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MAJOR ARTICLE

Safety and Immunogenicity of Sabin Strain Inactivated Poliovirus Vaccine Compared With Salk Strain Inactivated Poliovirus Vaccine, in Different Sequential Schedules With Bivalent Oral Poliovirus Vaccine: Randomized Controlled Noninferiority Clinical Trials in China

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Background. A new Sabin strain inactivated poliovirus vaccine (sIPV) proved to be immunogenic and safe in all IPV primary immunization in the previous study, with the corresponding profiles in sequential immunizations unclear.

Methods. Two clinical trials on the "IPV + 2 bivalent oral polio vaccine (2bOPV)" (Trial A) and "2IPV + bOPV" (Trial B) vaccination were conducted. Both clinical trials were randomized, controlled, double-blinded, noninferiority trials, and wild-strain IPV (wIPV) was adopted as the control vaccine. In each clinical trial, 240 healthy infants were enrolled and randomly assigned to receive sequential vaccinations containing sIPV or wIPV. Immunogenicity and safety were assessed using per-protocol and safety populations, respectively.

Results. For Trial A, the seroconversion rates in the experimental and control groups were 100% and 99.1%, respectively, against type 1; both 100.0% against type 3. For Trial B, the seroconversion rates in experimental and control groups were 99.2% and 100.0%, respectively, against type 1; both 100% against type 3. No serious adverse events related to vaccines were reported.

Conclusions. The new sIPV demonstrated an immunogenicity noninferior to that of the wIPV and a good safety profile in sequential vaccination with bOPV.

Clinical trial numbers. NCT:03822754; NCT:03822767.

Keywords. inactivated vaccine; noninferiority clinical trial; poliovirus; Sabin strain; sequential vaccination.

Poliomyelitis (polio) is a severe infectious disease that mainly affects children under 5 years old. In 1988, when the Global Polio Eradication Initiative (GPEI) was founded, polio was endemic in more than 125 countries and paralyzed 350 000 children every year. Since then, the GPEI has overseen a 99% reduction in annual polio cases [1]. The last poliomyelitis case caused by wild poliovirus type 2 (WPV2) was reported in India in 1999, and WPV2 was officially certified as eradicated in 2015. In addition, wild poliovirus type 3 (WPV3) has not been detected since 2012, when the last WPV3 poliomyelitis case was reported [2]. Today, wild poliovirus remains endemic only in 2 countries, including Afghanistan and Pakistan [3]. The world is closer than ever to being polio-free.

In the last mile toward polio eradication, the threat of vaccine-associated paralytic poliomyelitis (VAPP) and circulating vaccine-derived poliovirus (cVDPVs) became a significant concern. To eliminate all poliomyelitis including VAPP, the Polio Eradication and Endgame Strategic Plan 2013–2018 of GPEI recommended withdrawal of OPV in a phased manner starting with type 2 and the introduction of at least 1 dose of IPV in a routine immunization program, eventually converting to all-IPV immunization [4–8]. By April 2016, all 155 OPV-using countries discontinued use of Sabin poliovirus type 2 and replaced trivalent oral polio vaccine (tOPV) with bivalent oral polio vaccine (bOPV) [8]. Furthermore, developed countries that had eliminated WPV transmission shifted toward all-IPV immunization to prevent VAPP [7]. Nevertheless, the feasibility of switching to the all-IPV schedule depends on multiple

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factors, including the existing population's immunity level, the financial burden, and the IPV supply. An all-IPV schedule can cause higher vulnerability to imported wild poliovirus, especially when bordering polio-endemic countries, because of the absence of strong mucosal immunity, which can block the spread of the virus [9–11]. Besides, wild-strain IPV (wIPV) production can also pose concern for poliovirus transmission due to the potential release of vaccine strain virus, especially in developing countries where population immunity is seldom sufficiently high [12]. On the other hand, the high production cost, owing to the strict safety requirements, makes wild-strain IPV production unaffordable for developing countries, which was a barrier for production scale-up [6, 12, 13]. Actually, the IPV supply remains a serious issue and will continue to be so for several years [8, 14]. To address the above-mentioned problems, the Netherlands Vaccine Institute (NVI) has transferred technology optimized to develop Sabin strain IPV (sIPV) to several manufacturers, mainly in developing countries, to fill the gap of IPV supply with sIPV, which has a higher biosafety and reduced production cost [14, 15].

As one of the technology transfer recipients in China, Sinovac Biotech (Beijing) developed a new sIPV with proven good immunogenicity and safety in the all-sIPV schedule in the pivotal phase III clinical trial [16]. However, given the fact that "IPV then OPV" sequential schedules were adopted by many countries during the transition period before the all-IPV era, 2 supplementary phase III clinical trials on sequential vaccinations were conducted to provide enhanced evidence for the sIPV's postmarketing use.

METHODS

Study Design

As supplements of the phase III pivotal clinical trial of the new sIPV (NCT: 03526978), 2 clinical trials for different "IPV & bOPV" sequential schedules were conducted, with 1 for "IPV + 2bOPV" (Trial A: NCT:03822754) and another for "2IPV + bOPV" (Trial B: NCT: 03822767). Both were designed by Jiangsu Provincial Center for Disease Control and Prevention (CDC) and performed in Guanyun and Pizhou County of Jiangsu Province, respectively. Information from both clinical trials was registered on the Drug Clinical Trial Registration and Information Disclosure Platform of China Center for Drug Evaluation (http://www.chinadrugtrials.org.cn) before the recruitment of participants (Trial A: CTR20180526; Trial B: CTR20180599). In each clinical trial, 240 infants were randomly assigned to the experimental or control group in a 1:1 ratio and received the sequential vaccination of sIPV or the control wIPV with bOPV.

Participants

Healthy participants aged 2 months (60~90 days) were recruited in the clinics. The exclusion criteria included (1) axillary temperature >37℃; (2) acute disease within 7 days; (3) allergy to vaccine component; (4) any known immunodeficiency; (5) congenital malformation, developmental disorders, or genetic defects; (6) receipt of blood products within 3 months; (7) vaccination history of polio vaccine; (8) receipt of attenuated live vaccine within 14 days; (9) receipt of subunit or inactivated vaccine within 7 days; (10) other conditions that were deemed not suitable for study entry by the investigators.

Ethics Statement and Informed Consent

The protocols and informed consent forms were reviewed by the Ethics Committee of the Jiangsu CDC. Written informed consent was obtained from each participant's guardian before enrollment.

Randomization and Masking

Computer-generated random numbers based on a preset block length were used to mask the study vaccines. Each participant was assigned a unique number by order of entry and received the vaccine marked with the same number.

Vaccine and Vaccination

The investigational sIPV (0.5 mL/dose), developed by Sinovac Biotech, is a sterile liquid vaccine for intramuscular injection. It was generated from Sabin poliovirus type 1, type 2, and type 3 strains grown on Vero cells. The antigen contents were 15, 45, and 40 D antigen units, respectively, which was determined by enzyme linked immunosorbent assay, established based on the national standard reference of China. The vaccines were prepared in a good manufacturing practice–accredited facility and verified by the National Institute for Food and Drug Control (NIFDC) of China. The control wIPV (0.5 mL/dose) was produced by Sanofi Pasteur. Type 1 (Mahoney strain), 2 (MEF-1 strain), and 3 (Saukett strain) polioviruses grown on Vero cells were used to generate the control vaccine, with antigen contents of 40, 8, and 32 D antigen units, respectively.

Concomitant Vaccination

During the trial, routine immunization of subunit vaccines or inactivated vaccines should be separated by at least 7 days (14 days for bOPV), and that of live attenuated vaccines should be separated by at least 14 days (28 days for bOPV) from the injection of trial vaccines. Participants could receive rabies vaccine and tetanus vaccine if necessary.

Immunogenicity Assessment

About 3.0 mL of blood was drawn from each participant immediately before the first dose and 30 days after the third dose of the vaccination. After coagulation, the serum was separated, frozen, and stored at the study site at –20°C until shipment to the NIFDC, where the sera-neutralizing antibodies (NAb) were quantified using the microneutralization

test method, which is recommended by the World Health Organization (WHO), with the operators blinded to the sample groups. The primary end point was the seroconversion rate after the third dose. The secondary end points were the seroprotective rate and the geometric mean titer (GMT) of the NAb. Immunogenicity assessment was conducted based on the per-protocol population, all of whom received the 3-dose vaccination within the required time window, had the effective pre- and postvaccination sera NAb results, and did not deviate from the protocol.

Safety Assessment

For the first 7 days (14 days for bOPV), guardians of the participants were required to record the injection site adverse events (eg, pain, redness, or swelling) and systemic adverse events (eg, fever, vomiting, or diarrhea) on the diary card. For days 8–30 (days 15–30 for bOPV), the adverse events (AEs) were reported spontaneously. Data of serious adverse events (SAEs) were collected throughout the trial. The relationships between the AEs and the vaccination were determined by the investigators in blindness. Safety assessment was conducted based on the safety population, who received at least 1 dose of vaccine and provided the corresponding safety information.

Participant Compliance

Acceptably high compliance of the participants was maintained by the following measures: (1) ensuring that the recruitment guide and informed consent were brief enough to facilitate understanding; (2) thoroughly informing volunteers of study content and procedure; (3) strictly screening and enrolling participants based on the inclusion/exclusion criteria; (4) ensuring effective contact between the participants and investigators and timely disposition of the reported AEs during follow-up.

Statistical Analysis

The sample size of the study was calculated by NCSS-PASS Software (NCSS, Kaysville, UT) based on the noninferiority test for seroconversion rates of type 1 and 3 antibodies. We assumed that (1) the seroconversion rates were higher than 95%; (2) the noninferiority margin was 10%; (3) the 1-tailed α level was .025; (4) the β level was .2 with a statistical power of 90% (ie, 1-[β/2]) for each poliovirus type; (5) the withdrawal rate of the participants was no more than 15%; and (6) the number of participants in each arm was equal, which resulted in a total sample size of 240, with 120 in each arm.

Seroprotective rates were calculated based on the internationally accepted threshold value of ≥1:8. Seroconversion was defined as a change from seronegative (<1:8) to seroprotective (≥1:8) or a 4-fold

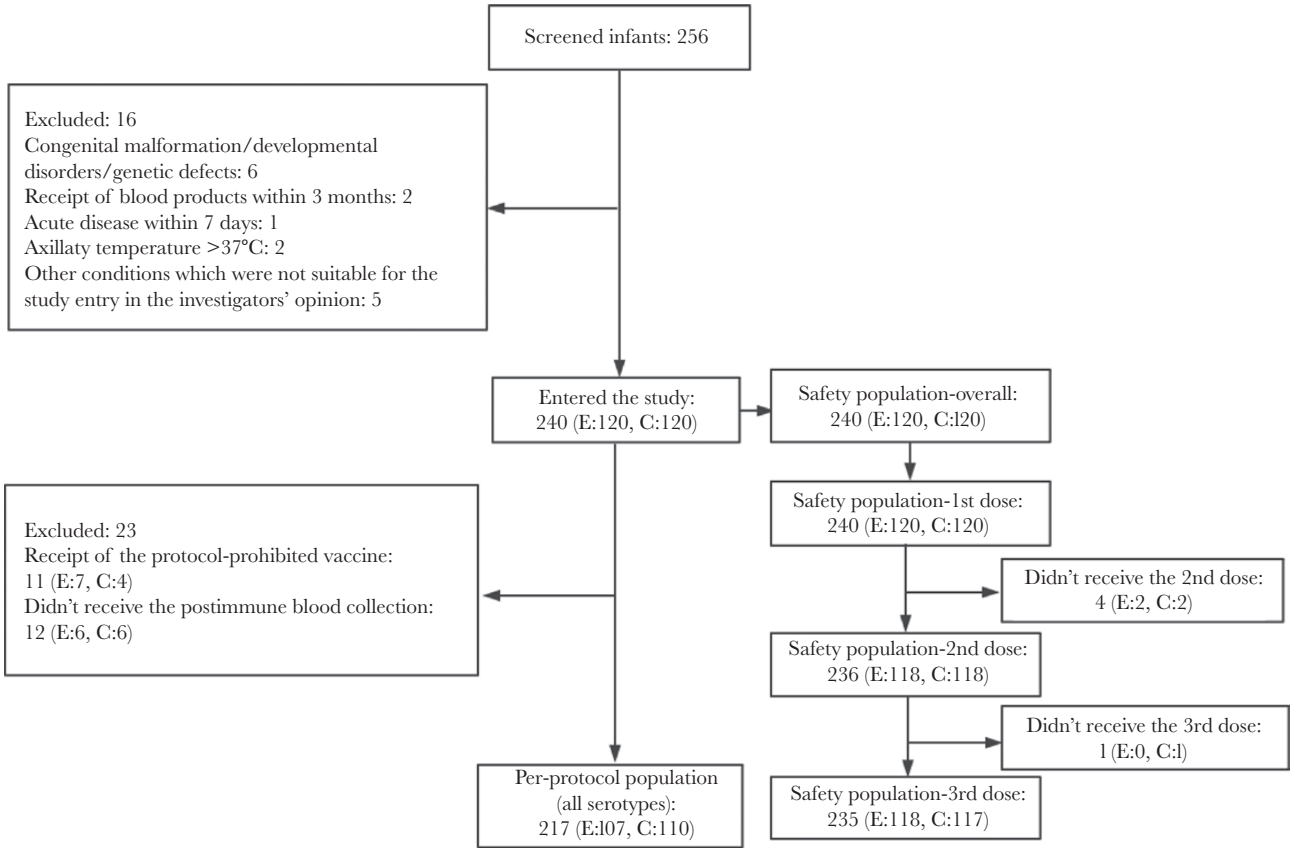

Figure 1. Profile of the clinical trial for the "IPV+2bOPV" sequential vaccination. Abbreviations: C, control group; E, experimental group.

increase from baseline titers if seroprotective. For the calculation of the seroconversion rate, the prevaccination antibodies were adjusted based on the following formula to reduce the influence of the maternal antibodies: the actual examined titers/2^n, n = intervals between the pre- and postvaccination sampling (in days)/28. The Pearson chi-square test or Fisher exact test was adopted for the analysis of binary outcomes. Where at least 1 theoretical frequency of the cross table was lower than 5, the Fisher exact test was used. Ninety-five percent confidence intervals (CIs) were computed with the Clopper Pearson method.

The NAb GMTs and their 95% CIs were calculated. Arbitrary values of 1:4 and 1:16 385 were given to the NAb titers that were below 1:8 or beyond 1:16 384, respectively, for the calculation of the GMTs. Ninety-five percent CIs of the GMT were computed based on standard normal distribution using log-transformation. The Student *t* test was adopted to compare the antibody levels between groups. All statistical analyses were performed using SAS 9.4 Software (SAS Institute, Cary, NC).

RESULTS

Study Participants

For Trial A, 256 infants were screened, 240 were recruited, and 5 dropped out during the study (2.1%). All subjects were vaccinated with at least 1 dose, and thereafter were included in the safety population. There were 217 subjects included in the per-protocol population, and the other 23 subjects who met 1 of the following conditions were excluded: (1) receipt of another vaccine within the protocol-prohibited time window; (2) did not complete postimmune blood collection (Figure 1).

For Trial B, 246 infants were screened, 240 were recruited, and 6 dropped out during the study (2.5%). All subjects were vaccinated with at least 1 dose, and thereafter were included in the safety population. There were 228 subjects included in the per-protocol population, and the other 12 subjects who met the following conditions were excluded: (1) did not finish all 3 doses of vaccination; (2) did not receive the vaccine within the required time window; (3) receipt of another vaccine within the protocol-prohibited time window (Figure 2).

No significant differences in age, sex, height, or weight were observed between groups in the safety population or the per-protocol population. No statistically significant difference for seroprotective rate or GMTs between groups was observed at enrollment (Table 1).

Immunogenicity

For Trial A, after 3 doses, the seroconversion rates in the experimental and control groups were 100% and 99.1%, respectively

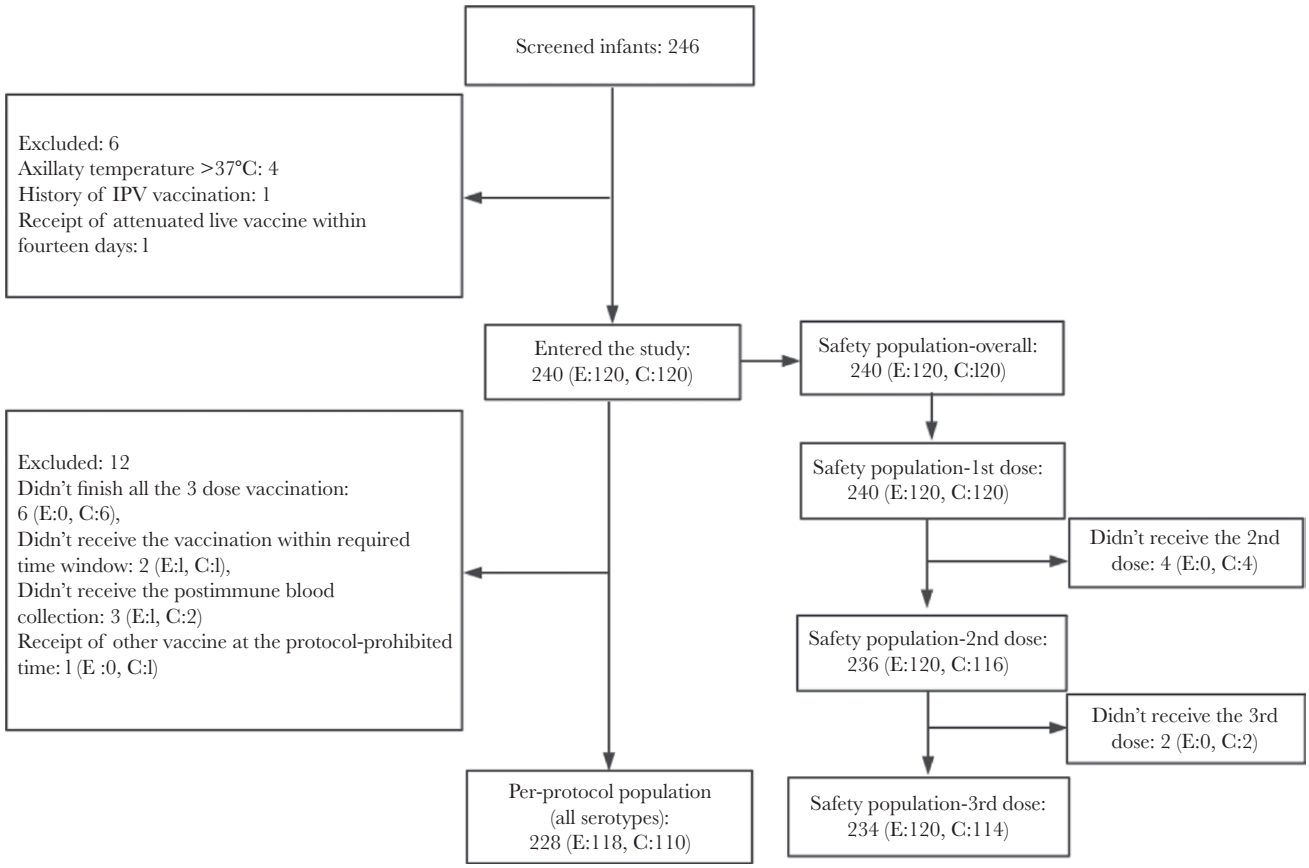

Figure 2. Profile of the clinical trial for the "2IPV+bOPV" sequential vaccination. Abbreviations: C, control group; E, experimental group.

(P = .3229), against type 1; both 100.0% against type 3; 83.2% and 78.2%, respectively (P = .3517), against type 2. For both types 1 and 3, noninferiority of the immunogenicity for the experimental group was achieved vs the control group. Among the participants who were seronegative before vaccination, the postimmune seroconversion rates against types 1 and 3 in the 2 groups were all 100%, and in the experimental and control groups, the rates were 93.2% and 88.7%, respectively (P = .5049), against type 2. The NAb GMTs (1:) in experimental and control groups were 5761.2 and 3196.8, respectively, against type 1 (P < .0001); 2074.8 and 2097.1, respectively, against type 3 (P = .9333); 27.7 and 21.9, respectively, against type 2 (P = .1466). Additionally, the fold increases of GMT (GMI) in the experimental group were significantly higher than in the control group against types 1 (P = .0003) and 2 (P = .0400) (Table 2).

For Trial B, after 3 doses, the seroconversion rates in the experimental and control group were 99.2% and 100.0%, respectively, against type 1 (P = .3332); both 100% against type 3; 94.9% and 98.2%, respectively, against type 2 (P = .0005). For both types 1 and 3, noninferiority of the immunogenicity for the experimental group was achieved vs the control group. Among the participants who were seronegative before the vaccination, the seroconversion rates against types 1 and 3 in the 2 groups were all 100%, and in the experimental and control groups, the rates were 98.4% and 100%, respectively (P = .5049), against type 2. The NAb GMTs (1:) of antibodies in the experimental and control groups were 10 119.2 and 5801.7, respectively, against type 1 (P < .0001); 7255.1 and 6124.2, respectively, against type 3 (P = .2236); 133.9 and 84.2, respectively, against type 2 (P = .0016). Additionally, the GMI of the experimental group was significantly higher than in the control group against types 1 (P = .0003) and 2 (P = .0110) (Table 2).

Safety

In Trial A, only 1 participant in the control group reported an SAE, which was infectious pneumonia unrelated to the vaccine. The proportion of participants who reported vaccine-related AEs was 65.8% (E vs C, 69.2% vs 62.5%; P = .3408) and 28.3%, 33.9%, and 41.3% after the first, second, and third doses, respectively. In Trial B, 5 participants in the control group reported SAEs unrelated to the vaccine, most of which were infectious pneumonia. The proportion of participants who reported vaccine-associated AEs was 78.8% (E vs C, 82.5% vs 75.0%; P = .2066) and 54.6%, 49.2%, and 44.0% after the first, second, and third doses, respectively. The most common vaccine-related AE was fever in both trials, with reports in 64.6% (E vs C, 68.3% vs 60.8%; P = .2802) and 74.6% (E vs C, 76.7% vs 72.5%; P = .5534) of participants in Trials A and B, respectively. All the vaccine-related AEs were

Table 1. Baseline Characteristics of Infants Participating in Clinical Trials of IPV & bOPV Sequential Vaccination in China, 2018

		Clinical Trial A: "IPV + 2bOPV"			Clinical Trial B: "2IPV + bOPV"		
Population	Characteristics	E (sIPV + 2bOPV)	C (wIPV + 2bOPV)	*P* Value	E (2sIPV + bOPV)	C (2wIPV + bOPV)	*P* Value
SP	No.	120	120	-	120	120	-
	Age, mean ± SD, d	74.2 ± 8.7	75.3 ± 8.1	.3420	75.6 ± 8.9	74.1 ± 8.4	.1909
	Male, No. (%)	68 (56.8)	63 (52.5)	.5168	56 (46.7)	52 (43.3)	.6038
	Han ethnicity, No. (%)	120 (100.0)	120 (100.0)	1.0000	120 (100.0)	120 (100.0)	1.0000
	Height, cm	59.8 ± 3.0	59.9 ± 2.4	.7012	60.3 ± 2.7	60.2 ± 2.4	.8276
	Weight, kg	6.2 ± 0.9	6.2 ± 0.8	.7428	6.2 ± 0.8	6.1 ± 0.8	.2969
PPP	No.	107	110	-	118	110	-
	Age, mean ± SD, d	74.0 ± 8.8	75.4 ± 8.2	.2278	75.6 ± 9.0	74.4 ± 8.4	.2966
	Male, No. (%)	59 (55.1)	55 (50.0)	.4484	55 (46.6)	46 (41.8)	.4667
	Han ethnicity, No. (%)	107 (100.0)	110 (100.0)	1.0000	118 (100.0)	110 (100.0)	1.0000
	Height, cm	59.6 ± 3.0	59.8 ± 2.5	.4541	60.2 ± 2.7	60.0 ± 2.2	.6440
	Weight, kg	6.1 ± 0.9	6.2 ± 0.8	.8134	6.2 ± 0.8	6.1 ± 0.8	.2390
	Poliovirus type 1						
	Seroprotective, no	71	66		72	67	
	Seroprotective rate (95% CI), %	66.4 (56.6 to 75.2)	60.0 (50.2 to 69.2)	.3320	61.0 (51.6 to 69.9)	60.9 (51.1 to 70.1)	.9867
	GMT (1:) (95% CI)	13.2 (10.6 to 16.4)	12.3 (9.7 to 15.6)	.6792	12.2 (10.0 to 14.9)	12.8 (10.2 to 16.0)	.7456
	Poliovirus type 3						
	Seroprotective, no	30	29		39	31	
	Seroprotective rate (95% CI), %	28.0 (19.8 to 37.6)	26.4 (18.4 to 35.6)	.7817	33.1 (24.7 to 42.3)	28.2 (20.0 to 37.6)	.4258
	GMT (1:) (95% CI)	6.5 (5.4 to 7.7)	6.3 (5.3 to 7.5)	.8222	6.5 (5.6 to 7.6)	6.2 (5.3 to 7.3)	.6429
	Poliovirus type 2						
	Seroprotective, no	63	57		57	55	
	Seroprotective rate (95% CI), %	58.9 (49.0 to 68.3)	51.8 (42.1 to 61.5)	.2956	48.3 (39.0 to 57.7)	50.0 (40.3 to 59.7)	.7981
	GMT (1:) (95% CI)	10.2 (8.5 to 12.3)	10.2 (8.3 to 12.5)	.9739	8.3 (7.0 to 9.8)	8.2 (7.0 to 9.6)	.9172

Abbreviations: bOPV, bivalent oral polio vaccine; C, control group; CI, confidence interval; E, experimental group; GMT, geometric mean titer; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine; PPP, per-protocol population; sIPV, Sabin strain inactivated poliovirus vaccine; SP, safety population; wIPV, wild-strain inactivated poliovirus vaccine.

Table 2. Immunogenicity Among Study Participants After IPV & bOPV Sequential Vaccination

	Clinical Trial A: "IPV + 2bOPV"					Clinical Trial B: "2IPV + bOPV"				
	E (n = 107) sIPV + 2bOPV	C (n = 110) wIPV + 2bOPV	*P* Value	Difference (95% CI)	Noninferiority	E (n = 118) 2sIPV + bOPV	C (n = 110) 2wIPV + bOPV	*P* Value	Difference (95% CI)	Noninferiority
Poliovirus type 1										
Seroprotective rate (95% CI), %	100.0 (96.6 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.4)	Yes	100.0 (96.9 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.1)	Yes
Seroconversion rate (95% CI), %	100.0 (96.6 to 100.0)	99.1 (95.0 to 100.0)	.3229	0.9 (–0.9 to 2.7)	Yes	99.2 (95.4 to 100.0)	100.0 (96.7 to 100.0)	.3332	–0.9 (–2.5 to 0.8)	Yes
GMT (1:) (95% CI)	5761.2 (4847.5 to 6847.2)	3196.8 (2745.8 to 3721.7)	<.0001	–	–	10 119.2 (8464.0 to 12 098.0)	5801.7 (4848.1 to 6942.8)	<.0001	–	–
GMI (95% CI)	1802.3 (1397.3 to 2324.6)	924.4 (719.0 to 1188.3)	.0003	–	–	3259.7 (2565.1 to 4142.2)	1768.3 (1408.2 to 2220.6)	.0003	–	–
Poliovirus type 3										
Seroprotective rate (95% CI), %	100.0 (96.6 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.4)	Yes	100.0 (96.9 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.1)	Yes
Seroconversion rate (95% CI), %	100.0 (96.6 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.4)	Yes	100.0 (96.9 to 100.0)	100.0 (96.7 to 100.0)	1.0000	0.0 (–3.3 to 3.1)	Yes
GMT (1:) (95% CI)	2074.8 (1700.3 to 2531.6)	2097.1 (1791.1 to 2455.4)	.9333	–	–	7255.1 (6093.8 to 8637.7)	6124.2 (4939.9 to 7592.4)	.2236	–	–
GMI (95% CI)	584.6 (464.7 to 735.3)	580.2 (479.7 to 702.0)	.9606	–	–	2323.00 (1855.7 to 2908.0)	1844.76 (1447.6 to 2350.8)	.1678	–	–
Poliovirus type 2				–						
Seroprotective rate (95% CI), %	87.9 (80.1 to 93.4)	88.2 (80.6 to 93.6)	.9401	–	–	99.2 (95.4 to 100.0)	100.0 (96.7 to 100.0)	1.0000	–	–
Seroconversion rate (95% CI), %	83.2 (74.7 to 89.7)	78.2 (69.3 to 85.5)	.3517	–	–	94.9 (89.26 to 98.11)	98.2 (93.59 to 99.78)	.0005	–	–
GMT (1:) (95% CI)	27.7 (21.6 to 35.5)	21.9 (18.0 to 26.8)	.1466	–	–	133.9 (108.7 to 164.9)	84.2 (69.2 to 102.6)	.0016	–	–
GMI (95% CI)	9.4 (7.1 to 12.5)	6.4 (5.0 to 8.1)	.0400	–	–	47.9 (37.5 to 61.1)	31.5 (25.4 to 38.9)	.0110	–	–

Abbreviations: bOPV, bivalent oral polio vaccine; C, control group; CI, confidence interval; E, experimental group; GMI, fold increases of geometric mean titer; GMT, geometric mean titer; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine; sIPV, Sabin strain inactivated poliovirus vaccine; wIPV, wild-strain inactivated poliovirus vaccine.

Table 3. Safety Profiles After the IPV& bOPV Sequential Vaccination

	Clinical Trial A: "IPV + 2bOPV"				Clinical Trial B: "2IPV + bOPV"			
	E (n = 120) sIPV + 2bOPV	C (n = 120) wIPV + 2bOPV	Total (n = 240)	*P* Value	E (n = 120) 2sIPV + bOPV	C (n = 120) 2wIPV + bOPV	Total (n = 240)	*P* Value
SAEs, No. (%)	0 (0.0)	1 (0.8)	1 (0.4)	1.0000	0 (0.0)	5 (4.2)	5 (2.1)	.0599
Vaccine-related AEs, No. (%)	83 (69.2)	75 (62.5)	158 (65.8)	.3408	99 (82.5)	90 (75.0)	189 (78.8)	.2066
Injection site, No. (%)								
Redness	0 (0.0)	0 (0.0)	0 (0.0)	-	4 (3.3)	3 (2.5)	7 (3.0)	1.0000
Induration	0 (0.0)	0 (0.0)	0 (0.0)	-	2 (1.7)	0 (0.0)	2 (0.8)	0.4979
Swelling	0 (0.0)	0 (0.0)	0 (0.0)	-	2 (1.7)	0 (0.0)	2 (0.8)	.4979
Systemic, No. (%)								
Fever	82 (68.3)	73 (60.8)	155 (64.6)	.2802	92 (76.7)	87 (72.5)	179 (74.6)	.5534
Diarrhea	5 (4.2)	7 (5.8)	12 (5.0)	.7686	27 (22.5)	23 (19.2)	50 (20.8)	.6338
Vomiting	2 (1.7)	2 (1.7)	4 (1.7)	1.0000	11 (9.2)	7 (5.8)	18 (7.5)	.4632
Inappetence	1 (0.8)	0 (0.0)	1 (0.4)	1.0000	12 (10.0)	8 (6.7)	20 (8.3)	.4844
Activity decline	0 (0.0)	1 (0.8)	1 (0.4)	1.0000	9 (7.5)	7 (5.8)	16 (6.7)	.7967
Allergy	0 (0.0)	0 (0.0)	0 (0.0)	-	1 (0.8)	1 (0.8)	2 (0.8)	1.0000

Abbreviations: AE, adverse event; bOPV, bivalent oral polio vaccine; C, control group; E, experimental group; IPV, inactivated poliovirus vaccine; OPV, oral polio vaccine; SAE, severe adverse event; sIPV, Sabin strain inactivated poliovirus vaccine; wIPV, wild-strain inactivated poliovirus vaccine.

solicited, and most of them were minor or moderate and self-healing within 1 week (Table 3).

DISCUSSION

The investigational sIPV manifested good safety profiles in sequential schedules with bOPV. The postimmune seroprotective rates and seroconversion rates against poliovirus types 1 and 3 were all >99%. The good immunogenicity of the "IPV & OPV" immunization was in accordance with historical findings in China and Chile [17–19]. Combined with the previous phase III study of the all-sIPV immunization, the new sIPV proved noninferiority to the commercial IPV in various vaccination schedules.

After the "2IPV + bOPV" schedule, the GMTs of the experimental group were noticeably higher than those of the control group for all serotypes. The sIPV can generate higher GMTs than wIPV, which has been demonstrated in other studies [16, 20]. As the serum-neutralizing assay was conducted using the Sabin strain virus, the sIPV antibodies had a stronger neutralizing capacity than the vaccine strain virus, which may explain the higher GMT in the experimental group in these studies.

Combined with our previous phase III study, we found that the GMTs after different primary vaccination schedules demonstrated a specific trend: "2sIPV + bOPV" > "sIPV + 2bOPV" > "sIPV only." The same trend was also detected for the wIPV [17]. Furthermore, Tang's study based on a meta-analysis reported that the GMTs were superior in sequential "IPV & OPV" schedules, which is in accordance with our findings [21].

It was shown that both the 1- and 2-dose sIPV sequential schedules can induce good immunogenicity against types 1 and 3; however, the former schedule induced a type 2 seroconversion rate <60%. One-dose sIPV cannot confer sufficient immunity for type 2, which poses concern for the countries at continuous importation risk of VDPV2. For example, China implemented the conversion from a 1- to a 2-dose IPV schedule at the beginning of 2019 to elevate immunity against type 2 poliovirus. Monovalent OPV2 and IPV should be reserved to cope with the outbreaks, especially for the countries that use 1-dose IPV for their routine vaccination.

There are several limitations to this study. First, the results of different vaccination schedules were obtained from separate clinical trials conducted in 2 different fields, which may have an impact on the comparability between different schedules to some degree. However, both clinical trials were designed by the same primary investigators and conducted simultaneously in the same province, ensuring the homogeneity to the utmost extent. Second, the sample size in this study was estimated based on the NAb seroconversion rates against type 1 and type 3 polioviruses, the main observation end points of this study, so the current sample size was not sufficient to examine the noninferiority of sIPV-induced immunogenicity against type 2. Third, the cross-neutralizing capacity of sIPV against the wild-strain virus was not revealed by this study; however, this will be examined in our future work.

In summary, this study revealed the good immunogenicity and safety of the new sIPV in sequential schedules with bOPV. Combined with previous work, it can be concluded that the new sIPV is comparable to commercial wIPV both in the all-IPV and IPV-OPV sequential schedules. The investigational sIPV could be an alternative to IPV in multiple vaccination strategies.

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