Immune persistence of an inactivated poliovirus vaccine derived from the Sabin strain: a 10-year follow-up of a phase 3 study

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Summary

Background In a previous phase 3 clinical trial, we showed that an inactivated poliovirus vaccine derived from the Sabin strain (sIPV) can induce neutralising antibodies against currently circulating and reference wild poliovirus strains. However, the immune persistence of sIPV remains to be evaluated.

Methods In this study, 400 participants who were eligible for an early phase 3 clinical trial (Jan 1, 2012–Aug 31, 2014) in Pingle County, GuanXi Province, China, were initially involved in one site. Of the participants in the previous phase 3 clinical trial, sera of 287, 262, 237, and 207 participants were sampled at the ages of 4, 6, 8, and 10 years, respectively, after the prime-boost regimen. Neutralising antibodies against attenuated Sabin strains were detected using these serum samples to determine immune persistence. The serum neutralising antibodies titre of 1:8 against poliovirus types 1, 2, and 3 is considered to be a seroprotection level for polio. The trial is registered at ClinicalTrials.gov, NCT01510366.

Findings The protective rates against poliovirus types 1, 2, and 3 in the sIPV group were all 100% at 10 years after the booster immunisation, compared with 98.1%, 100%, and 97.1%, respectively, in the wIPV control group after 10 years. After the booster at 18 months, the geometric mean titres (GMTs) of neutralising antibodies against poliovirus types 1, 2, and 3 in the sIPV group were 13,265.6, 7856.7, and 6432.2, respectively, and the GMTs in the control group (inoculated with inactivated poliovirus vaccine derived from wild strain (wIPV)) were 3915.6, 2842.6, and 4982.7, respectively. With increasing time after booster immunisation, the GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 gradually decreased in both the sIPV and wIPV groups. At the age of ten years, the GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 in the sIPV group were 452.3, 392.8, and 347.5, respectively, and the GMTs in the wIPV group 108.5, 154.8, and 229.3, respectively, which were still at a higher-than-protective level (1:8).

Interpretation Both sIPV and wIPV maintained sufficiently high immune persistence against poliovirus types 1, 2, and 3 for at least 10 years after booster immunisation.

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Translation: For the Chinese translation of the abstract see Supplementary Materials section.

Keywords: Inactivated poliovirus vaccine (IPV); IPV produced using wild poliovirus seed strains (wIPV); IPV derived from the Sabin strain (sIPV); Immune persistence

Research in context

Evidence before this study

We did not perform a literature search before starting this work, due to being the original creators of relevant research. Despite this, the evidence before this study is that the immune persistence of sIPV remains unknown. We showed that an inactivated poliovirus vaccine derived from the Sabin strain (sIPV) can induce neutralising antibodies against circulating and reference wild poliovirus strains.

Added value of this study

Our findings show that sIPV maintained sufficiently high immune persistence against poliovirus types 1, 2, and 3 for at least 10 years after booster immunisation, which was not numerically inferior to those induced by inactivated poliovirus vaccine produced using wild poliovirus seed strains (wIPV).

Implications of all the available evidence

Although these findings suggest that the preparation of inactivated poliovirus vaccines using attenuated Sabin strains is feasible, the effectiveness of sIPV still needs to be further validated through large-scale population vaccination trials.

Introduction

Poliomyelitis is a serious viral disease that typically infects children under 5 years of age and is expected to be the second human viral disease to be eradicated by vaccination strategies after smallpox.[1–3] Recently, sporadic cases of type 1 wild poliovirus have been reported in Afghanistan and Pakistan.[4] Wild poliovirus type 2 and type 3 were globally certified as eradicated in 2015 and 2019, respectively.[5,6] However, in 2022, circulating vaccine-derived poliovirus (cVDPV) was detected in sewage samples in London; one cVDPV2 case was reported in New York, which is the first paralytic poliomyelitis case in the United States since 2013.[7–9] Although the episodes of cVDPV are rare, cVDPV outbreaks resulted in nearly 800 cases over the past ten years globally.[10] Because oral poliovirus vaccine (OPV) can cause vaccine-associated paralytic poliomyelitis (VAPP), inactivated poliovirus vaccine (IPV) might be a better alternative vaccine, and it has practical significance to protect infants against polioviruses after the cessation of OPV and global eradication of wild polioviruses.[11–13]

In May 2008, the World Health Assembly resolution 61.1 requested that the Director-General of the WHO develop appropriate strategies for the management of potential risks to poliomyelitis eradication.[14] The Sabin strain IPV (sIPV) is recommended for use in developing countries and regions according to the 2013 Polio Eradication and Endgame Strategic Plan and has been used in China since 2015.[15–17] According to a phase 3 clinical trial of sIPV conducted at our institute, a three-dose primary immunisation with sIPV administered to 2-, 3-, and 4-month-old infants induced a good immune response, and the geometric mean titres (GMTs) of type 1, 2, and 3 neutralising antibodies were greatly increased by booster immunisation in 18-month-old children.[18] Furthermore, a clinical trial of sIPV conducted by our institute showed that sIPV had good safety in large-scale populations.[19] However, the persistence of serum-neutralising antibodies after completing the primary and booster regimens of sIPV is unclear.[20]

In this study, the serum neutralising antibody levels of participants who had completed the primary and booster regimens in a previous phase 3 clinical trial were evaluated.[18] Serum samples were collected from children at the ages of 4, 6, 8, and 10 years. Protective rates and GMTs of neutralising antibodies against polio types 1, 2, and 3 in the sIPV and inactivated poliovirus vaccine derived from wild strain (wIPV) groups were analysed.

Methods

Study design

The protocol is provided in the Supplementary Materials. This is a long-term follow-up study of the previous phase 3 clinical trial, and the aim of this report was to determine the immune persistence of sIPV.[18] At a significance level of $\alpha = 0.05$, we used the following function to estimate sample size: $n = (1.65^*/M)^2\rho\,(1\text{-}\rho)$. The margin of error was set at 7%, and an estimated value of the proportion was set at 90%; thus, the minimum sample size in each vaccine group at each age was calculated to be 84. In this study, 400 participants who were eligible for an early phase 3 clinical trial in Pingle County, GuanXi Province, China, were initially involved.[18] Venous blood samples were collected at the ages of 4, 6, 8, and 10 years from 139, 124, 109, and 102 participants in the sIPV group and 148, 138, 128, and 105 participants in the control wIPV group, respectively, to determine the neutralising antibody titres against poliovirus types 1, 2, and 3. The participants involved in this immune persistence study were detailed in Fig. 1.

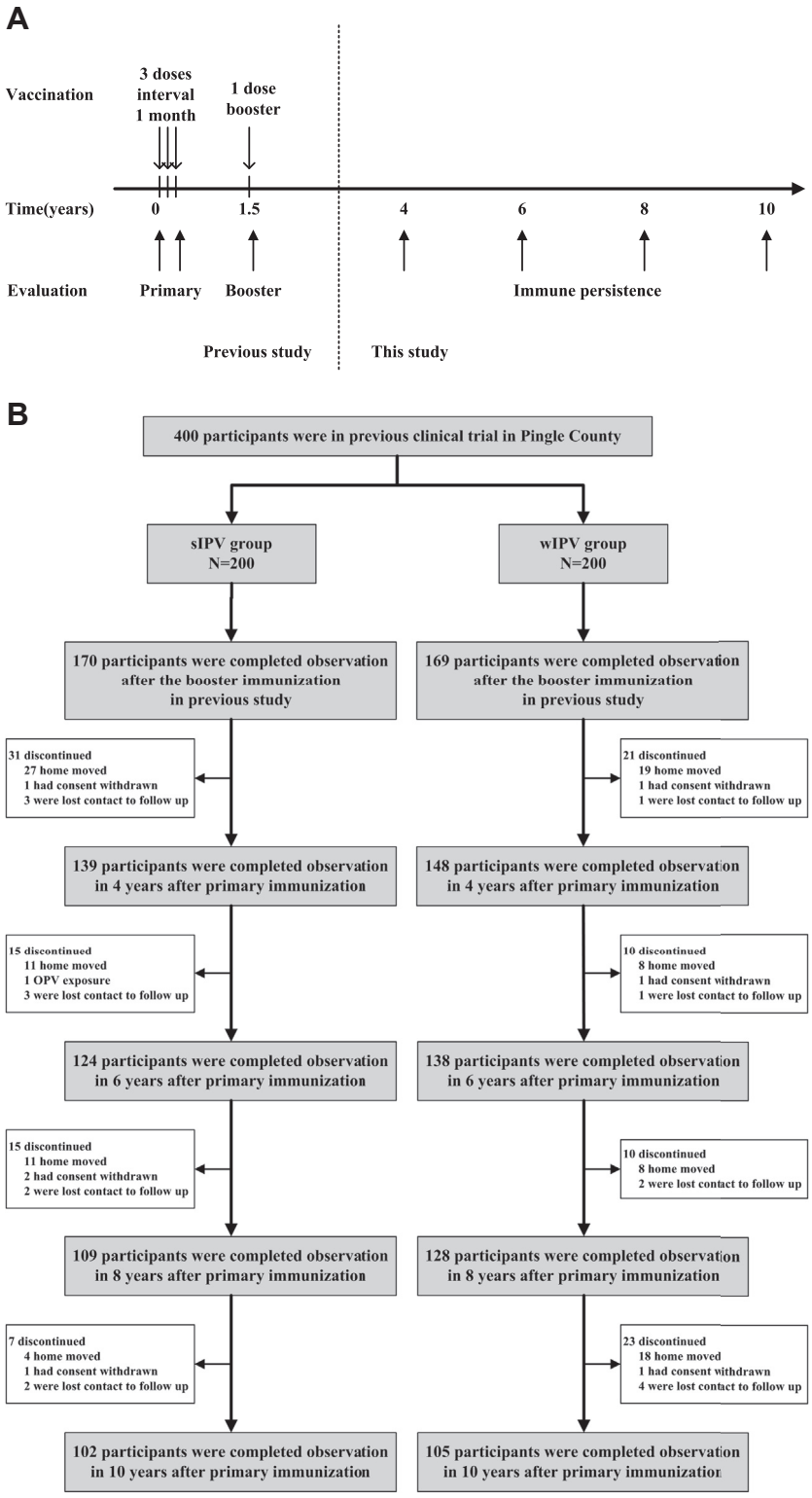

Fig. 1: Study design (A) and participant flow (B). (A) Prime-boost regimen and immune persistence study of the sIPV clinical trial. (B) Flow chart of the clinical sIPV immune persistence study.

Ethics

The study was designed by the Institute of Medical Biology, Chinese Academy of Medical Biology, and the Centre for Disease Control and Prevention, Guangxi Zhuang Autonomous Region (Guangxi CDC), and assessed by the National Institutes for Food and Drug Control. The trial was registered at ClinicalTrials.gov (NCT01510366) and conducted with approval by the Ethics Committee of Guangxi CDC (GXIRB2015-0029). An informed consent form was signed by the guardians of all participants, based on the principle of written informed consent and voluntary participation.

Vaccines

sIPV was generated from types 1 and 2 Sabin poliovirus strains, working seed lots of Sabin SO+2 and the type 3 strain of RSO2 (Pfizer) and grown in Vero cells attached to Cytodex 1 microcarriers in a 550 L bioreactor. The vaccines were prepared in a GMP-accredited facility and approved by the National Institutes for Food and Drug Control, China (approval number SZ201101226). The control wIPV was purchased from Sanofi-Pasteur (lot number H0059-1). The vaccination procedure and the results of booster immunisation were part of a previous phase 3 clinical trial.[18,21]

Neutralisation test

The neutralisation assay was performed by the National Institutes for Food and Drug Control. The titres of neutralising antibodies against poliovirus types 1, 2, and 3 were determined by microneutralisation assay, according to the Manual for the Virological Investigation of Polio.[22] Briefly, samples were serially diluted twofold and neutralised for 3 h at 35 °C using a 100 cell culture infective dose ($CCID_{50}$) of Sabin strain poliovirus type 1, 2, or 3 in 96-well plates. Hep-2 cells (0.1 ml of 15,000 cells per well) were added to the serum/virus mixture. After incubation for 7 days, cytopathic effects (CPEs) were observed.

Statistical analysis

Ages are presented as medians with 1st and 3rd quartiles. Protective rates are presented as percentages with 95% confidence intervals (95% CIs). We assigned neutralising antibody titres below the limit of detection (i.e., 1:8) an arbitrary value of 1:4. The neutralising antibody titres were converted into $\log_2$ titres to calculate geometric mean titres (GMTs) and 95% CIs. Reduction times of GMTs were calculated as GMTs at 30 days after the booster divided by GMTs at 4, 6, 8, or 10 years old. Differences between groups were examined using the Mann–Whitney U test, independent-samples t test, or Fisher's exact test according to the distribution characteristics of the data. Statistical analyses were performed using SPSS V.23.0 (SPSS, Chicago, Illinois, USA). p values of <0.05 were considered to reflect statistical significance. We used the CONSORT checklist when writing our report.[23]

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report.

Results

Participants

The prime-boost regimen of the previous phase 3 study and the serum sampling time points for immune persistence evaluation in this study are shown in Fig. 1A.[18] As shown in Fig. 1B, 170 participants in the sIPV group and 169 participants in the control wIPV group completed the booster observation at 18 months of age in the previous phase 3 clinical trial. A total of 139, 124, 109, and 102 participants in the sIPV group completed serum sampling at 4, 6, 8, and 10 years after the primary immunisation, respectively; 148, 138, 128, and 105 participants in the control wIPV group provided serum samples at 4, 6, 8, and 10 years after the primary immunisation, respectively. The participants available for serum samples were included in this immune persistence evaluation study. The reasons for drop-out during follow-up include loss of contact, change in home address, consent withdrawn and OPV exposure. There were no significant differences in gender ratio, age, or body weight between the two groups (Table 1).

Protective rates

As shown in Table 2, 30 days after booster immunisation in the previous study,[18] 100% protective rates against poliovirus types 1, 2, and 3 were observed in both the sIPV and wIPV groups.

At the age of four years, 100% protective rates were observed in the sIPV group for poliovirus types 1, 2, or 3. In the wIPV group, 100%, 100%, and 99.1% protective rates against poliovirus types 1, 2, and 3, respectively, were observed.

At the age of six years, 100% of participants in the sIPV group possessed neutralising antibodies against poliovirus types 1, 2, and 3. In the control group, 100%, 100%, and 98.1% of participants possessed neutralising antibodies against poliovirus types 1, 2, and 3, respectively.

At the age of eight years, 100% of participants in the sIPV group maintained neutralising antibodies against poliovirus types 1, 2, and 3. In the control group, 99.1%, 100%, and 98.1% participants possessed neutralising antibodies against poliovirus types 1, 2, and 3, respectively.

At the age of ten years, the protective rates against poliovirus types 1, 2, and 3 were still 100% in the sIPV

	sIPV group, N = 102	wIPV group, N = 105	p value
Male, number (%)	52 (51.0)	53 (50.5)	0.942
Female, number (%)	50 (49.0)	52 (49.5)	0.942
Age, years, median (1st quartile, 3rd quartile)			
4 years	4.0 (4.0, 4.1)	4.0 (3.9, 4.1)	0.538
6 years	6.0 (6.0., 6.1)	6.0 (6.0, 6.1)	0.540
8 years	8.0 (7.9, 8.1)	8.0 (7.9, 8.0)	0.733
10 years	10.1 (10.0, 10.2)	10.1 (10.0, 10.1)	0.538
Weight, kg, median (1st quartile, 3rd quartile)			
4 years	15.3 (15.0, 15.6)	15.3 (15.0, 15.7)	0.923
6 years	19.7 (19.2, 20.1)	19.8 (19.3, 20.3)	0.757
8 years	24.1 (23.4, 24.7)	24.5 (23.6, 25.4)	0.446
10 years	30.7 (30.0, 31.5)	31.3 (30.3, 32.2)	0.377

Table 1: **Participant characteristics.**

Types	sIPV group, % (95% CI), N = 102	wIPV group, % (95% CI), N = 105	p value
Type 1			
30 days after booster	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 4 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 6 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 8 years	100.0 (96.4–100.0)	99.1 (94.8–99.8)	1.000
Age of 10 years	100.0 (96.4–100.0)	98.1 (93.3–99.5)	0.498
Type 2			
30 days after booster	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 4 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 6 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 8 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 10 years	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Type 3			
30 days after booster	100.0 (96.4–100.0)	100.0 (96.5–100.0)	1.000
Age of 4 years	100.0 (96.4–100.0)	99.1 (94.8–99.8)	1.000
Age of 6 years	100.0 (96.4–100.0)	98.1 (93.3–99.5)	0.498
Age of 8 years	100.0 (96.4–100.0)	98.1 (93.3–99.5)	0.498
Age of 10 years	100.0 (96.4–100.0)	97.1 (91.9–99.0)	0.247

Note: A serum neutralising antibody titre of 1:8 is considered to be a level of effective antibody protection against poliovirus. *p* values were calculated with Fisher's exact test.

Table 2: **Protective rates against poliovirus types 1, 2, and 3 at the ages of 4, 6, 8, and 10 years.**

group. In the wIPV group, 98.1%, 100%, and 97.1% protective rates against poliovirus types 1, 2, and 3, respectively, were observed. Therefore, the protective rates in the sIPV group were not numerically inferior to those in the wIPV group.

Neutralising antibody titres

The GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 in children were high on Day 30 after booster immunisation in the previous study.[18] Over time, the titres of neutralising antibodies against poliovirus types 1, 2, and 3 decreased gradually in both the sIPV and wIPV groups (Table 3). At the age of ten years, the GMTs of neutralising antibodies in the sIPV group were 1:452.3 for type 1, 1:392.8 for type 2 and 1:347.5 for type 3. A similar trend was observed in the wIPV group (1:108.5 for type 1, 1:154.8 for type 2 and 1:229.3 type 3) (Table 3). However, the GMTs of both the sIPV and wIPV groups at the age of 10 years were far above the level for conferring protection (≥1:8).

The GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 in the sIPV group were significantly higher than the GMTs in the wIPV group at each time point except for type 3 at the age of 4 years (Table 3). There were no significant differences in the reduction times of GMTs between the two groups except GMTs against poliovirus type 2 at the age of four years,

Types	GMTs (1:X), 95% CI			Reduction times of GMTs, 95% CI		
	sIPV group, N = 102	wIPV group, N = 105	*p* value	sIPV group, N = 102	wIPV group, N = 105	*p* value
Type 1						
30 days after booster	13265.6 (11915.9–14768.1)	3915.6 (3351.5–4574.2)	0.000	–	–	–
Age of 4 years	2593.4 (2023.7–3323.1)	692.1 (559.6–856.0)	0.000	5.1 (4.0–6.6)	5.7 (4.4–7.3)	0.575
Age of 6 years	2398.5 (1991.9–2888.3)	649.3 (550.7–765.6)	0.000	5.5 (4.6–6.7)	6.0 (5.0–7.3)	0.523
Age of 8 years	504.2 (407.7–623.5)	147.4 (124.9–174.1)	0.000	26.3 (21.4–32.4)	26.6 (21.9–32.2)	0.948
Age of 10 years	452.3 (378.3–540.6)	108.5 (89.9–130.8)	0.000	29.3 (24.5–35.1)	36.1 (28.6–45.6)	0.165
Type 2						
30 days after booster	7856.7 (6738.9–9160.4)	2842.6 (2385.2–3387.7)	0.000	–	–	–
Age of 4 years	645.1 (486.7–855.1)	356.7 (294.3–432.4)	0.001	12.2 (9.0–16.4)	8.0 (6.2–10.2)	0.030
Age of 6 years	477.3 (396.1–575.0)	209.1 (172.8–253.0)	0.000	16.5 (13.7–19.8)	13.6 (10.8–17.1)	0.200
Age of 8 years	466.3 (389.9–557.6)	195.8 (161.2–237.8)	0.000	16.9 (14.0–20.3)	14.5 (11.4–18.4)	0.332
Age of 10 years	392.8 (322.4–478.5)	154.8 (128.0–187.3)	0.000	20.0 (16.5–24.3)	18.4 (14.4–23.4)	0.585
Type 3						
30 days after booster	6432.2 (5524.8–7489.2)	4982.7 (4293.4–5782.6)	0.018	–	–	–
Age of 4 years	672.0 (522.8–863.6)	549.7 (433.1–697.8)	0.251	9.6 (7.4–12.4)	9.1 (7.0–11.7)	0.763
Age of 6 years	507.4 (413.7–622.3)	300.3 (233.1–386.4)	0.002	12.7 (10.4–15.4)	16.6 (13.4–20.6)	0.070
Age of 8 years	415.5 (340.8–506.6)	273.2 (212.7–350.9)	0.010	15.5 (12.8–18.8)	18.2 (14.7–22.6)	0.264
Age of 10 years	347.5 (275.0–439.2)	229.3 (176.7–297.6)	0.020	18.5 (14.8–23.1)	21.7 (17.3–27.3)	0.321

Table 3: **GMTs and reduction times of neutralising antibodies against poliovirus types 1, 2, and 3 at the ages of 4, 6, 8, and 10 years.**

in which the reduction times of GMTs in the sIPV group were higher than those in the wIPV group (Table 3).

Neutralising antibody titres at the ages of 4, 6, 8, and 10 years were further visualised as reverse cumulative distribution curves. The shape and distribution of the curves of the sIPV and wIPV groups were consistent with the data shown in Table 3 (Figs. 2 and 3).

Discussion

In the post-poliomyelitis eradication era, cessation of OPV is scheduled according to WHO guidelines.[24–26] However, cessation of OPV decreases the population immunity level.[27,28] Although a previous phase 3 clinical trial showed the substitutability of IPV in China,[18,27] its immune persistence remained unclear. Therefore, we evaluated the neutralising antibody persistence of sIPV over 10 years in children who had completed the phase 3 clinical trial.

Our study showed that the protective rates and neutralising antibody titres induced by sIPV against poliovirus types 1, 2, and 3 were maintained for at least 10 years and were not numerically inferior to those induced by wIPV. The use of IPV could prevent all types of polio and VAPP in China.[29,30] This study showed that sIPV induces good antibody persistence and is thus an alternative substitute for OPV.

In this study, there were significant differences in the GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 between the two groups from the time of booster immunisation to the age of 10 years, except for that of poliovirus type 3 at the age of 4 years. This was likely because the detecting strain used in our neutralisation assay was the attenuated Sabin strain, since serum samples obtained from participants in the previous phase II trial had a similar capacity to neutralise different circulating wild strains between the sIPV group and wIPV group.[31] Further analyses indicated that the downtrend of 10-year neutralising antibody persistence was not significantly different between the sIPV group and wIPV group except for GMTs against poliovirus type 2 at the age of four years. At four years after booster immunisation, the GMTs of neutralising antibodies against poliovirus types 1, 2, and 3 decreased rapidly (80.5%–91.8% reduction in the sIPV group and 82.3%–89.0% reduction in the wIPV group). From the age of 6–10 years after booster immunisation, the decrease in GMTs slowed for poliovirus types 1, 2, and 3 (2.3%–79.0% reduction in the sIPV group, 6.2%–77.3% reduction in the wIPV group). However, the GMTs of poliovirus types 1, 2, and 3 in both groups were maintained at a higher-than-protective level (1:8) at the age of 10 years (1:347.5–452.3 in the sIPV group and 1:108.5–229.3 in the wIPV group).

China began to produce OPV in 1960, and circulating Sabin strains in the environment might have enhanced the immunity among participants.[32,33] Although the GMTs of neutralising antibodies did not indicate that the overall antibody levels increased over time in either the sIPV or wIPV groups, the levels of neutralising antibodies in some participants

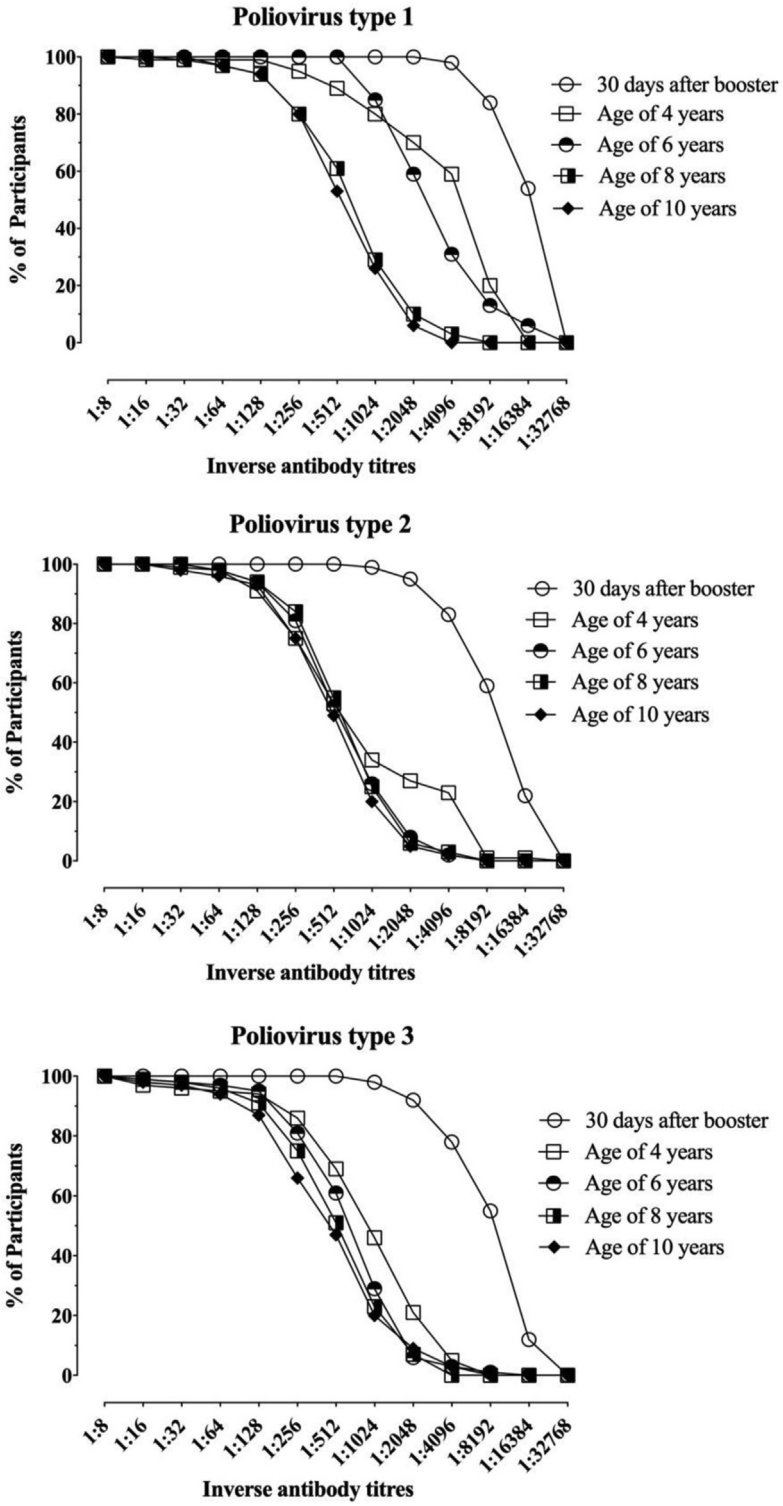

Fig. 2: Reverse cumulative distribution curves of neutralising antibodies against poliovirus types 1, 2, and 3 in the sIPV group.

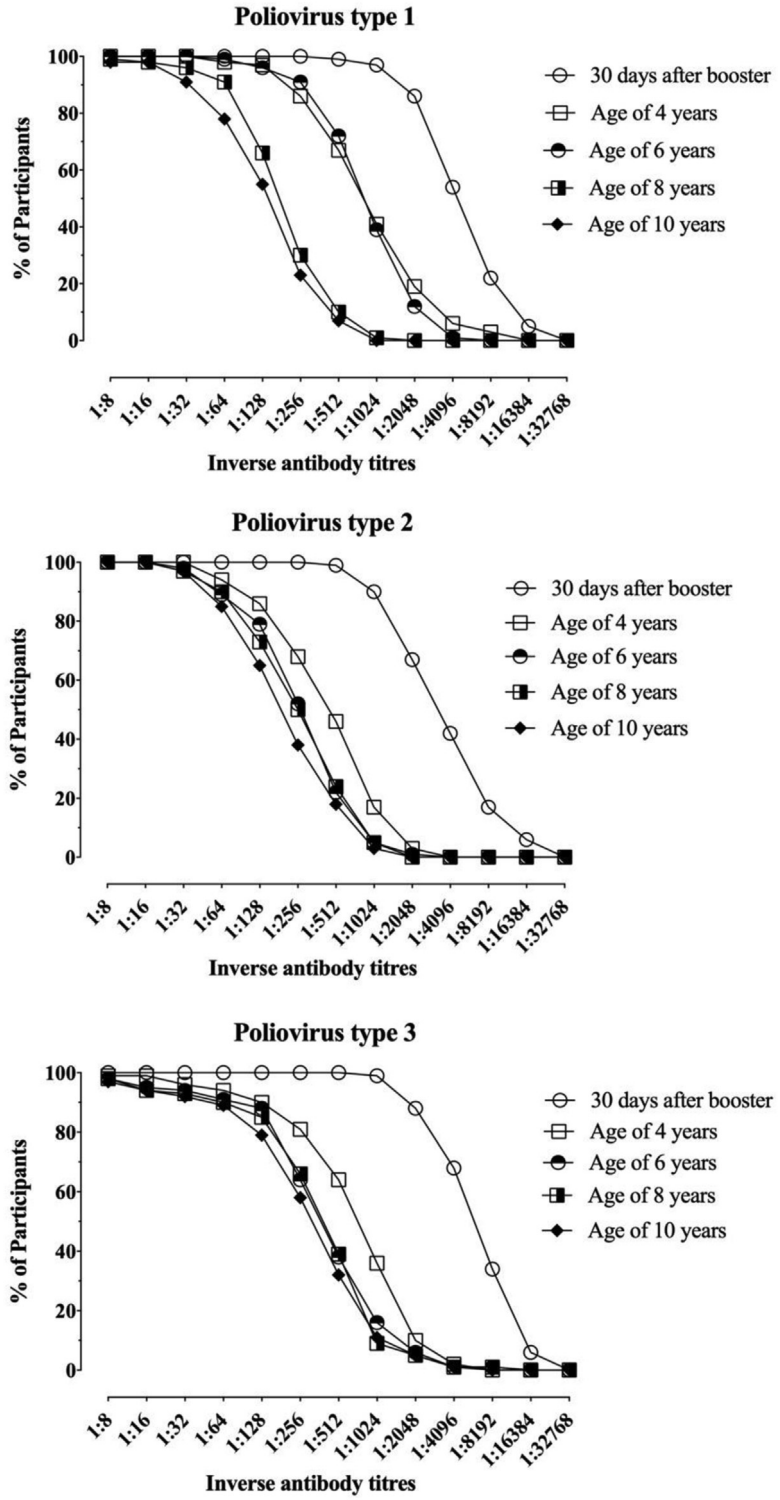

Fig. 3: Reverse cumulative distribution curves of neutralising antibodies against poliovirus types 1, 2, and 3 in the wIPV group.

(individual data not shown) did increase slightly over time.

Although we have made every effort to prevent participants detachment, due to the observation period spanning 10 years, the missed follow-up rate was 25.5%, which is a major limitation of this report.

In conclusion, sIPV and wIPV induced good persistent immunity (≥10 years) after primary and booster immunisations. These findings suggest that the preparation of inactivated poliovirus vaccines using attenuated Sabin strains is entirely feasible. High immune persistence of sIPV is critical for eradicating poliomyelitis in the postpolio era, particularly in developing countries.

Contributors

LM and WC designed the study and performed clinical trial. ZY, JW, JZ, HY, and JL performed the neutralisation assays. JG performed literature search. SO, SS, and FS performed clinical site work and data collection. ZZ and YW did the statistical analysis. RZ, LX, and XD wrote the paper. WL was responsible for vaccine interpretation. CL and LM accessed and verified the underlying data. GL did general arrangement and revised the manuscript. All authors read and approved the final version of the manuscript.

Data sharing statement

All data could be requested from corresponding author. Qualified researchers should submit a proposal to the corresponding author outlining the reasons for requiring the data. Use of data must also comply with the requirements of our institutes. A signed data access agreement with the sponsor is required before accessing shared data.

Declaration of interests

We declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102151.

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