The Lancet Regional Health - Western Pacific 10 (2021) 100133

Contents lists available at ScienceDirect

The Lancet Regional Health - Western Pacific

journal homepage: www.elsevier.com/locate/lanwpc

Research Paper

Immunogenicity of two-dose and three-dose vaccination schedules with Sabin inactivated poliovirus vaccine in China: An open-label, randomized, controlled trial

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ARTICLE INFO

Article history:
Received 3 December 2020
Revised 22 February 2021
Accepted 4 March 2021
Available online 16 April 2021

Keywords:
Inactivated polio vaccine
Seroprevalence
Sabin Strain

ABSTRACT

Background: We assessed immunogenicity of three-dose and two-dose immunization schedules with a Sabin-strain inactivated poliovirus vaccine (sIPV) produced by one Chinese vaccine manufacturer.

Methods: This was an open label, randomized, controlled trial conducted in 16 vaccination clinics in Shandong province. Infants were allocated randomly to either a 3-dose study arm (sIPV administered at 2, 3, and 4 months of age) or a 2-dose arm (sIPV administered at 4 and 8–11 months of age). Poliovirus neutralizing antibodies were measured in sera collected prior to the first sIPV dose and one month after the last dose.

Findings: We enrolled 560 infants; 536 (95.7%) completed the study. Final seropositivity rates were >98% for all three serotypes in both study arms. There were no statistically significant differences in seropositivity between the 2-dose and the 3-dose schedule. Final median reciprocal titres of polio antibodies were high overall (>1:768 for all serotypes) and statistically significantly higher in 2-dose recipients compared with 3-dose recipients ($p < 0.001$).

Interpretation: This study offers evidence that two doses of sIPV administered at 4 and 8–11 months of age and three doses of sIPV administered at 2, 3, and 4 months of age both provide serological protection against poliomyelitis. Median reciprocal titres of polio antibodies were high overall, and were more related to the interval between doses than the number of doses, with the longer interval of the 2-dose schedule producing higher reciprocal titres than the shorter-interval 3-dose schedule. The protection provided by the 3-dose schedule is achieved earlier in life than the protection with the 2-dose schedule. Countries planning to use an IPV-only schedule in the post-eradication era can consider this 2-dose sIPV option as an immunogenic and dose-sparing strategy.

Funding: World Health Organization (from a grant from International PolioPlus Committee, Rotary International, Evanston, IL, USA).

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https://doi.org/10.1016/j.lanwpc.2021.100133

Research in context

Evidence before this study

Salk-strain inactivated poliovirus (IPV) vaccine is known to be safe and immunogenic in three-dose and two-dose infant vaccination schedules. Sabin-strain IPV is known to be immunogenic in three-dose infant vaccination schedules and in two-dose sequential infant vaccination schedules that also include two doses of live Sabin-strain poliovirus vaccine. We searched Pubmed using the term, "Sabin inactivated poliovirus vaccine," and of the 259 results, there were no studies of two-dose, Sabin-strain IPV infant vaccination schedules that did not include live, Sabin-strain poliovirus vaccine.

Added value of the study

We conducted a randomized, open-label clinical trial comparing immunogenicity and seropositivity of Sabin-strain IPV when given in either a two-dose or a three-dose infant vaccination schedule. Our study showed that Sabin-strain IPV was highly immunogenic and had high seropositivity rates (greater than 98% for against all three polio serotypes one month after the last dose) in both two-dose and three-dose vaccination schedules.

Implications of all the available evidence

The World Health Organization (WHO) anticipates recommending routine IPV vaccination of infants for at least ten years following certification of eradication of polio. WHO's seropositivity target for IPV in the post-eradication era is 90% or greater. Our finding that a reduced, two-dose vaccination schedule meets the WHO seropositivity target implies that a two-dose Sabin-strain IPV schedule will be able to be used in routine infant polio vaccination schedules to maintain polio-free status following polio eradication.

1. Introduction

The effort to eradicate polioviruses, led by the Global Polio Eradication Initiative (GPEI), continues to make progress towards its goal, albeit, in 2019, transmission of wild poliovirus type 1 intensified in the last two endemic countries (Afghanistan and Pakistan); and outbreaks of circulating vaccine derived polioviruses (cVDPVs) were detected in Africa and Asia. In China, one cVDPV type 2 isolate was detected from Xinjiang province in 2018 through environment surveillance and one case of acute flaccid paralysis caused by a genetically-related cVDPV type 2 was detected in Sichuan province in 2019 [1]. The Xinjiang VDPV2 was successfully controlled with a Sabin-strain inactivated poliovirus vaccine (sIPV) campaign and the cVDPV2 outbreak in Sichuan was stopped with an sIPV-only campaign, without use of monovalent oral poliovirus vaccine type 2 (mOPV2) in either place [2]. Wild poliovirus types 2 and 3 have been certified by the Global Certification Commission as eradicated in 2015 and 2019, respectively; and the African continent was certified as wild poliovirus free in 2020 [1,3–5].

The Polio Endgame Strategy 2019–2023 calls for withdrawal of all live poliovirus containing vaccines, such as oral poliovirus vaccine (OPV), because live Sabin poliovirus contained in OPV may, in rare circumstances, mutate, regain neurovirulence, and circulate just like wild poliovirus [6,7]. The withdrawal of OPV started in 2016 when trivalent OPV (tOPV) was replaced by bivalent OPV (bOPV, containing only serotypes 1 and 3) worldwide. This switch was preceded by introduction of at least one IPV dose in immunization schedules in many but not all countries [7]. With global wild poliovirus eradication nearing, countries are starting to consider removing bOPV entirely from their routine immunization schedules and replacing bOPV with inactivated poliovirus vaccine (IPV). IPV is manufactured either from Salk strains or, more recently, from Sabin strains (referred to as sIPV) [8].

At present, China's polio vaccination schedule includes two IPV doses (administered at 2 and 3 months of age) plus two bOPV doses (administered at 4 months and 4 years of age). China manufactures sIPV in several production plants. Most of the IPV used in China is sIPV, and is produced by inactivation of the attenuated poliovirus Sabin strains. Past studies from China provided evidence of safety and immunogenicity of different IPV (and sIPV) schedules [9–12]. In our study we compare immunogenicity of a two-dose with a three-dose sIPV schedule with the objective of providing China's National immunization Program evidence for making policy decisions about a future, post-eradication, IPV-only immunization schedule, with results potentially applicable to other countries.

2. Methods

This was an open-label, randomized, controlled trial assessing immunogenicity of a two-dose sIPV schedule in Chinese children compared with a three-dose schedule using sIPV produced by the Chinese Academy of Medical Sciences affiliated Institute of Medical Biology, Kunming, China (IMBK). IPV is formulated based on the content of D-antigen, the native antigenic form of poliovirus, and IPV potency is defined as the content of protective D-antigen [13]. IMBK vaccine contains 30, 32, and 45 D Antigen units for poliovirus types 1, 2, and 3, respectively.

The study was conducted in 16 vaccination clinics from four counties in Dezhou and Liaocheng prefectures, Shandong province. Infants were recruited in the clinics where they receive routine immunization services. Study participants were selected from registration lists at each clinic at one month age and were enrolled at two months age. At enrollment, after obtaining informed consent, study participants were randomized to receive either three doses of sIPV at 2, 3, and 4 months of age (study arm A1) or 2 sIPV doses at 4 and at 8–11 months of age (study arm A2), using a 1:1 block randomization scheme with a block size of eight (four per group). Selection of the age of administration of the second sIPV dose in study arm A2 was part of the randomization process, using a 1:1:1:1 randomization scheme for the 2nd dose to be given at 8, 9, 10, or 11 months. The randomization assignment number was computer-generated by China CDC investigators and placed into envelopes so that the local investigator could only access the randomization list when they opened the envelope, immediately after enrolling a participant. Each dose of sIPV was allowed to be co-administered with other vaccines according China's national immunization schedule - i.e., diphtheria-tetanus-acellular pertussis combined vaccine given at 3, 4, and 5 months; the 3rd dose of hepatitis *B* vaccine given at 6 months; measles-rubella combined vaccine and Japanese encephalitis vaccines given at 8 months; and meningococcal group *A* vaccine given at 6 and 9 months.

Two samples of peripheral blood were obtained from each infant - one just before the first dose of sIPV and the second one month after the last dose (for arm A1, the blood was collected at 2 and 5 months of age; for arm A2, the blood was collected at 4 months and at 9–12 months of age) [14]. Blood specimens were collected at the clinics between May 2018 and September 2019.

Blood specimens were allowed to clot, centrifuged to separate serum, and transported to the Shandong Provincial Center for Disease Control and Prevention (CDC) Laboratory where they were stored at −20 °C until shipment to the National Institute of Food and Drug Control (NIFDC), where the sera were tested for the presence of poliovirus neutralizing antibodies using standard neutral-

ization assays [15]. Immunogenicity analysis was based on the per-protocol dataset for all enrolled subjects having two serum samples. The highest detectable titre reported was 1: ≥ 16,384; the minimum (non-detectable) titre was < 1:8. Because the maximum dilution was capped at 1:16,384, we present median titres rather than mean titres. Final titres in the 2-dose study arm were stratified into four subgroups depending on when the second sIPV dose was administered (either at 8, 9, 10, or 11 months of age). For each serotype, seropositivity was defined as the reciprocal titre of poliovirus neutralizing antibodies ≥ 8; seroconversion in children with no maternal antibodies (at baseline blood sample) was defined as the change from seronegative to seropositive (from reciprocal titre of < 8 to ≥ 8); for subjects with maternal antibodies, seroconversion was defined as a 4-fold rise in reciprocal titres over an expected decline in maternal antibodies with estimated half-life of 28 days. The primary end point was serotype-specific seroprevalence of polio antibodies one month after the last sIPV dose.

Adverse events following vaccination were identified by site investigators and reported to China CDC according to the national surveillance guidelines for adverse events following immunization (AEFI). Infants were observed for 30 min following the administration of the vaccine for immediate adverse events; parents were instructed to report adverse events to the health centers. Adverse events were defined as any medical condition in the study participants during the study period. Serious adverse events were defined as any medical condition resulting in either hospitalization or death. Safety analysis was based on the per-protocol dataset for all enrolled subjects who finished all sIPV doses.

We calculated the sample size by setting 90% seroconversion as the minimum rate acceptable for the program, and we assumed a 95% seroconversion rate against all three types of poliovirus in both groups. We used a power of 0.80, and significance level of 0.05 (alpha, two-side), estimating that no more than 15% of subjects would become lost to follow-up. We considered there will be no significant difference between study arms. Therefore, each arm needed 281 subjects - a total of 562 participants. The sample size determination, with its programmatic implications, was a decision taken jointly by China CDC and World Health Organization (WHO) investigators.

Seroprevalence was expressed as percentages with 95% exact confidence intervals. Comparisons of seroprevalence were made using Fisher's exact test. Median titres were determined for the comparative arms with bias-corrected (BC) 95% confidence intervals. Median titres were compared between study arms by applying the Kolmogorov-Smirnov two sample test. Median titres were calculated for children who received two sIPV doses at 4 and 8 months, 4 and 9 months, 4 and 10 months and, 4 and 11 months. Comparison of these four groups was made using Kruskal Wallis test. Pair-wise comparisons adjusting for multiple testing will be done only if Kruskal Wallis test was significant as this was not the main scope of this study. Cumulative proportions from the reverse cumulative distributions between the two study groups were compared using the Tarone-Ware test. Data were analyzed using R 4.0.0.

The study was approved by the Ethical Review Committee of China CDC in Beijing and the Ethical Review Committee of the World Health Organization, Geneva. All activities followed guidelines of Good Clinical Practice; the trial protocol was registered at ClinicalTrials.gov (NCT03597919).

2.1. Role of the funding source

Main Funding was from the World Health Organization. Three of the authors are employees of the funder; collectively, assisted in study design, trial implementation, and monitoring, and contributed to the data analysis, interpretation and writing of the report. China CDC was responsible for conducting the trial as well as study design, data collection, data analysis, interpretation, and writing of the report, partially supported by the grant from China National Science and Technology Major Projects (2018ZX09734004).

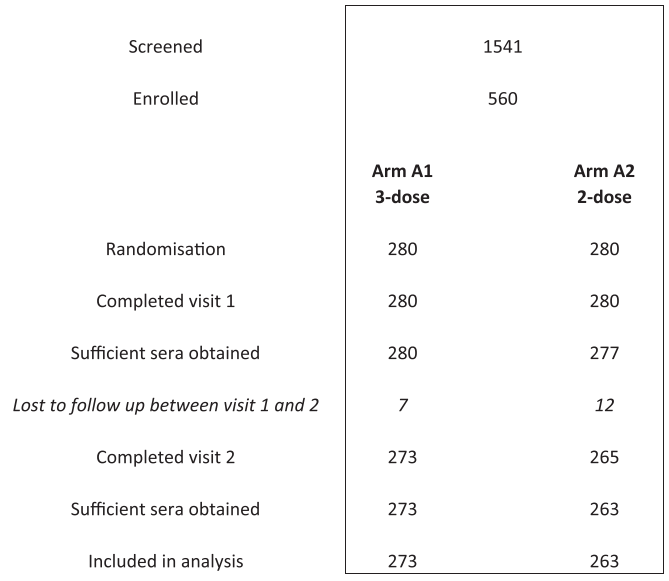

Fig. 1. Consort flowchart of the enrollment (A1: 3-dose study arm; A2: 2-dose study arm).

3. Results

There were 560 infants enrolled and randomized into either the 3-dose or 2-dose study arm. Analyzable blood specimens were obtained from 536 (96%) of the enrolled infants; these infants were included in the analyses (Fig. 1). There were no significant differences in baseline demographic characteristics between groups (Table 1).

Seroprevalence of polio antibodies at baseline (maternal antibodies measured in the infants) ranged between 14% for type 3 and 75% for type 1. The median age of first blood draw in the 3-dose arm was 66 days, compared to 125 days in the 2-dose arm; baseline seroprevalence was significantly higher among infants enrolled in 3-dose study arms compared to those enrolled in 2-dose study arms due to decline of maternal antibodies with infant age (p <0.001 for all serotypes). Median titres of antibodies at baseline were significantly higher in the 3-dose arm infants than in 2-dose arm infants for types 1 and 2 poliovirus; baseline titres were significantly different for all serotypes (p <0.001 respectively; Table 2).

Seroprevalence and seroconversion against the three types of poliovirus were > 95% in both arms (Tables 2 and 3). There were no statistically significant differences in final seroprevalence between the 2-dose and a 3-dose schedules for serotypes 1 and 2. For serotype 3, seroconversion was 1.9% higher in the 3-dose study arm than in the 2-dose arm and this difference was statistically significant.

Final titres of polio antibodies are presented in Table 2. Median titres were significantly higher in the 2-dose study arm than the 3-dose study arm for all three serotypes. Reverse cumulative titre distributions are presented in Fig. 2. There was a significant difference in the distribution of final titres for all serotypes - the distribution of final titres was always higher in the 2-dose arm than in the 3-dose arm (p <0.001 for all titre distributions). The final an-

Table 1
Baseline Demographic Characteristics (A1: 3-dose study arm; A2: 2-dose study arm).

	Group A1 $N = 273$ n (%)	Group A2 $N = 263$ n (%)
Gender	146 (53.5%)	154 (58.6%)
Male		
Age at first blood draw [months, IQR]	66 (62–70)	125 (123–130)
Breastfed when received first dose of sIPV		
Yes	235 (86.1%)	222 (84.4%)
No	6 (2.2%)	5 (1.9%)
Partial	32 (11.7%)	36 (13.7%)

Table 2
Baseline and Final Seroprevalences with Median Antibody Titres (A1: 3-dose study arm; A2: 2-dose study arm).

		Group A1 (2-month old)		Group A2 (4-month old)		P value
			95% CI		95% CI	
Baseline						
Type 1	Seroprevalence%	75.1	69.5–80.1	55.9	49.7–62.0	< 0.001
	Median Titres	24	16–24	8	< 8-< 8	< 0.001
Type 2	Seroprevalence%	64.8	58.9–70.5	42.6	36.5–48.8	< 0.001
	Median Titres	12	8–16	< 8	< 8-< 8	< 0.001
Type 3	Seroprevalence%	33.0	27.4–39.0	14.1	10.1–19.0	< 0.001
	Median Titres	<8	< 8-< 8	< 8	< 8-< 8	< 0.001
Final						
Type 1	Seroprevalence%	100.0	–	100.0	–	1.000
	Median Titres	3072	2677–4096	12,288	12,140-≥ 16,384	< 0.001
Type 2	Seroprevalence%	99.6	98.0–99.9	99.2	97.3–99.9	0.548
	Median Titres	256	256–384	2048	1852–3072	< 0.001
Type 3	Seroprevalence%	100.0	–	98.1	95.6–99.4	0.022
	Median Titres	768	746–768	1536	1024–1736	< 0.001

Table 3
Seroconversion (A1: 3-dose study arm; A2: 2-dose study arm).

	Group A1 (2 month old)		Group A2 (4-month old)		P value
	%	95% CI	%	95% CI	
Type 1	99.6	98.0–99.9	100.0	–	1.000
Type 2	97.1	94.3–98.5	99.2	97.3–99.8	0.111
Type 3	100.0	–	98.1	95.6–99.2	0.028

tibody titres did not significantly differ by age of second sIPV dose ($p = 0.49$, $p = 0.61$, $p = 0.11$, for types 1, 2 and 3 respectively); there was no observable trend (Table 4).

Fevers were observed in 16 subjects within 30 min after vaccination (6 infants in the 2-dose arm, 10 in the 3-dose arm). Among infants with fever, 14 have low-grade fevers (37.1–37.2 °C), two had temperatures above 38 °C (38.8 °C and 39.9 °C). One infant in the 2-dose arm had a temperature of 38.4 °C on the second day after vaccination. All reported fevers were temporary. No other adverse events were observed, and no serious adverse events were reported.

4. Discussion

Our study showed that a 3-dose and a 2-dose sIPV schedule both provide very high seroprevalence (> 98%) of polio antibodies against all three poliovirus serotypes, there was significantly higher seroconversion for type 3 in the 3-dose study group, however the increase represents < 2% in seroconversion having little programmatic impact. On the other hand, the final median antibody titres as well as titre distributions were significantly higher in children who received two sIPV doses at 4 and 8–11 months of age compared to children who received three sIPV doses at 2, 3 and 4 months of age. There was no significant difference in final titre by age of the second dose in the 2-dose schedule. When IPV is administered early in life, interference of maternal antibodies reduces immunogenicity of the vaccine. In our study, the early-age 3-dose schedule provided same immunogenicity as a later-age 2-dose schedule [16].

Our study showed that sIPV immunogenicity is similar to Salk-strain IPV immunogenicity [17–19]. Data from the clinical trial for regulatory approval of this sIPV, which used the same 3-dose schedule as the A1 arm of our study, showed seroconversion rates for poliovirus type 1, 2, and 3 were 100%, 96%, and 99% respectively, and GMT were 3716, 316, and 808 respectively [20]- similar with our study results.

Our study had the limitation that bOPV is used in China's routine immunization program, implying that Sabin strain poliovirus types 1 and 3 may circulate in the community and could influence the immunogenicity of the sIPV-only schedule through a boosting effect. This limitation does not apply to type 2 immunogenicity because bOPV does not include a type 2 component. This limitation applies similarly to both arms of the study, and we do not believe it to be a bias between the study schedules. A second limitation is that this study did not include another sIPV developed and made in China by China National Biotec Group (CNBG). The CNBG sIPV has different D-antigen content (15, 45 and 45 D antigen units for poliovirus types 1, 2, and 3), making our results not directly applicable to this vaccine.

Our findings have implications for the polio eradication program, as it provides evidence that a two-dose sIPV schedule administered at 4 and 8–11 months provides equivalent protection against poliomyelitis with a 3-dose schedule and can be considered as a dose-sparing strategy when countries start planning the switch to an all-IPV post-eradication schedule. Protection provided with the 2-dose schedule is achieved later in life than protection with the 3-dose schedule, which may be problematic in areas where high risk of importation of wild poliovirus or VDPV still exists. China's National immunization Program will consider using an IPV-only schedule in the future. Our study provides evidence to support decision making.

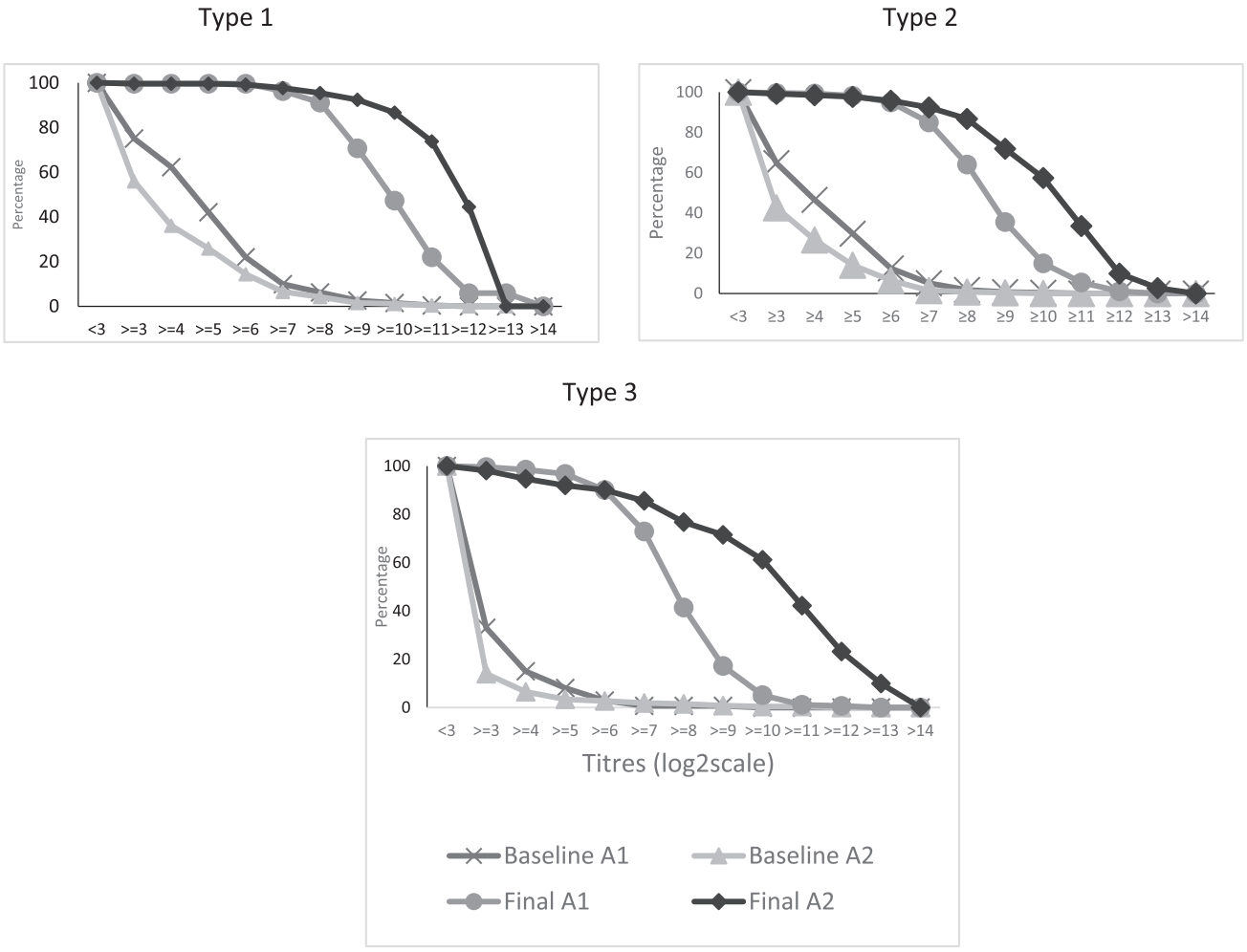

Fig. 2. Reverse Cumulative Distribution of Polio Antibody Titres (A1: 3-dose study arm; A2: 2-dose study arm.

Table 4
Final median antibody titres and 95%CI in the 2-dose sIPV study arm by age of administration of second sIPV.

Age of receipt of 2nd sIPV	8 months $N = 65$	9 months $N = 72$	10 months $N = 60$	11 months $N = 66$	p value
Type 1	12,288 (11,982-≥ 16,384)	12,288 (9049–14,336)	12,288 (7926-≥ 16,384)	≥ 16,384 (12,961-≥ 16,384)	0.489
Type 2	2048 (1659–2048)	2048 (1622–3072)	2560 (1596–3072)	1792 (1398–3584)	0.608
Type 3	1024 (537–1536)	2048 (1569–3072)	1024 (508–3072)	1536 (417–2048)	0.107

Declaration of Competing Interest

All authors of this manuscript have indicated that they have no conflicts of interest that relate to the content of this manuscript.

Acknowledgments

We sincerely thank all the infants and their parents who participated in the study, all investigators in the field for their superb work. We sincerely thank Tigran Avagyan from WHO Western Pacific region Office, and Zuo Shuyan from WHO China Office for helping us design the study.

Contributors

ZA and AX had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. ZA, O, AX, RS, YW, QX, and NW designed and concepted the study. YW, QX, JW, and HY collected data. YW, VJ, ZY, and QX analyzed data. OM, YW, VJ, ZY, and QX wrote the first draft. ZA, AX, RL, CL, NW, ZY, and ZF interpreted the findings and commented on and revised drafts of the manuscript. All authors contribute to reviewing, revising, and approving the final manuscript. YW, QX, VJ and ZY contributed equally.

Data sharing

Data will become publicly available upon request from the corresponding author beginning 3 months and ending 1 year after publication.

Role of the funding source

Three of the authors are employees of the funder; collectively, assisted in study design, trial implementation, and monitoring, and contributed to the data analysis, interpretation and writing of the report. China CDC was responsible for conducting the trial as well as study design, data collection, data analysis, interpretation, and writing of the report, partially supported by the

grant from China National Science and Technology Major Projects (2018ZX09734004).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.lanwpc.2021.100133.

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