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Immunogenicity of pentavalent rotavirus vaccine in Chinese infants

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ABSTRACT

Background: A phase III, randomized, double-blind, placebo-controlled clinical study was conducted in China to assess the efficacy, safety, and immunogenicity of the pentavalent rotavirus vaccine (RotaTeq™, RV5) among Chinese infants. The efficacy and safety data have been previously reported. This report presents the immunogenicity data of the study.

Methods: 4,040 infants aged 6–12 weeks were randomly assigned in a 1:1 ratio to receive 3 oral doses of RV5 or placebo. Trivalent oral poliovirus vaccine (tOPV) and diphtheria, tetanus, and acellular pertussis vaccine (DTaP) were administered in a staggered-use (N = 3,240) or concomitant-use (N = 800) schedule. Immunogenicity of RV5 was evaluated in 800 participants (400 participants from each staggered- and concomitant-use immunogenicity subgroup). Geometric mean titers (GMTs) and seroresponse rates (≥3-fold rise from baseline to PD3) were measured for anti-rotavirus IgA in the staggered- and concomitant-use subgroups and measured for serum neutralizing antibodies (SNAs) to human rotavirus serotypes G1, G2, G3, G4, P1A[8] in the staggered-use subgroup. Immune responses to tOPV and DTaP co-administered with RV5 were also evaluated in the concomitant-use immunogenicity subgroup. (ClinicalTrials.gov registry: NCT02062385)

Results: The PD3 GMT and seroresponse rate of anti-rotavirus IgA were higher in the RV5 group (82.42 units/mL, 89.4%) compared to the placebo group (0.33 units/mL, 10.1%). Rotavirus type-specific SNA responses were also higher in the RV5 group compared to the placebo group. In the concomitant-use subgroup, the seroprotection rates of anti-poliovirus type 1, 2, 3 in the participants who received RV5 were non-inferior to those who received placebo, and the antibody responses to DTaP antigens were comparable between the two vaccination groups.

Conclusions: RV5 was immunogenic in Chinese infants. Immune responses induced by tOPV and DTaP were not affected by the concomitant use of RV5.

1. Introduction

Rotavirus is the most common cause of severe diarrhea in children under 5 years old worldwide. World Health Organization (WHO) estimated that approximately 215,000 rotavirus-associated child deaths occurred worldwide in 2013, and more than 90% of rotavirus deaths occurred in 72 low-income and low-middle-income countries eligible for the Global Alliance for Vaccines and Immunization (Gavi) support [1].

Rotavirus causes substantial morbidity and mortality in China. It was estimated that 12.1 million diarrhea episodes among Chinese children under 5 years old were attributable to rotavirus infections in 2007 which resulted in 3.5 million outpatient visits and 220,000 hospital admissions [2]. From 2003 to 2012, the estimated total number of deaths caused by rotavirus disease among Chinese children was 53,559 [3]. Although the annual number of rotavirus-associated deaths decreased significantly in the past decade in China, a substantial number of Chinese children continue to die from rotavirus disease, especially in rural areas. In 2012, the estimated mortality rate associated with rotavirus disease was 0.17 deaths per 1000 live births in China, with 0.33 deaths per 1000 live births in rural areas vs. 0.03 deaths per 1000 live births in urban areas [3].

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Two live, oral rotavirus vaccines, RV5 (RotaTeq™, Merck & Co., Inc., Kenilworth, NJ, USA) and RV1 (Rotarix™, GlaxoSmithKline Biologicals Inc., Rixensart, Belgium), have been licensed in many countries worldwide since 2006. In 2009, WHO has recommended rotavirus vaccine to be included in all national immunization programs [4,5]. As of August 2018, 96 countries have introduced rotavirus vaccines, including 89 national introductions, 3 ongoing phased introductions, and 4 pilot or sub-national introductions, but 57% of all children worldwide still lack access to rotavirus vaccines [6]. In China, one domestic Lanzhou lamb rotavirus (LLR) vaccine (G10P[15]) has been available in the private market since 2000 [7,8]. However, the clinical efficacy and safety data of LLR vaccine are not publicly available [9]. Several post-marketing studies were conducted in some areas of China to investigate effectiveness of LLR vaccine, but the results remained controversial [10–13]. A recent cross-sectional, ecological study provided some evidence of the population-level impact of LLR vaccine in preventing RVGE among Chinese children under 4 years old [14]. However, the authors acknowledged that further research based on more rigorous design is necessary to confirm the impact of LLR vaccine.

To investigate the efficacy, safety, and immunogenicity of RV5 among Chinese infants, a phase III, randomized, double-blind, placebo-controlled clinical study was conducted in China during the 2014–2015 rotavirus season. As reported by Mo et al, the primary and secondary efficacy objectives of the study were met [15]. Efficacy of RV5 against any-severity and severe RVGE regardless of serotypes observed among Chinese infants was 69.3% (95% confidence interval [CI]: 54.5, 79.7) and 78.9% (95% CI: 59.1, 90.1), respectively (Vesikari scoring system was used as the primary method and a Vesikari score $\geq$11 was classified as severe). The Clark scoring system was also used as a supplemental method in the study, and the efficacy against severe RVGE with Clark score $\geq$17 was 95.5% (95% CI: 71.9, 99.9). The safety data showed that RV5 was generally well-tolerated in Chinese infants. Secondary objectives of the study were to characterize the immune responses to RV5 as measured by serum anti-rotavirus IgA and serum neutralizing antibodies (SNAs) to human rotavirus serotypes G1, G2, G3, G4, and P1A[8] contained in the RV5. Other secondary objectives were to assess the immune responses to trivalent oral poliovirus vaccine (tOPV) and diphtheria, tetanus, and acellular pertussis vaccine (DTaP) when concomitantly administered with RV5. This report describes the results of the immunogenicity analyses.

2. Materials and methods

2.1. Study design and participants

As previously reported, this was a phase III, randomized, double-blind, placebo-controlled clinical study [15]. The study was implemented from 30 May 2014 to 11 June 2015. This study was approved by the investigator's institutional review board. Written informed consent was obtained from each participant's parent or guardian before enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with Good Clinical Practice guidelines. The study was registered at ClinicalTrials.gov (NCT02062385).

4,040 eligible Chinese infants aged 6–12 weeks of age were randomly assigned in a 1:1 ratio to receive 3 oral doses of RV5 or placebo at approximately 2, 3, and 4 months of age. The 1st dose of RV5 or placebo was administered as early as 6 weeks of age and the 3rd dose was administered by 32 weeks of age. Each dose of RV5 or placebo was administered with a minimum interval of 4 weeks.

Administration of tOPV and DTaP were allowed in this study according to the Expanded Program of Immunization (EPI) schedule in China. Three doses of tOPV and DTaP were administered either in a staggered-use (N = 3,240) or concomitant-use (N = 800) schedule. In the staggered-use group, 1 oral dose of tOPV was given approximately 14 days following each dose of RV5 or placebo at around 2.5, 3.5, and 4.5 months of age, and 1 dose of DTaP was administered at around 3.5, 4.5, and 5.5 months of age. In the concomitant-use group, each dose of tOPV was given on the same day as each dose of RV5 or placebo, and the 1st and 2nd dose of DTaP were given on the same day of the 2nd and 3rd dose of RV5 or placebo respectively, and the 3rd dose of DTaP was administered alone at around 5 months of age (Table 1).

All participants were followed for efficacy and safety. The immunogenicity was evaluated in a subset of 800 participants enrolled in the immunogenicity subgroup, with 400 participants from each staggered-use or concomitant-use subgroup.

2.2. Vaccines

Each dose of RV5 consisted of a 2 mL, oral solution of 5 live human-bovine reassortant rotavirus strains (G1, G2, G3, G4, and P1A[8]), which contained a minimum of $2.0–2.8 \times 10^6$ infectious units (IU) per dose depending on the serotype, and not greater than 116×10^6 IU per dose in aggregate. The reassortants were suspended in a buffered stabilizer solution. Placebo contained the same constituents as the vaccine without viral antigens.

tOPV (1 g per dose, manufactured by the Institute of Medical Biology, Chinese Academy of Medical Sciences) and DTaP (5 mL per dose, manufactured by Wuhan Institute of Biological Products Co., Ltd. or Changchun Changsheng Life Sciences Ltd.) were obtained through the participants' routine health care as scheduled by EPI in China.

RV5, placebo, and tOPV were administered orally. DTaP was administered by intramuscular injection.

2.3. Immunogenicity assessment

Approximately 1.5 mL serum samples were collected from each participant enrolled in the immunogenicity subgroup before Dose 1 (baseline) and approximately 30 days post-dose 3 (PD3) of study vaccinations.

The immunogenicity of RV5 was measured by serum anti-rotavirus IgA and rotavirus type-specific SNAs. Anti-rotavirus IgA responses were evaluated among all participants enrolled in the immunogenicity subgroup. SNA responses were only evaluated in the staggered-use immunogenicity subgroup due to the limited volume of serum samples. The immune responses to tOPV and DTaP antigens were evaluated in the concomitant-use immunogenicity subgroup.

Geometric mean titers (GMTs) and seroresponse rates (defined as $\geq$ 3-fold rise in titers from baseline to PD3 as described elsewhere [16,17]) were measured for anti-rotavirus IgA and rotavirus type-specific SNAs. GMTs and seroprotection or seropositivity rates were measured for neutralizing antibodies (NAs) against poliovirus types 1, 2, and 3, and for antibodies against DTaP antigens including diphtheria toxoid, tetanus toxoid, pertussis toxin (PT), and pertussis filamentous hemagglutinin (FHA). Seroprotection for poliovirus was defined as NAs titers $\geq$ 1:8 dilution units. The seroprotection criteria for diphtheria and tetanus were defined as: (1) anti-diphtheria: antibody titers $\geq$ 0.1 IU/mL; (2) anti-tetanus: antibody titers $\geq$ 0.1 IU/mL; and the seropositivity criteria for pertussis were defined as: (3) anti-PT: antibody titers $\geq$ 20 EU/mL; (4) anti-FHA: antibody titers $\geq$ 20 EU/mL.

The serum samples were stored at -20 °C or lower until the samples were shipped on dry ice to the laboratories for antibody

Table 1
Summary of the RV5/placebo, tOPV and DTaP vaccination schedule for the staggered-use and concomitant-use immunogenicity subgroup.

Age at Vaccination (month)	Staggered-use Immunogenicity Subgroup (N = 400)			Concomitant-use Immunogenicity Subgroup (N = 400)		
	RV5/placebo	tOPV	DTaP	RV5/placebo	tOPV	DTaP
2	X			X	X	
2.5		X				
3	X			X	X	X
3.5		X	X			
4	X			X	X	X
4.5		X	X			
5						X
5.5			X			

RV5 = pentavalent rotavirus vaccine (RotaTeq^{TM}); tOPV = trivalent oral poliovirus vaccine; DTaP = diphtheria, tetanus, and acellular pertussis vaccine; X = vaccine administration; N = number of participants included in the respective subgroup.

detection. The rotavirus IgA assay and type-specific SNAs assay were validated and performed at Cincinnati Children's Hospital Medical Center (CCHMC), OH, USA. The rotavirus IgA assay is a standard enzyme-linked immunosorbent assay (EIA) designed to measure IgA antibody to rotavirus present in serum. The quantity of anti-rotavirus IgA is determined by comparison of the background-adjusted optical density from sample wells against a standard curve generated using a human serum pool with a predetermined anti-rotavirus IgA concentration. The type-specific SNAs assay detects and quantifies the amount of anti-rotavirus neutralizing antibodies present in serum by measuring the amount of type-specific rotavirus antigen remaining after neutralization of the virus strain. The amount of rotavirus antigen present in the cell lysate is inversely related to the amount of neutralizing antibody present in the serum. The reported neutralizing antibody titer is calculated from the inverse of the extrapolated dilution that causes a 60% reduction in infectious virus. The poliovirus serum NAs assay and the diphtheria, tetanus and pertussis serum antibody assays were performed at the laboratories of National Institutes of Food and Drug Control (NIFDC), Beijing, China.

2.4. Statistical analyses

The immunogenicity analyses were performed in the per-protocol immunogenicity (PPI) populations. The PPI populations were antigen specific. Eligible participants were those who received all 3 scheduled doses without intervening laboratory confirmed diseases specific to the analyzed antigen before collection of PD3 serum samples and had valid laboratory data with serum samples collected within protocol-specified day ranges.

One of the secondary objectives of this study was to evaluate the immunogenicity of tOPV when concomitantly administered with RV5 and the hypothesis for this objective was that the seroprotection rates in participants who received tOPV concomitantly with RV5 were non-inferior to those in participants who received tOPV concomitantly with placebo. The non-inferiority analyses were performed at 0.025 significance level for each component of tOPV using the method proposed by Miettinen and Nurminen [18]. The statistical criterion for non-inferiority corresponded to the 2-sided 95% CIs on the difference in seroprotection rates (tOPV+RV5 minus tOPV+placebo) excluding a decrease of 10 percentage points or more (i.e. the lower bound of 95% CI >-0.10).

Under the assumptions of an 85% evaluability rate and expected seroprotection rates of 96%, 91%, 95% for poliovirus types 1, 2, and 3, 200 participants per vaccination group enrolled in the concomitant-use immunogenicity subgroup will have overall 82% of power to demonstrate the non-inferior immune responses to tOPV measured by seroprotection rates.

There were no hypotheses for the immunogenicity objectives of RV5 and DTaP, therefore the immune responses to RV5 and DTaP were descriptively summarized. The point estimates and 95% CIs were calculated for GMTs and seroresponse rates. The 2-sided 95% CIs of GMTs were based on the natural log-transformed titers and t-distribution. The 2-sided 95% CIs of binomial responses were provided using the exact method by Clopper-Pearson.

3. Results

3.1. Study participants

A total of 800 participants were enrolled in the immunogenicity subgroup, with 400 participants from each staggered- or concomitant-use subgroup (Fig. 1). 754 participants received 3 doses of RV5 or placebo, including 371 participants from the staggered-use subgroup and 383 participants from the concomitant-use subgroup. In the concomitant-use immunogenicity subgroup, 383 participants received 3 doses of tOPV and 382 participants received 3 doses of DTaP concomitantly with RV5 or placebo.

3.2. Serum anti-rotavirus IgA responses

Among 754 participants in the immunogenicity subgroup who received 3 doses of RV5 or placebo, 733 participants were included in the per-protocol analysis for anti-rotavirus IgA (355 participants in the staggered-use subgroup and 378 participants in the concomitant-use subgroup). There were 16 participants in the staggered-use subgroup excluded from the per-protocol analysis: 8 participants with protocol violations, 4 participants with PD3 serum samples collected out of day range, and 4 participants with missing PD3 serum samples. Five participants in the concomitant-use subgroup were excluded from the per-protocol analysis: 3 participants with PD3 serum sample collection out of day range and 2 participants with missing PD3 serum samples.

In the PPI population, the baseline GMTs of anti-rotavirus IgA were comparable between the RV5 and placebo vaccination groups. The PD3 GMTs of anti-rotavirus IgA was 82.42 units/mL in the RV5 group, which was higher than 0.33 units/mL in the placebo group (Table 2). The seroresponse rate of anti-rotavirus IgA in the RV5 group (89.40%) was higher than that in the placebo group (10.11%) (Table 2).

Anti-rotavirus IgA responses among recipients of RV5 were also summarized by the concomitant-use and staggered-use subgroups (Table 3). The GMT of anti-rotavirus IgA in the concomitant-use subgroup was lower than that in the staggered-use subgroup (50.49 units/mL [95% CI: 36.48, 69.87] vs. 138.75 units/mL [95% CI: 105.39, 182.67]), and the seroresponse rate in the concomitant-use subgroup was also lower than that in the staggered-use subgroup, but the confidence intervals overlapped (85.63% [95% CI: 79.52, 90.48] vs. 93.14% [95% CI: 88.33, 96.41]).

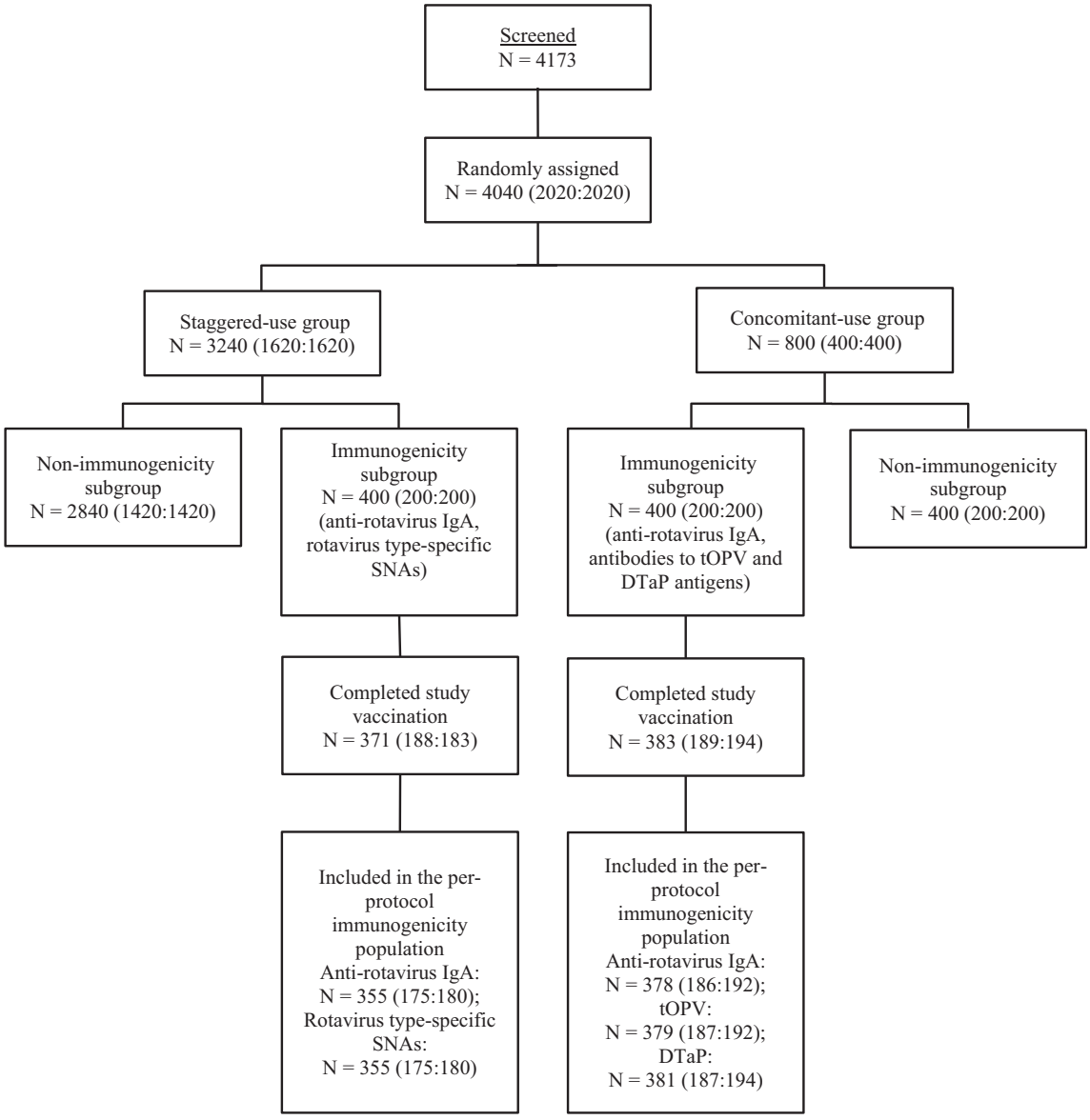

Fig. 1. Participant disposition and the number of participants included in per-protocol immunogenicity populations. The numbers in parentheses are the participant number in the group of RV5 vs. placebo.

Table 2
Summary of anti-rotavirus IgA responses in the per-protocol immunogenicity population (Concomitant-use and staggered-use immunogenicity subgroup).

Antibody	Parameter	RV5 (N = 361)			Placebo (N = 372)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
Anti-rotavirus IgA	Baseline GMT	349	0.15	(0.13, 0.18)	356	0.17	(0.14, 0.21)
	PD3 GMT	361	82.42	(66.19, 102.63)	372	0.33	(0.26, 0.42)
	Proportion of participants with a ≥ 3-fold rise	349	89.40%	(85.68%, 92.42%)	356	10.11%	(7.18%, 13.72%)

RV5 = pentavalent rotavirus vaccine (RotaTeq™); N = number of participants included in the per-protocol immunogenicity population; n = number of participants contributing to the per-protocol immunogenicity analyses; CI = confidence interval; GMT = geometric mean titer; PD3 = post-dose 3. Units for IgA are units/mL.

3.3. Serum neutralizing antibody (SNA) responses to human rotavirus serotypes contained in RV5 (G1, G2, G3, G4, P1A[8])

Rotavirus type-specific SNAs were evaluated in the staggered-use immunogenicity subgroup.

The GMTs and seroresponse rates among recipients of RV5 were generally higher than those among recipients of placebo (Table 4).

3.4. Immune responses to poliovirus types 1, 2, and 3 among participants who concomitantly received tOPV with RV5 or placebo

Immune responses to tOPV were evaluated in the concomitant-use immunogenicity subgroup. Among 383 participants in the concomitant-use subgroup who received 3 doses of tOPV concomitantly with RV5 or placebo, 379 participants were included in the

Table 3
Summary of anti-rotavirus IgA responses to RV5 by different subgroups in the per-protocol immunogenicity population.

Antibody	Parameter	Concomitant-use Subgroup (N = 186)			Staggered-use Subgroup (N = 175)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
Anti-rotavirus IgA	Baseline GMT	174	0.11	(0.09, 0.14)	175	0.20	(0.15, 0.27)
	PD3 GMT	186	50.49	(36.48, 69.87)	175	138.75	(105.39, 182.67)
	Proportion of participants with a ≥ 3-fold rise	174	85.63%	(79.52%, 90.48%)	175	93.14%	(88.33%, 96.41%)

RV5 = pentavalent rotavirus vaccine (RotaTeq™); N = number of participants included in the per-protocol immunogenicity population; n = number of participants contributing to the per-protocol immunogenicity analyses; CI = confidence interval; GMT = geometric mean titer; PD3 = post-dose 3. Units for IgA are units/mL.

Table 4
Summary of SNA responses to serotypes G1, G2, G3, G4, and P1A[8] in the per-protocol immunogenicity population (Staggered-use immunogenicity subgroup).

Serotype	Parameter	RV5 (N = 175)			Placebo (N = 180)		
		n	Observed Response	95% CI	n	Observed Response	95% CI
G1	Baseline GMT	175	43.41	(38.69, 48.71)	180	49.65	(44.33, 55.60)
	PD3 GMT	175	141.88	(120.49, 167.07)	180	17.94	(15.93, 20.20)
	Proportion of participants with a ≥ 3-fold rise	175	51.43%	(43.77%, 59.04%)	180	0.00%	(0.00%, 2.03%)
G2	Baseline GMT	175	24.03	(20.76, 27.81)	180	30.35	(25.62, 35.95)
	PD3 GMT	175	25.16	(20.96, 30.21)	180	10.67	(9.37, 12.17)
	Proportion of participants with a ≥ 3-fold rise	175	19.43%	(13.85%, 26.08%)	180	0.56%	(0.01%, 3.06%)
G3	Baseline GMT	175	23.93	(20.11, 28.47)	180	23.73	(19.87, 28.34)
	PD3 GMT	175	21.97	(18.64, 25.89)	180	8.33	(7.39, 9.38)
	Proportion of participants with a ≥ 3-fold rise	175	13.71%	(8.99%, 19.72%)	180	0.00%	(0.00%, 2.03%)
G4	Baseline GMT	175	33.82	(29.99, 38.14)	180	43.34	(37.23, 50.44)
	PD3 GMT	175	76.94	(67.25, 88.01)	180	14.84	(13.18, 16.72)
	Proportion of participants with a ≥ 3-fold rise	175	37.14%	(29.97%, 44.76%)	180	0.00%	(0.00%, 2.03%)
P1A[8]	Baseline GMT	175	39.18	(33.88, 45.31)	180	43.73	(37.69, 50.72)
	PD3 GMT	175	125.01	(103.00, 151.72)	180	11.98	(10.44, 13.74)
	Proportion of participants with a ≥ 3-fold rise	175	46.86%	(39.29%, 54.53%)	180	0.56%	(0.01%, 3.06%)

RV5 = pentavalent rotavirus vaccine (RotaTeq™); N = number of participants included in the per-protocol immunogenicity population; n = number of participants contributing to the per-protocol analyses; CI = confidence interval; GMT = geometric mean titer; PD3 = post-dose 3; SNA = serum neutralizing antibody. Units for SNAs are dilution units.

per-protocol analysis for tOPV. Four participants were excluded from the analysis: 3 participants with PD3 serum sample collection out of day range and 1 participant with missing PD3 serum sample.

As shown in Table 5 and Fig. 2, GMTs and seroprotection rates against poliovirus types 1, 2, and 3 post-vaccination were comparable between the tOPV+RV5 and tOPV+placebo groups. Seroprotection rates against poliovirus types 1, 2, and 3 were 98.93%, 100%, and 98.93%, respectively in the tOPV+RV5 group, while the corresponding rates in the tOPV+placebo group were 100%, 100%, and 98.96%, respectively. For each poliovirus type, the lower bound of 2-sided 95% CIs on the differences in seroprotection rates between the two vaccination groups was >-10%. Concomitant use of tOPV and RV5 met the criteria for non-inferiority to concomitant use of tOPV and placebo in eliciting protective immune responses against each type of poliovirus.

3.5. Immune responses to DTaP antigens among participants who concomitantly received DTaP with RV5 or placebo

Of 382 participants in the concomitant-use immunogenicity subgroup who received 3 doses of DTaP concomitantly with RV5 or placebo, 381 participants were included in the per-protocol analysis for DTaP. One participant was excluded from the analysis due to PD3 serum sample collected out of day range. All participants included in the per-protocol analysis were vaccinated with DTaP vaccine manufactured by Wuhan Institute of Biological Products Co., Ltd.

The immune responses to DTaP antigens post-vaccination as measured by GMTs and seroprotection/seropositivity rates were comparable between the DTaP + RV5 and DTaP + placebo groups (Fig. 2).

4. Discussion

The immunogenicity of RV5 among Chinese infants was investigated in the present study. And the immunogenicity of tOPV and DTaP concomitantly administered with RV5 was also investigated in the study.

Although a definitive immunological correlate of protection against rotavirus disease has not been established with any rotavirus vaccines, the anti-rotavirus IgA and SNA responses were used by regulatory agencies, as well as WHO, as a means of predicting efficacy [19]. There have been some studies suggesting that anti-rotavirus IgA can serve as a correlate of protection based on aggregated clinical data [20,21] or individual participant data [22]. However, a recent study based on 5 clinical studies of RV5 showed that G1 SNA titer correlated most closely with the efficacy of RV5 at both individual and population level compared to anti-rotavirus IgA [23].

In the present study, the seroresponse rate of anti-rotavirus IgA was 89.4%, which is numerically lower than those observed in the developed countries, such as USA, EU, Taiwan, Korea, and Latin America, where 92%-98% of participants seroconverted to anti-rotavirus IgA post-vaccination [24–29]. However, the seroresponse rate of anti-rotavirus IgA in Chinese infants was comparable or higher than those observed in other Asian and African countries with a lower socioeconomic level (87.8% in Bangladesh and Vietnam; 78.3% in Ghana, Kenya, and Mali) [16,17]. A similar finding was observed in the results of SNA responses in the present study.

Table 5
Summary of non-inferiority of seroprotection rates to poliovirus types 1, 2, and 3 in the per-protocol immunogenicity population (Concomitant-use Immunogenicity Subgroup).

Antibody	tOPV + RV5 (N = 187)		tOPV + Placebo (N = 192)		Estimated Difference (Percentage Points) (95% CI)	P-value*	Non-inferiority Conclusion
	n	Observed Response	n	Observed Response			
Poliovirus type 1	187	98.93%	192	100.00%	−1.07% (−3.82%, 0.91%)	<0.0001	Non-inferior
Poliovirus type 2	187	100.00%	192	100.00%	0.00% (−2.02%, 1.97%)	<0.0001	Non-inferior
Poliovirus type 3	187	98.93%	192	98.96%	−0.03% (−2.89%, 2.77%)	<0.0001	Non-inferior

RV5 = pentavalent rotavirus vaccine (RotaTeq™); tOPV = trivalent oral poliovirus vaccine; N = number of participants included in the per-protocol immunogenicity for tOPV; n = number of participants contributing to the per-protocol analyses; CI = confidence interval; Seroprotection rate = proportion of participants who achieved the seroprotection criteria: neutralizing antibody titers [NA] ≥ 1:8.

* A 95% CI on the difference excluding a decrease of 10 percentage points or more and associated one sided P-value < 0.025 implies that the difference is statistically significantly less than the pre-specified clinically relevant decrease of 10 percentage points and allows for a conclusion of non-inferiority.

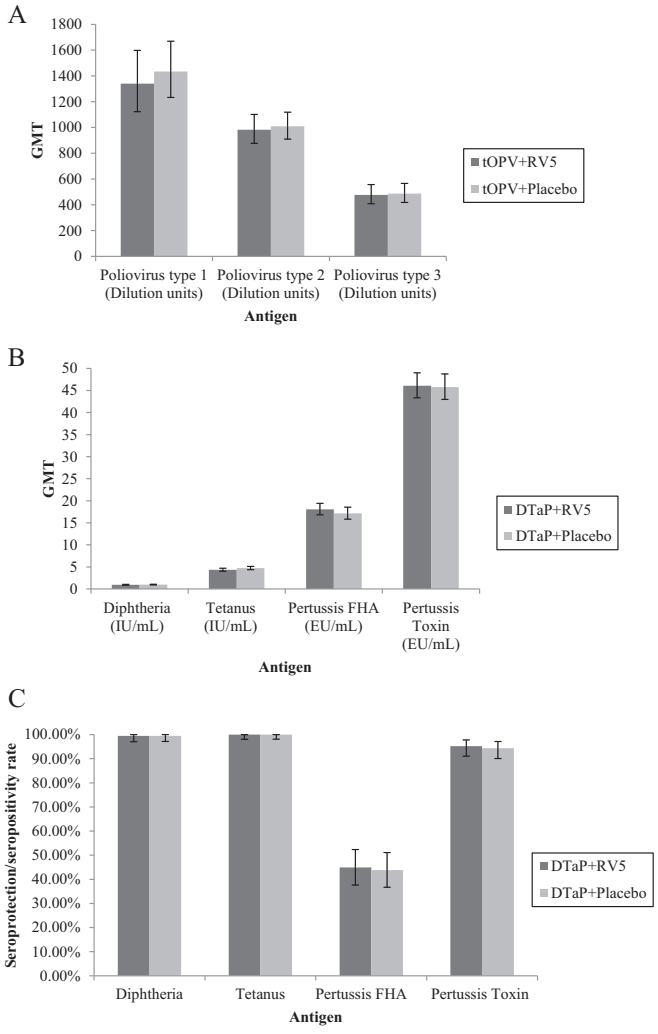

Fig. 2. Summary of immunogenicity for the concomitantly administered vaccines in the per-protocol immunogenicity populations. Brackets represent the 95% confidence intervals for the within-group measurement. (A) PD3 GMTs of neutralizing antibodies to poliovirus types 1, 2, and 3. (B) PD3 GMTs of antibodies to diphtheria, tetanus and acellular pertussis vaccine antigens. (C) PD3 seroprotection or seropositivity rates of antibodies to diphtheria, tetanus and acellular pertussis vaccine antigens.

The seroresponse rates of SNAs to the five vaccine serotypes in Chinese infants were generally lower than those observed in USA, EU, Taiwan, Korea, and Latin America [24,26–29]. However, the seroresponse rates of SNAs for most vaccine serotypes were higher than those in other Asian and African developing countries [16,17]. Despite the relatively lower immune responses to RV5 in Chinese infants compared to those in the developed countries, high efficacy of RV5 against rotavirus disease was observed in Chinese infants. The efficacy against severe RVGE with Clark score ≥17 in Chinese infants was 95.5%, which is similar to those observed in the developed countries where the same scoring system was used for the assessment of RVGE severity [15].

There are several factors that affect the immune responses to live oral vaccines, including high level of maternal antibody, immune and non-immune components of breast milk, the amount of gastric acid in the digestive tract, micronutrient malnutrition, interfering gut flora, and diarrheal and immune system diseases [30]. In addition, concomitant use of tOPV may reduce the level of some immune responses to RV5. Concomitant use of RV5 and tOPV was evaluated in a multicenter, open-label clinical study conducted in Mexico, Brazil, Costa Rica, and Guatemala, and the results showed that the GMT of anti-rotavirus IgA in the concomitant-use group was decreased by 46% compared to the staggered-use group, and the seroresponse rate of anti-rotavirus IgA in the concomitant-use group (~93%) was slightly lower, but non-inferior to that in the staggered-use group (~97%); the SNA responses to G1 and P1A[8] in the concomitant-use group were lower, but non-inferior, to those in the staggered-use group, while SNA responses to G2, G3 and G4 were generally comparable between the two vaccination groups [27]. tOPV interference was also observed for RV1 [31,32]. A similar finding was observed in the present study that both GMT and seroresponse rate of anti-rotavirus IgA in the concomitant-use group were lower than those in the staggered-use group. Based on the results of the previous studies [27,33], IgA responses induced by RV5 were mainly influenced by tOPV rather than DTaP. However, a few studies measuring immunogenicity and efficacy of RV5 and RV1 with or without concomitantly administered tOPV suggested that concomitant use of tOPV did not significantly interfere with the efficacy of rotavirus vaccines [27,31,34].

Another important immunogenicity objective of the present study was to investigate whether concomitant administration of RV5 could interfere with the immune responses to routine pediatric vaccines included in the EPI of China. In the concomitant-use group, participants received RV5 or placebo concomitantly with tOPV and DTaP. The immunogenicity data showed that concomitant use of RV5 did not interfere with the immune responses to tOPV and DTaP, which is consistent with the results of prior clinical studies in other countries [27,33,35].

To be aligned with the WHO's Polio Eradication and Endgame Strategic Plan 2013–2018, a nationwide switch from tOPV to bivalent OPV (bOPV containing poliovirus types 1 and 3) was implemented in China in May 2016, and phased introduction of at least 1 dose of IPV in China began with Beijing in December 2014 [36]. At least 1 dose of IPV has been introduced in all provinces of China in the past two years and 2-dose IPV sequential schedule or all IPV schedule will be implemented in China in the near future. However, concomitant administration of IPV and RV5 has been evaluated in the previous clinical studies and RV5 didn't show any interference with the immune responses to IPV [33,35].

One limitation of this study is that type-specific SNAs were not evaluated in the concomitant-use subgroup due to the limited volume of serum samples. Another limitation is that the immunogenicity results were from a subset of participants in the efficacy study and the participants enrolled in the immunogenicity subgroup were not randomly selected from the whole efficacy study population.

In conclusion, the present study demonstrated that 3-dose regimen of RV5 was immunogenic in Chinese infants and the immune responses induced by tOPV and DTaP were not affected by the concomitant use of RV5. These findings support the concomitant administration of tOPV and DTaP with RV5 to facilitate the vaccination schedule of infants in China.

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Conflict of interest information

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