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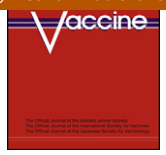

Efficacy, safety and immunogenicity of a human rotavirus vaccine (RIX4414) in Hong Kong children up to three years of age: A randomized, controlled trial

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ABSTRACT

Background: A phase III, double-blind, randomized, controlled trial was conducted in Hong Kong to evaluate the efficacy, safety and immunogenicity of a human rotavirus vaccine, RIX4414 (*Rotarix*™) against severe rotavirus gastroenteritis in children up to three years of age.
Methods: Healthy infants aged 6–12 weeks were enrolled between 08-December-2003 and 31-August-2005 and received two oral doses of either RIX4414 vaccine ($N = 1513$) or placebo ($N = 1512$) given 2 months apart. Vaccine efficacy was assessed from two weeks post-Dose 2 until the children were two and three years of age. Anti-rotavirus IgA seroconversion rate was calculated pre-vaccination and 1–2 months post-Dose 2 using ELISA (cut-off = 20 U/mL) for 100 infants. Safety was assessed until the children were two years of age; serious adverse events (SAEs) were recorded throughout the study period.
Results: In children aged two and three years of life, vaccine efficacy against severe rotavirus gastroenteritis was 95.6% (95% CI: 73.1%–99.9%) and 96.1% (95% CI: 76.5%–99.9%), respectively. The seroconversion rate 1–2 months after the second dose of RIX4414 was 97.5% (95% CI: 86.8%–99.9%).

Abbreviations: ARSN, Asian Rotavirus Surveillance Network; ATP, According-to-protocol; $CCID_{50}$, Cell culture infectious dose; DTPa, Diphtheria-tetanus-acellular pertussis; DTPw, Diphtheria-tetanus-whole cell pertussis; ELISA, Enzyme-linked immunosorbent assay; GMCs, Geometric mean concentrations; Hib, *Haemophilus influenzae* type b; ICD, International Classification of Diseases; IPV, Inactivated polio vaccine; OPV, Oral polio vaccine; RT-PCR, Reverse transcriptase polymerase chain reaction; RVGE, Rotavirus gastroenteritis; SAE, Serious adverse event; U/mL, Units per milliliter; WHO, World Health Organization.

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At least one SAE was recorded in 439 and 477 infants who were administered RIX4414 and placebo, respectively (p-value = 0.130). Six intussusception cases were reported (RIX4414 = 4; placebo = 2) and none was assessed to be vaccine-related.
Conclusion: RIX4414 was efficacious, immunogenic and safe in the prevention of rotavirus gastroenteritis for at least two years post-vaccination in Hong Kong children.

1. Introduction

In 2008, diarrhea attributable to rotavirus infection was estimated to have resulted in 453,000 deaths worldwide (95% CI: 420,000–494,000) in children aged less than 5 years [1]. An estimated 41% (188,000) of these deaths occurred in the Asian region [1]. The World Health Organization (WHO) recommends that rotavirus vaccines should be used in all countries, and considered a priority especially in countries with high rotavirus-related mortality [2].

Rotavirus is prevalent throughout Asia and is an important cause of gastroenteritis requiring hospitalization and medical care in children aged less than 5 years [3]. Data derived through passive surveillance of rotavirus underestimated the disease burden in Hong Kong [4] and highlighted the need for active rotavirus surveillance [5]. The first phase of the Asian Rotavirus Surveillance Network (ARSN) conducted across: China, Hong Kong, Indonesia, Malaysia, Myanmar, South Korea, Taiwan, Thailand and Vietnam between 2001–2003 [3,5], showed that rotavirus accounted for 30–55% of hospitalization in children aged less than 5 years with the lowest rotavirus-positivity rate (30%) recorded in Hong Kong [3].

In 2006, two new rotavirus vaccines, RIX4414 (*Rotarix*™; GlaxoSmithKline, Belgium) and (*Rotateq*™; Merck Vaccines) became available [1]. In studies undertaken in the Americas and Europe, both were reported to be highly efficacious and were not associated with any safety concerns in children during the first two years of life [6–9].

This three-year study was conducted in high-income regions of Southeast and East Asia (Singapore, Hong Kong and Taiwan) to evaluate the efficacy, safety and immunogenicity of the RIX4414 vaccine. The overall efficacy results have been previously presented elsewhere [10,11] and this publication describes specific data pertaining to the efficacy, safety and immunogenicity of RIX4414 vaccine in a pediatric population in Hong Kong.

2. Materials and methods

2.1. Study design and infants

This phase III, randomized, double-blind, placebo-controlled study (NCT00197210) was conducted at eight public hospitals in Hong Kong. The study protocol and related documents were approved by the ethics committee of the individual study centers and the study was conducted in accordance with Good Clinical Practice guidelines. Parents or legal guardians of the participating infants provided written consent before any study-related procedure was undertaken.

Healthy infants 6–12 weeks of age were equally randomized (1:1 blocking scheme) to receive two doses of either RIX4414 vaccine/placebo at 2 and 4 months of age.

Participants received a combined diphtheria-tetanus-acellular pertussis [DTPa], inactivated poliovirus [IPV] and *Haemophilus influenzae* type b [Hib] vaccine (*Infanrix*™ *IPV/Hib*; GlaxoSmithKline, Belgium) concomitantly with the study vaccines according to the local vaccination schedules. Alternatively, if requested, participants could receive diphtheria-tetanus-whole cell pertussis [DTPw], and oral poliovirus vaccine [OPV] at Maternal and Child Health Centres for routine vaccination. According to Hong Kong government policy, infants received a birth dose of Bacillus Calmette-Guérin, hepatitis B and OPV vaccines. Two weeks lapsed between the administration of any OPV dose and the RIX4414 vaccine/placebo; the second and third doses of hepatitis B vaccines were administered at 1 and 6 months of age. Infants were ineligible to participate if they had previously received any investigational drug/vaccine 30 days before the study, had allergy to any of the vaccine components, or were immunosuppressed or had a history of chronic gastrointestinal disease.

2.2. Study objectives and end points

The first co-primary objective of this study was to evaluate the efficacy of the RIX4414 vaccine against severe rotavirus gastroenteritis from two weeks after the second vaccine dose until two years of age. The second co-primary objective was to assess the safety of the vaccine with regard to occurrence of definite intussusception within 31-days following each vaccine dose.

2.3. Vaccine

Each dose of the lyophilized formulation of RIX4414 (*Rotarix*™, GlaxoSmithKline, Belgium) vaccine contained at least $10^{6.0}$ median cell culture infectious dose ($CCID_{50}$) of live, attenuated human G1P[8] rotavirus. The placebo had the same constituents and appearance as the active vaccine but without the vaccine viral strain. Both, the RIX4414 vaccine and placebo were reconstituted in a calcium carbonate buffer before oral administration. RIX4414 vaccine lot numbers RVC018A42, RVC019A43 and RVC021A44 were used. Lot numbers DD05A003A, DD05A003B and DD05A003C were used for the calcium carbonate buffer and RVC020A41PL was used for placebo.

2.4. Assessment of efficacy

The surveillance for gastroenteritis episodes started from the first dose of RIX4414 vaccine/placebo and continued until the children were three years of age. A gastroenteritis episode was defined as the occurrence of diarrhea [three or more, looser than normal stools within a day] with or without vomiting. If there was an interval of five or more symptom-free days between the two gastroenteritis episodes, they were considered as two different episodes. Hospital/medical facility surveillance ensured that all gastroenteritis cases requiring hospitalization and/or re-hydration therapy (equivalent to WHO plan B [oral re-hydration therapy for children with some dehydration in a medical facility] or C [intravenous re-hydration for severe dehydration in a medical facility]) [12] were recorded. Study personnel accessed computerized admission databases in the study centers on a daily basis to determine whether any study participants had been admitted to public hospitals. In addition, study personnel contacted families by telephone at least every month to determine any admissions to private hospitals.

For each qualifying episode of gastroenteritis, parents/guardians of infants completed a gastroenteritis diary card every day until

two days after the gastroenteritis symptoms had ceased. Diarrheal stool samples were collected as soon as possible (within 7 days) after hospitalization for the treatment of dehydration. The severity of the gastroenteritis episodes was assessed using a 20-Point Vesikari Scale where a score of ≥11 was considered to be severe [13].

Stool samples were stored between −20 °C and −70 °C until transported to GlaxoSmithKline Biologicals laboratory where they were analyzed for rotavirus using enzyme-linked immunosorbent assay (ELISA; *RotaClone*™ assay, Meridian Biosciences, USA). Rotavirus-positive stool samples were subsequently transported to Delft Diagnostic Laboratory, the Netherlands (where they were stored at 4 °C) and tested using reverse transcriptase polymerase chain reaction (RT-PCR) followed by reverse hybridization to determine the G and P types [14].

2.5. Assessment of safety

Vaccine safety was assessed with respect to serious adverse events (SAEs), intussusception cases, hospitalizations and deaths starting from Dose 1 until the children were two years of age. Although safety was not an endpoint during the follow-up period between Year 2 and Year 3, investigators were asked to report any unusual or vaccine-related SAEs during this period.

2.6. Assessment of immunogenicity

Blood samples from a subset of 100 infants were collected before vaccination and one to two months post-Dose 2 of RIX4414 vaccine/placebo. All children were invited to participate in the immunogenicity subset, and the first 100 infants with parental consent had blood taken to measure the serum anti-rotavirus IgA antibody concentrations using an in-house ELISA [15]; cut-off was 20 Units per milliliter (U/mL).

2.7. Statistical analyses

All statistical analyses were performed using SAS 8.2 (SAS Institute Inc., USA) and 95% Confidence Interval (CI) was calculated using Proc StatXact-5 (Cytel Software Corporation, USA).

The details of the sample size calculation have been previously presented [10,11].

Primary vaccine efficacy analysis was performed from two weeks post-Dose 2 until two years of age. Secondary vaccine efficacy analysis was performed from two weeks post-Dose 2 until three years of age. Both vaccine efficacy analyses were performed on the according-to-protocol (ATP) efficacy cohort with 95% CI. The ATP efficacy cohort included infants who had received two doses of RIX4414 vaccine/placebo, who had entered the efficacy follow-up period and who had no rotavirus other than the vaccine strain in their gastroenteritis stool samples. Estimates of vaccine efficacy against severe rotavirus gastroenteritis caused by wild-type rotavirus, against rotavirus gastroenteritis requiring hospitalization and against all-cause severe gastroenteritis were calculated during the period starting from two weeks post-Dose 2 until two and three years of age, respectively.

One to two months post-Dose 2 of RIX4414 vaccine/placebo, the anti-rotavirus IgA antibody seroconversion rate (anti-rotavirus IgA antibody concentration ≥20 U/mL in infants previously seronegative) and corresponding geometric mean concentrations (GMCs) were measured with 95% CI estimated.

3. Results

3.1. Demography

A total of 3025 infants (RIX4414 = 1513; placebo = 1512) were enrolled in Hong Kong between 08-December-2003 and 31-August-2005 and were followed until three years of age for vaccine efficacy. The ATP cohort for efficacy at the two- and three-year follow-up periods included 2993 infants. The reasons for excluding subjects from the analyses are presented in Fig. 1. There was no difference between the treatment groups with respect to age, gender and race. The mean age of infants was 11.6 weeks (standard deviation [SD]: 2.37) at Dose 1 and 17.8 weeks (SD: 1.53) at Dose 2 of RIX4414/placebo.

According to Hong Kong's routine immunization schedule, the majority of infants (99.8%) in the RIX4414 and placebo groups received a birth dose of OPV before Dose 1 of RIX4414 vaccine/placebo. Only one infant received OPV between Doses 1 and 2 of the RIX4414 vaccine. All other infants in the RIX4414 and placebo groups received DTPa-IPV-Hib concomitantly with both doses of RIX4414 vaccine/placebo.

3.2. Vaccine efficacy

Vaccine efficacy for severe rotavirus gastroenteritis was 95.6% (95% CI: 73.1%–99.9%) up until two years of age (Table 1). Vaccine efficacy against rotavirus gastroenteritis requiring hospitalization was 91.3% (95% CI: 64.7%–99.0%) while vaccine efficacy against gastroenteritis due to any etiology requiring hospitalization was 36.8% (95% CI: 12.5%–54.6%) in the first two years of life (Table 1). Similar efficacy results were obtained during the follow-up period until three years of age (Table 1).

The cumulative incidence of severe rotavirus gastroenteritis during the first two years of life was 0.1% (1/1494) among RIX4414 recipients and 1.5% (23/1499) among placebo recipients; the difference was statistically significant (p-value < 0.001). Similar results for cumulative incidence during the first three years of life are shown in (Table 1).

The RV types isolated during severe rotavirus gastroenteritis episodes up until three years of age were wild-type G1P[8] (placebo = 10), G3P[8] (RIX4414 = 1; placebo = 11) and G9P[8] (placebo = 3).

3.3. Safety

No case of intussusception was reported within the 31-days following each vaccine dose. Six cases of intussusception were reported in the follow-up period until two years of age; four cases in the RIX4414 group and two cases in the placebo group. All these cases occurred between 2 and 19 months after the second dose of RIX4414 vaccine/placebo. Five of the children (RIX4414 = 3; placebo = 2) underwent surgery (laparotomy) and one in the RIX4414 group underwent an air enema procedure for the reduction of intussusception. No case was considered by the investigator to be vaccine-related and all the infants recovered within two months (range: 2–37 days). No further case of intussusception was reported during the Year 3 follow-up period. No death was reported throughout the study.

In the follow-up period from Dose 1 until two years of age, at least one SAE was recorded in 439 infants in the RIX4414 group and 477 infants in the placebo group (p-value = 0.130) (data not shown). Based on the discharge diagnosis International Classification of Diseases (ICD) codes, gastroenteritis-related symptoms that required hospitalization at least once were recorded in 119 RIX4414 infants and 147 infants in the placebo group (Table 2).

Table 1
Efficacy of RIX4414 from two weeks post-Dose 2 until two and three years of age (ATP cohort for efficacy).

Gastroenteritis type	RIX4414			Placebo			Vaccine efficacy % (95% CI)	*p*-value[d]
	N[a]	*n*[b]	%[b] (95% CI)[c]	*N*[a]	*n*[b]	%[b] (95% CI)[c]		
Severe rotavirus gastroenteritis from two weeks post-Dose 2 until three years of age	1494	1	0.1 (0.0–0.4)	1499	26	1.7 (1.1–2.5)	96.1 (76.5–99.9)	<0.001
Severe rotavirus gastroenteritis from two weeks post-Dose 2 until two years of age	1494	1	0.1 (0.0–0.4)	1499	23	1.5 (1.0–2.3)	95.6 (73.1–99.9)	<0.001
Severe rotavirus gastroenteritis from two weeks post-Dose 2 until Year 1	1494	0	0.0 (0.0–0.2)	1499	8	0.5 (0.2–1.0)	100.0 (41.2–100.0)	0.008
Severe rotavirus gastroenteritis from Year 1–Year 2	1494	1	0.1 (0.0–0.4)	1498	15	1.0 (0.6–1.6)	93.3 (56.6–99.8)	<0.001
Severe rotavirus gastroenteritis from Year 2–Year 3	1461	0	0.0 (0.0–0.3)	1464	3	0.2 (0.0–0.6)	100.0 (<0.0–100.0)	0.250
Severe rotavirus gastroenteritis from two weeks post-Dose 2 until three years of age								
G1	1494	0	0.0 (0.0–0.2)	1499	11	0.7 (0.4–1.3)	100.0 (60.0–100.0)	<0.001
G3[e,f]	1494	1	0.1 (0.0–0.4)	1499	13	0.9 (0.5–1.5)	92.3 (48.6–99.8)	0.002
G9	1494	0	0.0 (0.0–0.2)	1499	4	0.3 (0.1–0.7)	100.0 (<0.0–100.0)	0.125
Hospitalization due to rotavirus gastroenteritis from two weeks post-Dose 2 until three years of age	1494	2	0.1 (0.0–0.5)	1499	27	1.8 (1.2–2.6)	92.6 (70.4–99.1)	<0.001
Hospitalization due to rotavirus gastroenteritis from two weeks post-Dose 2 until two years of age	1494	2	0.1 (0.0–0.5)	1499	23	1.5 (1.0–2.3)	91.3 (64.7–99.0)	<0.001
Hospitalization due to rotavirus gastroenteritis from two weeks post-Dose 2 until Year 1	1494	0	0.0 (0.0–0.2)	1499	8	0.5 (0.2–1.0)	100.0 (41.2–100.0)	0.008
Hospitalization due to rotavirus gastroenteritis from Year 1-Year 2	1494	2	0.1 (0.0–0.5)	1498	15	1.0 (0.6–1.6)	86.6 (42.5–98.5)	0.002
Hospitalization due to rotavirus gastroenteritis from Year 2–Year 3	1461	0	0.0 (0.0–0.3)	1464	4	0.3 (0.1–0.7)	100.0 (<0.0–100.0)	0.125
Hospitalization due to gastroenteritis of any cause from two weeks post-Dose 2 until three years of age	1494	83	5.6 (4.4–6.8)	1499	119[*]	7.9 (6.6–9.4)	30.0 (6.6–47.8)	0.011
Hospitalization due to gastroenteritis of any cause from two weeks post-Dose 2 until two years of age	1494	63	4.2 (3.3–5.4)	1499	100[*]	6.7 (5.5–8.1)	36.8 (12.5–54.6)	0.004
Hospitalization due to gastroenteritis of any cause from two weeks post-Dose 2 until Year 1	1494	21	1.4 (0.9–2.1)	1499	44	2.9 (2.1–3.9)	52.1 (17.7–73.0)	0.005
Hospitalization due to gastroenteritis of any cause from Year 1–Year 2	1494	42	2.8 (2.0–3.8)	1498	59	3.9 (3.0–5.1)	28.6 (-7.8–53.1)	0.105
Hospitalization due to gastroenteritis of any cause from Year 2–Year 3	1461	20	1.4 (0.8–2.1)	1464	21	1.4 (0.9–2.2)	4.6 (<0.0–50.9)	1.000

[a] *N* = number of infants included in each group.
[b] *n*/% = number/percentage of infants recording at least one severe rotavirus gastroenteritis episode/rotavirus gastroenteritis requiring hospitalization or severe gastroenteritis regardless of any cause in each group.
[c] 95% CI = 95% confidence interval.
[d] *p*-value = two-sided Fisher's exact test (significant level of $\alpha = 0.05$).
[e] One infant from the placebo group counted in G1 and G3 categories since both RV strains were isolated.
[f] One infant from the placebo group counted in G3 and G9 categories since both RV strains were isolated.
[*] Number of hospitalizations did not represent the sum of hospitalizations from the individual years because a subject might have reported a gastroenteritis episode requiring hospitalization in each year; however, only the first gastroenteritis episode requiring hospitalization was considered in the combined year follow-up.

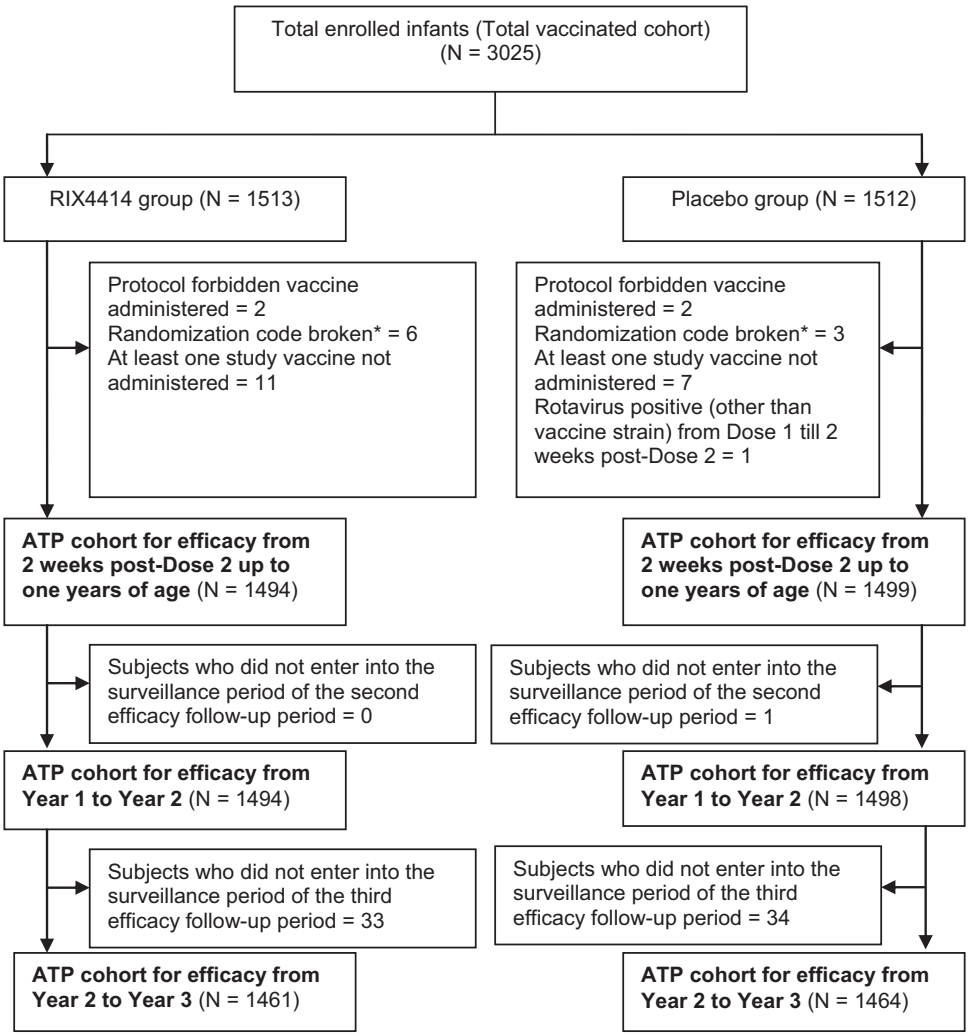

Fig. 1. CONSORT flowchart.
Footnotes: * The randomization code was broken for the following reasons: Kawasaki disease (RIX4414 = 2; Placebo = 2); Non-fatal SAEs—Constipation (Placebo = 1), anorexia (RIX4414 = 1), poor weight gain (RIX4414 = 1), rash (RIX4414 = 1) and gastroenteritis (RIX4414 = 1).

Table 2
Gastroenteritis-related serious adverse events recorded from Dose 1 up to two years of age.

	RIX4414 N[a] = 1513		Placebo N[a] = 1512		Difference (RIX4414 minus Placebo)	p-value
	n[b]	per 10,000 (95% CI)[c]	n[b]	per 10,000 (95% CI)	Value (95% CI)	
Diarrhea	2	13.2 (1.6–47.7)	3	19.8 (4.1–57.9)	−6.6 (−46.4 to −30.3)	0.654
Hemorrhagic diarrhea	1	6.6 (0.2–36.8)	0	0.0 (0.0–24.4)	6.6 (−18.7 to −37.3)	0.317
Enteritis	3	19.8 (4.1–57.8)	2	13.2 (1.6–47.7)	6.6 (−30.3 to −46.3)	0.655
Frequent bowel movements	1	6.6 (0.2–36.8)	0	0.0 (0.0–24.4)	6.6 (−18.7 to −37.3)	0.317
Infectious diarrhea	1	6.6 (0.2–36.8)	0	0.0 (24.4–6.6)	6.6 (−18.7 to −37.3)	0.317
Campylobacter intestinal infection	0	0.0 (0.0–24.4)	2	13.2 (1.6–47.7)	−13.2 (−48.1 to −12.1)	0.157
Salmonella gastroenteritis	19	125.6 (75.8–195.4)	25	165.3 (107.3–243.1)	−39.8 (−130 to −47.5)	0.361
Shigella gastroenteritis	1	6.6 (0.2–36.8)	0	0.0 (0.0–24.4)	6.6 (−18.7 to −37.3)	0.317
Bacterial gastroenteritis (unspecified)	2	13.2 (1.6–47.7)	0	0.0 (0.0–24.4)	13.2 (−12.1–48.1)	0.157
Caliciviral gastroenteritis	6	39.7 (14.6–86.1)	7	46.3 (18.6–95.2)	−6.6 (−60.3 to −45.5)	0.780
Norwalk virus	1	6.6 (0.2–36.8)	0	0.0 (0.0–24.4)	6.6 (−18.7 to −37.3)	0.317
Viral gastroenteritis (unspecified)	3	19.8 (4.1–57.8)	7	46.3 (18.6–95.2)	−26.5 (−77.7 to −17.4)	0.205
Dehydration	1	6.6 (0.2–36.8)	3	19.8 (4.1–57.9)	−13.2 (−52.3 to −19.2)	0.317
Food poisoning	0	0.0 (0.0–24.4)	1	6.6 (0.2–36.8)	−6.6 (−37.4 to −18.7)	0.317
Gastritis	7	46.3 (18.6–95.1)	9	59.5 (27.3–112.7)	−13.3 (−71.9 to −42.9)	0.615
Vomiting	2	13.2 (1.6–47.7)	2	13.2 (1.6–47.7)	−0.0 (−36.2 to −36.2)	0.999
Miscellaneous gastrointestinal symptoms	70	462.7 (362.4–581.0)	90	595.2 (481.3–726.6)	−133 (−295–27.2)	0.103
At least one symptom	119	–	147	–	–	–

[a] N = number of subjects having received at least one dose.
[b] n = number of subjects reporting at least once the specified SAE.
[c] 95% CI = 95% confidence interval.
Note: The gastroenteritis-related symptoms reported at least once were based on discharge diagnosis ICD codes.

Eight vaccine-related SAEs, all occurring after the first vaccine dose, were recorded (six in the RIX4414 group and two in the placebo group). They comprised rash (RIX4414 = 1), gastroenteritis (RIX4414 = 3; placebo = 1), constipation (placebo = 1), anorexia (RIX4414 = 1) and poor weight gain with frequent bowel movement (RIX4414 = 1). All infants, except the one with constipation, were hospitalized for these SAEs and all recovered.

3.4. Immunogenicity

One to two months post-Dose 2, the anti-rotavirus IgA antibody seroconversion rate in the subset of 100 infants was 97.5% (95% CI: 86.8%–99.9%) in the RIX4414 group, with a GMC of 314.6 U/mL (95% CI: 215.1–460.1). None of the infants in the placebo group seroconverted for anti-rotavirus IgA antibodies and the GMCs in this group were below 20 U/mL.

4. Discussion

This was the first study to report detailed efficacy, safety and immunogenicity data for the RIX4414 vaccine specifically in children from Hong Kong. Further data on rotavirus and all-cause gastroenteritis may be useful in making informed decisions on the use of rotavirus vaccination in this setting.

The results established that the RIX4414 vaccine provided high and sustained protection against severe rotavirus gastroenteritis caused by wild-type rotavirus strains particularly during the first two years of life (vaccine efficacy = 95.6%). Although possible protection was observed during the third year (vaccine efficacy = 96.1%), the group difference did not reach statistical significance. The efficacy of the RIX4414 shown in this study was comparable to that observed in two-year efficacy studies conducted in Latin America (vaccine efficacy = 80.5% [95% CI: 71.3%–87.1%]) and Europe (vaccine efficacy = 90.4% [95% CI: 85.1%–94.1%]) [8,9].

RIX4414 vaccine had an acceptable safety profile. As anticipated, the number of infants who reported gastroenteritis-related symptoms at least once in the placebo group (n = 147) was higher than that in the RIX4414 group (n = 119). There were no clinical or statistical differences between the groups from Dose 1 up to three years of age with respect to gastroenteritis symptoms or etiologies (Table 2) except for rotavirus gastroenteritis, which was significantly lower in the vaccine group (Table 1). Additionally, none of the six intussusception cases (RIX4414 = 4; placebo = 2) reported here were vaccine-related. The vaccine's immunogenicity was demonstrated by the high anti-rotavirus IgA seroconversion rate (97.5%) in the subset of 100 infants one to two months post-Dose 2. The fact that no seroconversion was found in the placebo group when tested between approximately 4 and 6 months of age indicated that natural rotavirus infection in early infancy was quite uncommon in Hong Kong.

Consistent with a previous report from Hong Kong, G1 and G3 were the most prevalent circulating rotavirus strains followed by G9 in children [3]. However, unlike previously, we did not observe the circulating G2 rotavirus strain in this study [3]. RIX4414 demonstrated efficacy against the three circulating rotavirus strains (92.3–100%).

ARSN data for Hong Kong reported that approximately one-third of all diarrhea-related hospital admissions were due to rotavirus [5], with significant health care and societal costs [16]. An economic evaluation using a Markov model and 2002 cost assumptions estimated that the introduction of routine rotavirus vaccination at a cost of US$40–$92 per course could be potentially cost-saving from a government perspective alone [17]. In this study, the percentage of hospitalization due to severe rotavirus gastroenteritis in the first three years of life was 1.7% (26/1499 or 1 in 58) in the placebo recipients and 0.1% (1/1494) in the RIX4414 recipients. In contrast, the previous ARSN surveillance data estimated a 2.4% (1 in 41) cumulative risk of a rotavirus-associated admission by three years of age and 4.2% (1 in 24) by five years of age [5]. The present data could reduce previous estimates of the potential economic benefit of vaccination [17], although, the previous economic evaluation did not take into account vaccine efficacy against hospitalization due to diarrhea of any etiology (30% in the first three years of life, preventing 2.3 admissions per 100 children vaccinated or 1 in 43). It is also possible that vaccination could prevent nosocomial infections [18]. Furthermore, vaccinating infants against rotavirus provides indirect protection to unvaccinated older children and adults through reduced transmission of the virus in the community resulting in fewer infections in the population [19]. This amplifies the economic benefit of rotavirus vaccination by reducing rotavirus-related hospitalization costs in older age groups who are ineligible for rotavirus vaccination [19,20].

This study had some limitations. First, while it was possible to routinely capture all admissions to public hospitals via a computerized system in this trial, admissions to private hospitals might have been missed or notified late. Although such cases should have been recorded in the diary cards maintained by parents, the retrospectively obtained information could be less complete and stool samples might not have been collected. This limitation could contribute to the apparent low rotavirus admission rates and vaccine efficacy against all-cause diarrhea. Second, this study was not powered to draw more definitive conclusions on the potential benefits of introducing rotavirus vaccines in Hong Kong. Nevertheless, substantial reductions in rotavirus-associated hospitalization rates have been observed following universal rotavirus vaccination in both developed countries (Australia [20,21], Austria [22], Belgium [23,24], United States [25]) and developing countries (Brazil [26,27], El Salvador [28,29], Mexico [30], Nicaragua [31], Panama [32]). In addition, Brazil and Mexico have witnessed reductions in all-cause mortality from gastroenteritis following the introduction of rotavirus vaccination [27,33,34]. Third, although there were multiple comparisons (without adjustment) of SAEs, calculated p-values less than 0.05 were used to highlight potential differences which would require further attention. Therefore, statistically significant findings should be interpreted with caution and clinical significance must be considered.

5. Conclusion

The study provided specific data about rotavirus vaccination in Hong Kong that could help public health officials with their consideration of universal rotavirus vaccination. There were no safety concerns or cases of vaccine-related intussusception in this study. Two oral doses of RIX4414 administered concomitantly with routine childhood vaccines offered high and sustained protection against severe rotavirus gastroenteritis caused by circulating rotavirus strains and against all-cause gastroenteritis in Hong Kong children during their first two years of life and possibly extending to their third year.

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