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A Field Study of the Safety and Efficacy of Two Candidate Rotavirus Vaccines in a Native American Population

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A double-blind, randomized, placebo-controlled trial was conducted to evaluate the safety and efficacy of a rhesus rotavirus vaccine and RIT 4237, a bovine rotavirus vaccine, in a Navajo population. Infants aged 2–5 months were randomized to receive one dose of either 10^4 pfu of the rhesus rotavirus vaccine or 10^8 pfu of the RIT 4237 vaccine or placebo. Eleven (10.2%) of 108 infants in the rhesus vaccine group, 11 (10.4%) of 106 in the RIT 4237 group, and 9 (8.4%) of 107 in the placebo group experienced rotavirus diarrhea during the follow-up period of 17 months. Thus, in this population, neither vaccine was efficacious in preventing rotavirus diarrhea.

Diarrhea is a leading cause of childhood mortality in developing countries, and rotavirus infections are one of the major causes of childhood diarrhea in both developing and developed countries [1–3]. Moreover, clinical illness caused by rotavirus diarrhea tends to be more severe (requiring hospitalization) than diarrhea caused by other organisms [4]. Therefore, development of an effective rotavirus vaccine has been assigned a high priority by the Institute of Medicine [5, 6]. A bovine rotavirus vaccine, the RIT 4237 derived from the Lincoln strain, and the rhesus rotavirus (RRV) vaccine derived from the rhesus monkey rotavirus strain MMU-18006 [7, 8] have undergone clinical trials in different geographic regions [9]. Both vaccines have been shown to provide varying levels of protection in some populations but none in others [9]. However, no study has directly compared the relative efficacy of these two vaccines in the same population. Therefore, we conducted a double-blind, randomized, controlled study to evaluate the safety and efficacy of RIT 4237 and RRV vaccines in preventing rotavirus diarrhea in a native American population.

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Study protocol was approved by the ethical review committees of the Indian Health Service, Johns Hopkins University School of Hygiene and Public Health, and National Institute of Allergy and Infectious Diseases and by the health boards of the three service units.

The opinions expressed herein are those of the authors and do not necessarily reflect the views of the Indian Health Service.

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Methods

Study site and population. The study population consisted of Navajo infants <6 months of age living on the Navajo reservation, which occupies 64,750 km^2. Most of the reservation is located in Arizona and New Mexico. Health care is provided by the Indian Health Service (IHS) at no cost to the population via hospitals and clinics located throughout the reservation in eight geographic regions known as service units. For this study, infants from three service units in Arizona—Tuba City, Fort Defiance, and Kayenta—were recruited.

Recruitment. From September 1985 to February 1987, parents or guardians of infants residing at one of the study sites were contacted. Infants 2–5 months old were enrolled into the study if the infant had no known chronic underlying illness or immunodeficiency.

Randomization. By use of a table of random numbers, infants were randomized in blocks of nine to one of three groups. Infants were given either RRV vaccine, RIT 4237 vaccine, or placebo.

Administration of vaccine and placebo. The passage history of RRV and RIT vaccines has been described previously [7, 8]. Infants in the RRV group received 10^4 pfu of vaccine suspended in 1 ml of a soy-based lactose-free formula (Nursoy; Wyeth Laboratories, Philadelphia). The Nursoy did not contain any detectable rotavirus-specific antibodies. Infants randomized to the RIT 4237 group were given 10^8 pfu of vaccine suspended in 1 ml of Nursoy, whereas placebo recipients were given 1 ml of Nursoy. Before administration of the vaccine or placebo, 30 ml of Nursoy buffered with 400 mg of sodium bicarbonate was given orally. The vaccines or placebo were given ≥3 weeks before or after the infant's oral polio immunization.

Monitoring of adverse reactions. Infants were visited by a field worker daily for 5 days after immunization. During these visits a standard questionnaire was administered to monitor adverse reactions to the vaccine or placebo. In addition, parents were requested to record their infant's rectal temperatures twice daily for 5 days after immunization.

Monitoring of diarrheal illness. The parents or guardians were requested to record daily the occurrence of all diarrheal illness of

the child, using a standard form. They were also asked to collect a stool sample if the infant had diarrhea. A field worker visited each home weekly from the day the vaccine or placebo was administered until the study was stopped. During the home visit, the field worker reviewed the information recorded by the parents or guardians on the standard form. In addition, a stool sample was collected if a diarrheal episode occurred on the day of the home visit or if diarrhea occurred within the previous week. A stool sample also was obtained if the infant was seen any time in the hospital or clinic for a diarrheal illness. Whole stools were collected whenever possible.

One aliquot of stool was placed in a culturette containing modified Stuart's bacterial transport medium (American Scientific Products, Tempe, AZ) for the detection of bacterial pathogens. A second aliquot was tested for the presence of rotavirus antigen as described below. If whole stool was not available, two rectal swabs were obtained. One swab was placed in a culturette to test for the presence of bacterial pathogens and the other in 1 ml of 10% PBS to test for the presence of rotavirus antigen. Stool samples were transported to the laboratory within 4 h after collection.

Routine collection of serum and stool samples. Serum samples were collected at vaccination and 1 and 12 months later. These samples were tested for the presence of rotavirus-specific IgA antibodies by ELISA as described previously [10–12]. Stool samples were collected from all infants immediately before administration of vaccine or placebo. These samples were also tested for the presence of rotavirus antigen by ELISA as described previously [10–12].

Processing of stool for bacterial pathogens. Stool cultures were routinely examined for *Shigella*, *Salmonella*, *Campylobacter*, *Aeromonas*, and *Plesiomonas* species, enterotoxigenic *Escherichia coli* (ETEC), and rotavirus. Stools or rectal swabs were inoculated directly onto xylose-lysine-deoxycholate (XLD) agar, Hektoen agar, MacConkey agar, and Butzler *Campylobacter* agar and into tubes of Gram-negative (GN) broth, Selenite F broth, and alkaline peptone water (APW). Plates were incubated at 37°C for 18–24 h, except for the *Campylobacter* agar, which was incubated at 42°C for 48 h in an anaerobic jar with a gas-pak hydrogen–carbon dioxide generator. After overnight incubation, the GN broth was subcultured on XLD and Hektoen agar plates, the Selenite F broth on an XLD plate, and the APW on an ampicillin (10 μg/ml) blood agar plate. Suspicious colonies were isolated and identified by conventional methods. For the identification of ETEC, five lactose-positive colonies were picked from the MacConkey plates, put in nutrient agar slants in screw-capped bottles, and stored at room temperature until assayed for heat-labile and heat-stable enterotoxins by ELISA [13, 14]. Only a 20% random sample was tested for ETEC.

For rotavirus antigen detection, duplicate rectal swabs or aliquots of stool were placed in PBS and frozen at −70°C. These were periodically transported to the Laboratory of Infectious Diseases at the National Institute of Allergy and Infectious Diseases (Bethesda, MD) for rotavirus-confirmatory ELISA assays.

Stool specimens were not routinely examined for ova and parasites, since previous experience (unpublished data) has shown that parasitic infections in children of this age in this population are extremely rare.

Rotavirus strains were serotyped by ELISA using serotype-specific monoclonal antibodies (VP7) as described by Taniguchi et al. [15].

Definitions. Diarrhea was defined as three or more watery stools in a 24-h period. Infants were considered to have a serologic response to vaccination if there was a fourfold rise in antibody titers in the post compared with the prevaccination sample. For calculating vaccine efficacy, only cases that occurred 14 days after vaccination were included.

Decision to stop or continue trial. An independent committee consisting of two pediatric infectious disease experts, one epidemiologist, and one biostatistician from Johns Hopkins University (Baltimore) was assembled to monitor the progress of the study and to make recommendations for stopping or continuing the trial. No member of the monitoring committee participated in any aspect of conducting the trial. Every 6 months the number of cases of rotavirus diarrhea and adverse reactions seen after administration of vaccine or placebo were reported to the committee.

Statistical methods. Two-tailed Fisher's exact test and χ^2 test were used for comparison of frequencies and proportions. A log rank test was used to test for a difference in time to vaccine failure. Analysis of variance was done on appropriate variables among the groups.

Results

During the study period 332 infants were enrolled. Eleven (3.3%) moved off the reservation or were not available for follow-up; thus, 321 (96.7%) completed the study protocol.

In February 1987, when 31 cases of rotavirus diarrhea had occurred, the monitoring committee decided to break the study code because of the possibility of having a statistically significant difference in the attack rates of rotavirus diarrhea among the groups. After examining the distribution of cases of rotavirus diarrhea, the committee recommended terminating the trial since there was no evidence of protection by either vaccine.

Selected characteristics of the groups. One hundred eight infants were in the RRV group, 106 were in the RIT 4237 group, and 107 in the placebo group (table 1). The male-to-female ratio, number enrolled at each study site, age at time of immunization, and number breast-fed at time of immunization were similar among the groups.

Adverse reactions. During the first 5 days after vaccina-

Table 1. Comparison of baseline covariates by study group.

	Vaccine group		
	RRV	RIT 4237	Placebo
No. of infants	108	106	107
No. male	54	59	54
No. enrolled at			
Tuba City	43	45	44
Fort Defiance	43	41	40
Kayenta	22	20	23
Age (months) at immunization			
2	0	2	0
3	51	39	42
4	25	15	21
5	32	50	44
No. breast-feeding at immunization	44	42	44

NOTE. No difference between groups was statistically significant. RRV = rhesus rotavirus.

Table 2. Adverse reactions to vaccination 1–5 days after immunization.

Reaction	Vaccine group		
	RRV	RIT 4237	Placebo
Diarrhea	18 (17)	16 (15)	19 (18)
Temperature ≥38.3°C	12 (11)	9 (8)	8 (7)
Runny nose	41 (38)	40 (38)	35 (33)

NOTE. Data are no. (%) exhibiting reaction. No difference between groups was statistically significant. RRV = rhesus rotavirus.

tion, the number of infants experiencing diarrhea, temperatures ≥38.3°C, or runny nose was similar in the three groups (table 2). The incidence of adverse reactions did not vary with age in any group. Also, there was no clustering of adverse reactions on any day after immunization.

Diarrheal illness. During the 17-month study period, infants in the RRV, RIT 4237, and placebo groups experienced 3.9, 4.1, and 3.8 episodes of diarrhea per person-year, respectively (table 3). There were 11 episodes of rotavirus diarrhea in the RRV group, 11 in the RIT 4237 group, and 9 in the placebo group. The proportion of cases and the time interval between administration of vaccine or placebo and disease were not significantly different for the three groups ($P = .87$ and $P = .90$, respectively). One infant with rotavirus diarrhea in the RIT 4237 group had a simultaneous *Campylobacter* infection. No others had simultaneous infections with other bacterial pathogens. The proportion of infants with rotavirus diarrhea who had associated symptoms, such as fever ≥38.3°C, vomiting, more than five watery stools per day, and duration of illness ≥5 days was similar in the three groups. Of the 11 infants in each vaccine group, 4 receiving RRV vaccine and 5 receiving RIT 4237 vaccine had rotavirus diarrhea >6 months after immunization, whereas all 9 infants in the control group had rotavirus diarrhea within 6 months of receiving placebo and none after 6 months ($P = .07$). Among the diarrheal episodes for which stool samples were tested, causative agent was identified in 43 (11%) of 390 in the RRV group, 42 (11%) of 387 in the RIT 4237 group, and 58 (16%) of 359 in the placebo group. Rotavirus, ETEC, and *Campylobacter* species were the most common pathogens identified.

Serologic responses. Of the 97 infants in the RRV group, 61 (63%) and 40 (47%) of the 85 RIT 4237 and 16 (17%) of 92 placebo recipients had a seroresponse 1 month after im-

Table 3. Diarrheal episodes among children receiving rotavirus vaccine or placebo.

	Vaccine group		
	RRV	RIT 4237	Placebo
No. of infants	108	106	107
Person-years of observation	130	125	125
No. of episodes of diarrhea during study period	397	404	383
No. of episodes/person-years at risk	3.9	4.1	3.8
No. of episodes of rotavirus diarrhea*	11	11	9
No. of such episodes with symptom			
Fever ≥38.3°C	1	4	2
Vomiting	8	3	5
≥5 watery stools/day	8	6	8
≥4 days duration	6	6	8
≥5 days duration	2	3	2
No. requiring hospitalization	2	3	0
Time (months) after immunization when rotavirus diarrhea occurred			
1–3	5	4	7
4–6	2	2	2
7–13	4	5	0
No. of pathogens identified in diarrheal episodes	390	387	359
Rotavirus†	14 (4)	14 (3)	10 (3)
ETEC‡	12/107 (11)	8/86 (9)	13/89 (15)
Campylobacter species	7 (2)	11 (3)	1 (0.3)
Shigella species	6 (2)	3 (1)	5 (1)
Salmonella species	2 (0.5)	2 (0.5)	11 (3)
Aeromonas species	2 (0.5)	4 (1)	2 (0.5)

NOTE. Data in parentheses are percentages. No difference between groups was statistically significant. RRV = rhesus rotavirus; ETEC = enterotoxigenic *Escherichia coli*.

* Does not include cases within 14 days or second cases for the same child.

† Includes cases that occurred within 14 days of vaccination and second cases for the same child.

‡ Only a random sample of stool specimens was tested.

Table 4. Serologic responses by vaccine group and breast-feeding practice.

	Vaccine group						
	RRV		RIT 4237		Placebo		*P*
No. with acute and convalescent titers done	97		85		92		
No. (%) with serologic response	61	(63)*	40	(47)	16	(17)	<.001
Proportion (%) of breast-fed infants with serologic response	32/45	(71)†	15/34	(44)‡	5/41	(12)§	<.001
Proportion (%) of non-breast-fed infants with serologic response	29/52	(56)	25/51	(49)	11/51	(22)	<.001

NOTE. RRV = rhesus rotavirus.
* $P = .046$ compared with RIT 4237 group. P = † .18, ‡ .82, § .37 compared with non-breast-fed infants in same vaccine group.

munization ($P < .001$) (table 4). There were no statistically significant differences in the seroresponse to vaccination in breast-fed compared with non-breast-fed infants in any group.

Serotypes of rotavirus diarrhea. Sufficient antigen was present in 15 (48%) of the 31 rotavirus-positive specimens for serotyping (6 RRV group, 6 RIT 4237 group, and 3 placebo group). Most specimens were stool swabs. Nine were serotype 1 (4 RRV group, 2 RIT 4237 group, and 3 placebo group), four were serotype 2 (2 RRV group, 2 RIT 4237 vaccine group, and 0 placebo group), and one each was serotype 3 (RIT 4237 group) and serotype 4 (RIT 4237 group).

Discussion

These data indicate that neither RRV nor RIT 4237 vaccine protected infants from rotavirus diarrhea in this population.

Recent studies from Venezuela have demonstrated that RRV vaccine was 93% efficacious in preventing rotavirus diarrhea in children aged 1–5 months [16]. Moreover, in that study the vaccine was 100% efficacious in preventing rotavirus diarrhea in infants aged 1–10 months. In contrast, the RRV vaccine failed to protect young infants in our study and in a recent study in Rochester, New York [9]. We found no evidence of protection by the RRV vaccine when the diarrheal episodes were classified by use of different parameters of severity including those suggested by Hjelt et al. [17] and Flores et al. [16].

The lack of protection by RRV vaccine in our study may be due to the lack of heterotypic protection provided by this vaccine. In Venezuela, where this vaccine was highly efficacious, the prevalent rotavirus serotype was type 3, the same serotype as the vaccine. In contrast, in Arizona most rotaviruses belonged to serotypes 1 or 2. There were not enough cases of serotype 3 disease for us to evaluate the efficacy of RRV vaccine in preventing diarrhea due to serotype 3 rotavirus.

Our study and studies in The Gambia [18] and Rwanda [19] have shown that the RIT 4237 vaccine provided little or no protection. In contrast, it was 50%–58% efficacious for preventing all rotavirus diarrheas and 82%–88% efficacious against severe rotavirus diarrhea in Finland [20, 21]. In a recent study in Peru [22], three doses of RIT 4237 vaccine were shown to provide 58%–75% protection against severe rotavirus illness.

The lack of protection provided by the RIT 4237 vaccine cannot be explained by the difference in prevalent serotypes in this study compared with previous studies. In one of the Finnish studies, the RIT 4237 vaccine was shown to provide protection against rotavirus belonging to subgroup II, which includes serotypes 1, 3, and 4 [21]. In the other [20], this vaccine was shown to protect against infections due to serotype 1, with a trend towards protection against serotypes 2 and 3. In the Peru study, up to 89% protection was provided against severe diarrhea due to serotype 1 rotavirus. The protective efficacy of this vaccine in these populations might be because children were older when vaccinated and thus may have undergone prior natural infection, causing a broader antibody response to vaccination. Since the oral polio vaccine was given at least 3 weeks before or after the rotavirus vaccines, it is unlikely to have interfered with the immune responses to the rotavirus vaccines.

It is difficult to directly compare the seroresponses seen in our and other studies in different geographic regions because different laboratory tests were used. In addition, the ages of the individuals vaccinated were different in the various studies. In a recent study in Finland [8], several laboratory tests were used (complement fixation, IgG and IgM ELISA, and neutralization) to assess the seroresponse in infants immunized with either the RRV or RIT 4237 vaccine. A seroresponse was noted by at least one serologic test in 88% of infants in the RRV group and 75% in the RIT 4237 group. In our study, 63% of RRV vaccine recipients and 47% of RIT 4237 vaccine recipients had rotavirus-specific IgA responses; we used no other laboratory serologic tests.

Breast-feeding did not seem to alter the seroresponses to either vaccine in our study. In a previous study conducted in Finland, breast-fed infants were shown to have a poorer seroresponse than did formula-fed infants[23]. The reasons for the difference in seroresponse among breast-fed infants in the Finnish study and ours is not known.

It is possible that both vaccines provided partial protection for the first 6 months but that this protection did not extend beyond the 6-month period. This conclusion is suggested by the finding that none of the placebo recipients had disease 6 months after immunization whereas ~40% of the episodes in the vaccine groups occurred after 6 months.

In contrast to our findings, studies from developed countries have shown that about one-third of infants experience adverse reactions to a comparable dose of RRV vaccine [8]. The low rate of adverse reactions seen in Navajo infants may be related to high levels of preexisting maternal antibodies in this population (data not shown) and the younger age at which they were vaccinated.

We conclude that in the Navajo population neither RRV nor RIT vaccine provided protection against rotavirus diarrhea. The lack of protection may be related to the prevalent serotypes of rotavirus in this population, the lack of heterotypic protection provided by the vaccines, and the relatively young age of the infants at the time of vaccination; thus, the infants may not have had a broad antibody response following vaccination.

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