**Interference of Oral Rotavirus Vaccine on Oral Poliovirus Vaccine with or without an Inactive Poliovirus Vaccine Replacement Dose Among Bangladeshi Infants: a Secondary Analysis of a Randomized Controlled Trial**

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# Abstract

*Background:* Bivalent oral rotavirus vaccine (Rotarix) and oral poliovirus vaccines (OPV) are concurrently administered in low-income countries, and recent polio endgame strategies aim to replace all OPV and introduce inactivated poliovirus vaccine (IPV) doses. This combination of Rotarix, OPV, and IPV has yet to be studied in low-income countries.

*Objectives:* (1) To investigate possible interference from concurrent administration of Rotarix with one IPV replacement dose in the trivalent OPV schedule (IPV-OPV) or without this replacement dose (OPV only) on OPV effectiveness among infants in Bangladesh at 52 weeks of life. (2) To descriptively compare mean treatment effect estimates from different statistical models and identify any potential differences in the model choices.

*Methods:* Between May 2011 and November 2014, 700 Bangladeshi infant-mother pairs from Dhaka, Bangladesh were enrolled into an open-label, randomized controlled trial with a 2x2 factorial design to compare Rotarix interference in infants who received an IPV replacement dose at 39 weeks (IPV-OPV) to infants who only received the trivalent OPV series (OPV only). One-hundred seventy-five infants were randomized to each of the four study arms: Rotarix with IPV-OPV, no Rotarix with IPV-OPV, Rotarix with OPV only, and no Rotarix with OPV only. The main comparison groups were no Rotarix with IPV-OPV and Rotarix with OPV only. The primary outcome was poliovirus immunity as measured by fecal excretion of any and all three shed poliovirus types up to 25 days post-52 week trivalent OPV dose. Adjusted generalized linear models (GLM) with gaussian and Poisson log link functions (linear probability model and modified Poisson regression, respectively) as well as targeted maximum-likelihood estimation (TMLE) models were built to perform intention-to-treat (ITT) analysis and estimate risk differences and risk ratios.

*Results:* There were no meaningful differences in any shed poliovirus from the adjusted GLM and TMLE models among infants who received no Rotarix with IPV-OPV compared to infants who received Rotarix with OPV (RD: 0.0497; 95% CI: -0.0645−0.1638; *P*=0.3938). Relative risks were similarly null and nonsignificant between these two comparison groups (RR: 1.0683; 95% CI: 0.8403−1.3583; *P*=0.5896).Results for shedding analysis by each poliovirus type as well as comparisons across the other factorial groups who received different combinations of Rotarix, IPV-OPV, or OPV were similar.

*Conclusion:* This study’s analysis indicates that incorporation of IPV dose into OPV vaccination schedules is possible while maintaining OPV’s existing intestinal immunity, without any interference from concurrent Rotarix administration.

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# Background

Rotavirus is a pathogen that causes diarrhea-associated mortality in infants and young children globally, with a higher death burden in low-income and middle-income countries (LMICs), particularly in Africa, Oceania, and South Asia.1 Poliovirus similarly affects children under age five and spreads mainly through the fecal-oral route and multiplies in the intestine, from where it can invade the nervous system and cause paralysis.2 Since 1988, global incidence of wild poliovirus cases reduced by 99.9%, and of the three strains of wild poliovirus types, poliovirus type 2 and 3 are declared to be eradicated; however, LMICs remain at risk for polio outbreaks, especially from vaccine-derived poliovirus types, due to weak public health and immunization services.3

Currently, oral rotavirus vaccine is the only prevention for rotavirus disease.4 To protect against poliovirus types 1, 2, and 3, there are two poliovirus vaccine options, inactivated poliovirus vaccine (IPV) or oral poliovirus vaccine (OPV).5 Since 2009, the World Health Organization (WHO) recommended the rotavirus vaccine to be administered in infancy concurrently with other vaccines, including the poliovirus vaccine, for prevention of multiple diseases at once in LMIC settings.6 Oral vaccines, including both the oral rotavirus vaccine and OPV, have historically been preferred in LMICs because of their capacity to induce immune responses at both systemic and mucosal sites, relatively low cost of manufacturing, and ease of administration.7 However, there has been a recent movement since 2016 to introduce at least one IPV dose because studies have showed it decreases risk of vaccine-associated paralytic polio and better prevents disease.5,8,9 This sets the stage for eventual withdrawal of all OPV, but studying the immune response from concurrent Rotarix administration with IPV dose in the OPV series during this transition period may be important so that potential consequences can be anticipated and mitigated.

Concurrent administration of Rotarix and OPV as well as immune responses from IPV versus OPV have been studied separately, but the combination of all three vaccines has not been extensively studied. The Performance of Rotavirus and Oral Polio Vaccines in Developing Countries (PROVIDE) was a randomized controlled trial (RCT) with a 2x2 factorial design to evaluate oral vaccine efficacy in low-income communities of Dhaka, Bangladesh.10 As a secondary data analysis of the PROVIDE study’s RCT data, this study aimed to focus on OPV vaccine performance providing poliovirus immunity, specifically in the prevention of poliovirus shedding in fecal cultures. The primary objective was to investigate possible interference from concurrent administration of Rotarix with one IPV replacement dose in the OPV schedule (IPV-OPV) or without (OPV only) on OPV effectiveness among infants in Bangladesh at 52 weeks. We hypothesized that the combination of no Rotarix and IPV-OPV will have an effect on shed poliovirus, compared to other combinations of Rotarix and IPV replacement dose receival. The secondary objective was to qualitatively compare the mean treatment effect estimates from statistical models and identify any potential differences in the model choices to gain perspective on analytical methods for RCT data.

# Methods

## Study Design

The PROVIDE study was conducted in the Mirpur area of Dhaka, Bangladesh from May 2011 to November 2014.10 Detailed description of the study design and recruitment has been previously described and available in reference.10 In brief, a birth cohort of 700 infants were recruited and followed for 104 weeks from birth. All enrolled children received OPV at weeks 6, 10, and 14. Children were randomly assigned to receive Rotarix scheduled at 10 and 17 weeks. At 39 weeks, children were again randomly assigned to receive OPV or IPV dose. Lastly, at 52 weeks, all children received an additional OPV booster dose. Infants were equally distributed across all four factorial groups and intervention arms, defined by the receival of Rotarix or none at 10 and 17 with receival of IPV or OPV at 39 weeks. A diagram highlighting randomization of vaccine interventions to create the four factorial group study arms is presented in Figure 1. Children also received all other vaccines according to the Bangladesh Expanded Program on Immunizations (EPI) during the conduct of the trial. The data collected on laboratory specimens at 52 weeks, and baseline household and individual characteristics of all 700 participants were used for analysis in this study.

## Fecal Poliovirus Shedding

The primary binary outcome variable was the presence of poliovirus shedding in stool specimens. This was an appropriate measure to approximate vaccine response for OPV because poliovirus isolation comes most likely from stool and is the most sensitive method to diagnose a poliovirus infection.11 Fecal cell cultures underwent qPCR at week 14 and week 52 for poliovirus to measure the presence and absence of viral shedding. In order to quantify the combined effects of both Rotarix versus none (at weeks 10 and 17) and IPV-OPV versus OPV (at week 39), only the week 52 specimens collected and measured for fecal shedding of any poliovirus type were analyzed. Each of the three Sabin poliovirus types at week 52 were also analyzed independently. While stool was collected at five discrete time points at week 52 (on day 0 before vaccination, and days 4, 11, 18, and 25 after the last OPV challenge dose), only the first positive cell culture was run for PCR.

## Statistical Analysis

The primary outcome variable, presence of poliovirus shedding in stool specimens for any and all three poliovirus types at 52 weeks, was first analyzed with descriptive statistics across the four intervention arms.

We then evaluated risk difference (RD) and relative risk (RR) measures of association between the interventions received and poliovirus shedding to assess treatment effects with generalized linear models (GLM) and targeted maximum likelihood estimators (TMLE) for ITT analyses. All models made contrasts across the intervention arms for all possible factorial group combinations, though the two main comparison groups of interest were no Rotarix with IPV-OPV and Rotarix with OPV only. Models were evaluated with and without adjustment for baseline characteristics, as there have been evidence showing that adjustment for baseline characteristics could potentially increase power for RCTs with dichotomous outcomes.12,13 Linear probability models apply ordinary least squares to binary outcomes and are appropriate for binary outcomes in RCTs because treatment status is categorical and not subject to misspecification of the functional form.14 Thus, we used GLMs with a noncanonical gaussian link function to obtain unadjusted and adjusted RDs that estimated the mean marginal effect of treatments. A GLM with a log link function (log-binomial regression model) estimated the unadjusted RR, whereas a modified Poisson regression model with sandwich estimation produced valid, adjusted RR with robust standard errors to overcome nonconvergence.15 TMLE models with the binary outcome returned ITT estimates on the absolute (unadjusted and adjusted average treatment effect), relative (unadjusted and adjusted RR), and log-odds ratio scale. The default super-learner algorithm library for the TMLE models included the simple mean, main terms GLM, main terms Bayes GLM with non-informative priors, generalized additive models (degree 2), and lasso and elastic-net regularized GLMs.

A likelihood ratio test between a GLM fit to all potential covariates (baseline characteristics) and a null model was used to identify covariates to include in the adjusted GLM and TMLE models; these variables were ones with associated p-value less than the threshold chosen for inclusion (*P<*0.2*).* A list of prescreened covariates selected for inclusion in the adjusted analyses for any and all poliovirus types can be found in Supplemental Materials 3.

Lastly, by default, the TMLE model restricted the data to complete observations in intervention arms, so we evaluated the same TMLE models with inverse probability of censoring weighting (IPCW) to adjust for individuals missing outcome values and to address potential selection bias.

These models were created using the “washb” R package, and details regarding functions within the package can be found in reference.16 All p-values were considered statistically significant at a level of α=0.05 using 2-sided tests. All analyses were performed in R 4.1.2.

# Results

## Study Population

Initially, 700 infants were enrolled and randomly assigned equally across the four intervention arms (n=175). Of the 595 (85%) infants who completed follow-up, 150 (25.2%) infants received Rotarix with complete OPV, 153 (25.7%) infants received Rotarix with IPV-OPV, 151 (25.4%) infants received no Rotarix with complete OPV, and 141 (23.7%) received no Rotarix with IPV-OPV. The remaining 105 (15%) participants who were enrolled at the beginning of the study withdrew, and 94 (13%) of these withdrawn participants were missing data on stool specimens to measure poliovirus shedding, the primary outcome variable. Baseline characteristics between those who withdrew and remained in the study were similar, and summary statistics of these study participants are presented in Supplemental Material 1. Baseline characteristics across the four intervention arms were also similar; a summary of these characteristics across each arm is presented in Table 1. In addition, the distribution of the outcome variable were similar across intervention arms for any shed poliovirus and for each shed poliovirus type. The distributions for any shed poliovirus and each individual poliovirus type across the four intervention arms are visualized in Supplemental Material 2.

## Statistical Model Comparison

The secondary objective of this study was to descriptively compare different statistical models and identify any differences in treatment effect estimates. We found no meaningful differences in ITT estimates on both the absolute and relative scales across all models, including those with and without covariate adjustments (Figure 2). This result was also observed for all shed poliovirus types (Supplemental Material 4). Adjustments for prescreened covariates in both the GLM and TMLE models had similar size of treatment effect and standard error as their unadjusted counterparts. This suggested that baseline characteristics related to shed poliovirus were balanced between arms and that no further increase in power resulted from adjusting covariates. In addition, when comparing the GLM and TMLE estimators themselves, the semi-parametric TMLE models based on ensemble learning methods with improved robustness also had similar estimates and precision as the simpler, parametric GLMs. Lastly, the estimates of TMLE with IPCW were similar to the ones of TMLE without the IPCW extension, which suggests there was no differential censoring across study arms. Given there were no differences between the model choices, we reported the results of our primary analysis from the adjusted GLM with gaussian link function in the remaining section.

## Poliovirus Shedding

Though there were four intervention arms, we hypothesized that the arm receiving no Rotarix with IPV-OPV would have an effect on poliovirus shedding when compared to the other three remaining arms. The main comparison of interest were the treatment effects from no Rotarix with IPV-OPV and Rotarix with OPV only, but we also assessed individual effects of Rotarix and IPV-OPV by comparing the hypothesized group of interest (no Rotarix with IPV-OPV) with the other two intervention arms (Rotarix with IPV-OPV and no Rotarix with OPV only). Among infants who did not receive Rotarix with IPV-OPV compared to infants who received other combinations of the two vaccines, the adjusted linear probability model’s estimates (RDs) for positive poliovirus shedding were close to null and nonsignificant (Table 2). Compared to infants who received Rotarix with OPV, infants who did not receive Rotarix with IPV-OPV showed no mean treatment response differences in any shed poliovirus (RD: 0.0497; 95% CI: -0.0645−0.1638; *P*=0.3938). We observed similar response differences contrasting these two intervention combinations for poliovirus type 1 (RD: 0.0407; 95% CI: -0.0683−0.1497; *P*=0.4647), poliovirus type 2 (RD: 0.0241; 95% CI: -0.0737−0.1218; *P*=0.6292), and poliovirus type 3 (RD: 0.0162; 95% CI: -0.0793−0.1117; *P*=0.7395). In addition, the contrast that allowed for the two interventions to be considered independently (i.e. Rotarix versus no Rotarix and IPV-OPV versus OPV only) also produced similar mean treatment response differences that remained close to null and nonsignificant. These results were consistent with the nonsignificant chi-squared test that was run prior to the regression models, which compared the four intervention arms and any shed poliovirus (χ2 = 0.51884; df = 3; *P* = 0.9147). The results of the regression models were the same on the relative scale (Supplemental Material 5) and across different models, as previously discussed.

# Discussion

Infants who received no Rotarix with IPV-OPV had no meaningful differences in the risk for any positive poliovirus shedding, compared to infants who received Rotarix with the complete OPV-only series. We observed similar null differences for individual shed poliovirus types. In other words, we found no evidence of Rotarix interference in any and all shed poliovirus for infants who received an IPV replacement dose to the OPV series. In addition, we observed no differences in the analytical methods comparing ITT estimates on both the relative and absolute scale as well as across the different unadjusted and adjusted model choices, suggesting results of our analysis were robust.

Our study extends previous work on IPV doses with OPV by looking at potential interferences from the combination of IPV doses with or without Rotarix on shed poliovirus. Compared to prior literature on OPV-only administration, our results are consistent with other findings on the lack of Rotarix interference. A phase II randomized controlled study in urban Dhaka at Mirpur, Bangladesh found no statistically significant impact of the Rotarix vaccine on the immune response to OPV in terms of seroprotection rates to poliovirus types 1, 2 and 3.17 Although the outcome measured a different treatment response, it aligns with our findings on the null differences in shed poliovirus at 52 weeks between the Rotarix versus no Rotarix arms when concurrently administered with IPV-OPV or OPV. This indicates that the response to IPV-OPV and OPV remains immunogenic and safe for preventing poliovirus when administered simultaneously with Rotarix; lower immunogenicity and stool shedding for rotavirus, however, may need further investigation.18–21

On the other hand, there are some differences in our findings on the null effects of IPV- OPV compared to OPV-only from prior studies. Many studies have shown IPV dose’s protection against paralytic polio, enhanced response to type 2 polioviruses, and possible reduction in the duration and amount of viral shedding, which resulted in the global introduction of at least one IPV dose with OPV.22 Unlike our findings, a study in northern India demonstrated that a single dose of IPV in OPV-vaccinated children improved both humoral and intestinal immunity, and therefore reduced any poliovirus shedding in children aged 6–11 months, 5 and 10 years.23 One reason for the differences in our findings could be variations in age and geography of immunogenicity to OPV. Furthermore, all participants in the PROVIDE study received additional OPV doses along with other EPI vaccines, which may have influenced high antibody titers in both the IPV-OPV and OPV arms and similar shed poliovirus excretion levels. Our findings are consistent with results of another study in India that found no difference in fecal excretion rates and shedding for any of the poliovirus serotypes between the OPV arm and the IPV boost am.24 Researchers, however, did find that the IPV boost improved the quantity of serum neutralizing antibodies.24 This was also reported in another analysis of the PROVIDE study that found no differences in intestinal immunity but a significantly higher seroprevalence and seroconversion rates in the IPV dose arm.25 Although neither IPV nor OPV is superior to the other in improving mucosal immunity, as observed in the lack of differences in poliovirus shedding across intervention arms in this current study, IPV may enhance humoral immunity.

Generalized linear models (GLM), including the linear probability model, log-binomial regression, and modified Poisson regression used in this study, are at risk of model misspecification which can lead to bias.26 In contrast, TMLE are asymptotically unbiased and normal, even when the working models are mis-specified.26,27 In our model comparisons, we found similar precision and estimates of treatment effects from both GLM and TMLE models. This suggests that there may have not been any model misspecification with the GLMs and that the RCT design of the PROVIDE study were specified and planned well enough for these estimators to be efficient for this study’s analysis. Yet another reason for the similar performance of the TMLE model to the GLMs could be that the super learner library did not include enough complex multivariate regression models that could capture potential interactions or nonlinear relationships. However, given that the sample size and the number of covariates were relatively small and that both the unadjusted and adjusted TMLE models produced similar results, we are confident with the libraries included in the TMLE super learner algorithm.

There are several potential limitations in our study. First, we did not measure other outcome variables such as oropharyngeal excretion, all-cause mortality, or serum neutralizing antibodies that may have been better proxies of poliovirus immunity. This was especially true for evaluating the IPV replacement dose at 39 weeks in the OPV series, as other studies have shown significant differences in serum neutralizing antibodies without any effects on shed poliovirus. However, given the primary objective was to observe the combined effects of Rotarix and IPV on OPV effectiveness, and not IPV effectiveness, the analysis of shed poliovirus may have been appropriate to evaluate rates of mucosal immunity and estimate poliovirus reservoir. Second, the small sample size may be limiting in that the probability distribution of the true underlying amount of shed poliovirus for each group may be large and thus only large differences across arms would be able to be detected, if any difference did actually exist. However, the precision around treatment response difference estimates were relatively narrow, suggesting effect sizes and power calculations may have been correctly specified. Third, related to sample size, 13% of the study population were missing the outcome. Upon further investigation with an IPCW extension in the TMLE model, there were no meaningful differences in the estimates or the confidence intervals compared to the TMLE model without IPCW, suggesting there was no differential censoring across study arms. Finally, while treatment responses were measured up to one year of age, potential long-term changes or waning immunity past this timeframe were not addressed.

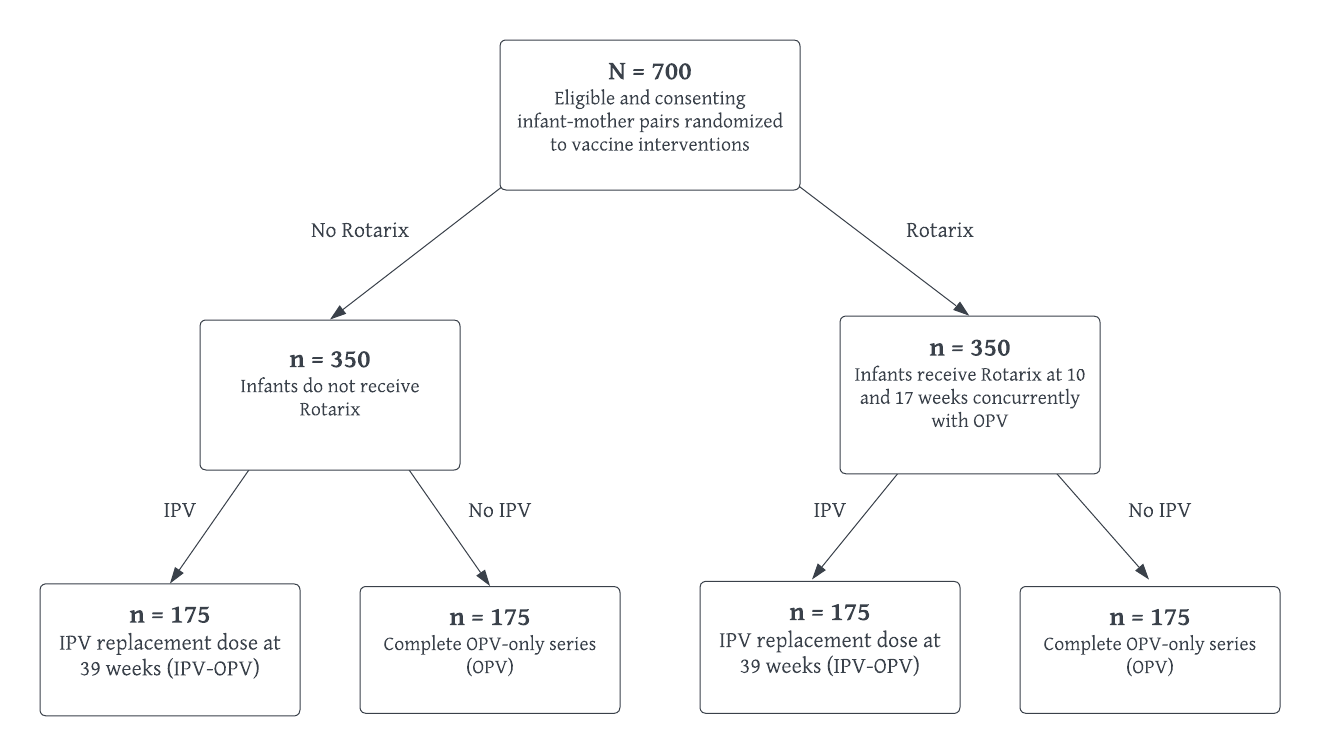
In conclusion, our study shows that incorporation of an IPV dose into the OPV vaccination schedule is possible while maintaining OPV’s existing intestinal immunity, without any interference from concurrent Rotarix administration in LMIC settings. Though IPV does not appear to be superior in decreasing shed poliovirus in fecal cultures, the global switch to IPV with coadministration of Rotarix may be warranted to prevent poliomyelitis and provide humoral immunity to poliovirus. Further studies on coadministration of Rotarix and IPV-only schedules, its long term effects, and ways to improve IPV’s mucosal immunity may be needed to effectively and safely eradicate poliovirus globally.

# Acknowledgements

We thank the contributing investigators who conducted the original PROVIDE RCT (Am J Trop Med Hyg. 2015 Apr;92(4):744-51. doi: [10.4269/ajtmh.14-0518](https://doi.org/10.4269/ajtmh.14-0518). PMID: 25711607), the families who participated in the study, the Bill and Melinda Gates Foundation that supported the work, and ClinEpiDB as the mechanism through which we were able to access the study’s data (William A. Petri, Rashidul Haque, Beth D. Kirkpatrick, et al. Dataset: PROVIDE Randomized Controlled Trial. ClinEpiDB. 03 March 2022, Release 21 <https://clinepidb.org/ce/app/workspace/analyses/DS_fe95d702c3/new>).

# Tables and Figures

*Figure 1*: Flowchart of the randomization of vaccine interventions in the PROVIDE study

Abbreviations: IPV, inactivated poliovirus vaccine; IPV-OPV, inactive poliovirus vaccine replacement dose with oral poliovirus vaccine; OPV, oral poliovirus vaccine; PROVIDE, Performance of Rotavirus and Oral Polio Vaccines in Developing Countries.

*Table 1*: Baseline characteristics of infants in each study arm of the PROVIDE study, May 2011-November 2014

Table

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Abbreviations: HAZ, height for age; IPV-OPV, inactive poliovirus vaccine replacement dose with oral poliovirus vaccine; OPV, oral poliovirus vaccine; PROVIDE, Performance of Rotavirus and Oral Polio Vaccines in Developing Countries Randomized Controlled Trial; SCC, secondary school certificate; SD, standard deviation; WAZ, weight for age.

*Table 1: Baseline characteristics of infants in each study arm of the PROVIDE study, May 2011-November 2014 (cont.)*

Table

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Note: The Bangladeshi Taka to USD conversion is 1 Taka to 0.0097 US

*Figure 2*: Estimates from different models comparing infants who received Rotarix with OPV to infants who received no Rotarix with IPV replacement dose

*Chart, table

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Abbreviations: GLM, generalized linear model; IPCW, inverse probability of censoring weights; IPV-OPV, inactive poliovirus vaccine; OPV, oral poliovirus vaccine; TMLE, targeted maximum likelihood estimator.

Note: Covariates included in adjusted models for any shed poliovirus were: mode of birth, maternal age at first pregnancy (years), mother’s education level, washing hands before feeding self, food availability; the dashed vertical lines on plots indicate the null value on the estimate’s corresponding scale.

*Table 2*: Risk differences from adjusted linear probability models of any and all shed polio serotypes across intervention group contrasts

Text

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Abbreviations: CI, confidence interval; IPV-OPV, inactive poliovirus vaccine replacement dose with oral poliovirus vaccine; OPV, oral poliovirus vaccine; RD, risk difference.

Note: Covariates included in the adjusted models are summarized in Supplemental Table 1 for all shed polio serotypes.

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