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Assessing the immunogenicity of three different inactivated polio vaccine schedules for use after oral polio vaccine cessation, an open label, phase IV, randomized controlled trial

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Abstract

Background: After global oral poliovirus vaccine (OPV) cessation, the Strategic Advisory Group of Experts on Immunization (SAGE) currently recommends a two-dose schedule of inactivated poliovirus vaccine (IPV) beginning ≥14-weeks of age to achieve at least 90% immune response. We aimed to compare the immunogenicity of three different two-dose IPV schedules started before or at 14-weeks of age.

Methods: We conducted a randomized, controlled, open-label, inequality trial at two sites in Dhaka, Bangladesh. Healthy infants at 6-weeks of age were randomized into one of five arms to receive two-dose IPV schedules at different ages with and without OPV. The three IPV-only arms are presented: Arm C received IPV at 14-weeks and 9-months; Arm D received IPV at 6-weeks and 9-months; and Arm E received IPV at 6 and 14-weeks. The primary outcome was immune response defined as seroconversion from seronegative (<1:8) to seropositive (≥1:8) after vaccination, or a four-fold rise in antibody titers and median reciprocal antibody titers to all three poliovirus types measured at 10-months of age.

Findings: Of the 987 children randomized to Arms C, D, and E, 936 were included in the intention-to-treat analysis. At 10-months, participants in Arm C (IPV at 14-weeks and 9-months) had ≥99% cumulative immune response to all three poliovirus types which was significantly higher than the 77–81% observed in Arm E (IPV at 6 and 14-weeks). Participants in Arm D (IPV at 6-weeks and 9-months) had cumulative immune responses of 98–99% which was significantly higher than that of Arm E (p value < 0.0001) but not different from Arm C.

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Contributors

All authors contributed to the design of the study. Study implementation was managed in Bangladesh by KZ, AA, and MY, and supported by all authors. MAP and MSO contributed to laboratory testing. SK and AA contributed to data analysis. All authors contributed to interpretation of study results. All authors reviewed and approved the final article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Interpretation: Results support current SAGE recommendations for IPV following OPV cessation and provide evidence that the schedule of two full IPV doses could begin as early as 6-weeks.

Keywords

Poliovirus; Inactivated poliovirus vaccine; Immunization schedule

1. Introduction

The Global Commission for Certification of Poliomyelitis Eradication declared wild poliovirus (WPV) type 2 eradicated in 2015 [1,2] and WPV type 3 eradicated in 2019 [3]. In April 2016, the global polio community switched from trivalent oral poliovirus vaccine (tOPV) to bivalent OPV (bOPV) for all immunization activities, removing type 2 poliovirus from the vaccine [4] as a first step in cessation of OPV use. Successful cessation of OPV use is required to end transmission of all live vaccine polioviruses and to ensure eradication of paralysis due to all polioviruses. After certification of global eradication of wild poliovirus type 1, the use of bOPV will be discontinued to prevent the risks of vaccine-associated paralytic polio (VAPP) and circulating vaccine-derived polioviruses (cVDPV) [5,6]. The polio end game strategy requires new vaccination schedules that expand the use of inactivated poliovirus vaccine (IPV) in order to reduce risks of inadvertent poliovirus transmission, such as a breach in facility containment, to effectively immunize populations against paralytic polio [7].

After global OPV cessation, the World Health Organization's Strategic Advisory Group of Experts on Immunization (SAGE) recommends a two full-dose or fractional (one-fifth) dose schedule of IPV to achieve at least 90% immune response [8]. Currently, SAGE recommends the first dose be given at or after 14-weeks of age and the second dose at least 4-months thereafter [8]. Administration of the first dose is recommended at or after 14-weeks because the immune response to IPV is higher after maternal antibodies have declined by infant age 14-weeks [8]. A clinical trial conducted in Cuba before the global switch from tOPV to bOPV reported close to 100% immune response after two full-doses of IPV at 4 and 8-months of age (type 1: 100%; type 2: 100%; type 3: 99%) [9]. A trial in Latin America reported 100% type 2 immune response after two full doses of IPV at 14-weeks and 36-months, along with bOPV at 6, 10 and 14-weeks of age [10]. A trial in conducted in Panama and the Dominican Republic among OPV naïve infants comparing full and fractional two dose and three dose schedules given at either 14-weeks and 36-weeks or 10-weeks, 14-weeks and 36-weeks found seroconversion rates of between 97 and 100% for all three polio virus types for the two full-dose schedule given at 14 and 36-weeks [11]. However, no published clinical trial has assessed the SAGE-recommended IPV-only schedule to multiple two full dose schedules given at or before 14-weeks of age in a post-switch environment.

An ideal IPV schedule will optimize individual immunity with overall vaccination coverage in routine immunization (RI). The current Expanded Programme on Immunization (EPI) schedule recommends the first dose of vaccines containing diphtheria-tetanus-pertussis-

(DTP) vaccine (generally as part of pentavalent vaccination that includes Hepatitis B Vaccine and Hemophilus Influenza B) at 6-weeks, second dose at 10-weeks, and the third dose at 14-weeks of age. Globally in 2018, 5.9 million more children received their first dose of DTP than received their third dose, 90% vs. 86% of eligible children, respectively [12]. Therefore, an IPV only schedule that is aligned with the first dose of DTP at 6-weeks is likely to achieve higher vaccination coverage than a schedule that starts later in the EPI schedule. Furthermore, an IPV dose schedule where the initial dose is given at the earliest possible contact with RI could provide protection from VAPP for a certain percentage of vaccinated children while OPV is still in use [13].

Multiple clinical trials have demonstrated immune response of approximately 90% to all three poliovirus types with two full-doses of IPV when only the first dose or the first and second dose are administered before or at 14-weeks of age, and the time period between doses is less than four months. A clinical trial in Cuba with full-dose IPV given at 8 and 16-weeks reported immune response rates of 90%, 89% and 90% for types 1, 2, and 3, respectively [14], while a trial in Oman reported >90% immune response to two full doses of IPV at two and four months of age [15]. More recently, a clinical trial in Bangladesh reported achieving over 90% immune response for all poliovirus types with two full-doses of IPV at 6 and 14-weeks of age (type 1: 95%; type 2: 91%; type 3: 97%) [16]. Another trial in Bangladesh found >95% type 2 polio immune response with two full-doses of IPV at both 6 and 18-weeks, and 14 and 18-weeks of age [17].

To assess the immune response to IPV only schedules that start before 14-weeks of age, we conducted a study in Bangladesh with the primary objective to compare the 10-month immune response and antibody titers to poliovirus types 1, 2, and 3 for three different two full-dose IPV schedules administered at 14-weeks and 9-months, 6-weeks and 9-months, and 6 and 14-weeks among bOPV-naïve infants. The 14-week and 9-month schedule adapts the SAGE recommendations to align with the EPI schedule of third DTP dose and first measles-rubella (MR) vaccine dose; the 6-week and 9-month schedule aligns with first DTP dose and first MR dose, and the 6-week and 14-week schedule aligns with first and third DTP doses. As a secondary objective, we compared 18-week immune responses and antibody titers to one or two full-dose IPV only schedules given before or at 14-weeks of age.

2. Methods

2.1. Trial design and participants

We conducted a randomized, controlled, open-label, superiority trial at two sites (Mirpur and Mohakhali) in urban Dhaka, Bangladesh. Sites were selected for their prior experience with conducting polio vaccine clinical trials. Trial enrollment began in November 2017, over a year after Bangladesh switched from tOPV to bOPV use in April 2016. The trial had two primary objectives, the first to assess immunogenicity of IPV-only schedules and a second to assess duration of immunity of both IPV only and bOPV and IPV schedules (follow-up until 18-months plus 1-week of age). The protocol a priori included analyses of collected sera from children in the IPV-only arms upon completion of participant visits at 10-months of age. This article presents immunogenicity results of children in the three

IPV-only arms through 10-months of age. The trial protocol and amendments were approved by icddr,b's (formerly known as the International Centre for Diarrhoeal Disease Research, Bangladesh) institutional review board (IRB) (Human Welfare Assurance #00001822). The study protocol and amendments were shared with the Human Research Protection Office of the US Centers for Disease Control and Prevention (CDC) but approval deferred to icddr,b's IRB under Federal-wide Assurance. CDC staff had no interaction with participants nor any access to personally identifiable information.

Study staff assigned to specific communities identified and recruited expectant mothers; interested parents were invited to participate. Eligibility criteria included participants of singleton birth aged six-weeks (42–48 days), full term (>37-weeks gestation), who would remain in the trial area for the duration of the 73-weeks of follow-up. Exclusion criteria were evidence of a medical condition in the infant that contraindicated blood collection by venipuncture or administration of IPV, a chronic medical condition identified by a trial medical officer (not including stunting or wasting), severe illness or infection at enrollment that would require hospitalization, acute vomiting and intolerance to liquids within 24 h of enrollment, receipt of any polio vaccine (OPV or IPV), and known allergy or sensitivity to polio vaccine or its contents. Written informed consent was obtained from parents, and parents could withdraw consent for participation at any time. Trial staff discontinued participants from the trial if a polio vaccine was received outside the trial; if they identified a medical condition in which participation posed a risk to the infant's health; if they identified an immunodeficiency disorder or bleeding disorder; or if they were unable to collect blood at the enrollment visit.

2.2. Randomization and masking

Participants were randomly allocated (1:1:1:1:1) to one of five trial groups, with each group representing a different immunization schedule. This article describes the IPV-only Arms C, D, and E (Fig. 1). Participants in Arm C received full-dose IPV at 14-weeks and 9-months; those in Arm D received full-dose IPV at 6-weeks and 9-months; and participants in Arm E received full-dose IPV at 6-weeks and 14-weeks (Table 1). Arms A and B received bOPV at 6, 10, and 14-weeks and IPV 14-weeks and 18-months (Arm A) and 14-weeks, 18-weeks, and 18-months (Arm B) (analysis of serologic testing results for children in all five arms through 18-months of age not included in this manuscript). At each trial clinic, block randomization was used with varying block sizes of one to four per block. The randomization list was generated using R (blockrand) by CDC; trial staff and parents had no prior knowledge of arm assignment until after enrollment procedures were completed. CDC laboratory staff were unaware of trial arm assignment

Upon enrollment at 6-weeks of age, staff obtained participant's clinical history (i.e. breastfeeding, health status), completed a physical examination (temperature, weight, and length), collected a blood sample, and administered IPV for participants in Arm D and E only (Table 1). All participants received the recommended vaccinations, except poliovirus vaccines, according to the EPI schedule of the Bangladesh Ministry of Health and Family Welfare including Penta and pneumococcal conjugate vaccine (PCV) administered at 6, 10 and 14-weeks and measles-rubella vaccine administered at 9 and 15-months. Participants

were monitored for 30 min after receiving IPV for any systemic or injection-site adverse events. Weight was measured twice by use of an electronic scale with a precision to 100 g and length measured twice by use of measuring board with precision to 1 mm. The mean of the two measurements was used to assess for evidence of wasting (reduced weight for age) or stunting (reduced length for age) according to the child-growth standard curves from the WHO's Multicenter Growth Reference Trial [18]. Wasting and stunting were defined as participants with measurements two or more standard deviations below the mean of the reference population.

Participants returned to clinics at 14-weeks, 18-weeks, 9-months, and 10-months of age to complete trial activities. An additional clinic visit at 10-weeks of age was conducted for administering routine immunizations (excluding polio). At each visit, trial staff collected clinical histories, completed physical examinations, collected blood specimens (18-weeks for all Arms; 9-months for Arms C and D only; and 10-months for all Arms), administered IPV (14-weeks for Arms C and E; 9-months for Arms C and D), and monitored for adverse events. All blood samples were collected before administration of IPV.

The IPV used in the trial was manufactured by Sanofi Pasteur (Lyon, France) and each full dose contained serotype 1 (40 D-antigen units of the Mahoney strain), serotype 2 (8 D-antigen units of the MEF-1 strain), and serotype 3 (32 D-antigen units of the Saukett strain). IPV in prefilled syringes was used for all 6-week and 14-week injections (batch M746522V). For the 9-month IPV doses, 251 participants received IPV from prefilled syringes (batch M746522V) and 375 participants received IPV from multidose vials (batch P3D98). The multidose vials were equally distributed between trial sites and arms C and D. All IPV doses were administered as intramuscular full dose (0.5 mL) to the outer, upper right thigh of participants. Participants received all routine immunization vaccines (except for the polio vaccines) according to the EPI schedule of the Bangladesh Ministry of Health and Family Welfare. Upon completion of participation, all participants received three doses of bOPV at 4-week intervals beginning at 18-months of age to ensure compliance with national guidelines for polio vaccination. All vaccines remained in cold chain as per the manufacturer's recommendations.

Blood samples (1 mL at 6-weeks, 18-weeks, and 9-months, and 1.5 mL at 10-months) were transported to the icddr,b laboratory by the end of each day; samples were stored and transported at 2–8 °C. Samples were centrifuged within 24 h of collection and sera were aliquoted for testing (stored at −20 °C) and long-term storage (stored at −70 °C). Upon completion of the 10-month visits, serum samples were sent to the CDC laboratory in Atlanta, GA, USA, for testing. The polio microneutralization assay was used to measure antibody titers to poliovirus 1, 2, and 3, with a lower limit of quantitation of 1:8 and the upper limit of quantitation of 1:1448, as described previously [19]. Values outside this range are expressed as <1:8 and ≥1:1448.

2.3. Outcomes

The primary outcome was immune response and median reciprocal antibody titers measured at 10-months of age, after receipt of two doses of IPV. Immune response was defined as seroconversion from seronegative (<1:8) at baseline (6-weeks of age) to seropositive (≥1:8)

after vaccination, or a four-fold rise in antibody titers between baseline and 4-weeks post-vaccination after adjusting for the exponential decay of maternal antibodies assuming a half-life of 28 days. Cumulative immune response was defined as the proportion of participants who had an immune response at any timepoint (18-weeks, 9-months, or 10-months). The secondary outcome was immune response and median reciprocal antibody titers after one or two doses of IPV measured at 18-weeks of age. We also measured immune response and median reciprocal antibody titers at 9-months of age for Arms C and D to evaluate immune response and antibody titers before administration of the second IPV dose.

Systemic and injection-site adverse events were monitored during the trial. Adverse events were defined as any illness occurring in participants during the trial period. Serious adverse events were defined as death, admission to hospital or prolongation of a stay in hospital, paralysis or severe disability, and anaphylaxis. During clinic visits, parents were asked about any illnesses since the last visit and participants were monitored for 30 minutes after receiving IPV for any adverse events. Parents were instructed to seek medical care if their infant became ill between trial visits. All adverse event reports were reviewed by the principal investigator and all serious adverse events reports were shared within 24 h to icddr,b's IRB, the Data Safety Monitoring Board, Sanofi Pasteur, and CDC.

2.4. Statistical analyses

To address the primary objective, immune response, a sample size of 329 per arm was targeted for enrollment, accounting for 20% attrition. To assess the immunogenicity of the three different IPV-only schedules, we assumed 90% immune response to all three types after two doses [16,17]. With 90% power and a two-sided alpha of 0.05, we powered the trial to detect a 10% difference in immune response for each pairwise comparison assuming equality. A 95% confidence interval around the difference in immune response was calculated and differences between arms was assessed by Fisher's exact test to ascertain differences in immune response. The Kruskal-Wallis test was used to assess differences in measured reciprocal antibody titer distributions among responders between arms. Multiple comparison correction was not applied to the analyses because a priori hypotheses were tested at different outcome endpoints. Reverse cumulative distribution function curves were created to visualize the differences in antibody titers among those with an immune response. The y-axis shows proportion of participants with antibody titers at least of the value represented on x-axis in the logarithmic scale. Descriptive analyses (medians and proportions) of baseline characteristics and adverse events are also presented. All data, analysis, and results were reviewed and verified by two co-authors independently.

The primary analytical approach was a modified intention-to-treat, defined as participants who had adequate blood specimens for serology at baseline, 18-weeks, 9-months (Arms C and D only), and 10-months. Per-protocol analysis was also completed, and no appreciable differences were observed in results (data not shown); therefore, the intention-to-treat results are presented. Analyses were completed using R (version 3.5.1). This trial is registered with ClinicalTrials.gov, number NCT03202719.

2.5. Role of funding source

The staff of the sponsor of this trial participated in the trial design, protocol development, data analysis, data interpretation, and manuscript development. The staff of the sponsor did not participate in data collection. All authors had full access to all trial data except for personally identifiable information, and the corresponding author had final responsibility for submission for publication.

3. Results

Between November 2017 and April 2018, a total of 2400 parents were approached and 1645 consented for their infant to be enrolled in the study. Of these 1645 participants, 987 were randomized into arms C, D, and E (Fig. 1). The intention-to-treat population included 936 infants (95%); baseline characteristics are summarized in Table 2. At ten months of age, participants who received IPV at 14-weeks and 9-months of age (Arm C) had ≥99% cumulative immune response to all three poliovirus types and this was significantly higher than participants who received IPV at 6 and 14-weeks (Arm E) where cumulative immune responses varied between 77% and 81% for the three poliovirus types (Table 3, Fig. 2). Participants in Arm D, who received IPV at 6-weeks and 9-months of age, had cumulative immune responses ranging from 98% to 99% depending on poliovirus type. This was statistically significantly higher than those of participants in Arm E, but not statistically different to participants in Arm C. At 10-months among those that serologically responded, participants in arms that received the second dose of IPV at 9-months (Arms C and D) had statistically significantly higher median antibody titers than those who received the IPV schedule with a second dose at 14-weeks (Arm E) (Table 4). Median antibody titers for Arms C and D were ≥1448 for all three poliovirus serotypes, but median antibody titers for the three poliovirus serotypes ranged from 45 to 114 for Arm E (Table 4 and Fig. 2).

The immune response at 18-weeks among those who received two doses (Arm E) were significantly higher than among those who received one dose at 14-weeks (Arm C) or at 6-weeks (Arm D) for poliovirus types 1 and 3 (Tables 3 and 4). Immune response for type 2 was similar among participants who received a single dose of IPV at 14-weeks (Arm C) and those who received two doses at 6 and 14-weeks (Arm E), 67% (95% CI: 61–72%) and 74% (95% CI: 69–79%), respectively (Table 3 and Fig. 3). The median reciprocal antibody titers for types 1, 2, and 3 at 18-weeks were statistically significantly higher for those who received two doses of IPV at 6 and 14-weeks (Arm E) than those who received one dose at 14-weeks (Arm C) or at 6-weeks (Arm D). Median recipro cal antibody titers at 18-weeks for the three types ranged from 910 to ≥1448 for Arm E but ranged from 14 to 36 for the three types for Arms C and D (Table 4 and Fig. 2).

No trial vaccine was administered between 14-weeks and 9-months of age in any arm. Among participants with no detectable immune response at 18-weeks of age to type 2, 28 of 101 (28%) in Arm C and 71 of 244 (29%) in Arm D had an immune response at 9-months of age (Table 3). The immune response at 9-months of age among participants in Arms C and D with no detectable immune response at 18-weeks were 39 of 176 (22%) and 63 of 228 (28%) for type 1 and 17 of 131 (13%) and 50 of 220 (23%) for type 3, respectively.

During follow-up to age 10-months, there were 256 adverse events in 226 infants across the three arms, of which 22 were SAEs including one death due to diarrhea (in Arm D). The SAE were equally distributed across arms; Arm C = 8, Arm D = 9, and Arm E = 5. All SAEs were determined to be unrelated to vaccination with IPV. The most common adverse events reported were mild and acute respiratory infections in 91 participants (35%), acute diarrhea and gastroenteritis in 77 participants (30%), fever in 46 (18%), pneumonia in 12 (5%), chickenpox in 4 (2%) and meningitis in 2 (1%). Additional adverse events included tinea capitis in 9 participants (4%), scabies in 5 (2%), and oral thrush in 4 (2%), conjunctivitis 3 (1%). Remaining adverse events included one each of the following: congenital heart defect, burn, and allergic reaction (not related to IPV).

4. Discussion

This study provides direct comparison of the immunogenicity of three different potential IPV-only schedules to inform immunization policy after the global cessation of OPV from routine immunization schedules. Two regimens were found to meet the immune response threshold. The cumulative immune response at 10-months of age by serotype of 98–99% for participants receiving IPV at 14-weeks and 9-months (Arm C) and IPV at 6-weeks and 9-months (Arm D), surpassing the 90% threshold recommended by SAGE. In comparison, IPV at 6-weeks and 14-weeks of age schedule (Arm E) failed to reach 90% immune response for any serotype.

Although SAGE recommended a two dose IPV schedule with the first dose administered at or later than 14-weeks of age, our findings show that a two dose IPV schedule starting at 6-weeks of age is as immunogenic as an IPV schedule starting at 14-weeks of age. No difference was observed at 10-months in the cumulative immune response of an IPV schedule of 6-weeks and 9-months compared to 14-weeks and 9-months for all three serotypes. A schedule that leverages the increased coverage of DTP1 (6-weeks) compared to DTP3 (14-weeks) could achieve higher vaccination coverage and therefore population immunity [20]. In contrast, when immune responses at 18-weeks of age were used to compare immunogenicity of different schedules in young infants who have maternal antibodies, two doses given at 6 and 14-weeks of age led to immune responses in 74–79% of participants for all types. This was higher than the 24–32% observed in those who received a single dose at 6-weeks of age and the 42–67% among those who received a single dose at 14-weeks of age, showing the benefit of early vaccination. These findings highlight the tradeoffs of different immune schedules whereby schedules that provide two early doses with DPT1 and DPT3 may achieve higher population coverage and higher immune response for a younger age, but schedules that provide a second dose at least 4-months after the first will overall achieve a higher immune response though by a later age. These tradeoffs should be considered by policy makers when choosing post OPV cessation immunization schedules.

The type 2 immune response after a single dose of IPV at 14-weeks of age of 67% was notably higher than in a previous study (53%) conducted at the same study clinics [17]. The difference in type 2 response observed between participants who received one dose of IPV at 14-weeks of age (67%) and participants who received two doses at 6 and 14-weeks (74%) was notably small. These findings in a post-bOPV switch environment suggests

limited benefit of the 6-week IPV dose on type 2 immune response but should be interpreted with caution. Serconversion at 9-months to types 1 and 3 was observed among 22–28% and 13–23% of children with no detectable antibody titer at 18-weeks for each serotype, respectively. This was an expected finding by incidental exposure to Sabin strains in low-level community transmission following bOPV administration. However, we observed type 2 immune response between 18-weeks of age and 9-months of age among infants who received one dose of IPV at 14-weeks of age (28%) and at 6-weeks of age (29%) and did not demonstrate a type 2 immune response at 18-weeks of age. We also observed type 2 immune response of 14% between 18-weeks of age and 10-months of age among infants who received two IPV doses at 6 and 14-weeks of age and did not demonstrate a type 2 immune response at 18-weeks. All study activities were conducted after global cessation of type 2 OPV use. This implies that type 2 immune responses occurred during a period when participants neither received study vaccines nor should have been exposed to type 2 vaccine virus circulating in the environment. These findings in our study suggest potentially a limited background exposure of study participants to type 2 poliovirus antigen during a vaccination-free period between 18-weeks of age and 9 or 10-months of age during 2018. A study conducted by the co-authors in the same area at a time when tOPV was used reported a type 2 immune response of 91% after two doses of IPV at 6 and 14-weeks, far higher than the 74% observed in the current study; therefore the type 2 exposures during vaccine free periods occurring in our study are likely lower than that observed when tOPV was being used for routine childhood vaccination in Bangladesh [16]. Our study findings may be interpreted as occurring with some background exposure to poliovirus type 2 antigen, but the effect is likely balanced across all three arms. These findings have triggered an ongoing public health investigation in Bangladesh by the Ministry of Health and Family Welfare.

Our study had some strengths and limitations. First, as a randomized trial, bias due to known and unknown confounders was minimized. Second, loss to follow-up was small such that 95% of the original enrollment population was included in the 10-month analyses. Trial staff were blinded to arm assignment until after enrollment and CDC laboratory staff were blinded throughout the study. The study was conducted among OPV-naïve infants in a post-tOPV environment, which allows us to assess the immunogenicity of IPV for type 2 in the absence of OPV2 with limited effect on the titers for types 1 and 3 due to bOPV. However, because the study was conducted with bOPV in use in the community, we observed type 1 and 3 responses during the vaccination-free period. Generally, secondary exposure to bOPV is thought to have a minimal effect on titers for serotypes 1 (5%) and 3 (3%) (K. Zaman, unpublished data). This may result in a small over-estimate of the immunogenicity of different IPV schedules. The effect should also be balanced across all three arms.

The findings of this of study have implications for immunization policy in the post-OPV cessation period. Our findings support the SAGE recommendation that two full doses of IPV given at or after 14-weeks of age and four months thereafter can achieve at least 90% immune response for all three poliovirus types. The trial also provides evidence that the schedule of two full IPV doses could begin as early as 6-weeks of age, potentially increasing the number of infants who get at least one IPV dose. However, similar to previous studies, the age of administration and duration between doses are important factors. In our trial, a

schedule at 6 and 14-weeks of age did not achieve at least 90% immune response. Future analyses should focus on combining the latest routine immunization coverage data from different sources with findings from clinical trials on different IPV schedules to develop a range of estimates of population immunity. This would help policy markers identify the optimal IPV-only schedule that would maximize population immunity for polio in the post-OPV era.

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References

[1]. Centers for Disease Control and Prevention. Apparent global interruption of wild poliovirus type 2 transmission. MMWR Morb Mortal Wkly Rep. 2001;50 (12):222–4. [PubMed: 11300627]

[2]. Adams A, Salisbury DM. Eradicating polio. Science 2015;350(6261):609. [PubMed: 26542542]

[3]. Global Polio Erradication Iniative. Report from the Twentieth Meeting of the Global Commission for Certification of Poliomyelitis Eradication; 2019.

[4]. Hampton LM, Farrell M, Ramirez-Gonzalez A, Menning L, Shendale S, Lewis I, et al. Cessation of trivalent oral poliovirus vaccine and introduction of inactivated poliovirus vaccine - worldwide, 2016. MMWR Morb Mortal Wkly Rep 2016;65(35):934–8. [PubMed: 27606675]

[5]. Kew O, Morris-Glasgow V, Landaverde M, Burns C, Shaw J, Garib Z, et al. Outbreak of poliomyelitis in Hispaniola associated with circulating type 1 vaccine-derived poliovirus. Science 2002;296(5566):356–9. [PubMed: 11896235]

[6]. Nathanson N, Kew OM. From emergence to eradication: the epidemiology of poliomyelitis deconstructed. Am J Epidemiol 2010;172(11):1213–29. [PubMed: 20978089]

[7]. No authors listed Meeting of the Strategic Advisory Group of Experts on Immunization, November 2013 - Conclusions and Recommendations. Weekly Epidemiologic Record. 2013;89:20.

[8]. No authors listed. Meeting of the Strategic Advisory Group of Experts Polio Working Group, April 2017 -Conclusions and Recommendations. Weekly Epidemiologic Record. 2017;92:301–20.

[9]. Resik S, Tejeda A, Sutter RW, Diaz M, Sarmiento L, Alemañi N, et al. Priming after a fractional dose of inactivated poliovirus vaccine. N Engl J Med 2013;368 (5):416–24. [PubMed: 23363495]

[10]. Asturias EJ, Bandyopadhyay AS, Self S, Rivera L, Saez-Llorens X, Lopez E, et al. Humoral and intestinal immunity induced by new schedules of bivalent oral poliovirus vaccine and one or two doses of inactivated poliovirus vaccine in Latin American infants: an open-label randomised controlled trial. Lancet 2016;388(10040):158–69. [PubMed: 27212429]

[11]. Bandyopadhyay AS, Gast C, Rivera L, Sáez-Llorens X, Oberste MS, Weldon WC, et al. Safety and immunogenicity of inactivated poliovirus vaccine schedules for the post-eradication era: a randomised open-label, multicentre, phase 3, non-inferiority trial. Lancet Infect Dis 2021;21(4):559–68. [PubMed: 33284114]

[12]. Peck M, Gacic-Dobo M, Diallo MS, Nedelec Y, Sodha SS, Wallace AS. Global routine vaccination coverage, 2018. MMWR Morb Mortal Wkly Rep 2019;68 (42):937–42. [PubMed: 31647786]

[13]. Global Polio Eradication Initiative. Background and Technical Rational for Introduction of One Dose of Inactivated Polio Vaccine (IPV) in Routine Immunization Schedules. 2015 January 2015.

[14]. The Cuba IPVSCG. Randomized, placebo-controlled trial of inactivated poliovirus vaccine in Cuba. N Engl J Med 2007;356(15):1536–44. [PubMed: 17429085]

[15]. Mohammed AJ, AlAwaidy S, Bawikar S, Kurup PJ, Elamir E, Shaban MMA, et al. Fractional doses of inactivated poliovirus vaccine in Oman. N Engl J Med 2010;362(25):2351–9. [PubMed: 20573923]

[16]. Anand A, Zaman K, Estívariz CF, Yunus M, Gary HE, Weldon WC, et al. Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial. Vaccine 2015;33(48):6816–22. [PubMed: 26476367]

[17]. Snider CJ, Zaman K, Estivariz CF, Yunus M, Weldon WC, Wannemuehler KA, et al. Immunogenicity of full and fractional dose of inactivated poliovirus vaccine for use in routine immunisation and outbreak response: an open-label, randomised controlled trial. Lancet 2019;393(10191):2624–34. [PubMed: 31104832]

[18]. de Onis M, Onyango AW, Van den Broeck J, Chumlea WC, Martorell R. Measurement and standardization protocols for anthropometry used in the construction of a new international growth reference. Food Nutr Bull 2004;25 (1_suppl_1):S27–36. [PubMed: 15069917]

[19]. Weldon WC, Oberste MS, Pallansch MA. Standardized methods for detection of poliovirus antibodies. Methods Mol Biol 2016;1387:145–76. [PubMed: 26983734]

[20]. Anand A, Pallansch MA, Estivariz CF, Gary H, Wassilak SG. Estimating the likely coverage of inactivated poliovirus vaccine in routine immunization: evidence from demographic and health surveys. J Infect Dis 2014;210(Suppl 1): S465–74. [PubMed: 25316869]

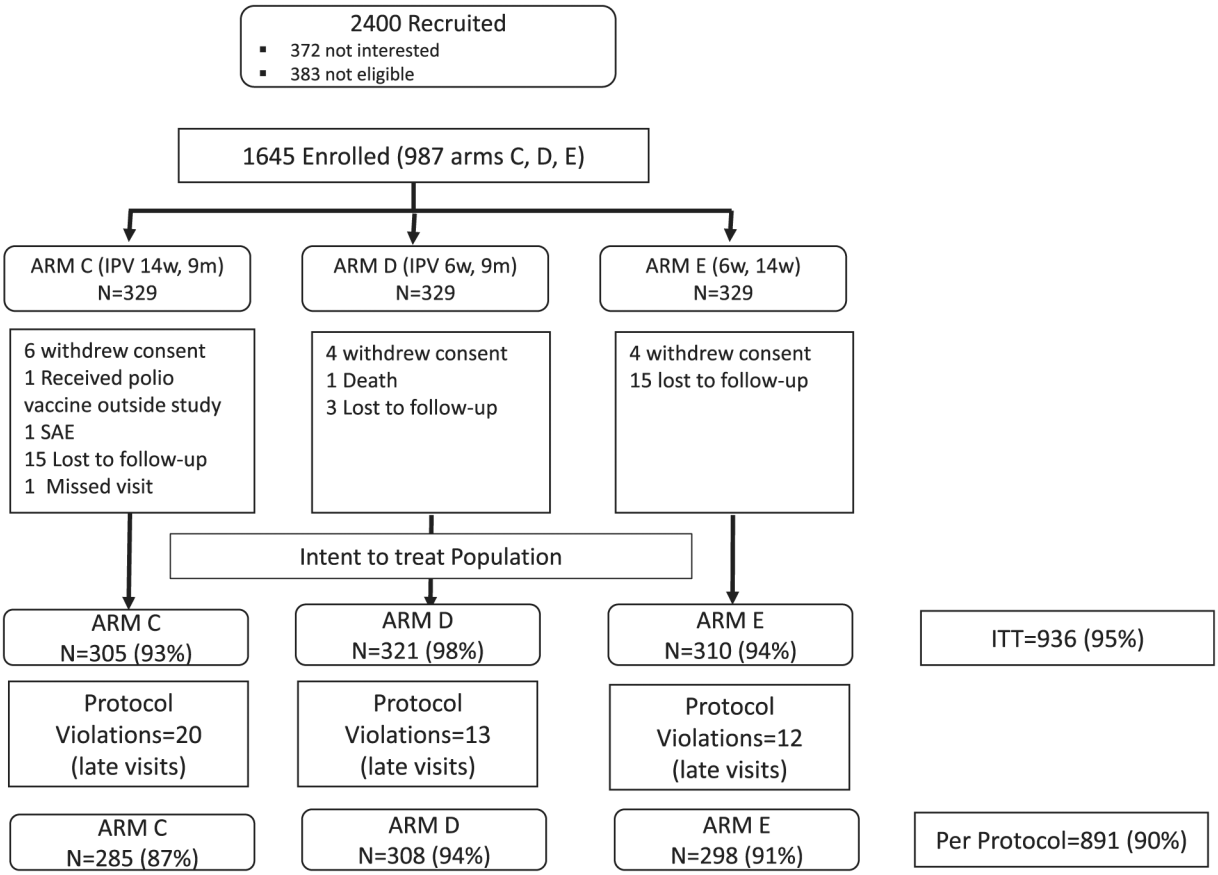

Fig. 1.

Inactivated poliovirus vaccine (IPV), 14-weeks (14w), 9-months (9m), 6-weeks (6w).

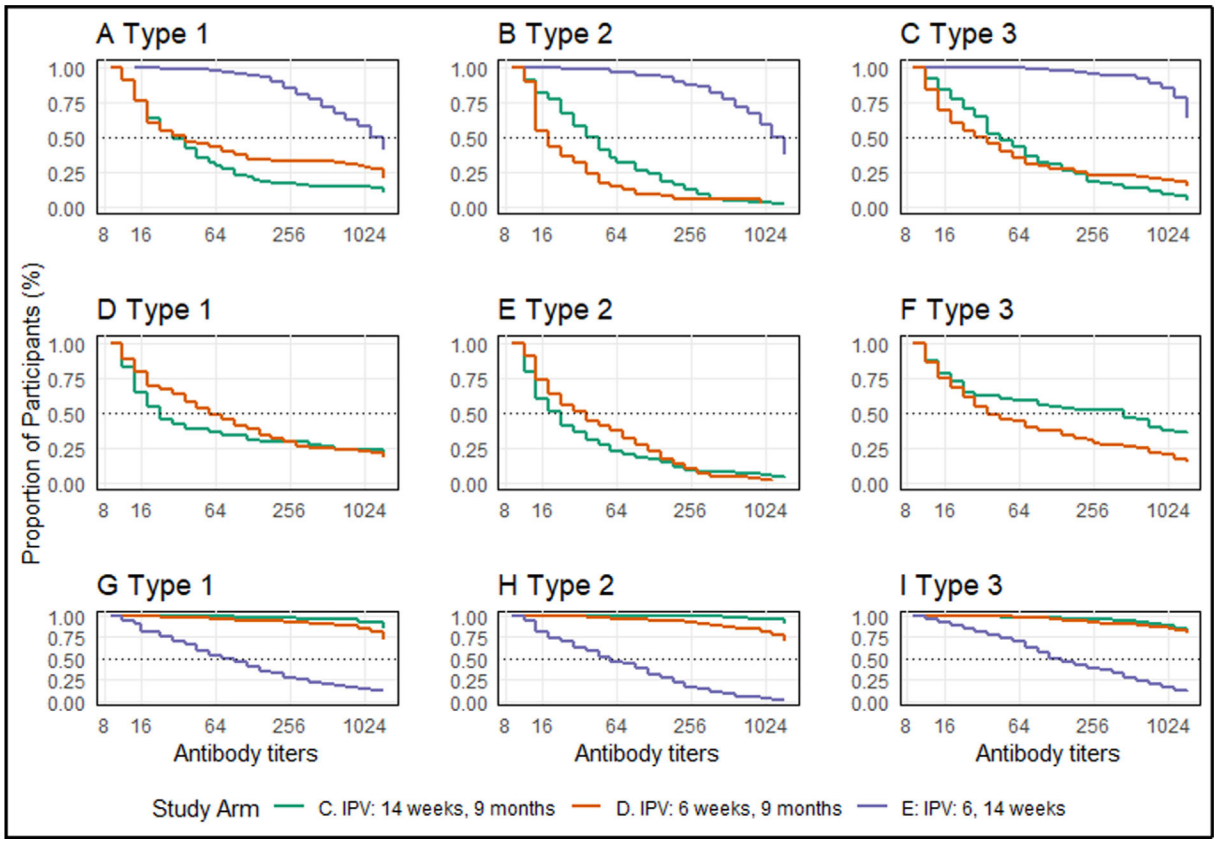

Fig. 2.

(A-C) Proportion of participants (y axis) with measurable reciprocal antibody titers and greater titers (x axis) among vaccine responders at 18-weeks, (D-F) 9-months, and (G-I) 10-months for types 1, 2 and 3.

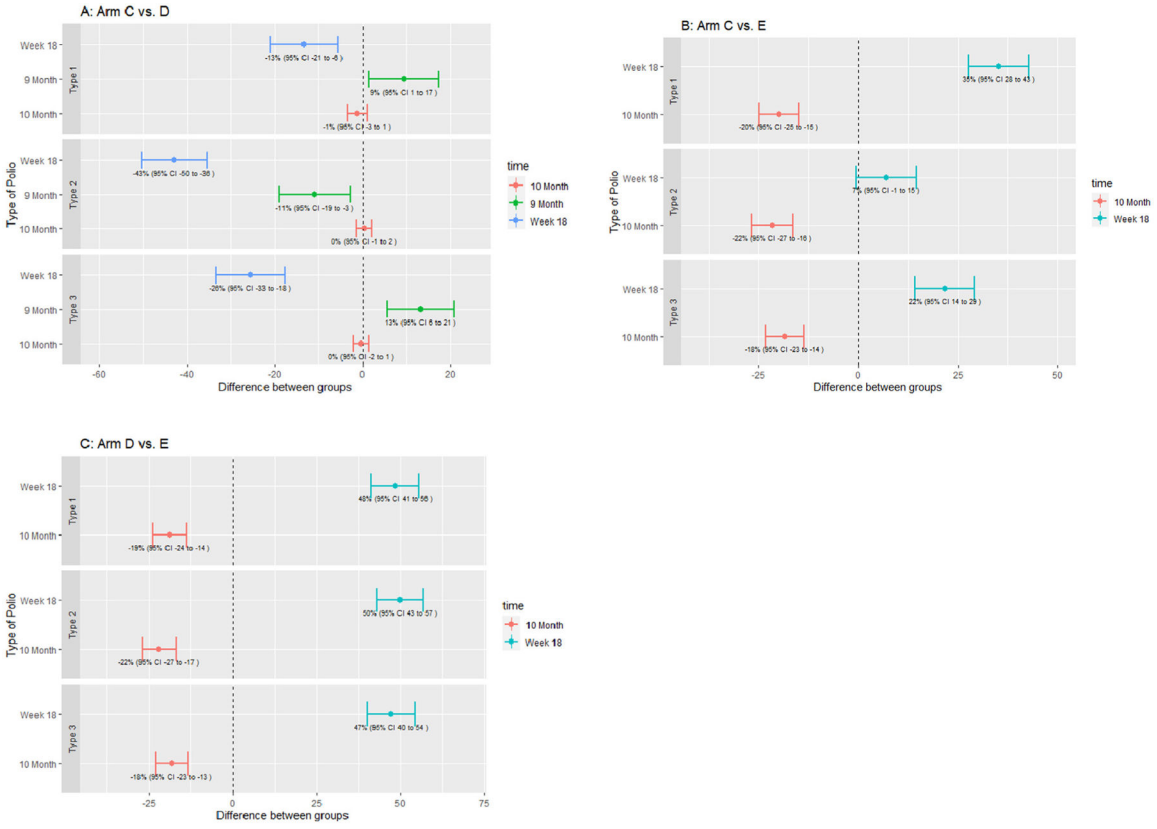

Fig. 3.

Summary of reciprocal antibody titers among immune responders by time point, poliovirus type and arm.

Table 1

Blood collection and IPV administration during clinic visits by Study Arm.

	6-weeks	14-weeks	18-weeks	9-months	10-months
Arm C (IPV 14-weeks + 9-months)	Blood	IPV	Blood	Blood + IPV	Blood
Arm D (IPV 6-weeks + 9-months)	Blood + IPV		Blood	Blood + IPV	Blood
Arm E (IPV 6 + 14-weeks)	Blood + IPV	IPV	Blood		Blood

Inactivated poliovirus vaccine (IPV).

Table 2

Baseline Characteristics of Trial Participants by Trial Arm.

	C (IPV 14w 9m) N = 305	D (IPV 6w, 9m) N = 321	E (IPV 6w, 14w) N = 310
Age at enrollment (days)	43 (42–48)	43 (42–48)	43 (42–48)
Female	148 (49)	158 (49)	153 (49)
Maternal education - primary or less	164 (54)	168 (52)	160 (52)
Exclusive breastfeeding	60 (20)	67 (21)	60 (19)
Stunting present	39 (13)	32 (10)	38 (12)
Wasting present	21 (7)	15 (5)	19 (6)
Baseline Seropositive			
Type 1	150 (49)	150 (47)	153 (49)
Type 2	149 (49)	169 (53)	171 (55)
Type 3	95 (31)	122 (38)	114 (37)
Baseline Titers			
Type 1	4.34 (3.17–10.5)	4.50 (3.17–10.5)	4.83 (3.17–10.5)
Type 2	4.50 (3.17–9.83)	4.17 (3.17–9.50)	4.17 (3.17–9.83)
Type 3	4.17 (3.17–10.5)	5.00 (3.17–10.5)	4.17 (3.17–10.5)

Data are n(%) or median (range). Inactivated poliovirus vaccine (IPV), 14-weeks (14w), 9-months (9m), 6-weeks (6w).

Table 3

Immune Response by Poliovirus Type, Time Point and Arm.

	Arm C (IPV 14w & 9m)	Arm D (IPV 6w & 9m)	Arm E (IPV 6w & 14w)	Fisher's Exact Test
Polio Type 1				
Immune response at 18-weeks	129/305 (42)	93/321 (29)	240/310 (77)	C vs. D: p = 0.0007; C vs. E: p < 0.0001 D vs. E: p < 0.0001
Immune response at 9-months	39/176 (22)	63/228 (28)	N/A	C vs. D: p = 0.1822
Immune response at 10-months	134/137 (98)	158/165 (96)	5/70 (7)	
Cumulative immune response by 10-months	302/305 (99)	314/321 (98)	245/310 (79)	C vs. D: p = 0.3815; C vs. E: p < 0.0001 D vs. E: p < 0.0001
Polio Type 2				
Immune response at 18-weeks	204/305 (67)	77/321 (24)	229/310 (74)	C vs. D: p < 0.0001; C vs. E: p = 0.0637 D vs. E: p < 0.0001
Immune response at 9-months	28/101 (28)	71/244 (29)	N/A	C vs. D: p = 0.0827
Immune response at 10-months	70/73 (96)	171/173 (99)	11/81 (14)	
Cumulative immune response by 10-months	302/305 (99)	319/321 (99)	240/310 (77)	C vs. D: p = 0.9542; C vs. E: p < 0.0001 D vs. E: p < 0.0001
Polio Type 3				
Immune response at 18-weeks	174/305 (57)	101/321 (32)	244/310 (79)	C vs. D: p < 0.0001; C vs. E: p < 0.0001 D vs. E: p < 0.0001
Immune response at 9-months	17/131 (13)	50/220 (23)	N/A	C vs. D: p = 0.0051
Immune response at 10-months	112/114 (98)	167/170 (98)	7/66 (11)	
Cumulative immune response by 10-months	303/305 (99)	318/321 (99)	251/310 (81)	C vs. D: p = 1.0; C vs. E: p < 0.0001 D vs. E: p < 0.0001

Data are n(%). Inactivated poliovirus vaccine (IPV), 14-weeks (14w), 9-months (9m), 6-weeks (6w).

Table 4

Median Reciprocal Antibody Titers and Interquartile Range for Immune Responders by Poliovirus Type, Timepoint and Arm.

	Arm C (IPV 14w & 9m)	Arm D (IPV 6w & 9m)	Arm E (IPV 6w & 14w)	Kruskal-Wallis Test
Polio Type 1				
Antibody Titers at 18-weeks	23 (9, >=1448)	28 (9, >=1448)	910 (14, >=1448)	C vs. D: p = 0.2751; C vs. E, D vs. E: p < 0.0001
Antibody Titers at 9-months	18 (9, >=1448)	45 (9, >=1448)	N/A-	C vs. D: p = 0.0338
Antibody titers at 10-months	>=1448 (9, >=1448)	>=1448 (9, >=1448)	57 (9, >=1448)	C vs. D, C vs. E, D vs. E: p < 0.0001
Polio Type 2				
Antibody Titers at 18-weeks	28 (9, >=1448)	14 (9, 910)	910 (11, >=1448)	C vs. D, C vs. E, D vs. E: p < 0.0001
Antibody Titers at 9-months	18 (9, >=1448)	28 (9, 1152)	N/A	C vs. D: p = 0.0031
Antibody titers at 10-months	>=1448 (28, >=1448)	>=1448 (11, >=1448)	45 (9, >=1448)	C vs. D, C vs. E, D vs. E: p < 0.0001
Polio Type 3				
Antibody Titers at 18-weeks	36 (9, >=1448)	23 (9, >=1448)	>=1448 (11, >=1148)	C vs. D: p = 0.1216; C vs. E, D vs. E: p < 0.0001
Antibody Titers at 9-months	181 (9, >=1448)	28 (9, >=1448)	N/A	C vs. D: p = 0.0259
Antibody titers at 10-months	>=1448 (11, >=1448)	>=1448 (9, >=1448)	114 (9, >=1448)	C vs. D: p = 0.7666; C vs. E, D vs. E: p < 0.0001

Data are median (IQR). Inactivated poliovirus vaccine (IPV), 14-weeks (14w), 9-months (9m), 6-weeks (6w).