MAJOR ARTICLE

# Randomized Trial of Type 1 and Type 3 Oral Monovalent Poliovirus Vaccines in Newborns in Africa

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**(See the editorial commentary by Cochi and Linkins, on pages 169–71.)**

***Background.*** The Global Polio Eradication Initiative aims to eradicate wild poliovirus by the end of 2012. Therefore, more-immunogenic polio vaccines, including monovalent oral poliovirus vaccines (mOPVs), are needed for supplemental immunization activities. This trial assessed the immunogenicity of monovalent types 1 and 3, compared with that of trivalent oral poliovirus vaccine (tOPV), in South Africa.

***Methods.*** We conducted a blinded, randomized, 4-arm controlled trial comparing the immunogenicity of a single dose of mOPV1 (from 2 manufacturers) and mOPV3 (from 1 manufacturer), given at birth, with the immunogenicity of tOPV.

***Results.*** Eight hundred newborns were enrolled; 762 (95%) were included in the analysis. At 30 days after vaccine administration, seroconversion to poliovirus type 1 was 73.4% and 76.4% in the 2 mOPV1 arms, compared with 39.1% in the tOPV arm ($P < .0000001$), and seroconversion to poliovirus type 3 was 58.0% in the mOPV3 arm, compared with 21.2% in the tOPV arm ($P < .0000001$). The vaccines were well tolerated, and no adverse events were attributed to trial interventions.

***Conclusion.*** A dose of mOPV1 or mOPV3 at birth was superior to that of tOPV in inducing type-specific seroconversion in this sub-Saharan African population. Our results support continued use of mOPVs in supplemental immunization activities in countries where poliovirus types 1 or 3 circulate.

***Clinical Trials Registration.*** ISRCTN18107202.

In 1988, the World Health Assembly, the governing body of the World Health Organization (WHO), resolved to eradicate poliomyelitis globally by 2000 [1]. To achieve this goal, the Global Polio Eradication Initiative was created and guided the implementation of the polio eradication strategies [2, 3], which relied almost exclusively on trivalent oral poliovirus vaccine (tOPV). Progress toward eradication was gratifying. Between 1988 and 2005, the number of polio-endemic countries decreased from >125 to 4, and the number of polio cases decreased from >350 000 to <1700 (a decrease of >99%) [4]. Wild type 2 poliovirus was last seen in 1999 but is still seen as circulating type 2 vaccine-derived poliovirus. However, eradication remained elusive. The Global Polio Eradication Strategic Plan 2010–2012 aims to interrupt the transmission of wild poliovirus worldwide by the end of 2012 [5].

Because of the low immunogenicity of tOPV in northern India [6] and to further accelerate progress, the technical oversight committee of the Global Polio Eradication Initiative recommended the development of more-immunogenic polio vaccines, including monovalent type

Received 29 April 2011; accepted 13 July 2011; electronically published 8 December 2011.

Presented in part: Internal World Health Organization meetings.

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**The Journal of Infectious Diseases 2012;205:228–36**



DOI: 10.1093/infdis/jir721

1 oral poliovirus vaccine (mOPV1) and monovalent type 3 oral poliovirus vaccine (mOPV3) [7]. The superiority of these vaccines compared with tOPV was established in trials in Egypt [8] and India [9, 10] and was confirmed by field effectiveness studies [11] and seroprevalence surveys (WHO, unpublished results, 2011). However, immunogenicity data from sub-Saharan infants are lacking.

The introduction and subsequent widespread use of the first mOPV1 and mOPV3 in 2005 decreased the incidence of poliovirus type 1 and 3 transmission in many areas. MOPV1 aided the interruption of poliovirus type 1 transmission in Egypt [12], where, despite very high coverage with tOPV [13], transmission had been ongoing. It may, however, have inadvertently facilitated the spread of poliovirus type 3, particularly in India [14], because of the use of a vaccine not containing poliovirus type 3 and the resultant decreased immunity to this serotype. In sub-Saharan Africa, these monovalent vaccines played an important role in controlling the spread of type 1 poliovirus after importation into West Africa resulted in outbreaks in many countries in this region during 2009–2010 [15]. Introduction of bivalent OPV in late 2009 and programmatic improvements led to a dramatic decrease in the circulation of both type 1 and type 3 polioviruses in Nigeria, the single remaining polio-endemic country in Africa [16, 17]. Bivalent OPV is seen as the most important critical factor for poliovirus eradication by end 2012 [18].

Neonatal immunization with tOPV was first investigated in 1960 [19]. This was followed in the mid-1980s by trials in India [20] and China [21] that showed better immune responses when the vaccine was administered in a schedule that started with a dose in the first week of life. Since 1985, the WHO has recommended a supplemental birth dose (''zero-dose'') of tOPV in countries where poliomyelitis is endemic [22, 23]. This practice continues in most developing countries. Polio vaccines are immunogenic in children with human immunodeficiency virus (HIV) infection. It is associated with a good antibody response (albeit one that is lower than that in uninfected children) and is recommended by the WHO and the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices as part of the immunization schedule for children infected with HIV [24–27]. It is not associated with an increased risk for vaccine-associated paralytic poliomyelitis [25].

In South Africa, mOPV1 (and not tOPV) was used for supplemental vaccination at birth in the late 1980s [28] to better control type 1 poliovirus transmission. When the capacity to produce mOPV1 became unavailable, it was replaced with tOPV, which became the principal tool to control and eliminate poliovirus. The tOPV was administered as part of the National Immunization Schedule at birth and at 6, 10, and 14 weeks of age, with booster doses at 18 months and 5 years of age [29]. The last case of poliomyelitis due to wild poliovirus occurred in South Africa in 1989.

The current study aimed to provide the first immunogenicity data on birth doses of mOPV1 and mOPV3 among newborns residing in sub-Saharan Africa and to corroborate existing data on mOPV1 (with lower potency) from South Africa [28]. In addition, the immunogenicity data from this trial will also inform the WHO prequalification process for the United Nations Children's Fund purchase of mOPV3 vaccine generally.

## METHODS

### Trial Design

This was a blinded, randomized, controlled, 4-arm study comparing mOPVs to tOPV. The mOPV1, mOPV3, and tOPV (control) vaccines were manufactured by GlaxoSmithKline Biologicals (GSK), and a second version of mOPV1 was manufactured by Panacea Biotec (Panacea). The design was double blinded for the GSK vaccines but only single blinded (ie, not blinded to the study staff) for the Panacea vaccine, because of the different vial shapes used by the 2 manufacturers.

### Participants

The trial was conducted at 2 birthing units, the Community Health Clinic in Worcester and Ceres Hospital, in the Western Cape Province of South Africa. Pregnant women planning to deliver at either of these sites were approached during antenatal visits and were invited to consider participation in the trial. They received detailed information about the trial, and written informed consent was obtained. Once newborns were delivered, they were enrolled if they met the inclusion criteria; these newborns constituted the trial population. Initially, it was decided not to enroll infants who had been born at the secondary referral hospital. This decision was amended when it was observed that otherwise healthy mothers were often referred for maternal indications that did not affect the health of the neonate or eligibility criteria.

The study protocol received ethical approval from the University of Cape Town Faculty of Health Sciences Human Research Ethics Committee (Cape Town, South Africa) and from the Ethics Review Committee of the WHO (Geneva, Switzerland). The study was also approved by the Medicines Control Council, the South African national regulatory authority, prior to the study start. This trial was conducted in accordance with the Declaration of Helsinki, Fifth Revision (published in 2000 and the latest revision in use at the start of the trial); the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; good clinical practice guidelines; and all relevant local regulatory requirements in South Africa. The Current Controlled Trials number for the study is ISRCTN18107202.

The inclusion criteria were that the newborns had to weigh $\geq$2.5 kg at birth, with an Apgar score of $\geq$9 at 5 minutes of age. The family had to reside within 50 km of the birthing unit and could not have plans to move out of the area during the 1-month

study period. High-risk newborns, those requiring hospitalization and a diagnosis or suspicion of B-cell immunodeficiency disorder in the newborn or the immediate family were excluded from participating in the trial.

After birth, cord blood was collected, and vaccine with the next consecutive number (on the vaccine vial label) was allocated to the study subject. The number on the vaccine vial coded for the vaccine type contained in the vial (ie, mOPV1, mOPV3, or tOPV from GSK or mOPV1 from Panacea). Two drops of the vaccine were administered orally to the child ≤3 hours after delivery. The child was observed for adverse events for 30 minutes after vaccine administration. The mother was issued a diary card to record any adverse events that might occur before the next study visit. At 30 days of age, the children were followed up for a venous blood draw, at which time any adverse events that had occurred between birth and the follow-up visit were recorded. All serious adverse events (SAEs) were reviewed by an independent data safety and monitoring board. Subjects then exited the study, and their parents were advised to take their children to the nearest community health clinic to receive the remainder of their vaccines according to guidelines of the South African National Expanded Program on Immunization. At the time of the study, the national immunization schedule recommended tOPV at birth and at 6, 10, and 14 weeks of age for primary immunization, with a booster dose at 18 months of age.

### Outcomes

The primary outcome of this study was immunogenicity, defined as the immune response to a single dose of each of the study vaccines (mOPV1 GSK, mOPV1 Panacea, mOPV3 GSK, and tOPV GSK) administered at birth. The proportion of subjects who seroconverted between birth and 30 days of age was compared to determine whether the mOPVs were able to induce superior levels of seroconversion than the relevant type-specific serotypes of tOPV. The secondary outcome was safety, determined on the basis of the occurrence of adverse events. Subjects were monitored for adverse events between birth and 30 days of age.

Serum samples collected at birth and at 30 days of age were tested and assessed for the presence of neutralizing antibodies to poliovirus types 1, 2, and 3, using a standard microneutralization assay [30, 31]. Samples were tested in triplicate and at doubling dilution from 1:8 to 1:1024. Reciprocal titers were expressed as <8 to ≥1448. A reciprocal titer of ≥8 was considered indicative of the presence of detectable neutralizing antibody (ie, seropositivity). A 4-fold increase in antibody titer over the expected decay of maternally derived antibody (assuming a half-life decay of 30 days) was used to indicate seroconversion between birth and 30 days of age. For participants with no detectable neutralizing antibody at baseline, a rise from a reciprocal titer of <8 to one of ≥8 also qualified as seroconversion. All assays were conducted at the CDC, Atlanta, Georgia, which houses one of the 7 global specialized laboratories in the Global Polio Laboratory Network.

### Sample Size

The purpose of this study was to demonstrate the superior immunogenicity of mOPV1 or mOPV3 over that of tOPV in terms of poliovirus type 1 and 3 seroconversion, respectively. Superiority was defined as a 20% difference in seroconversion rates between mOPV1 and tOPV, for type 1 poliovirus, and between mOPV3 and tOPV, for type 3 poliovirus. The level of statistical significance ($\alpha$) used was .05 (2-tailed test), and power was 90%. Given these assumptions, it was estimated that a minimum sample size of 139 participants per study arm was needed. To account for dropouts, attrition, and insufficient sera for laboratory testing, the sample size per group was increased to 200 per study arm, for a total of 800 study participants.

### Randomization

The randomization allocation (1:1:1:1) was performed at GSK (Rixensart, Belgium) by use of MATEX, a program developed for use in SAS(R) [32] by GSK, using a block-randomization scheme with a block size of 20. This block-randomization technique was used at both study sites simultaneously to ensure the adequate distribution of study arms, independently of the number of participants attending the 2 study sites. The vials were sequentially numbered. The treatment randomization codes were retained by GSK. Codes were only broken once all serology results were available for analysis.

### Data Management

An electronic database (Microsoft Access) was used for data entry and storage, using a double data entry system that included 2 passes of the data. The clinical and immunology data were merged using 2 different merging algorithms and 2 different software systems and were then compared.

### Statistical Methods

A $\chi^2$ test was used to compare the proportion of study subjects who seroconverted in each study arm. To use a conservative measure of $P$, a 2-tailed $\chi^2$ test (Yates corrected) was applied. Nonparametric tests (ie, the Wilcoxon rank-sum test) were used to compare distribution of antibody titers between study groups. A similar test was used to compare the difference in titers at day 0 and day 30 (assuming the null hypothesis that the difference should be 0). All analyses were conducted as modified intention-to-treat analyses, with the attempt to include all available evaluable subjects in the analyses.

All data analysis was performed using R [33] and SAS, version 9.232 [32], statistical packages.

## RESULTS

### Study Population

A total of 1620 mothers consented to enroll their children at birth; of these, 820 infants were excluded as follows: 674 did not meet the inclusion criteria, 16 had parental consent withdrawn at birth, 68 were excluded for other reasons, and 62 were screened but not

enrolled because the required number of participants had already been enrolled by the time of their birth (Figure 1).

Enrollment took place from July 2008 to August 2009. Follow-up was completed in September 2009.

There was an excellent retention of enrolled subjects. Seven hundred and sixty-two of the 800 participants (95%) enrolled were included in the analysis (Figure 1). Thirty-eight (5%) were excluded from the analysis: 31 were lost to follow-up, 4 exited because parental consent was withdrawn, 2 were withdrawn because of protocol violations, and 1 was excluded because of an ongoing SAE (not vaccine related) at the time of the day 30 follow-up visit.

### Participant Characteristics

There were no significant differences in the baseline demographic characteristics (ie, sex, birth weight, maternal education level, and interval from birth to study vaccine administration) between the 4 study groups (Table 1). The baseline seroprevalence of neutralizing antibodies to the 3 poliovirus serotypes detected in cord blood at birth is presented in Table 2. There were no significant differences in the baseline seroprevalence or in antibody titers to the 3 polio vaccine virus serotypes between the 4 study arms. The maternal education level was high in the study population, with a median education duration of 10–11 years. There was no intergroup variation.

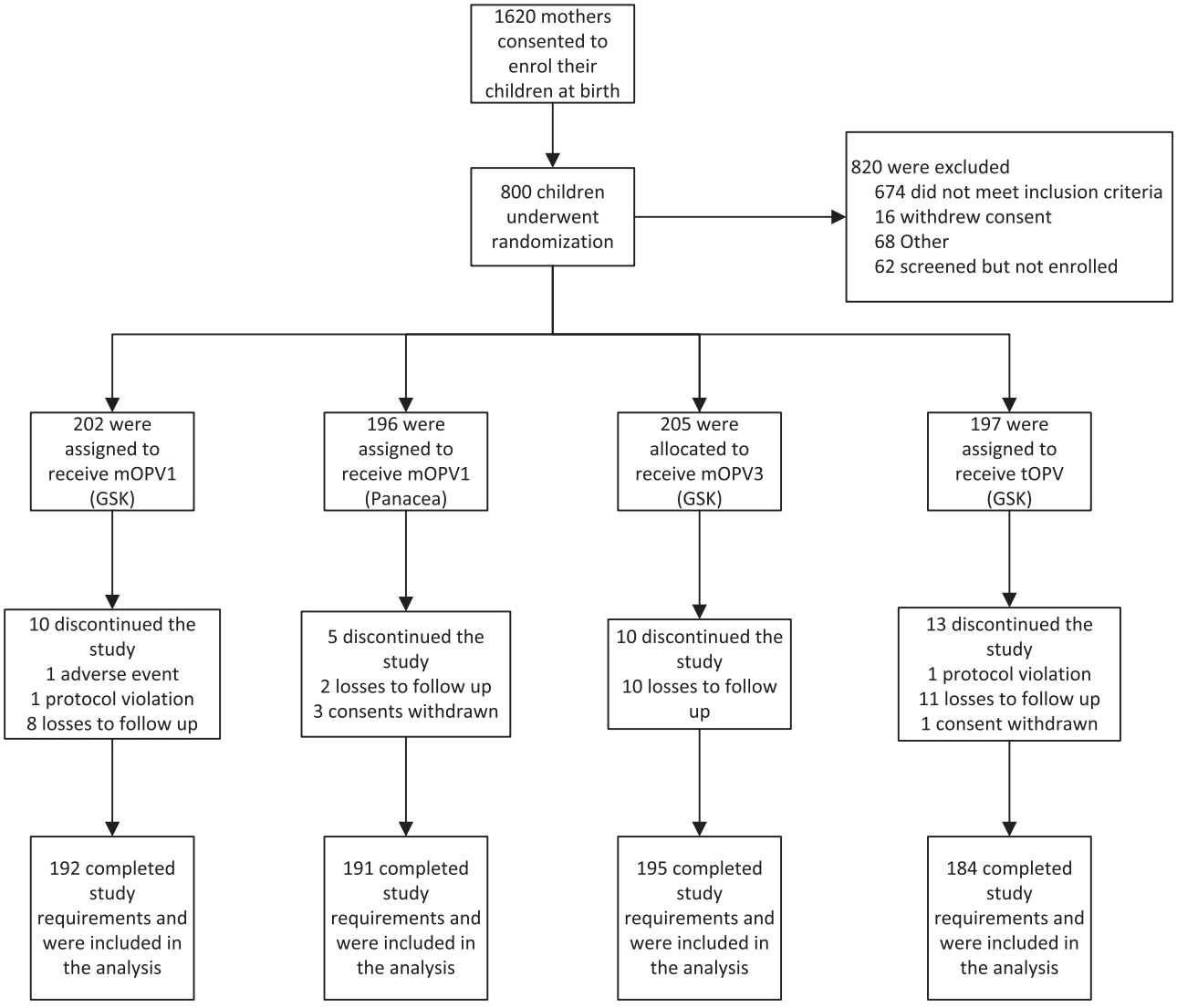


**Figure 1.** Consolidated Standards of Reporting Trials flow diagram showing the number of mothers screened, the number of children randomized to receive 1 of 4 oral poliovirus vaccines (OPVs; monovalent type 1 OPV manufactured by GlaxoSmithKline Biologicals [mOPV1 GSK], monovalent type 1 OPV manufactured by Panacea Biotec [mOPV1 Panacea], monovalent type 3 OPV [mOPV3], and trivalent OPV [tOPV]), and the number of children included in the analysis.

**Table 1. Baseline Demographic Characteristics of Enrolled Infants, by Study Group at Birth**

| Characteristic | mOPV1 GSK (n = 192) | mOPV1 Panacea (n = 191) | mOPV3 GSK (n = 195) | tOPV GSK (n = 184) |
|---|---|---|---|---|
| Female sex, subjects, no. (%) | 84 (43.8) | 102 (53.4) | 91 (46.7) | 87 (47.3) |
| Birth weight, kg, median (95% CI) | 3.1 (3.0–3.2) | 3.1 (3.0–3.2) | 3.1 (3.0–3.2) | 3.1 (3.0–3.2) |
| Interval from birth to receipt of study vaccine, min, median (95% CI) | 82 (74.5–87.5) | 78 (74–85) | 80 (75.5–91.5) | 79 (73–87) |
| Duration of maternal education, y, median (95% CI) | 11 (10–11) | 10 (10–11) | 11 (10–11) | 10 (10–11) |

Abbreviations: CI, confidence interval; mOPV1 GSK, monovalent type 1 oral poliovirus vaccine manufactured by GlaxoSmithKline Biologicals; mOPV1 Panacea, monovalent type 1 oral poliovirus vaccine manufactured by Panacea Biotec; mOPV3, monovalent type 3 oral poliovirus vaccine; tOPV, trivalent oral poliovirus vaccine.

### Serological Analysis

The seroconversion rates at day 30 after vaccine administration for each poliovirus type by study arm are shown in Table 3 and Figure 2. Seroconversion for both mOPV1 arms was >70% (73.4% in the mOPV1 GSK arm and 76.4% in the mOPV1 Panacea arm) against type 1 poliovirus, compared with 39% in the tOPV arm ($P < .0000001$). There was no difference in the seroconversion rates between the mOPV1 GSK and mOPV1 Panacea groups ($P = .58$). mOPV3 was more immunogenic than the type 3 component of the trivalent vaccine, with seroconversion rates of 58% and 21%, respectively ($P < .0000001$).

There was a >50-fold increase (from 26 to ≥1448) in median antibody titers between birth and 30 days of age in the mOPV1 groups, compared with a 2-fold increase (from 45 to 91) in the tOPV group and a 2-fold decrease (from 28 to 14) in the mOPV3 group, against type 1 poliovirus. Median antibody titers to type 3 poliovirus showed a 20-fold increase (from 11 to 227) in the mOPV3 group; there was no change in the tOPV group, and there were undetectable levels in the mOPV1 groups. There was a 12-fold increase (from 74 to 910) in median antibody titer to type 2 poliovirus in the tOPV group, compared with 2–4-fold decreases (from 45 to 14 and from 74 to 28, respectively) in the mOPV1 GSK arm and the mOPV1 Panacea arm.

### Safety Assessment

There were no vaccine-related adverse events during the 30-minute period following vaccination.

There were no significant differences in adverse events among the 4 study groups during the study period between birth and 30 days of age. There were 24 SAEs in 22 participants. All SAEs required inpatient hospitalization and were deemed unrelated to the vaccine by the site investigator. The data and safety monitoring board reviewed all SAEs and concluded that none were causally related to trial interventions. There were 6 SAEs in the mOPV1 GSK group, 6 in the mOPV3 GSK group, 2 in the mOPV1 Panacea group, and 10 in the tOPV GSK group. Six participants had more than one clinical diagnosis per hospitalization (SAE). The clinical diagnoses are shown in Table 4.

## DISCUSSION

This trial provides the first immunogenicity data on mOPV1 and mOPV3 among newborns from a largely black population in sub-Saharan Africa. Both mOPV1 formulations were superior to the type 1 component of tOPV in inducing seroconversion; similarly, mOPV3 was superior to the type 3 component of tOPV in inducing seroconversion. The immunogenicity of mOPV1 and mOPV3 in our study was substantially higher than that reported

**Table 2. Baseline Seroprevalences and Baseline Titers of Serotype Among Enrolled Infants, by Study Group at Birth**

| Characteristic | mOPV1 GSK (n = 192) | mOPV1 Panacea (n = 191) | mOPV3 GSK (n = 195) | tOPV GSK (n = 184) |
|---|---|---|---|---|
| Type 1 poliovirus | | | | |
| Seroprevalence, subjects, % | 78.9 | 81.3 | 78.5 | 78.3 |
| Reciprocal titer, median (95% CI) | 28 (18–45) | 26 (18–45) | 28 (18–40) | 45 (23–57) |
| Type 2 poliovirus | | | | |
| Seroprevalence, subjects, % | 90.6 | 89.1 | 90.3 | 91.3 |
| Reciprocal titer, median (95% CI) | 45 (36–72) | 74 (45–91) | 45 (28–80) | 74 (45–91) |
| Type 3 poliovirus | | | | |
| Seroprevalence, subjects, % | 58.3 | 57.8 | 62.1 | 63.0 |
| Reciprocal titer, median (95% CI) | 11 (9–14) | 11 (9–14) | 11 (11–18) | 11 (11–18) |

Abbreviations: CI, confidence interval; mOPV1 GSK, monovalent type 1 oral poliovirus vaccine manufactured by GlaxoSmithKline Biologicals; mOPV1 Panacea, monovalent type 1 oral poliovirus vaccine manufactured by Panacea Biotec; mOPV3, monovalent type 3 oral poliovirus vaccine; tOPV, trivalent oral poliovirus vaccine.

**Table 3. Poliovirus Type–Specific Seroconversion Rates at Day 30 of Age and Median Antibody Titers at Birth and Day 30 of Age, by Study Group**

| Vaccination response | mOPV1 GSK (n = 192) | mOPV1 Panacea (n = 191) | mOPV3 GSK (n = 195) | tOPV GSK (n = 184) | *P* Value |
|---|---|---|---|---|---|
| Type 1 poliovirus | | | | | |
| Seroconversion, subjects | | | | | |
| No. | 141 | 146 | 16 | 72 | |
| Percentage (95% CI) | 73.4 (66.9–79.3) | 76.4 (70.0–82.1) | 8.2 (4.9–12.7) | 39.1 (32.3–46.3) | <.0000001[a], .58[b] |
| Titer, by time, median (IQR) | | | | | |
| Birth | 28 (18–45) | 26 (18–45) | 28 (18–40) | 45 (45–91) | |
| Day 30 | ≥1448 (≥1448 to ≥1448) | ≥1448 (1176 to ≥1448) | 14 (11–18) | 91 (57–181) | |
| Type 2 poliovirus | | | | | |
| Seroconversion, subjects | | | | | |
| No. | 18 | 8 | 31 | 116 | |
| Percentage (95% CI) | 9.4 (5.8–14.1) | 4.2 (2.0–7.8) | 15.9 (11.3–21.5) | 63.0 (55.9–69.8) | |
| Titer, by time, median (IQR) | | | | | |
| Birth | 45 (36–72) | 74 (45–91) | 45 (28–80) | 74 (45–91) | |
| Day 30 | 14 (11–23) | 18 (11–28) | 28 (18–36) | 910 (576–1176) | |
| Type 3 poliovirus | | | | | |
| Seroconversion, subjects | | | | | |
| No. | 8 | 5 | 113 | 39 | |
| Percentage (95% CI) | 4.2 (2.0–7.8) | 2.6 (1.0–5.7) | 58.0 (50.9–64.7) | 21.2 (15.8–27.6) | <.0000001[c] |
| Titer, by time, median (IQR) | | | | | |
| Birth | 11 (9–14) | 11 (9–14) | 11 (11–18) | 11 (11–18) | |
| Day 30 | <8 (<8 to <8) | <8 (<8 to <8) | 227 (143–362) | 11 (9–11) | |

Abbreviations: CI, confidence interval; IQR, interquartile range; mOPV1 GSK, monovalent type 1 oral poliovirus vaccine manufactured by GlaxoSmithKline Biologicals; mOPV1 Panacea, monovalent type 1 oral poliovirus vaccine manufactured by Panacea Biotec; mOPV3, monovalent type 3 oral poliovirus vaccine; tOPV, trivalent oral poliovirus vaccine.

[a] mOPV1 GSK or mOPV1 Panacea versus tOPV (type 1).

[b] mOPV1 GSK versus mOPV1 Panacea.

[c] mOPV3 versus tOPV (type 3).

from other contemporary clinical trials [8, 10]. The vaccines were well tolerated, and no SAEs were attributable to trial interventions.

A birth dose of mOPV1 in our trial led to seroconversion against poliovirus type 1 in >70% of study subjects, compared with only 39% seroconversion against poliovirus type 1 following receipt of tOPV. These levels are considerably higher than those reported in a previous study in Egypt, where 56% seroconverted after receiving a birth dose of mOPV1 against poliovirus type 1 [8], and are also much higher than the response reported from 3 trials conducted in India, where the seroconversion rates were only 10%–20% following receipt of a birth dose of mOPV1 [10]. mOPV1 Panacea—the same vaccine used in our study—resulted in low seroconversion rates at birth in India for unknown reasons. A second dose of mOPV1, given at 30 days of age, led to a 90% seroconversion rate in the study from India. In our trial, the two mOPV1 vaccines resulted in similar seroconversion rates and antibody titer profiles.

Similarly, a birth dose of mOPV3 led to seroconversion against poliovirus type 3 in 58% of subjects, compared with 21% in the tOPV arm. This is again much better than that reported from a trial in India, where only 12% of subjects seroconverted following a birth dose with mOPV3, again for unknown reasons unknown. However, a dose of mOPV3 administered at the age of 30 days led to seroconversion in 81% of subjects in India [10].

The reciprocal median antibody titers following a dose of mOPV1 were above the final dilution tested (reciprocal titer, ≥1448), suggesting, by another measure, the strong immunogenicity of the vaccine in this study population. In contrast, the reciprocal median titer (against poliovirus type 1) following a birth dose of tOPV was considerably lower (reciprocal titer, 91). As expected, the poliovirus type 2 immunogenicity of the tOPV was high (seroconversion rate, 63%; reciprocal median titer, 910). The higher immunogenicity of type 2 poliovirus in tOPV, compared with that of the type 1 and 3 components, resulted in the elimination of wild poliovirus type 2 in 1999. Following a birth dose of mOPV3, the reciprocal median titers increased to 227, compared with 11 (against poliovirus type 3) in the tOPV group. These titers are comparable to those found in other reported trials [8, 10], including the trial conducted in Egypt in 2008 [8].

The following considerations should be borne in mind in interpreting our findings. First, the study is located in an

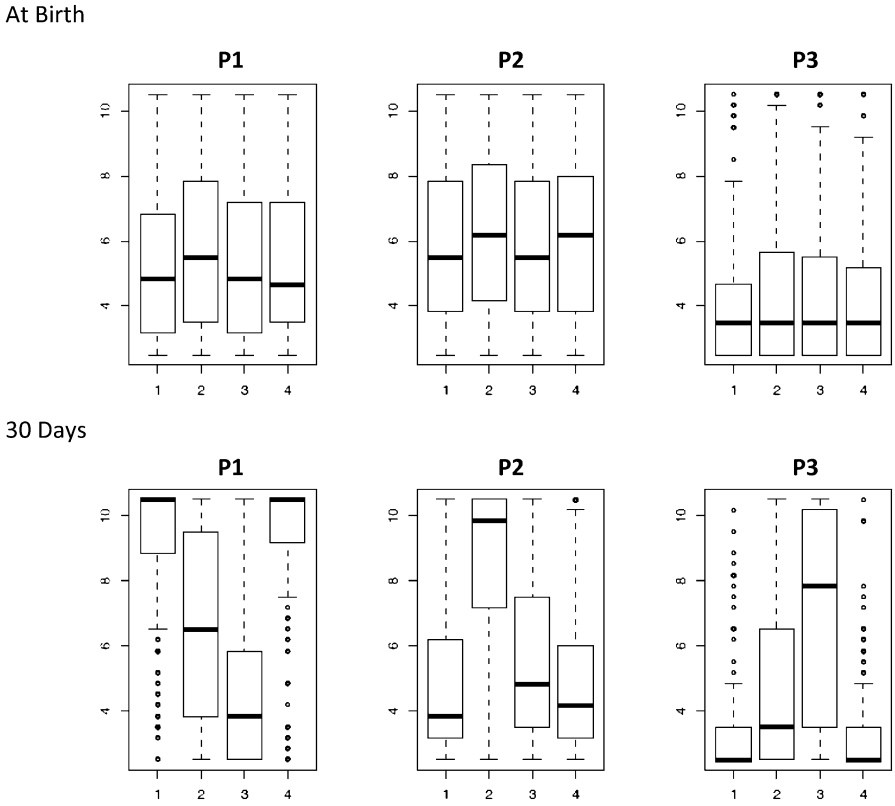


**Figure 2.** Overall median reciprocal titers of antibodies to poliovirus types 1 (P1), 2 (P2), and 3 (P3) prior to vaccination at birth and 30 days after vaccination with 1 of the following oral poliovirus vaccines (OPVs): monovalent type 1 OPV manufactured by GlaxoSmithKline Biologicals (1), trivalent OPV manufactured by GlaxoSmithKline Biologicals (2), monovalent type 3 OPV manufactured by GlaxoSmithKline Biologicals (3), and monovalent type 1 OPV manufactured by Panacea Biotec (4). The upper and lower limits of the boxes denote the interquartile range, the bold lines denote median values, the whiskers denote the minimum and maximum values of the distribution, and the circles denote outliers.

area with a Mediterranean climate (which is similar to the climate in Egypt but definitely not a tropical climate). Second, although the socioeconomic status of the study population was low (the parents of most infants were agricultural workers), the maternal education levels were high. Because of these factors, we may not be able to directly extrapolate the seroconversion data from this trial to the tropical settings in Africa.

**Table 4. Clinical Diagnoses Reported in Hospitalized (Serious Adverse Event) Children**

| Diagnosis | mOPV1 GSK | mOPV1 Panacea | mOPV3 GSK | tOPV GSK |
|---|---|---|---|---|
| Neonatal jaundice | 1 | 0 | 0 | 2 |
| Acute gastroenteritis | 0 | 1 | 0 | 0 |
| Sepsis syndrome[a] | 2 | 2 | 1 | 3 |
| Meningitis | 2 | 2 | 0 | 1 |
| Conjunctivitis/bilateral eye infection | 1 | 1 | 1 | 0 |
| Pneumonia/LRTI | 1 | 1 | 0 | 4 |
| Urinary tract infection | 0 | 1 | 0 | 1 |
| Omphalitis | 0 | 0 | 0 | 1 |
| Transient tachypnea of newborn | 0 | 0 | 0 | 1 |
| Overall[b] | 7 | 8 | 2 | 13 |

Abbreviations: LRTI, lower respiratory tract infection; mOPV1 GSK, monovalent type 1 oral poliovirus vaccine manufactured by GlaxoSmithKline Biologicals; mOPV1 Panacea, monovalent type 1 oral poliovirus vaccine manufactured by Panacea Biotec; mOPV3, monovalent type 3 oral poliovirus vaccine; tOPV, trivalent oral poliovirus vaccine.

[a] Defined as suspected sepsis, proven sepsis, or septic shock.

[b] Several children had >1 clinical diagnosis per serious adverse event.

Monovalent and bivalent oral poliovirus vaccines are currently only recommended for supplemental immunization activities (ie, they are not for routine vaccination, including birth doses). mOPV1 has been used until recently as a birth dose (eg, in Hong Kong, Kuwait, and South Africa) and could be used, or substituted by bivalent OPV, at birth again [34]. mOPVs and bivalent OPV have immunogenicity that is superior to that of tOPV to the type-specific serotypes, especially since wild poliovirus type 2 appears to have been eradicated globally in 1999 [35].

Another interesting observation from our study is that mOPV1 and mOPV3 given at birth were considerably more immunogenic in South Africa than in India [10] and were more immunogenic than mOPV1 in Egypt [8], for reasons that are currently unclear. At this juncture, it appears that a birth dose administered in India results in low seroconversion [10, 36], a phenomenon that has not been observed elsewhere. Polio and other enteric vaccines are less effective in poor populations in Africa and India. This is hypothesized to be caused, in an additive manner, by a combination of environmental factors (eg, undernutrition, environmental enteropathy, and coinfection by pathogenic organisms) and genetic factors, with the genetic factors predominating in early life [37]. The difference in immunogenicity to OPV is thought to result from genetic factors mainly and to a lesser degree by coinfection with different pathogenic organisms.

This study demonstrates that mOPV1 is superior to the type 1 component of tOPV and that mOPV3 is superior to the type 3 component of tOPV when administered at birth. The performance of the mOPV1 vaccines did not differ by manufacturer, demonstrating that OPV vaccine potencies predict immunogenicity. To accelerate the elimination of the final chains of poliovirus transmission, the most-immunogenic vaccines must be employed and the highest vaccination coverage must be attained, both with routine vaccine coverage and during supplemental immunization activities. The immunogenicity data of mOPV3 documented in this study facilitated the prequalification of this product by the World Health Organization for United Nations Children's Fund purchase.

In conclusion, both mOPV1 and mOPV3 vaccines have a continued important role in the control and elimination of the remaining chains of poliovirus type 1 and type 3 transmission in Africa and in other regions, particularly where a single poliovirus serotype has been imported and is circulating and where type-specific control efforts through supplemental immunization activities are indicated. It is also administered as a short-interval additional dose, which consists of 2 doses of mOPV administered within 2 weeks of each other, to swiftly increase population immunity [38].

## Notes

***Acknowledgments.*** We thank the South African Tuberculosis Vaccine Initiative (SATVI) staff involved in the study, including the staff at the 2 study sites (Lauren Mactavie, Anne Swarts, Bongani Diamond, Carmen Segelaar, Cecilia Yeko, Cynthia Gwintsa, Elizabeth Filander, Glenda Harrison, Lorraine Coetzee, Madeleine Cupido, Margareth Erasmus, Menno Januarie, Mzwandile Clive Maqubela, Nicoleen Jass, Nokuzola Williams, Nomsa Mangweni, Patiswa Plaaitjie, Rachel Oelofse, and Sheily Ndwayana); the pharmacist (Loren Traut); the regulatory affairs team (Ashley Veldsman, Benita Diener, and Judy Huna); the communications and marketing manager (Linda Rhoda); the administration staff (Lucrecia Adams, Claire Khai, Rieyaat Hassiem, Liana Swarts, and Alvin Coetsee); the SATVI laboratory staff (Hadn Africa, Esme Janse van Rensburg, Christiaan Hopley, Lebohang Makhethe, and Mzwandile Erasmus), for processing specimens; the data management staff (Fajwa Opperman, Petroween Van Rooyen, and Petrus Tyambetyu); the CDC laboratory staff (including Deborah Moore, Yiting Zhang, and Eric Rhoden), for providing excellent technical assistance in performing the neutralization tests; and Triclinium Clinical Trial Project Management, for monitoring the trial.

Vaccines used this study were supplied by GlaxoSmithKline and Panacea Biotec.

***Financial support.*** This work was supported by the Bill & Melinda Gates Foundation (37460), the GAVI Alliance, the WHO Polio Eradication Initiative, and GlaxoSmithKline (unconditional grant).

***Potential conflicts of interest.*** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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