Efficacy, Immunogenicity, and Safety of Two Doses of a Tetravalent Rotavirus Vaccine RRV-TV in Ghana With the First Dose Administered During the Neonatal Period

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Background. Oral rhesus/rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) was licensed in 1998 but withdrawn in 1999 due to a rare association with intussusception, which occurred disproportionately in infants receiving their first dose at ≥90 days of age. This study examined RRV-TV for the prevention of rotavirus gastroenteritis (RV-GE) in Ghana, West Africa, with infants receiving the first dose during the neonatal period and the second before 60 days of age.

Methods. In a double-blinded, randomized, placebo-controlled trial in Navrongo, Ghana, we recruited neonates to receive 2 doses of RRV-TV or placebo and followed them to age 12 months.

Results. In the intention-to-treat population of 998 infants, we measured a vaccine efficacy of 63.1% against RV-GE of any severity associated with any of the 4 serotypes represented in the vaccine and 60.7% against RV-GE associated with any rotavirus serotype.

Conclusions. RRV-TV in a 2-dose schedule with the first dose during the neonatal period is efficacious in preventing RV-GE in rural Ghana. Neonatal dosing results in early protection and may be the optimum schedule to avoid or significantly reduce intussusception, now reported to be associated in international settings with the 2 most widely marketed, licensed, live virus, oral rotavirus vaccines.

Keywords. rotavirus; rotavirus infections; rotavirus vaccines; Ghana; randomized controlled trial; diarrhea; infantile; gastroenteritis; humans; infant; vaccines; attenuated.

Rotaviruses are the single most important cause of severe diarrheal illnesses of infants and young children in both developed and developing countries, accounting for 453,000 deaths annually in the under-5-year age-group, mostly in developing countries [1]. Two licensed rotavirus (RV) vaccines, RotaTeq (Merck) and Rotarix (GSK), have reduced the burden of rotavirus diarrhea when used in developed countries [2–5]. However, both have been less efficacious in trials in Africa and poorer countries within Asia [6–8]. In addition, neither vaccine is licensed for administration to neonates, leaving a protection gap in the first months of life [9, 10].

Concern that all RV vaccines might induce intussusception has been present since the withdrawal of the first licensed RV vaccine, the oral rhesus/rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) or
RotaShield (Wyeth-Ayerst), in 1999 [11–16]. Recent publications have now demonstrated evidence of an association between RotaTeq, Rotarix, and intussusception [17–22]. Subsequent analysis of the RotaShield experience reported that excess risk occurred in large part following “catch-up” vaccination, with administration of the first dose at ≥90 days of age [16, 23–25]. Between 3 and 9 months of age is a period of high susceptibility for non-vaccine-associated intussusception and was an age accounting for a disproportionate number of RotaShield-associated cases of intussusception [16, 23–25]. Prelicensure trials of RotaTeq and Rotarixstringently avoided administration of the first dose at this older age, with the mean age for the first dose of RotaTeq and Rotarix being 68.6 and 67.4 days, respectively [26, 27]. In data from actual commercial use, the median age of infants who developed intussusception following the first dose of Rotarix was 99 days (range, 45–356 days), and the incidence ratio of intussusception for 3 through 7 days after the first dose was 5.0 times as high as that for the same period after the second dose [18]. While there has been debate on the age-dependence of intussusception related to the first dose of a rotavirus vaccine [28], regulatory approval of RotaTeq and Rotarix required age-restrictions on their dosing schedules and age limitations are still required. According to their labels, the first doses of RotaTeq and Rotarix are not administered until infants are at least 6 weeks of age but may be administered to infants as old as 15 and 20 weeks, respectively.

Background rates of intussusception vary markedly by age, with an 8- to 10-fold increase between infants aged 1–3 and 4–6 months [29]. Assuming that rotavirus vaccine-associated intussusception risk—relative to background intussusception risk—is stable with age, administering vaccines early in life would minimize the excess ratio of intussusception [23, 30].

RRV-TV was originally developed to be administered as 3 doses at 2, 4, and 6 months of age. In this study, we describe the efficacy of a 2-dose schedule [31, 32] of RRV-TV with the first dose given neonatally, between birth and 29 days, and the second dose at 30–59 days. The RRV-TV schedule has 3 major potential advantages: (1) protection of infants against RV-GE at a younger age than the currently licensed rotavirus vaccines, an important factor given the high burden of rotavirus disease in the first months of life [9, 10, 33]; (2) elimination or significant reduction of the risk of rotavirus-vaccine associated intussusception because it is being given at a relatively refractory period for developing intussusception under natural conditions; and (3) achievement of a higher compliance rate of vaccination since some infants in resource-poor countries may have contact with a healthcare provider only at or near the time of the child’s birth, when oral polio vaccine (OPV) and Bacille Calmette-Guérin (BCG) may be first administered [34].

In addition, a 2-dose schedule of RRV-TV is efficient: RRV-TV is stable at room temperature ≤25°C [35], it could be effectively utilized in resource-poor areas, and it is a potentially cost-effective vaccine. Therefore, given the pressing need to reduce the burden of rotavirus gastroenteritis among infants in developing countries, we conducted a double-blinded, randomized, placebo-controlled trial in Ghana to evaluate the efficacy, immunogenicity, and safety of 2 doses of RRV-TV.

**METHODS**

**Study Site**

In Ghana, 28.5% of the population lives below the country’s established poverty line, the gross domestic product per capita is $2500 in 2010 US dollars, and the human immunodeficiency virus (HIV) prevalence is 1.8% among adults [36]. The Kassena-Nankana and Bongo districts of the Upper East Region, where the study was conducted, are rural with >84% of the population in the poorest households (lowest and second wealth quintile) in Ghana. The neonatal mortality rate is 17 deaths per 1000 live births; the infant mortality rate is 46 deaths per 1000 live births [37].

**Enrollment Procedures**

Using the Navrongo Demographic Surveillance System, we identified pregnant women and sought to recruit their neonates from birth to 29 days old, if they were healthy, having no symptoms of active gastroenteritis, and available for follow-up by home visits until 1 year of age.

We randomized neonates in a 1:1 ratio to receive 2 doses of either RRV-TV or placebo at 0 to 29 days of age and again at 30–59 days of age and at least 21 days after receiving the first dose. Each dose of RRV-TV had a potency of 4 × 10^5 plaque forming units (PFU) in 2.5 mL buffered liquid (vaccine and placebo were prepared at IDT Biologika GmbH, Dessau-Roßslau, Germany). The RRV-TV used in this clinical trial has been shown to be free of porcine circovirus type 1 and 2. The placebo was the same formulation but without the virus and was visually indistinguishable from RRV-TV.

Investigators, subjects, the subjects’ parents/guardians and caregivers, and the sponsor representatives remained blinded to the treatment-assignment until after the database was locked. All study participants continued to receive their routine Expanded Program on Immunization (EPI) vaccines without modification as the standard of care. The Ghana EPI policy includes OPV and BCG at birth, OPV and Diphtheria-Pertussis-Tetanus-Haemophilus influenzae type b-Hepatitis B Vaccine (DPT-Hib-HepB) at 6, 10, and 14 weeks of age. The actual vaccinations times in this region of rural Ghana varied significantly from the EPI schedule. The mean age of the first dose of RRV-TV or placebo was 1.8 weeks, and 28% of the first doses of RRV-TV or placebo were administered within ±7 days of the first dose of OPV, but, in most cases, the doses of RRV-TV or placebo were not given on the same day as the other EPI vaccines. Breastfeeding was not restricted at the time of receiving...
RRV-TV or placebo. No HIV testing was done or offered in the study; therefore, the HIV status of the subjects was unknown at study initiation.

Subject Follow-Up

Trained field workers visited the subjects at home 2 and 4 days after each RRV-TV/placebo dose then weekly until 1 year of age. Episodes of gastroenteritis (GE), defined as 3 or more watery stools within a 24-hour period with or without vomiting, were captured upon their presentation to medical facilities/clinics in the study area. Stool samples were obtained from all who reported with GE between receipt of first RRV-TV/placebo dose and the last scheduled visit, at 12 months of age, plus or minus 14 days. Trained field workers collected information about the GE event through interviews with the parent or caregiver. The GE severity was graded using the 20-point Vesikari scoring system [38]. RV-GE was defined a priori as a GE occurring more than 2 weeks after the subject’s last dose of rotavirus vaccine or placebo and for which RV was identified in a stool sample taken no more than 7 days after the start of the subject’s diarrhea. Events of GE were counted as different episodes if separated by at least 5 days free of vomiting and diarrhea.

For safety monitoring, subjects were visited at home 2 and 4 days after dosing and then weekly to document any adverse events. Axillary temperatures were taken at each of these visits since RRV-TV was associated with febrile reactions in some infants typically 3–4 days after the administration of the first dose [31]. No febrile reactions to vaccination were detected. Furthermore, timing of the visits was also appropriate for detection of intussusception because intussusception has been associated with RRV-TV, RotaTeq, and Rotarix within 7 days of vaccination and appears to peak around 3–4 days after that first dose [14, 20, 22]. In addition, parents and guardians were asked to bring their children to the hospital or clinic if their children developed symptoms of GE or were unwell.

Laboratory Tests

All the Enzyme Immunoassay (EIA) and rotavirus genotyping were performed at the World Health Organization (WHO) Regional Rotavirus Laboratory at the Noguchi Memorial Institute for Medical Research, University of Ghana. Serological assays for the serum antirotavirus immunoglobulin A (IgA) were performed by EIA in the laboratory for Clinical Studies, Division of Infectious Diseases, Children’s Hospital Medical Center, Cincinnati, Ohio. Serological assays for the OPV-specific neutralization antibodies were performed at the CDC, Atlanta, Georgia. Stool specimens were transported on ice to the study laboratory, where they were frozen at −20°C until testing. Rotavirus antigen in stool was detected by EIA (ProSpecT, Oxoid Ltd, United Kingdom). All stool samples positive for rotavirus(es) by EIA were further characterized by reverse transcription-polymerase chain reaction (RT-PCR) to determine the rotavirus P and G genotypes [39, 40]. A subset of serum specimens obtained from 246 (250 planned) study participants was tested for IgA rotavirus antibody by EIA [41] as described in the online Supplementary data. A subset of 228 (250 planned) serum samples was also tested for poliovirus neutralizing antibodies as described in the Supplementary data.

Statistical Analysis

The primary objective of the study was to evaluate the efficacy of 2 doses of RRV-TV against RV-GE of any severity, in which the stool sample contained at least one of the serotypes represented in RRV-TV (G1 to G4). The efficacy period began 2 weeks after the last dose of vaccine/placebo and continued until the end of that subject’s study participation. We considered the intention-to-treat (ITT) population as the primary efficacy analysis population, although we also assessed efficacy in the per-protocol (PP) population. The ITT population consisted of all randomized subjects, regardless of whether or not they received the treatment to which they were assigned. The PP population, determined before unblinding the treatment allocation, consisted of all randomized subjects who completed the study without major protocol deviations. The statistical test for significance for vaccine efficacy consisted of the two-sided Fisher’s exact test (α = 0.05) The Supplementary data provide further details regarding the statistical analysis, as well as specifics concerning the protection of human subjects.

A secondary objective of the study was to evaluate the efficacy of 2 doses of RRV-TV against severe RV-GE, in which the stool sample contained at least one of the serotypes present in RRV-TV (G1 to G4).

RESULTS

Study Subjects

Of 1029 neonates screened, 998 were enrolled and randomized (Figure 1). The ITT population consisted of 998 subjects, 500 in the RRV-TV group and 498 in the placebo group. The PP population consisted of 889 subjects, 447 RRV-TV and 442 placebo. Demographic characteristics for the 2 groups are listed in Table 1. All subjects were breastfed.

Efficacy

In the ITT population, as shown in Table 2, when only RV-GE episodes where an associated stool sample contained at least one of the serotypes (G1–G4) represented in RRV-TV were counted, the RRV-TV group had 10 cases (2.0%), whereas the placebo group had 27 (5.4%) for a vaccine efficacy (VE) of 63.1% (95% confidence interval [CI], 24.6%–82.0%). In the same population, when all RV-GE episodes regardless of the serotype were counted, the RRV-TV group had 15 cases (3.0%), whereas the placebo group had 38 (7.6%) for a VE of 60.7%
Figure 1. Flow diagram of the progress through the phases of the trial. [1] Inclusion criteria: Investigator’s judgment regarding protocol adherence, aged 0 to 29 days, written parental permission, healthy, birth weight >2000 g or, if birth weight unknown, gestation period >37 weeks. [2] Exclusion criteria: Use or planned use of other investigational drug or vaccine, participation or planned participation in another clinical study of drug or vaccine, plans for nonroutine vaccine within 14 days of rhesus/rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) or placebo dose, chronic administration of immunosuppressants since birth, clinically significant history of chronic gastrointestinal disease, including any uncorrected congenital malformation of the gastrointestinal tract, intussusception, or other medical condition determined to be serious by the investigator, confirmed or suspected immunosuppressive or immunodeficient condition, history of allergic disease or reaction likely to be exacerbated by any component of the vaccine, acute disease at the time of enrollment. Gastroenteritis (GE) within 7 days, rotavirus gastroenteritis (RV-GE), family history of congenital or hereditary immunodeficiency, receipt of immunoglobulins and/or blood products (except hepatitis B immune globulin [HBIG]), neurologic disorders or seizures, or clinically significant pulmonary, cardiovascular, hepatic or renal functional abnormality. [3] Subjects were lost to follow-up rather than from parental withdrawal of consent, treatment failure, investigator opinion, protocol deviations, request of the sponsor, or breaks in the randomization code. [4] Some subjects had more than one major protocol deviation.
The analyses were limited to the VP7 genotypes; no G2 or G4 strains were detected during the trial. In the PP population, also shown in Table 2, when only RV-GE episodes where an associated stool sample contained at least one of the serotypes represented in RRV-TV, the RRV-TV group had 9 cases (2.01%), whereas the placebo group had 26 (5.9%) for a VE of 65.8% (95% CI, 27.8%–83.8%). When all the RV-GE episodes regardless of the serotype were counted, the RRV-TV group had 13 cases (2.91%), whereas the placebo group had 36 (8.14%), for a VE of 64.3% (95% CI, 33.6%–80.8%).

Although the investigators recognized the importance of determining severe RV-GE, this study was not powered to show a reduction in severe RV-GE as a primary endpoint. Severe RV-GE would be the primary endpoint of a future, and larger, Phase III clinical study. Of the severe RV-GE episodes (Vesikari score ≥11) in which the stool sample contained at least one of the serotypes represented in RRV-TV, in the ITT population, the RRV-TV group had 5 cases (1.00%) cases, whereas the placebo group had 10 (2.01%), for a VE of 50.2% (95% CI, −44.7%–82.9). When RV-GE episodes of any serotype were

### Table 1. Baseline Characteristics of the Randomized Subjects

<table>
<thead>
<tr>
<th></th>
<th>RRV-TV group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 500</td>
<td>N = 498</td>
</tr>
<tr>
<td>Gender</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>11.5 (7.28) d</td>
<td>11.8 (7.43) d</td>
</tr>
<tr>
<td>Birth weight (mean ± SD)</td>
<td>2.93 (0.392) kg</td>
<td>2.91 (0.387) kg</td>
</tr>
<tr>
<td>Gestational age (mean ± SD)</td>
<td>39.0 (0.97) wk</td>
<td>39.1 (0.96) wk</td>
</tr>
<tr>
<td>Body length (mean ± SD)</td>
<td>50.47 (3.471) cm</td>
<td>50.56 (3.078) cm</td>
</tr>
<tr>
<td>Body weight (mean ± SD)</td>
<td>3.16 (0.553) kg</td>
<td>3.13 (0.513) kg</td>
</tr>
<tr>
<td>Axillary temperature (mean ± SD)</td>
<td>36.85 (0.322)°C</td>
<td>36.85 (0.324)°C</td>
</tr>
</tbody>
</table>

Abbreviations: RRV-TV, rhesus/rhesus-human reassortant rotavirus tetravalent vaccine; SD, standard deviation.

### Table 2. Vaccine Efficacy (VE) of RRV-TV against RV-GE by Serotype

<table>
<thead>
<tr>
<th>Incidence of RV-GEa</th>
<th>RRV-TV</th>
<th>Placebo</th>
<th>VE, % (95% CI)</th>
<th>Pvalue†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat</td>
<td>(N = 500)</td>
<td>(N = 498)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV with any serotype</td>
<td>15</td>
<td>38</td>
<td>60.7 (29.5–78.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Serotype G1 alone</td>
<td>9</td>
<td>18</td>
<td>50.2 (−9.8–77.4)</td>
<td>.082</td>
</tr>
<tr>
<td>Serotype G3 alone</td>
<td>1</td>
<td>9</td>
<td>88.9 (13.0–96.6)</td>
<td></td>
</tr>
<tr>
<td>Serotype G9 alone</td>
<td>2</td>
<td>2</td>
<td>66.8 (−218–96.5)</td>
<td>.373</td>
</tr>
<tr>
<td>Serotype G10 alone</td>
<td>1</td>
<td>3</td>
<td>Not Estimated</td>
<td></td>
</tr>
<tr>
<td>Serotype G12 alone</td>
<td>0</td>
<td>1</td>
<td>Not Estimated</td>
<td></td>
</tr>
<tr>
<td>Untyped RV serotypes</td>
<td>2</td>
<td>2</td>
<td>0.4 (−604–85.9)</td>
<td>.100</td>
</tr>
<tr>
<td>Dual serotypesb</td>
<td>0</td>
<td>3</td>
<td>Not Estimated</td>
<td>.124</td>
</tr>
<tr>
<td>Pooled G1–G4</td>
<td>10</td>
<td>27</td>
<td>63.1 (24.6–82.0)</td>
<td>.004</td>
</tr>
<tr>
<td>Pooled G9, 10, 12</td>
<td>3</td>
<td>6</td>
<td>50.2 (−98.0–87.5)</td>
<td>.341</td>
</tr>
<tr>
<td>Per protocol</td>
<td>(N = 447)</td>
<td>(N = 442)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV with any serotype</td>
<td>13</td>
<td>36</td>
<td>64.3 (33.6–80.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Serotype G1 alone</td>
<td>8</td>
<td>17</td>
<td>53.5 (−6.7–79.7)</td>
<td>.070</td>
</tr>
<tr>
<td>Serotype G3 alone</td>
<td>1</td>
<td>9</td>
<td>89.0 (13.6–98.6)</td>
<td>.011</td>
</tr>
<tr>
<td>Serotype G9 alone</td>
<td>1</td>
<td>2</td>
<td>50.6 (−443–95.5)</td>
<td>.622</td>
</tr>
<tr>
<td>Serotype G10 alone</td>
<td>1</td>
<td>2</td>
<td>50.6 (−443–95.5)</td>
<td>.622</td>
</tr>
<tr>
<td>Serotype G12 alone</td>
<td>0</td>
<td>1</td>
<td>Not Estimated</td>
<td>.497</td>
</tr>
<tr>
<td>Untyped RV serotypes</td>
<td>2</td>
<td>2</td>
<td>0.1 (−605–86.0)</td>
<td>.100</td>
</tr>
<tr>
<td>Dual serotypesb</td>
<td>0</td>
<td>3</td>
<td>Not Estimated</td>
<td>.122</td>
</tr>
<tr>
<td>Pooled G1–G4</td>
<td>9</td>
<td>26</td>
<td>65.8 (27.8–83.8)</td>
<td>.003</td>
</tr>
<tr>
<td>Pooled G9, 10, 12</td>
<td>2</td>
<td>5</td>
<td>60.5 (−103–92.3)</td>
<td>.285</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RRV-TV, rhesus/rhesus-human reassortant rotavirus tetravalent vaccine; RV-GE, rotavirus gastroenteritis.

a No subject had more than 1 episode of RV-GE.
b Pairs included G1 and G10, G9 and G10, and G10 and G12.
† P-values were calculated using the 2-sided Fisher exact test (α = 0.05). For serotypes where no cases of RV-GE were observed for one of the treatment groups, no estimate of vaccine efficacy could be made.
counted, in the ITT population, the RRV-TV group had 7 severe RV-GE cases (1.4%) cases, whereas the placebo group had 15 (3.0%), for a VE of 53.5% (95% CI, −13.0 to 80.9). In the PP population in which the stool sample contained at least one of the serotypes represented in RRV-TV, the RRV-TV group had 4 severe RV-GE cases (0.8%), whereas the placebo group had 10 (2.3%), for a VE of 60.5% (95% CI, −9.9 to 87.5%). When episodes of any serotype were counted, in the ITT population, the RRV-TV group had 7 severe RV-GE cases (1.3%) cases, whereas the placebo group had 14 (3.2%), for a VE of 57.6% (95% CI, −9.3 to 83.6).

### Immunogenicity

We tested a subset of individuals for serum IgA rotavirus antibody at visit 1 (baseline), visit 2, and visit 3 (Table 3). Infants who received RRV-TV vaccine showed markedly higher serum anti-RV antibody titers both at visit 2 and visit 3. The ratio of anti-RV antibody GMT of visit 3 to baseline was more than 20 times larger for the RRV-TV group. A seroresponse to the vaccine, defined as a ≥4-fold rise in serum anti-RV IgA antibody titers, was observed in 59 of 123 (48%) vaccinees and 1 of 122 (0.8%) placebo recipients after dose 1 ($P < .001$) and in 68 of 120 (56.7%) vaccinees and 4 of 116 (3.4%) placebo recipients after dose 2 ($P < .001$). The immunogenicity of 2 doses of RRV-TV observed in this study (56.7% in RRV-TV recipients as compared to 3.4% in placebo recipients) is comparable to that observed in a study of Rotarix in Malawi and South Africa, but given at a later age [6]. Although serological responses to OPV in a subset of RRV-TV vaccinees and placebo recipients are described in more detail in the Supplementary data, no differences were found when examining the change from baseline to the visit 4 titers for any of the 3 types across the 2 groups.

### Safety

Rates of frequent adverse events recorded after administration of RRV-TV or placebo were similar between treatment groups as shown in Table 4. The most commonly experienced adverse events were malaria (RRV-TV, 77%; placebo, 78.3%), respiratory tract infections (RRV-TV, 55.6%; placebo, 55.8%), non-RV-related gastroenteritis (RRV-TV, 38.0%; placebo, 41.4%), and pyrexia (RRV-TV, 30.6%; placebo, 32.7%). For dose 1 on day 2, the mean change in baseline body temperature was $–0.22°C$ for the RRV-TV group and $–0.20°C$ for the placebo group.

### Table 4. Summary of Most Frequently Experienced Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>RRV-TV group N = 500, no. (%)</th>
<th>Placebo group N = 498, no. (%)</th>
<th>All subjects N = 998, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one AEPI*</td>
<td>482 (96.4)</td>
<td>480 (96.4)</td>
<td>962 (96.4)</td>
</tr>
<tr>
<td>Various infections and infestations</td>
<td>462 (92.4)</td>
<td>462 (92.8)</td>
<td>924 (92.6)</td>
</tr>
<tr>
<td>Malaria</td>
<td>385 (77.0)</td>
<td>390 (78.3)</td>
<td>774 (77.5)</td>
</tr>
<tr>
<td>Respiratory tract infections</td>
<td>278 (55.6)</td>
<td>278 (55.8)</td>
<td>556 (55.7)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>190 (38.0)</td>
<td>206 (41.4)</td>
<td>396 (39.7)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>191 (38.2)</td>
<td>179 (35.9)</td>
<td>370 (37.1)</td>
</tr>
<tr>
<td>Mucous stools</td>
<td>107 (21.4)</td>
<td>82 (16.5)</td>
<td>189 (18.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>64 (12.8)</td>
<td>63 (12.7)</td>
<td>127 (12.7)</td>
</tr>
<tr>
<td>Enteritis</td>
<td>35 (7.0)</td>
<td>24 (4.8)</td>
<td>59 (5.9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>153 (30.6)</td>
<td>163 (32.7)</td>
<td>316 (31.7)</td>
</tr>
<tr>
<td>Cough</td>
<td>126 (25.2)</td>
<td>145 (29.1)</td>
<td>271 (27.2)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>88 (17.6)</td>
<td>76 (15.3)</td>
<td>164 (16.4)</td>
</tr>
<tr>
<td>Rash</td>
<td>58 (11.6)</td>
<td>58 (11.6)</td>
<td>116 (11.6)</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>25 (5.0)</td>
<td>24 (4.8)</td>
<td>49 (4.9)</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; AEPI, adverse event post immunization; RRV-TV, rhesus/rhesus-human reassortant rotavirus tetravalent vaccine; RV-GE, rotavirus gastroenteritis.

* AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 12.0 dictionary.

* Each subject was counted once per system organ class and preferred term. Percentages are based on the total number of subjects in the treatment group from the safety population.

* Only non-RV-GE events are included; RV-GE is analyzed as part of study efficacy.
(P = .59). All temperatures were measured as axillary temperatures. Fevers were defined as >37.5°C. No febrile reactions to vaccination were detected.

The most common serious adverse event category in both groups was infections and infestations (6.8% in RRV-TV recipients and 8.8% in placebo recipients). No subject had intussusception. Overall, 29 deaths occurred during the study: 14 (2.8%) among the RRV-TV group and 15 (3.0%) among the placebo group (see Supplementary Table 1). An independent data safety monitoring board judged all serious adverse events to be unrelated to study intervention.

**DISCUSSION**

In this study, 2 doses of RRV-TV administered during the first and second months of life significantly reduced the incidence of RV-GE episodes in infants in rural Ghana. The intent was to conduct a clinical study in a real-world situation that would be encountered by a rotavirus vaccination program in a resource-poor area of Africa. Prior to this study of 998 neonates, safety data were available from 662 neonatal subjects who received rotavirus vaccine. (Sources include authors’ unpublished data and others [24, 42, 43]). Of these, 421 neonatal subjects received vaccine at a virus concentration identical to the RRV-TV dose used in Ghana. All these studies were double-blinded, placebo-controlled studies, but because they were primarily based on 3 doses of RRV-TV, the results are not directly comparable to this study. In Ghana, we measured a VE (60.7% ITT and 64.3% PP) against RV-GE of any severity associated with any serotype, in the context of an impoverished, breastfeeding population also receiving their routine EPI vaccines. Efficacy in this environment, starting with the first dose of RRV-TV in the neonatal period (when passively received maternal antibodies would be at their highest levels) demonstrates the potential of this approach both to reduce the burden of rotavirus disease in similar settings and simultaneously address the risk of intussusception.

The protection against RV-GE afforded by administration of 2 doses of RRV-TV beginning in the neonatal period in this population is comparable to that provided by Rotarix (2 or 3 doses) and RotaTeq (3 doses), which were recently evaluated among post-neonatal infant populations in Africa and Asia [6–8]. In Africa, vaccine efficacy for RotaTeq against rotavirus gastroenteritis in Kenya, Ghana, and Mali was 30.5% (95% CI, 16.7%–42.2%) for RV-GE of any severity and 64.2 (95% CI, 40.2%–79.4%) for severe RV-GE [8]. Rotarix demonstrated efficacy in South Africa and Malawi of 53.4% (95% CI, 42.1%–62.2%) against RV-GE of any severity and 61.2% (95% CI, 44.0%–73.2%) against severe RV-GE [6].

Administration of rotavirus vaccine during the neonatal period among infants in developing countries confers a number of potential advantages compared with administration in later infancy. First, initial contact with the EPI services occurs during the neonatal period, because BCG and OPV are scheduled to be given at this time. The second and final dose of RRV-TV also fits within the EPI schedule because its timing is within the same time frame as the second dose of OPV and the first dose of DPT-Hib-HepB scheduled at 6 weeks of age. Second, the burden of RV-GE is high in the first 6 months of life among children in developing countries, making early immunization advantageous in maximizing protection [10]. Third, because intussusception rarely occurs naturally in neonates, this makes the neonatal period an attractive time to administer the first dose of a live, oral rotavirus vaccine. Neonatal immunization had been evaluated in a rotavirus vaccine vaccine trial [44], and this strategy was proposed by rotavirus researchers a number of years ago as a means to minimize or eliminate the risk of intussusception [12, 23, 24]. Of note, Vesikari et al demonstrated in a double-blind placebo-controlled safety and immunogenicity trial of 90 infants who received RRV-TV vaccine at 0–4–6, 0–2–4, or 2–4–6 months of age that infants receiving the first dose in the neonatal period do not develop fever [43]. The efficacy results of the trial we report here support the neonatal strategy. Although this clinical trial was not powered to evaluate the relative risks of intussusception, there were no cases of intussusception in either RRV-TV or placebo groups.

Currently the US Advisory Committee on Immunization Practices (ACIP), US Food and Drug Administration (FDA), and the European Medicines Agency (EMA) recommend age-limits at which the first dose of a rotavirus vaccine should be administered. Recently, the WHO concluded that without age restrictions thousands of deaths due to rotavirus could be prevented, whereas there may only be a small additional increase in intussusception [45]. The WHO recommended that countries should develop country-specific plans for the removal of age restrictions.

Today it is known that, although the epidemiology of intussusception differs by geographical setting, the background rate of intussusception consistently peaks in infants aged approximately between 3 and 9 months across the world [46] including Ghana [47]. An alternative strategy related to age restrictions on administration of rotavirus vaccines should also encompass neonatal administration proposed here for the RRV-TV vaccine, which could potentially minimize or eliminate the risk of increased cases of intussusception and begin to provide protection to infants before the first dose of the currently licensed rotavirus vaccines is typically administered, thereby saving additional lives.

This first evaluation to our knowledge of a neonatally administered rotavirus vaccine in a developing country provides clear evidence to support further evaluation at which time additional parameters can be evaluated such as efficacy against severe RV-GE after 1 or 2 doses. Incorporation of this new rotavirus vaccine-dosing regimen into the EPI schedule would be programmatically feasible. An increased portfolio of rotavirus

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vaccines is desirable from both supply- and cost-perspectives; thus RRV-TV, which in this schedule offers protection earlier in life and is stable at room temperature <25°C [35, 48], represents an important addition.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyrighted. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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**Potential conflicts of interest.** T. V. has received advisory board fees from Merck, Sanofi Pasteur-Merck Sharp & Dohme, and Novartis, as well as served as a consultant to Pfizer and received payments for lecture service on speaker bureaus from Merck, Sanofi Pasteur-Merck Sharp & Dohme, Novartis, Pfizer, and Glaxo-Smith-Kline. N. C. received funds for serving on this study’s data safety monitoring board and has served on advisory boards for Glaxo-Smith-Kline and Sanofi Pasteur-Merck Sharp & Dohme and has had a grant from Glaxo-Smith-Kline for vaccine-related research. R. M. J. has in the last 3 years served as a site principal investigator at Mayo Clinic for 2 multisite vaccine studies funded by Pfizer, Inc, as well as a member of a data monitoring committee and a safety review committee for Merck & Co, Inc, for 3 vaccine studies. L. P. R. is the President of the nonprofit International Medica Foundation that has an exclusive license to RRV-TV from the US National Institutes of Health, Public Health Service. D. B. B. is an advisory board member for AstraZeneca and was an executive at Wyeth from 1999 to 2007; he has served as a consultant to many pharmaceutical companies on development and regulation of nonrotavirus products. L. P. R. is an employee of the International Medica Foundation, the sponsor of the clinical trial. All other 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.

**References**


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