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Immunogenicity and safety evaluation of bivalent types 1 and 3 oral poliovirus vaccine by comparing different poliomyelitis vaccination schedules in China: A randomized controlled non-inferiority clinical trial

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ABSTRACT

Background: The type 2 component of the oral poliovirus vaccine is targeted for global withdrawal through a switch from the trivalent oral poliovirus vaccine (tOPV) to a bivalent oral poliovirus vaccine (bOPV). The switch is intended to prevent paralytic polio caused by circulating vaccine-derived poliovirus type 2. We aimed to assess the immunogenicity and safety profile of 6 vaccination schedules with different sequential doses of inactivated poliovirus vaccine (IPV), tOPV, or bOPV.

Methods: A randomized controlled trial was conducted in China in 2015. Healthy newborn babies randomly received one of the following 6 vaccination schedules: cIPV-bOPV-bOPV(I-B-B), cIPV-tOPV-tOPV (I-T-T), cIPV-cIPV-bOPV(I-I-B), cIPV-cIPV-tOPV(I-I-T), cIPV-cIPV-cIPV(I-I-I), or tOPV-tOPV-tOPV(T-T-T). Doses were administered sequentially at 4–6 week intervals after collecting baseline blood samples. Patients were proactively followed up for observation of adverse events after the first dose and 30 days after all doses. The primary study objective was to investigate the immunogenicity and safety profile of different vaccine schedules, evaluated by seroconversion, seroprotection and antibody titer against poliovirus types 1, 2, and 3 in the per-protocol population.

Results: Of 600 newborn babies enrolled, 504 (84.0%) were included in the per-protocol population. For type 1 poliovirus, the differences in the seroconversion were 1.17% (95% CI = −2.74%, 5.08%) between I-B-B and I-T-T and 0.00% (95% CI: −6.99%, 6.99%) between I-I-B and I-I-T; for type 3 poliovirus, differences in the seroconversion were 3.49% (95% CI: −1.50%, 8.48%) between I-B-B and I-T-T and −2.32% (95% CI: −5.51%, 0.86%) between I-I-B and I-I-T. The non-inferiority conclusion was achieved in both poliovirus type 1 and 3 with the margin of −10%. Of 24 serious adverse events reported, no one was vaccine-related.

Conclusions: The vaccination schedules with bOPV followed by one or 2 doses of IPV were recommended to substitute for vaccinations involving tOPV without compromising the immunogenicity and safety in the Chinese population. The findings will be essential for policy formulation by national and global authorities to facilitate polio elimination.

Introduction

Poliomyelitis, caused by a poliovirus infection, used to be one of most widespread childhood diseases worldwide. Poliomyelitis patients present the severe clinical symptoms, such as neuron damages, muscle weakness, paralysis, etc. Three serotypes of poliovirus, without cross-reactive of immunogenicity, have been identified in nature. Infection or vaccination with one poliovirus serotype does not confer immunity against the other serotypes.,[1,2] Although no specific antiviral therapy is available to cure poliomyelitis, a trivalent oral poliovirus vaccine (tOPV) and a trivalent conventional inactivated poliovirus vaccine (cIPV) have been used effectively worldwide to combat poliovirus infections since the 1950s. Because of the good vaccine efficacy, a poliomyelitis eradication campaign was launched by the World Health Organization in 1988. Through intensive tOPV vaccination, the number of poliomyelitis-endemic countries has fallen from an estimated 125 in 1988 to 2 in 2015. The number of poliomyelitis cases fell from estimated 350,000 cases in 1988 to 39 in 2015.[3,4] Currently, type 1 poliovirus (PV1) is the only serotype with a wild strain circulating in nature; and has caused 26 cases (9 in Afghanistan, 14 in Pakistan, and 3 in Nigeria) between January and September 2016.[5] Outbreaks caused by wild strains of type 2 poliovirus (PV2) and type 3 poliovirus (PV3) has not been reported since 1999 and 2012, respectively.[6]

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Poliovirus is transmitted by a fecal-oral cycle.[4] Feeding the oral poliovirus vaccine (OPV) elicits strong intestinal and systemic immunity, which is effective at both preventing poliomyelitis and reducing viral fecal-oral transmission. In contrast, muscular injection of inactivated poliovirus vaccine (IPV) induces excellent systemic immunity However, IPV is incapable of establishing adequate mucosal immunity on gut epithelia against poliovirus fecal shedding. Nonetheless, in contrast to the inactivated viral particles in IPV, OPV consists of live attenuated polioviruses which might revert to virulent circulating vaccine-derived strains, thereby resulting in vaccine-derived paralytic poliomyelitis in vaccinated persons. As naturally occurring poliomyelitis cases have largely decreased, these OPV-related polioviruses have become potential causative agents in a re-established poliomyelitis endemic. For example, although PV2 is no longer a naturally occurring virus, hundreds of paralytic poliomyelitis cases have been caused by vaccine-derived PV2 since 2000.[7,8] Natural circulation of vaccine-derived PV2 was still persistent in parts of northern Nigeria and Pakistan.[9] Between August 2011 and February 2012, an outbreak caused by type 2 circulating vaccine-derived poliovirus (cVDPV) occurred in Sichuan Province, China.[10] In Northeastern Nigeria, a cVDPV2 was identified in an environmental sample collected in March 2016, and the identification in August of polio cases caused by wild PV1 (WPV1) required further strengthening of surveillance and immunization. [11,12] As of 29 June 2016, the Global Polio Eradication Initiative (GPEI) had confirmed 12 cases of polio in Pakistan.[13] Laos with VDPV transmission in 2015 has reported 3 additional cVDPV cases in 2016 to date.[14] To avoid the threats by re-emergence of vaccine-derived poliomyelitis, a switch of prevention strategy from OPV to IPV has been implemented worldwide.[2,15]

To recognize the difficulty of synchronous switching to the exclusive global administering of IPV, the "Polio Eradication and Endgame Strategic Plan: 2013–2018," was introduced by the Global Polio Eradication Initiative.[2] By April of 2015, at least one dose of IPV must be introduced into routine immunization schedules. For removal of the potential threat from VDPV2 (naturally occurring PV2 has been eradicated since 1999), the trivalent OPV should be replaced by a bivalent OPV containing only serotypes 1 and 3 by April 2016.[6] According to the September 2016 Morbidity and Mortality Weekly Report, all 155 countries and territories using OPV in their immunization programs in 2015 reported that they had completely ceased use of tOPV by mid-May 2016. As of August 31, 173 (89%) of 194 WHO (World Health Organization) countries had introduced IPV into their immunization programs and 29 countries are expected to deplete their supplies of IPV before being resupplied in 2017. [11]

Given the blended dose of OPV and IPV is used in the transition period, the immunization schedules to maintain optimal safety and immunogenicity might have significant differences among regions and human populations worldwide. For Chinese infants, no studies on poliovirus vaccination schedule with bOPV have been reported for reference to date. Here, we aimed to evaluate the immunogenicity and safety profile of the bivalent types 1 and 3 oral poliovirus vaccine (bOPV). We then further compared the advantages and disadvantages of different childhood sequential vaccination schedules involving bOPV, trivalent types 1, 2, and 3 oral poliovirus vaccines (tOPV) and inactivated polio vaccine (IPV).

Results

We enrolled 600 newborn babies randomized assigned into 6 sequential vaccination schedules as follows: cIPV-bOPV-bOPV (I-B-B), cIPV-tOPV-tOPV (I-T-T), cIPV-cIPV-bOPV (I-I-B), cIPV-cIPV-tOPV (I-I-T), cIPV-cIPV-cIPV (I-I-I), and tOPV-tOPV-tOPV (T-T-T). In total, 552 (92.00%) babies completed the trial (96 in I-T-T, 90 in I-I-I, 91 in I-B-B, 90 in T-T-T, 93 in I-I-T and 92 in I-I-B), while 48 (8.00%) discontinued (Fig. 1). In total, 504 (84.00%) of all randomized subjects were involved in the per-protocol (PP) population analyses (86 in I-T-T, 82 in
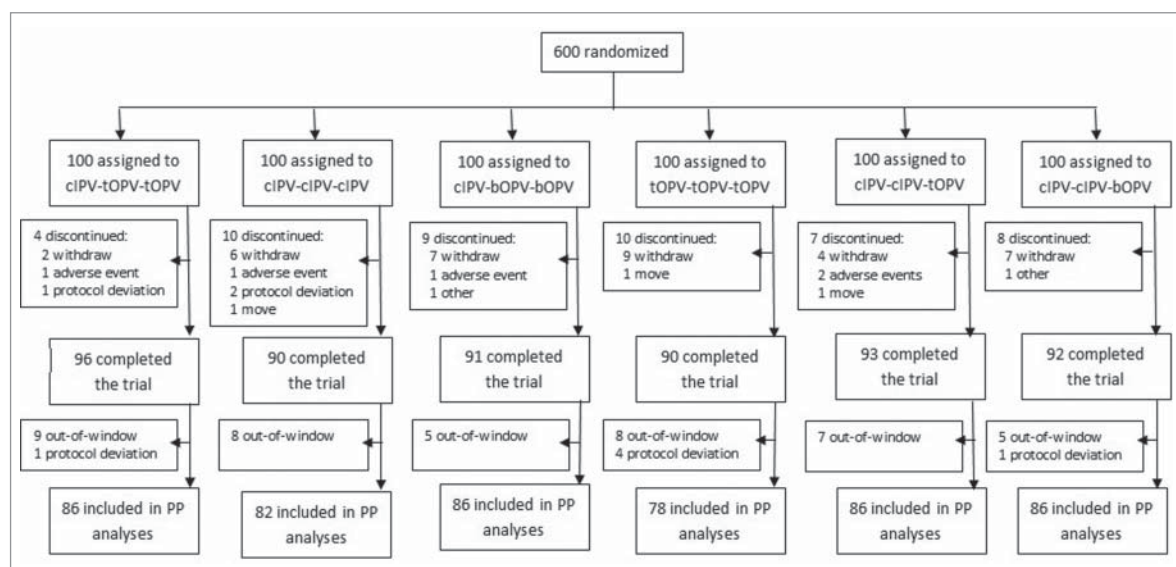

Figure 1. Trial profile, intent-to-treat and per-protocol (PP) analyses, China, 2014 PP = per-protocol. cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

I-I-I, 86 in I-B-B, 78 in T-T-T, 86 in I-I-T and 86 in I-I-B) according to the predefined requirements.

All 600 subjects who received at least one dose of study medication were included in the overall safety analyses and the safety analyses after the first dose of actual treatment as follows: 100 in I-T-T, 99 in I-I-I, 100 in I-B-B, 101 in T-T-T, 100 in I-I-T and 100 in I-I-B. There were 572 (95.33%) subjects in the safety analysis population for the second dose; and 565 (94.17%) subjects in the safety analysis population for the third dose.

Table 1 shows demographics, baseline characteristics, and seroprevalence in the various vaccine groups. There were no statistically significant differences among treatment groups.

Seroconversion, seroprotection, reciprocal titer and the times of reciprocal titer increase by vaccination groups based on PP population 30 days after the last vaccination are presented in Table 2. Differences in proportions of overall seroconversion to type 1 and 3 polioviruses were measured between I-T-T vs. I-B-B and I-I-T vs. I-I-B vaccination schedules, respectively, using 2-sided 95% confidence intervals (95% CIs) (Fig. 2).

Type 1 poliovirus: Overall seroconversion rates to PV1 in the PP population at 30 d after the last vaccination were as follows: 97.67% for I-T-T, 91.46% for I-I-I, 98.84% for I-B-B, 96.25% for T-T-T, 94.29% for I-I-T, and 94.29% for I-I-B. No statistically significant differences among the 6 arms were detected using the Chi-Square Test ($p = 0.2241$). The difference between I-B-B and I-T-T seroconversion rates was 1.17%, with the lower 95%CI bound of -2.74%, and the difference between I-I-B and I-I-T in seroconversion rate was 0.00% with the lower bound of 95% CI -6.99%. Since the lower bounds of both 95% CIs were greater than the pre-specified margin -10%, non-inferiority was demonstrated.

The seroconversion rates of PV1 for susceptible infants after vaccination were 100.00% for all 6 arms. No statistically significant differences among the 6 arms were detected for the 4-fold increased rates among unsusceptible subjects ($p = 0.2903$).

Seroprotection rates for PV1 were 98.84% for I-I-B and 100.00% for the other 5 groups. No statistically significant differences among the 6 arms were detected using Chi-Square Test ($p = 0.4319$).

The overall geometric mean of the reciprocal antibody titer (GMT) of PV1 antibody was significantly higher in the I-B-B group than in the I-T-T ($p = 0.0025$), and numerically higher in I-I-B than in I-I-T. Increases of GMT were numerically greater after both schedules of bOPV than after tOPV.

Type 3 poliovirus: Seroconversion rates to PV3 in the PP population at 30 days after the last vaccination were as follows: 95.35% for I-T-T, 97.56% for I-I-I, 98.84% for I-B-B, 100.00% for T-T-T, 100.00% for I-I-T, and 97.67% for I-I-B. No statistically significant difference among the 6 arms were detected using the Chi-Square test ($p = 0.1834$). The difference between the I-B-B and I-T-T seroconversion rates was 3.49% with the 95%CI lower bound of -1.50%. The difference between the I-I-B and I-I-T seroconversion rates was -2.32% with a 95% CI lower bound of -5.51%. Since the lower bounds of both 95% CIs were greater than the pre-specified margin of -10%, non-inferiority was demonstrated.

The seroconversion rates of PV3 in susceptible infants after vaccination were 97.22% for I-T-T, 100.00% for I-I-I, 98.72% for I-B-B, 100.00% for T-T-T, I-I-T, and I-I-B arms. No statistically significant differences among the 6 arms were detected using Chi-Square test ($p = 0.2339$). No statistically significant differences among the 6 arms were detected for the 4-fold increase rates among unsusceptible subjects ($p = 0.5124$).

Seroprotection rates of PV3 were 97.67% for I-T-T, 98.84% for I-B-B, 100.00% for I-I-I, T-T-T, I-I-T, and I-I-B arms. No statistically significant differences among the 6 arms were detected using Chi-Square test ($p = 0.2393$).

The GMT of PV3 antibody was lower for the I-T-T group than for the I-B-B ($p = 0.0413$) and was numerically higher in the I-I-B group than in I-I-T ($p = 0.1706$). Group I-B-B exhibited a statistically higher increase of GMT ($p = 0.0261$).

Table 1. Baseline characteristics and seroprevalence of per-protocol population by arms.

	cIPV-tOPV-tOPV (n = 86)	cIPV-cIPV-cIPV (n = 82)	cIPV-bOPV-bOPV (n = 86)	tOPV-tOPV-tOPV (n = 78)	cIPV-cIPV-tOPV (n = 86)	cIPV-cIPV-bOPV (n = 86)
Age, mean ± SD (days)	73.67 ± 9.24	72.32 ± 8.63	72.77 ± 8.21	73.60 ± 8.90	73.21 ± 9.37	74.79 ± 9.36
Male sex, n (%)	36(41.86)	35(42.68)	41(47.67)	37(47.44)	44(51.16)	38(44.19)
Ethnicity, n (%)						
Han	68(79.07)	73(89.02)	70(81.40)	58(74.36)	74(86.05)	73(84.88)
Miao	5(5.81)	1(1.22)	3(3.49)	4(5.13)	0(0.00)	0(0.00)
Zhuang	5(5.81)	1(1.22)	5(5.81)	3(3.85)	2(2.33)	6(6.98)
Yao	8(9.30)	7(8.54)	6(6.98)	13(16.67)	9(10.47)	6(6.98)
Others	0(0.00)	0(0.00)	2(2.33)	0(0.00)	1(1.16)	1(1.16)
Weight, mean ± SD (kg)	5.33 ± 0.75	5.28 ± 0.66	5.26 ± 0.67	5.40 ± 0.64	5.23 ± 0.68	5.27 ± 0.69
Length, mean ± SD (cm)	58.97 ± 2.29	58.62 ± 2.44	58.63 ± 2.44	59.22 ± 2.32	58.72 ± 2.31	58.58 ± 2.26
Type 1 Poliovirus						
Seropositive, n(%)	31(36.05)	43(52.44)	46(53.49)	41(52.56)	45(52.33)	45(52.33)
GMT(95%CI)	8.27(6.39–10.71)	10.43(8.06–13.51)	11.27(8.86–14.35)	9.48(7.36–12.21)	9.99(7.85–12.71)	10.87(8.36–14.13)
Type 2 Poliovirus						
Seropositive, n(%)	26(30.23)	28(34.15)	25(29.07)	37(47.44)	30(34.88)	23(26.74)
GMT(95%CI)	6.66(5.56–7.97)	6.95(5.71–8.46)	5.65(4.96–6.43)	7.45(6.26–8.86)	6.37(5.46–7.44)	6.10(5.12–7.28)
Type 3 Poliovirus						
Seropositive, n(%)	14(16.28)	14(17.07)	8(9.30)	11(14.10)	10(11.63)	18(20.93)
GMT(95%CI)	4.87(4.37–5.44)	5.12(4.47–5.85)	4.56(4.11–5.07)	5.04(4.36–5.82)	4.85(4.21–5.58)	5.79(4.85–6.92)

cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine. GMT = geometric mean reciprocal titer.

Table 2. Seroprotection, seroconversion and titer in per-protocol population 30 days after the last vaccination.

	cIPV-tOPV-tOPV (n = 86)	cIPV-cIPV-cIPV (n = 82)	cIPV-bOPV-bOPV (n = 86)	tOPV-tOPV-tOPV (n = 78)	cIPV-cIPV-tOPV (n = 86)	cIPV-cIPV-bOPV (n = 86)
Type 1 Poliovirus						
Seroconversion	84(97.67, 91.85–99.72)	75(91.46, 83.20–96.50)	85(98.84, 93.69–99.97)	75(96.15, 89.17–99.20)	81(94.19, 86.95–98.09)	81(94.19, 86.95–98.09)
Seroconversion in susceptible infants	55(100.0, 93.51–100.0)	39(100.0, 90.97–100.0)	40(100.0, 91.19–100.0)	37(100.0, 90.51–100.0)	41(100.0, 91.40–100.0)	41(100.0, 91.40–100.0)
Seroconversion in non-susceptible infants	29(93.55, 78.58–99.21)	36(83.72, 69.30–93.19)	45(97.83, 88.47–99.94)	38(92.68, 80.08–98.46)	40(88.89, 75.95–96.29)	40(88.89, 75.95–96.29)
Seroprotection	86(100.0, 95.80–100.0)	82(100.0, 95.50–100.0)	86(100.0, 95.80–100.0)	78(100.0, 95.38–100.0)	86(100.0, 95.80–100.0)	85(98.84, 93.69–99.97)
GMT	1100.89(875.60–1384.2)	301.42(246.33–368.85)	1822.01(1444.3–2298.5)	1459.89(1124.9–1894.6)	864.44(630.70–1184.9)	1167.98(849.70–1605.5)
GMI	133.04(94.64–340.06)	28.89(20.43–40.86)	161.66(116.63–224.07)	153.98(106.49–222.65)	86.55(58.05–129.04)	107.46(69.83–165.39)
Type 2 Poliovirus						
Seroconversion	82(95.35, 88.52–98.72)	70(85.37, 75.83–92.20)	48(55.81, 44.70–66.52)	76(97.44, 91.04–99.69)	81(94.19, 86.95–98.09)	71(82.56, 72.87–89.90)
Seroconversion in susceptible infants	60(100.0, 94.04–100.0)	54(100.0, 93.40–100.0)	47(77.05, 64.50–86.85)	41(100.0, 91.40–100.0)	56(100.0, 93.62–100.0)	63(100.0, 94.31–100.0)
Seroconversion in non-susceptible infants	22(84.62, 65.13–95.64)	16(57.14, 37.18–75.54)	1(4.00, 0.10–20.35)	35(94.59, 81.81–99.34)	25(83.33, 65.28–94.36)	8(34.78, 16.38–57.27)
Seroprotection	85(98.84, 93.69–99.97)	82(100.0, 95.60–100.0)	59(68.60, 57.70–78.19)	78(100.0, 95.38–100.0)	86(100.0, 95.80–100.0)	85(98.84, 93.69–99.97)
GMT	279.19 (218.50–356.74)	136.94(106.68–175.77)	11.01(8.97–13.51)	271.39(216.87–339.62)	662.66(480.02–914.79)	53.49(43.82–65.29)
GMI	41.94 (30.60–57.50)	19.70 (3.40–28.96)	1.95 (1.48–2.57)	36.43 (27.56–48.16)	103.99 (69.92–154.66)	8.76 (6.42–11.97)
Type 3 Poliovirus						
Seroconversion	82(95.35, 88.52–98.72)	80(97.56, 91.47–99.70)	85(98.84, 93.69–99.97)	78(100.0, 95.38–100.0)	86(100.0, 95.38–100.0)	84(97.67, 91.85–99.72)
Seroconversion in susceptible infants	70(97.22, 90.32–99.66)	68(100.0, 94.72–100.0)	77(98.72, 93.06–99.97)	67(100.0, 94.64–100.0)	76(100.0, 95.26–100.0)	68(100.0, 94.72–100.0)
Seroconversion in non-susceptible infants	12(85.71, 57.19–98.22)	12(85.71, 57.19–98.22)	8(100.0, 63.06–100.0)	11(100.0, 71.51–100.0)	10(100.0, 69.15–100.0)	16(88.89, 65.29–98.62)
Seroprotection	84(97.67, 91.85–99.72)	82(100.0, 95.60–100.0)	85(98.84, 93.69–99.97)	78(100.0, 95.38–100.0)	86(100.0, 95.80–100.0)	86(100.0, 95.80–100.0)
GMT	480.91 (359.04–644.15)	370.52(293.54–467.68)	698.14(565.37–862.09)	477.11(382.39–595.31)	777.98(575.70–1051.4)	1068.89(755.90–1511.4)
GMI	98.68(72.31–134.66)	72.43(55.02–95.36)	153.00(121.20–193.14)	94.73(74.40–120.63)	160.38(116.90–220.03)	184.55(123.75–275.22)

Data for seroprotection and seroconversion are n(%, 95%CI); data for titer are GMT(95%CI); 95%CI was estimated by exact test. Seroprotection defined as neutralizing titer of at least 8. For susceptible infants who were seronegative (titer <8),seroconversion was defined as achieving an antibody titer of at least 8; for non-susceptible infants who were seropositive (titer> = 8),seroconversionwas defined as a titer four times higher than the expected fall in maternal antibody concentrations based on the pre-vaccination titer. cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine. GMT = geometric mean reciprocal titer. GMI = fold increase in GMT.
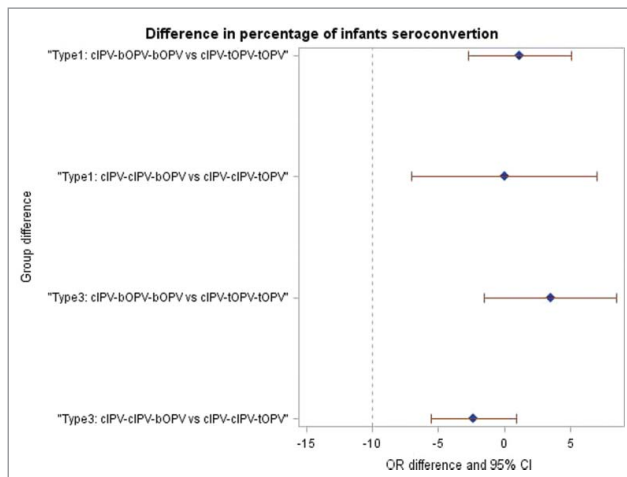
Figure 2. Differences in proportions of post-vaccination antibody seroconversion Differences in proportions of seroconversion to type 1 and 3 polioviruses were measured between cIPV-tOPV-tOPV vs. cIPV-tOPV-tOPV and cIPV-cIPV-tOPV vs. cIPV-cIPV-tOPV vaccination schedules using one-sided 95% CIs. cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

Type 2 poliovirus: Seroconversion rates to PV2 in the PP population at 30 days after the last vaccination were as follows: 98.35% for I-T-T, 85.37% for I-I-I, 55.81% for I-B-B, 97.44% for T-T-T, 94.19% for I-I-T, and 82.56% for the I-I-B group. Seroconversion rates of PV2 in susceptible infants were 77.05%% for I-B-B, and 100.00% for the other 5 arms. Seroprotection rate of PV2 in PP population at 30 days after vaccination were 98.84% for I-T-T, 68.60% for I-B-B, 98.84% for I-I-B, 100.00% for I-I-I, T-T-T and I-I-T.

Differences among the 6 arms for above immunogenicity endpoints of PV2 were statistically significant ($p<0.0001$).

The increase of GMT against PV2 using the I-I-T vaccination schedule was numerically higher (103.99 folds, 95%CI = 69.92–154.66), followed by I-T-T, T-T-T, I-I-I, I-I-B, and I-B-B schedules.

The reverse cumulative distribution curves, which are a summary measure of antibody distribution, show similar curves for arms with similar type-specific seroconversion rates (Fig. 3).

Overall, all vaccines given during the study were well tolerated; and no vaccine-related serious adverse event (SAE) were reported (Table 3). Among 24 subjects with SAEs unrelated to the vaccine, 4 subjects (4.00%) had 4 SAEs were in the I-T-T group. Three subjects (3.03%) had 4 SAEs in I-I-I group. Five subjects (5.00%) had 7 SAEs in I-B-B group. One subject (0.99%) had one SAE in T-T-T group. Four subjects (4.00%) had 4 SAEs in I-I-T group. Seven subjects (7.00%) had 8 SAEs in I-I-T. There were no statistically significant differences in SAEs among the arms ($p = 0.3628$). Infectious pneumonia was the main SAE (10 subjects, 1.67%), followed by bronchitis (4 subjects, 0.67%) and hand-foot-and-mouth disease (4 subjects, 0.67%). The incidences of solicited and unsolicited AEs are presented in Table 3.

Discussion

Eradication of wild type poliovirus has been achieved through intensive tOPV vaccination worldwide.[16,17] Although the usage
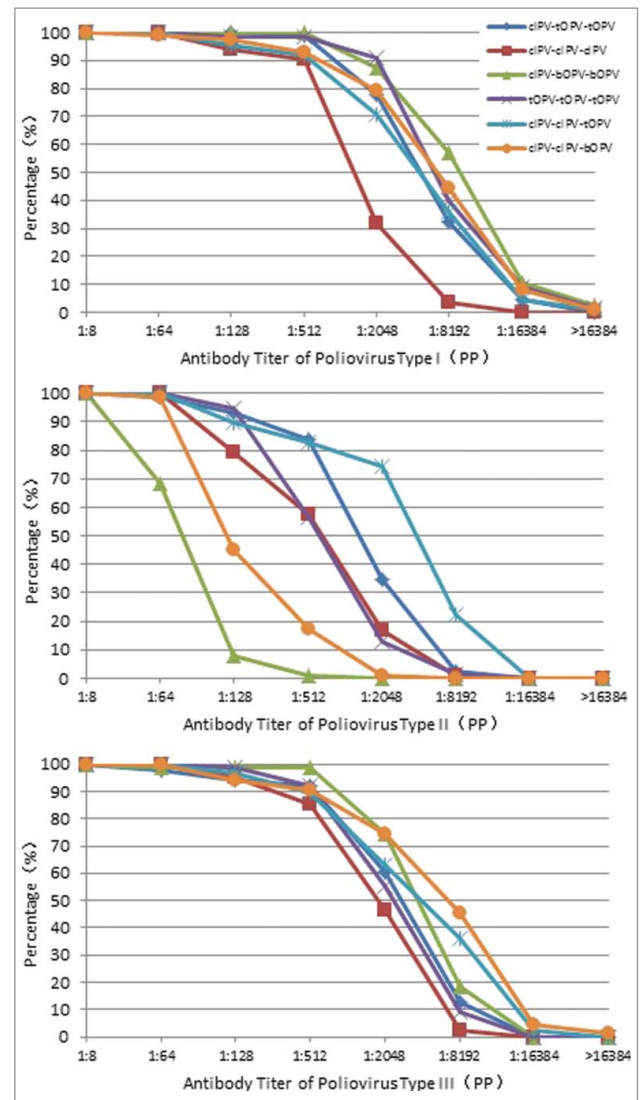

Figure 3. Reverse poliovirus antibody distribution curves PP = per-protocol. cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

of tOPV effectively disrupts the transmission of the live virus, eradication of all circulating vaccine-derived polioviruses from the reverse mutated OPV Sabin strains requires the transfer of the vaccination schedule from OPV to IPV. Sequential removal of OPV-derived Sabin poliovirus strains from populations is a key objective to achieve the eradication goal. The first step toward this goal is the removal of vaccine-derived Sabin PV2, because naturally circulating wild PV2 was eradicated in 1999.[6] Infection by vaccine-derived Sabin PV2 contributed to 26–31% of vaccine-associated paralytic poliomyelitis,[7] which presented a significant public health burdens worldwide. Accordingly, the Global Polio Eradication Initiative raises a roadmap for new immunization schedule consisting of multiple doses of bOPV following at least one dose of IPV. Given the blended use of IPV and bOPV, the safety and immunogenicity of a new immunization schedule have urgently needed re-evaluation for different global regions and human populations. Previous studies have assessed the immunogenicity and safety of a blended IPV-OPV immunization schedule in Bangladesh[18,19] Chile[20] Panama,[21] and India.[22,23]

In the current study, we have evaluated the immunogenicity and safety of bOPV by comparing different poliomyelitis vaccination schedules in China using a randomized controlled non-inferiority clinical trial. In general, bOPV was non-inferior to tOPV in terms of immunogenicity since the lower bounds of the 95% CIs for the differences between the treatment arms (I-B-B vs. I-T-T and I-I-B vs. I-I-T) were greater than pre-specified non-inferiority margin of −10%.

Reciprocal antibody titer against PV1 and PV3 were higher after both schedules with bOPV than after tOPV. The lowest reciprocal titer was identified in the I-I-I arm. A low GMT with PV1 was observed in the I-I-I arm. This finding was expected and was consistent with the results of previous studies using 3-dose cIPV manufactured by Sanofi Pasteur. In a comparison study among Chinese population, the GMT after vaccinated by cIPV was 386 (297–502), while the GMT after vaccine with tOPV was 3315 (2703–4064). [24]

Compared with I-I-B, I-B-B possessed a significantly higher PV1 reciprocal titer, while the PV3 reciprocal antibody titer in I-I-B was higher than in the I-B-B group. In the context of the final stage of polio eradication, PV2 immunity is of concern as well. Both vaccination schedules with bOPV have shown certain efficacy of seroconversion and seropositivity against PV2 compared with other arms. The results favor I-I-B compared with the I-B-B vaccination schedule. Additionally, there was no significant difference in safety between the I-I-B and I-B-B vaccination schedules. Therefore, with at least one dose of IPV, adequate prevention of PV2 infection could be achieved, and the I-I-B vaccination schedule might be preferred choice if conditions allowed.

Our findings were consistent with the results of a study using different poliovirus vaccination schedules in Chile in which the seroconversion rates against PV1 (99% for I-B-B, 100% for I-I-B and 100% for I-I-I) and PV3 (98% for I-B-B, 100% for I-I-B and 99% for I-I-I) were non-inferior in vaccination schedules containing IPV and bOPV, compared with an all-IPV schedule, and proportions of infants with protective antibodies were high after all schedules.[21,15] Comparable results in an India Polio study showed that the seroconversion rates against PV1 were 99% for bOPV, bOPV-IPV and B-I-I arms; and the seroconversion rates against PV3 were 96%, 99% and 99% for bOPV, bOPV-IPV and B-I-I arms, respectively.[22,23] The improved seroconversions to types 1 and 3 were also consistent with results from Bangladesh[18,19] Panama[21] and Pakistan.[25]

The safety results suggest that the immunization schedules with IPV and bOPV were well tolerated. No vaccine related SAEs were observed, and all local and systemic reactions were mild; which was consistent with previous studies globally. No SAEs were attributed to the vaccines in safety results in the studies in India, Bangladesh, Panama and Pakistan. Only one SAE was considered vaccine related (intestinal intussusception) in Chilean population.[15]

Current data indicated that the sequential schedules are suitable for China, as they achieved adequate immunogenicity, whereas the cIPV-only schedule showed lower GMTs; which is in line with expectations. These results were supported by the results from studies comparing immunogenicity and tolerability among different schedules with IPV and tOPV but not bOPV in China.[26,27,28]

Table 3. Summary of adverse events and subjects with adverse events.

	cIPV-tOPV-tOPV (n = 100)	cIPV-cIPV-cIPV (n = 99)	cIPV-bOPV-bOPV (n = 100)	tOPV-tOPV-tOPV (n = 101)	cIPV-cIPV-tOPV (n = 100)	cIPV-cIPV-bOPV (n = 100)	Total (n = 600)
Serious adverse events							
Number of AEs	4	4	7	1	4	8	28
Number of subjects with AEs (n/N%)	4 (4.00%)	3 (3.03%)	5 (5.00%)	1 (0.99%)	4 (4.00%)	7 (7.00%)	24 (4.00%)
Systemic reactions*							
Number of AEs	248	256	242	239	289	257	1531
Number of subjects with AEs (n/N%)	83 (83.00%)	76(76.77%)	78 (78.00%)	78 (77.23%)	90 (90.00%)	90 (90.00%)	495 (82.50%)
Fever							
Number of AEs	186	188	173	170	202	180	1099
Number of subjects with AEs (n/N%)	80 (80.00%)	70 (70.71%)	71 (71.00%)	75 (74.26%)	86 (86.005)	85 (85.00%)	467 (77.83%)
Irritability/fussiness							
Number of AEs	10	16	13	15	20	20	94
Number of subjects with AEs (n/N%)	8 (8.005)	10 (10.00%)	9 (9.00%)	11 (10.89%)	15 (15.00%)	13 (13.00%)	66 (11.00%)
Somnolence							
Number of AEs	3	3	2	3	2	2	15
Number of subjects with AEs (n/N%)	3 (3.00%)	3 (3.03%)	2 (2.00%)	2 (2.97%)	2 (2.00%)	2 (2.00%)	15 (2.50%)
Vomit							
Number of AEs	7	7	8	3	14	3	42
Number of subjects with AEs (n/N%)	6 (6.00%)	7 (7.07%)	7 (7.00%)	2 (2.97%)	9 (9.00%)	3 (3.00%)	35 (5.83%)
Diarrhea							
Number of AEs	42	42	45	46	46	47	268
Number of subjects with AEs (n/N%)	34 (34.00%)	28 (28.28%)	31 (31.00%)	29 (28.71%)	29 (29.00%)	29 (29.00%)	180 (30.00%)
Allergic reaction							
Number of AEs	0	0	1	2	5	5	13
Number of subjects with AEs (n/N%)	0	0	1 (1.00%)	1 (0.99%)	5 (5.00%)	5 (5.00%)	12 (2.00%)
Local reaction: Redness on injection site							
Number of AEs	1	3	2	0	4	2	12
Number of subjects with AEs (n/N%)	1 (1.00%)	3 (3.03%)	2 (2.00%)	0	3 (3.00%)	2 (2.00%)	11 (1.83%)

*Systemic reactions involve fever, easy irritation, somnolence, vomit, diarrhea and allergic reaction.
cIPV = conventional inactivated poliovirus vaccine. bOPV = bivalent oral poliovirus vaccine. tOPV = trivalent oral poliovirus vaccine.

Our study had 2 major limitations. First, vaccination arm assignment in the study could not be masked because of the different vaccination formulations used. This limitation may not impact on the immunogenicity results, but may have affected the reports of adverse events. Another limitation is the generalizability of our findings to all areas in China which covers 56 ethnic groups and broad areas with different socioeconomic status as well as other developing countries.

In developing countries, the acceptability of injection is limited compared with the oral route mainly due to poor clinical practices, higher cost, and occasional pain and bleeding, which may reduce the pace of introducing IPV globally and may ultimately impact the elimination of poliovirus.[29,30] Increased availability and affordability of IPV in developing countries will be important prerequisites to ensure global withdrawal of the tOPV. The proportion of children using IPV is increasing each year in China, which is consistent with the introduction of IPV that is called for by the Polio Eradication Endgame Strategic Plan.[31] GPEI report indicated that 7 countries which have not already received their first IPV shipment through UNICEF (United Nations Children's Fund) and were considered at low risk for polio outbreaks will be delayed to introduce IPV until the first quarter of 2017. [32]

In conclusion, the current results support the application of the I-B-B and I-I-B vaccine schedules, substituting these vaccinations with pure tOPV or IPV and tOPV without compromising safety and immunogenicity. Our findings regarding bOPV and the different poliovirus vaccination schedules in the Chinese population would provide national and global policy makers with flexibility when choosing a vaccination schedule for eliminating vaccine-associated and vaccine-derived poliomyelitis.

Methods

Study design

This randomized controlled non-inferiority clinical trial was conducted between April 8 and August 23, 2015, at the Center of Diseases Control and Prevention (CDC) of Hezhou County and Zhongshan County in Guangxi Zhuang Autonomous Region of China. The study was approved by the ethics review committees of the CDC of Guangxi Zhuang Autonomous Region and authorized by the Center for Drug Evaluation of the China Food and Drug Administration for implementation (clinical trial authorization number: 2014L00500). The study was also registered in clinicaltrial.gov (NCT02785705).

Participants

Eligible participants were healthy full-term (37–42 weeks) infants aged 60–90 days who weighed more than 2.5 kg at birth with no obvious medical disorders, no polio vaccination, no immunoglobulin vaccination, with no other attenuated vaccine administered in the past 14 days and no other inactivated vaccine administered.

Participants were excluded if meet one or more of the following criteria: had or were at risk of immunodeficiency, severe allergic reaction, acute fever or infectious diseases, severe chronic diseases, family history of allergies, convulsions, seizures, encephalopathy or psychiatric diseases, oral steroids during at least 14 consecutive days of the preceding month, auxiliary temperature equal or greater than 38.0°C during the past 3 days, diarrhea (defection frequency equal or greater than 3 times per day) in the past 7 days, and participated in other drug clinical trials.

Participants could receive DTP vaccine during the study. However, they would need to have a 14-day interval from the polio vaccination.

Voluntary and informed consent for participation of newborn babies were obtained at enrollment from parents or guardians in accordance with ethical principles. Participants could withdraw from the study at any time point, on request by the mother or a legally acceptable representative. Reasons for withdrawal were collected where possible.

Randomization and masking

Serial numbers from 1–600 were equally randomized (1:1:1:1:1:1) into 6 sequential vaccination schedules as follows: cIPV-bOPV-bOPV(I-B-B), cIPV-tOPV-tOPV(I-T-T), cIPV-cIPV-bOPV(I-I-B), cIPV-cIPV-tOPV(I-I-T), cIPV-cIPV-cIPV (I-I-I), and tOPV-tOPV-tOPV(T-T-T). Sites were provided with sealed envelopes that contained the allocation assignments for emergency unblinding.

Considering that the formulations are different, the vaccines could not be completely masked (oral vs. injectable). cIPV, bOPV, and tOPV were coded as A, B, and C, respectively. However, the bOPV and tOPV vaccines could be masked; and laboratory investigators were blinded to group assignments. A statistician would analyze data unblinded with the allocation schedule after the database was locked.

Procedure

Healthy infants received following 3 doses sequentially at 4–6 weeks interval after collecting baseline blood sample as follows: I-B-B, I-T-T, I-I-B, I-I-T, I-I-I, and T-T-T. Subjects were proactively followed up for observation of adverse events from the first dose to 30 days after all doses. The blood samples were collected at pre-vaccination and 30 days after the third dose to test for antibodies to type 1, 2, and 3 polioviruses.

Serum samples were prepared within 24 hours after collection of blood (2.5mL). Half of the sample was used for antibodies testing, routine serum chemistry and hematological laboratory testing, and the other half was frozen and stored at −20°C using dry ice if needed. Immunogenicity was tested using the micro-neutralization assay, which has been described previously and applied, by National Institutes for Food and Drug Control. [18,33]

At least 8 site visits were required as follows: 2 for each vaccination, one 30 days after the full immunization schedule, and another visit 6 months after all 3 vaccinations. Investigators followed up with a phone call or optional visits for any further information needed. Investigators recorded medical histories and provided training and a diary card for parents to record safety data and concomitant medications. Parents or guardians were asked at each site visits to provide information about any

adverse event that occurred since the last visit, which were recorded on the diary card as well. The solicited adverse events were collected within 2 weeks and unsolicited adverse events were collected for 30 d after each vaccination. Serious adverse events were recorded for 6 months post all 3 vaccinations.

Tiantan Biological Product Co. (Beijing, China) manufactured the bOPV and tOPV vaccines used in this trial which is the pivotal study for bOPV registration in China. The cIPV was produced by Sanofi Pasteur (Lyon, France). Both tOPV and cIPV are licensed in China.

Outcomes

The primary immunogenicity outcome was the proportion of infants with seroconversion which was defined as antibody titers at 30 days after all 3 vaccinations equal or larger than 8 for susceptible infants or post-vaccination reciprocal titers 4 times higher than the pre-vaccination titers for unsusceptible infants. Here, susceptible infants are those whose pre-vaccination reciprocal titers were less than 8. Otherwise, the subjects were categorized as unsusceptible. The seroconversion rates of susceptible infants and 4-folder increased rate among unsusceptible infants were also calculated, respectively.

Other immunogenicity outcomes included the overall seroprotection rate, which was defined as the proportion of subjects with reciprocal titers of at least 8, the geometric mean of reciprocal antibody titer (GMT) and the fold increase in GMT (GMI).

The primary safety outcome was the proportion of infants with serious adverse events 6 months after the vaccination with the different vaccination schedules. Solicited adverse events, including both systemic reactions (including fever, irritability/fussiness, somnolence, vomiting, diarrhea, and allergic reactions) and local reactions (including tenderness, redness, swelling, and callous around the injection sites), within 30 days after the vaccination were presented and compared across all arms.

Statistical analyses

A sample size of at least 85 was needed for each arm based on the assumptions of 95% seroconversion rates for PV1 and PV3 and a 10% non-inferiority margin to achieve 85% power with one-sided α level of 0.025. The trial would be considered successful if both PV1 and PV3 achieved non-inferiority. It is planned that 100 subjects would be recruited for each arm in the case of any dropouts.

The PP population included all subjects who completed all 3 vaccinations, had complete pre- and post-vaccination immunogenicity data, met all inclusion criteria and no exclusion criteria, had good compliance, etc. The PP population was the primary population in the immunogenicity analyses presented in this article.

The non-inferiority analyses were conducted between the 2 arms with the same vaccination schedule. Non-inferiority was considered if all lower bounds of 95% CIs of the differences between the I-B-B arm and I-T-T arm, I-I-B arm and I-I-T arm for both PV1 and PV2 are greater than −10%. No α adjustments were needed for these multiple comparisons.

The Clopper-Pearson method [34] was used to compute the 95% confidence intervals (CIs) for the rates. Their differences among the groups were compared using Fisher's exact test or the Chi-Square test. GMT and GMI were compared using an analysis of variance (ANOVA) after a log-transformation. Two-sided p-values and 95% CIs for immunogenicity assessments were provided.

For safety assessment, serious adverse events (SAEs) within 6 months and adverse events (AEs) within 30 days after the vaccination were assessed and compared among the 6 arms using Fisher's exact test.

We conducted the statistical analyses using SAS software (version 9.2).

Clinical trials registration

NCT02785705.

Abbreviations

AEs	Adverse Events
bOPV	bivalent Oral Poliovirus Vaccine
cIPV	trivalent conventional Inactivated Poliovirus Vaccine
CDC	Center of Diseases Control and Prevention
cVDPV	circulating Vaccine-Derived Poliovirus
DTP	Diphtheria-Tetanus-Pertussis vaccine
GPEI	Global Polio Eradication Initiative
GMT	Geometric Mean of Reciprocal Antibody Titer
GMI	Fold Increase in GMT
IPV	Inactivate Poliovirus Vaccine
I-B-B	cIPV-bOPV-bOPV
I-T-T	cIPV-tOPV-tOPV
I-I-B	cIPV-cIPV-bOPV
I-I-T	cIPV-cIPV-tOPV
I-I-I	cIPV-cIPV-cIPV
OPV	Oral Poliovirus Vaccine
PP	Per-Protocol
PV1	Type 1 Poliovirus
PV2	Type 2 Poliovirus
PV3	Type 3 Poliovirus
SAEs	Serious Adverse Events
T-T-T	tOPV-tOPV-tOPV
tOPV	trivalent Oral Poliovirus Vaccine
UNICEF	United Nations Children's Fund
WPV1	Wild Type 1 Poliovirus
WHO	World Health Organization
95% CIs	95% Confidence Intervals

Disclosure of potential conflicts of interest

The authors declare no conflicts of interests.

Acknowledgments

Author contributions

Jingjun Qiu: drafted the manuscript and provided statistical analysis.

Yunkai Yang: trial design and coordinate trial conduction

Ling Wang: trial design and statistical analysis

Zhiwei Jiang: provided the main part of statistical analysis.

Wei Wang: trial conduction

Hongyan Wang: process optimization

Shaohong Guo: trial conduction

Chanjuan Li: trial design and statistical analysis

Prof. Jielai Xia: contributed to the study concept and design.

Dr. Zhaojun Mo: trial design, conduct and evaluation

Prof. Shuyuan Wei: contributed to the study concept and design

All authors contributed to the interpretation of data, final review and approval of the manuscript.

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