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Boosting of Mucosal Immunity After Fractional-Dose Inactivated Poliovirus Vaccine

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Abstract

Background.—Inactivated poliovirus vaccine (IPV) boosts mucosal immunity in persons previously vaccinated with oral poliovirus vaccine (OPV). We assessed whether fractional-dose IPV (fIPV, 1/5th of full dose) administered intradermally also boosts mucosal immunity.

Methods.—Children 10–12 years old were enrolled in Sri Lanka and randomized to receive one dose IPV, fIPV, or no IPV vaccine. One month later, they received OPV challenge. Blood was collected at enrolment and before challenge; stool was collected at 3, 7, and 14 days post-challenge. Sera were analysed for presence of poliovirus neutralizing antibodies; stool was analysed for poliovirus.

Results.—We analysed 304/309 (98%) enrolled subjects. There were 16/97 (16%), 9/99 (9%), and 72/95 (76%) subjects excreting poliovirus after challenge in the IPV, fIPV and “No IPV Vaccine” study arms, respectively ($P < .001$ for comparison of IPV [or fIPV] vs “No IPV Vaccine”; $P = .1$ for comparisons of fIPV vs IPV). Relative decrease in excretion prevalence was 80% and 88% to IPV and fIPV, respectively, compared with the “No IPV Vaccine” control arm.

Conclusions.—Single fIPV dose boosted mucosal immunity to a similar degree as single full dose of IPV. This finding provides further evidence in support of fIPV for poliovirus outbreak response at the time of IPV global supply shortage.

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Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Clinical trials registration.—Australia New Zealand Clinical Trial Registry ACTRN12616000124437p.

Keywords

poliovirus; eradication; immune response; Sri Lanka

Poliovirus eradication is closer than ever to its goal. In 2017, there have been 22 reported cases of poliomyelitis caused by wild poliovirus type 1 from 2 endemic countries (Afghanistan and Pakistan) [1]; wild poliovirus type 2 was declared eradicated in 2015 by the Global Certification Commission [2]; and wild poliovirus type 3 has not been detected since November 2012, a period surpassing 5 years [3].

Sri Lanka's routine immunization program is considered one of the most successful, reaching 99% coverage with the third dose of oral poliovirus vaccine (OPV) in the past several years [4]. The schedule used until April 2016 called for trivalent OPV doses at 2, 4, 6, and 18 months, followed by a school entry dose at 5 years. A seroprevalence survey of poliovirus neutralizing antibodies conducted in Sri Lanka in 2014 showed >95% seroprevalence for poliovirus serotypes 1 and 2 (PV1 and PV2) in all studied age groups (9–11 months, 3–4 years, 7–9 years, and 15 years); and >75% seroprevalence for PV3 [5].

Immunity to polioviruses is mediated by 2 components: (1) humoral immunity, measured by the presence of circulating neutralizing antibodies in sera, provides protection against paralytic disease but may not protect individuals from acquiring poliovirus infection and transmitting the virus to others; and (2) mucosal (pharyngeal or intestinal) immunity that decreases the likelihood of acquiring poliovirus infection and prevents or limits the replication and excretion of the virus. Mucosal immunity is usually measured by evaluating resistance to excretion of polioviruses following a challenge with OPV [6–8].

OPV is an effective vaccine that induces both mucosal and humoral immunity. However, the mucosal immunity appears to wane rapidly, especially in tropical developing countries with low hygiene and sanitation. Significant mucosal immunity waning has been observed within a year of vaccine administration in Northern India [9]. Inactivated poliovirus vaccine (IPV) effectively induces humoral immunity but does not appear to induce mucosal immunity (ie, the generation of secretory IgA). However, importantly for outbreak response, boosting of intestinal mucosal immunity with IPV has been observed in individuals previously vaccinated with OPV [10–13]. The World Health Organization (WHO) recommends use of IPV as a tool for control of poliovirus outbreaks [14–16]. However, starting in 2016 the Global Polio Eradication Initiative (GPEI) has been experiencing an acute IPV supply shortage that affected initially almost 50 countries and caused either delays in IPV introduction or stock-outs in countries that had already introduced IPV in their routine immunization programs. Subsequently, IPV was prioritized for use in routine immunization rather than for outbreak response activities [17]. Although the supply situation is improving, the IPV shortage is likely to last for several more years and in some countries will result in several birth cohorts having no protection against PV2.

In order to expand the available IPV supplies, intradermal administration of one-fifth of a full IPV dose (0.1 mL instead of 0.5 mL, referred to as fractional IPV or fIPV) has been evaluated. The use of a 2-dose fIPV schedule for routine immunization is recommended by WHO's Strategic Advisory Group of Experts (SAGE) [18]; a schedule of 2 doses of fIPV provides superior immunogenicity compared to 1 full dose of IPV and stretches the existing supply of IPV [19–21]. Some countries have implemented a 2-dose fIPV schedule in routine immunizations programs, including Bangladesh, India, Sri Lanka, Nepal, and others. Furthermore, a single dose of fIPV has been used in vaccination campaigns for outbreak response activities in India and Pakistan [22].

There is a substantial body of evidence on the humoral immune response following fIPV administration [19]. However, the data on mucosal immunity are limited, and there are no data for mucosal response following a single dose of fIPV in children who had a history of receiving multiple doses of OPV. In this trial we assessed boosting of mucosal immunity by 1 dose of either full or fractional IPV in previously OPV-vaccinated children in Sri Lanka. The studied children were between 10 and 12 years of age and had received their last OPV as part of the Sri Lankan routine immunization program at least 5 years prior to the study. Given the length of time between the last dose of OPV (at school entry contact) and the age of the children, we assumed that their mucosal immunity had waned [8, 9, 23]. The children in our study had not received any previous IPV.

METHODS

We conducted a community-based, open-label, randomized clinical trial in Sri Lanka. Children between 10 and 12 years of age residing in Kalutara District of Sri Lanka were eligible for enrolment. Public Health Midwives and Public Health Inspectors, using lists of families residing in their catchment areas, randomly selected children in the target age group using simple random sampling. The exclusion criteria were contraindication for venipuncture, sick child requiring hospitalization for acute or chronic condition, and diagnosis or suspicion of congenital immunodeficiency disorder in the subject or an immediate family member. After receiving consent from parents and assent from children, the children were enrolled and randomized into 1 of 3 study arms. In study arm A, children received 1 full dose of IPV intramuscularly; in arm B, 1 dose of fIPV intradermally; and in arm C, they did not receive any IPV. Four weeks later, children in all study arms received 1 challenge dose of trivalent OPV (tOPV). We collected 2 blood samples, at enrolment and on the day of tOPV challenge, and we collected 3 stool samples, on days 3, 7, and 14 following the tOPV challenge. The enrolment took place on 2–3 April 2016; the tOPV administration was done on 28–29 April 2016, which coincided with the last nationwide tOPV vaccination campaign in Sri Lanka. The vaccines used in the study were the same as those used by the Sri Lankan immunization program (tOPV was produced by Sanofi Pasteur, France, and IPV by Bilthoven Biologicals, the Netherlands).

The blood specimens were allowed to clot at the primary care center. Sera were then separated and transported to Colombo, where they were stored at −20°C until the shipment to the Centers for Disease Control and Prevention (CDC) in Atlanta. The sera were tested for the presence of poliovirus neutralizing antibodies using standard neutralization assays

at CDC [24]. Seropositivity was defined as reciprocal titers of poliovirus neutralizing antibodies ≥1:8; seroconversion was defined as the change from seronegative to seropositive (from reciprocal titer of <1:8 to ≥1:8); and boosting was defined as ≥4-fold increase in titers. In this study, humoral immune response refers to either boosting or seroconversion. The analysis of immune response was restricted to children with a baseline serological titer of ≤1:362 to ensure that a 4-fold boosting response could be achieved because the highest titer reported was ≥1:1448.

Stool specimens were collected at the residence of the children and tested at the Medical Research Institute (the Polio Regional Reference Laboratory) in Colombo, Sri Lanka, for the presence of poliovirus using standard poliovirus detection methodology [25]. Presence or absence of poliovirus in stool samples was reported by serotype. Mucosal immunity was defined as resistance to excretion of poliovirus after tOPV challenge [8].

The target sample size for each arm was calculated to be 100 children per arm accepting alpha = 0.05 and power = 80%; and assuming at least 20% difference in poliovirus excretion rates between arms. Data was analyzed using EpiInfo 8. The proportion of excretion in different study arms was compared by X^2 test for quantitative variables. P value was calculated to assess differences in between study arms. The median titers across the study arms and 95% confidence intervals for median titers were calculated using the bootstrap method [26].

The study was approved by the Ethical Review Committees of the Sri Lanka Medical Association, the Ministry of Health, Sri Lanka and the WHO, Geneva, Switzerland.

RESULTS

A total of 309 children met the study eligibility criteria, were enrolled, and were randomized to 1 of the 3 study arms. The analysis was restricted to 304/309 (98%) children; the remaining 5 children received an OPV dose during a local polio vaccination outbreak response earlier in 2016 and were therefore excluded from the analysis. All of the 304 subjects provided a baseline blood sample, and 302/304 (99%) provided the second blood sample; there were 294/304 (97%), 300/304 (99%), and 299/304 (98%) children who provided analyzable stool samples on days 3, 7, and 14 post-tOPV challenge, respectively (Supplementary Figure 1).

The mean number of OPV doses the enrolled subjects received through the Sri Lankan routine immunization program prior to the enrolment was 5 and the median interval from the latest OPV dose was >5 years in all study arms (minimum = 51 months, maximum = 95 months). The baseline seroprevalence of antipolio antibodies was 98%, 98%, and 79% for PV1, PV2, and PV3 respectively. There were no statistical differences neither in the demographic indicators nor in the baseline seroprevalence between the study arms (Table 1).

The humoral immune response in the IPV or fIPV study arms was close to 100% (Table 2). There were 7%, 7%, and 13% of the children in the no IPV arm who experienced immune response for PV1, PV2, and PV3, respectively, despite not receiving any poliovirus vaccine. However, their antibody titers from sera collected in the end of the study were

low (approximately 1:11) indicating borderline immune response. Reverse cumulative distribution of titers for all 3 serotypes demonstrated that the boost in titers was the same following either IPV or fIPV administration (Figure 1A–C).

Excretion of polioviruses 3, 7, and 14 days after tOPV challenge is shown in Figure 2. There was no statistical difference in poliovirus excretion between full and fractional IPV study arms. There was statistically higher incidence of excretion of polioviruses in the no IPV arm than in either of the 2 IPV arms at all time points ($P < .001$ for PV1 and PV3; $P < .02$ for PV2).

Overall, 16/97 (16%), 9/99 (9%), and 72/95 (76%) subjects excreted any poliovirus (serotypes 1, 2, or 3) at any time point after tOPV challenge in the IPV, fIPV, and no IPV study arms, respectively ($P < .001$ for comparison of IPV [or fIPV] vs no IPV; $P = .1$ for comparisons of fIPV vs IPV). The relative decrease in shedding was 80% in the full IPV arm and 88% in the fIPV arm compared with the no IPV arm.

There were 2/99 (2%), 3/97 (3%), and 15/95 (16%) children who excreted more than 1 serotype at any time point after tOPV challenge in the IPV, fIPV, and no IPV study arms, respectively ($P < .001$ for comparison of IPV [or fIPV] vs no IPV; $P = .4$ for comparisons of fIPV vs IPV).

There were no children in the IPV or fIPV arms who excreted the same poliovirus serotype on all 3 occasions (days 3, 7, and 14); in the no IPV arm there were 5/95 (5%), 0/95 (0%), and 2/95 (2%) children excreting the same serotype (PV1, PV2, or PV3, respectively), on all 3 study visits.

The excretion prevalence in the no IPV arm was unexpectedly low for PV2 when compared with PV1 and PV3. The highest prevalence of excretion was at day 7: 33% for PV3, followed by PV1 (29%), compared with a low excretion rate of 10% for PV2 (Figure 2).

We analyzed the association of baseline antibody titers and homologous poliovirus excretion in the no IPV study group (Figure 3). For the purposes of this analysis, we divided the children into 2 groups for each serotype: those with titer equal to or less than the median titer were assigned to the low-titer group; and those with baseline titer greater than the median titer were assigned to the high-titer group. There were 51% and 29% of children excreting PV1 at any point after the tOPV challenge in the low and high-titer groups respectively ($P = .03$); this was 20% vs 10% for PV2 ($P = .09$); and 48% vs 33% for PV3 ($P = .1$).

DISCUSSION

Our study provides several new insights. A single fIPV dose boosted mucosal immunity in previously OPV-vaccinated children to the same degree as a full IPV dose. Our study further confirmed that 1 fIPV dose or 1 full IPV dose equally boosted humoral immunity in almost all study subjects; the boosting was equal in terms of titer distribution as well as in terms of proportion of children with immune response. We confirmed the inverse relationship of antibody titer and excretion prevalence in previously OPV-vaccinated children (the higher

the antibody titer, the lower the excretion prevalence) [27]. And finally, not demonstrated elsewhere, our results seem to suggest that PV2 mucosal immunity is more prevalent compared with PV1, and especially with PV3.

The ability of a single dose of fIPV to boost mucosal immunity equally (both in terms of prevalence and duration of excretion after a tOPV challenge) to a full dose among previously OPV-vaccinated children is a new finding. Previously, limited data from Oman after 3 fIPV doses [28] administered to polio-vaccine–naive infants did not suggest that fIPV differentially boosted mucosal immunity compared to full-dose IPV. The relative decreases in shedding in our study (approximately 80%–90%) were similar to those reported in the 10-year age group in India [11].

In addition to the mucosal immunity boost, both IPV and fIPV provided almost universal humoral immune response reflected in a significant increase in antibody titers in almost all children. These findings are in line with a body of literature that demonstrates that IPV immunization after OPV, whether fIPV or full-dose IPV, appears to close most of the immunity gaps, and is able to boost the antibody titer to high levels [7, 28, 29].

Furthermore, children in the no IPV study arm with higher baseline antibody titers induced by prior tOPV vaccination were less likely to excrete poliovirus after being exposed to the tOPV challenge. Similar findings have been reported previously [6, 27]. The significant association for PV1 remained when we controlled for time since the last documented OPV administration. We hypothesize that (1) high antibody titer indicated secondary exposure to tOPV from recently vaccinated contacts boosted the mucosal immunity; (2) mucosal immunity to serotype 2 is more prevalent than that to serotypes 1 and 3; or (3) that the high antibody titer facilitated faster mucosal response when poliovirus infection occurred. Further study is needed to distinguish which of these is the most likely explanation for our findings.

Sabin type 2 is the most transmissible of the 3 poliovirus serotypes contained in tOPV, and may be transmitted to a greater degree from recently vaccinated contacts than the other 2 serotypes [30]. Over time, this may result in more prevalent mucosal immunity to poliovirus type 2. Therefore, if the findings from Sri Lanka can be generalizable to other populations, they may help explain the relatively infrequent emergence of vaccine-derived poliovirus type 2 following the withdrawal of Sabin type 2 from OPV in April 2016 [31]. However, it may also suggest that the future withdrawal of the serotypes 1 and 3 from OPV, respectively, may not profit from this effect.

Our study had limitations: tOPV was used for routine immunization in Sri Lanka, therefore children in our study were exposed to the vaccine poliovirus from recently vaccinated contacts, for example younger siblings. This may have biased the assessment of mucosal immunity. Indeed, we found lower than anticipated excretion of PV2 in the no IPV study arm, suggesting secondary transmission of PV2 [32]. The excretion of PV1 and PV3 was about 40% lower than reported from India [11], suggesting that the rapidity of waning may have been in general somewhat slower in Sri Lanka, for unknown reasons. In addition, this study was not blinded and therefore children knew whether they had received an IPV or not; however, we do not believe that this knowledge could have influenced poliovirus excretion.

Together, both the mucosal and humoral boosting effects of a single fIPV dose provide strong support for using fIPV for outbreak control, especially in children who have a history of prior OPV immunization. The use of fIPV stretches limited IPV supplies, allowing vaccination of a much larger geographic area and target population, and controlling outbreaks more efficiently. Therefore fIPV should become the vaccine of choice for mass vaccination campaigns, both for outbreak response and for catch up IPV vaccination of cohorts missed due to the supply shortages. SAGE does not recommend use of any IPV for poliovirus outbreak control, except in special situations and then only fIPV [33]. Our findings fully support this recommendation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments.

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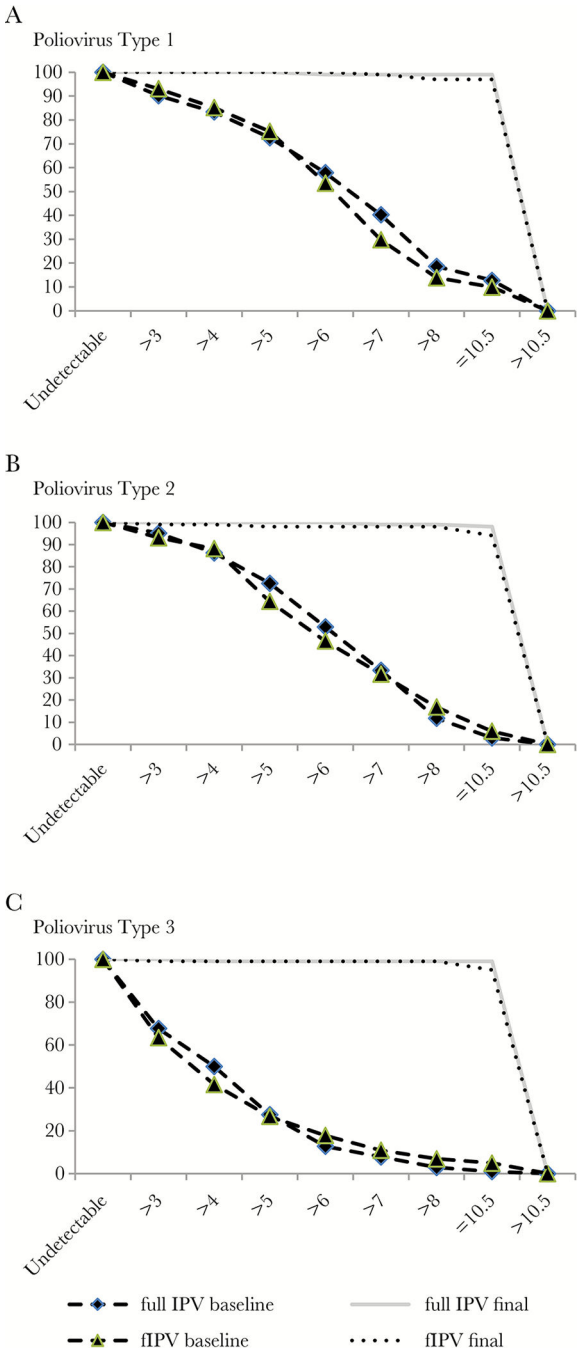

Figure 1.

Reverse cumulative curves of antibody titer distribution: x axis, reciprocal titer; y axis, % of those reaching or exceeding the titer on x axis. Abbreviations: fIPV, fractional-dose inactivated poliovirus vaccine; IPV, inactivated poliovirus vaccine.

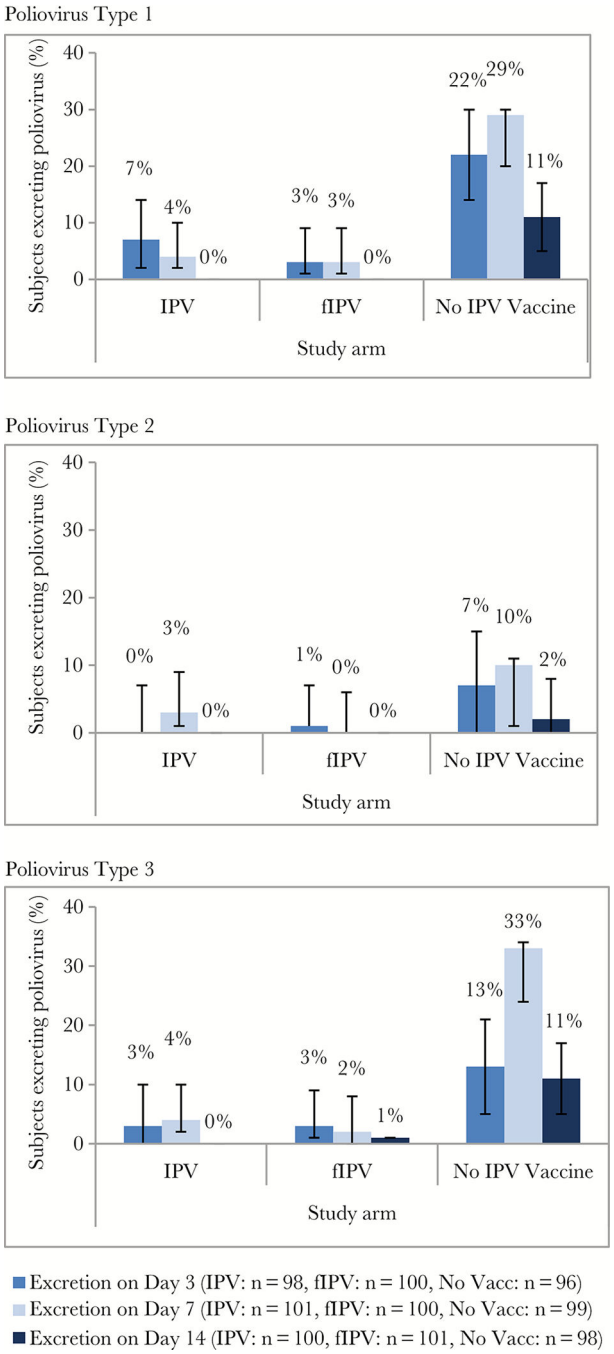

Figure 2.

Poliovirus excretion 3, 7, and 14 days after trivalent oral poliovirus vaccine challenge. Abbreviations: fIPV, fractional-dose inactivated poliovirus vaccine; IPV, inactivated poliovirus vaccine; No vacc, no vaccine.

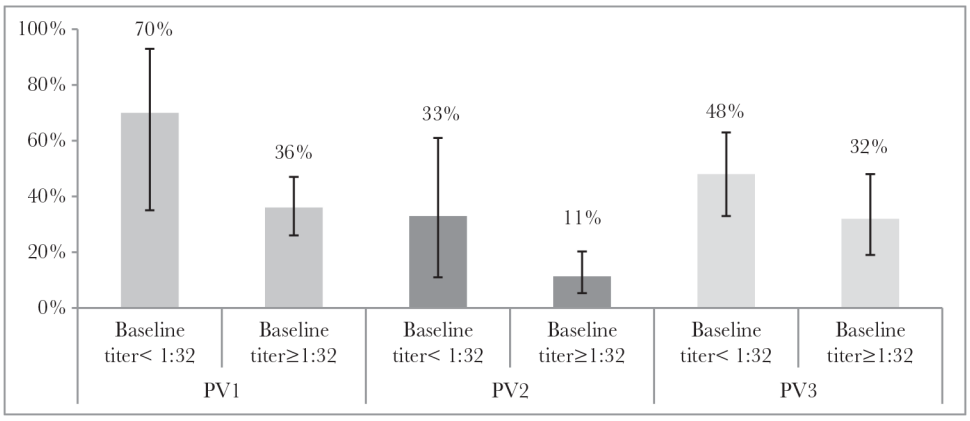

Figure 3.

Poliovirus excretion (%) in the no IPV study arm and its association with the baseline antibody titer (excretion at any time point after challenge, day 3, 7, or 14). Abbreviation: PV, poliovirus serotype.

Table 1.

Demographic Indicators, Vaccination History, and Baseline Seroprevalence of the Study Population

	Arm A (Full-Dose IPV) N = 102	Arm B (fIPV) N = 101	Arm C (No IPV) N = 101	Total N = 304	P Value(Ref: Arm C)
Gender: female, No./total (%)	50/102 (49)	60/101 (59)	46/101 (46)	156/304 (51)	*P* > .12
Age, y median (IQR)	11 (10–11.5)	11 (10.5–12.5)	11 (10.5–11.5)	11 (10.5–11.5)	*P* > .6
Mothers' education at least ordinary level, No./total (%) (11 grades)	70/102 (69)	78/101 (77)	76/101 (75)	224/304 (74)	*P* > .4
OPV history, mean number of doses	5	5	5	5	*P* = 1
Months since last OPV, median (IQR)	69.5 (61–76.5)	68 (61.5–73.5)	72 (65–78)	70 (62.5–76.5)	*P* > .1

Abbreviations: fIPV, fractional-dose inactivated poliovirus vaccine; IPV, inactivated poliovirus vaccine; IQR, interquartile range; OPV, oral poliovirus vaccine.

Table 2.

Baseline and Final Seroprevalence, Median Titers (Reciprocal Dilution), and Immune Response

	Arm A (Full Dose IPV)	Arm B (fIPV)	Arm C (no IPV)
Baseline seroprevalence, median titer			
PV1, No./total (% positive, 95% CI)	100/102 (98, 93–99)	99/101 (98, 93–99)	100/101 (99, 95–100)
Median titer (95% CI)	(227–455)	(227–455)	(181–455)
PV2, No./total (% positive, 95% CI)	102/102 (100)	98/101 (97, 92–99)	97/101 (96, 90–99)
Median titer (95% CI)	(90–181)	(80–181)	(101–227)
PV3, No./total (% positive, 95% CI)	82/102 (80, 71–88)	79/101 (78, 69–86)	78/101 (77, 68–85)
Median titer (95% CI)	(22–36)	(18–36)	(18–45)
Final seroprevalence, median titer			
PV1, No./total (% positive, 95% CI)	102/102 (100)	101/101 (100)	98/99 (99, 95–100)
Median titer (95% CI)	≥1448 (≥1448 to ≥1448)	≥1448 (≥1448 to ≥1448)	362 (227–576)
PV2, No./total (% positive, 95% CI)	102/102 (100)	101/101 (100)	96/99 (97, 92–99)
Median titer (95% CI)	≥1448 (≥1448 to ≥1448)	≥1448 (≥1448 to ≥1448)	181 (135–241)
PV3, No./total (% positive, 95% CI)	102/102 (100)	100/101 (99, 95–100)	86/99 (87, 79–93)
Median titer (95% CI)	≥1448 (≥1448 to ≥1448)	≥1448 (≥1448 to ≥1448)	36 (18–56)
Immune response (seroconversion or boosting in those with baseline titer ≤ 362)			
PV1, No./total (% with response, 95% CI)	53/54 (98, 90–100)	55/56 (98, 90–100)	4/54 (7, 2–18)
PV2, No./total (% with response, 95% CI)	87/87 (100)	78/79 (99, 93–100)	5/72 (7, 2–15)
PV3, No./total (% with response, 95% CI)	96/97 (99, 94–100)	88/89 (99, 94–100)	12/92 (13, 7–22)

Abbreviations: CI, confidence interval; fIPV, fractional-dose inactivated poliovirus vaccine; IPV, inactivated poliovirus vaccine; PV1, poliovirus type 1; PV2, poliovirus type 2; PV3, poliovirus type 3.