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Efficacy and safety of a pentavalent live human-bovine reassortant rotavirus vaccine (RV5) in healthy Chinese infants: A randomized, double-blind, placebo-controlled trial

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ABSTRACT

Background: A randomized, double-blind, placebo-controlled multicenter trial was conducted in healthy Chinese infants to assess the efficacy and safety of a pentavalent live human-bovine reassortant rotavirus vaccine (RotaTeq™, RV5) against rotavirus gastroenteritis (RVGE).
Methods: 4040 participants aged 6–12 weeks were enrolled and randomly assigned to either 3 oral doses of RV5 (n = 2020) or placebo (n = 2020), administered ~4 weeks apart. The participants also received OPV and DTaP in a concomitant or staggered fashion. The primary objective was to evaluate vaccine efficacy (VE) against naturally-occurring RVGE at least 14 days following the third dose. Key secondary objectives included: VE against naturally-occurring severe RVGE and VE against severe and any-severity RVGE caused by rotavirus serotypes contained in the vaccine, occurring at least 14 days after the third dose. All adverse events (AEs) were collected for 30 days following each dose. Serious AEs (SAEs) and intussusception cases were collected during the entire study. (ClinicalTrials.gov registry: NCT02062385).
Results: VE against RVGE of any-severity caused by any serotype was 69.3% (95% CI: 54.5, 79.7). The secondary efficacy analysis showed an efficacy of: 78.9% (95% CI: 59.1, 90.1) against severe RVGE caused by any serotype; 69.9% (95% CI: 55.2, 80.3) and 78.9% (95% CI: 59.1, 90.1) against any-severity and severe RVGE caused by serotypes contained in the vaccine, respectively. Within 30 days following any vaccination, 53.5% (1079/2015) and 53.3% (1077/2019) of participants reported at least one AE, and 5.8% (116/2015) and 5.7% (116/2019) reported SAEs in the vaccine and placebo groups, respectively. No SAEs were considered vaccine-related in recipients of RV5. Two intussusception cases were reported in recipients of RV5 who recovered after receiving treatment. Neither was considered vaccine-related.
Conclusions: In Chinese infants, RV5 was efficacious against any-severity and severe RVGE caused by any serotype and generally well-tolerated with respect to AEs.

1. Introduction

Rotaviruses are globally the leading cause of severe, dehydrating diarrhea in young children. As of April 2016, the World Health Organization (WHO) estimates that globally 215,000 (range, 197,000–233,000) child deaths occurred due to rotavirus infection during 2013, and four countries (India, Nigeria, Pakistan and the Democratic Republic of the Congo) accounted for approximately half (49%) of all rotavirus deaths in children under age five in 2013 [1].

China has experienced significant morbidity and mortality associated with rotavirus. In 2007, there were an estimated 12.1 million rotavirus diarrhea episodes, which resulted in

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3.5 million outpatient visits and 220 thousand pediatric hospital admissions [2]. It was estimated that a total of 53,559 diarrheal deaths among Chinese children <5 years of age were attributed to rotavirus from 2003 to 2012 and 2791 deaths were attributed to rotavirus in 2012 with a mortality rate of 0.17 per 1000 live births [3]. Two studies showed that rotavirus was responsible for approximately 50% in 2001–2003 and approximately 48% in 2003–2007 of emergency department or inpatient visits of children with diarrhea in China [4,5]. On average, rotavirus accounted for 41% of hospitalized acute gastroenteritis (AGE) cases and 25% of outpatient AGE cases in China [6].

Rotavirus diarrhea has also imposed a high economic burden in China. It was estimated that the total annual direct cost, social cost and private cost for outpatient and inpatient visits due to rotavirus diarrhea in 2007 were US $271.4 million, 365.0 million and 290.0 million, respectively [2]. If a vaccine was introduced in the national immunization program, it would be a cost-effective measure to reduce deaths, hospitalizations and outpatient visits associated with rotavirus infection in China [7]. Although the Lanzhou lamb rotavirus vaccine (LLR) had been licensed in China for more than 15 years, its efficacy data generated in a randomized controlled trial was not available publicly [8]. A pentavalent live human-bovine reassortant rotavirus vaccine (RotaTeq™, RV5) manufactured by Merck & Co., Inc., Kenilworth, NJ, USA, has proved highly efficacious against rotavirus gastroenteritis (RVGE) and associated hospitalizations in large-scale, well-controlled clinical trials worldwide [8], but it has not been licensed in China.

Here we report the efficacy against RVGE and safety of RV5 in healthy Chinese infants during the 2014–2015 RV season. The primary objective was to evaluate vaccine efficacy (VE) of RV5 against naturally-occurring RVGE at least 14 days following the third dose. The key secondary objectives included safety of RV5 with respect to all adverse events (AEs) within 30 days after each dose, VE against naturally-occurring severe RVGE occurring at least 14 days after the third dose, and VE against severe and any-severity RVGE caused by rotavirus serotypes contained in the vaccine occurring at least 14 days after the third dose.

2. Methods

2.1. Study design and participants

This study was a randomized, double-blind, placebo-controlled multicenter trial. No important change to methods was made after trial commencement. This study aimed to enroll 4040 participants with an allocation ratio of 1:1 to receive orally either RV5 or placebo. The participants were enrolled in five sites (Liujiang, Liucheng, Sanjiang, Rongan and Luzhai) in Guangxi Zhuang Autonomous Region, China. Healthy infants aged 6–12 weeks at the time of the first dose were eligible to be enrolled. The key exclusion criteria included any history of congenital abdominal disorders, rotavirus gastroenteritis, intussusception (IS), chronic diarrhea, failure to thrive, abdominal surgery, immunocompromised, or previous rotavirus vaccination; any clinical evidence of active gastrointestinal illness; receipt of systemic corticosteroid treatment, blood transfusion or blood products. Participants with fever (axillary temperature $\geq$37.5 °C) at the time of vaccination or within the last 24 h were to be deferred for vaccination.

The study was approved by Institutional Review Board of Guangxi Center for Disease Control and Prevention and conducted in compliance with Good Clinical Practice, the Declaration of Helsinki, and local regulations in China. Informed consent form was written by all the participants' parents or legal representatives. The trial was registered with ClinicalTrials.gov registry: NCT02062385.

2.2. Interventions

The eligible participants were randomly assigned to either 3 oral doses of RV5 (n = 2020) or placebo (n = 2020) administered approximately 4 weeks apart. RV5 consisted of 5 live human-bovine reassortant rotavirus strains (G1, G2, G3, G4, and P1A[8]) which were suspended in a 2 mL, buffered stablilizer solution. The placebo contained the same solution as RV5 except for no reassortant rotavirus strains.

To assess the impact of RV5 on the antibody response to oral poliovirus vaccine (OPV) and diphtheria, tetanus and acellular pertussis vaccine (DTaP), a subgroup (n = 800) received OPV and DTaP concomitantly administered with RV5 and other participants received staggered dosing of the two vaccines. Both OPV and DTaP are recommended by the Expanded Program of Immunization in China. The results regarding the immunogenicity will be reported separately.

2.3. Assessment of efficacy

Active surveillance for AGE was performed during the entire study to capture all potential RVGE cases through weekly contact with parent/legal guardian via telephone/email during the first rotavirus season (01 Oct 2014 through 31 Mar 2015) and biweekly contact during the "off-season" period (01 Apr through 11 Jun 2015). Inquiries were made about any vomiting, diarrhea, or hospitalization of the participants.

AGE was defined as 3 or more watery or looser-than-normal stools within a 24-h period and/or forceful vomiting. The parent/legal guardian was required to record and report all suspected AGEs. A stool specimen was to be collected no later than 7 days, preferably within 3 days after the onset of AGE. The stool samples were tested for detection of rotavirus antigen by a solid phase sandwich type enzyme immunoassay (EIA) which utilized monoclonal antibody against cognate genome 6 (VP6) (Premier Rotaclone). All rotavirus antigen EIA-positive samples underwent further evaluation by reverse transcription polymerase chain reaction (RT-PCR) to detect VP6 which was for identification of wild-type rotavirus. G (VP7) and P (VP4) genotypes were assayed by RT-PCR as described previously [9]. RT-PCR was conducted by LabCorp (Beijing, China). If an AGE case was detected with wild-type rotavirus in a stool specimen taken within 7 days after the onset of symptoms, it was deemed as a RVGE case.

RVGE severity was primarily determined by Vesikari scoring system with a score of 11 or more classified as severe [10]. However, Clark scoring system was also used in the supportive efficacy analysis with a score of 17 or more classified as severe [10].

2.4. Assessment of safety

Maximum axillary temperatures were measured daily through 7 days following each vaccination and recorded on the Vaccine Report Card (VRC). All AEs were collected for 30 days following each dose. Pre-specified solicited AEs including diarrhea and/or vomiting were collected from Day 1 through Day 14 following each vaccination and recorded on the VRC. Unsolicited systemic AEs were collected by VRC from Day 1 through Day 14 and by parent/legal guardian reporting from Day 15 through Day 30. Serious AEs (SAEs), deaths and cases of IS were collected during the entire study. No injection-site AEs were collected in this study as RV5 and placebo were given orally.

2.5. Sample size, randomization and blinding

The study design was RVGE case driven. Under the following assumptions: an 85% evaluability rate, a 60% true efficacy against

severe RVGE, and a true underlying attack rate of 2% for severe RVGE, a total of 48 targeted severe RVGE cases, of which no more than 16 are in the RV5 group, would be able to demonstrate the efficacy of RV5 against severe RVGE with 1-sided $\alpha = 0.025$ and power≈80%. To accrue the targeted severe RVGE cases, a total of 4040 participants with 2020 per vaccination group were sufficient. This sample size would be able to demonstrate the efficacy of RV5 against any-severity RVGE with 1-sided $\alpha = 0.025$ and power >90%, from which 100 targeted any-severity RVGE cases would be accrued.

The participants were randomly assigned according to a computer-generated allocation schedule with a block size of 4 which was designed to randomize the participants into a concomitant cohort or a staggered cohort individually. When a participant entered the study, the site used the lowest randomization number available from the corresponding cohort's allocation schedule. Throughout the study, the participants' parent/guardian, investigator, lab personnel and sponsor personnel or delegate(s) remained blinded to the allocation. RV5 and placebo were identical in appearance, packaging, and labeling with the randomization number so that blinding was maintained.

2.6. Statistical analysis

The per-protocol efficacy (PPE) population was used for the primary efficacy analysis which included participants who received the 3 scheduled doses, adhered to guidelines for the administration, and did not have important deviations from the protocol that might substantially affect the results of the primary efficacy endpoint. Only RVGE cases that occurred at least 14 days after the third dose were included in the PPE analysis.

For the primary hypothesis, RV5 was considered efficacious if the lower bound of the 2-sided 95% confidence interval (CI) for efficacy was >0%. To calculate the CI and associated p-value, an exact conditional method based on a Poisson distribution was used. Unless otherwise stated, all statistical tests were conducted at $\alpha = 0.05$ (2-sided) level. No multiplicity adjustment was needed.

An intention-to-treat (ITT) analysis on efficacy against any-severity RVGE was also done, which included all participants who received at least one dose of vaccine or placebo. RVGE cases that occurred at least 14 days after the first dose were included in the ITT analysis.

All randomized participants who received at least one dose of RV5 or placebo were included for safety analysis. Fever (axillary temperature ≥37.5 °C, or equivalent), vomiting, diarrhea, and IS were considered AEs of special interest and subject to inferential testing between groups with p-values and 95% CIs provided. A separate safety analysis was performed in the concomitant cohort.

3. Results

3.1. Study population

This study enrolled 4040 healthy Chinese infants with 2020 in each group from 30 May 2014 through 7 Oct 2014. 4037 (99.9%) participants received at least one dose, 3878 (96.0%) participants received all three doses and 3876 (95.9%) participants completed the study (Fig. 1). The proportion of participants that discontinued

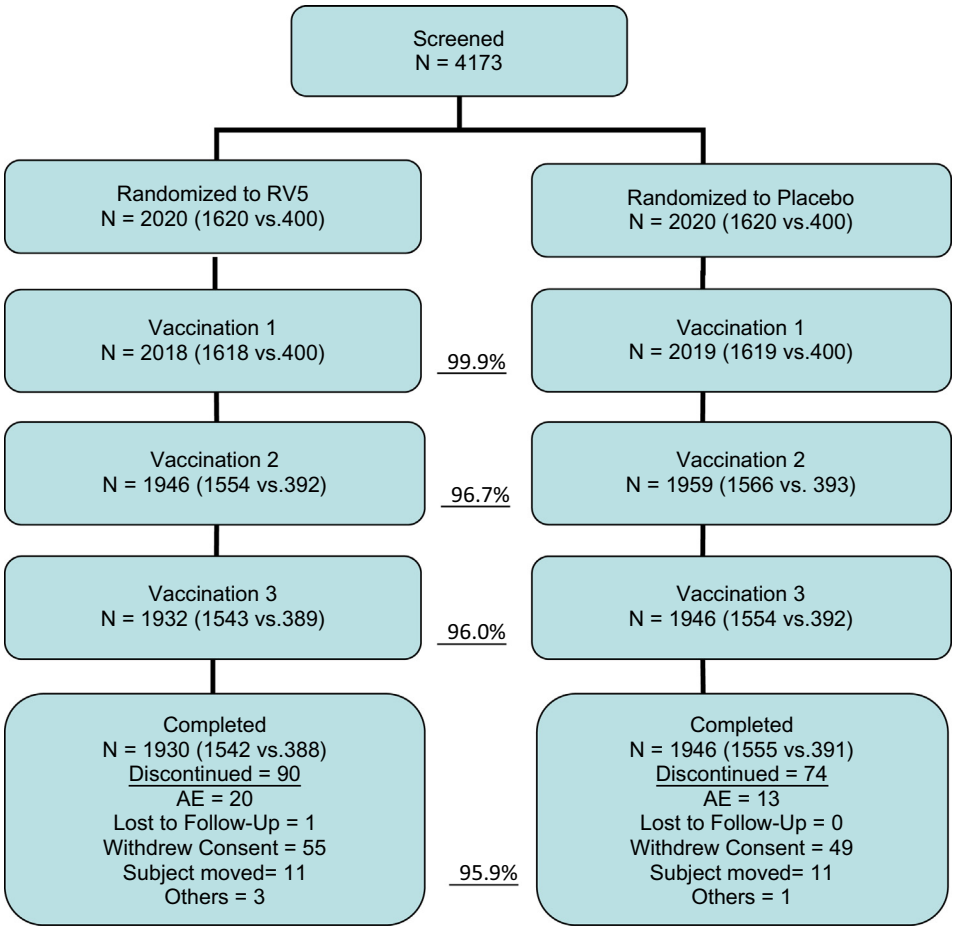

Fig. 1. Participants flow. The numbers in parentheses are the participants number in staggered cohort vs. concomitant cohort.

from the study was low and similar in the two groups (4.5% in RV5 group vs 3.7% in placebo group). The most common reason for study discontinuation was withdrawal by parent/guardian. A total of 800 participants with 400 participants in each group received OPV and DTaP concomitantly with RV5 or placebo.

The efficacy follow-up was from 30 May 2014 through 11 Jun 2015. The study ended when the targeted number of severe (48) and any-severity (1 0 0) RVGE cases had been accrued. A total of 148 participants had RV-positive stool samples. The most common G serotype was G9 (57.4%, 85/148) and all of them were combined with P1A[8]. The second most common G serotype was G1 (33.1%, 49/148). The most common P serotype was P1A[8] (91.9%, 136/148). Other serotypes were less common in this study.

The demographic and medical characteristics of the participants at baseline are shown in the Table 1. All participants were Asian in race. 433 (10.7%) participants reported at least one medical condition prior to vaccination with hyperbilirubinaemia neonatal (2.4%) and neonatal pneumonia (2.0%) as the two most common medical conditions. These conditions appeared to be evenly distributed across the two groups.

3.2. Vaccine efficacy

A total of 3864 (95.6%) participants with 1927 in the RV5 group and 1937 in the placebo group who had assessable efficacy follow-up results and no major protocol violations were included in the PPE population, from which 143 any-severity RVGE cases regardless of serotype were detected with 34 in the RV5 group and 109 in the placebo group, translating into a vaccine efficacy of 69.3% (95% CI: 54.5, 79.7) against RVGE of any-severity regardless of serotype at least 14 days after the third vaccination. In the secondary efficacy analysis, 11 and 52 severe RVGE cases regardless of serotype, 33 and 108 any-severity RVGE cases caused by vaccine serotypes, 11 and 52 severe RVGE cases caused by vaccine serotypes were observed in the RV5 and placebo groups, respectively, translating into an efficacy of: 78.9% (95% CI: 59.1, 90.1) against severe RVGE regardless of serotype; 69.9% (95% CI: 55.2, 80.3) and 78.9% (95% CI: 59.1, 90.1) against any-severity and severe RVGE caused by vaccine serotypes at least 14 days after the third vaccination, respectively (Table 2). In the supportive analysis using Clark scoring system, 1 and 22 severe RVGE cases regardless of serotype were observed in the RV5 and placebo groups, respectively, translating into an efficacy of 95.5% (95% CI: 71.9, 99.9).

Vaccine efficacy of RV5 against RVGE caused by specific serotype is shown in Table 3. RV5 was efficacious at least 14 days after the third vaccination against any-severity RVGE caused by G1, G9 or P1A[8] and against severe RVGE caused by G9 or P1A[8] with VEs varying from 67.4% to 88.3%. VE against RVGE caused by other serotypes did not show statistical significance which is likely due to insufficient RVGE cases.

Among ITT population, a total of 147 any-severity RVGE cases regardless of serotype were observed at least 14 days following the first vaccination with 35 and 112 in the RV5 and placebo groups, respectively, translating into a VE of 69.0% (95% CI: 54.4, 79.4) against RVGE of any-severity regardless of serotype at least 14 days after the first vaccination.

At least 14 days after the third vaccination, RV5 had an efficacy of: 74.0% (95% CI: 38.9, 90.5) and 79.1% (95% CI: 44.2, 93.8) against any-severity and severe hospitalized RVGE regardless of serotype, respectively; 14.1% (95% CI: 1.9, 24.8) and 49.9% (95% CI: 29.0, 65.1) against all-cause gastroenteritis and all-cause severe gastroenteritis, respectively.

3.3. Vaccine safety

A total of 4034 (99.9%) participants with 2015 in the RV5 group and 2019 in the placebo group had safety follow-up; therefore were included in the safety analysis. 2156 (53.4%) participants with 1079 (53.5%) in the RV5 group and 1077 (53.3%) in the placebo group reported at least one AE within 30 days following any vaccination. There were 116 participants in each group who reported SAEs and no SAE was considered vaccine-related in recipients of RV5. A total of 29 participants discontinued from subsequent vaccination due to an AE. The incidences of AEs, SAEs, deaths, vaccination-related AEs, vaccination-related SAEs, and any discontinuation, appeared comparable within the two vaccination groups (Table 4).

AEs of special interest are shown in Table 5. Approximately 22% of participants reported fever in both groups. There was no statistical difference between RV5 and placebo groups with respect to the incidences of fever, vomiting, diarrhea and IS. Within 7 days post Dose 1, 5.31% (107/2015) and 4.75% (96/2019) of participants reported diarrhea in the RV5 and placebo groups, respectively, and the difference in rate [0.56% (95% CI: −0.80%, 1.92%)] did not show statistical significance. Two IS cases were reported in the RV5 group. One participant developed intussusception on Day 32 Postdose 1 when she was 77-day old as diagnosed by abdominal ultrasonography, and recovered 2 days later after receiving treatment of air enema on the second day of onset. Another participant developed intussusception on Day 53 Postdose 3 when he was 173-day old, concomitantly vaccinated with OPV and DTaP. The diagnosis was confirmed by abdominal ultrasonography.

Table 1
Demographic and medical characteristics of the participants at baseline.

	RV5	Placebo
Gender		
Male	1029 (50.9%)	1062 (52.6%)
Female	991 (49.1%)	958 (47.4%)
Age (Day)		
Mean ± SD	59.6 ± 10.3	59.4 ± 10.1
Median	60.0	60.0
Range	41.0–84.0	41.0–83.0
With at least one medical condition	211 (10.4)	222 (11.0)

SD: standard deviation.

Table 2
Vaccine efficacy of RV5 against rotavirus gastroenteritis at least 14 days after the third vaccination.

	RV5		Placebo		Efficacy% (95% CI)
Efficacy against	RVGE cases	Days of follow-up	RVGE cases	Days of follow-up	
Any-severity RVGE regardless of serotype	34	428477	109	422252	69.3 (54.5, 79.7)
Severe RVGE regardless of serotype	11	431061	52	429345	78.9 (59.1, 90.1)
Any-severity RVGE caused by vaccine serotypes	33	428556	108	422392	69.9 (55.2, 80.3)
Severe RVGE caused by vaccine serotypes	11	431061	52	429345	78.9 (59.1, 90.1)

RVGE: rotavirus gastroenteritis.
Vaccine serotypes includes G1, G2, G3, G4, and G serotypes that contain P1A[8] (e.g., G9).
Sever RVGE: RVGE case with severity score≥11 on the Vesikari scoring system.

Table 3
Vaccine efficacy of RV5 by serotypes against rotavirus gastroenteritis at least 14 days after the third vaccination.

	RV5		Placebo		Efficacy% (95% CI)
Efficacy against	RVGE cases	Days of follow-up	RVGE cases	Days of follow-up	
Any-severity RVGE					
G1	10	431389	39	430335	74.4 (47.8, 88.6)
G2	1	432536	4	434924	74.9 (−154.0, 99.5)
G3	2	432429	2	434954	−0.6 (−1288, 92.7)
G4	0	432674	2	435032	100.0 (−435.4, 100.0)
G9	20	430224	61	428019	67.4 (45.2, 81.4)
P1A[8]	31	428828	101	423009	69.7 (54.3, 80.4)
Severe RVGE					
G1	5	432059	14	433529	64.2 (−5.3, 89.9)
G2	0	432674	2	435222	100.0 (−435.6, 100.0)
G3	2	432429	0	435218	NA (NA, 81.1)
G4	0	432674	2	435032	100.0 (−435.4, 100.0)
G9	4	432206	34	431216	88.3 (67.1, 97.0),
P1A[8]	10	431195	48	429527	79.2 (58.5, 90.6)

RVGE: rotavirus gastroenteritis.
Sever RVGE: RVGE case with severity score ≥11 on the Vesikari scoring system.
Serotype P1A[8] is not mutually exclusive with G1, G2, G3, G4 or G9.

Table 4
Adverse event summary within 30 days following any vaccination in all subjects as treated population.

	RV5 (N = 2015)		Placebo (N = 2019)		Total (N = 4034)	
	n	(%)	n	(%)	n	(%)
With one or more AE	1079	(53.5)	1077	(53.3)	2156	(53.4)
With vaccination-related[†] AE	359	(17.8)	354	(17.5)	713	(17.7)
With serious AE	116	(5.8)	116	(5.7)	232	(5.8)
With serious vaccination-related AE	0	(0.0)	3	(0.1)	3	(0.1)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued[‡] due to an AE	17	(0.8)	12	(0.6)	29	(0.7)
Discontinued due to a vaccination-related AE	4	(0.2)	4	(0.2)	8	(0.2)
Discontinued due to a serious AE	10	(0.5)	5	(0.2)	15	(0.4)
Discontinued due to a serious vaccination-related AE	0	(0.0)	0	(0.0)	0	(0.0)

All events were collected within 30 days after any vaccination and before the next vaccination.
[†] Determined by the investigator to be related to the vaccination.
[‡] Study medication withdrawn.

Table 5
Adverse Events of Special Interest in All Subjects as Treated Population.

	RV5			Placebo			Risk difference, RV5-placebo,% (95% CI)[†]	P-value (2-sided)
	n	N	%	n	N	%		
Fever								
Post Dose 1	154	2015	7.64	165	2019	8.17	−0.53 (−2.20, 1.14)	
Post Dose 2	146	1946	7.50	173	1959	8.83	−1.33 (−3.06, 0.39)	
Post Dose 3	191	1932	9.89	182	1946	9.35	0.53 (−1.33, 2.40)	
Post Any Dose	440	2015	21.84	461	2019	22.83	−1.00 (−3.57, 1.57)	0.4473
Vomiting								
Post Dose 1	40	2015	1.99	49	2019	2.43	−0.44 (−1.37, 0.47)	
Post Dose 2	11	1946	0.57	16	1959	0.82	−0.25 (−0.82, 0.29)	
Post Dose 3	5	1932	0.26	11	1946	0.57	−0.31 (−0.78, 0.11)	
Post Any Dose	54	2015	2.68	71	2019	3.52	−0.84 (−1.93, 0.24)	0.1252
Diarrhoea								
Post Dose 1	218	2015	10.82	189	2019	9.36	1.46 (−0.40, 3.33)	
Post Dose 2	143	1946	7.35	162	1959	8.27	−0.92 (−2.61, 0.77)	
Post Dose 3	97	1932	5.02	124	1946	6.37	−1.35 (−2.83, 0.11)	
Post Any Dose	406	2015	20.15	406	2019	20.11	0.04 (−2.44, 2.52)	0.9748
Intussusception[*]								
Post Dose 1	1	2015	0.05	0	2019	0.00	0.05 (−0.14, 0.28)	
Post Dose 2	0	1946	0.00	0	1959	0.00	0.00 (−0.20, 0.20)	
Post Dose 3	1	1932	0.05	0	1946	0.00	0.05 (−0.15, 0.29)	
Post Any Dose	2	2015	0.10	0	2019	0.00	0.10 (−0.09, 0.36)	0.1568

Calculation of percentage: The number of subjects evaluated divided by the number of subjects with follow-up.
Fever is defined as axillary temperature ≥37.5 °C.
N = Number of participants with assessable safety results; n = Number of participants with event.
[†] Based on Miettinen & Nurminen method.
[*] Intussusception was collected throughout the study. Other events were collected within 30 days after any vaccination and before next vaccination. CI = Confidence interval.

The participant recovered one week later after receiving treatment of air enema and subsequent surgical reduction. Neither case was considered vaccination-related by the investigator.

In the concomitant administration cohort, 47.0% (188/400) and 49.8% (199/400) of participants reported at least one AE in RV5 and placebo groups within 30 days following any vaccination, respectively. The incidences of those various safety indicators appeared comparable between the two groups (Table 6). It was also shown that the AE incidence in concomitant administration cohort was similar to that in the overall population.

4. Discussion

This randomized, double-blind, placebo-controlled, phase III study showed that vaccination with 3 doses of RV5 in healthy Chinese infants was efficacious against RVGE regardless of serotype and disease severity, and also efficacious against severe RVGE regardless of serotype. The primary and key secondary objectives for efficacy were met. This study also showed that RV5 was efficacious in healthy Chinese infants against any-severity and severe RVGE caused by serotypes contained in the vaccine.

During the first RV season, the VE against RVGE of any-severity regardless of serotype observed in this study (69.3%) was similar to that observed in Japan (75.3%) and Finland (72.0%) [11,12], and also similar to the VEs against RVGE of any-severity caused by serotypes G1, G2, G3 and G4 observed in Finland and United States (72.5% and 74.0%) [13,14]. Due to different scoring systems for RVGE severity, the VE against severe RVGE by Vesikari scoring system in this study cannot be compared with those observed in previous trials conducted in developed countries where Clark scoring system was used [11–14]. However, when Clark scoring system was used in the supportive analysis, the efficacy against severe RVGE regardless of serotype observed in this study (95.5%) was similar to those observed in developed countries (100.0%, 100.0%, 98.0%) [11,13,14]. Both our study and the trial conducted in five developing countries from Asia and Africa adopted Vesikari scoring system [15,16]. The VEs regardless of serotype observed in this study were higher (69.3% vs. 51.2% against any-severity RVGE, 78.9% vs. 58.9% against severe RVGE) than those observed in the five countries [17]. The VE against severe RVGE regardless of serotype observed in this study was higher (78.9% vs. 51.0%) than that observed in the two Asian countries (Vietnam and Bangladesh) [15]. In addition, the VE against all-cause severe gastroenteritis after 3 doses of RV5 observed in this study was higher (49.9% vs. 23.0%) than that observed in the five countries [17]. It was found that the VE increased with escalating RVGE severity which was consistent with the results observed in previous trials. Rotavirus vaccine generally showed higher efficacy in developed countries than in developing countries. Taking into account the fact that Guangxi Zhuang Autonomous Region where this study was conducted is relatively less developed in China, the results in this study are applicable for most of regions in China where the socioeconomic status is at least as good as the study sites.

One limitation of this study is that we did not assess the efficacy of RV5 during the second RV season because the targeted number of severe (48) and any-severity (1 0 0) RVGE cases had been accrued in the first RV season which triggered the predefined conditional termination of the study ahead of the second RV season. In previous trials, the efficacy of RV5 in the second season was lower than in the first season but still significant [12,14,17].

A systematic review and meta-analysis showed that the predominant G serotype circulating in China was G1 before 2000, G3 since 2001 and G9 after 2011, and that P1A[8] was the predominant P serotype from 1980 to 2011 [18]. The studies conducted in Gansu, Beijing and Guangxi of China in recent years also showed that G9 has become the predominant G serotype in those areas, which was mostly combined with P1A[8] [19,20]. The RV serotypes distribution observed in this study is consistent with previous findings in China, indicating that the study population is representative of the general population of healthy Chinese infants. The vast majority of serotypes observed in this study were those contained in the vaccine; therefore the VEs against RVGE caused by any serotype or caused by vaccine serotypes were almost identical. This study also demonstrated that RV5 was efficacious against any-severity and severe RVGE caused by G9-containing strains, indicating that RV5 affords protection against the most commonly circulating strains in China.

RV5 was well tolerated in Chinese healthy infants. No statistical differences in the incidences of AEs, SAEs, vaccination-related AEs and vaccination-related SAEs were observed between the two groups. After Dose 1, approximately one half of diarrhea cases occurred within 7 days in both groups (107/217 in RV5 group, 96/189 in placebo group). Regardless of within 7 days or within 30 days, the two groups did not show a statistical difference in diarrhea rate. Co-administration of OPV and DTaP did not increase the incidences of AE in RV5 recipients when compared to placebo recipients. It is difficult to draw conclusions regarding the two cases of IS observed in the RV5 group as the study was not powered to evaluate the risk of IS. No increased risk of IS was identified in a large-scale, well-controlled trial conducted previously [14]. Some post-licensure studies did detect a small increased risk of IS (1–2 excess case per 100,000 recipients) after the first dose of RV5 [21–24]. On the contrary, other post-licensure studies found no increased risk of IS after receiving RV5 [25–27]. The consensus from expert groups is that the well-documented benefits from rotavirus vaccination far outweigh the potential small increased risk of IS [21–31]. Another limitation of this study is that fecal shedding of vaccine strains was not assessed. However, shedding

Table 6
Adverse event summary within 30 days following any vaccination in concomitant administration cohort.

	RV5 (N = 400)		Placebo (N = 400)		Total (N = 800)	
	n	(%)	n	(%)	n	(%)
With one or more AE	188	(47.0)	199	(49.8)	387	(48.4)
With vaccination-related[†] AE	101	(25.3)	118	(29.5)	219	(27.4)
With serious AE	20	(5.0)	22	(5.5)	42	(5.3)
With serious vaccination-related AE	0	(0.0)	1	(0.3)	1	(0.1)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued[‡] due to an AE	1	(0.3)	0	(0.0)	1	(0.1)
Discontinued due to a vaccination-related AE	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to a serious AE	1	(0.3)	0	(0.0)	1	(0.1)
Discontinued due to a serious vaccination-related AE	0	(0.0)	0	(0.0)	0	(0.0)

All events were collected within 30 days after any vaccination and before the next vaccination.
[†] Determined by the investigator to be related to the vaccination.
[‡] Study medication withdrawn.

of vaccine strain virus is limited after vaccination with RV5, and primarily occurs following Dose 1. As indicated in the US prescribing information, 32 of 360 (8.9%), 0 of 249 (0.0%) and 1 of 385 (0.3%) vaccine recipients shed vaccine virus after Dose 1, 2 and 3, respectively, as detected by EIA and confirmed by plaque assay and RNA electropherotyping. Similar results were observed in the phase I trial with RV5 conducted in China where 1 of 23 (4.3%), 2 of 21 (9.5%) and 1 of 22 (4.5%) vaccine recipients shed vaccine virus after Dose 1, 2 and 3, respectively, as detected by EIA and confirmed by plaque assay and VP6 PCR (unpublished data). Overall, no new safety concern was identified for RV5 in this study and the data are consistent with the known safety profile of the vaccine.

RV5 is currently licensed in >120 countries worldwide; post-licensure studies in developed countries have demonstrated that depending on the population studied, vaccine effectiveness was up to 100% associated with decreased hospitalizations for RVGE, and that hospitalizations and emergency-department visits were reduced by up to 90% since the introduction of RV5 [32]. In addition, the indirect effect (i.e., herd immunity) and the long-term and broadly heterologous protection afforded by RV5 after its introduction in the USA had been observed [33–35], indicating that the full effect of RV5 may be greater than would be expected based on the results in controlled clinical trials.

The high disease burden of RVGE in China, the proven efficacy and safety profile of RV5 in Chinese infants, and the well documented vaccine effectiveness and public health impact of RV5 after approved in other countries warrant an urgent introduction of RV5 to the Chinese infant immunization schedule.

5. Conclusions

In healthy Chinese infants, RV5 was efficacious against naturally-occurring any-severity and severe RVGE regardless of serotype at least 14 days following the third vaccination and generally well-tolerated with respect to all AEs. Concomitant use of RV5 with OPV and DTaP was generally well tolerated.

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Potential conflict of interest

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