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The effect of diarrheal disease on bivalent oral polio vaccine (bOPV) immune response in infants in Nepal

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Abstract

Background: A globally-coordinated phase out of all type 2 containing oral polio vaccine (OPV) is planned for April 2016 during which bivalent 1 + 3 OPV (bOPV) will replace trivalent OPV (tOPV) in routine immunization schedules and campaigns. Diarrhea impairs the immune response to tOPV, but the effect of diarrhea on bOPV is unknown.

Methods: Infants aged 6 weeks to 11 months, who had received <3 doses of OPV and had mild-moderate diarrhea or no diarrhea, were recruited at five health facilities in Nepal. Neutralizing antibody titers to poliovirus types 1 and 3 were measured before and 28 days after bOPV administration. The effect of diarrhea and other factors on seroconversion or boosting in antibody titers to poliovirus was assessed by multivariable analysis.

Results: Infants with diarrhea, versus those without diarrhea, had reduced response for poliovirus types 1 (56% [87/156] vs 66% [109/164]) and 3 (34% [70/209] vs 52% [122/236]). After adjusting for other factors, infants with diarrhea had significantly reduced response for type 3 (odds ratio [OR] = 0.44, 95% CI 0.29–0.68), as did infants with >5 loose stools per day (OR = 0.36, 95% CI 0.21–0.62).

Conclusions: Diarrhea reduced the immune response to bOPV. Provision of additional doses of polio vaccine is necessary to maintain high population immunity in areas with high prevalence of diarrheal disease.

Clinical trial registry: This study is registered at clinicaltrials.gov as NCT01559636.

Keywords

Bivalent oral polio vaccine; Seroconversion; Poliomyelitis; Diarrhea; Nepal

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1. Introduction

Since the Global Polio Eradication Initiative (GPEI) was launched in 1988, global polio cases have been reduced by 99% [1]. Despite these gains, polio remains endemic in two countries—Pakistan and Afghanistan—with a number of countries reporting outbreaks following importations [2].

Trivalent oral polio vaccine (tOPV) has been used for routine immunization and supplementary immunization activities (SIAs) in developing countries, but several studies have shown lower immunogenicity of tOPV in these settings [3–6]. Reasons include higher levels of maternal antibodies, undernutrition, and high force of infection because of crowding, poor sanitation, and hygiene [3,7–9]. Some studies also found that diarrheal illness impaired seroconversion to tOPV, particularly to poliovirus types 2 and 3 [10–13] and certain enteric pathogens may also play a role in reducing the immune response to tOPV [10,14]. To ensure children with diarrhea at the time of vaccination are fully protected, WHO recommends provision of an additional dose of OPV after the diarrhea resolves [15], but in resource-poor settings, this is not always feasible.

To accelerate interruption of polio transmission, in 2009, the Strategic Advisory Committee of Experts on Immunization (SAGE) recommended using bivalent oral poliovirus vaccine (bOPV) in supplementary immunization activities because of higher immunogenicity for poliovirus types 1 and 3 as compared to tOPV [16,17]. Additionally, to reduce the burden of type 2 vaccine-derived polioviruses, a globally-coordinated phase out of all type 2 containing OPV is planned for April 2016 during which bOPV will replace tOPV in routine and supplementary immunization [18]. However, the impact of diarrheal illness and enteric pathogens on bOPV immunogenicity is unknown, and it is uncertain if provision of an additional dose of bOPV is necessary for children with diarrhea at the time of vaccination.

Diarrhea remains a leading cause of death in children globally [19], and a major cause of morbidity and mortality in children <5 years old in Nepal, with up to 24% of infants under 12 months of age reporting diarrhea [20]. At the time of the study, the recommended immunization schedule in Nepal included tOPV at 6, 10 and 14 weeks of age and additional bOPV doses were provided up to 5 years of age through campaigns conducted annually. Coverage with 3 OPV doses in 12–23 month olds was 92% in 2013 [21]. In November 2014, Nepal introduced inactivated polio vaccine (IPV) routinely at 14 weeks of age as per SAGE's recommendation for all countries using only OPV [22].

Our primary objective was to determine if infants with diarrhea were less likely to demonstrate an immunological response to a bOPV dose compared with infants without diarrhea. Secondary objectives included examining risk factors for poor seroconversion, such as severity of illness and concurrent enteropathogens, as well as determining polio seroprevalence after completion of the OPV primary series. Results from this study will provide critical information for GPEI strategic plans.

2. Methods

2.1. Study design and procedures

We conducted a prospective interventional cohort study at five participating study sites throughout Nepal (eastern Nepal: Kosi Zonal Hospital in Biratnagar, and B.P. Koirala Institute of Health Sciences [BPKIHS] in Dharan; central: Kanti Children's Hospital in Kathmandu; western: Western Regional Hospital in Pokhara, and Nepalgung Medical College in Nepalgunj). Infants were recruited until target enrollment numbers were met.

We recruited study participants among infants aged 6 weeks to 11 months who presented to outpatient clinics and emergency rooms between August 2012 and July 2013, and had prior receipt of <3 OPV doses (any polio vaccine type from routine immunization or supplemental immunization activities); infants requiring hospital admission were excluded from participation. Diarrhea was defined as ≥3 loose stools in the 24 h prior to study entry. Infants without diarrhea included those who were healthy, or presenting with mild non-diarrheal illness. After obtaining written informed consent, a study physician conducted an interview with the infant's caregiver. The infant's immunization status was cross-checked with immunization cards when available. Then, the infant was weighed, measured, had a blood and stool sample taken, and was administered one dose of bOPV (lot number: 2044711; manufacturer: Bio Farma Bandung, Indonesia). Participants returned 28 days after vaccination for a short interview and had a second blood sample drawn. An independent safety monitor reviewed all adverse events.

2.2. Laboratory testing

Blood specimens were allowed to clot and were centrifuged within 6 h of collection. Sera were separated and transported to Kathmandu, where they were stored at −20 °C until shipment to the Centers for Disease Control and Prevention (CDC) in Atlanta, USA. Neutralizing antibody titers to poliovirus were measured at the Polio Global Specialized Laboratory of CDC. Serum samples were tested in triplicate using a standard microneutralization assay for poliovirus antibodies according to established protocols [23,24]. A serum sample was considered positive if antibodies were present at ≥1:8 dilution. Samples with all three replicates negative at the lowest dilution were assigned a titer of 1:5.7; those with all three replicates positive at the highest dilution were assigned titers of 1:1448. Seroconversion was defined as a change from seronegative (neutralizing antibody titer <1:8) to seropositive (neutralizing antibody titer ≥1:8) 28 days after receipt of bOPV [25]. Boosting was defined as ≥4-fold increase in antibody titers 28 days after receipt of bOPV [25]. Seroconversion or boosting of titer is referred to as "response" in this paper.

Stool samples were stored at −20 °C and shipped to the CDC lab for testing for norovirus genogroup I and II and rotavirus using realtime RT-PCR [26,27]. Detailed stool testing methods and results will be reported elsewhere.

2.3. Statistical analyses

Sample sizes were calculated based on the primary outcome of interest, i.e., the difference in the percentage of diarrhea-positive and diarrhea-negative infants who responded after

bOPV. We set a significance level of 0.05 (two-tailed) and power of 0.80 and estimated that presence of diarrhea would result in a difference of 20% in the percentage of infants responding. If the percent responding to bOPV in the non-diarrhea group is 60%, we estimated we needed approximately 90 children per arm. Assuming that only 35% of the children were seronegative or had sufficiently low titers at baseline, based on the binomial distribution we needed to enroll approximately 320 children per arm to achieve a 90% probability of obtaining 90 seronegative or low titer infants.

Participating infants who reported receipt of additional doses of OPV during the study period, such as during campaigns (four bOPV campaigns were conducted during the study enrollment period at four of the participating sites) were excluded from analysis (Fig. 1). Additionally, as 1:1448 is the maximum dilution that can be detected, infants with baseline polio titers too high to observe a 4-fold boost (i.e., titers >1:362) were excluded from analysis. Seroprevalence of infants 6 weeks up to 6 months of age with zero prior doses of OPV was adjusted for maternal antibodies assuming exponential decay with a half-life of 28 days [28–30].

We determined participants seronegative or with boostable titers for either type 1 or 3 separately (Figure 1), and present immune response by type 1 and 3 analysis groups. Immune response was analyzed by variables determined a priori to have possible impact, including presence of diarrhea, maximum number of stools per day, nutritional status, breastfeeding, age, prior OPV doses, and facility. The percentage of infants responding to bOPV by these key factors was determined using standard binomial proportions with 95% Wilson score confidence intervals, and characteristics of diarrhea versus non-diarrhea participants compared using two-tailed Fisher's exact test. Variables significant at $p \leq 0.05$ or with high epidemiologic plausibility were included in the multivariable logistic regression models. The first logistic regression models (one each for type 1 and 3 response) examined our primary objective, the effect of diarrhea and other factors on immune response to bOPV.

After a relationship between maximum number of stools per day and bOPV response was observed, we created a second set of models in which the maximum number of stools per day replaced diarrhea status as the primary variable of interest. We also examined the effect of rotavirus and norovirus infection on immune response, in infants who had a stool sample available for laboratory testing. Finally, we calculated immune response for a subset of infants without diarrhea who had received three doses of OPV (i.e., two doses before enrollment plus the bOPV study dose), to estimate polio immunity in infants who have completed the OPV primary series according to the Nepalese schedule.

This study received ethical approval from CDC, the Tribhuvan University Institute of Medicine, and Nepal Health Research Council. Data were double-entered into a Microsoft Access database and analyzed using SAS v9.3 and R v3.1.2.

3. Results

We screened 6866 infants for inclusion in the study (Fig. 1); 5266 (77%) were ineligible because they had received >2 OPV doses, 1276 (19%) did not fulfill other study criteria and

324 (5%) did not consent to the study. Of the 682 participants who began the study, 95% (299/315) in the diarrhea arm and 91% (335/367) in the non-diarrhea arm completed the study. After excluding those with baseline titers that were too high to measure a four-fold titer increase, 156 and 164 infants remained in the diarrhea and non-diarrhea arms for the type 1 analyses, and 209 and 236 remained in the two arms for the type 3 analyses. For the effect of rotavirus and norovirus infection on immune response, infants without stool samples were excluded from testing, leaving 147 (94%) infants in the type 1 diarrhea group, 161 (98%) infants in the type 1 non-diarrhea group, 198 (95%) infants in the type 3 diarrhea group, and 227 (96%) infants in the type 3 non-diarrhea group.

Most infants were aged 6 weeks to 6 months (≥79% in each group), and were exclusively breastfed (≥79% in each group) (Table 1). Participants in diarrhea versus non-diarrhea arms differed slightly by age group, study facility, and lifetime prior episodes of diarrhea ($p < 0.05$ for these characteristics). For infants with diarrhea, the median duration of diarrhea was 6 days (IQR 4–10), and the median of the maximum number of stools per day was 6 (IQR 5–7) in both types 1 and 3 analysis groups.

In univariate analyses examining the effect of diarrhea on the immune response, for type 1, 56% (95% CI 48–63%) of infants in the diarrhea arm, and 66% (95% CI 59–73%) of infants in the non-diarrhea arm responded after receipt of bOPV ($p = 0.067$) (Table 2). For type 3, 34% (95% CI 27–40%) of infants in the diarrhea arm, and 52% (95% CI 46–59%) of infants in the non-diarrhea arm responded after receipt of bOPV ($p < 0.001$). When infants with diarrhea were divided into two groups (those with 3–5 and >5 maximum number of stools per day), an association was found between increasing number of stools per day and decreasing percentage of infants responding to bOPV, for both poliovirus types 1 and 3, although only the type 3 response was significant ($p < 0.001$) (Appendix A). Immune response by other participant characteristics differed by age group, facility, and number of prior OPV doses ($p < 0.05$ for these characteristics), for both type 1 and 3 analysis groups (Table 3). Finally, there was no response to type 2 after bOPV administration (Appendix B).

The first set of multivariable analysis models calculated the odds of responding to bOPV for poliovirus types 1 and 3 (Table 4). For type 1 poliovirus, diarrhea was not associated with the response (odds ratio [OR] 0.72, $p = 0.217$). For type 3 poliovirus, diarrhea was significantly associated with a decreased response (OR = 0.4, $p < 0.001$), and facility was also significantly associated with decreased odds of response ($p = 0.004$).

The second set of multivariable analysis models replaced diarrhea status with maximum number of stools per day, and adjusted for the remaining factors as in the model in Table 4. The inverse relationship between number of stools per day and immune response remained significant for type 3 ($p < 0.001$). Infants with 3–5 stools per day had lower odds of response for poliovirus type 3 compared with infants without diarrhea (OR = 0.53, 95% CI 0.31–0.92); infants who had >5 stools per day had lower odds of response for type 3 compared with infants without diarrhea (OR = 0.36, 95% CI 0.21–0.62).

Infants with norovirus infection, but not rotavirus infection, also had decreased immune response for type 1 and type 3 (Table 5). After adjusting for other factors, infants with

diarrhea and norovirus infection were significantly associated with a decreased type 1 response (OR 0.15 [95% CI 0.04–0.59], $p = 0.007$), compared with infants without diarrhea or norovirus infection.

In a subset of infants without diarrhea ($n = 137$), who received three doses of any OPV, the percent seropositive for poliovirus type 1 was 93% (95% CI: 88–96%), and for type 3 was 76% (95% CI: 68–82%).

4. Discussion

In Nepal, infants aged 6 weeks to 11 months with diarrhea showed decreased immune response to one dose of bOPV for both poliovirus types 1 and 3 as compared with infants without diarrhea, although the difference was statistically significant for only type 3. Infants with a higher number of loose stools per day had decreased response for type 3, and infants with norovirus infection had decreased response for type 1.

To our knowledge, this is the first study focusing on the impact of diarrheal disease on the immune response to bOPV. These results are consistent with previous studies that showed decreased seroconversion for poliovirus type 3 in children with diarrhea after receipt of trivalent OPV [10–12]. Diarrhea may affect OPV seroconversion in one or more ways, including direct interference from concurrent enteropathogens, nonspecific interference via induction of interferon or other immunomodulators, destruction of receptor sites by local inflammation, rapid gastrointestinal transit, or some combination of the above mechanisms that inhibit colonization and replication of the vaccine virus [3,10,14]. Our finding that a higher number of loose stools per day in children with diarrhea was associated with decreased response to bOPV, and the effect persisted for type 3 when controlling for other factors, is consistent with the mechanism of rapid gastrointestinal transit.

Our study findings also indicate that concurrent enteropathogens play a role in the immune response to bOPV. Infants with norovirus infection and diarrhea, but not rotavirus infection, had a significant decrease in type 1 response, indicating that norovirus might infect similar cells in the gastrointestinal tract as bOPV. While we are not aware of any prior studies that have specifically examined the effect of norovirus infection on OPV response, concurrent enteric pathogens (including viruses, bacteria, and parasites) have been associated with decreased response to OPV [10,31–34] and a recent meta-analysis concluded that concurrent non-polio enterovirus infection significantly reduced the odds of per-dose seroconversion for type 1 poliovirus, but not for type 2 or 3 [14]. As such, there might be an analogous effect of norovirus infection that could explain the diminished immune response for type 1 poliovirus, but this needs further investigation. Since clinical trials for a norovirus vaccine are in the pipeline, future studies should try to dissect whether immune responses to norovirus infection are affected by bOPV compared to cohorts that have received IPV, for example.

WHO advises provision of an additional OPV dose to children who have diarrhea at the time of vaccination [15]. Our study affirms this recommendation for bOPV. However, in practice this might not always be achieved, particularly in resource-poor settings and in regions where the diarrhea season is lengthy. Given that revaccination after the diarrhea

episode is not always feasible, and because diarrheal disease affects a large number of children globally, the importance of ensuring high population immunity for both types 1 and 3 in other ways becomes paramount. Additionally, the remaining immunity gap for type 3 after three doses of any OPV in infants without diarrhea was substantial in our study population, with close to one in four infants remaining susceptible to polio type 3 after three doses of OPV. In 2014, SAGE recommended the introduction of at least one dose of inactivated polio vaccine (IPV) in the routine immunization schedule for all countries using only OPV [22], and Nepal adopted this recommendation in September 2014. While the primary purpose of the recommendation is to maintain immunity against type 2 poliovirus during and after the global switch from tOPV to bOPV, provision of IPV will likely help to reduce immunity gaps to types 1 and 3 in areas with lower effectiveness of OPV, including Nepal, if immunization coverage rates for the 3rd OPV dose do not decrease with the introduction of IPV.

This study has limitations. First, although this study included infants from diverse backgrounds and living conditions and were recruited from five study sites in Nepal, results may not be generalizable to other settings. Second, although we excluded children who received an OPV dose between the baseline and post-vaccination blood collection, we could not control for community transmission of vaccine poliovirus received by other infants in routine immunization or in campaigns conducted during the study implementation. However, type 2 seroprevalence was similar between groups at baseline and did not change after bOPV administration, suggesting little to no impact from community transmission of tOPV. Furthermore, exposure to community vaccine polioviruses administered through routine immunization or campaigns would have occurred equally in study groups. Third, because of relatively small numbers of infants in specific sub-groups, we could not detect some associations that might be related to decreased immune response, such as severe stunting, severe wasting, no breastfeeding, and specific gastrointestinal infections. Fourth, we excluded infants with severe clinical illness, because it was not ethically acceptable to administer bOPV while they were hospitalized, so we could not determine whether these infants might have had different seroconversion responses. However, we did find that a greater number of loose stools, a clinical indicator of more severe diarrhea, was associated with decreased immune response.

In conclusion, diarrhea was associated with a lower type 1 and type 3 immune response among infants in Nepal following a dose of bOPV, although only the type 3 response was statistically significant. Immunization programs should continue to provide an additional dose of bOPV to children who present with diarrhea at the time of immunization. Additionally, provision of IPV with the third dose of OPV in routine immunization at high coverage and supplemental doses of OPV through routine immunization and campaigns are necessary to ensure high population immunity against poliovirus in areas with high diarrheal disease incidence, including Nepal.

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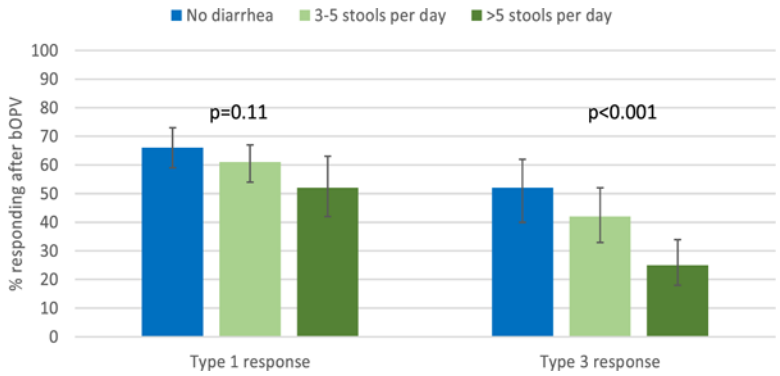
Appendix A.: Percent of infants responding to bOPV, by number of stools per day

Error bars show 95% Wilson score confidence intervals. *p* values are calculated from Fisher's exact test.



Appendix B.: Seroprevalence and median antibody titers for type 2 poliovirus at baseline and 28 days after bOPV vaccination, by diarrhea status

	Diarrhea (*N* = 294)		Non-diarrhea (*N* = 326)		*p*-Value
	n	**% (95% CI)[a]**	***n***	**% (95% CI)[a]**	
Baseline					
Seropositive for type 2, *n*, % (95% CI)	224	76 (71, 81)	249	76 (72, 81)	1.000[b]
Antibody titers, median (IQ range)		724 (11, 1448)		455 (9, 1448)	0.238[c]
28 days after bOPV vaccination					
Seropositive for type 2, *n*, % (95% CI)	218	74 (69, 79)	252	77 (72, 82)	0.398[b]
Antibody titers, median (IQ range)		724 (6, 1448)		576 (11, 1448)	0.781[c]

[a] Wilson score confidence interval.

[b] Two-tailed Fisher's exact test.

[c] Two-tailed Wilcoxon rank sum test.

References

[1]. Moturi EK, Porter KA, Wassilak SGF, Tangermann RH, Diop OM, Burns CC, et al. Progress Toward Polio Eradication — Worldwide, 2013–2014. MMWR Wkly 2014;63(21):468–72.

[2]. Global Polio Eradication Initiative Available at: http://www.polioeradication.org/Dataandmonitoring/Poliothisweek.aspx.

[3]. Patriarca PA, Wright PF, John TJ. Factors affecting the immunogenicity of oral poliovirus vaccine in developing countries: review. Rev Infect Dis 1991;13(September–October (5)):926–39. [PubMed: 1660184]

[4]. John TJ, Jayabal P. Oral polio vaccination of children in the tropics. I: The poor seroconversion rates and the absence of viral interference. Am J Epidemiol 1972;96(4).

[5]. Lee LH, Wenner HA, Rosen L. Prevention of poliomyelitis in Singapore by live vaccine. Br Med J 1964;1:1077–80. [PubMed: 14113821]

[6]. Commission Poliomyelitis, Western Region Ministry of Health, Nigeria. Poliomyelitis vaccination in Ibadon, Nigeria during 1964 with oral vaccine. Bull WHO 1966;34:865–76. [PubMed: 5296535]

[7]. Grassly NC, Fraser C, Wenger J, Deshpande JM, Sutter RW, Heymann DL, et al. New strategies for the elimination of polio from India. Science 2006; 314(5802):1150–3. [PubMed: 17110580]

[8]. Sutter RW, Kew OM, Cochi SL. Poliovirus vaccine – live. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines Philadelphia: Saunders; 2008. p. 631–85.

[9]. Saleem AF, Mach O, Quadri F, Khan A, Bhattia Z, Rehman N, et al. Immunogenicity of poliovirus vaccines in chronically malnourished infants: a randomized controlled trial in Pakistan. Vaccine 2015;33:2757–63. [PubMed: 25917673]

[10]. Myaux JA, Unicomb L, Besser RE, Modlin JF, Uzma A, Islam AM, et al. Effect of diarrhea on the humoral response to oral polio vaccination. Pediatr Infect Dis J 1996;15(3):204–9. [PubMed: 8852907]

[11]. Posey DL, Linkins RW, Oliveria MJ, Monteiro D, Patriarca PA. The effect of diarrhea on oral poliovirus vaccine failure in Brazil. J Infect Dis 1997;175(Suppl. 1):S258–63. [PubMed: 9203726]

[12]. WHO. Factors affecting the immunogenicity of oral poliovirus vaccine: a prospective evaluation in Brazil and the Gambia. World Health Organization Collaborative Study Group on Oral Poliovirus Vaccine. J Infect Dis 1995;171(May (5)):1097–106. [PubMed: 7751683]

[13]. Haque R, Snider C, Liu Y, Ma JZ, Liu L, Nayak U, et al. Oral polio vaccine response in breast fed infants with malnutrition and diarrhea. Vaccine 2014;32(January (4)):478–82. [PubMed: 24300591]

[14]. Parker EPK, Kampmann B, Kang G, Grassly NC. Influence of enteric infections on response to oral poliovirus vaccine: a systematic review and meta-analysis. J Infect Dis 2014 Sep 15;210(6):853–64. [PubMed: 24688069]

[15]. Expanded Programme on Immunization, World Health Organization. Immunization policy Geneva: WHO; 1986. WHO/EPI/GEN/86/7 REV 1. Available at: http://apps.who.int/iris/bitstream/10665/59368/1/WHO_EPI_GEN_86_7_REV_1.pdf?ua=1 [accessed 07.07.15].

[16]. Advisory Committee on Poliomyelitis Eradication: recommendations on the use of bivalent oral poliovirus vaccine types 1 and 3. Wkly Epidemiol Rec 2009;84(July (29)):289–300 http://www.who.int/wer. [PubMed: 19630188]

[17]. Sutter RW, John TJ, Jain H, Agarkhedkar S, Ramanan PV, Verma H, et al. Immunogenicity of bivalent types 1 and 3 oral poliovirus vaccine: a randomised, double-blind, controlled trial. Lancet 2010;376(November (9753)):1682–8, 10.1016/S0140-6736(10)61230-5 [Epub 2010 Oct 25]. [PubMed: 20980048]

[18]. Polio Eradication and Endgame Strategic Plan 2013–2018 Available at: http://www.polioeradication.org/Resourcelibrary/Strategyandwork.aspx#sthash.iuwbAO2t.dpuf.

[19]. GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2015;385(January (9963)):117–71, 10.1016/S0140-6736(14)61682-2 [Epub 2014 Dec 18]. [PubMed: 25530442]

[20]. Nepal Demographic and Health Survey 2011 Population Division, Ministry of Health and Population, Government of Nepal, Kathmandu, Nepal. Available at: http://dhsprogram.com/pubs/pdf/FR257/FR257%5B13April2012%5D.pdf.

[21]. WHO vaccine-preventable diseases: monitoring system 2013 global summary Nepal. Available at: http://apps.who.int/immunization_monitoring/globalsummary/estimates?c=NPL.

[22]. Polio vaccines: WHO position paper, January 2014. Wkly Epidemiol Rec 2014;89(February (9)):73–93. Available at: http://www.who.int/wer/2014/wer8909.pdf. [PubMed: 24707513]

[23]. World Health Organization. Manual for the virological investigation of polio. 1997 WHO EPI/GEN/97.01.EPV1, Expanded Program on Immunization

[24]. Report of a WHO informal consultation on polio neutralization antibody assays Geneva: World Health Organization; 1991 [WHO/EPI/RD/91.3 Rev 1].

[25]. Sutter RW, Brink EW, Cochi SL, Kew OM, Orenstein WA, Biellik RJ, et al. A new epidemiologic and laboratory classification system for paralytic poliomyelitis cases. Am J Public Health 1989;79:495–8. [PubMed: 2929811]

[26]. Vega E, Barclay L, Gregoricus N, Shirley SH, Lee D, Vinjé J. Genotypic and epidemiologic trends of norovirus outbreaks in the United States, 2009–2013. J Clin Microbiol 2014;52(January (1)):147–55. [PubMed: 24172151]

[27]. Mijatovic-Rustempasic S, Tam KI, Kerin TK, Lewis JM, Gautam R, Quaye O, et al. Sensitive and specific quantitative detection of rotavirus A by one-step real-time reverse transcription-PCR assay without antecedent double-stranded-RNA denaturation. J Clin Microbiol 2013;51(September (9)):3047–54. [PubMed: 23850952]

[28]. Gelfand HM, Fox JP, LeBlanc DR, Elveback L. Studies on the development of natural immunity to poliomyelitis in Louisiana V. Passive transfer of polioantibody from mother to fetus, and natural decline and disappearance of antibody in the infant. J Immunol 1960;85(1):46–55. [PubMed: 13827179]

[29]. Resik S, Tejeda A, Mas Lago P, et al. Randomized controlled clinical trial of fractional doses of inactivated poliovirus vaccine administered intradermally by needle-free device in Cuba. J Infect Dis 2010;201:1344–52. [PubMed: 20350164]

[30]. World Health Organization. Annex 3—Recommendations to assure the quality, safety and efficacy of poliomyelitis vaccines (inactivated). Technical Rep Ser 2015;993:89–174.

[31]. Maldonado YA, Pena-Cruz V, de la Luz Sanchez M, Logan L, Blandón S, Cantwell MF, et al. Host and viral factors affecting the decreased immunogenicity of Sabin type 3 vaccine after administration of trivalent oral polio vaccine to rural Mayan children. J Infect Dis 1997;175:545–53. [PubMed: 9041324]

[32]. Faden H, Duffy L. Effect of concurrent viral infection on systemic and local antibody responses to live attenuated and enhanced-potency inactivated poliovirus vaccines. Am J Dis Child 1992;146:1320–3. [PubMed: 1415071]

[33]. Triki H, Abdallah MV, Ben Aissa R, Bouratbine A, Ben Ali Kacem M, Bouraoui S, et al. Influence of host related factors on the antibody response to trivalent oral polio vaccine in Tunisian infants. Vaccine 1997;15:1123–9. [PubMed: 9269056]

[34]. Mahmoud AA, Imam IZ, Abozid SS, El Mished AM, Mitkis FA. The influence of bacillary dysentery on the efficiency of oral poliovaccine in Egypt. Gaz Egypt Paediatr Assoc 1976;24:82–91. [PubMed: 192625]

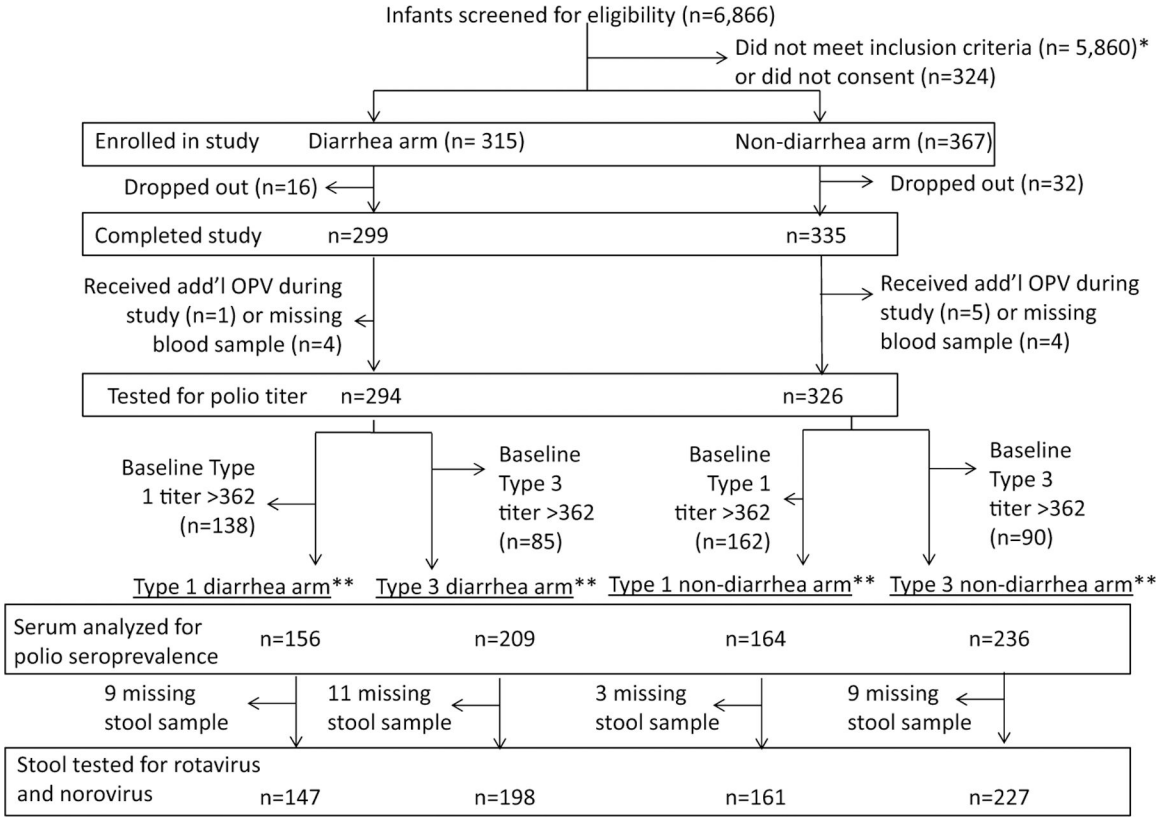


Fig. 1.

Participants screened, enrolled in diarrhea and non-diarrhea arms, completing study, tested for polio titer, serum analyzed for response to poliovirus types 1 and 3 after receipt of bOPV, and stool tested for rotavirus and norovirus. *Of the 5860 infants who did not meet inclusion criteria, reasons were as follows: 5266 had >2 doses OPV, 103 did not meet age criteria, 2324 had last OPV dose given <4 weeks, 788 residence was too far, 843 were not available during study period, 170 had <3 loose stools in 24 h, 18 had history of reaction to medication or OPV, 652 required hospitalization for illness. An infant may have been excluded for more than one reason. **Numbers are not mutually exclusive, as some infants' serum was analyzed for both types 1 and 3 in the diarrhea and non-diarrhea arms, or had stool samples tested for rotavirus and norovirus in both type 1 and type 3 diarrhea and non-diarrhea arms

Table 1

Characteristics of infants in type 1 and 3 analysis groups, with and without diarrhea.

	Poliovirus type 1 analysis group					Poliovirus type 3 analysis group				
	Diarrhea (*N* = 156)		Non-diarrhea (*N* = 164)		*p*-Value[b]	Diarrhea (*N* = 209)		Non-diarrhea (*N* = 236)		*p*-Value[b]
	n	% (95% CI)[a]	*n*	% (95% CI)		*n*	% (95% CI)	*n*	% (95% CI)	
Age					0.003					0.005
6 weeks to <3 months	62	40 (32, 48)	96	58 (51, 66)		71	34 (28, 41)	109	46 (40, 53)	
3 to <6 months	68	44 (36, 51)	47	29 (22, 36)		99	47 (41, 54)	77	33 (27, 39)	
6 to <12 months	26	17 (12, 23)	21	13 (8, 19)		39	19 (14, 24)	50	21 (16, 27)	
Female sex	69	44 (37, 52)	64	39 (32, 47)	0.365	93	44 (38, 51)	91	39 (33, 45)	0.211
Mother's education					1.000					0.902
Less than primary school	82	53 (45, 61)	86	52 (45, 60)		113	54 (47, 61)	123	52 (46, 58)	
Completed primary or some secondary	28	18 (13, 25)	30	18 (13, 25)		37	18 (13, 23)	43	18 (14, 24)	
Completed secondary or higher	45	29 (22, 37)	48	29 (23, 37)		58	28 (22, 34)	70	30 (24, 36)	
Study facility					<0.001					<0.001
Kanti	20	13 (8, 19)	36	22 (16, 29)		25	12 (8, 17)	55	23 (18, 29)	
Kosi Zonal	33	21 (15, 28)	30	18 (13, 25)		47	22 (17, 29)	43	18 (13, 24)	
Western Regional	29	19 (13, 25)	14	8 (5, 14)		34	16 (12, 22)	19	8 (5, 12)	
Nepalgunj Medical College	27	17 (12, 24)	48	29 (23, 37)		42	20 (15, 26)	64	27 (22, 33)	
BPKIHS	47	30 (24, 38)	36	22 (16, 29)		61	29 (23, 36)	55	23 (18, 29)	
Prior doses of OPV					0.055					0.192
0	49	31 (25, 39)	73	44 (37, 52)		56	27 (21, 33)	81	34 (29, 41)	
1	60	38 (31, 46)	52	32 (25, 39)		80	38 (32, 45)	76	32 (27, 38)	
2	47	30 (24, 38)	39	24 (18, 31)		73	35 (29, 42)	79	34 (29, 40)	
Breastfeeding					0.728					0.132
Exclusive	129	83 (76, 88)	136	83 (76, 88)		175	84 (78, 88)	186	79 (73, 84)	
Some	26	17 (12, 23)	25	15 (10, 22)		34	16 (12, 22)	46	20 (15, 25)	
None/don't know	1	1 (0, 4)	3	2 (1, 5)		0	0 (0, 2)	4	2 (1, 4)	
Stunting [c]					0.337					0.104
Severe	18	12 (7, 18)	14			24	12 (8, 16)	23	10 (7, 14)	
Moderate	19	12 (8, 18)	14			29	14 (10, 19)	19	8 (5, 12)	

	Poliovirus type 1 analysis group					Poliovirus type 3 analysis group				
	Diarrhea (*N* = 156)		Non-diarrhea (*N* = 164)		*p*-Value[b]	Diarrhea (*N* = 209)		Non-diarrhea (*N* = 236)		*p*-Value[b]
	n	% (95% CI)[a]	*n*	% (95% CI)		*n*	% (95% CI)	*n*	% (95% CI)	
Mild or none	119	76 (69, 82)	136			156	75 (68, 80)	194	82 (77, 87)	
Wasting [d]					0.066					0.107
Severe	12	8 (4, 13)	26	16 (11, 22)		20	10 (6, 14)	35	15 (11, 20)	
Moderate	22	14 (10, 20)	18	11 (7, 17)		28	13 (9, 19)	21	9 (6, 13)	
Mild or none	122	78 (71, 84)	120	73 (66, 79)		161	77 (71, 82)	180	76 (70, 81)	
Lifetime prior episodes of diarrhea					0.004					0.001
0–2	133	85 (79, 90)	156	95 (91, 98)		177	85 (79, 89)	223	94 (91, 97)	
3+	23	15 (10, 21)	8	5 (2, 9)		32	15 (11, 21)	13	6 (3, 9)	

[a] Wilson score confidence interval.

[b] Two-tailed Fisher's exact test, testing the null hypothesis that there is no difference between diarrhea and non-diarrhea participants.

[c] Severe = 3 or more standard deviations (SDs) below mean length for age; moderate = 2–3 SDs below mean length for age; mild or none = 2 SDs below to greater than mean length for age.

[d] Severe = 3 or more standard deviations (SDs) below mean weight for length; moderate = 2–3 SDs below mean weight for length; mild or none = 2 SDs below to greater than mean weight for length.

Table 2

Seroprevalence and median antibody titers for type 1 and 3 poliovirus at baseline and 28 days after bOPV vaccination, and proportion of children who had an immune response, by study arm.

	Poliovirus type 1 analysis group					Poliovirus type 3 analysis group				
	Diarrhea (*N* = 156)		Non-diarrhea (*N* = 164)		*p*-Value	Diarrhea (*N* = 209)		Non-diarrhea (*N* = 236)		*p*-Value
	n	% (95% CI)[a]	*n*	% (95% CI)[a]		*n*	% (95% CI)[a]	*n*	% (95% CI)[a]	
Baseline										
Seropositive, *n*, % (95% CI)	80	51 (44, 59)	71	43 (36, 51)	0.179[b]	81	39 (32, 46)	67	29 (23, 35)	0.026[b]
Antibody titers, median (IQ range)		8 (6, 32)		6 (6, 25)	0.156[c]		6 (6, 45)		6 (6, 10)	0.017[c]
28 days after bOPV vaccination										
Seropositive, *n*, % (95% CI)	123	79 (72, 84)	136	83 (76, 88)	0.394[b]	122	58 (52, 65)	155	66 (60, 72)	0.118[b]
Antibody titers, median (IQ range)		323 (14, 1448)		576 (28, 1448)	0.414[c]		36 (6, 455)		161 (6, 910)	0.008[c]
Immune response, *n*, % (95% CI)	87	56 (48, 63)	109	66 (59, 73)	0.067[b]	70	34 (27, 40)	122	52 (46, 59)	<0.001[b]

[a] Wilson score confidence interval.

[b] Two-tailed Fisher's exact test.

[c] Two-tailed Wilcoxon rank sum test.

Table 3

Immune response after bOPV vaccination, by participant characteristics.

	Type 1 Poliovirus (*N* = 320)			Type 3 Poliovirus (*N* = 445)		
	Total *n*	**% Responding (95% CI)[a]**	***p*-Value[b]**	**Total *n***	**% Responding (95% CI)**	***p*-Value[b]**
Age			<0.001			<0.001
6 weeks to 3 months	158	73 (66, 80)		180	53 (46, 60)	
3–6 months	115	56 (46, 64)		176	41 (34, 48)	
6–12 months	47	36 (24, 50)		89	27 (19, 37)	
Sex			0.816			0.771
Male	187	61 (54, 68)		261	42 (37, 49)	
Female	133	62 (54, 70)		184	44 (37, 51)	
Mother's education			0.568			0.847
Less than primary school	168	59 (51, 67)		236	42 (36, 48)	
Completed primary or some secondary	58	66 (53, 76)		80	45 (35, 56)	
Completed secondary or higher	93	64 (54, 73)		128	44 (36, 53)	
Facility			0.010			<0.001
BPKIHS	83	64 (53, 73)		116	50 (41, 59)	
Kanti	56	79 (66, 87)		80	62 (52, 72)	
Kosi Zonal	63	56 (43, 67)		90	34 (25, 45)	
Nepalganj Medical College	75	49 (38, 60)		106	28 (21, 38)	
Western Regional	43	65 (50, 78)		53	43 (31, 57)	
Prior OPV doses			<0.001			0.007
0	122	75 (66, 81)		137	49 (41, 57)	
1	112	59 (50, 69)		156	48 (40, 56)	
2	86	46 (36, 57)		152	33 (26, 41)	
Breastfeeding			0.672			0.536
Exclusive	265	62 (56, 68)		361	44 (39, 50)	
Some	51	57 (43, 70)		80	38 (28, 48)	
None or don't know	4	75 (30, 99)		4	50 (15, 85)	
Stunting			0.567			0.757
Severe	32	56 (39, 72)		47	40 (28, 55)	

	Type 1 Poliovirus (*N* = 320)			Type 3 Poliovirus (*N* = 445)		
	Total *n*	**% Responding (95% CI)[a]**	***p*-Value[b]**	**Total *n***	**% Responding (95% CI)**	***p*-Value[b]**
Moderate, mild or normal	288	62 (56, 68)		398	44 (39, 48)	
Wasting			0.381			0.885
Severe	38	68 (52, 81)		55	42 (30, 55)	
Moderate, mild or normal	282	61 (55, 66)		390	43 (38, 48)	
Lifetime number prior episodes of diarrhea			0.700			1.000
0–2	289	62 (56, 67)		400	43 (38, 48)	
3+	31	58 (41, 74)		45	42 (29, 57)	

[a]Wilson score confidence interval.

[b]Two-tailed Fisher's exact test.

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Table 4

Logistic regression analysis of factors associated with an immune response following a bOPV dose.

Factor	Poliovirus type 1			Poliovirus type 3		
	Odds ratio	95% confidence interval	*p*-Value	Odds ratio	95% confidence interval	*p*-Value
Diarrhea status			0.217			<0.001
Diarrhea	0.72	0.42, 1.20		0.44	0.29, 0.68	
Non-diarrhea	Ref.			Ref.		
Age in weeks			0.082			0.238
6–12	2.97	1.12, 7.87		1.73	0.81, 3.72	
13–25	2.21	0.99, 4.91		1.69	0.91, 3.14	
26–51	Ref.			Ref.		
Facility			0.065			0.004
BPKIHS	1.02	0.44, 2.37		1.23	0.61, 2.46	
Kanti	1.72	0.61, 4.85		1.46	0.67, 3.16	
Kosi Zonal	0.87	0.36, 2.08		0.70	0.33, 1.46	
Nepalganj Medical College	0.45	0.19, 1.06		0.44	0.21, 0.91	
Western Regional	Ref.			Ref.		
Prior OPV doses			0.110			0.297
0	1.98	0.90, 4.36		1.40	0.73, 2.70	
1	1.07	0.54, 2.12		1.55	0.89, 2.70	
2	Ref.			Ref.		
Breastfeeding			0.093			0.700
Some	1.96	0.89, 4.17		1.13	0.61, 2.07	
Exclusive	Ref.			Ref.		
Stunting			0.702			0.969
None/mild/moderate	1.17	0.52, 2.64		1.01	0.52, 1.99	
Severe	Ref.			Ref.		
Wasting			0.597			0.792
None/mild/moderate	0.80	0.36, 1.80		0.92	0.48, 1.75	
Severe	Ref.			Ref.		
Lifetime prior episodes of diarrhea			0.238			0.789

Factor	Poliovirus type 1			Poliovirus type 3		
	Odds ratio	95% confidence interval	*p*-Value	Odds ratio	95% confidence interval	*p*-Value
0–2	1.71	0.70, 4.18		1.10	0.54, 2.23	
3+	Ref.					

Table 5

Immune response after bOPV vaccination, by rotavirus and norovirus infection.

	Type 1			Type 3		
	Total *N*	**% Responding (95% CI[a])**	***p*-Value[b]**	**Total *N***	**% Responding (95% CI[a])**	***p*-Value[b]**
Rotavirus						
Negative	261	63 (57, 68)	0.516	362	44 (39, 49)	0.582
Positive	47	58 (43, 70)		63	40 (28, 52)	
Norovirus						
Negative	287	64 (59, 70)	0.002	393	46 (41, 50)	0.003
Positive	21	29 (14, 50)		32	19 (9, 35)	

[a]Wilson score.

[b]Two-tailed Fisher's exact test.