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Safety, immunogenicity and lot-to-lot consistency of a new Bivalent Oral Polio Vaccine (bOPV) in healthy Infants: Results of a Phase III, observer blind, randomized, controlled clinical study

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ABSTRACT

Background: Poliomyelitis infection continues to be endemic in few countries despite rigorous efforts for eradication. A new Bivalent Oral Polio Vaccine (BBio bOPV) was tested in a Phase III Clinical study.
Methods: An observer blind, randomized, controlled clinical study was conducted comparing BBio bOPV with a licensed bOPV (SII bOPV). Initially in Part 1, 40 children 5–6 years of age were given a single dose of either vaccine in 1:1 ratio. In Part 2, 1080 infants of 6–8 weeks of age were received in 1:1:1:1 ratio one of the 3 lots of BBio bOPV or SII bOPV at 6, 10 and 14 weeks of age. Blood samples were collected to assess neutralizing antibody responses against Polio Type 1 and 3 viruses. Safety of the vaccines were recorded.
Results: All children were seroprotected against both Type 1 and Type 3 polioviruses post-vaccination. More than 96% of the infants demonstrated seroconversion as well as seroprotection against both types of polioviruses. The geometric mean titres (GMT) for Type 1 and Type 3 antibodies were comparable between the groups. The 3 lots of BBio bOPV generated similar GMTs of Type 1 and Type 3 antibodies. In total 387 participants reported at least one adverse event and 18 serious adverse events. None of these events were vaccine related.
Conclusions: The new bOPV vaccine demonstrated immunogenicity that was non-inferior to a licensed bOPV vaccine. Consistency in immune response by 3 consecutively manufactured lots was also demonstrated. The vaccine did not cause any adverse event.
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1. Introduction

Since launch of Global Poliomyelitis Eradication Initiatives (GPEI) in 1988, widespread use of poliovirus vaccines led to reduction in polio cases from about 350,000 in 1988 to 33 in 2018 [1]. Inactivated polio vaccines (IPV) as well as trivalent Oral Polio Vaccine (tOPV) have played a big role in this reduction though OPV has been the vaccine of choice in eradication activities, because of oral administration, its superiority in conferring intestinal immunity, and low cost [2].

No case of wild type 2 poliovirus has been reported since 1999 [3]. Because of issues of circulating vaccine-derived poliovirus (cVDPV) and vaccine-associated paralytic polio (VAPP) cases associated with type 2, interference by the type 2 with the immune response of type 1 and 3 vaccines and [4] global eradication of type 2 strain in September 2015, the World Health Organization (WHO) recommended that withdrawal of the type 2 component in the OPV should occur in April 2016 [5]. Bivalent OPV (bOPV) is superior to tOPV in giving immunity against type 1 and 3 viruses [6]. It was also recommended that this global switch from tOPV to bOPV should happen along with introduction of at least one dose of IPV [6].

UNICEF envisages that bOPV vaccines will be required till 2022 and anticipates total demand for 2018–2022 period, to reach 4.2 billion doses [7]. Presently around 145 countries in the world use OPV in their immunization programmes [8]. Though there are eight WHO prequalified bOPV manufacturers, only four of them manufacture the bulk vaccine and the remaining four fill and finish the bulk received from one of the bulk manufacturers [9].

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Considering the global need for bOPV, a new bOPV has been developed from bulk stage by Bilthoven Biologicals, the Netherlands. In line with the WHO recommendations [10], the vaccine was tested in a Phase III clinical study in children and in infants.

2. Materials and methods

This was an observer blind, randomized, controlled clinical study conducted in 2 parts at Matlab Health Research Centre of International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh (icddr,b). In the first part of the study, safety and seroprotection rates with BBio bOPV were assessed in comparison with SII bOPV in healthy children of 5–6 years of age. The children were given a single dose of either BBio bOPV or SII bOPV in 1:1 randomization. They were followed for one month for any safety events and a blood sample was collected at one month after the vaccination. If no safety concern was identified, then the study proceeded to the Part 2.

In the Part 2, the 1080 infants were randomized in 1:1:1:1 ratio to BBio bOPV (Lot A), BBio bOPV (Lot B), BBio bOPV (Lot C) or to SII bOPV. All the participants received 3 doses of the study vaccines at 6, 10 and 14 weeks of age along with DTwP-HepB-Hib and pneumococcal conjugate vaccines (PCV). Solicited reactions were collected by using structured diary cards. Safety follow up was maintained till one month after the last dose. All adverse events and serious adverse events reported during this period were collected. One month after the last dose, blood sample was collected to assess immune response induced by the study vaccines. The primary objectives of the Part 2 of this study were to compare seroconversion and seroprotection rates against type 1 and type 3 polio viruses with the BBio bOPV to that of SII bOPV. The secondary objectives were to demonstrate manufacturing consistency of BBio bOPV by evaluating geometric mean titres (GMT) of type 1 and type 3 polio antibodies induced by three lots of BBio bOPV manufactured as per current Good Manufacturing Practice (cGMP). Safety assessment was also a secondary objective.

2.1. Randomization and blinding

For treatment allocation, a randomization blocking scheme (1:1 in Part 1 and 1:1:1:1 in Part 2 of this study) was used. Randomization was done by using computer generated randomization list. As an observer blind study, an unblinded medical officer/nurse administered the study vaccines who was not involved in the safety evaluations. The study staff involved in safety evaluation, parents/legal guardians of the participants and the laboratory personnel conducting serological analysis were blinded to the treatment allocations.

2.2. Study products

BBio bOPV (Bilthoven Biologicals, Netherlands) is a suspension of type 1 and type 3 live attenuated poliomyelitis viruses (Sabin strains) propagated in Vero cell culture. Each dose of 2 drops (0.1 ml) contains 10^6 $CCID_{50}$ live attenuated polio virus Type 1 and $10^{5.8}$ $CCID_{50}$ live attenuated polio virus Type 3 along with formulation buffer and water for injection. Batch number BLP-002 (Expiry 02 Sep 2016) was used in the part 1 of the study and Batch numbers BLP005 (Expiry Apr 2018), BLP006 (Expiry Apr 2018) and BLP007 (Expiry Apr 2018) were used in the part 2 of the study.

SII bOPV (Serum Institute of India Pvt Ltd, India) is a suspension of type 1 and type 3 live attenuated polio viruses (Sabin), grown on Primary Monkey Kidney culture. Each dose of 2 drops (0.1 ml) contains $10^{6.0}$ $CCID_{50}$ Polio virus Type 1 and $10^{5.8}$ $CCID_{50}$ Type 3. Batch no. 180O6030 (Expiry Feb 2018) was used in the Part 1 of the study and Batch number 180O6048 (Expiry Mar 2018) was used in the part 2 of the study.

All the study vaccines were transported and stored at or below −20 °C.

2.3. Study population

In the Part 1 of the study, healthy children of 5–6 years who had received at least 3 doses of tOPV were included. In part 2 healthy infants of 6 to 8 weeks age who had not received OPV previously were included. Children with immunodeficiency, acute or persistent diarrhoea, vomiting, history of allergy to the study vaccines, malnutrition ($\leq$3 SD weight for length) or any other clinically significant medical condition were excluded.

2.4. Immunogenicity assessment

In Part 1 antibody titres against polio virus type 1 and type 3 were measured 28 days after a single dose of bOPV. In the part 2 the antibody titres were measured at baseline and at 28 days after the third dose of bOPV. The testing was conducted at Bilthoven Biologicals, the Netherlands by microneutralization assay. Seroprotection was defined as neutralizing antibody titre $\geq$1:8. Seroconversion was defined as a titre 4 times higher than the expected drop in maternal antibody concentrations between successive serum samples (the half life of antibody decay is assumed to be 28 days) in previously seropositive participants or reciprocal neutralization antibody titre $\geq$8 in previously seronegative participants. The microneutralization assay was standardized as per WHO guidance [11].

Titers below the lowest limit of quantitation (i.e., below the starting dilution of assay) were set to half that limit (1:4).

2.5. Safety evaluations

Throughout the study period adverse events (AEs) were collected form study participants. The AEs were classified for severity as mild, moderate, severe as per predefined criteria. Causality association with study vaccination was determined based on the temporal relationship, biological plausibility and study physician's clinical judgement. An independent Data Safety Monitoring Board (DSMB) was appointed by icddr,b, Ethical Review Committee which oversaw the safety data in the study.

2.6. Statistical analysis

Quantitative demographic variables like age, length, and weight were described as number of participants, mean, standard deviation, median and range. Qualitative demographic variables like gender were described by number of participants and percentage for each group.

Safety Analysis was conducted on the intention to treat (ITT) data set. The analysis included frequency of adverse events expressed in terms of percentage and 95% of confidence interval (CI).

The immunogenicity analysis was conducted on the per protocol (PP) data set as well as on the ITT data set. Seroprotection (antibody titre $\geq$ 1:8) in each group was calculated in percentage along with 95% CI. Seroprotection was compared between groups by using Farrington and Manning method. In all the groups Geometric Mean Titre (GMT) of antibodies were calculated along with 95% CI.

In the Part 1 of the study there was no formal hypothesis. In the Part 2 of the study, 226 evaluable infants were required in each BBio bOPV vaccine lot groups to demonstrate lot-to-lot consistency of the vaccine at 90% power. The consistency would be demonstrated if the ratios of GMTs between each of the 3 lots were between 0.5 and 2. With an estimated dropout rate of 15%, the target enrolment was 270 subjects per lot. Evaluable sample size of 678 infants for the BBio bOPV 3 lots combined and 226 infants

for the control group (1080 infants randomized to account for 15% dropout rate) provided more than 99% power to demonstrate non-inferiority of BBio bOPV to SII bOPV for both serotypes 1 and 3. Non-inferiority was to be proven if the upper bound of the 95% CI of the difference in seroconversion rates was <10% for both the serotypes. Statistical testing for non-inferiority of proportion of seroconversion was done using Farrington and Manning method.

ITT Population was defined as participants who received at least one dose of vaccine. The PP population was defined as participants who met all eligibility criteria, received all 3 doses of the vaccines as per randomization scheme, developed no premature discontinuation criteria and did not take any prohibited concomitant medications like immunosuppressive drugs and other polio vaccines.

2.7. Ethical considerations

The study was approved by the Ethical Review Committee of icddr,b, Dhaka. The participants were enrolled only after written Informed Consent of their parents/legal guardians. The study followed the principles of the Declaration of Helsinki and the ICH Good Clinical Practices (GCP) guidelines.

3. Results

3.1. Part 1

A total of 41 healthy children of 5–6 years of age were screened and 40 were randomized in 1:1 ratio to BBio bOPV or to the control vaccine (SII bOPV). All 40 participants completed the study. There were no major protocol deviations.

Table 1
Geometric mean titres (95% CI) of polio antibodies in the Part 1 study (PP Set).

	BBio bOPV (N = 20)	Control (N = 20)	GMT ratio
Polio Virus Type 1	693.1 (250.7, 1916.2)	582.8 (267.4, 1270.5)	1.19 (0.34, 4.11)
Polio Virus Type 3	222.2 (137.8, 358.0)	282.6 (135.3, 590.4)	0.79 (0.34, 1.84)

The age of the study participants ranged from 63 months to 83 months. 60% of the participants were females. A total of 12 AEs were reported in the study; 4 in the BBio bOPV group and 8 in the SII bOPV group. Of these, 4 were within 4 days of study vaccination. No AEs were related to study products. There was no serious adverse event reported. At one month after study vaccinations, all the 40 participants had seroprotective titres against both polio viruses Type 1 and Type 3. The GMTs of polio Type 1 and Type 3 antibodies were similar in both the groups (Table 1).

3.2. Part 2:

A total of 1096 infants were screened of which 16 were screen failures. A total 1080 infants were randomized in 1:1:1:1 ratio to group 1A, group 1B, group 1C and to the control group. All 1080 participants received their first vaccination.

A total of 1060 participants completed the study. The 20 early withdrawals were due to either lost to follow-up (n = 9) or due to consent withdrawal by parents/legal guardians (n = 10) and received another investigational drug/polio vaccine during the study (n = 1).

The ITT population and the safety population included all 1080 participants while the PP population included 1039 participants. The exclusions from the PP data set were because of blood sample not collected (n = 41), not receiving all 3 doses of the study vaccines (n = 10) and receipt of another polio vaccine during the study (n = 1) (Fig. 1).

The participants' age ranged from 6 to 8 weeks. The male female distribution was almost similar. The weights of the participants ranged from 3.1 kg to 6.2 kg. The lengths ranged from 49 cm to 62 cm. All the participants were Bangladeshi infants (Table 2).

Out of 1080 participants, all received PCV and, 1076 received DTwP-HepB-Hib vaccine at 6, 10, 14 weeks of age while 1073 received BCG vaccine at 6 weeks of age. While 1080 participants

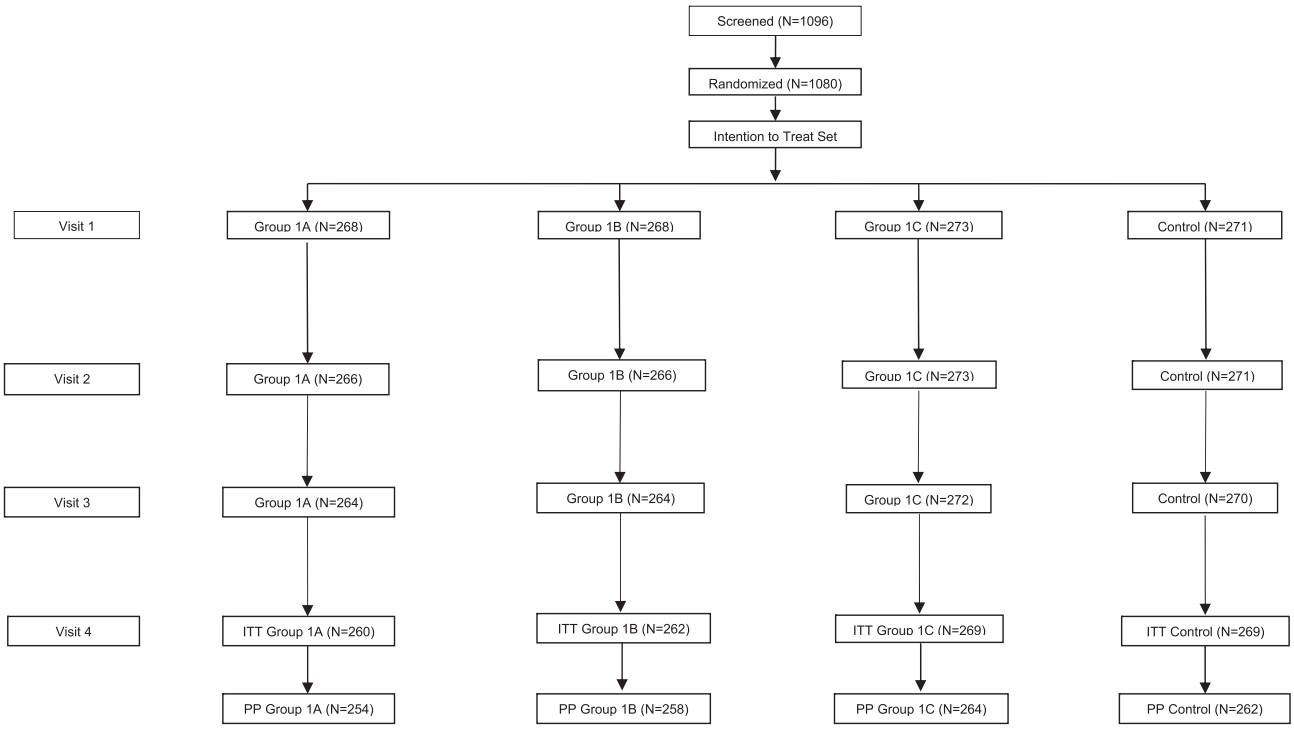

Fig. 1. Subject Disposition Flow Chart By Visit (ITT SET).

Table 2
Demographics and baseline characteristics in the Part 2 study (ITT Set).

	Group 1A (N = 268)	Group 1B (N = 268)	Group 1C (N = 273)	Control (N = 271)
Age (weeks)	7.0	6.9	6.9	7.0
Mean (SD)	(0.59)	(0.57)	(0.55)	(0.56)
Male (%)	131 (48.9%)	134 (50.0%)	150 (54.9%)	134 (49.4%)
Weight (kg)	4.54	4.55	4.45	4.49
Mean (SD)	(0.537)	(0.523)	(0.539)	(0.498)
Length (cm)	55.3	55.4	55.0	55.0
Mean (SD)	(2.06)	(2.00)	(2.13)	(1.90)

received the first dose, 1076 received the second dose and 1070 received all three doses of the study vaccines.

In the PP population, the seroconversion rates were more than 96% for both the viruses in both the groups. In terms of seroprotection (antibody titres $\geq$ 1:8) for both the viruses, the seroprotection rates were more than 97% in the both the groups (Table 3).

Table 4 gives the lot-to-lot consistency of BBio bOPV in the PP population for polio virus Type 1 and 3 antibodies. The ratios of GMTs among the three groups were close to 1 with 95% CI within the predefined limits of 0.5–2, thus demonstrating the lot-to-lot consistency.

A comparison was done for the GMTs between the pooled BBio group and the control group for both the Type 1 and Type 3 antibodies. In both the cases, the ratios were close to 1 (Table 5).

There were a total of 250 participants who reported at least one AE within 4 days of each vaccination. Of these 146 reported having at least one AE after the first dose, 84 reported having at least one AE after the second dose and 62 reported having at least one AE after the third dose. There were 387 participants who reported at least one AE throughout the study duration, of which 19 were SAEs reported in 18 participants. The incidence of AEs and SAEs were comparable between study and control groups (Table 6).

Of the total 387 participants who reported at least one AE throughout the study, most of them were due to infections and infestations, injection site reactions for concomitant vaccines and fever. 347 reported mild, 20 were moderate and 19 were of severe grading. In case of one adverse event, severity assessment could not be made. In 387 participants, adverse events resolved without sequelae, while in 10 participants adverse events did not resolve at the time of last follow up. None of the AEs were causally related to the study vaccines.

Of the 19 SAEs, 18 were lower respiratory tract infections and one was respiratory tract infection and all were unrelated to the study vaccination. All of them recovered without any sequelae. There were no deaths reported in the study.

Table 3
Seroconversion and seroprotection in the Part 2 study, n, % (95% CI) (PP Set).

		Pooled BBio bOPV (N = 777)	Control (N = 262)	Pooled BBio bOPV vs. Control
Polio Virus Type 1	Seroconversion	762 (98.1%) (96.8%, 98.9%)	261 (99.6%) (97.9%, 100.0%)	−1.5% (−3.7%, 0.6%)
	Seroprotection	771 (99.2%) (98.3%, 99.7%)	262 (100.0%) (98.6%, 100.0%)	−0.8% (−2.9%, 1.3%)
Polio Virus Type 3	Seroconversion	764 (98.3%) (97.2%, 99.1%)	254 (96.9%) (94.1%, 98.7%)	1.4% (−1.1%, 3.8%)
	Seroprotection	772 (99.4%) (98.5%, 99.8%)	255 (97.3%) (94.6%, 98.9%)	2.0% (−0.3%, 4.4%)

Table 4
GMCs and GMC ratios for lot-to-lot consistency of BBio bOPV groups in the Part 2 study (PP population).

GMC			GMC			Ratio of GMCs	
Group	N	Value (95% CI)	Group	N	Value (95% CI)	Groups	Value (95% CI)
Polio type 1 antibody							
Group 1A	255	1046.1 (871.0, 1256.4)	Group 1B	258	967.4 (816.2, 1146.5)	Group 1A versus Group 1B	1.08 (0.84, 1.39)
Group 1A	255	1046.1 (871.0, 1256.4)	Group 1C	264	1006.6 (832.5, 1217.2)	Group 1C versus Group 1A	0.96 (0.74, 1.25)
Group 1B	258	967.4 (816.2, 1146.5)	Group 1C	264	1006.6 (832.5, 1217.2)	Group 1B versus Group 1C	0.96 (0.74, 1.24)
Polio type 3 antibody							
Group 1A	255	605.0 (528.8, 692.2)	Group 1B	258	558.7 (481.3, 648.5)	Group 1A versus Group 1B	1.08 (0.89, 1.32)
Group 1A	255	605.0 (528.8, 692.2)	Group 1C	264	652.6 (567.2, 750.9)	Group 1C versus Group 1A	1.08 (0.89, 1.31)
Group 1B	258	558.7 (481.3, 648.5)	Group 1C	264	652.6 (567.2, 750.9)	Group 1B versus Group 1C	0.86 (0.70, 1.05)

Table 5
Comparison of geometric mean titres of BBio bOPV and SII bOPV in the Part 2 study (PP Set).

	Pooled BBio bOPV (N = 777)	Control (N = 262)	Ratio	P value
Polio Virus Type 1	1006.0 (906.4, 1116.6)	958.6 (821.2, 1119.1)	1.05 (0.86, 1.28)	0.6369
Polio Virus Type 3	604.6 (557.3, 655.9)	478.0 (404.8, 564.3)	1.26 (1.07, 1.50)	0.0068

Table 6
Key safety analysis of adverse events (ITT Set); n(%) (95% CI).[1]

	Pooled BBio bOPV (N = 809)	Control (N = 271)	p-value[2]
AE within 4 Days of Each Vaccination	196 (24.2%)	54 (19.9%)	0.158
	(21.3%, 27.3%)	(15.3%, 25.2%)	
AE throughout Participation	301 (37.2%)	86 (31.7%)	0.108
	(33.9%, 40.6%)	(26.2%, 37.6%)	
SAE throughout Participation	11 (1.4%)	7 (2.6%)	0.177
	(0.7%, 2.4%)	(1.0%, 5.2%)	

[1] CI is obtained using Clopper and Pearson method.
[2] P-value is obtained using two-sided Fishers exact test.

4. Discussion

This Phase III clinical study was conducted in two parts. In the Part 1, 40 healthy children of 5–6 years of age received a single dose of either BBio bOPV or SII bOPV. No safety issues were seen in the one month follow-up. In the Part 2, 1080 infants of 6 to 8 weeks of age received either one of three lots of BBio bOPV or SII bOPV. The seroconversion and seroprotection rates were more than 96% for both the polio antibodies in both the study groups. Non-inferiority of BBio bOPV against SII bOPV was proven. The GMTs were also similar among the three consecutive cGMP lots of BBio bOPV. No safety concerns were reported in both the parts of the study.

We found seven published studies which had bOPV only arms. Of these, two studies assessed two dose schedule, three studies assessed three dose schedules while two studies assessed four dose schedules (including birth dose). A study in India in 900 infants found that cumulative two-dose seroconversion with bOPV was 86% to poliovirus type 1 and 74% to poliovirus type 3 [12]. In Pakistan, a study found seroconversion to type-1 poliovirus of 79% with two doses of bOPV given 4 weeks apart [13]. Response to type 3 was not assessed in this study.

A study in Bangladesh assessed three dose schedules of OPVs in 1000 infants. Seroconversion with bOPV was seen in >97% infants (type 1) and in >94% infants (type 3) [14]. In a multi-country study in Latin America, 940 infants were randomly assigned to the five treatment groups. Three doses of bOPV elicited type 1 and 3 seroconversion rates of at least 97.7% [15]. A study in Bangladesh investigated different polio vaccination schedules in 975 infants. The arm which received three doses of bOPV showed seroconversion of 98.5% against type 1 and 94% against type 3 [16].

One study in India assessed four dose (birth, 6, 10, 14 weeks) bOPV schedules with/out IPV in 900 infants. Seroconversion against type 1 was 98.7% and against type 3 was in 97.4% in the bOPV only group [17]. A four dose schedule of bOPV study in Pakistan showed 97% and 94% seroconversion against type 1 and 3, respectively [18].

In our study, the seroconversion rates were more than 96% for both type 1 and type 3 viruses in both the groups. Thus our results are in line with other studies which used only bOPV in three dose or four dose schedules. The results are higher than two dose bOPV schedules reported in India and Pakistan.

Few adverse events were reported in the study participants including 19 serious adverse events. None of these were causally related to the study vaccines. There were no deaths reported in the study. Our safety results are also in line with the other bOPV studies [12–18].

Though OPV has been in use for several decades, there is no published study which has assessed its lot-to-lot consistency. These studies are required by WHO for any new vaccine [19]. Thus ours is the first study which investigated this aspect for bOPV and demonstrated the manufacturing consistency of BBio bOPV immunologically.

To conclude the new bOPV manufactured by Bilthoven Biologicals has been found non-inferior to the licensed and WHO prequalified SII bOPV vaccine in terms of seroconversion. The seroprotection rates and the GMTs were also similar. Between the two vaccines, there were no safety issues identified in this study. Thus the BBio bOPV has been proven safe and immunogenic in the target infant population in Bangladesh. As the use of bOPV is expected to be continued until at least 2022, availability of new bOPV bulk manufacturer will be helpful in securing adequate supplies of bOPV for global demand in the polio endgame strategy.

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Declaration of Competing Interest

RK, IVS, DM, XB are employed by BBio which is the manufacturer of the study vaccine. BG and PSK are employed by SIIPL which supplied the control vaccine for the study free of cost, filled the study vaccine for part 2 study in vials and which collaborated with BBio in the conduct of the study.

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