Immunogenicity of three doses of bivalent, trivalent, or type 1 monovalent oral poliovirus vaccines with a 2 week interval between doses in Bangladesh: an open-label, non-inferiority, randomised, controlled trial

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Summary

Background The provision of several doses of monovalent type 1 oral poliovirus vaccine (mOPV1) and bivalent OPV1 and 3 (bOPV) vaccines through campaigns is essential to stop the circulation of remaining wild polioviruses. Our study aimed to assess the shortening of intervals between campaigns with bOPV and mOPV1 and to assess the immunogenicity of bOPV in routine immunisation schedules.

Methods We did an open-label, non-inferiority, five-arm, randomised controlled trial in Bangladesh. We recruited healthy infants aged 6 weeks at 42 immunisation clinics and randomly assigned them (with blocks of 15, three per group) to receive a short three-dose schedule of bOPV (bOPV short) or mOPV1 (mOPV1 short) with the first dose given at age 6 weeks, the second at age 8 weeks, and the third at age 10 weeks; or to a standard three-dose schedule of bOPV (bOPV standard) or mOPV1 (mOPV1 standard) or trivalent OPV (tOPV standard) with the first dose given at age 6 weeks, the second at 10 weeks, and the third at age 14 weeks. The primary outcome was the proportion of infants with antibody seroconversion for type 1, type 2, and type 3 polioviruses. The primary, modified intention-to-treat analysis included all patients who had testable serum samples before and after receiving at least one OPV dose. We used a 10% margin to establish non-inferiority for bOPV groups versus mOPV1 groups in seroconversion for type 1 poliovirus, and for bOPV1 short versus bOPV1 standard for types 1 and 3. This trial is registered at ClinicalTrials.gov, number NCT01633216, and is closed to new participants.

Findings Between May 13, 2012, and Jan 21, 2013, we randomly assigned 1000 infants to our study groups. 927 completed all study visits and were included in the primary analysis. Seroconversion for type-1 poliovirus was recorded in 183 (98%, 95% CI 95–100) of 186 infants given bOPV short, 179 (97%, 94–99) of 184 given bOPV standard, 180 (96%, 92–98) of 188 given mOPV short, 178 (99%, 97–100) of 179 given mOPV1 standard, and 175 (92%, 87–96) of 190 given tOPV standard. Seroconversion for type 2 was noted in 16 infants (9%, 5–14) on bOPV short, 29 (16%, 11–22) on bOPV standard, 19 (10%, 7–15) on mOPV short, 33 (18%, 13–25) on mOPV1 standard, and 182 (96%, 92–98) on tOPV standard. Seroconversion for type 3 was noted in 175 infants (94%, 90–97) on bOPV short, 176 (96%, 92–98) on bOPV standard, 18 (10%, 6–15) on mOPV short, 25 (14%, 10–20) on mOPV1 standard, and 167 (88%, 83–92) on tOPV standard. The short schedules for mOPV1 and bOPV elicited a non-inferior antibody response compared with the bOPV standard schedule. 104 adverse events were reported in 100 infants during follow up. 36 of these events needed admission to hospital (32 were pneumonia, two were vomiting or feeding disorders, one was septicaemia, and one was diarrhoea with severe malnutrition). One of the infants admitted to hospital for pneumonia died 5 days after admission. No adverse event was attributed to the vaccines.

Interpretation Our trial showed that three doses of mOPV1 or bOPV with a short schedule of 2 week intervals between doses induces an immune response similar to that obtained with the standard schedule of giving doses at 4 week intervals. These findings support the use of these vaccines in campaigns done at short intervals to rapidly increase population immunity against polioviruses to control outbreaks or prevent transmission in high-risk areas.

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Introduction

The trivalent oral poliovirus vaccine (tOPV), which includes attenuated strains of serotypes 1, 2, and 3 poliovirus, has long been the vaccine of choice for eradication of poliomyelitis. However, this vaccine has low effectiveness in developing countries because several doses need to be given through routine immunisation services and vaccination campaigns to reach the high degree of herd immunity needed to stop the transmission of polioviruses.[1,2] Furthermore, interference of the type-2 strain with intestinal replication of types 1 and 3 means an interval of 4–6 weeks is needed between initial tOPV doses to elicit the adequate immune responses.[3,4]

The Global Polio Eradication Initiative (GPEI) introduced monovalent OPV type 1 (mOPV1) in 2005, mOPV type 3 (mOPV3) in 2006, and bivalent OPV 1 and 3 (bOPV) in 2009 after several trials showed higher immunogenicity per dose than tOPV against the respective serotypes of poliovirus.[5–7] Combined use of mOPV1 and bOPV in vaccination campaigns probably contributed to the elimination of endemic wild poliovirus from India in 2011[8] and no type-3 wild poliovirus detected globally since November, 2012.[9] However, frequent provision of bOPV and mOPV in campaigns while maintaining use of tOPV in routine immunisation services might enable the emergence of circulating vaccine-derived type-2 polioviruses in countries with weak routine immunisation systems and low tOPV coverage.[10–12] To eliminate vaccine-associated paralytic poliomyelitis and the emergence of circulating vaccine-derived polioviruses, in November, 2013, the Strategic Advisory Group of Experts on immunisation (SAGE) from WHO endorsed the introduction of at least one dose of inactivated poliovirus vaccine in routine immunisation, and a phased cessation of OPV with a global switch from tOPV to bOPV before global cessation of OPV.[13,14]

An additional challenge for the GPEI is to interrupt poliovirus transmission in areas where access for vaccination teams is restricted because of armed conflict,[15,16] and in areas where years of absence of natural infection and suboptimum routine immunisation services have created a large pool of susceptible children.[17,18] In these settings, the GPEI has used a strategy of delivering two to three doses of mOPV1 or bOPV at 1–2 week intervals between doses, in campaigns to rapidly increase population immunity.[16,18] But information is scarce on whether a 1–2 week interval between doses will decrease the efficacy of mOPV1 or bOPV, as with tOPV.[3,4]

We therefore did a study that compared the immune response conferred by three doses of mOPV1, bOPV, or tOPV provided with a short schedule with that provided with the standard schedule for primary immunisation. The aims of this study were to assess the shortening of intervals between immunisation campaigns with bOPV and mOPV1, and to assess the immunogenicity of bOPV in routine immunisation schedules. The results will help to guide strategies for the eradication of poliomyelitis.

Methods

Study design and participants

We did an open-label, non-inferiority, five-arm, randomised controlled clinical trial in Bangladesh at 41 outreach immunisation clinics in Matlab, a rural area in Chirpur district, and one immunisation clinic in Mirpur, an urban area in the Dhaka district. The study was approved by the institutional review board of the International Center for Diarrheal Diseases Research, Bangladesh (icddr,b).

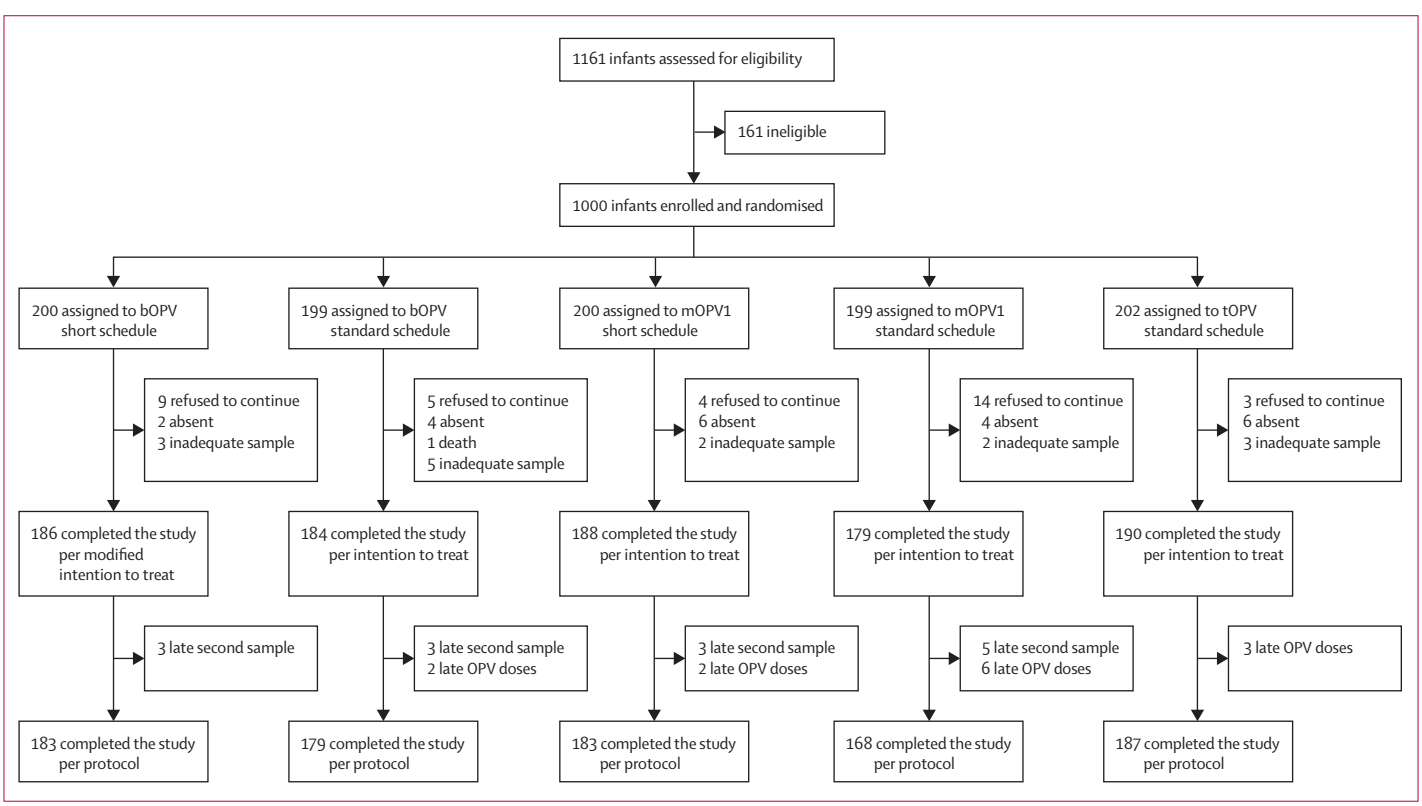

Figure 1: **Trial profile**
bOPV=bivalent oral poliovirus vaccine. mOPV1=monovalent oral poliovirus vaccine. tOPV=trivalent oral poliovirus vaccine.

Participants in the study were healthy infants aged 6 weeks (42–50 days) at enrolment who lived in the study clinic's catchment area. Exclusion criteria were suspicion of immunodeficiency, contraindications for venepuncture, previous receipt of OPV or inactivated poliovirus vaccine, and vomiting or acute illness at enrolment that would contraindicate giving OPV as per Bangladesh immunisation guidelines. Infants were withdrawn from the trial if they received OPV from another source or if their parents refused to let them continue.

To recruit participants for our trial, field study workers identified newborn babies in the catchment areas and scheduled visits to a study site by the time infants were aged 6 weeks. During this visit, physicians assessed eligibility and obtained informed, written consent from parents.

	bOPV short (n=186)	bOPV standard (n=184)	mOPV1 short (n=188)	mOPV1 standard (n=179)	tOPV standard (n=190)
Sex					
Male	101 (54%)	86 (47%)	81 (43%)*	90 (50%)	101 (53%)
Female	85 (46%)	98 (53%)	107 (57%)	89 (50%)	89 (47%)
Rural setting, Matlab	85 (46%)	104 (57%)	109 (58%)	99 (55%)	111 (58%)
Age (days)	44 (43–46)	44 (42–47)	44 (42–46)	44 (43–47)	44 (42–46)
Exclusive breastfeeding	182 (98%)	176 (96%)	183 (97%)	174 (97%)	176 (93%)*
Years that the mother spent in education					
No formal school attendance	18 (10%)	19 (10%)	19 (10%)	27 (15%)	17 (9%)
Completed primary education (up to age 10 years)	91 (49%)	84 (46%)	79 (42%)	71 (40%)	85 (45%)
Completed middle education (up to age 13 years)	46 (25%)	52 (28%)	55 (29%)	49 (27%)	50 (26%)
Completed high school or above (up to age 18 years or more)	31 (17%)	29 (16%)	35 (19%)	32 (18%)	38 (20%)
Stunted growth, low length for age†	31 (17%)	38 (21%)	18 (10%)‡	27 (15%)	37 (19%)
Wasting, low weight for length†	11 (6%)	19 (10%)	21 (11%)	19 (11%)	21 (11%)
Type-1 poliovirus					
Seropositive	119 (64%)	129 (70%)	133 (71%)	124 (69%)	119 (63%)
Antibody titres	11 (6–23)	14 (7–28)	14 (7–28)	11 (7–32)	11 (6–28)
Type-2 poliovirus					
Seropositive	143 (77%)	141 (77%)	145 (77%)	135 (75%)	144 (76%)
Antibody titres	15 (9–57)	14 (9–45)	18 (9–57)	14 (9–45)	18 (9–45)
Type-3 poliovirus					
Seropositive	79 (42%)	89 (48%)	93 (49%)	80 (45%)	85 (45%)
Antibody titres	6 (6–11)	7 (6–16)	7 (6–18)	7 (6–14)	6 (6–14)

Data are number (%) or median (IQRs). bOPV=bivalent oral poliovirus vaccine. mOPV1=monovalent oral poliovirus vaccine type 1. tOPV=trivalent oral poliovirus vaccine. *p=0·03 versus bOPV short. †Length for age and weight for length were compared with the SD of an international reference population recommended by WHO.[19] ‡p=0·04 versus bOPV short, 0·004 versus bOPV standard, and 0·006 versus tOPV standard.

Table 1: **Baseline characteristics of the intention-to-treat population**

Randomisation

After obtaining parental consent, study staff randomly assigned the infants to one of five intervention groups through a blocked randomisation scheme using a list prepared by the study statistician with blocks of 15 (three per group). The statisticians who assigned the numbers had no involvement with the patients. The five groups were short schedules for bOPV (bOPV short) and mOPV1 (mOPV1 short), and standard schedules for bOPV (bOPV standard), mOPV1 (mOPV1 standard), and tOPV (tOPV standard). Study group allocation could not be masked because of the different vaccination schedules used.

Procedures

Infants received the first dose of vaccine (bOPV, mOPV1, or tOPV) at the first (baseline) visit aged 6 weeks and were scheduled to return for the next two doses, at either age 8 weeks and 10 weeks (bOPV short and mOPV1 short), or at age 10 weeks and 14 weeks (bOPV standard, mOPV1 standard, and tOPV standard). At the first visit, study staff also recorded infants' immunisation and breastfeeding history from the parents and immunisation cards, measured their weight and length, and obtained a blood sample. During the second and third visits, staff asked about breastfeeding, presence of diarrhoea and clinical events, and vaccines received since the last visit, repeated the weight and height measurements, and gave the second and third OPV doses. During a fourth visit, which was scheduled 28–40 days after the third OPV dose, study staff obtained a second blood sample and gave the first of three tOPV doses to children who had received bOPV or mOPV1 in the study. If study visits coincided with an immunisation session and children were the correct age, they also received pentavalent vaccine (diphtheria and tetanus toxoids, whole-cell pertussis and *Haemophilus influenzae* type b vaccines, manufactured by Berna Biotech Korea, Gyeonggi-do, South Korea) in Matlab and Mirpur; and rotavirus vaccine manufactured by GlaxoSmithKline Biologicals (Rotarix; Rixensart, Belgium), in Matlab. We measured weight with electronic scales precise to 100 g (Seca, UNICEF, Australia) and length using measuring boards for infants precise to 1 mm. We used the mean of two consecutive measurements of length and weight to establish whether stunting (reduced length for age) and wasting (reduced weight for length) were present, using child-growth standard curves from the WHO Multicenter Growth Reference Study.[19] Stunted growth or wasting were defined as at least 2 SDs less than the mean of the reference population during any visit.

GlaxoSmithKline (Rixensart, Belgium) manufactured the three OPV vaccines used in this study. Each dose of vaccine (two drops or roughly 0·1 mL) contained at least 1×10^6 median cell culture infective doses ($CCID_{50}$) of attenuated Sabin serotype-1 poliovirus for mOPV1; 1×10^6 $CCID_{50}$ of Sabin serotype 1 and $1\times10^{5\cdot8}$ $CCID_{50}$ of Sabin serotype 3 for bOPV; and 10^6 $CCID_{50}$ of Sabin serotype 1, 1×10^5 $CCID_{50}$ of Sabin serotype 2, and $1\times10^{5\cdot8}$ $CCID_{50}$ of

	bOPV short (n=186)	bOPV standard (n=184)	mOPV1 short (n=188)	mOPV1 standard (n=179)	tOPV standard (n=190)	p value*
Type 1 poliovirus						
Proportion of infants with seroconversion	183 (98%, 95–100)†	179 (97%, 94–99)†	180 (96%, 92–98)†	178 (99%, 97–100)†	175 (92%, 87–85)†	0·006 bOPV short *vs* tOPV standard; 0·03 bOPV standard *vs* tOPV standard; 0·0002 mOPV1 standard *vs* tOPV standard
Reciprocal titres	≥1448 (724–≥1448)	≥1448 (1152–≥1448)	≥1448 (910–≥1448)	≥1448 (1448–≥1448)	≥1448 (724–≥1448)	0·003 bOPV short *vs* bOPV standard; 0·002 mOPV1 short *vs* mOPV1 standard; 0·005 bOPV standard *vs* tOPV standard; <0·0001 mOPV1 standard *vs* tOPV standard
Type 2 poliovirus						
Proportion of infants with seroconversion	16 (9%, 5–14)	29 (16%, 11–22)	19 (10%, 7–15)	33 (18%, 13–25)	182 (96%, 92–98)	0·04 bOPV short *vs* bOPV standard; 0·02 mOPV1 short *vs* mOPV1 standard
Reciprocal titres	6 (6–11)	6 (6–10)	6 (6–14)	6 (6–11)	≥1448 (724–≥1448)	NA
Type 3 poliovirus						
Proportion of infants with seroconversion	175 (94%, 90–97)	176 (96%, 92–98)	18 (10%, 6–15)	25 (14%, 10–20)	167 (88%, 83–92)	0·04 bOPV short *vs* tOPV standard; <0·02 bOPV standard *vs* tOPV standard
Reciprocal titres	910 (362–≥1448)	910 (455–≥1448)	6 (6–6)	6 (6–6)	646 (228–≥1448)	0·008 bOPV short *vs* tOPV standard; <0·001 bOPV standard *vs* tOPV standard

Data are proportions of infants with seroconversion and reciprocal antibody titres after three OPV doses, by poliovirus type and study arm (n=927), either n (%, 95% CI) or median (IQR) and p values. bOPV=bivalent oral poliovirus vaccine. mOPV1=monovalent oral poliovirus vaccine type 1. tOPV=trivalent oral poliovirus vaccine. *p values are reported for comparisons of interest (ie, they exclude comparisons between study vaccines without a specific serotype). Also excluded are comparisons between bOPV short with bOPV standard, mOPV1 short with mOPV1 standard, bOPV short with mOPV1 short, and bOPV standard with mOPV1 standard groups for poliovirus types 1 and 3 because comparisons were done using non-inferiority assumptions. †Wilson 95% CIs of proportions.

Table 2: **Seroconversion and reciprocal antibody titres**

Sabin serotype 3 for tOPV. UNICEF purchased and donated the study vaccines. All vaccines were shipped by the manufacturer and stored in appropriate cold-chain conditions in Mirpur and Matlab. We used cold boxes to transport vaccines to outreach clinics in Matlab.

We obtained 1 mL of blood by venepuncture from each infant and stored it at 2–8°C. We separated serum within 6 h of collection and stored it at –20°C until study completion. We tested samples for neutralising antibody titres against types 1, 2, and 3 poliovirus using a modified microneutralisation assay that has been previously described.[20,21] The dilution series ran from 1/8 to 1/1024. Titres not detected at the lower limit were assigned a value of 1/6 and titres above the upper limit were assigned a value of 1/1448. We defined seropositivity as a reciprocal antibody titre of at least 8, and seroconversion as a change from seronegative at baseline to seropositive after receiving three doses of OPV, or a post-vaccination titre that was at least four-times higher than the expected titre, assuming a half-life of 28 days for maternal antibodies detected at baseline.

Outcomes

The primary outcomes of the study were the proportions of infants with antibody seroconversion against a specific poliovirus type. Secondary outcomes were non-inferiority for bOPV groups versus mOPV1 groups in seroconversion for type-1 poliovirus, and for bOPV1 short versus bOPV1 standard for type 3, comparison of distribution of reciprocal antibody titres and adverse events by study group, and factors that affected the likelihood of seroconversion.

We monitored adverse events at the study sites for 30 min after each vaccine dose was given, and parents were asked to bring the children to a reference hospital or study site if signs of illness occurred during the 8–12 week follow-up. All adverse events were reviewed by the principal investigator (KZ) and serious adverse events were reported within 24 h.

Statistical analysis

We set the non-inferiority margin at 10% using a 0·05 one-tailed test. The test vaccine study group was deemed non-inferior to the control study group if the lower bound of the 95% CI of the differences in seroconversion was not less than –10%. The study was powered to detect non-inferiority in seroconversion for type-1 poliovirus for both bOPV groups versus both mOPV1 groups, and in seroconversion for type-1 and type-3 polioviruses for bOPV short versus bOPV standard. A sample of 154 participants per group was needed to show non-inferiority with an expected seroconversion of 90% for bOPV standard and 90% power at the point of equality for the two groups. The sample was inflated to 200 children per group to account for about 20% attrition. Because bOPV and mOPV1 were expected to have similar or better immunogenicity than tOPV, we used χ^2, or Fisher's exact test for comparisons between tOPV and other vaccines, and defined statistical significance as a two-tailed p value less than 0·05. We compared proportions between study groups with χ^2, Fisher's, or Cochran-Armitage trend tests, and used non-parametric Wilcoxon rank-sum tests to compare the distribution of antibody titres in the groups. We used logistical regression to calculate adjusted odds

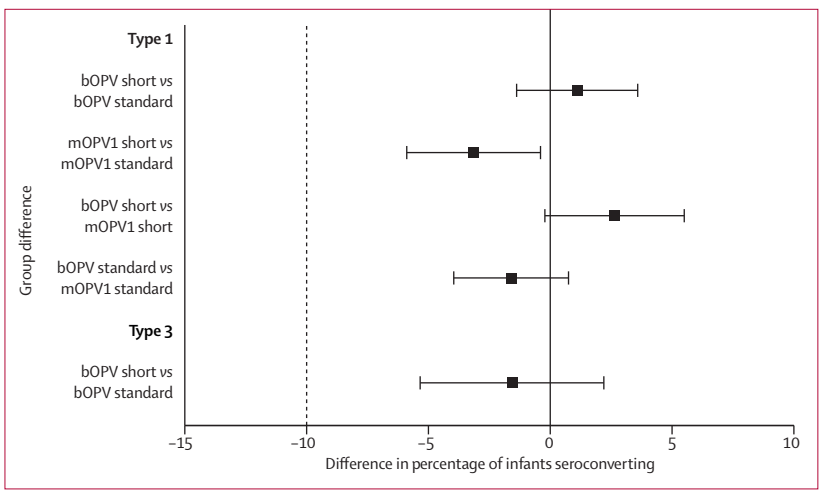

Figure 2: **Differences in proportions of post-vaccination antibody seroconversion**
Differences in proportions of seroconversion to types 1 and 3 polioviruses were measured between test groups (bOPV short schedule and mOPV1 short schedule) and control groups (bOPV standard schedule and mOPV1 standard schedule) using one-sided 95% CIs. bOPV=bivalent oral poliovirus vaccine. mOPV1=monovalent oral poliovirus vaccine.

ratios (ORs) for the effect of risk factors on seroconversion rates[1,22,23] (methods for calculating the logistic regression analysis are in the appendix). Analyses were done for infants who completed the study per modified intention to treat (primary analysis) and per protocol, with SAS version 9.3.[24] The icddr,b safety monitoring board oversaw the study and reviewed safety data.

See Online for appendix

This trial is registered at ClinicalTrials.gov (number NCT01633216).

Role of the funding source

The funder of the study participated in study design, data analysis, data interpretation, and writing of the report, but not in data collection. The corresponding author had full access to all the data in the study and had final responsibility to submit for publication.

Results

Between May 13, 2012, and Jan 21, 2013, we enrolled and randomly assigned 1000 infants to our study groups (figure 1). 927 infants completed all study visits and were included in the modified intention-to-treat analysis (528 in Matlab, 399 in Mirpur) and 900 completed the study per protocol. No significant differences were noted in baseline seroprevalence or other characteristics between infants who completed or discontinued the study (data not shown). Of the 27 infants with protocol violations, 13 attended the second or third visit more than 2 days (range 3–9) after the scheduled date, and 14 gave a blood sample more than 40 days (range 41–67) after the last OPV dose; none missed a study vaccine dose. Immunogenicity outcomes of the per-protocol and intention-to-treat populations did not differ significantly; results are presented for the modified intention-to-treat population.

No significant differences were noted in baseline seroprevalence to polioviruses (table 1). Because of differences in vaccination schedules, in Matlab only 28 (5%) of 527 infants received both Rotarix doses concomitantly with OPV; 162 (31%) received one Rotarix dose concomitantly with OPV and 337 (64%) received Rotarix separately from OPV doses (median 6 days for OPV1-Rotarix1 and 8 days for OPV3-Rotarix2).

Seroconversion for type-1 poliovirus was recorded in 183 (98%, 95% CI 95–100) of 186 infants given bOPV short, 179 (97%, 94–99) of 184 given bOPV standard, 180 (96%, 92–98) of 188 given mOPV1 short, 178 (99%, 97–100) of 179 given mOPV1 standard, and 175 (92%, 87–96) of 190 given tOPV standard. Compared with tOPV, proportions of seroconversion were higher after bOPV short (p=0·006), bOPV standard (p=0·03), and mOPV1 standard (p=0·0002; table 2).

Seroconversion for type 2 was noted in 16 infants (9%, 5–14) on bOPV short, 29 (16%, 11–22) on bOPV standard, 19 (10%, 7–15) on mOPV1 short, 33 (18%, 13–25) on mOPV1 standard, and 182 (96%, 92–98) on tOPV standard. Proportions of seroconversion were higher for bOPV short versus bOPV standard (p=0·04) and for mOPV1 short versus mOPV1 standard (p=0·02).

Seroconversion for type 3 was noted in 175 infants (94%, 90–97) on bOPV short, 176 (96%, 92–98) on bOPV standard, 18 (10%, 6–15) on mOPV1 short, 25 (14%, 10–20) on mOPV1 standard, and 167 (88%, 83–92) on tOPV standard. Seroconversion to type-3 poliovirus was non-inferior with bOPV short compared with bOPV standard (table 2, figure 2).

Antibody titres against type-3 poliovirus were higher after both schedules of bOPV than after tOPV (table 2), but differences for titres against type 1 are difficult to interpret because final titres were very high for all study groups, and microneutralisation testing did not differentiate between values for titres of 1448 or more (table 2).

With logistic regression analysis (table 3, appendix), after tOPV exclusive breastfeeding increased the likelihood of seroconverting to type-1 poliovirus, and residence in Matlab (rural area) was associated with an increased likelihood of seroconverting to type 3; a high concentration of type-specific maternal antibodies was associated with a decreased likelihood of seroconverting to type-3 poliovirus but not to type 1 (table 3). After giving bOPV standard, stunting of growth during any visit reduced the likelihood of seroconversion to type 3 (adjusted OR 0·15, 95% CI 0·02–0·86, p=0·03; data not shown).

We noted no adverse events within 30 min of giving an OPV dose, but 104 adverse events were reported in 100 infants during follow-up. 68 events were classified as mild to moderate (appendix), and 36 (35%) needed treatment in hospital. The events treated in hospital included pneumonia (32, 89%), vomiting or feeding disorders (two, 6%), septicaemia (one, 3%), and diarrhoea with severe malnutrition (one, 3%). One infant admitted to hospital for pneumonia died 5 days after admission; all other events resolved with symptomatic treatment. No adverse event was attributed to trial vaccines by the

principal investigator, and we noted no significant differences in adverse events between study groups.

Discussion

Our trial showed that giving three doses of mOPV1 or bOPV according to a short schedule of 2 week intervals between doses induces an immune response similar to that induced with a standard schedule of 4 week intervals between doses. The trial also substantiated the high immunogenicity and safety of bOPV against both type-1 and type-3 polioviruses, given with the infant routine immunisation schedule recommended by WHO (panel).

At least 94% of infants seroconverted to type-1 and type-3 polioviruses after receiving bOPV with both short and standard schedules, and we noted no between-group differences in reported adverse events. The results of this study support those from a trial in India,[7] in which only two vaccine doses were given. As in that trial, the immune response elicited by bOPV standard schedule in our trial for type-1 poliovirus was non-inferior to mOPV1 short schedule, and superior to tOPV.[7] For type-3 poliovirus, the immune responses from bOPV short and standard were higher than that from tOPV, with high proportions of seroconversion (94–96%) and high antibody titres (median 910). On the basis of the results of these two trials, we expect a high proportion of children to be immune after three doses of bOPV.

Provision of three doses of either mOPV1 or bOPV with only a 2 week interval between doses seroconverted and elicited high antibody titres against type-1 poliovirus in 96–98% of children vaccinated. Giving mOPV1 at short intervals was not expected to affect its immunogenicity, but studies in the 1960s[5,28,29] suggested potential interference in replication of types 1 and 3 strains when doses are given at intervals shorter than 4 weeks. However, the results of our study support the use of bOPV in short-interval campaigns, alone or in addition to mOPV1, to accelerate the development of high population immunity. bOPV offers the advantage of closing immunity gaps to type-3 poliovirus without compromising the ability to stop the transmission of type-1 wild poliovirus.

Seroconversion to types 1 and 3 after three tOPV doses was higher in this trial than expected in a tropical, non-industrialised country.[1] In a study done in Dhaka in 2008,[27] 90% (95% CI 81–96) of infants had seroconversion for type-1 poliovirus and 68 % (56–79) for type 3 after three tOPV doses with the standard schedule. On one hand, results from our study support those from other studies in which chronic malnutrition reduced seroconversion to type 3[1,8] and exclusive breastfeeding increased seroconversion to type 1.[26] Simultaneous receipt of at least one rotavirus vaccine dose did not interfere with immune responses to mOPV1 or bOPV as it has been shown previously with tOPV, but most infants received both vaccines on different days.[25,27] On the other hand, the use of rotavirus vaccine in Matlab, together with community interventions such as the encouragement of breastfeeding or use of safe water, implemented in the area for years,[30] could have reduced local prevalence of diarrhoeal diseases, which could explain the beneficial effect of residing in Matlab for type-3 seroconversion.

Our study had several limitations. First, the study might not be representative of all areas in Bangladesh or other countries. Second, group assignment in the study could not be masked because of the different vaccination schedules used; this factor is unlikely to have affected the immunogenicity data, but could possibly have affected

	Conversion to serotype 1	Conversion to serotype 3
Male sex	1·34 (0·36–4·92), 0·66	0·95 (0·32–2·83), 0·92
Rural setting, Matlab	0·96 (0·17–5·47), 0·96	6·19 (1·72–22·29), 0·01
Mother's education <5 years	0·73 (0·20–2·66), 0·63	2·27 (0·76–6·75), 0·14
Moderate to severe stunting in any visit	0·39 (0·11–3·32), 0·81	0·64 (0·21–2·01), 0·44
Moderate to severe wasting in any visit	0·85 (0·22–1·38), 0·14	1·34 (0·38–4·71), 0·65
Exclusive breastfeeding at all visits	5·48(1·18–25·41), 0·03	0·86 (0·21–3·58), 0·84
Breastfeeding <15 min before giving OPV	0·81 (0·15–4·22), 0·80	0·49 (0·12–1·95), 0·31
High concentration of maternal antibodies for type-specific polioviruses, >1/72	0·35 (0·10–1·24), 0·10	0·11 (0·03–0·37), 0·0004
Received two or more doses of OPV during rainy months, June to September	1·06 (0·32–3·57), 0·92	0·36 (0·11–1·16), 0·09

Data are odds ratios (95% CIs), p values; obtained after three doses of tOPV (n=187). These were estimated controlling for all variables tested with univariate analysis and shown in the table (methods in appendix). OPV=oral poliovirus vaccine. tOPV=trivalent OPV.

Table 3: **Logistic regression analysis for risk factors affecting seroconversion**

Panel: Research in context

Systematic review

We searched PubMed for papers published from Jan 1, 1959, to July 31, 2014, with the terms "oral polio vaccine", "monovalent oral polio vaccine", "bivalent oral polio vaccine", "trivalent oral polio vaccine", and "clinical trials" for studies comparing the immunogenicity of polio vaccines. Publications not written in English or Spanish were excluded. Because a large number of studies used trivalent oral poliovirus vaccine (tOPV), we used expert reviews as references to summarise general tOPV results[1,4,5] We selected clinical trials[6,7,25–27] that had used bivalent OPV (bOPV), monovalent OPV (mOPV), and tOPV for direct comparisons with the results of our study because other studies had used vaccines with different formulations and total virus content. Finally, we used published and unpublished reports from the Global Polio Eradication Initiative to obtain updated epidemiological information about worldwide transmission of polioviruses.

Interpretation

To our knowledge, our study has shown for the first time that provision of three doses of type-1 mOPV (mOPV1) or type-1 and type-3 bOPV given at 2 week intervals induces similar immune responses as doses given at 4 week intervals. These results support the use of both vaccines in campaigns done at short intervals to rapidly increase population immunity against polio to accelerate the control of outbreaks after importations, and to stop transmission in areas with difficult access because of armed conflict. bOPV offers the advantage of closing immunity gaps to type-3 poliovirus without compromising the ability to stop type-1 poliovirus. This study also showed that bOPV is more effective than tOPV against type-1 and type-3 polioviruses in the classic routine immunisation schedule. These findings support the replacement of tOPV with bOPV in routine immunisation for infants worldwide, to eliminate the risk of type-2 vaccine-derived polioviruses as part of the polio eradication strategy.

reports of adverse events. Finally, community transmission of Sabin strains from non-study participants who received tOPV through routine immunisation services probably caused type-2 seroconversion during the bOPV and mOPV1 series, and might have increased seroconversion rates to other serotypes; however, this effect is expected to be similar across groups.

In conclusion, provision of three doses of mOPV1 or bOPV at 2 week intervals induced similar immune responses as provision of doses at the standard 4 week intervals. These findings lend support to the use of these vaccines in campaigns done at short intervals to rapidly increase population immunity against polioviruses to control outbreaks or prevent transmission in high-risk areas. bOPV given in a short schedule or a standard schedule produced higher proportions of seroconversion to type-1 and type-3 poliovirus than tOPV, which supports the replacement of tOPV with bOPV in routine immunisation schedules for infants worldwide to eliminate the risk of type-2 vaccine-derived polioviruses.

Contributors

CFE prepared the manuscript, and all authors reviewed and approved it. CFE, AA, HEG, SGFW, SYC, SPL, JDH, and MAP did the study design, trial implementation strategy, and interpreted the data. KZ, MR, JI, and TIB oversaw the trial implementation. WCW and MAP did the laboratory tests and interpreted the data. CFE and HEG contributed to data analyses.

Declaration of interests

We declare no competing interests.

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