Efficacy and safety of high-dose rhesus-human reassortant rotavirus vaccine in Native American populations

Mathuram Santosham, MD, MPH, Lawrence H. Moulton, PhD, Raymond Reid, MD, MPH, Janné Croll, BS, Robert Weatherholt, BS, Richard Ward, PhD, John Forro, PhD, Edward Zito, PhD, Michael Mack, PhD, George Brenneman, MD, and Bruce L. Davidson, MD, MPH

Objectives: We compared the efficacy, safety, and immunogenicity of a rhesus rotavirus tetravalent vaccine (RRV-TV), a rhesus rotavirus monovalent (serotype 1) vaccine (RRV-S1), and placebo in healthy American Indian infants for two rotavirus seasons.

Study design: Infants aged 6 to 24 weeks were enrolled in a randomized, double-blind efficacy study. Infants were orally administered RRV-TV (4×10^5 plaque-forming units per dose), RRV-S1 (4×10^5 plaque-forming units per dose), or placebo at 2, 4, and 6 months of age. Stools collected during episodes of gastroenteritis were tested for detection of rotavirus antigen. A total of 1185 infants received at least one dose of a study vaccine or placebo, and 1051 received all three doses according to the protocol.

Results: During the first year of surveillance, the estimates of vaccine efficacy (with 95% confidence interval) for preventing rotaviral gastroenteritis were 50% (26, 67) for RRV-TV and 29% (–1, 50) for RRV-S1. In this population only 6% of rotaviral gastroenteritis episodes among placebo recipients were associated with type G1 disease. For severe disease the estimates of vaccine efficacy were higher: 69% (29, 88) for RRV-TV and 48% (–4, 75) for RRV-S1.

Conclusions: These data indicate that RRV-TV is moderately efficacious in preventing all episodes of gastroenteritis caused by rotavirus and is most efficacious against the severe disease characteristic of rotaviral illness. (J Pediatr 1997;131:632-8)

Diarrhea is a leading cause of morbidity and death in developing countries.[1,2] Even in the United States, there are approximately 300 to 400 deaths and 200,000 hospitalizations per year for diarrhea.[3] Rotavirus is the leading cause of diarrhea both in developed and developing countries,[4-7] especially in infants less than 1 year of age. Recently both a monovalent rhesus RV vaccine and reassortant RRV vaccines have undergone evaluation in developed and developing countries.[8-14] The tetravalent (G1-G4) RVV contains the three reassortant viruses expressing human VP7 serotypes G1, G2, and G4 combined with RRV, which has a VP7 immunologically similar to that of human serotype G3.[15] These are the four prevalent

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G serotypes that cause the majority of human disease. The monovalent formulation of the vaccine contains the rhesus-human strain G1 reassortant RV.

Both the monovalent and the tetravalent formulations of the RRVs appear to be safe and to provide moderate protection against mild disease and greater protection against severe disease in the general U.S. population.[8,9]

CI	Confidence interval
ELISA	Enzyme-linked immunosorbent antigen reduction
GE	Gastroenteritis episode
PFU	Plaque-forming units
RRV	Rhesus rotavirus vaccine
RRV-S1	Rhesus-human strain G1 reassortant rotavirus
RRV-TV	Rhesus rotavirus tetravalent vaccine
RV	Rotavirus

Certain American Indian populations are known to be at high risk of having severe RV diarrhea.[16,17] We evaluated the safety and efficacy of three doses of RRV-TV and RRV-S1 given at 4×10^5 plaque-forming units per dose among four American Indian populations.

From the Departments of International Health, Biostatistics, and Maternal and Child Health, Johns Hopkins University School of Hygiene and Public Health, and the Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, Maryland; J. N. Gamble Institute of Medical Research, Cincinnati, Ohio; Wyeth-Ayerst Research, Radnor, Pennsylvania; and the Division of Pulmonary and Critical Care Medicine, Philadelphia, Pennsylvania.

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Reprint requests: Mathuram Santosham, MD, Center for American Indian and Alaskan Native Health, Department of International Health, Johns Hopkins University School of Hygiene and Public Health, 615 N. Wolfe St., Baltimore, MD 21205.

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METHODS

The study was conducted from Jan. 1, 1992, to Jan. 31, 1994. The study population consisted of infants residing on the Gila River Indian Reservation (Arizona), the Navajo Indian Reservation (Arizona and New Mexico), the San Carlos Apache Indian Reservation (Arizona), and the Fort Apache Indian Reservation (Arizona). The study protocol was approved by the Johns Hopkins University Committee on Human Research, the Indian Health Service, and the Tribal Councils and Health Boards of the respective tribes.

Infants aged 6 to 24 weeks with no underlying illness whose parents signed a written informed consent were included in the study. Infants were excluded if they had evidence of a clinically significant chronic disease, if there was an individual with immunosuppression in the household, or if the subject was involved in any other vaccine trial. Infants were randomly assigned in blocks of six to receive either RRV-TV (containing 1×10^5 PFU of each of serotypes G1, G2, and G4 RRV reassortants and the RRV G3 strain), or 4×10^5 PFU of RRV-S1 (containing serotype 1 only), or placebo consisting of tissue culture medium. The vaccines and placebo were resuspended in 3 ml of sodium-citrate bicarbonate buffer, and 2.5 ml of the suspension was administered orally. The vaccine or placebo doses were separated by at least 3 weeks. Simultaneous administration of routine childhood immunizations such as diphtheria, tetanus, and pertussis vaccination and oral polio vaccination was permitted but not required. The vaccine or placebo doses were administered between Jan. 1, 1992, and Oct. 5, 1992. Blood samples (3 to 5 ml) were obtained just before administration of the first dose of the vaccine or placebo, 1 month after the third dose, and in January 1993. Sera from 201 randomly selected children were assayed for neutralizing antibodies against RRV and human rotavirus strains G1 (Wa), G2 (DS-1), G3 (P), and G4 (ST-3) by an enzyme-linked immunosorbent antigen reduction assay as described previously.[18] In addition, sera from all subjects who had a sufficient volume of all three specimens were analyzed for anti-rotavirus IgA.[19] A fourfold or greater rise in antibody titer, in comparison with the preimmunization titer, was considered to be a seroresponse.

Surveillance for Vaccine Safety

The parents/guardians of the study participants were asked to record the following information for 5 days after vaccination for each infant: (1) rectal temperature in the evening, (2) number and consistency of stools, (3) vomiting, (4) level of activity (decreased, irritable, or normal), (5) occurrence of any skin rash, and (6) respiratory symptoms. In addition, the parents/guardians were instructed to bring the infant to the hospital or clinic for evaluation if seizures, high fever, or any other unusual symptoms developed. This information was recorded on a standard form by the parents/guardians. Study personnel (field-workers) who were fluent both in English and in the native language visited each of the homes and reviewed the data forms with the parents/guardians. In addition, field-workers conducted daily home visits in a sample of infants who lived in close proximity to the hospital (n = 160) for the first 5 days after each dose of the vaccine to collect the same information. All hospitalizations and deaths of study subjects were recorded during the study.

Surveillance for Gastroenteritis

Field-workers made weekly home visits to study subjects to collect information regarding gastroenteritis episodes. If the parent/guardian reported a GE (three or more looser-than-normal or watery stools or at least one occurrence of vomiting in a 24-hour period) during the previous week or since the last visit, the following information was collected: (1) number and consistency of stools, (2) presence of blood in the stools, and (3) vomiting frequency. If a GE occurred, stool specimens were collected anytime from the onset of the GE up to 7 days after the GE resolved. These specimens were stored at –20° C until collected by a field-worker. The field-worker transported the stool specimens to the clinic or hospital and stored them at –70° C. The specimens were then shipped monthly to the J. N. Gamble Institute of Medical Research (Cincinnati, Ohio) for processing. During GEs, the field-workers visited the home daily until the GE was resolved. The stool specimens were assayed for the presence of rotavirus antigen by ELISA as described previously.[20] Rotavirus isolates were serotyped by ELISA by means of serotype-specific monoclonal antibodies.[21,22]

If rotavirus antigen was detected in a stool collected during a GE or within 7 days after the illness resolved, the GE was attributed to rotavirus.

As previously described, a 20-point scoring system was used to grade the severity of the diarrhea.[9] The scoring was based on a point system that ranged from 0 to 3 for each of the following: duration of diarrhea, maximum number of diarrheal stools in a 24-hour period, duration of vomiting, maximum number of vomiting episodes in a 24-hour period, presence of dehydration, presence of fever, and medical intervention by a physician. A diarrheal episode was considered to be severe if the score was greater than 14.

Initially, consent was obtained from parents/guardians of study participants to continue surveillance for a 1-year period. However, at the end of the first year, a decision was made to extend the surveillance for an additional year, and a second consent was obtained.

Data Analysis and Statistical Methods

Enrollment characteristics and adverse reaction data were analyzed with the Fisher Exact Test, t test, and linear regression methods, and chi-square test where appropriate. Immunogenicity analyses were performed by means of exact methods. Vaccine efficacy was calculated as $(1-R_v/R_u) \times 100\%$, where R_v and R_u are the incidence rates of GEs in the vaccinated and unvaccinated (placebo) groups, respectively. RV-specific incidence rates were calculated with the use of the first episode of rotaviral gastroenteritis for a child, whereas all-cause gastroenteritis rates used all GEs. Person-time denominators for the primary efficacy period were calculated by time from 14 days after the third dose until the earliest of (1) loss to follow-up, (2) death, or (3) end of first year of surveillance. The

intent-to-treat analysis performed for the first year of surveillance began its time line at receipt of first dose. Exact CIs for RV-specific efficacy were calculated by the binomial distribution[23]; an overdispersed Poisson model was used for the 2-year RV and all-cause gastroenteritis efficacy analyses.[24] Adjustments for other covariates were carried out with Cox proportional hazards modeling of time-to-episode. Calculations were performed with SAS (Cary, N.C.) and EGRET (Maple Valley, Wash.) software. All CIs were calculated at the 95% level.

RESULTS

A first dose of vaccine or placebo was given to 1185 infants (396 RRV-TV, 398 RRV-S1, and 391 placebo). Three doses of the vaccine or placebo were given to 1059 infants. Of these, eight infants received vaccine or placebo outside the protocol-defined time intervals and were excluded from primary efficacy analyses. Among the 1185 infants who received at least one dose of the vaccine, 1084 (91%) completed year 1 of surveillance, and the parents/guardians of 1027 (95%) of the infants who completed year 1 of surveillance consented to a second year of surveillance. Of those who had consent for a second year of surveillance, 913 (89%) completed the study. The proportions of infants who received three doses of the vaccine or placebo and the proportions that completed years 1 and 2 of surveillance, respectively, in each of the groups were similar.

Sixty-eight percent (n = 805) of the infants were Navajo, 18% (n = 219) were Apache, 7.5% (n = 90) were Pima, and 6% (n = 71) belonged to one of the other American Indian tribes. At enrollment, there were no significant differences between the treatment groups with respect to tribal affiliation (p = 0.63), geographic site (p = 0.99), breast-feeding status (p = 0.82), age at enrollment (p = 0.14), or total body weight at enrollment (p = 0.25). The proportions of male subjects were 53%, 43%, and 53% in the RRV-TV, RRV-S1, and placebo groups, respectively (p = 0.005). The age at enrollment was similar in the three groups (mean, 12 weeks; range, 3 to 24 weeks). The mean birth weight of the study participants was 3400 gm. The proportions of infants whose birth weight was above 2500 gm were 96%, 97%, and 96% in the RRV-TV, RRV-S1, and placebo groups, respectively.

Adverse Reactions

The proportions of infants who had diarrhea or vomiting during the 5-day period after each of the doses of the vaccine or placebo ranged from 3% to 7% and did not differ significantly among the groups (Fig. 1). The proportions of infants who had temperatures greater than 38° C after the first, second, and third doses of the vaccine or placebo are shown in Fig. 1. The only statistically significant difference occurred after the second dose, at which time 18% of the RRV-TV recipients had a temperature greater than 38° C, in comparison with 12% among the placebo recipients (p = 0.02). The overall proportion of infants with a temperature greater than 39° C after a dose was only 2%. There were 81, 87, and 98 hospitalizations in the RRV-TV, RRV-S1, and placebo groups, respectively. There were four deaths, all in the RRV-TV group. The causes of death were as follows: *Haemophilus influenzae* type b meningitis in one infant, sudden infant death syndrome in one, asphyxia in one, and unknown in one. None of the deaths occurred within 1 month after receipt of vaccines.

Immunogenicity of the Vaccines

With the use of sera obtained 1 month after the third dose, 93%, 88%, and 19% of the infants had seroconversion (fourfold or greater antibody increase) for RV IgA by ELISA in the RRV-TV, RRV-S1, and placebo groups, respectively (Table I). By neutralization assay, 24% of RRV-TV, 37% of RRV-S1, and 2% of placebo group infants had seroconversion against the G1 serotype. The RRV-TV group had the highest seroconversion rates by neutralization assay for all other serotypes, achieving statistically significantly higher rates than the RRV-S1 vaccine group for serotypes G2 and G3.

RV-specific Vaccine Efficacy

Stool samples were available from 2582 (66%) of 3900 GEs that occurred from 14 days after the third dose. The proportions of GEs for which stool samples were available were similar among the groups (66%, 66%, and 67% for RRV-TV, RRV-S1, and placebo groups, respectively). Of the samples positive for RV, 77% (209/270) were able to be typed.

Twenty-three children had more than one episode of RV gastroenteritis, including one child who had three GEs. For 15 of these children, GEs were separated by more than 4 weeks. Of these, eight had more than one GE that could be typed; only two of the eight had a second GE associated with the same serotype as their first GE.

YEAR 1 EFFICACY

During the primary efficacy period, the rates of RV gastroenteritis were 19, 28, and 39 per 100 child-years in the RRV-TV, RRV-S1, and placebo groups, respectively (Table II). The predominant type was G3; there were only eight cases of serotype G1 disease (2 RRV-TV, 1 RRV-S1, and 5 placebo). For severe RV gastroenteritis (score, >14), these rates were 4, 7, and 13 per 100 child-years, respectively.

Vaccine efficacy (with 95% CI) for preventing RV gastroenteritis was 50% (26, 67) for RRV-TV and 29% (–1, 50) for RRV-S1 (p = 0.10 for difference in percentages of efficacy). For severe disease the point estimates of vaccine efficacy were higher: 69% (29, 88) for RRV-TV and 48% (–4, 75) for RRV-S1. All severe GEs were of type G3. For serotype G3 disease, vaccine efficacy was 53% (25, 72) for RRV-TV and 20% (–20, 46) for RRV-S1. The efficacy percentages for serotype G1 disease were 59% (–149, 96) and 81% (–73, 99) for RRV-TV and RRV-S1, respectively.

Cox regression models were fit by adjusting for gender and breast-feeding status and time-varying age specification, stratified on geographic area. In these analyses, male incidence rates were 50% higher than female rates (p < 0.05), but there was no evidence of differing efficacy by gender. Efficacy for RRV-TV was somewhat higher, 59% (39, 72), than the 50% of the unadjusted analysis, mainly because study sites were accounted for. The adjusted efficacy for RRV-1 remained unchanged at 29% (1, 50).

The intent-to-treat (effectiveness) analysis was based on all enrolled infants regardless of number or timing of receipt of doses and included all first RV episodes after the first dose. Effectiveness estimates for the RRV-TV and RRV-S1 groups were 47% (26, 63) and 29% (3, 48), respectively, compared with the placebo group.

YEAR 2 AND OVERALL EFFICACY

The number of rotaviral GEs in year 2 of surveillance declined dramatically in all groups (Table II, Fig. 2). The point estimates (and 95% CIs) of vaccine efficacy for all RV diarrhea were –3% (–93, 45) for RRV-TV and 4% (–80, 49) for RRV-S1. For severe RV diarrhea, the point estimates were higher: 44% (–121, 88) for RRV-TV and 35% (–139, 84) for RRV-S1. Combining data on all rotaviral episodes from both surveillance years, including the repeated episodes, resulted in 2-year efficacy estimates of 39% (19, 54) for RRV-TV and 27% (5, 44) for RRV-S1.

AGE-SPECIFIC EFFICACY

We analyzed the age-specific incidence of rotaviral disease from 14 days after dose 3 through the second year of surveillance. Analyses by 6-month age groupings demonstrated significant efficacy of the vaccines during the first year of life (Table III): 57% (34, 73) and 33% (3, 54) for RRV-TV and RRV-S1, respectively. Although the point estimates for efficacy after 12 months of age indicated no vaccine efficacy, the variability of the estimates was too high to rule out moderate efficacy at these higher ages.

Vaccine Efficacy Against Gastroenteritis of All Causes

During the primary efficacy period, the estimates of vaccine efficacy (95% CI) for gastroenteritis of all causes were 7% (–7, 14) for RRV-TV and 8% (–4, 19) for RRV-S1. For all severe episodes, the point estimates were slightly greater: 22% (–3, 42) for RRV-TV and 9% (–20, 31) for RRV-S1. Efficacy estimates for the second year of surveillance, when the number of episodes declined greatly, were slightly lower than during the first year (Table IV).

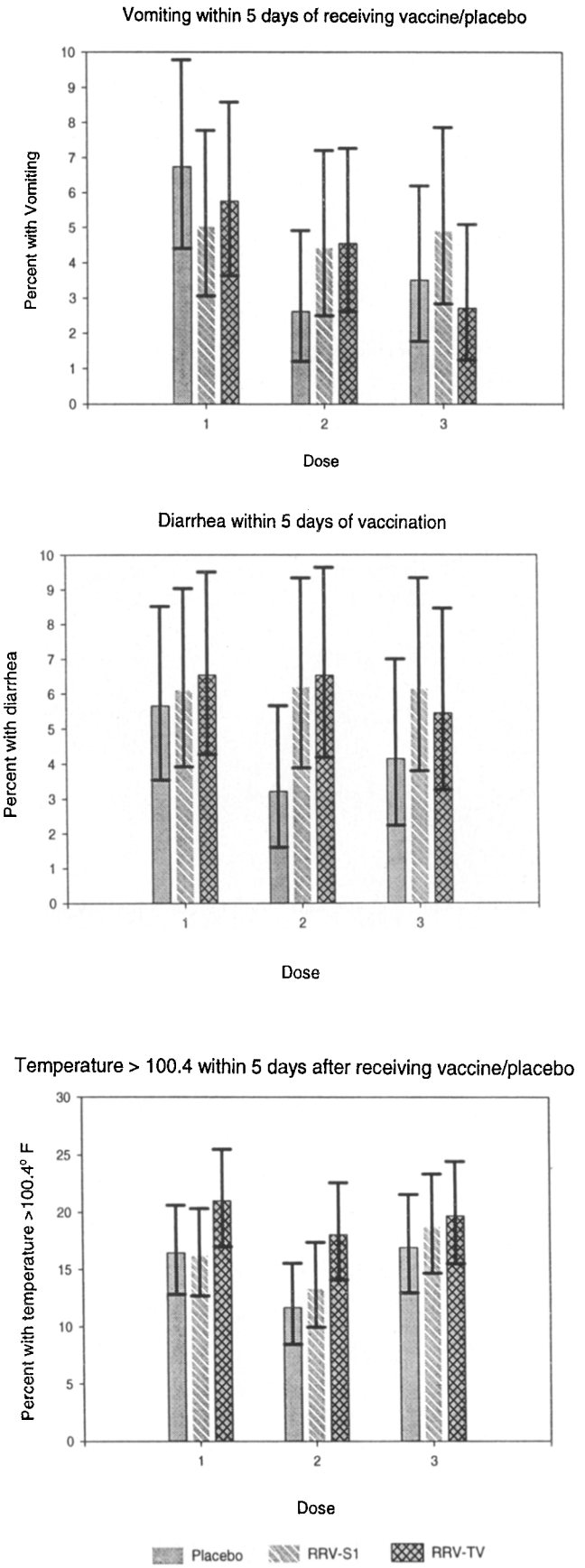

Fig. 1. Percentage of vaccine and placebo recipients having vomiting, diarrhea, and fever during safety surveillance period.

Table I. Number (percentage) of children with fourfold or greater rises in serum rotavirus antibody

Treatment group	*n*	Rotavirus IgA	*n*	Neutralizing antibody assay RRV (G3)	Wa (G1)	DS-1 (G2)	P (G3)	ST-3 (G4)
RRV-TV	217	201 (93)	58	48 (83)	14 (24)	14 (24)*	15 (26)*	11 (19)
RRV-S1	243	214 (88)	73	60 (82)	27 (37)	5 (27)	8 (11)	9 (12)
Placebo	228	46 (20)	70	5 (7)	2 (3)	0 (0)	4 (6)	3 (4)

*$p < 0.05$ in comparison with RRV-S1.

Table II. Vaccine efficacy and incidence of rotavirus gastroenteritis

	% Efficacy (95% CI)*		Rate/100 child-years (*n* cases)		
	RRV-TV	RRV-S1	RRV-TV	RRV-S1	Placebo
Year 1					
All serotypes	50 (26, 67)	29 (–1, 50)	19.0 (39)	28.0 (59)	39 (80)
Serotype 1	59 (–149, 96)	81 (–73, 99)	1.0 (2)	0.5 (1)	2 (5)
Serotype 3	53 (25, 72)	20 (–20, 46)	13.0 (27)	23.0 (49)	29 (59)
Severe (15+)	69 (29, 88)	48 (–4, 75)	4.0 (8)	7.0 (14)	13 (26)
Year 2					
All serotypes	–3 (–93, 45)	4 (–80, 49)	9.0 (23)	8.0 (23)	8 (22)
Serotype 1	—	—	0.8 (2)	0.4 (1)	0 (0)
Serotype 3	–9 (–203, 60)	–42 (–272, 43)	4.0 (10)	5.0 (14)	4 (9)
Severe (15+)	44 (-121, 88)	35 (-139, 84)	2.0 (4)	2.0 (5)	3 (7)

*Efficacy relative to placebo group; exact CIs based on analysis of child-years.

Table III. Age-specific vaccine efficacy and incidence of rotavirus gastroenteritis

	% Efficacy (95% CI)*		Rate/100 child-years (*n* cases)		
	RRV-TV	RRV-S1	RRV-TV	RRV-S1	Placebo
5-11	57 (34, 73)	33 (3, 54)	16 (31)	26 (52)	38 (74)
12-17	–16 (–131, 41)	–9 (–116, 45)	14 (21)	13 (21)	12 (18)
18-23	1 (–182, 65)	17 (–141, 72)	8 (9)	7 (8)	8 (9)

*Efficacy relative to placebo group; exact CIs based on analysis of child-years.

Table IV. Vaccine efficacy and incidence of gastroenteritis episodes from all causes

	% Efficacy (95% CI)*		Rate/100 child-years (*n* cases)		
	RRV-TV	RRV-S1	RRV-TV	RRV-S1	Placebo
Year 1					
All GEs	7 (–7, 14)	8 (–4, 19)	330 (667)	325 (696)	353 (733)
Severe (15+)	22 (–3, 42)	9 (–20, 31)	31 (62)	36 (77)	39 (82)
Year 2					
All GEs	6 (–10, 19)	0 (–17, 15)	119 (556)	126 (640)	127 (598)
Severe (15+)	17 (–17, 40)	2 (–36, 30)	8 (36)	9 (45)	9 (43)

*Efficacy relative to placebo group; CIs from overdispersed Poisson models.

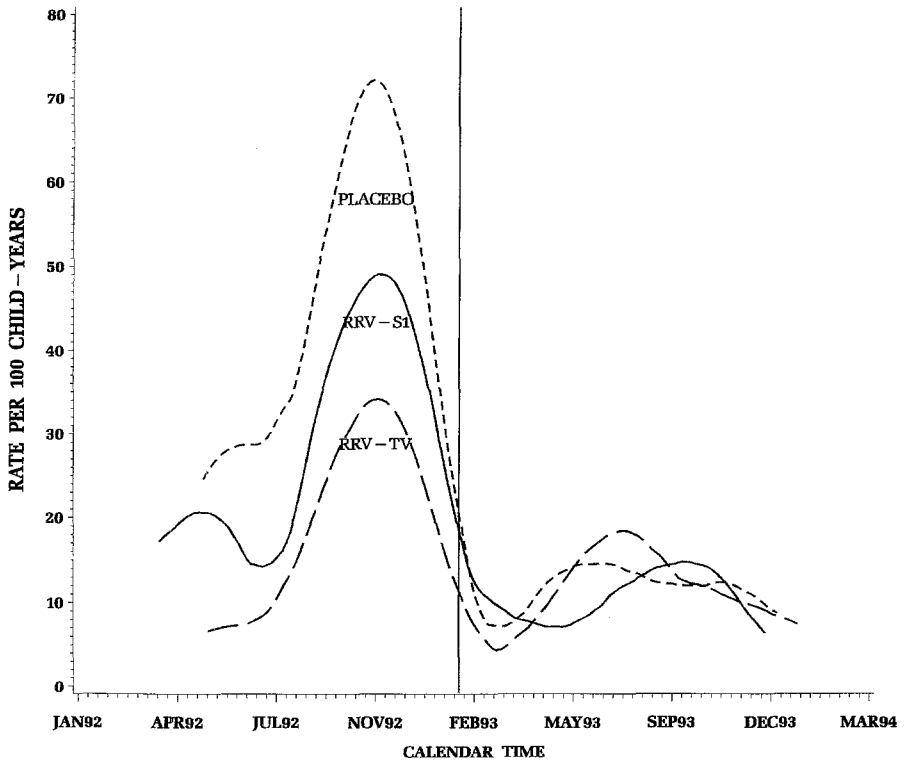

Fig. 2. Incidence rates, by study group, of RV gastroenteritis smoothed over calendar time. *Vertical line* marks beginning of second year of surveillance.

DISCUSSION

The results of this study confirm the findings of two other multicenter studies conducted in the general U.S. population to evaluate the safety and efficacy of RRV-TV and RRV-S1.[8,9] Both the RRV-TV and the RRV-S1 vaccines were well tolerated by the American Indian infants. The rates of adverse reactions observed by us were similar to those seen in the two previous U.S. studies.[8,9] The point estimate of efficacy seen in this study for RRV-TV against all RV disease in year 1 was the same as in the multicenter study in a general U.S. population, with the use of the same dose of the vaccine.[9] For RRV-S1, the point estimate of vaccine efficacy in the current study was only 29%, compared with 54% in the multicenter study.[9] This difference is most likely the result of a lack of protection against serotype G3 infection, the predominant serotype in our study. In year 2 the small number of cases of RV gastroenteritis prevents the drawing of firm conclusions about the efficacy of either vaccine. However, there was little suggestion that either vaccine was efficacious in the second year. Although the numbers of serotype G1 episodes were small, RRV-S1 vaccine appeared to be as efficacious as RRV-TV vaccine against serotype G1 disease during the first year of the study. RRV-TV was more efficacious against serotype 3 disease, however, with point estimates of vaccine efficacy 53% for RRV-TV, in comparison with 20% for RRV-S1. This finding, similar to the findings of the multicenter study, suggests that the monovalent RRV-S1 vaccine may be efficacious in preventing serotype 1 disease but provides little heterotypic protection.

The efficacy of both vaccines was higher when analysis for severe disease was based on the severity scoring system. The point estimate of vaccine efficacy for severe (score, >14) RV diarrhea was 69% for RRV-TV and 48% for RRV-S1 in year 1 of surveillance. In year 2 the number of cases of severe RV disease were too few to permit meaningful assessment of efficacy. In the multicenter study, the vaccine efficacy for severe disease was 80% for RRV-TV and 69% for RRV-S1. In that study the efficacy for preventing dehydration-associated rotavirus illness was 100%.[9] There were so few cases of dehydration in our populations, probably because of the aggressive use of oral rehydration therapy, that we could not make this specific efficacy assessment.

This study confirms the findings of the previous U.S. study in which the RRV-TV was found to be efficacious and safe when it was used in a dosage of 4×10^5 PFU. In a previous U.S. multicenter trial, the efficacy of RRV-TV and RRV-S1, given at a dosage of 4×10^4 PFU[8] was found to be similar to the efficacy of the same vaccines given at a dosage of 4×10^5 PFU.[9] However, the efficacy of the vaccine in Peru and Brazil given at a dosage of 4×10^4 PFU was only 30% and 35%, respectively.[25,26] Variations in age-specific attack rates may account for these differing observations. A study is currently in progress in Venezuela to evaluate the efficacy of RRV-TV and RRV-S1 given at a dosage of 4×10^5 PFU.

In the U.S. multicenter trial conducted 1 year earlier than the current study using the same vaccines,[9] serotype 1 was detected in 70% and serotype 3 in 22% of cases among placebo recipients. In our placebo group the results were 6% for serotype 1 and 86% for serotype 3. These differences, coupled with the year-to-year variation in serotype distribution, suggest that RRV-TV would be a better choice than RRV-S1 for use on a national level.

On the basis of the available data in the U.S. studies, a substantial number of severe diarrheal illnesses can be prevented if RRV-TV is used routinely in infancy.

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