



Effect of a single inactivated poliovirus vaccine dose on intestinal immunity against poliovirus in children previously given oral vaccine: an open-label, randomised controlled trial

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Summary

Background Intestinal immunity induced by oral poliovirus vaccine (OPV) is imperfect and wanes with time, permitting transmission of infection by immunised children. Inactivated poliovirus vaccine (IPV) does not induce an intestinal mucosal immune response, but could boost protection in children who are mucosally primed through previous exposure to OPV. We aimed to assess the effect of IPV on intestinal immunity in children previously vaccinated with OPV.

Methods We did an open-label, randomised controlled trial in children aged 1–4 years from Chinnallapuram, Vellore, India, who were healthy, had not received IPV before, and had had their last dose of OPV at least 6 months before enrolment. Children were randomly assigned (1:1) to receive 0·5 mL IPV intramuscularly (containing 40, 8, and 32 D antigen units for serotypes 1, 2, and 3) or no vaccine. The randomisation sequence was computer generated with a blocked randomisation procedure with block sizes of ten by an independent statistician. The laboratory staff did blinded assessments. The primary outcome was the proportion of children shedding poliovirus 7 days after a challenge dose of serotype 1 and 3 bivalent OPV (bOPV). A second dose of bOPV was given to children in the no vaccine group to assess intestinal immunity resulting from the first dose. A per-protocol analysis was planned for all children who provided a stool sample at 7 days after bOPV challenge. This trial is registered with Clinical Trials Registry of India, number CTRI/2012/09/003005.

Findings Between Aug 19, 2013, and Sept 13, 2013, 450 children were enrolled and randomly assigned into study groups. 225 children received IPV and 225 no vaccine. 222 children in the no vaccine group and 224 children in the IPV group had stool samples available for primary analysis 7 days after bOPV challenge. In the IPV group, 27 (12%) children shed serotype 1 poliovirus and 17 (8%) shed serotype 3 poliovirus compared with 43 (19%) and 57 (26%) in the no vaccine group (risk ratio 0·62, 95% CI 0·40–0·97, $p=0\cdot0375$; 0·30, 0·18–0·49, $p<0\cdot0001$). No adverse events were related to the study interventions.

Interpretation The substantial boost in intestinal immunity conferred by a supplementary dose of IPV given to children younger than 5 years who had previously received OPV shows a potential role for this vaccine in immunisation activities to accelerate eradication and prevent outbreaks of poliomyelitis.

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Introduction

The Global Polio Eradication Initiative (GPEI) has relied on oral poliovirus vaccine (OPV) to successfully eliminate wild poliovirus transmission from most of the world. However, three countries remain persistently infected with indigenous poliovirus (Afghanistan, Pakistan, and Nigeria), and export of virus has led to large outbreaks in Africa, Asia, and Europe in the past decade. Response to these outbreaks and elimination of transmission in the remaining reservoirs are major challenges for the GPEI.¹

OPV has been the vaccine of choice for the GPEI because of its ease of administration in mass campaigns, low cost, and ability to induce strong intestinal mucosal immunity against poliovirus shedding and transmission. However, poor immunogenicity of OPV in areas with poor sanitation and hygiene has restricted its effectiveness in the prevention of transmission.² Additionally, intestinal mucosal immunity induced by OPV wanes substantially

within a year of vaccination.³ Therefore, although children and adults vaccinated with OPV are protected against poliomyelitis if they mount a neutralising antibody response to all three serotypes they might still be susceptible to infection and transmit wild poliovirus.^{4,5} Infected adults have been implicated in international spread and outbreaks of poliomyelitis, and incomplete intestinal immunity in OPV-vaccinated individuals might contribute to persistent transmission in infected areas.^{6,7}

The injected inactivated poliovirus vaccine (IPV) has excellent immunogenicity that does not vary between populations.⁸ However, it does not induce an effective mucosal immune response—poliovirus-specific IgA is undetectable in serum or saliva in most children after administration of IPV^{9,10}—and offers restricted protection against poliovirus shedding in the intestine after challenge with OPV, most likely explained by transudated serum IgG.¹¹ The effect of IPV on transmission of

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See [Comment](#) page 1480

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poliovirus, particularly in areas with efficient faecal–oral transmission is therefore likely to be limited compared with OPV.¹² This view is supported by the recent widespread silent circulation of wild poliovirus in Israel, where routine immunisation with IPV replaced a combined IPV/OPV schedule in 2005, and where virus was detected in stool from children vaccinated with IPV but not associated with poliomyelitis.¹³

The administration of IPV with OPV during routine immunisation of infants did not reduce poliovirus shedding in stool after subsequent challenge with OPV when compared with infants immunised with OPV alone.^{14–16} However, adults who received OPV as children show increases in poliovirus-specific IgA and memory CD4+ T cells expressing the gut-homing integrin $\alpha 4\beta 7$ after administration of IPV.^{9,17} This finding suggests that IPV might boost intestinal immunity in children and adults who have been mucosally primed through earlier exposure to live poliovirus (vaccine or wildtype) and therefore have poliovirus-specific memory lymphocytes with a gut-homing phenotype, but whose intestinal immunity has waned. If so, IPV could be used as a complement to OPV in several ways: to prevent international spread by boosting intestinal immunity among travellers, to accelerate eradication in infected areas with poor OPV immunogenicity through use in campaigns, and to maximise herd immunity in advance of the planned global withdrawal of serotype 2 OPV in 2016.

Several countries have implemented routine infant immunisation schedules with IPV followed by OPV, which is associated with a strong humoral and mucosal immune response.^{15,18} However, few studies have examined the results of immunisation with IPV in children previously vaccinated with OPV.^{19–21} These studies show a significant boost to serum antibodies, but only one study²¹ examined intestinal immunity. In this study, low poliovirus shedding was identified in stool after challenge at 15 months of age with serotype 3 monovalent OPV (13%), with no statistically significant difference between study groups receiving a supplemental dose of IPV or OPV at 9 months of age.²¹ Because of the paucity of data for the effect of IPV on intestinal immunity and the absence of studies of IPV given to OPV-immunised children older than 12 months whose immunity might have waned, we aimed to assess the effect of IPV on both systemic and intestinal mucosal immunity in Indian children aged 1–4 years who had received OPV at least 6 months previously.

Methods

Study design and participants

In this open-label, randomised controlled trial children aged 1–4 years old who had received at least five doses of trivalent OPV through routine and supplementary immunisation with the last dose given at least 6 months before enrolment were recruited from Chinnallapuram,

a densely populated urban area of Vellore, India. Children underwent clinical examination and parents or guardians were interviewed to obtain basic sociodemographical data and a medical history. Children were eligible for enrolment if they were aged between 12 and 59 months of age, were available for 11 weeks of follow-up, and had no medical condition that precluded study involvement. Children were excluded if they had received OPV in the past 6 months or IPV at any time previously.

Written informed consent was obtained from the parent or legal guardian of every child. The trial was done in accordance with the principles of good clinical practice and the ethical principles in the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the Christian Medical College and the Drugs Controller General of India. Oversight of the study was provided by an independent data safety and monitoring board.

Randomisation and masking

Children were randomly assigned (1:1) to receive either a dose of IPV or no vaccine at enrolment. The randomisation sequence was computer generated with a blocked randomisation procedure with block sizes of ten by an independent statistician. The allocation code for every participant was concealed in sequentially numbered opaque covers that were opened at the time of enrolment by study staff. All biological samples were given a unique ID linked to the study participant ID, such that laboratory staff did blinded assessments.

Procedures

Children received either an intramuscular dose of 0.5 mL IPV in a prefilled syringe (Sanofi Pasteur, Mumbai, India), containing 40 D antigen units of serotype 1, 8 D antigen units of serotype 2, and 32 D antigen units of serotypes 3, or no vaccine at enrolment. A dose of bOPV (Panacea Biotec, New Delhi, India) containing at least 10^6 and 10^{5-8} median cell culture infectious doses of Sabin serotype 1 and 3 poliovirus was given to all children 28 days later and stool samples were collected 0, 7, 14, and 21 days later to assess poliovirus shedding. Children who received no vaccine at baseline were given a second dose of bOPV 56 days after enrolment and further stool samples were collected at 0, 7, 14, and 21 days. In children who received IPV, a 3 mL venous blood sample was collected at enrolment and 28 days later. For children who received no vaccine at enrolment, a blood sample was collected at the time of administration of the first dose of bivalent OPV (bOPV) and 28 days later (study days 28 and 56).

Children were observed for 30 min after vaccine administration to identify any potential allergic or adverse reactions. Surveillance for serious adverse events was done during home visits by field workers and at the study clinic by the study physician.

Serum was tested for poliovirus-specific neutralising antibodies to types 1, 2, and 3 with a modified micro-neutralisation assay.²² Samples were tested in two-fold serial dilutions from 1:8 to 1:1024. Shedding of poliovirus in stool samples was assessed with quantitative real-time PCR and a subset was also assessed by culture following the WHO protocol (appendix).^{23,24}

Outcomes

The primary outcome was the proportion of children shedding poliovirus 7 days after a challenge dose of serotype 1 and 3 bOPV in the IPV group compared with in the no vaccine group. Secondary outcomes were shedding of poliovirus at 14 and 21 days after challenge, after a second dose of bOPV in the no vaccine group compared with shedding after the first dose, and the serum neutralising antibody response to IPV and bOPV.

Statistical analysis

The study was powered to detect a 40% reduction in shedding of poliovirus serotype 1 or 3 in the IPV group compared with in the no vaccine group 7 days after administration of the bOPV challenge dose. We expected 30% of children in the no vaccine group to shed each serotype of poliovirus on the basis of findings from published challenge studies.¹¹ We calculated that for 85% power with the two-sided Fisher's exact test, we would need to recruit roughly 450 children.

A per-protocol analysis was planned for all children who provided a stool sample at 7 days after bOPV challenge. The proportion of children shedding serotype 1 or 3 poliovirus and exact binomial 95% CI were calculated at every timepoint.²⁵ Fisher's exact test was used to compare the proportion of shedding 7 days after challenge between study groups for the primary analysis. McNemar's exact test for paired data was used to compare shedding 7 days after the first and second challenge within the no vaccine study group. The mean and SE of the virus copy number were calculated on a log scale and differences assessed with the non-parametric Wilcoxon rank sum test. Wald 95% CI were calculated about risk ratios for the paired and unpaired shedding data.²⁶ The correlation in shedding of poliovirus serotype 1 and 3 was determined with Fisher's exact test, and the odds ratio (OR) with exact 95% CI presented as a measure of association.

The median titre of serum neutralising antibodies to each poliovirus serotype was calculated for every sample from the neutralisation assay with the Spearman-Kärber method.²⁴ Geometric mean titres (GMTs) of antibodies were calculated by assigning a value of 1:6 and 1:1448 for the censored values below and above the limits of the dilution series. Seroconversion was defined as a four-fold rise in median antibody titre or a change from undetectable to detectable antibodies at 1:8 dilution. The correlation between seroconversion and shedding of poliovirus was assessed with Fisher's exact test and ORs

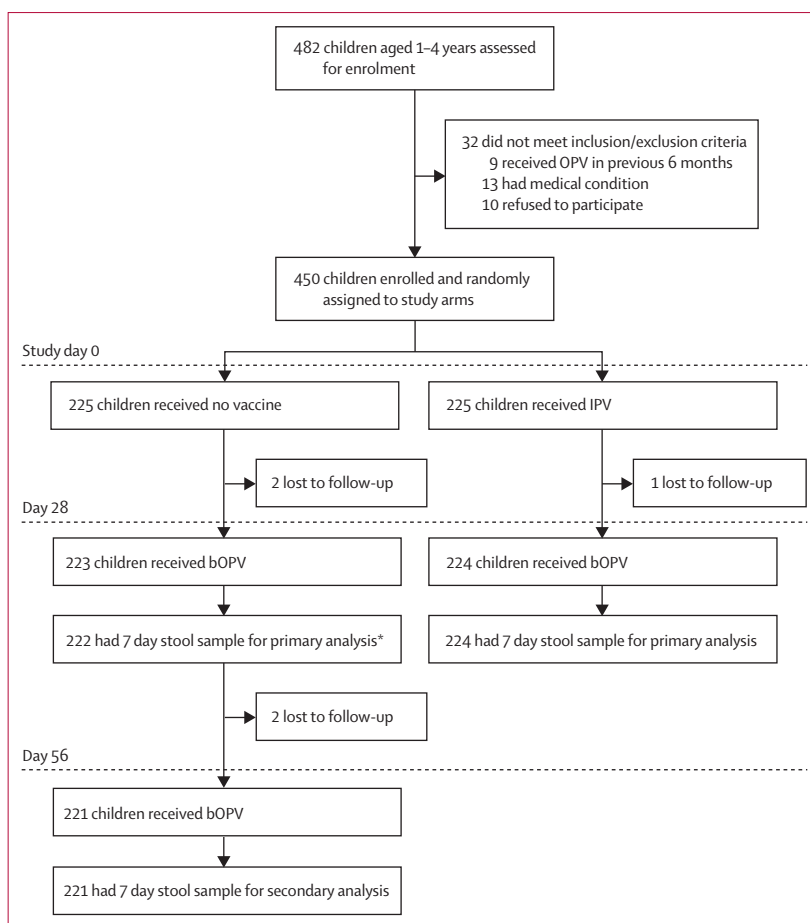


Figure 1: Trial profile

Children randomly assigned to the inactivated poliovirus vaccine group were enrolled in the study for a total of 7 weeks, and children randomly assigned to the no vaccine group were enrolled for 11 weeks. OPV=oral poliovirus vaccine. IPV=inactivated poliovirus vaccine. bOPV=bivalent oral poliovirus vaccine. *One child in the no vaccine group did not provide a day 7 stool sample for the primary analysis.

	No vaccine group	Inactivated poliovirus vaccine group
Demographic characteristics		
Age (years)	2.51 (0.08)	2.64 (0.08)
Women	114 (51%)	104 (46%)
Weight (kg)	11.58 (0.16)	11.97 (0.17)
Height (cm)	88.1 (0.7)	89.4 (0.7)
Concrete house type	149 (66%)	149 (66%)
Mother's education primary only or uneducated	74 (33%)	71 (32%)
Vaccination history		
Number of oral poliovirus vaccine doses received	10.24 (0.19)	10.4 (0.19)
Time since last oral poliovirus vaccine (months)	6.27 (0.051)	6.20 (0.019)
Data are mean (SE) or n (%).		

Table 1: Characteristics of the study participants at enrolment

See Online for appendix

	No vaccine group		IPV group (n=224)
	First challenge (n=222)	Second challenge (n=221)	
Serotype 1			
Proportion (%) shedding on day 7 (95% CI)	19.4% (14.4–25.2)	19.0% (14.1–24.8)	12.1% (8.1–17.1)*
Mean log ₁₀ virus copy number per 0.2 g stool on day 7 (SE)	6.96 (0.54)	4.82 (0.52)*	5.00 (0.69)*
Serotype 3			
Proportion (%) shedding on day 7 (95% CI)	25.7% (20.1–31.9)	20.8% (15.7–26.8)	7.6% (4.5–11.9)†
Mean log ₁₀ virus copy number per 0.2 g stool on day 7 (SE)	6.34 (0.43)	5.47 (0.47)	6.56 (0.84)

IPV=inactivated poliovirus vaccine. *p<0.05 and †p<0.0001 significantly different from no vaccine group at first challenge.

Table 2: Shedding of poliovirus in stool samples detected by PCR

are presented as a measure of association. Antibody titres were compared between study groups with Wilcoxon’s rank sum test and within study groups with signed rank test (for paired data).

The trial is registered with the Clinical Trials Registry India (CTRI/2012/09/003005).

Role of the funding source

The funders had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data from the study and had final responsibility for the decision to submit for publication.

Results

Study recruitment took place between Aug 19, 2013, and Sept 13, 2013. All study procedures were completed by Dec 3, 2013, before annual national immunisation days in January and February. 450 children were enrolled in the trial and randomly assigned equally between the two study groups (figure 1). 447 children received the challenge dose of bOPV at study day 28, and 446 had stool collected 7 days later for the primary per protocol analysis (all of whom had received the primary intervention and challenge dose). Table 1 shows the demographic characteristics and vaccination history of the two study groups.

The proportion of children shedding poliovirus 7 days after challenge was significantly reduced in the IPV group compared with in the no vaccine group for both serotype 1 (risk ratio [RR] 0.62, 95% CI 0.40–0.97, p=0.0375) and serotype 3 (0.30, 0.18–0.49, p<0.0001; table 2, figure 2). The quantity of poliovirus shed at 7 days was lower in the IPV group than in the no vaccine group for serotype 1 (p=0.0332), but there was no significant difference for serotype 3 (p=0.64; table 2).

In the no vaccine group, the proportion of poliovirus shedding after the second bOPV dose was not significantly reduced compared with shedding after the first dose for either serotype (table 2; RR on day 7 after the second compared with first dose was 0.98, 95 CI 0.66–1.44, for serotype 1; 0.81, 0.56–1.16, for serotype 3). The quantity of poliovirus shed was significantly reduced for serotype 1 (p=0.010), but not for serotype 3 (p=0.097).

Three children in the no vaccine group and one child in the IPV group were shedding Sabin poliovirus at

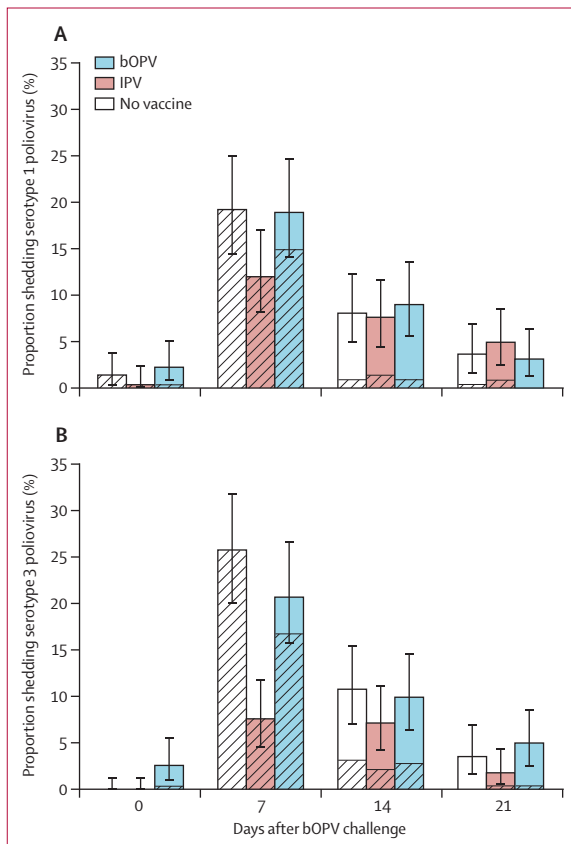


Figure 2: Proportion of children shedding poliovirus serotype 1 (A) and serotype 3 (B) in stool samples collected after administration of bivalent oral poliovirus (bOPV) challenge dose

The primary comparison of inactivated poliovirus vaccine and no vaccine groups corresponds to study days 28–49. The secondary analysis of the effect of a supplementary bOPV dose on shedding after challenge was assessed by examining shedding in the no vaccine group after a second bOPV dose corresponding to study days 56–79. The hatched area of the bars corresponds to the proportion of children who were newly shedding poliovirus on the given day (ie, whose earlier stool samples were all negative). Error bars show 95% CI. IPV=inactivated poliovirus vaccine.

enrolment (all serotype 1). Exclusion of these children did not significantly change the results (RR for shedding serotype 1 at day 7 in the IPV group compared with no vaccine group was 0.62, 95% CI 0.40–0.96, and after the second versus first bOPV dose in the no vaccine group 0.95, 0.65–1.41).

Shedding of serotype 1 or 3 poliovirus 7 days after challenge was significantly correlated in both study groups (OR 8.6, 95% CI 2.6–28.8, for IPV group; 20.8, 8.7–54.1, for the no vaccine group).

Of children in the no vaccine group who shed vaccine poliovirus 7 days after the first bOPV dose, we noted no significant difference for 7 days after the second dose compared with children who did not shed after the first dose (RR 0.82 [95% CI 0.39–1.72] for serotype 1 and 0.53 [0.26–1.09] for serotype 3). Some children shedding 7 days after the second dose could have been continuing to shed poliovirus from the initial challenge. Five (2%) children in the no vaccine group were shedding serotype 1 poliovirus at the second bOPV dose (study day 56) and six (3%) were shedding serotype 3 (figure 2). Exclusion of these children did not significantly change the risk ratio for shedding 7 days after the second compared with first dose in the no vaccine group (RR 1.00 [95% CI 0.67–1.50] for serotype 1 and 0.83 [0.56–1.21] for serotype 3).

Figure 3 shows the distributions of serum neutralising antibodies to each poliovirus serotype before and after IPV or bOPV in the IPV group and no vaccine group, respectively. The GMT for poliovirus specific neutralising antibodies significantly increased for both vaccines and all serotypes 28 days after vaccination (table 3). The GMT post-vaccination was substantially greater after IPV than after bOPV ($p < 0.0001$ for all serotypes), which is shown by the greater proportion of children undergoing seroconversion.

For serotype 1, serum neutralising antibody titres at the time of bOPV challenge were significantly lower in children who subsequently shed this serotype of poliovirus than in non-shedders, both in the IPV group (GMT 970.8 vs 1139.9, $p = 0.025$) and in the no vaccine arm (GMT 63.7 vs 120.2, $p = 0.0017$). For serotype 3, this difference was not significant (IPV group 890.8 vs 1232.4, $p = 0.90$; no vaccine group 39.9 vs 55.0, $p = 0.072$). Serum neutralising antibodies at challenge did not differ significantly in children shedding poliovirus after the second bOPV dose in the no vaccine group compared with non-shedders for both serotypes (130.2 vs 178.9 for serotype 1 and 79.0 vs 107.4 for serotype 3; $p = 0.166$ and $p = 0.240$, respectively).

Seroconversion after bOPV as assessed in the no vaccine group was significantly associated with poliovirus shedding 7 days after vaccine administration (OR 23.3, 95% CI 9.6–60.7, for serotype 1; 30.1, 12.7–77.8, for serotype 3). Of those children who seroconverted to serotypes 1 or 3, 29 (66%) of 44 and 46 (69%) of 67 shed the corresponding serotype of poliovirus, respectively. Children who seroconverted after this dose of bOPV were

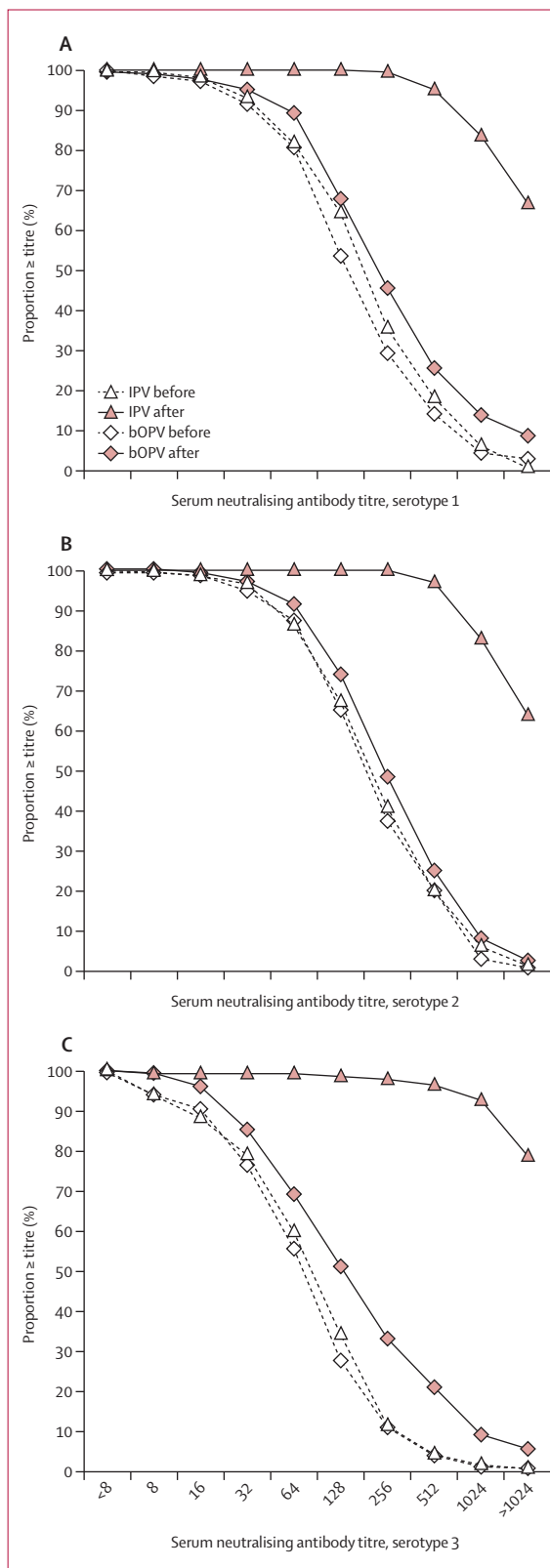


Figure 3: Reverse cumulative distribution of poliovirus specific serum neutralising antibody titres before and 28 days after a supplementary dose of inactivated poliovirus vaccine (IPV) or bivalent oral poliovirus vaccine (bOPV)

	Serotype 1	Serotype 2	Serotype 3
IPV			
Proportion $\geq 1:8$ on day of vaccination (%)	223/224 (99.6%)	223/224 (99.6%)	209/224 (93.3%)
Proportion $\geq 1:8$ 28 days after vaccination (%)	223/223 (100%)	223/223 (100%)	221/223 (99.1%)
GMT on day of vaccination	124.3	142.0	53.0
GMT 28 days after vaccination	1118.8*	1122.3*	1202.3*
Proportion seroconverting† (%)	172/223 (77%)	164/223 (74%)	209/223 (94%)
bOPV (first dose, no vaccine group)			
Proportion $\geq 1:8$ on day of vaccination (%)	216/219 (98.6%)	219/219 (100%)	206/219 (94.1%)
Proportion $\geq 1:8$ 28 days after vaccination (%)	217/219 (99.1%)	219/219 (100%)	217/219 (99.1%)
GMT on day of vaccination	106.1	137.4	50.3
GMT 28 days after vaccination	168.4*	173.7‡	100.7*
Proportion seroconverting† (%)	44/219 (20%)	29/219 (13%)	68/219 (31%)

GMT=geometric mean titre. * $p < 0.0001$ comparing prevaccination and post-vaccination titres. †Seroconversion was defined as a four-fold rise in median antibody titre or a change from undetectable to detectable antibodies at 1:8 dilution. ‡ $p = 0.0014$ comparing prevaccination and post-vaccination titres.

Table 3: Serum neutralising antibody titres before and after vaccination with inactivated poliovirus vaccine (IPV) or bivalent oral poliovirus vaccine (bOPV)

less likely to shed 7 days after the second dose compared with children who did not seroconvert, but this difference was not significant (RR 0.55, 95% CI 0.23–1.33 for serotype 1; 0.62, 0.33–1.17 for serotype 3).

The proportion of stool samples positive by PCR for a single poliovirus serotype that were tested and found positive by culture (positive predictive value of PCR for culture) was 87% (91/105) for serotype 1 and 89% (104/117) for serotypes 3 (appendix). 108 (98%) of 110 in a randomly selected subset of stool samples that were negative by PCR for serotypes 1 and 3 were also negative by culture. The proportion positive by culture did not vary by time since challenge (all $p > 0.17$), and was somewhat lower in the IPV group compared with in the no vaccine group, although this was not significant (RR 0.85, 95% CI 0.71–1.02 for serotype 1; 0.82, 0.65–1.04 for serotype 3). PCR positive samples that were culture negative had a lower virus copy number than did those that were culture positive (serotype 1: mean log copy number 3.27 vs 5.14, $p = 0.0494$; serotype 3: 2.65 vs 5.62, $p < 0.0001$).

No adverse events were related to the study interventions.

Discussion

A dose of IPV given to children aged 1–4 years previously vaccinated with OPV substantially increased humoral and intestinal mucosal immunity to poliovirus compared with no vaccine. Serum neutralising antibodies were substantially increased and these children were significantly less likely to shed poliovirus after challenge with bOPV. Most children had detectable serum neutralising antibodies to poliovirus at enrolment (>98% for serotype 1 and >93% and for serotype 3), showing that this is a boosting (anamnestic) response in children who had previously received at least five trivalent OPV doses as part of routine immunisation and who are mucosally primed. The titre of serum neutralising antibodies at the time of challenge was

correlated with protection against shedding, although this was only significant for serotype 1. The last dose of OPV received by these children was on average 7 months (range 6–17) before enrolment and it is likely that intestinal mucosal immunity to poliovirus had waned, consistent with recent findings of declining protection against infection within a year of exposure to OPV.³ By contrast, studies that coadministered IPV and OPV during routine immunisation had no interval during which waning could occur, which might explain the absence of any significant benefit in terms of mucosal immunity compared with OPV alone.^{14,16}

A dose of bOPV did not significantly reduce the proportion of children shedding poliovirus after a subsequent challenge, although the amount of virus shed was less (table 2). Shedding was less likely in children who seroconverted or shed poliovirus after the first bOPV dose than in those who did not show such evidence of vaccine take. The restricted effect of bOPV could therefore be attributable to its poorer immunogenicity compared with IPV in this low-income setting (table 3). Its performance might be better where risk factors for poor OPV immunogenicity are less common.²⁷ A small but statistically significant increase in antibody titre to serotype 2 after bOPV was noted (table 3). This increase could be caused by secondary exposure to OPV, but might also be attributable to heterologous boosting as a result of shared epitopes between serotypes.^{28,29}

The effect of IPV on poliovirus shedding was no longer significant at days 14 and 21 after challenge, when typically the amount of poliovirus shed was lower than at 7 days (appendix). Additionally, a proportion of children were newly shedding on day 14, having not previously shed poliovirus (figure 2). This finding suggests that an IPV boost suppresses the bulk of poliovirus replication at the peak of shedding, but might allow less replication that is detected later after challenge.

Panel: Research in context**Systematic review**

We previously did a systematic review of the effect of inactivated poliovirus vaccine (IPV) and oral poliovirus vaccine (OPV) on mucosal immunity to poliovirus, searching all records in PubMed and ISI Web of Knowledge up to May 9, 2011.¹¹ Immunisation with IPV alone did not reduce the prevalence of poliovirus shedding in stool 7 days after challenge with OPV. Similarly, administration of IPV with OPV during primary immunisation did not reduce poliovirus shedding after challenge when compared with OPV alone. Only one study examined immunisation with a supplementary dose of IPV, given to infants 2 months after primary immunisation with OPV.²¹ Findings from this study showed little poliovirus shedding after challenge 6 months later and no significant differences between study groups. Recent data from India suggest that intestinal mucosal to poliovirus wanes significantly within a year of vaccination with OPV.³ However, no studies were identified that examined the effect of IPV on intestinal immunity to poliovirus in OPV-vaccinated children older than 12 months whose immunity might have waned.

Interpretation

A dose of IPV given to Indian children aged 1–4 years who had been vaccinated with OPV at least 6 months previously was shown to boost humoral and intestinal immunity to poliovirus, offering substantially greater benefit compared with an additional dose of OPV. This finding supports uses of this vaccine to accelerate polio eradication by boosting herd immunity in endemic regions, prevent international spread by travellers, and minimise the risk of poliomyelitis outbreaks due to imported wildtype or vaccine-derived polioviruses.

At present, no good biomarkers are available for intestinal immunity to poliovirus and challenge studies remain the gold standard. However, challenge with a high dose of attenuated poliovirus clearly differs from natural exposure to highly infectious wildtype poliovirus. This difference restricts direct quantitative inference from our study to the effect of IPV on poliovirus transmission, although results from challenge studies do broadly correspond with epidemiological observations.¹¹ Additionally, some of the poliovirus detected by PCR could be defective or bound by antibody and uninfected. However, 87–89% of samples positive by PCR were also positive by culture and use of a higher threshold for virus copy number as an indicator for shedding, which might correlate more closely with results from virus culture, gave similar results (appendix).

The substantial benefit offered by IPV rather than further doses of OPV to boost intestinal immunity in children within the typical age range for mass vaccination campaigns that we noted in this setting supports an expanded role for IPV in the global eradication programme (panel). This role could include use in

campaigns to accelerate poliovirus eradication in infected areas and prevent reinfection in areas at risk of poliomyelitis outbreaks, and as a booster to prevent poliovirus carriage by travellers. Early programmatic experience will be essential to refine this enhanced role for IPV in the global eradication of poliomyelitis.

Contributors

JJ, JM, NCG, and GK conceived the study. JJ and ASK managed the trial. SG, MI-G, AA, and GK led the laboratory work. JJ and NCG led the statistical analysis. All authors contributed to the interpretation of the data, writing of the report, and approved the final report.

Declaration of interests

We declare no competing interests. NCG is a member of the WHO Strategic Advisory Group of Experts polio working group.

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