ORIGINAL ARTICLE

Human Neonatal Rotavirus Vaccine (RV3-BB) to Target Rotavirus from Birth

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ABSTRACT

BACKGROUND

A strategy of administering a neonatal rotavirus vaccine at birth to target early prevention of rotavirus gastroenteritis may address some of the barriers to global implementation of a rotavirus vaccine.

METHODS

We conducted a randomized, double-blind, placebo-controlled trial in Indonesia to evaluate the efficacy of an oral human neonatal rotavirus vaccine (RV3-BB) in preventing rotavirus gastroenteritis. Healthy newborns received three doses of RV3-BB, administered according to a neonatal schedule (0 to 5 days, 8 weeks, and 14 weeks of age) or an infant schedule (8 weeks, 14 weeks, and 18 weeks of age), or placebo. The primary analysis was conducted in the per-protocol population, which included only participants who received all four doses of vaccine or placebo within the visit windows, with secondary analyses performed in the intention-to-treat population, which included all participants who underwent randomization.

RESULTS

Among the 1513 participants in the per-protocol population, severe rotavirus gastroenteritis occurred up to the age of 18 months in 5.6% of the participants in the placebo group (28 of 504 babies), in 1.4% in the neonatal-schedule vaccine group (7 of 498), and in 2.7% in the infant-schedule vaccine group (14 of 511). This resulted in a vaccine efficacy of 75% (95% confidence interval [CI], 44 to 91) in the neonatal-schedule group ($P<0.001$), 51% (95% CI, 7 to 76) in the infant-schedule group ($P=0.03$), and 63% (95% CI, 34 to 80) in the neonatal-schedule and infant-schedule groups combined (combined vaccine group) ($P<0.001$). Similar results were observed in the intention-to-treat analysis (1649 participants); the vaccine efficacy was 68% (95% CI, 35 to 86) in the neonatal-schedule group ($P=0.001$), 52% (95% CI, 11 to 76) in the infant-schedule group ($P=0.02$), and 60% (95% CI, 31 to 76) in the combined vaccine group ($P<0.001$). Vaccine response, as evidenced by serum immune response or shedding of RV3-BB in the stool, occurred in 78 of 83 participants (94%) in the neonatal-schedule group and in 83 of 84 participants (99%) in the infant-schedule group. The incidence of adverse events was similar across the groups. No episodes of intussusception occurred within the 21-day risk period after administration of any dose of vaccine or placebo, and one episode of intussusception occurred 114 days after the third dose of vaccine in the infant-schedule group.

CONCLUSIONS

RV3-BB was efficacious in preventing severe rotavirus gastroenteritis when administered according to a neonatal or an infant schedule in Indonesia. (Funded by the Bill and Melinda Gates Foundation and others; Australian New Zealand Clinical Trials Registry number, ACTRN12612001282875.)

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Despite evidence of the success of rotavirus vaccines, more than 90 million infants still lack access to a rotavirus vaccine.[1,2] Barriers to global implementation of the vaccine include cost, suboptimal efficacy in low-income countries, and lingering safety concerns.[3,4] An oral rotavirus vaccine administered at birth has the potential to address some of these challenges.

Rotavirus disease occurs early in life in infants in low-income countries.[5] A rotavirus vaccine administered at birth could provide early protection and could maximize the opportunity to complete a full vaccine schedule.[6] Administration of an oral vaccine at the time of birth presents a unique opportunity that may assist the uptake of the vaccine, since the presence of gastric acid is limited at birth, and environmental enteropathy is not yet established.[7,8] Because intussusception is rare in newborns, administration of the vaccine at birth may offer a safety advantage.[9]

The oral human neonatal rotavirus vaccine (RV3-BB) was developed from the human neonatal rotavirus strain RV3 (G3P[6]), which was identified in the stool of infants with asymptomatic infection.[10] Wild-type infection with RV3 was reported to provide protection from severe gastroenteritis in the first 3 years of life and resulted in strong heterotypic serologic responses to community rotavirus strains.[11,12] RV3 appears to be naturally attenuated and adapted to the newborn gut; it has been shown to replicate effectively despite the presence of maternal antibodies and despite the baby being breast-fed.[13] Vaccination with RV3-BB is intended to take advantage of the intrinsic characteristics of this novel strain for use in a strategy of vaccination at the time of birth. In a phase 2a trial in New Zealand, RV3-BB was immunogenic when administered according to a neonatal or infant schedule, and no safety concerns were identified.[14]

The primary objective of this trial was to assess the efficacy of three doses of RV3-BB against severe rotavirus gastroenteritis up to the age of 18 months. Secondary objectives included assessment of the efficacy against severe rotavirus gastroenteritis, immunogenicity, and safety of RV3-BB administered according to a neonatal schedule (first dose administered at 0 to 5 days of age) or an infant schedule (first dose administered at 8 to 10 weeks of age), with each of these trial groups compared with placebo. The vaccine efficacy was also assessed against rotavirus gastroenteritis of any severity and against severe gastroenteritis of any cause, up to the age of 12 months.

METHODS

TRIAL DESIGN AND OVERSIGHT

This phase 2b, randomized, double-blind, placebo-controlled trial involving 1649 participants was conducted from January 2013 through July 2016 in primary health centers and hospitals in Central Java and Yogyakarta, Indonesia. Indonesia is a low-middle–income country; the per capita gross regional product in Yogyakarta and Central Java is $2,164 to $2,326 (in U.S. dollars), and the mortality rate is 30 to 38 deaths per 1000 live births among children younger than 5 years of age.[15,16]

The protocol, which is available with the full text of this article at NEJM.org, was approved by the ethics committees at Universitas Gadjah Mada, the Royal Children's Hospital Melbourne, and the National Agency of Drug and Food Control, Republic of Indonesia. The use of a placebo was deemed to be acceptable because vaccination against rotavirus disease is not currently being implemented under the Indonesian National Immunization Program and the cost of the vaccines limits private purchase.[17]

The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and was monitored by an independent contract research organization (Quintiles). The conduct of the trial was overseen by Murdoch Children's Research Institute, with local input from PT Bio Farma. An independent data and safety monitoring board regularly reviewed the safety data. Data management was performed by Biophics Thailand. Statistical analysis was conducted by INC Research, Australia, and by an independent statistical consultant. The National Health and Medical Research Council, the Bill and Melinda Gates Foundation, and PT Bio Farma funded the trial but had no role in the trial design, data collection, or data interpretation, or in the decision to submit the manuscript for publication. All the authors reviewed the manuscript and vouch for the accuracy and com-

pleteness of the data and analysis and for the fidelity of the trial to the protocol.

PARTICIPANTS, RANDOMIZATION, AND BLINDING

Pregnant women provided preliminary written informed consent before a sample of cord blood was obtained. Final written informed consent was obtained from the parent or guardian after birth, before eligibility for the infant's participation in the trial was confirmed. Infants were eligible if they were healthy, full-term babies 0 to 5 days of age who had a birth weight of 2.5 to 4.0 kg. Eligible infants were randomly assigned, in a 1:1:1 ratio, to one of three groups: a neonatal-schedule vaccine group, an infant-schedule vaccine group, or a placebo group. Randomization was performed according to a computer-generated code with a block size of 6, with stratification according to province. The doses of vaccine (RV3-BB) or placebo were drawn into syringes for dispensing by a pharmacist who was located at the central pharmacy in each province and was aware of the trial-group assignments. Investigators, trial monitors, data managers, statisticians, and other trial staff, as well as the families of the participants, remained unaware of the trial-group assignments for the duration of the trial.

Participants received four 1-ml oral doses of vaccine or placebo according to their trial-group assignment, with doses administered at 0 to 5 days of age (dose 1), 8 to 10 weeks of age (dose 2), 14 to 16 weeks of age (dose 3), and 18 to 20 weeks of age (dose 4) (see Fig. S1 in the Supplementary Appendix, available at NEJM.org). Each of the two vaccine groups received three doses of RV3-BB and one dose of placebo. In the neonatal-schedule vaccine group, doses 1, 2, and 3 were RV3-BB and dose 4 was placebo, and in the infant-schedule vaccine group, dose 1 was placebo and doses 2, 3, and 4 were RV3-BB. Doses 2, 3, and 4 were preceded by a 2-ml dose of an antacid solution (Mylanta Original). Feeding was withheld for 30 minutes before and after each dose. The vaccine or placebo was administered at the same time as vaccines that were provided as part of the Indonesian National Immunization Program. Participants were followed by means of weekly telephone contact and monthly visits until the age of 18 months. All the participants received oral polio vaccine, with the exception of a subgroup of 282 participants (the first cohort of participants recruited) who received an inactivated polio vaccine.

VACCINE

Clinical trial lots of RV3-BB were prepared at Meridian Life Science to a titer of 8.3×10^6 to 8.7×10^6 focus-forming units per milliliter in a serum-free medium that was supplemented with 10% sucrose. Placebo consisted of the same medium with 10% sucrose and was visually indistinguishable from RV3-BB. Vials of vaccine or placebo were stored at −70°C until they were thawed within 6 hours before administration.

EFFICACY

Gastroenteritis of any severity was defined as having three or more stools that were looser than normal for a given child within a 24-hour period. The severity of gastroenteritis was defined on the basis of the Vesikari clinical severity scoring system (scores range from 0 to 20, with higher scores indicating more severe disease) that takes into account clinical symptoms (diarrhea and vomiting), clinical signs (elevated body temperature and dehydration), and type of treatment, if any.[18] A modified Vesikari score was applied in cases in which intravenous, nasogastric rehydration or 6 hours of supervised oral rehydration was scored as hospitalization, regardless of whether the rehydration was administered at a primary health center or at a hospital. Rotavirus gastroenteritis was defined as gastroenteritis coincident with the presence of rotavirus antigen in the stool that was detected with the use of an enzyme-linked absorbent assay (ProSpecT Rotavirus Microplate Assay, Oxoid). Severe rotavirus gastroenteritis was defined as rotavirus gastroenteritis with a modified Vesikari score of at least 11.

VACCINE RESPONSE AND IMMUNOGENICITY

Vaccine response (often called "vaccine take"), as evidenced by serum immune response or shedding of RV3-BB in the stool, was assessed in the first cohort recruited (282 participants). A blood sample was obtained from the cord (which represented baseline for the neonatal schedule), immediately before dose 2 of vaccine or placebo (which represented baseline for the infant schedule), 28 days after dose 3, and 28 days after dose 4. Serum rotavirus IgA antibody titers and serum

neutralizing antibody titers were measured with the use of previously described methods.[14,19] The methods used to detect serologic responses to RV3-BB also detect responses to wild-type rotavirus strains. To determine the background exposure to wild-type rotavirus strains, serum immune response and shedding of RV3-BB in the stool were also assessed in participants in the placebo group. The shedding of RV3-BB in the stool was detected with the use of a rotavirus VP6–specific reverse-transcriptase–polymerase-chain-reaction assay and confirmed by sequence analysis.[14] Vaccine response was defined quantitatively as a serum immune response (a serum rotavirus IgA antibody titer or a serum neutralizing antibody titer three times as high as the titer at baseline) 28 days after administration of the vaccine or shedding of RV3-BB between days 3 and 7 after administration of the vaccine. Cumulative vaccine response was defined as evidence of vaccine response after dose 1, 2, or 3 in the neonatal-schedule vaccine group and after dose 2, 3, or 4 in the infant-schedule vaccine group.

SAFETY

Vital signs were evaluated before, and in the 30 minutes after, administration of the vaccine or placebo. Parents reported the participant's temperature and solicited gastrointestinal and systemic symptoms on diary cards for 7 days after each dose. Parents were instructed to contact the trial staff immediately if blood was present in the stool so that further investigations to exclude intussusception, including ultrasonography, could be performed if clinically indicated. All unsolicited adverse events that were reported up to 28 days after administration of a dose of the vaccine or placebo were assessed according to the Division of AIDS grading table, version 1.0 (updated August 2009)[20] for the grading of laboratory abnormalities reported as adverse events and according to standard criteria defined in the protocol for the grading of clinical adverse events. A serious adverse event was defined as an adverse event that resulted in death or in new or prolonged hospitalization or was considered to be medically significant or life threatening and occurred within 28 days after a dose of vaccine or placebo. Causality and severity grading of adverse events were determined by the local Indonesian investigators.

STATISTICAL ANALYSIS

In the primary analysis of efficacy, we compared the percentage of participants in the neonatal-schedule vaccine group and infant-schedule vaccine group combined (combined vaccine group) who had an episode of severe rotavirus gastroenteritis during the period from 2 weeks after the administration of dose 4 through 18 months of age with the percentage in the placebo group who had such an episode during the same time period, using Pearson's chi-square test. The primary analysis was conducted in the per-protocol population, which included only the participants who received all four doses of vaccine or placebo within the visit windows. In a secondary analysis, which was conducted in the intention-to-treat population (all participants who underwent randomization), we compared events of severe rotavirus gastroenteritis that occurred from randomization through 18 months of age. Vaccine efficacy is presented as 1 minus the relative risk of an event in the vaccine group as compared with that in the placebo group and multiplied by 100, and its exact 95% confidence interval was calculated with the use of the Clopper–Pearson method.[21]

Efficacy was assessed in the neonatal-schedule vaccine group from 2 weeks after dose 3 of the vaccine to 12 months and to 18 months and in the infant-schedule vaccine group from 2 weeks after dose 4 of the vaccine to 12 months and to 18 months. The assessment schedule resulted in two different presentations of data in the placebo group (denoted as neonatal-schedule placebo group and infant-schedule placebo group). In the analysis of vaccine response, data were considered to be missing for a given participant only if data on all the components of the outcome were missing for that participant. The Kaplan–Meier method was used to estimate the cumulative risk of a first episode of severe rotavirus gastroenteritis from the time of randomization, and the trial groups were compared with the use of a log-rank test. All statistical tests were two-sided.

On the basis of local surveillance data, we assumed that 3% of the participants in the placebo group would have an episode of severe rotavirus gastroenteritis during the trial,[22,23] and we calculated that an enrollment target of 549 participants in each of the three trial groups would provide the trial with 80% power to reject

the null hypothesis of no difference between the combined vaccine group and the placebo group if the true efficacy of the vaccine was 60%, at a one-sided alpha level of 0.1. The estimated sample size would allow for a rate of nonadherence to the trial regimen of 10%. We calculated that a minimum of 282 participants would be required to reject the null hypothesis of no difference in the percentage of participants with vaccine response, at a two-sided alpha level of 0.05, assuming that 25% of participants in the placebo group would be exposed to rotavirus[14] and that 50% of the participants in each of the two vaccine groups would have vaccine response, and allowing for a rate of nonadherence of 10%.

RESULTS

Of the 1649 newborns who underwent randomization (intention-to-treat population), 1640 received at least one dose of vaccine or placebo (safety population) and 1588 (96%) were followed until they were 18 months of age (Fig. 1). The primary efficacy analysis was performed in the 1513 participants (92%) who received all four doses of vaccine or placebo within the visit windows (per-protocol population). The demographic characteristics at baseline and the age of receipt of the first dose of vaccine or placebo were similar across the three trial groups (Table S1 in the Supplementary Appendix).

VACCINE EFFICACY

In the per-protocol population, severe rotavirus gastroenteritis was reported in 28 of the 504 participants (5.6%) in the placebo group as compared with 21 of the 1009 participants (2.1%) in the combined vaccine group, resulting in a vaccine efficacy of 63% (95% confidence interval [CI], 34 to 80) at 18 months of age (P<0.001). Similar results were observed in the intention-to-treat analysis (vaccine efficacy, 60%; 95% CI, 31 to 76; P<0.001) (Table 1).

When three doses of RV3-BB were administered according to the neonatal schedule, the vaccine efficacy against severe rotavirus gastroenteritis was 75% (95% CI, 44 to 91; P<0.001) at 18 months of age (Table 1) and 94% (95% CI, 56 to 99; P=0.006) at 12 months of age (Table S2 in the Supplementary Appendix). The vaccine efficacy against rotavirus gastroenteritis of any severity in the neonatal-schedule vaccine group at 18 months of age was 63% (95% CI, 37 to 81; P<0.001) (Table S2 in the Supplementary Appendix).

In the infant-schedule vaccine group, the vaccine efficacy against severe rotavirus gastroenteritis was 51% (95% CI, 7 to 76; P=0.03) at 18 months of age (Table 1) and 77% (95% CI, 31 to 92; P=0.008) at 12 months of age (Table S2 in the Supplementary Appendix). The vaccine efficacy against rotavirus gastroenteritis of any severity at 18 months of age when RV3-BB was administered according to the infant schedule was 45% (95% CI, 12 to 69; P=0.01) (Table S2 in the Supplementary Appendix).

The time from randomization to the first episode of severe rotavirus gastroenteritis was significantly longer among the participants who received RV3-BB than among those who received placebo (Fig. 2). G3P[8] rotavirus was detected in the stool of 46 of the 49 participants in whom severe rotavirus gastroenteritis was reported.

VACCINE RESPONSE AND IMMUNOGENICITY

Cumulative vaccine response (a serum immune response or shedding of RV3-BB in the stool after the administration of any dose of RV3-BB) was detected in 78 of 83 participants (94%) in the neonatal-schedule vaccine group and in 83 of 84 participants (99%) in the infant-schedule vaccine group. The difference in the proportion of participants who had a cumulative vaccine response between the neonatal-schedule vaccine group and the neonatal-schedule placebo group was 0.52 (95% CI, 0.39 to 0.64; P<0.001), and the difference in the proportions between the infant-schedule vaccine group and the infant-schedule placebo group was 0.52 (95% CI, 0.40 to 0.63; P<0.001) (Fig. 3, and Table S3 in the Supplementary Appendix). A cumulative serum immune response was observed after the administration of any dose of RV3-BB in 76% of the participants in the neonatal-schedule vaccine group and in 87% of the participants in the infant-schedule vaccine group. A serum IgA response was observed in 66% of the participants in the neonatal-schedule vaccine group and in 81% of the participants in the infant-schedule vaccine group. After the administration of two doses, cumulative vaccine response was observed in 87% of the participants in the infant-schedule vaccine group

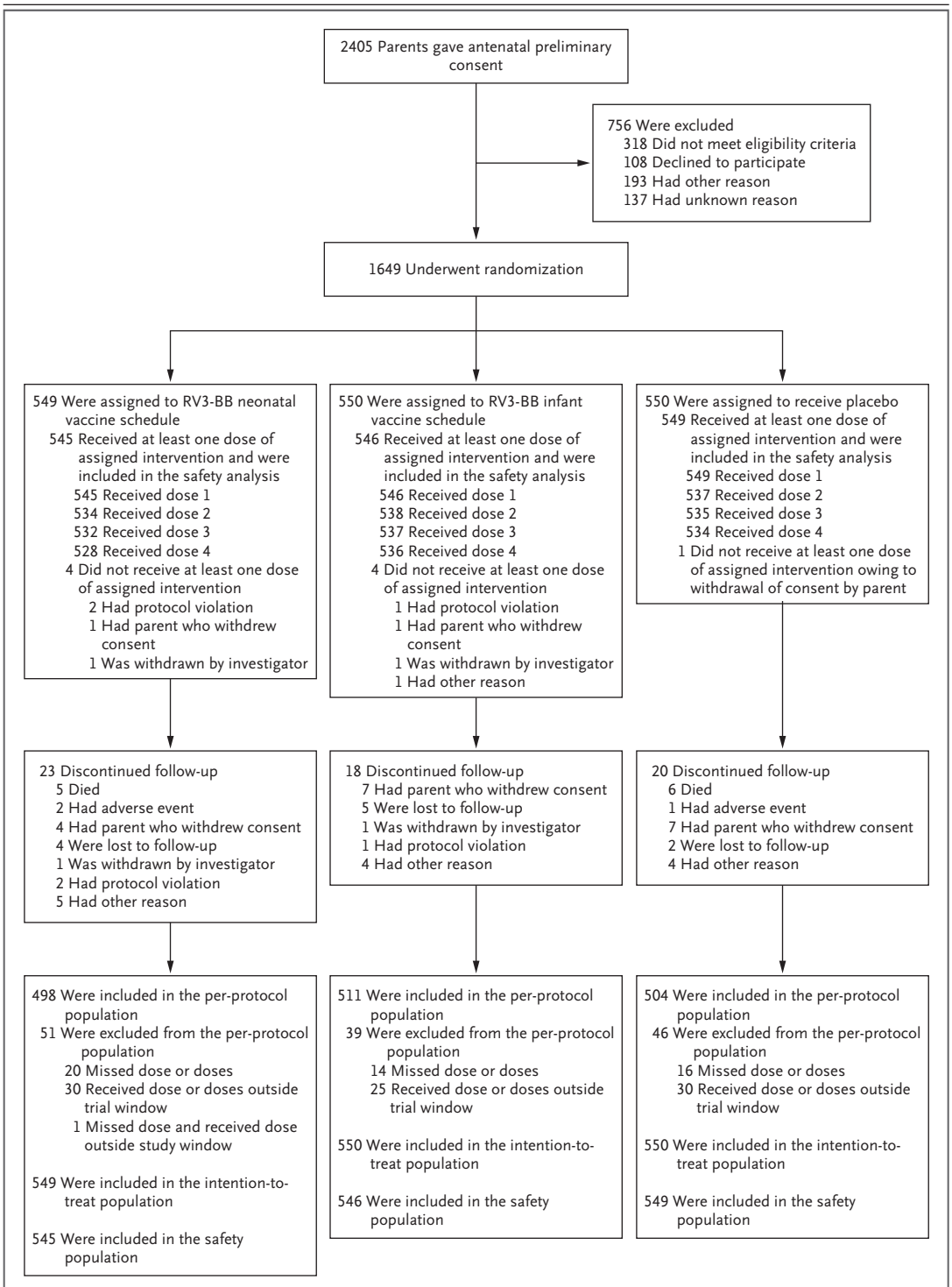
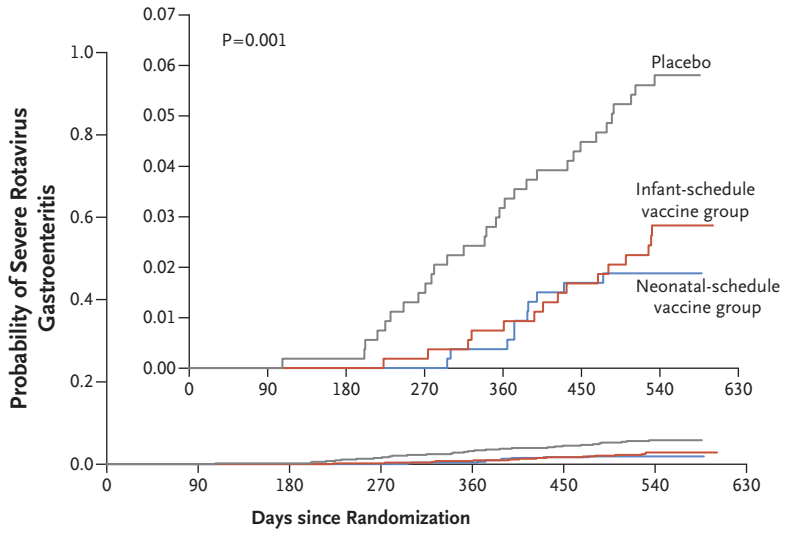


Figure 1. Randomization, Trial Assignment, and Follow-up.

Table 1. Vaccine Efficacy of RV3-BB against Severe Rotavirus Gastroenteritis at 18 Months of Age.*

Trial Group	Per-Protocol Population: No. of Participants	Per-Protocol Population: Participants with Episode of Severe Rotavirus Gastroenteritis	Per-Protocol Population: Vaccine Efficacy†	Per-Protocol Population: P Value	Intention-to-Treat Population: No. of Participants	Intention-to-Treat Population: Participants with Episode of Severe Rotavirus Gastroenteritis	Intention-to-Treat Population: Vaccine Efficacy†	Intention-to-Treat Population: P Value
		no. (%)	*% (95% CI)*			*no. (%)*	*% (95% CI)*	
Placebo group	504	28 (5.6)	—	—	550	31 (5.6)	—	—
Combined vaccine group	1009	21 (2.1)	63 (34–80)	<0.001	1099	25 (2.3)	60 (31–76)	<0.001
Neonatal-schedule vaccine group	498	7 (1.4)	75 (44–91)	<0.001	549	10 (1.8)	68 (35–86)	0.001
Infant-schedule vaccine group	511	14 (2.7)	51 (7–76)	0.03	550	15 (2.7)	52 (11–76)	0.02

* Severe rotavirus gastroenteritis was defined as rotavirus gastroenteritis that is scored as 11 or higher on the modified Vesikari clinical severity scoring system (scores range from 0 to 20, with higher scores indicating more severe disease).[18]
† The individual vaccine groups and the combined vaccine group were compared with the placebo group.



No. at Risk

Neonatal-schedule vaccine	549	541	537	534	531	522	468	0
Infant-schedule vaccine	550	540	539	538	532	526	452	0
Placebo	550	543	536	528	517	510	452	0

Figure 2. Severe Rotavirus Gastroenteritis from Randomization to 18 Months of Age in the Intention-to-Treat Population.

Severe rotavirus gastroenteritis was defined as rotavirus gastroenteritis that is scored as 11 or higher on the modified Vesikari clinical severity scoring system (scores range from 0 to 20, with higher scores indicating more severe disease).[18] The inset shows the same data on an expanded y axis.

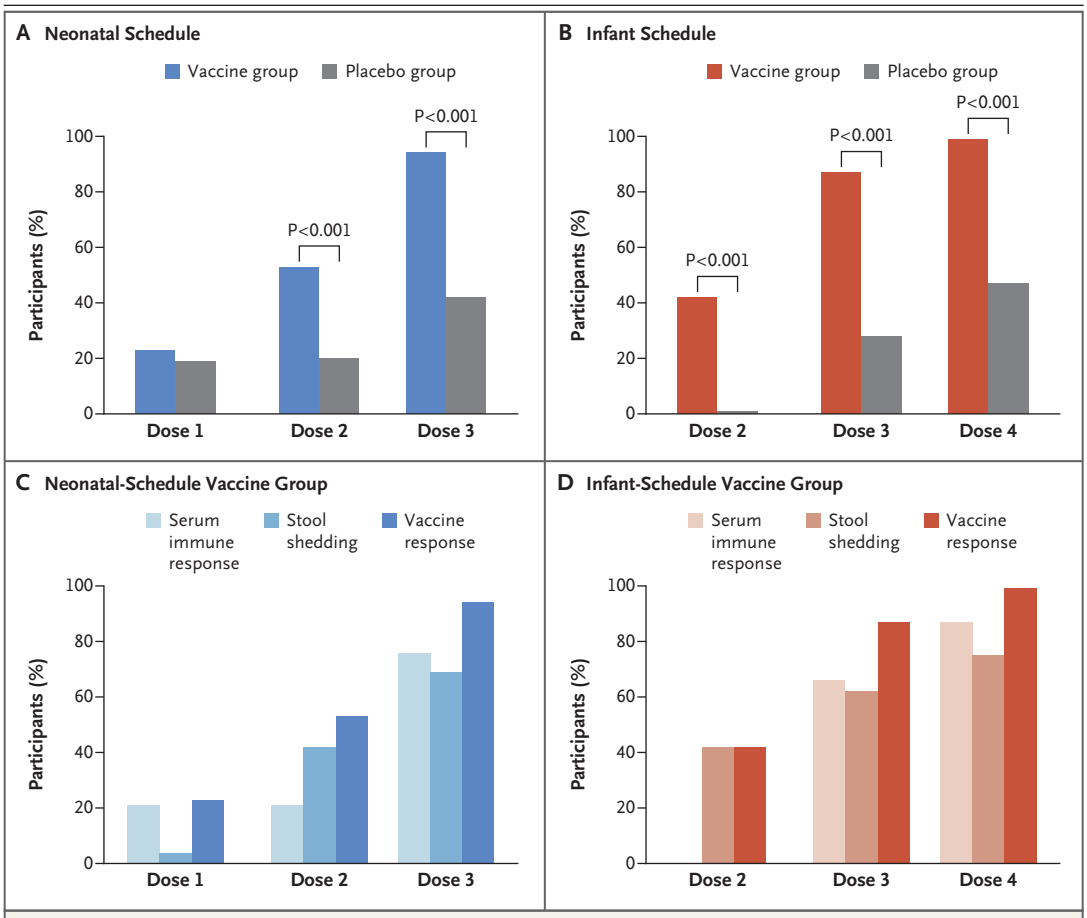


Figure 3. Cumulative Vaccine Response.

The cumulative vaccine response is presented according to the dose administration schedule in each vaccine group and the placebo group (Panels A and B) and according to individual components of vaccine response in the neonatal-schedule vaccine group and the infant-schedule vaccine group (Panels C and D). Vaccine response was defined quantitatively as a serum immune response (a serum rotavirus IgA antibody titer or a serum neutralizing antibody titer three times as high as the titer at baseline) 28 days after administration of the vaccine or shedding of RV3-BB between days 3 and 7 after administration of the vaccine. Cumulative vaccine response was defined as evidence of vaccine response after dose 1, 2, or 3 in the neonatal-schedule vaccine group and after dose 2, 3, or 4 in the infant-schedule vaccine group. In the neonatal-schedule vaccine group, doses 1, 2, and 3 were RV3-BB and dose 4 was placebo, and in the infant-schedule vaccine group, dose 1 was placebo and doses 2, 3, and 4 were RV3-BB. No assessment of serum immune response was conducted after administration of dose 2, which corresponded to the second dose of RV3-BB in the neonatal-schedule vaccine group and to the first dose of RV3-BB in the infant-schedule vaccine group.

as compared with 28% of the participants in the infant-schedule placebo group; the difference in the proportions of participants who had a cumulative vaccine response was 0.59 (95% CI, 0.45 to 0.71; P<0.001). This comparison could not be evaluated in the neonatal-schedule vaccine group because no blood sample was obtained at that time point. RV3-BB shedding was detected in 69% of the participants in the neonatal-schedule vaccine group and in 75% of the participants in the infant-schedule vaccine group.

SAFETY

The incidence of serious adverse events (Table 2) and unsolicited and solicited adverse events was similar across the trial groups (Tables S4 and S5 in the Supplementary Appendix). A total of 11 participants died (5 in the neonatal-schedule

Table 2. Adverse Events, According to Administration Schedule.

Events	Neonatal Schedule		Infant Schedule	
	Vaccine Group, Doses 1 to 3 (N=545)	Placebo Group, Doses 1 to 3 (N=549)	Vaccine Group, Doses 2 to 4 (N=538)	Placebo Group, Doses 2 to 4 (N=537)
Serious adverse events				
Events that occurred within 28 days after dose				
Total no. of events	28	24	6	17
No. of events, according to system organ class*				
Blood and lymphatic system disorders	1	1	0	0
Congenital, familial, and genetic disorders	3	2	0	1
Gastrointestinal disorders	6	6	1	8
Hepatobiliary disorders	6	3	0	0
Infections and infestations	8	6	5	2
Metabolism and nutrition disorders	2	1	0	0
Pregnancy, puerperium, and perinatal conditions	2	0	0	0
Respiratory, thoracic, and mediastinal disorders	0	5	0	6
Other important serious adverse events				
Intussusception	0	0	1†	0
Unsolicited adverse events				
Events that occurred within 28 days after dose				
Total no. of events	618	615	640	648
No. of common events, according to preferred term*‡				
Diarrhea	29	30	26	39
Upper respiratory tract infection	17	20	28	34
Constipation	27	22	24	24
Pyrexia	9	10	16	14
Miliaria	15	10	3	4

* Events were coded according to the *Medical Dictionary for Regulatory Activities*, version 19.0.
† This confirmed case occurred 114 days after the third dose of vaccine.
‡ Common events were events that were reported in at least 2% of participants in any group.

vaccine group and 6 in the placebo group); the serious adverse events that resulted in death are listed in Table S6 in the Supplementary Appendix. No episodes of intussusception were reported within the 21-day risk period after administration of any dose of vaccine or placebo, and one episode of intussusception occurred 114 days after the third dose of vaccine in the infant-schedule vaccine group.

DISCUSSION

Our results showed that the human neonatal vaccine RV3-BB provided protection against severe rotavirus gastroenteritis. When administered according to the neonatal schedule, RV3-BB had a vaccine efficacy of 94% at 12 months of age and 75% at 18 months of age, findings that support the administration of RV3-BB starting from the time of birth. These results compare favorably with the results of studies of licensed vaccines that were evaluated in similar low-income and low-middle–income countries in which the disease burden is high. The administration of two doses of Rotarix (GlaxoSmithKline) had a combined 1-year and 2-year vaccine efficacy of 34% in Malawi.[24] When a three-dose schedule was implemented, the combined 1-year and

2-year vaccine efficacy of Rotarix was 42.3% (in Malawi),[24] that of RotaTeq (Merck) was 17.6 to 63.9% (in Mali, Bangladesh, Vietnam, Ghana, and Kenya),[25,26] and that of Rotavac (Bharat Biotech) was 55.1% (in India).[27] Administration of three doses of Rotasil (Serum Institute of India) resulted in a vaccine efficacy of 66.7% after a mean follow-up of 9.8 months in Niger.[28]

The concept of vaccination at the time of birth is not new. Birth is an established immunization time point in many countries. The use of a neonatal dose was investigated in the early phase of development of the rotavirus vaccine but was not pursued because of concerns regarding inadequate immune responses and safety.[29-31] The VP4 proteins of human neonatal P[6] rotavirus strains have specific residues at the basal surface of VP8* that may allow them to adhere to cell-surface receptors in the newborn gut.[32] This characteristic may provide an advantage for the strategy of vaccination at the time of birth. The P[6] VP4 protein of RV3-BB may also offer an advantage in Africa and Asia where the Lewis-negative phenotype is common.[33] Lewis (*FUT3*) and secretor (*FUT2*) genes appear to mediate susceptibility to rotavirus infection.[33] P[8] rotaviruses infect only persons who are Lewis-positive and secretor-positive, whereas P[6] rotaviruses infect persons irrespective of the Lewis or secretor status.[34] This phenomenon may explain the high prevalence of disease caused by P[6] rotaviruses in Africa and the lower efficacy of vaccines with a P[8] genotype in this region.[35] RV3-BB is currently the only vaccine with a P[6] VP4 protein.

The incidence of adverse events was similar in the vaccine and placebo groups, and there were no evident safety concerns. Because intussusception is rare in newborns, the administration of a rotavirus vaccine at the time of birth may offer a safety advantage.[9] On the basis of a global baseline risk of intussusception that is estimated at 74 cases per 100,000 children younger than 1 year of age, we anticipated that 1.22 cases of intussusception would occur in our trial cohort.[36] Consistent with this estimate, one case of intussusception was identified in an 8.5-month-old infant in the infant-schedule vaccine group; the episode occurred 114 days after the third dose of vaccine. No episodes of intussusception were reported within the 21-day risk period[37] after administration of any dose of vaccine or placebo. However, this trial was not powered to detect the risk of a rare adverse event such as intussusception.

Unlike IgG, IgA is not transferred through the placenta, and the immune system of a newborn may not produce a significant serum IgA response after the administration of an oral vaccine, such as RV3-BB, at birth, despite evidence that the neonatal schedule is efficacious.[38] Similar dissonance has been shown with other vaccines administered during the newborn period.[39] An equinelike G3P[8] strain of rotavirus was responsible for most of the episodes of severe gastroenteritis in this trial and reflects the global emergence of this strain.[40] On the basis of the strong heterotypic serologic responses to community strains (G1 or G2 dominant) provided by the parent strain RV3,[11,12] it is anticipated that RV3-BB will also offer protection against a range of circulating rotavirus strains, but this assumption could not be assessed in the current trial.

Despite the success of rotavirus vaccines, challenges to global implementation remain and will need to be overcome if all infants are to be protected against rotavirus disease.

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APPENDIX

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