

COMMENTARY



The progress of postapproval clinical studies on Sabin IPV

Li Shi ^a and Mingbo Sun^{a,b}

^aInstitute of Medical Biology, Chinese Academy of Medical Sciences & Peking Union Medical College, Kunming, Yunnan, China; ^bYunnan Key Laboratory of Vaccine Research and Development on Severe Infectious Diseases, Kunming, Yunnan, China

ABSTRACT

As one of the powerful vaccines for completely eradicating all types of poliovirus in the polio endgame period, the novel IPV, which is prepared from attenuated polio Sabin strains (sIPV) and is expected to reduce the overall biosafety risk, was licensed in Japan (sIPV-containing diphtheria-tetanus-acellular pertussis combination vaccines, DTP-sIPV) and China (sIPV) in November 2012 and January 2015, respectively. Limited by the development progress and the manufactured sIPV ability, it has to date only been used in Chinese Expanded Programme on Immunization (EPI) by sequential scheduling with bOPV and in Japan with DTP-sIPV vaccination. We herein summarize postapproval clinical studies of sIPV in both full-dose schedules and sequential schedules, focusing on China, to evaluate sIPV safety and immunogenicity in large populations to provide important data for its broad application in developing countries worldwide.

ARTICLE HISTORY

Received 11 May 2021
Accepted 3 June 2021

KEYWORDS

sIPV; postapproval clinical studies; full-dose and sequential vaccination; safety; immunogenicity

According to the requirement of the “Polio Eradication and Endgame Strategic Plan,” at least one dose of inactivated poliomyelitis vaccine (IPV) was introduced into the routine immunization schedule worldwide in 2016¹. In addition to conventional IPV, which is prepared from wild polio strains (cIPV) and has been used since the 1960s, another new IPV made from attenuated polio Sabin strains (sIPV) was licensed in Japan (sIPV-containing diphtheria-tetanus-acellular pertussis combination vaccines, DTP-sIPV) and China (sIPV) in November 2012 and January 2015, respectively.² Since sIPV is expected to reduce the overall biosafety risk, the WHO recommends implementing and using sIPV in developing countries to reach the final target of polio eradication worldwide.³ In China, sIPV has been included in the Expanded Programme on Immunization (EPI) since May 2016. The first one was licensed in January 2015 and manufactured by the Institute of Medical Biology, Chinese Academy of Medical Sciences (CAMS) and was formulated to contain 30, 32, and 45 D-antigen units (DUs) for poliovirus serotypes I, II, and III, respectively. The second one was licensed in September 2017 and manufactured by the National Vaccine & Serum Institute of China National Biotech Group (CNBG); it was formulated to contain 15, 45, and 45 DU for poliovirus serotypes I, II, and III, respectively. We summarize postapproval clinical studies of sIPV in both full-dose schedules and sequential schedules, focusing on China, to provide data for reference use in the polio endgame period.

1. Safety in sequential vaccination

Immediately after sIPV licensing, safety and immunogenicity evaluations for sequential immunization of sIPV with trivalent

oral poliomyelitis vaccine (tOPV) and bivalent OPV (bOPV) were performed in several provinces in China. The primary sequential schedule included sIPV-tOPV-tOPV, sIPV-sIPV-tOPV, sIPV-bOPV-bOPV, and sIPV-sIPV-bOPV compared with 3 doses of tOPV or IPV (cIPV or sIPV) or cIPV-bOPV/tOPV at ages of 2, 3, and 4 months.^{4–15} These postmarket studies investigated the safety of sIPV, with no vaccine-related serious adverse events (SAEs). Most adverse reactions were mild and transient, and phase I–III clinical trials were carried out.¹⁶ In addition, the safety of sIPV was comparable to that of cIPV, though adverse reactions were higher than those of tOPV.^{4,6,12,15} In a post hoc analysis including two clinical trials of sIPV/cIPV-bOPV sequential vaccination using commercial sIPV in 1200 infants in Guangxi Province compared with 3 doses of tOPV vaccination, injected IPV in sequential vaccination was associated with a relatively higher incidence of adverse events.⁵ Shi XJ¹⁵ et al. performed active surveillance among 2313 individuals in Ningxia Province and found rates of common reactions of 2464.33 and 64.92 per 100,000 doses for sIPV and tOPV, respectively. In Adverse Events Following Immunization (AEFI) passive surveillance related to 111,906 dose sIPV vaccinations from December 2015 to December 2016, rates of common reactions and rare reactions were 51.68 and 1.67 per 100,000 doses; among 3228071 doses of tOPV vaccination from January 2008 to April 2015, rates of common reactions and rare reactions were 1.73 and 0.22 per 100,000 doses, respectively, for tOPV.¹⁵ The higher incidence of adverse events (AEs) with sequential immunization combining OPV with IPV than the full tOPV schedule may be related to the vaccination route, whereby IPV was administered by intradermal injection and OPV orally. There were no significant safety differences regarding the sequential schedule evaluation.^{4,5,8} For example, Huang ZY et al.⁸ evaluated the

safety of a population-based sequential vaccination schedule using sIPV-cIPV-bOPV, cIPV-sIPV-bOPV, 2 sIPV-bOPV, and 2cIPV-bOPV in 1917 infants in Shanghai city and found no significant differences in the rate of grade 3 reactions among different groups.

2. Immunogenicity evaluation of sequential vaccination

sIPV also showed good immunogenicity in sequential vaccination. Xiao ST et al¹⁰ evaluated the immunogenicity of 2 sIPV-tOPV sequential vaccination compared with tOPV-tOPV-tOPV and 3 sIPV-sIPV-sIPV in 214 infants in Shanghai and reported that sequential immunization with IPV and tOPV induced better immune effects than 3 doses of tOPV or sIPV. Shi XJ et al¹¹ reached the same conclusion when evaluating 180 infants in Ningxia using sIPV-tOPV-tOPV sequential vaccination and tOPV-tOPV-tOPV vaccination. When immunogenicity was evaluated in sequential vaccination of sIPV (containing 30, 32, and 45 DU for poliovirus serotype I, II, and III) and bOPV, seroconversion rates were 98.9–100% for polio type I and type III neutralizing antibodies with all sequential vaccinations; however, rates were only 79.4–95% for type II for 2 sIPV-bOPV sequential immunization and 42.5–74.6% for sIPV-2bOPV sequential immunization.^{4,5,7,13,14} Not only the seroconversion rate but also neutralizing antibody levels for type II were lower in sIPV-bOPV sequential vaccination than in full-dose sIPV vaccination. The geometric mean titers (GMTs) for type I and III were 2048–5309.9 and 1079–2048 with sIPV-2bOPV vaccination and 2048–7359.6 and 2048–2941.1 with 2 sIPV-bOPV vaccination, whereas GMTs for type II were only 11.7–19 and 64–73.4 with sIPV-2bOPV and 2 sIPV-bOPV vaccinations, respectively. With the higher content of type II antigens (containing 15, 45, and 45 DU for poliovirus serotype I, II, and III), GMTs for type II increased, to 38.1–41.6 and 200.4–270.4 for sIPV-2bOPV and 2 sIPV-bOPV vaccinations, respectively.^{6,13} Nonetheless, values were still lower than those induced by three doses of sIPV or tOPV.^{5,17} All these sequential vaccinations suggest that one dose of sIPV in the EPI schedule is not effective and that at least two doses of sIPV with 1 dose of bOPV should be included in a sequential schedule to improve immunity against type II poliovirus. In China, the 2IPV-bOPV primary schedule was introduced into the EPI in December 2019. Summaries of sIPV-bOPV sequential vaccination immunogenicity are shown in [Table 1](#).

3. Safety in large populations with the sIPV schedule

A full dose of the sIPV vaccination schedule in postmarket surveillance is important to guide sIPV use in polio endgames worldwide. He H et al⁴ evaluated the safety of sIPV in 163 infants and observed only temporary and mild AEs; Yan S et al⁶ reported that most common AEs consisted of fever and rash, and no SAEs were related to vaccines among 195 sIPV vaccinators. We evaluated the safety of sIPV in a large population of 49,702 infants in Shanghai, including 20,019 for active monitoring and 29,683 for passive monitoring, using the AEFI

monitoring system of the Shanghai CDC.¹⁷ The total rate of unsolicited AEs related to vaccination was 0.19%, and no grade 3 or 4 unsolicited vaccination-related reactions and no serious AEs related to vaccination were found in activating monitoring. AE rates were even lower in passive monitoring, with an incidence of 390.80/100,000 after 84,853 doses. Rare reactions in 6 participants were reported, including 4 cases of anaphylactic rash, 1 case of urticaria and 1 case of thrombocytopenic purpura, which suggested that we should pay more attention to these developments in future EPI mass vaccination. Of note, 42% cases of AEs occurred during concomitant administration with other vaccines, especially with the first dose of DTaP and DTaP-Hib, emphasizing that the effect of coadministering another vaccine with sIPV should be considered in routine vaccination.

4. Immunogenicity of the sIPV schedule in postmarket evaluation

To date, postmarket immunogenicity evaluations of sIPV have been reported in Japan and China. In Japan, sIPV was introduced into the national immunization program in November 2012, in which 3 doses of DTP-sIPV were administered to 3- to 90-month-old children at intervals of 20–56 days as the primary vaccination, followed by the fourth dose at least 6 months later; no booster was required after 2018.^{18,19} Hotta C et al¹⁸ reported that seroconversion rates reached 100% for all polio types after 4 doses of sIPV, and GMTs for type I, II and III polio were 173.3, 479.8 and 245.1, respectively. Comparing the neutralizing antibody titers induced by sIPV and tOPV, the polio type I neutralizing antibody titer was lower with IPV than OPV vaccination, whereas polio type II and III neutralizing antibody titers were significantly higher in IPV.¹⁸ In contrast to the DTP-sIPV antibody response in Japan, GMTs for anti-type II polio in China were lower than those for type I and type III. In a randomized, controlled, and open-label phase IV clinical trial of 3 doses of sIPV (manufactured by CNBG) involving 195 infants in China, seroconversion rates for 3 doses of sIPV vaccination reached 100%, 99.49% and 100% for type I, II and III, and GMTs were 4476.66, 510.18 and 1091.66, respectively.⁶ In our phase IV clinical trial of a consistency study for three commercial batches of sIPV (manufactured by IMBCAMS) in 1200 infants in China, seroconversion rates for type I, type II and type III were 99.83%, 98.93% and 99.44%, respectively, and GMTs were 3283.3, 231.1, and 932.0, respectively.¹⁷ The sIPV antigen content and manufacturing procedure may be related to the antibody level. sIPV contents for type I, II, and III polio with DTP-sIPV were 1.5, 50, and 50 sDU, 15, 45, and 45 DU and 30, 32, and 45 per dose, respectively, as manufactured by Kaketsuken, CNBG and IMBCAMS. Thus, a homologous reference measuring the antigen content of IPV is urgently needed to evaluate the potency of sIPV in clinical and postclinical trials worldwide.

With collaborative study among different laboratories, including the WHO, national regulatory departments in different countries and sIPV manufacturers, the first World Health Organization international standard for sIPV was established in 2019.²⁰ In addition, to guarantee a sufficient IPV supply for polio eradication using a full-dose sIPV

Table 1. The sIPV immunogenicity evaluation in postmarket studies of the sIPV primary schedule and sIPV-bOPV sequential schedule in China.

Vaccination schedule	sIPV antigen	Individuals Numbers	Location	Type 1		Type 2		Type 3		Ref.
				Seroconversion rate % (95%CI)	GMTs(95%CI)	Seroconversion rate % (95%CI)	GMTs(95%CI)	Seroconversion rate % (95%CI)	GMTs(95%CI)	
sIPV-bOPV-bOPV sIPV-sIPV-bOPV	Type I: 30 DU Type II: 32 DU Type III: 45 DU	358	Chongqing	99.7	2896 (2586–3244)	74.58	19(15–25)	100	1079 (972–1199)	7
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	158	Zhejiang	100	2048 (2048–2048)	62	12 (4–32)	100	2048 (1024–2048)	4
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	170	Guangxi	99.4 (96.8–100.0)	5,303.9 (4610.5–6101.5)	51.8 (44.0–59.5)	11.7 (9.8–14.0)	99.4 (96.8–100.0)	1285.7 (1124.2–1470.4)	5
	Type I: 15 DU Type II: 45 DU Type III: 45 DU	69	Hebei	100	4907.8	97.6	41.6	100	1692.15	13
	Type I: 15 DU Type II: 45 DU Type III: 45 DU	189	Inner Mongolia, Shanxi, and Hebei	100 (98.07–100)	5029.8 (4435.2–5704.2)	91.53 (86.62–95.08)	38.1 (32.1–45.2)	100 (98.07–100)	1406.7 (1235.6–1601.5)	6
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	70	Shanghai	100	840.9 (1715.6–1966.3)			100	1858.5 (1742.6–1973.5)	10
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	152	Zhejiang	100	2048 (2048–2048)	95	64 (32–224)	100	2048 (2048–2048)	4
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	180	Guangxi	98.9 (90.0–99.9)	7,359.6 (6379.2–8490.6)	79.4 (72.8–85.1)	73.4 (60.1–89.7)	99.4 (96.9–100.0)	2,941.1 (2493.7–3468.9)	5
	Type I: 30 DU Type II: 32 DU Type III: 45 DU	68	Hebei	100	7175.3	100	200.4	100	2986.3	13
	sIPV-sIPV-sIPV	Type I: 15 DU Type II: 45 DU Type III: 45 DU	185	Inner Mongolia, Shanxi, and Hebei		9310.9 (8132.9–10659.5)	98.4 (95.3–99.7)	270.4 (230.1–317.8)	100 (98.03–100)	4065.4 (3483.7–4744.3)
Type I: 30 DU Type II: 32 DU Type III: 45 DU		72	Shanghai	100	1085.6 (903.9–1267.2)			98.61	644.9 (518.7–771.1)	10
Type I: 30 DU Type II: 32 DU Type III: 45 DU		163	Zhejiang	100	2048 (2048–2048)	99	256 (128–512)	100	512 (256–1024)	4
Type I: 30 DU Type II: 32 DU Type III: 45 DU		1200	Yunnan	99.83 (98.1–100)	3283.3 (3091.7–3488.9)	98.93 (96.9–99.6)	231.1 (217.3, 245.9)	99.9 (98.5–100)	932.0 (880.6, 986.3.0)	18
Type I: 15 DU Type II: 45 DU Type III: 45 DU		195	Inner Mongolia, Shanxi, and Hebei	100 (98.1–100)	4476.7 (3982.0–5032.7)	99.5 (97.2–100)	510.2 (438.4–593.7)	100 (98.1–100)	1091.7 (942.2–1264.8)	6

sIPV: inactivated poliomyelitis vaccine made from Sabin strains; bOPV: bivalent oral poliomyelitis vaccine

schedule instead of a sequential schedule after bOPV withdrawal in the near future, with the exception of postapproval clinical studies of current sIPV administered intramuscularly, a clinical trial of fractional doses of sIPV administered intradermally should be performed as an appropriate vaccination route for polio endgame requirements.²¹

In conclusion, postapproval clinical studies of sIPV with both the full-dose sIPV schedule and sequential schedule indicate that commercial sIPV has good safety in large populations. Three doses of sIPV vaccination can induce high levels of GMTs against all three types of polio, revealing its good immunogenicity and the ability to neutralize multiple individual wild and vaccine-derived polioviruses,²² with no difference in response between male and female infants or among different populations.¹⁷ All these results indicate that sIPV is suitable for completely eradicating all types of poliovirus in the polio endgame period. In addition, with the increased manufacturing capability of sIPV, the 2sIPV-bOPV sequential schedule should be used as soon as possible instead of the present sIPV-2bOPV schedule worldwide, with transition to the full-dose sIPV schedule in the future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

ORCID

Li Shi  <http://orcid.org/0000-0001-9508-7863>

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