Early priming with inactivated poliovirus vaccine (IPV) and intradermal fractional dose IPV administered by a microneedle device: A randomized controlled trial

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**A B S T R A C T**

**Introduction:** Inactivated poliovirus vaccine (IPV) introduction and phased oral poliovirus vaccine (OPV) cessation are essential for eradication of polio.

**Methods:** Healthy 6-week old infants in Bangladesh were randomized to one of five study arms: receipt of trivalent OPV (tOPV) or bivalent OPV (bOPV) at ages 6, 10 and 14 weeks, intramuscular IPV or intradermal one-fifth fractional dose IPV (f-IPV) at ages 6 and 14 weeks, or f-IPV at ages 6 and 14 weeks with bOPV at age 10 weeks (f-IPV/bOPV). All participants received tOPV at age 18 weeks.

**Results:** Of 975 infants randomized, 95% (922) completed follow-up. Type 1 seroconversion after 3 doses at 6, 10 and 14 weeks was higher with bOPV compared with tOPV (99% vs 94%, \(p = 0.019\)). Seroconversions to types 1 and 3 after 2 IPV doses at ages 6 and 14 weeks were no different than after 3 doses of tOPV or bOPV at ages 6, 10 and 14 weeks. A priming response, seroconversion 1 week after IPV at 14 weeks among those who did not seroconvert after IPV at 6 weeks, was observed against poliovirus types 1, 2 and 3 in 91%, 84% and 97%, respectively. Compared with IPV, f-IPV failed non-inferiority tests for seroconversion with or 2 doses and priming after 1 dose.

**Discussion:** The findings demonstrate considerable priming with IPV at age 6 weeks, comparable immunogenicity of tOPV and bOPV, and inferior immunogenicity of one-fifth f-IPV compared with IPV. If IPV induced priming at age 6 weeks is similar to that at age 14 weeks, IPV could be administered at a younger age and possibly with a higher coverage.

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1. Introduction

Oral poliovirus vaccines (OPV) consist of live attenuated poliovirus strains that revert and cause paralysis, that is indistinguishable from paralysis caused by wild polioviruses (WPV), either due to vaccine-associated paralytic polo (VAPP) or circulating vaccine-derived polioviruses (cVDPV), in which the reverted vaccine virus also acquires the ability to circulate [1]. Since the last type 2 WPV (WPV2) was reported in 1999 in India [2] and about 87% of VDPVs during 2000–2013 were type 2 [3], the strategic advisory group of experts on immunization (SAGE) has recommended a phased cessation of OPV starting with type 2 OPV [4]. In countries using trivalent OPV (tOPV), a mixture of types 1, 2 and 3 OPV, in routine immunization (RI), SAGE has recommended a switch to bivalent OPV (bOPV), a mixture of OPV types 1 and 3 following introduction of 1 dose of inactivated poliovirus vaccine (IPV) generally at age \(\geq 14\) weeks [5]. It is expected that delaying IPV administration to age \(\geq 14\) weeks is likely to maximize IPV immunogenicity [5]; however, compared with vaccinating at age 6 weeks, vaccination at age \(\geq 14\) weeks is likely to be associated with lower vaccination coverage in some high-risk countries [6].

The principal objective of introducing IPV with bOPV is to mitigate the risk associated with increased susceptibility to WPV2 or cVDPV2. For IPV, priming is defined as a seroconversion response...
1 week after a second dose of IPV among those who did not seroconvert after the first IPV dose. One clinical trial in Cuba reported considerable immunogenicity (seroconversion [63%] and priming [35%]) with 1 dose of IPV at age 4 months [7]. The absence of immunogenicity data by age, including priming response after IPV, is the chief limitation in assessing the optimal age for IPV administration in RI. In 2012, SAGE also recommended collecting additional immunogenicity data on intradermal (ID) one-fifth dose of IPV (0.1 ml fractional IPV [f-IPV]) as a potential substitute for intramuscular IPV (0.5 ml) [8].

2. Methods

2.1. Randomization and masking

We conducted an open-label 5-arm randomized controlled trial from 27 November 2012 to 30 November 2013 in Mirpur, an urban neighborhood in Dhaka, Bangladesh. The trial enrolled participants from 5 different sections of Mirpur. During the duration of the trial no polio vaccination campaigns were conducted in or around the study site. Infants were assigned randomly to one of five arms using a block randomization scheme of 65 blocks with a block size of 18 and an allocation ratio of 4:4:3:3:4 (Fig. 1). The tOPV arm received tOPV at ages 6, 10 and 14 weeks; the bOPV arm received bOPV at ages 6, 10 and 14 weeks; the IPV arm received IPV at ages 6 and 14 weeks; the f-IPV arm received f-IPV at ages 6 and 14 weeks; and the f-IPV/bOPV arm received f-IPV at ages 6 and 14 weeks with bOPV at age 10 weeks. All participants received tOPV at age 18 weeks (Table 1 in Supplementary Appendix).

2.2. Study objectives

The study’s three primary objectives were to compare immunogenicity of (1) f-IPV and bOPV with bOPV alone; (2) 3 doses of tOPV with 3 doses of bOPV; and (3) 2 doses of intramuscular IPV with 2 doses of f-IPV.

2.3. Study design and procedures

Infants were recruited at age 6–7 weeks (42–51 days), if the parents were willing to participate, comply with study procedures, and provide written informed consent. Exclusion criteria included (1) receipt of any polio vaccine before enrollment; (2) diagnosis or suspicion of immunodeficiency or a bleeding disorder; (3) known allergy to polio vaccines or constituents; (4) any acute illness such as vomiting, diarrhea or infection immediately before enrollment; and (5) an infant who was part of a multiple birth. Enrolled participants were withdrawn from the study if requested by their parents or if they received polio vaccine outside of the study.

Study physicians administered all study vaccines and routine non-polio vaccines for infants as recommended by the Bangladesh Ministry of Health and Family Welfare. Intramuscular IPV (0.5 ml) was administered using a standard needle and syringe. Intradermal f-IPV (0.1 ml) was administered using NanoPass MicronJet 600
(MJ600), a microneedle device with three microneedles (0.6 mm in length) that attaches to an intradermal syringe. Multiple clinical trials have been conducted using MJ600 [9–12]. IPV and f-IPV were administered in the anterolateral thigh, opposite the side used for routine immunization of injectable vaccines.

Blood samples (1 ml) were obtained by venipuncture at ages 6, 14, and 18 weeks from all participants and at age 15 weeks from participants assigned to IPV or f-IPV arms before administering any scheduled study vaccine. Sera were stored at −20 °C and tested for antibodies to poliovirus types 1, 2 and 3 at the Centers for Disease Control and Prevention (CDC), Atlanta, USA using microneutralization assay. Titers below a dilution of 1:8 were considered negative for presence of poliovirus antibodies and the highest measurable titer was 1:1448. Parents were asked to collect a stool specimen (8 g) from participants 1 week after tOPV administration at age 18 weeks. Stool specimens were stored at −20 °C and tested at CDC for presence of poliovirus by type [13].

2.4. Analysis

No published studies were found to have administered f-IPV with bOPV, or 3 doses of bOPV. Therefore, for sample size calculations based on limited evidence, we assumed seroconversions of 85% for types 1 and 3 with f-IPV and bOPV and 95% with 3 doses of bOPV [14,15]. For tOPV, we assumed sero−conversions of 75% for type 1 and 65% for type 3 [16]. Therefore, a sample size of 207 per arm would be sufficient to obtain a power of 90% with two-sided α of 0.05 to detect a difference in seroconversion of at least 10% when comparing 3 doses of bOPV with 3 doses of tOPV, and 2 doses of f-IPV and 1 dose of bOPV with 3 doses of bOPV. No published studies were found to have reported immunogenicity of IPV or f-IPV with two doses 8 weeks apart at ages 6 and 14 weeks. For a non-inferiority comparison, we assumed a sero−conversion of 90% with both IPV and f-IPV with a non-inferiority margin of 10% [14,17]. For this comparison a sample size of 155 per arm is required for a power of 90% with one-sided α of 0.05. Hence, the effective sample size for the trial was 931, with an enrollment target of 1170 assuming 20% attrition (Table 1 in Supplementary Appendix).

Seroconversion was defined as either conversion from seronegative to seropositive or a four-fold increase in antibody titers between two specimens after adjusting for decay of maternal antibodies. The half-life of maternal antibodies was assumed to be 28 days [14,18]. The primary analytical approach was intent−to−treat for participants with serological results. The primary end−point was seroconversion at age 18 weeks. To compare immunogenicity across study arms, the proportion of participants who seroconverted were compared using Fisher’s exact test (two−tailed). Priming was defined as a seroconversion response at age 15 weeks after receipt of the second IPV/f-IPV dose among those who did not seroconvert by age 14 weeks after one IPV/f-IPV dose at age 6 weeks. Reverse cumulative distribution curves, which are constructed by representing on the vertical axis the percent of subjects with antibody titers equal to or greater than that marked in x-axis, were used to compare distribution of antibody titers by study arms [19].

2.5. Study oversight

The study protocol was reviewed by icddr,b’s Institutional Review Board (IRB). The study was conducted in compliance with good clinical practice guidelines. UNICEF assisted in the procurement of vaccines used in this study. OPV was manufactured by Sanofi Pasteur and IPV was manufactured by the Netherlands Vaccine Institute (NVI). NanoPass Technologies Ltd. donated the supplies of MJ600. UNICEF, Sanofi Pasteur, NanoPass, and NVI had no role in the study design, implementation, data analysis, or interpretation of study results. The study was registered with Clinicaltrials.gov (NCT01813604). Adverse events data were reviewed by the Data Safety Monitoring Board (DSMB) of icddr,b.

2.6. Role of funding source

The study was funded by the Global Immunization Division of the Centers for Disease Control and Prevention. CDC staff participated in the study design, sample testing, data analysis and decision to submit for publication.

3. Results

3.1. Baseline characteristics

The study enrolled and randomized 975 participants and of these, 922 (95%) with blood specimens available at ages 6 and 18 weeks were included in the primary end−point analysis (Fig. 1). Enrollment was stopped after enrolling 975 participants as the study had achieved its effective sample size due to lower than anticipated study attrition. No statistically significant differences were observed at baseline among participants who completed the study compared with those who did not (data not shown) except that median type 2 antibody titers at baseline were lower for those who completed the study (1:28 vs 1:41, Kruskal–Wallis = 0.036). No other significant differences in baseline characteristics, including seroprevalence to polioviruses, were observed among study arms (Table 1).

3.2. Humoral immunogenicity

The median bleb diameter after intradermal injection with MJ600 was 10 mm and 99% of the participants had no residual liquid present on the skin following the injection.

Seroconversion to poliovirus type 1 (PV1) after 2 and 3 doses was higher in the bOPV arm compared with the tOPV arm (2 doses: 93% vs 87%, p = 0.047; 3 doses: 99% vs 94%, p = 0.019; Table 2). PV1 seroconversion with 2 doses of IPV (95%) was statistically no different from that observed with 3 doses of tOPV or bOPV. PV1 seroconversion with 2 doses of f-IPV and 1 dose of bOPV was higher than that observed with 2 doses of f-IPV alone (p = 0.005) and no different from that with 3 doses of tOPV or bOPV.

Seroconversion at 18 weeks to PV2 was higher with 3 doses of tOPV compared with 2 doses of IPV (p = 0.002) or f-IPV in either f-IPV arms (p < 0.001). Seroconversion to PV3 was statistically no different with 3 doses of tOPV (95%) compared with 3 doses of bOPV (94%), 2 doses of IPV (97%) or f-IPV (89%), or 2 doses of f-IPV with 1 dose of bOPV (94%).

Compared with IPV, f-IPV failed the non-inferiority test for all serotypes for seroconversion observed with 1 or 2 doses (Fig. 2). Additionally, compared with IPV, f-IPV failed the non-inferiority test for all serotypes for priming response observed at 15 weeks.

Reverse cumulative distribution curves for antibody titers by study arm at age 18 weeks show that the highest titers were reached for PV1 in the bOPV arm, PV2 in the tOPV arm and PV3 in the IPV arm (Fig. 3). f-IPV was associated with the lowest titers for all three poliovirus types among those receiving type specific vaccines. One dose of IPV or f-IPV was not associated with a substantial change in distribution of antibody titers, despite the high degree of priming with 1 dose; however, within a week of the second dose of IPV or f-IPV, a rapid rise in antibody titers was observed (Fig. 1 in Supplementary Appendix).

3.3. Intestinal mucosal immunity

One week after receiving tOPV at age 18 weeks, 15%, 6%, and 8% of participants in the tOPV arm were excreting PV 1, 2, and
Table 1
Baseline characteristics among those who completed the study by study arms.

| Baseline characteristics | A (tOPV n = 203) | B (bOPV n = 200) | C (IPV n = 156) | D (f-IPV n = 152) | E (f-IPV/bOPV n = 211) | p-value
<table>
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<tr>
<td>Median age in days (range)</td>
<td>44(41, 53)</td>
<td>44(41, 53)</td>
<td>44(41, 53)</td>
<td>44(41, 53)</td>
<td>44(41, 53)</td>
<td>0.662</td>
</tr>
<tr>
<td>Male n (%)</td>
<td>95</td>
<td>46.8</td>
<td>99</td>
<td>49.5</td>
<td>79</td>
<td>50.6</td>
</tr>
<tr>
<td>Mother’s education n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No formal school</td>
<td>36</td>
<td>17.7</td>
<td>27</td>
<td>13.5</td>
<td>29</td>
<td>18.6</td>
</tr>
<tr>
<td>Primary school</td>
<td>88</td>
<td>43.4</td>
<td>92</td>
<td>46.0</td>
<td>68</td>
<td>43.6</td>
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<tr>
<td>Middle school</td>
<td>36</td>
<td>17.7</td>
<td>42</td>
<td>21.0</td>
<td>30</td>
<td>19.2</td>
</tr>
<tr>
<td>High school</td>
<td>33</td>
<td>16.3</td>
<td>34</td>
<td>17.0</td>
<td>27</td>
<td>17.3</td>
</tr>
<tr>
<td>Graduate</td>
<td>10</td>
<td>4.9</td>
<td>5</td>
<td>2.5</td>
<td>2</td>
<td>1.3</td>
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<tr>
<td>Type 1 seroprevalence n (%)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Median (range)</td>
<td>99</td>
<td>48.8</td>
<td>97</td>
<td>48.5</td>
<td>78</td>
<td>50.0</td>
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<tr>
<td>Type 2 seroprevalence n (%)</td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Median (range)</td>
<td>118</td>
<td>58.1</td>
<td>118</td>
<td>59.0</td>
<td>95</td>
<td>60.9</td>
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<tr>
<td>Type 3 seroprevalence n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Median (range)</td>
<td>51</td>
<td>25.1</td>
<td>56</td>
<td>28.0</td>
<td>42</td>
<td>27.6</td>
</tr>
<tr>
<td>Wasting present n (%)</td>
<td>31</td>
<td>15.3</td>
<td>38</td>
<td>19.0</td>
<td>28</td>
<td>18.0</td>
</tr>
<tr>
<td>Stunting present n (%)</td>
<td>40</td>
<td>19.7</td>
<td>37</td>
<td>18.5</td>
<td>28</td>
<td>18.0</td>
</tr>
<tr>
<td>Exclusive breastfeeding n(%)</td>
<td>180</td>
<td>88.7</td>
<td>170</td>
<td>85.0</td>
<td>134</td>
<td>85.9</td>
</tr>
</tbody>
</table>

| tOPV, trivalent oral poliovirus vaccine (OPV); bOPV, bivalent OPV; IPV, inactivated poliovirus vaccine; f-IPV, fractional IPV. |
| Fisher’s exact test. Kruskal–Wallis test used for mother’s education and rank test for medians. |
| Among those with titers >8. |

4. Discussion

The study demonstrated that considerable priming can be achieved with 1 dose of IPV at age 6 weeks. Cumulatively, 99% of children had either seroconverted or were primed against Type 2 poliovirus at age 6 weeks. This is consistent with the global implementation of at least 1 dose of IPV at age ≤14 weeks recommended by the World Health Organization. In this study, however, the percentage of participants inoculated against Type 2 IPV, the switch from IPV to OPV, or the change from OPV to IPV, was not statistically significant between the groups. This is consistent with previous studies showing that IPV is an effective booster for OPV. However, the results also suggest that IPV is more effective at maximizing the number of seroconverted participants. The percentage of participants seroconverted against Type 2 IPV in the IPV arm is significantly higher than in the OPV arm, suggesting that IPV is more effective at increasing seroconversion rates. This is consistent with previous studies showing that IPV is more effective at increasing seroconversion rates.

In conclusion, this study demonstrates that IPV is an effective booster for OPV and that the switch from OPV to IPV is not statistically significant between the groups. However, IPV is more effective at increasing seroconversion rates. This is consistent with previous studies showing that IPV is more effective at increasing seroconversion rates.

In summary, this study demonstrates that IPV is an effective booster for OPV and that the switch from OPV to IPV is not statistically significant between the groups. However, IPV is more effective at increasing seroconversion rates. This is consistent with previous studies showing that IPV is more effective at increasing seroconversion rates.

References


### Table 2

Humoral and intestinal immunogenicity by study arm.

<table>
<thead>
<tr>
<th>Type 1</th>
<th>A: tOPV</th>
<th>B: bOPV</th>
<th>C: IPV</th>
<th>D: f-IPV</th>
<th>E: f-IPV/bOPV</th>
<th>Fisher's exact test (a priori)</th>
<th>Fisher's exact test (post hoc)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serocconversion by 14 weeks: n (%)</td>
<td>178/205</td>
<td>189/203</td>
<td>93.1%**</td>
<td>57/161</td>
<td>20/155</td>
<td>12.9%**</td>
<td>173/211</td>
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<tr>
<td>Priming response by 15 weeks: n (%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>78/86</td>
<td>90.7%</td>
<td>91/109</td>
</tr>
<tr>
<td>Cumulative effect of one dose (seroconversion and priming): n (%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>124/132</td>
<td>93.9%</td>
<td>110/128</td>
</tr>
<tr>
<td>Poliovirus shedding at 19 weeks: n (%)</td>
<td>190/203</td>
<td>197/200</td>
<td>98.5%**</td>
<td>148/156</td>
<td>94.9%</td>
<td>133/152</td>
<td>87.5%**</td>
</tr>
<tr>
<td>Poliovirus shedding at 19 weeks: n (%)</td>
<td>31/203</td>
<td>7/196</td>
<td>3.6%</td>
<td>77/156</td>
<td>49.4%</td>
<td>73/151</td>
<td>48.3%</td>
</tr>
<tr>
<td>Serocconversion by 14 weeks: n (%)</td>
<td>190/205</td>
<td>14/203</td>
<td>6.9%**</td>
<td>62/161</td>
<td>38.5%**</td>
<td>30/155</td>
<td>19.4%</td>
</tr>
<tr>
<td>Priming response by 15 weeks: n (%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>66/79</td>
<td>83.5%</td>
<td>73/101</td>
</tr>
<tr>
<td>Cumulative effect of one dose (seroconversion and priming): n (%)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>119/132</td>
<td>90.2%</td>
<td>100/128</td>
</tr>
<tr>
<td>Poliovirus shedding at 19 weeks: n (%)</td>
<td>200/203</td>
<td>28/200</td>
<td>14%**</td>
<td>142/156</td>
<td>91%**</td>
<td>123/152</td>
<td>80.9%</td>
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<tr>
<td>Serocconversion by 18 weeks: n (%)</td>
<td>12/203</td>
<td>119/196</td>
<td>60.7%</td>
<td>89/156</td>
<td>57.1%</td>
<td>99/151</td>
<td>65.6%</td>
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<tr>
<td>Poliovirus shedding at 19 weeks: n (%)</td>
<td>174/205</td>
<td>181/203</td>
<td>89.2%**</td>
<td>54/161</td>
<td>33.5%**</td>
<td>22/155</td>
<td>14.2%**</td>
</tr>
<tr>
<td>Serocconversion by 14 weeks: n (%)</td>
<td>192/203</td>
<td>188/200</td>
<td>94.0%</td>
<td>152/156</td>
<td>97.4%</td>
<td>135/152</td>
<td>88.8%</td>
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<tr>
<td>Poliovirus shedding at 19 weeks: n (%)</td>
<td>16/203</td>
<td>7.9%</td>
<td>12/196</td>
<td>6.1%</td>
<td>50/156</td>
<td>32.1%</td>
<td>64/151</td>
</tr>
</tbody>
</table>

NS, not significant; tOPV, trivalent oral poliovirus vaccine (OPV); bOPV, bivalent OPV; IPV, inactivated poliovirus vaccine; f-IPV, fractional IPV.

1. Test comparison of IPV (Arm C) and f-IPV (Arm D) presented in Fig. 2.
2. Bonferroni correction. Significance at p < 0.0125.
3. Analysis restricted to those with serological results at 6, 14, 15 and 18 weeks.
as vaccination coverage in many high-risk countries is higher at age 6 weeks compared with age 14 weeks [6].

The study confirms that bOPV is more immunogenic than tOPV for poliovirus types 1 and 3 [15]; however, after 3 doses, the differences in seroconversion are small and high titers of antibodies were observed after administration of both vaccines. Prior field assessments of tOPV have reported substantially lower effectiveness though those estimates have been based on parental report of the number of vaccine doses received [20,21]. This study demonstrates a high immunogenicity of tOPV in a developing country with a tropical climate [22–24].

IPV demonstrated a higher immunogenicity compared with f-IPV for priming with one dose and seroconversion with one or two doses. These results address a prior identified information need by SAGE to collect more evidence on the comparative immunogenicity of f-IPV and IPV [8]. Also these results are consistent with other studies that have reported lower immunogenicity of a one-fifth IPV dose compared with IPV [7,14,25]. The findings of this study confirm the safety of NanoPass MJ-600 in intradermal f-IPV administration, a device that had not been previously used for f-IPV administration.

The stool excretion results demonstrate a minimal reduction in type 2 excretion with IPV and f-IPV recipients compared with bOPV recipients, who did not receive any type 2 vaccine. Also a vaccination schedule of f-IPV/bOPV reduced the percent of participants who excreted type 1 or 3 polioviruses 1 week after receiving tOPV compared to the use of IPV or f-IPV alone. Although the percent excreting poliovirus in the f-IPV/bOPV arm was significantly higher than those in the bOPV arm, the absolute difference was not large.

A prior study with tOPV demonstrated the substantial reduction in excretion of polioviruses with 1–2 doses of tOPV with minimal reduction with additional doses [26]. These findings taken together with noteworthy priming associated with IPV at age 6 weeks support evaluating polio vaccination schedules with IPV only as the first poliovirus vaccine followed by OPV.

This study has notable limitations. First, transmission of OPV received by other children in the community was observed. However, the effect of community transmission was low with only 14% type 2 seroconversion over 12 weeks in the bOPV arm [23,27]. Second, in the assessment of priming, the primary as well as secondary (challenge at 14 weeks) vaccines had different routes of administration and dosage between IPV and f-IPV arms, which limits comparison. Lastly, assessment of MJ600 performance was limited to safety and injection quality associated with the device and we could not compare immunogenicity of IPV administered by MJ600 with standard needle and syringe for intradermal administration.

Overall, findings from this study address several previously identified information gaps with regard to primary routine polio vaccine performance and could help simplify and expand polio vaccination policy options. The study supports the safety and comparable immunogenicity of tOPV and bOPV for types 1 and 3 poliovirus and demonstrates the lack of non-inferiority of one-fifth f-IPV to IPV. Most importantly, the study shows the promising degree of priming with an early (6 week) dose of IPV. A useful next step would be to compare priming at age 6 weeks to that with the SAGE-recommended IPV schedule at age ≥14 weeks.

**Fig. 3.** Reverse cumulative antibody titers at 18 weeks of age by study arm.
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Contributors
AA prepared the first draft of the manuscript and all authors reviewed and approved the manuscript. AA, CFE, HG, MAP, SW, MSO and WW contributed to the design of the study. The design team jointly developed the trial implementation strategy with KZ, SPL, JDH, MY and TBI. WW and MSO contributed to laboratory testing. AA and HG contributed to data analysis. All authors contributed to interpretation of study results.

Conflict of interest
All authors declare that they have no conflict of interest.

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Appendix A. Supplementary data
Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.09.039.

References