine has been given priority by WHO.[4,5] Although infections can arise early in life (ie, in infants aged <6 months),[6] epidemiological studies in Latin America showed that the peak incidence of rotavirus gastroenteritis occurred between 6 and 24 months of age.[7] Therefore, early and persistent vaccine-induced protection is clearly needed during the first 2 years of life.

A classification system has been established for group A rotavirus serotypes on the basis of outer surface VP7 glycoprotein and the protease-sensitive VP4 protein, defining the G and P types, respectively. At least 15 G types and 26 P types have thus far been identified; however, the five worldwide prevalent VP7 and VP4 combinations include G1, G3, G4, and G9 with P[8] strains and G2 P[4] strains.[8] A live attenuated human rotavirus vaccine RIX4414 (Rotarix, GlaxoSmithKline Biologicals, Rixensart, Belgium) derived from the most common circulating wild-type strain G1P[8], has now been licensed in many parts of the world.[9,10] Its efficacy during the first 2 years of life in a large European phase III study was 90·4% (95% CI 85·1–94·1) against severe rotavirus gastroenteritis and

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96·0% (83·8–99·5) against admission. For severe illness, high vaccine efficacy was shown against the most common virus types: 96·4% (90·4–99·1) for G1, 93·7% (52·8–99·9) for G3, 95·4% (68·3–99·9) for G4, 85·0% (71·7–92·6) for the emerging G9 type, and 85·5% (24·0–98·5) for G2.[11]

In a large Latin American study,[12] two oral doses of RIX4414 given at about 2 and 4 months of age proved to have a good safety profile and were highly efficacious for prevention of rotavirus gastroenteritis in healthy infants during the first year of life. Vaccine efficacy against severe illness was 84·7% (95% CI 71·7–92·4), with vaccination affording substantial reductions in hospitalisation for both severe rotavirus gastroenteritis (85·0%; 69·6–93·5) and gastroenteritis of any cause (42·4%; 28·6–53·1). Protection was shown against both G1 and non-G1P[8] strains, with efficacy of 91·8% (74·1–98·4) against G1 wild-type and 87·3% (64·1–96·7) against pooled non-G1P[8] strains (G3, G4, and G9). Protection was shown individually against G1P[8], G3P[8], and G9P[8] strains but not against the G4P[8] strain because of low circulation; a non-significant trend towards protection against G2P[4] strain was noted. Importantly, RIX4414 was not associated with an increased risk of intussusception compared with placebo after either vaccine dose.[12] We report a large subset of infants participating in this initial study who were followed up to 24 months of age to assess the safety and protective efficacy of the human rotavirus vaccine during the second year of life.

Methods

Participants and study design

We undertook a large, multicountry, randomised, double-blind, placebo-controlled, multicentre phase III study in Latin America between Aug 5, 2003, and Oct 20, 2005. Inclusion and exclusion criteria were as previously described.[12] The study was approved by the research ethics committees at all participating centres and was done in accordance with the Declaration of Helsinki and guidelines for good clinical practice. Written informed consent was obtained from parents or guardians before study entry. Parents or guardians had to sign a supplementary informed consent to continue participation during the second year.

GlaxoSmithKline Biologicals provided vaccine supplies that were numbered with a computer-generated randomisation list. We used a blocking scheme randomisation. Randomisation was done by a central internet randomisation system. Infants were randomly assigned in a 1 to 1 ratio to receive two doses either of RIX4414 or placebo. Treatment allocation remained concealed from investigators and parents of participating infants throughout the study. GlaxoSmithKline Biologicals did the masking and concealment. Each dose of RIX4414 contained $10^{6\cdot5}$ median cell-culture infective doses ($CCID_{50}$) of vaccine strain. Placebo contained the same constituents as the active vaccine but without the virus component; both were reconstituted with liquid calcium carbonate-based buffer before oral administration. A total of 63 225 healthy infants aged 6–13 weeks were enrolled to receive two oral doses of RIX4414 (n=31 673) or placebo (n=31 552) at about 2 and 4 months of age and were followed up for safety for up to 3 months after the first dose.[12] Infants received other routine paediatric immunisations during the study period in accordance with local recommendations. Oral poliovirus vaccination was provided at an interval of at least 2 weeks before or after a dose of RIX4414 or placebo.

Cases of severe gastroenteritis of any cause, intussusception, and serious adverse events were captured through active hospital-based surveillance during follow-up, as previously described.[12] Severe gastroenteritis was clinically defined as an episode of diarrhoea (the passage of three or more loose or watery stools within a 24-h period) with or without vomiting that needed overnight treatment in hospital or rehydration treatment (equivalent to WHO plan B or C),[12] or both, in a medical facility, such as hospital, clinic, or supervised rural health-care centre. Additionally, severity was calculated with the 20-point Vesikari scale.[13] In accordance with this scale, an episode of gastroenteritis with a score of 11 or more was regarded as severe.

Stool samples from infants with severe gastroenteritis were tested for the presence of rotavirus by ELISA (Rotaclone, Meridian Bioscience, Cincinnati, OH, USA) at GlaxoSmithKline Biologicals' laboratories (Rixensart, Belgium). All rotavirus-positive stool samples were tested by reverse transcriptase PCR followed by reverse hybridisation assay and sequencing (optional) at Delft Diagnostic Laboratory (Delft, Netherlands) to identify G and P types.

Statistical analysis

The primary endpoint was the assessment of efficacy from 2 weeks after dose two until 1 year of age as previously reported.[12] The secondary endpoint was the assessment of efficacy during the second year and for the combined 2-year period from 2 weeks after dose two until about 24 months of age. The cohorts consisted of participants who completed the full two-dose vaccination course and for whom compliance with the protocol was complete. If the vaccine efficacy was truly 60% in the second-year efficacy follow-up and an attack rate of 1% was assumed for severe rotavirus gastroenteritis, the study had at least 90% power to note a 95% CI for the vaccine efficacy that would be above 0% with a target sample size of 5600 children per group.

We calculated the percentage of participants reporting at least one episode of severe gastroenteritis (overall and by G type) with 95% CI. We compared groups with two-sided Fisher's exact test ($\alpha=0\cdot05$) and expressed the results as relative risk (RR) and absolute risk. We calculated vaccine efficacy with 95% CI for all three efficacy periods with the formula:

$$(1-RR)\times100=(1-\frac{ARV}{ARU})\times100$$

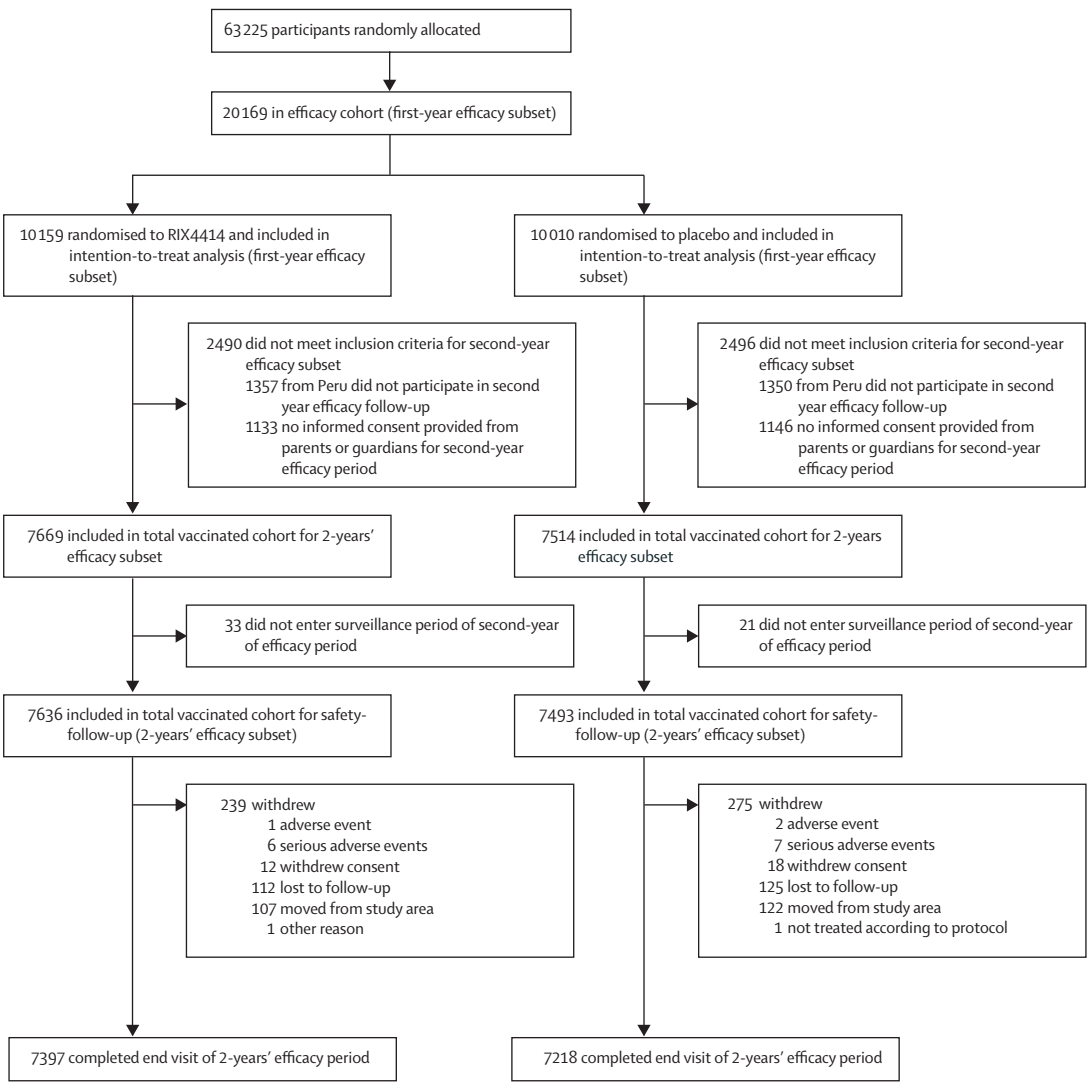

Figure 1: **Trial profile (total cohort)**

where ARU is the disease attack rate in the unvaccinated population (estimated from the placebo group)—ie, the number of infants reporting at least one severe gastroenteritis episode per total number in the placebo group, and ARV is the disease attack rate in the vaccinated group. 95% CIs for efficacy were derived from the exact CI for the Poisson rate ratio. When more than one G type was isolated for an episode, the child was counted in every G type category for analysis of efficacy by G type. Exploratory vaccine efficacy against gastroenteritis leading to hospital admission, severe gastroenteritis with Vesikari scores of at least 11, at least 19, and equal to 20, and severe gastroenteritis due to any cause was also calculated.

Secondary analysis of efficacy was done for participants in the total vaccinated cohort of all infants who had received at least one dose of RIX4414 or placebo for the first-year efficacy subset. Vaccine efficacy against severe rotavirus gastroenteritis and its 95% CI from dose one until 2 years of age were estimated by the Cox proportional-hazard model. The time was censored at the last contact in the study period.

The cumulative hazard of a first episode was estimated as minus-log transformation (of log data to non-log data) of the Kaplan-Meier survival curve during the period from dose one until 2 years of age in all the infants who received at least one dose of either vaccine or placebo. The p value for the cumulative-hazard curve was calculated with the log-rank test.

Analysis of safety was done for all infants who had received at least one dose of study vaccine and had entered the second year of follow-up. The incidence of serious adverse events during the second year of the study was compared between groups with the two-sided asymptotic score test for the null hypothesis of identical

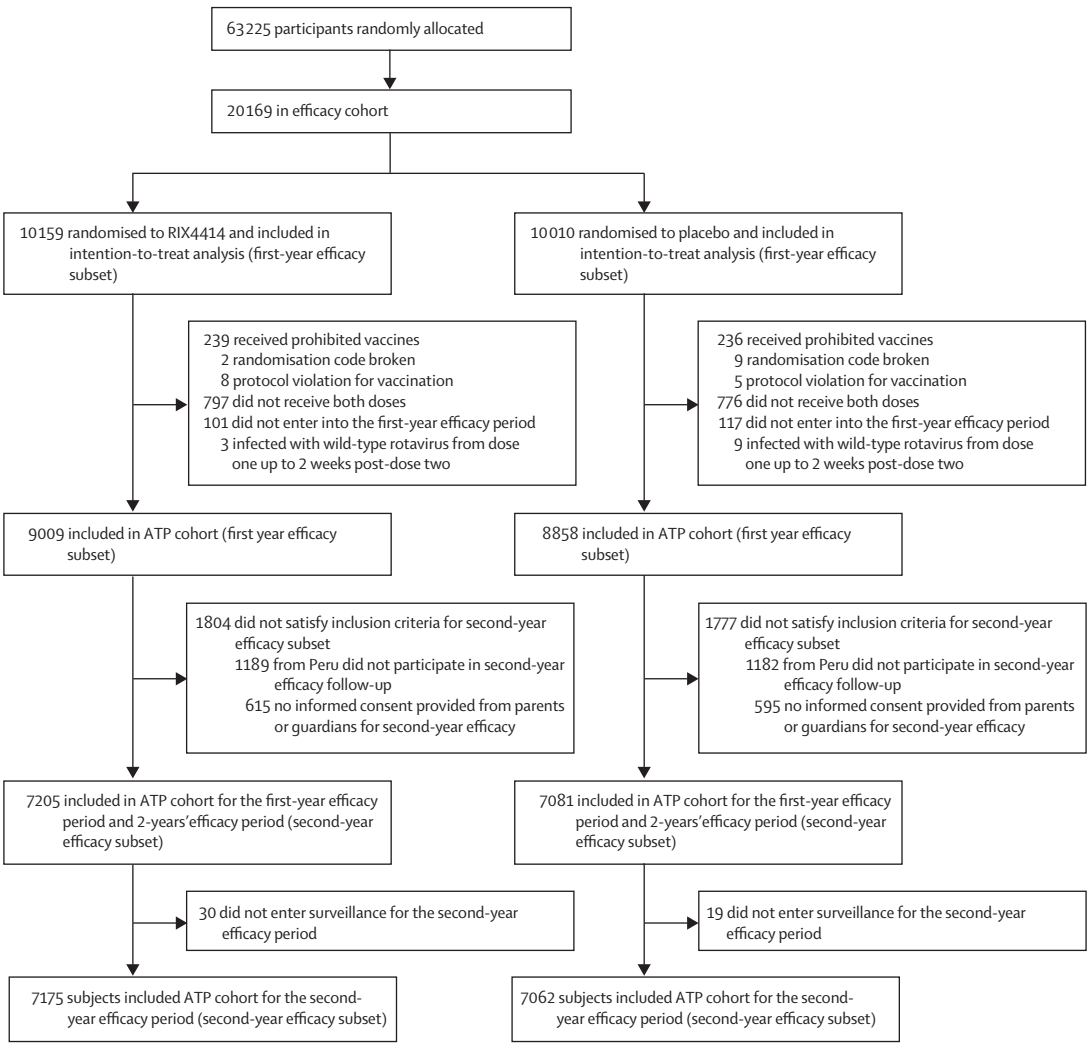

Figure 2: **Trial profile (according-to-protocol [ATP] cohort)**

incidence in both groups (α=0·05). In the 2-years' efficacy subset, the percentage of participants reporting definite intussusception (surgical, radiological, or post-mortem evidence), based on the Brighton Collaboration Working Group guidelines,[14] from dose one up to study end, was compared between groups with the two-sided asymptotic score tests for the null hypothesis of identical incidence in both groups (α=0·05). Two-sided asymptotic standardised 95% CIs were calculated for RR in the RIX4414 group compared with the placebo group.

Data analysis was done with SAS software (version 8.2) and Proc StatXact 5 on Windows NT (version 4.0).

This study is registered with ClinicalTrials.gov, number NCT00140673 (eTrack444563-023).

Role of funding source

The sponsor held the data and did the analyses, with continuous feedback from the authors, and was involved in all stages of the study, including study design. The report was written jointly by both the sponsor and the authors, who vouched for the accuracy and completeness of the reported data. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile for the total cohort. Vaccine efficacy during the first year of life was measured in 20169 infants. From this group, a subset of 15183 children from ten participating countries in Latin America (Argentina [n=1269], Brazil [630], Chile [415], Colombia [1708], Dominican Republic [1129], Honduras [1545], Mexico [4335], Nicaragua [1727], Panama [1057], and Venezuela [1368]) were included in the follow-up for efficacy for the second year of life (figure 1). A total of 14237 infants completed this follow-

up. 15 129 were included in the follow-up for safety during the second year of life. Demographic details for both initial cohorts have been described previously.[12] RIX4414 and placebo groups were similar with respect to age, sex, and ethnic origin). Median age was 8 (IQR 6–11) weeks at the time of the first vaccine dose and 15 (13–19) weeks at the time of the second vaccine dose, 7723 (51%) of 15 183 infants were boys and the study population was predominantly Hispanic (12 725 [84%] of 15 183). Figure 2 shows the trial profile for the according-to-protocol cohorts derived from the original first-year efficacy cohort[12] that met the inclusion criteria for and completed the second-year follow-up. Mean duration of follow-up was 8·3 months during the first-year efficacy period, 11·8 months during the second-year efficacy period and 20 months for the 2-years' efficacy period. Mean age at study end was 24 (SD 1·34) months.

No child from the total vaccinated cohort had more than one episode of severe rotavirus gastroenteritis during the 2 years of follow-up. Incidence of severe gastroenteritis in the placebo group was higher during the second-year efficacy period than during the first year (table 1). Fewer episodes were reported in the RIX4414 group than in the placebo group during both individual efficacy periods and during the 2-years' efficacy period. Similar vaccine efficacy results were obtained during the three efficacy periods and in the overall cohort of infants who had received at least one dose of vaccine or placebo; efficacy against severe rotavirus gastroenteritis from dose one until 2 years of age in the first-year efficacy subset was 80·3% (95% CI 72·4–85·9). The cumulative hazard of severe illness was significantly lower in the vaccine group than in the placebo group throughout the 2-years' efficacy period (figure 3). The difference between groups led to roughly fivefold reduction in risk of severe gastroenteritis in the vaccine group compared with the placebo group at 2 years of age.

Fewer infants in the RIX4414 group were admitted for severe rotavirus gastroenteritis than in the placebo group during the 2-years' efficacy period (p<0·0001; table 2). Vaccine efficacy against hospital admission for rotavirus gastroenteritis was 85·4% (95% CI 67·4–94·4) during the first-year efficacy period, 81·5% (67·7–90·1) during the second-year efficacy period, and 83·0% (73·1–89·7) during the 2-years' efficacy period.

G1P[8] wild-type was the predominant strain during the first rotavirus season (detected in 30 [52%] of 58 stools tested in the placebo group during the first-year efficacy period), followed by G9P[8] (10 [17%] of 58) (figure 4). A shift in type predominance was noted during the second virus season (figure 4), with the G9P[8] type gaining predominance (56 [54%] of 103) and with a marked increase in G4P[8] strains (16 [16%] of 103). Wild-type G1P[8] was noted in 21 (24%) of 103 stools tested in the placebo group during the second-year efficacy period. Circulation of the G2P[4] strain was low during both years of follow-up (in the placebo group,

	Severe RVGE (95% CI)	Vaccine efficacy (95% CI)	p value
First year*			
RIX4414	10/7205 (0·1%; 0·1–0·3)	83·1% (66·6–92·3)	<0·0001
Placebo	58/7081 (0·8%; 0·6–1·1)		
Second year†			
RIX4414	22/7175 (0·3%; 0·2–0·5)	79·0% (66·4–87·4)	<0·0001
Placebo	103/7062 (1·5%; 1·2–1·8)		
2 years‡			
RIX4414	32/7205 (0·4%; 0·3–0·6)	80·5% (71·3–87·1)	<0·0001
Placebo	161/7081 (2·3%; 1·9–2·6)		

Data are n/N (%), unless otherwise indicated. *Mean duration 8·3 months. †Mean duration 11·8 months. ‡Mean duration 20·0 months.

Table 1: **Proportion of participants reporting at least one severe rotavirus gastroenteritis (RVGE) episodes (per protocol clinical definition) and vaccine efficacy against severe RVGE during three efficacy periods (according-to-protocol cohorts for the 2-years' efficacy subset)**

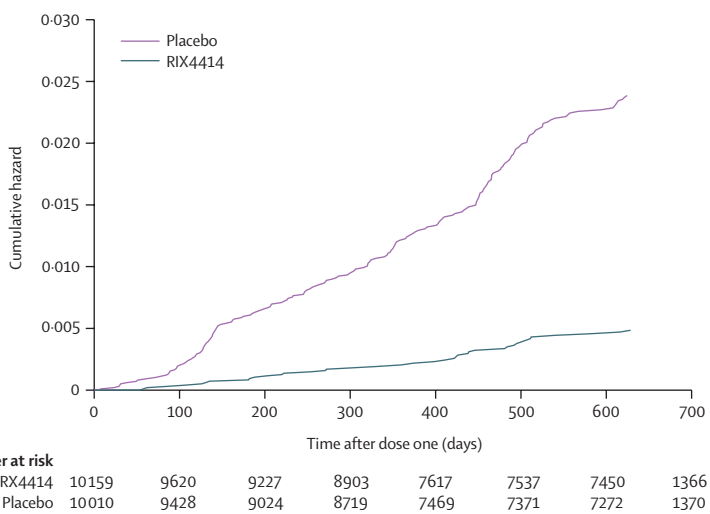

Figure 3: **Cumulative hazard of a first episode of severe rotavirus gastroenteritis (total vaccinated cohort)**
The difference between receiving placebo and receiving vaccine was significant (p<0·01 by the log-rank test).

seven cases during the first-year efficacy period and only one case during the second-year efficacy period).

Fewer participants in the RIX4414 group had severe gastroenteritis episodes with a score of at least 11 on the Vesikari scale during the 2-years' efficacy period (table 3). Vaccine efficacy was consistent with results obtained with the protocol-specified clinical case definition of severe rotavirus gastroenteritis (children given WHO plan B and C or needing hospital admission, or both). Efficacy increased with disease severity (table 3).

Fewer episodes of severe gastroenteritis from any cause were recorded in the RIX4414 group than in the placebo group during the first and the second year efficacy periods and during the 2-years' efficacy period (p<0·0001). Severe gastroenteritis from any cause (including documented rotavirus) was reported by fewer children in the RIX4414 group than in the placebo group during the 2-years' efficacy

	RIX4414 (N=7205)		Placebo (N=7081)		Relative risk† (95% CI)	Absolute risk	Vaccine efficacy (95% CI)
	Infants with ≥1 episode*	1000 infants-year ratio	Infants with ≥1 episode*	1000 infants-year ratio			
Severe gastroenteritis according to the clinical case definition‡							
All-cause gastroenteritis							
Severe	342	28·5	551	46·7	0·610 (0·531-0·699)	0·078	39·0 (30·1–46·9)
Admission	265	22·1	429	36·4	0·607 (0·519-0·709)	0·061	39·3 (29·1–48·1)
Rotavirus gastroenteritis§							
Severe	32	2·7	161¶	13·6	0·195 (0·129-0·287)	0·023	80·5 (71·3–87·1)
Admission	22	1·8	127	10·8	0·170 (0·103-0·269)	0·018	83·0 (73·1–89·7)
Serotype specific rotavirus gastroenteritis‖							
G1P[8]**	10††	0·8	55‡‡	4·7	0·179 (0·081-0·354)	0·008	82·1 (64·6–91·9)
Pooled P[8], non-G1 (G3, G4, G9)	19§§	1·6	96¶¶	8·1	0·195 (0·112-0·321)	0·014	80·5 (67·9–88·8)
Pooled non-G1 (G2, G3, G4, G9)	24	2·0	105‖‖	8·9	0·225 (0·138-0·353)	0·015	77·5 (64·7-86·2)
Non-G1, non-P[8] (G2P[4])	5	0·4	8	0·7	0·614 (0·158-2·129)	0·001	38·6 (<0–84·2)
Severe rotavirus gastroenteritis with a score of ≥11 on the Vesikari scale* **							
Serotype specific gastroenteritis							
G1P[8]**	9†††	0·7	51†††	4·3	0·173 (0·075-0·356)	0·007	82·7 (64·4–92·5)
Pooled P[8], non-G1 (G3, G4, G9)	17†††	1·4	94†††	8·0	0·178 (0·099-0·300)	0·013	82·2 (70·0–90·1)
Pooled non-G1 (G2, G3, G4, G9)	21	1·7	101	8·6	0·204 (0·121-0·329)	0·014	79·6 (67·1-87·9)
Non-G1, non-P[8] (G2P[4])	4	0·3	7	0·6	0·562 (0·121-2·209)	0·001	43·8 (<0–87·9)

Participants who had episodes with more than one isolated G type were counted in each one of the detected rotavirus type category. *No child from total vaccinated cohort had more than one episode of severe rotavirus gastroenteritis during the 2 years of follow-up. †Relative risk is ratio of the incidence of participants reporting at least one episode in the vaccine group over the incidence of those reporting at least one episode in the placebo group. ‡Case definition according to the study protocol: severe gastroenteritis was clinically defined as an episode of diarrhoea (passage of three or more looser than normal or watery stools within a 24-h period) with or without vomiting that needed overnight treatment in a hospital or rehydration treatment (equivalent to WHO plan B [oral rehydration] or WHO plan C [intravenous rehydration]), or both, in a medical facility, such as hospital, clinic, or supervised rural health-care centre. §One isolate from the placebo group could not be serotyped because of insufficient quantity of sample, one isolate from the placebo group could not be typed by RT-PCR and the G-type of one P[6] rotavirus isolate from the placebo group could not be typed but vaccine strain was ruled out. ¶One rotavirus gastroenteritis was not tested by RT-PCR because of insufficient quantity and one could not be typed. ‖G3P[6] type alone isolated in stool sample from one infant in the placebo group. **All G1 types isolated were wild-type rotavirus. ††G1P[8] type alone isolated in stool samples from eight infants; G1P[8] and G9P[8] types isolated in a stool sample from two infants. ‡‡G1P[8] type alone isolated in stool samples from 53 infants; and G1P[8] and G9P[8] types isolated in a stool sample from two infants. §§Includes G3P[8] alone in three infants; G4P[8] alone in seven infants; G9P[8] alone in seven infants; and G1P[8] and G9P[8] in two infants. ¶¶Includes G3P[8] alone in 13 infants; G4P[8] alone in 17 infants; G9P[8] alone in 63 infants; G1P[8] and G9P[8] in two infants; and G4P[4] and G9P[8] in one infant. ‖‖G3P[6] type isolated in stool sample from one infant. ***Scores on the Vesikari scale range from 0 to 20, with higher scores indicating more severe cases; an episode with a score of 11 or greater was thought to be severe. †††Participants appeared in more than one category if more than one G-type was identified in the stool sample.

Table 2: **Efficacy of RIX4414 against severe rotavirus gastroenteritis and severe gastroenteritis during the 2-years' efficacy period (ATP cohort for the 2-years' efficacy subset)**

period (table 2). Vaccine efficacy against severe gastroenteritis from any cause was 40·6% (26·9–51·8) during the first year, 38·3% (26·4–48·4) during the second year, and 39·0% (30·1–46·9) during the 2-years' efficacy period. Fewer children in the RIX4414 group were admitted for severe gastroenteritis from any cause during any efficacy period (p<0·0001). Total number of children in the RIX4414 group who needed treatment in hospital for severe gastroenteritis of any cause during the 2-years' efficacy period was less than that in the placebo group (p<0·0001; table 2). Vaccine efficacy against hospital admission for severe gastroenteritis of any cause was 42·0% (27·2–53·9) during the first year, 37·8% (23·5–49·5) during the second year, and 39·3% (29·1–48·1) during the 2-years' efficacy period (table 2).

Data for the incidence of intussusception and serious adverse events during the first year of this study have been reported in detail elsewhere.[12] Fewer serious adverse events per 10 000 infants were reported in the RIX4414 group than in the placebo group during the second year of follow-up (678 *vs* 787, respectively; p 0·01). All serious adverse events during the second year of follow-up were assessed as not related to vaccination by the respective investigators. The most frequently reported events per 10 000 participants according to MedDRA system organ class were infections and infestations (503 *vs* 622, p=0·001) with gastroenteritis as a most frequently reported cause (214 *vs* 336, p<0·0001). Other commonly reported causes of infections per 10 000 were pneumonia (127 *vs* 134; p=0·727), bronchiolitis (47 *vs* 44; p=0·777), bronchopneumonia (34 *vs* 40; p 0·544), urinary tract infections (20 *vs* 11; p 0·157), bronchitis (18 *vs* 17; p 0·886), and pharyngitis (13 *vs* 15; p 0·794). 13 infants withdrew from the study during the second year of follow-up because of serious adverse events (six in

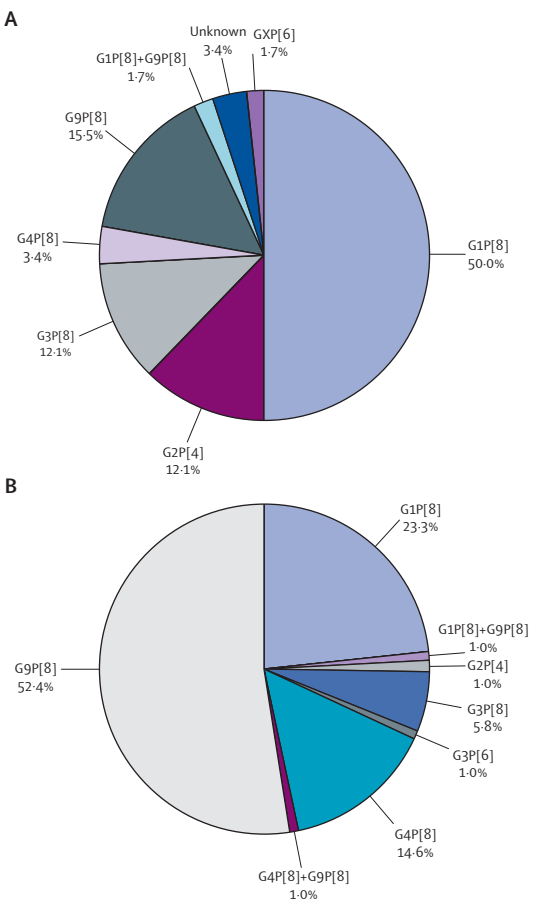

Figure 4: **Rotavirus serotype distribution in stools tested in the placebo group in each year of follow-up (according-to-protocol cohort for the 2-years' efficacy subset)**
(A) First year of follow-up (n=58). (B) Second year of follow-up (n=103).

	Severe RVGE (95% CI)	Vaccine efficacy (95% CI)	p value
≥11*			
RIX4414	28/7205 (0·4%; 0·3–0·6)	82·1% (73·1–88·5)	<0·0001
Placebo	154/7081 (2·2%; 1·8–2·5)		
≥19*			
RIX4414	1/7205 (0; 0·0–0·1)	97·3% (83·8–99·9)	<0·0001
Placebo	36/7081 (0·5%; 0·4–0·7)		
≥20*			
RIX4414	0/7205 (0; 0·0–0·1)	100·0% (60·8–100·0)	0·0004
Placebo	11/7081 (0·2%; 0·1–0·3)		

Data are n/N (%), unless otherwise indicated. *Severity assessed with Vesikari scale.

Table 3: **Proportion of participants reporting severe rotavirus gastroenteritis (RVGE) episodes with a score of ≥11, ≥19 and ≥20 on the Vesikari scale and efficacy of vaccine during the 2-years' efficacy period (according-to-protocol cohort for efficacy)**

RIX4414 group and seven in placebo group). Only three participants withdrew during this period because of non-serious adverse events (one in the RIX4414 group and two in the placebo group), which did not result in death or persistent or substantial disability or incapacity, were not life-threatening, did not need or extend hospital admission, and were not congenital anomalies.

No cases of intussusception were reported during the second year of follow-up. In the 2-years' efficacy subset, the RR (RIX4414 *vs* placebo) for definite intussusception diagnosed during the first 2 years of life after administration of first vaccine dose was 0·36 (95% CI 0·12–1·06). Intussusception was reported in four of 7669 vaccine recipients and 11 of 7514 infants given placebo during the first year of life. No increased risk of definite intussusception was seen in the RIX4414 group versus the placebo group during the 2-years' follow-up (p 0·065).

11 deaths occurred during the second year of follow-up (five in RIX4414 group and six in placebo group). Causes of death were respiratory disorders (n=2), septic shock (1), injury (1), and unspecified death (1) in the RIX4414 group, and pneumonia (2), bacterial meningitis (2), cardiac disorders (1), and road traffic accident (1) in the placebo group. All deaths were thought to be unrelated to vaccination.

Discussion

Two oral doses of RIX4414 when given in early infancy afforded sustained high protection against severe rotavirus gastroenteritis during the first 2 years of life when disease burden is highest. Vaccine efficacy did not differ in the two individual efficacy periods, showing that protective efficacy of the human rotavirus vaccine persists throughout the second rotavirus season despite the high viral attack rate.

The complete protection afforded against very severe rotavirus gastroenteritis episodes (Vesikari score 20) by two oral doses of RIX4414 was consistent with data showing two wild-type virus infections to be fully protective against subsequent episodes of severe disease.[15] Similar to our findings, a previous phase IIb, dose-ranging study of 405 Mexican infants given RIX4414 showed sustained protective efficacy during two consecutive follow-up periods with high vaccine efficacy in prevention of severe rotavirus gastroenteritis.[16] Roughly twice as many severe episodes of rotavirus gastroenteritis were reported in unvaccinated infants during the second year of this study compared with those reported during the first year. This finding is in agreement with the results of previous epidemiological studies in Latin America that showed a large proportion of children received care for rotavirus gastroenteritis during the second year of life[17] and substantiates the need for early and sustained protection against severe rotavirus gastroenteritis for at least the first 2 years of life.

Importantly, RIX4414 afforded broad protection against a changing pattern of wild-type rotavirus strains during the 2-years' efficacy period. Although G1P[8] is the most

common human rotavirus strain, type prevalence is known to vary within the same region with time, resulting in peaks of some strains.[8,18–19] The second year of this study had a shift in strain predominance from G1P[8] to G9P[8], including a large increase in G4P[8]. RIX4414 provided a high degree of protection against severe rotavirus gastroenteritis caused by both G1 wild-type and other strains bearing P[8]-type specificity [G3, G4, and G9] (table 2). Protection against G2P[4] rotavirus seemed to be low; however, circulation of strains bearing these type-specificities was low during both years of the study.

Results of a European study (n=3994) showed RIX4414 to have an efficacy of 58·3% (95% CI 10·1–81·1) against rotavirus gastroenteritis of any severity and 85·5% (24·0–98·5) against severe illness due to G2P[4] strains during two consecutive rotavirus seasons,[11] confirming that RIX4414 provides protection against these fully heterotypic (non-G1, non-P[8]) strains. In a study done in Aracaju, northeastern Brazil,[20] investigators claimed that "vaccine does not afford complete protection against infection" by G[2]P4 strains. However, although the sample size was small, vaccine coverage was low, and predominance of G2P[4] strains was 100%, this study clearly showed evidence of reduced risk of severe rotavirus diarrhoea among vaccinated children in Aracaju. Indeed, severe rotavirus diarrhoea occurred in three (7%) of 44 vaccinated children compared with five (26%) of 19 non-vaccinated patients ($p<0·05$), with a calculated odds ratio of 0·20 (exact 95% CI 0·03–1·24). Furthermore, rather than a vaccine-related replacement event (which biologically and epidemiologically seems unlikely), the 100% G2 predominance in Aracaju most probably indicates a cyclical pattern of occurrence of this serotype in Brazil.[21] Nevertheless, the issue of crossprotection draws attention to the need for further prospective surveillance studies to assess both vaccine effect and strain surveillance,in compliance with recent WHO recommendations.[1] The fact that we could not fully assess the efficacy of the vaccine against rotavirus serotype G2 is, in our view, the main limitation of our study and is explained in part by the low circulation of G2 type during the 2-year follow-up period.

Worldwide, rotavirus is estimated to account for about 39% of all hospital admissions for childhood diarrhoea.[2] With the high burden rotavirus disease places on health systems, an exploratory analysis of efficacy against gastroenteritis-related admissions was undertaken. The protection against hospital admission for severe rotavirus gastroenteritis noted during the first year of this study was maintained during a second rotavirus season, with an efficacy of 83·0% against gastroenteritis-related hospital admissions during the 2-year efficacy period. Vaccination also substantially reduced overall rates of admissions for severe gastroenteritis from any cause (table 2). Such a striking reduction in admissions for rotavirus gastroenteritis and overall gastroenteritis during the first 2 years of life would be expected to substantially reduce the burden of rotavirus disease in hospital systems during early childhood, with large reductions in associated costs.[22]

Analysis of safety during the second year of follow-up provided further evidence of the good safety profile of RIX4414. No cases of intussusception were reported during this period. The incidence of serious adverse events was lower during the second year of follow-up than that during the first year of the study;[12] all serious adverse events reported during the second year of follow-up were thought to be unrelated to vaccination. As in the first year of the study, the overall serious adverse event profile during the second year of follow-up was in favour of RIX4414 vaccine with respect to prevention of gastroenteritis-related serious adverse events.

Results confirm the occurrence of rotavirus disease early in life and the continued high burden of gastroenteritis during the second year of life in Latin America. Two oral doses of RIX4414 given in early infancy showed good safety profile, were well tolerated, and provided sustained high protection against severe rotavirus gastroenteritis caused by a change in circulating rotavirus strains during the first 2 years of life when disease burden is highest. The importance of these results should not be underestimated because this study was done in developing countries from Latin America with challenging socioeconomic circumstances. Inclusion of this vaccine in routine paediatric immunisation schedules can be expected to greatly reduce the burden of rotavirus disease worldwide.

Contributors

All authors participated in the design or implementation, analysis, and interpretation of the study. ACL, EOB, MOR, FRV, AB, SD, PG, and BDV took part in all phases of the study. AB, EOR (second year of the study), BDV, and PG led the clinical team at GlaxoSmithKline Biologicals. SD did the data analysis. MOR was the coordinating principal investigator for the study. HA was the principal investigator for Argentina; ACL for Brazil; EN for Chile; PL for Colombia; LR for Dominican Republic; DMRM was the principal investigator for Honduras; FRV, GMRP, and NPR for Mexico; FE for Nicaragua; EOB (first year of the study) and XSL (second year of the study) for Panama; and IPS for Venezuela. BS participated in acquisition of data and had full access to data. CAD participated in acquisition of data, analysis and interpretation of data, critical draft revision, and final approval of the version to be published. PR participated in study conception and design, and critical draft revision and final approval of the version of the report to be published.

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Conflict of interest statement

AB, PG, BDV, SD, RR, NS, YC, PR, EOB, RC, and SACC are or were employees of GlaxoSmithKline Biologicals. BDV is now affiliated with Sanofi-Pasteur (Lyon, France). AB is now affiliated with Sanofi-Pasteur (Swiftwater, PA, USA). XSL received consulting fees in the past three years. ACL, PL, MMP, EN, RFV, and LPRS received honoraria or paid expert testimony or travel grants from GlaxoSmithKline. MOR received consulting fees in the past 3 years and honoraria or paid expert testimony or travel grants from GlaxoSmithKline. FRV, GMRP, NPR, IPS, DMRM, FE, LR, HA, MEN, VR, MLG, TDL, JS, CAD, BS, and JCT declare that they have no conflict of interest.

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