

INTUSSUSCEPTION AMONG INFANTS GIVEN AN ORAL ROTAVIRUS VACCINE

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ABSTRACT

Background Intussusception is a form of intestinal obstruction in which a segment of the bowel prolapses into a more distal segment. Our investigation began on May 27, 1999, after nine cases of infants who had intussusception after receiving the tetravalent rhesus–human reassortant rotavirus vaccine (RRV-TV) were reported to the Vaccine Adverse Event Reporting System.

Methods In 19 states, we assessed the potential association between RRV-TV and intussusception among infants at least 1 but less than 12 months old. Infants hospitalized between November 1, 1998, and June 30, 1999, were identified by systematic reviews of medical and radiologic records. Each infant with intussusception was matched according to age with four healthy control infants who had been born at the same hospital as the infant with intussusception. Information on vaccinations was verified by the provider.

Results Data were analyzed for 429 infants with intussusception and 1763 matched controls in a case–control analysis as well as for 432 infants with intussusception in a case–series analysis. Seventy-four of the 429 infants with intussusception (17.2 percent) and 226 of the 1763 controls (12.8 percent) had received RRV-TV ($P=0.02$). An increased risk of intussusception 3 to 14 days after the first dose of RRV-TV was found in the case–control analysis (adjusted odds ratio, 21.7; 95 percent confidence interval, 9.6 to 48.9). In the case–series analysis, the incidence–rate ratio was 29.4 (95 percent confidence interval, 16.1 to 53.6) for days 3 through 14 after a first dose. There was also an increase in the risk of intussusception after the second dose of the vaccine, but it was smaller than the increase in risk after the first dose. Assuming full implementation of a national program of vaccination with RRV-TV, we estimated that 1 case of intussusception attributable to the vaccine would occur for every 4670 to 9474 infants vaccinated.

Conclusions The strong association between vaccination with RRV-TV and intussusception among otherwise healthy infants supports the existence of a causal relation. Rotavirus vaccines with an improved safety profile are urgently needed. (N Engl J Med 2001; 344:564–72.)

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ROTAVIRUS causes severe gastroenteritis and affects most infants in the United States. There are an estimated 3.5 million cases annually among children less than five years of age in this country, leading to 500,000 office visits, 50,000 hospitalizations, and approximately 20 deaths.¹ The morbidity and mortality associated with rotavirus infection are much greater in developing countries.²

In prelicensing trials in the United States, the tetravalent rhesus–human reassortant rotavirus vaccine (RRV-TV; RotaShield, Wyeth Lederle Vaccines, Philadelphia) was 80 percent or more effective in preventing severe rotavirus gastroenteritis in infants.^{3–5} Although side effects (fever, irritability, decreased appetite, and abdominal cramping) were more common among recipients of RRV-TV three to five days after the first dose than among recipients of placebo, the vaccine was generally well tolerated.⁶ In 27 prelicensing trials of candidate rotavirus vaccines, 5 cases of intussusception, a rare form of bowel obstruction in which a portion of the bowel prolapses into a more distal portion, were reported among 10,054 infants who received the vaccine (0.05 percent), as compared with 1 case among 4633 recipients of placebo (0.02 percent, $P>0.45$).⁷

On August 31, 1998, the Food and Drug Administration approved RRV-TV, which was recommended for use at two, four, and six months of age.^{4,8} Intussusception was listed as a possible adverse reaction in the manufacturer's product insert and in the published recommendations of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics.^{4,8} In October 1998, distribution of RRV-TV began. Between this time and May 27, 1999, the Vaccine Adverse Event Reporting System received nine reports of intussusception among infants given RRV-TV, as compared with only four reports overall

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in the seven years before the introduction of this vaccine. This information prompted the temporary suspension of vaccination against rotavirus and the initiation of a case-control investigation to evaluate the potential association between the vaccine and intussusception.^{9,10} We report here the results of that case-control investigation.

METHODS

The investigation was carried out in the 19 states (California, Georgia, Illinois, Indiana, Maryland, Michigan, Minnesota, Missouri, Nebraska, New Jersey, New York, North Carolina, Ohio, Pennsylvania, South Carolina, Tennessee, Texas, Virginia, and Wisconsin) where 80 percent of the RRV-TV had been distributed, according to the manufacturer. Because the investigation was initiated in response to a public health emergency, it did not require review by an institutional review board at the CDC. Nevertheless, all safeguards for the protection of subjects and the preservation of confidentiality were observed, and oral informed consent was obtained from the parents or guardians of all the infants.

Infants with Intussusception

To select infants with intussusception for the study, we ranked hospitals in the 19 states according to the number of discharge diagnoses of intussusception during the three years before the study period. Hospitals accounting for approximately 75 percent of these discharge diagnoses were selected to provide cases for the study. Infants at these hospitals who had had intussusception were then identified from medical records with the use of a code from the *International Classification of Diseases, Ninth Revision* (intussusception [560.0]), from logbooks of radiologic procedures, or from medical records with use of *Current Procedural Terminology* (therapeutic enema for the reduction of intussusception [code 74283], barium enema [74270], or air-contrast barium bowel examination [74280]).

Infants were eligible for the study if they had been hospitalized with intussusception during the study period (November 1, 1998, to June 30, 1999), if they were at least 1 but less than 12 months old at the time of hospitalization, and if the diagnosis had been confirmed by a radiologic procedure, at surgery, or at autopsy. Infants were excluded if the family did not reside in the United States. To preserve the independence of the results, we also excluded infants who were members of the Northern California Kaiser Permanente Medical Group, in which postlicensure surveillance was being conducted for adverse events after vaccination with RRV-TV.⁹

Controls

Controls were infants born in the same hospital in which the infants with intussusception had been born, with whom they were matched according to age. By matching according to birth hospital and age, we were able to adjust for age, season, and variations in the use of RRV-TV among the different counties and states in the study. A list of infants born on the same day as a given infant with intussusception was generated, and the infants were ranked randomly. Priority for enrollment was then given to the first four infants on the ranked list. If four controls were not available from the first list, additional controls were obtained by generating a randomly ranked list of infants born the day before or the day after the infant with intussusception; this procedure was repeated, if necessary, for a maximum of seven days before or after the birth of the infant with intussusception. Controls were not eligible for the study if they were adopted, had been hospitalized since birth, were the second-born of a pair of twins, or had died or if their parents or guardians did not live in the United States.

Data Collection

Information on each episode of intussusception was abstracted from hospital records. For all the infants, the parents or guardians

provided the following information: demographic characteristics, the number of children in the household, the infant's medical and vaccination history, contact information for medical and vaccine providers, type of child care, type of milk used for feeding, and age at the first feeding with solid food other than cereal. For questions regarding the time of events such as vaccination, the reference date was the date of hospitalization (for infants with intussusception) or the date on which the matched control was the same age as the infant with intussusception at the time of hospitalization (for controls). For all infants, the medical providers were interviewed to obtain information on conditions associated with intussusception and on symptoms of illness at visits within two weeks before the reference date and to obtain information regarding all vaccinations, including the date, type, manufacturer, and lot number of each dose. Records of hepatitis B vaccinations at birth hospitals were not sought, and thus results for hepatitis B vaccination are not presented.

Statistical Analysis

Case-Control Analysis

We used univariate and conditional logistic-regression models to estimate the matched odds ratios for intussusception during predefined risk periods within the first 21 days after vaccination (0 to 2, 3 to 14, 3 to 7, 8 to 14, and 15 to 21 days after vaccination).¹¹ In the univariate analyses, variables that differed between the infants with intussusception and the controls at a significance level of $P \leq 0.2$ were considered potential confounders and were assessed in the models. Variables that affected the odds ratios for intussusception by approximately 10 percent or more when removed from the analyses were included in the final model.

To determine whether classification of the infants into subgroups according to age or other variables modified the risk of intussusception among infants who received the rotavirus vaccine, we calculated separate odds ratios for each such subgroup (e.g., age subgroups of 1 to 3 months and of 4 to 11 months). Other variables examined in this way were sex, race or ethnic group, type of milk or formula used for feeding, age at the first feeding with solid food, time of administration of a live attenuated poliovirus vaccine (concurrent with or subsequent to the rotavirus vaccine), time of administration of other vaccines, type of child care, number of children in the household younger than five years of age, lot number of each dose of vaccine, gestational age at birth (premature or term), and birth weight (low or normal).

Case-Series Analysis

In the case-series analysis, we examined whether most cases of intussusception occurred shortly after vaccination with RRV-TV or whether they were distributed more uniformly through time. We used a conditional Poisson regression model to estimate the incidence-rate ratios within the predefined risk periods after vaccination, with adjustment for age. Infants with intussusception functioned as their own controls, with implicit adjustment for unrecognized confounders.¹² Unvaccinated infants with intussusception were included in the model to adjust for changes in the background incidence of intussusception according to age (in months).

Attributable Fraction

We developed a model to estimate the number of cases of intussusception that would be attributable to RRV-TV, in excess of the background number of cases, if a national program of vaccination were fully implemented. The model assumed a cohort of 3.8 million infants and a 90 percent rate of vaccination with RRV-TV. The ages at which each dose was given were taken from population-based estimates of ages for the primary series of vaccines (diphtheria, tetanus, and whole-cell pertussis or diphtheria, tetanus, and acellular pertussis [Klevens M, CDC: unpublished data]), which were recommended for infants of the same ages as those for the RRV-TV vaccine.

The background incidence rates of intussusception according

to month of age were derived from data on cases with a confirmed diagnosis recorded by the Vaccine Safety Datalink project from 1991 to 1997.¹³ The annualized incidence of intussusception in this data base was 34.2 cases per 100,000 child-years. The adjusted odds ratios derived from the case-control analysis and the incidence-rate ratios derived from the case-series analysis were used to predict the number of cases in excess of the background number that resulted from the administration of RRV-TV during the 21-day period after each dose.

RESULTS

Of 446 eligible infants with intussusception, 429 were included in the case-control analysis. The other 17 infants with intussusception were excluded because information from the parents (13 infants) or medical providers (1 infant) was incomplete or because controls were unavailable (3 infants). Ninety-four percent of the infants with intussusception were matched with at least 4 controls, and a total of 1763 controls had sufficient information for analysis. Seventy-nine

percent of the controls who were randomly ranked from 1 to 4 were enrolled. Data from all the controls were included in the results; the results were essentially unchanged when the analyses were restricted to the controls ranked from 1 to 4.

The infants with intussusception and the controls differed significantly with respect to some characteristics. A higher proportion of the infants with intussusception were male and were Hispanic or black. The mother's level of education was lower among these infants; they more often had Medicaid health coverage, and they less often had started consuming solid food before the reference date (Table 1). Seventy-four of the 429 infants with intussusception (17.2 percent) and 226 of the 1763 controls (12.8 percent) received RRV-TV during the study period (P=0.02). Infants with intussusception and controls who were at least four months old by the end of the study pe-

TABLE 1. CHARACTERISTICS OF THE INFANTS WITH INTUSSUSCEPTION AND THEIR AGE-MATCHED CONTROLS.*

VARIABLE	INFANTS WITH INTUSSUSCEPTION (N=429)	CONTROLS (N=1763)	ODDS RATIO (95% CI)	P VALUE
	number (percent)			
Sex				
Male	262 (61.1)	890 (50.5)	1.6 (1.3-1.9)	<0.001
Female†	167 (38.9)	873 (49.5)	1.0	
Race or ethnic group‡				
Hispanic	110 (26.7)	353 (20.2)	2.3 (1.6-3.4)	<0.001
Black	81 (19.7)	271 (15.5)	2.0 (1.4-2.8)	<0.001
Other or mixed	45 (10.9)	178 (10.2)	1.5 (1.0-2.1)	0.04
Non-Hispanic white†	176 (42.7)	946 (54.1)	1.0	
Mother's level of education§				
Less than high school	103 (25.1)	312 (18.0)	2.3 (1.6-3.4)	<0.001
High-school graduate or some college or technical school	230 (56.1)	936 (54.0)	1.7 (1.2-2.2)	0.001
College graduate†	77 (18.8)	487 (28.1)	1.0	
Type of health insurance¶				
Medicaid or subsidized	182 (44.1)	593 (34.0)	1.7 (1.3-2.2)	<0.001
Private, military, self-paid, or other†	231 (55.9)	1151 (66.0)	1.0	
Type of milk or formula				
Cow's milk-based formula	286 (68.6)	1077 (61.3)	1.2 (0.9-1.6)	0.18
Soy-based formula	34 (8.2)	209 (11.9)	0.7 (0.5-1.1)	0.13
Other formula	12 (2.9)	93 (5.3)	0.6 (0.3-1.1)	0.10
Breast milk for most feedings†	85 (20.4)	379 (21.6)	1.0	
Intake of solid food**				
≥5 wk before reference date	121 (31.2)	613 (37.1)	0.7 (0.5-0.9)	0.01
<5 wk before reference date	65 (16.8)	295 (17.9)	0.8 (0.6-1.1)	0.19
No solid food before reference date†	202 (52.1)	745 (45.1)	1.0	

*Odds ratios have been adjusted for the matching variables (age and the hospital where the infant was born). CI denotes confidence interval. Because of rounding, not all percentages total 100. P values are for the comparison with the reference group.

†Infants in this category served as the reference group.

‡Data were available for 412 infants with intussusception and 1748 controls.

§Data were available for 410 infants with intussusception and 1735 controls.

¶Data were available for 413 infants with intussusception and 1744 controls.

||Data were available for 417 infants with intussusception and 1758 controls.

**Data were available for 388 infants with intussusception and 1653 controls.

riod had similar rates of receipt of a first dose of childhood vaccines other than RRV-TV (diphtheria, tetanus, and whole-cell or acellular pertussis vaccine: 90.8 percent in infants with intussusception and 92.3 percent in controls, $P=0.31$; poliovirus vaccine: 93.6 percent and 94.0 percent, respectively, $P=0.76$; and *Haemophilus influenzae* type b vaccine: 91.9 percent and 93.0 percent, $P=0.47$).

Variables used to adjust the odds ratios were related both to the risk of intussusception (Table 1) and to vaccination with RRV-TV. Variables that were related to vaccination with RRV-TV were examined among the controls. When compared with controls who did not receive RRV-TV, controls who received RRV-TV were more often white (73.8 percent vs.

51.2 percent), more often had private health insurance (82.1 percent vs. 63.6 percent), and more often received inactivated poliovirus vaccine rather than live attenuated poliovirus vaccine (88.2 percent vs. 73.7 percent), and their mothers' level of education was higher (at least college graduation, 44.9 percent vs. 25.6 percent) ($P\leq 0.001$ for all comparisons).

Of the 74 infants who had intussusception and who had received RRV-TV, 67 had intussusception after the first, second, or third dose. Most of these 67 cases of intussusception occurred shortly after vaccination (Fig. 1). None of the infants with intussusception were hospitalized within two days after vaccination. The clustering of cases was most prominent 3 to 14 days after the first dose (43 cases) and 3 to

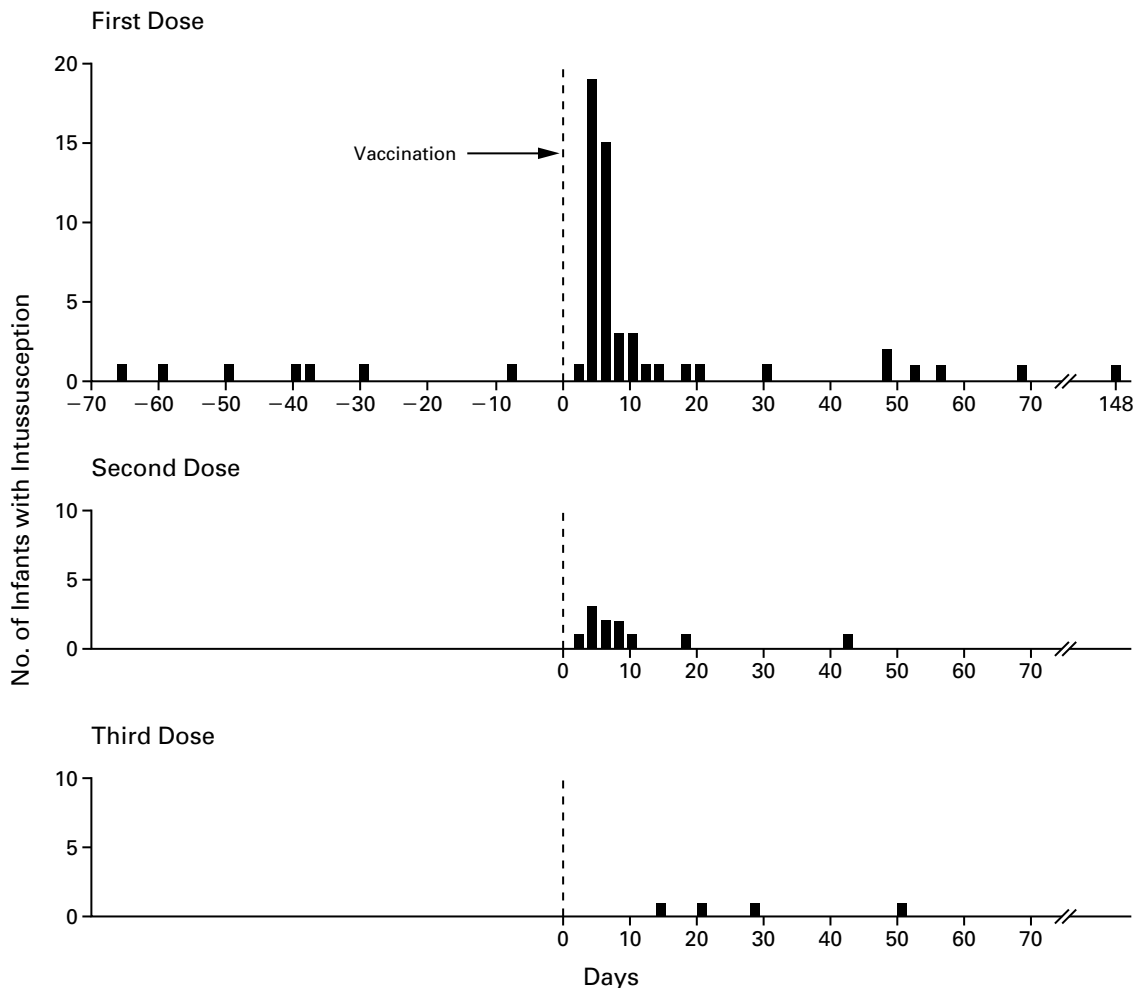


Figure 1. Interval between Vaccination with RRV-TV and Intussusception in 74 Infants.

Intussusception occurred before the first dose of RRV-TV in seven infants. In 52 infants, intussusception occurred at some time after the first dose of RRV-TV but before any subsequent dose; after intussusception, 27 of these 52 infants (52 percent) received one or two additional doses of RRV-TV. In 11 infants, intussusception occurred after the second dose; 4 of them (36 percent) received a subsequent dose of RRV-TV. In four other infants, intussusception occurred after the third dose of RRV-TV. Each infant is shown only once.

14 days after the second dose (9 cases). One infant was hospitalized with intussusception 3 to 14 days after the third dose. Fourteen cases of intussusception occurred more than 14 days after the first, second, or third dose.

The risk of intussusception was greatest among infants who were ever vaccinated with RRV-TV and for 3 to 14 days after vaccination (Table 2). Three to 14 days after vaccination with RRV-TV, the adjusted odds ratio was 10.6 (95 percent confidence interval, 5.7 to 19.6). Three to 14 days after the first dose, the odds ratio was 21.7 (95 percent confidence interval, 9.6 to 48.9), and 3 to 14 days after the second dose, it was 3.3 (95 percent confidence interval, 1.1 to 9.8) (Table 2). Table 3 shows the corresponding incidence-rate ratios estimated from the case-series analysis of 432 infants with intussusception who had sufficient data for analysis.

We found no evidence that age or other variables, except for feeding with breast milk, modified the risk of intussusception among infants given RRV-TV. The risk of intussusception three to seven days after the

first dose of RRV-TV was lower among infants fed breast milk (adjusted odds ratio, 10.7; 95 percent confidence interval, 1.4 to 78.7) than among other vaccinated infants (adjusted odds ratio, 43.3; 95 percent confidence interval, 12.7 to 148.1). However, the difference between these two estimates was not statistically significant ($P=0.22$).

Infants with intussusception who had received the first or second dose of RRV-TV 14 or fewer days before the onset of this condition were younger than other infants with intussusception (mean age at the time of hospitalization, 4.1 vs. 6.4 months, $P<0.001$; range, 2.0 to 7.0 vs. 1.0 to 11.0 months) (Fig. 2). The clinical characteristics of the infants vaccinated 14 or fewer days before hospitalization for intussusception were similar to those of other infants with intussusception (need for laparotomy: 23 of 52 [44.2 percent] vs. 208 of 377 [55.2 percent], respectively, $P=0.14$; need for bowel resection: 8 of 52 [15.4 percent] vs. 67 of 377 [17.8 percent], $P=0.67$; and lymphoid hyperplasia, 7 of 18 [38.9 percent] vs. 72 of 120 [60.0 percent], $P=0.13$ and other anatomical masses: 2 of

TABLE 2. MATCHED ODDS RATIOS IN THE CASE-CONTROL ANALYSIS OF INTUSSUSCEPTION AFTER VACCINATION WITH RRV-TV.*

DOSE	RISK PERIOD†	No. OF INFANTS WITH INTUSSUSCEPTION VACCINATED DURING RISK PERIOD	No. OF CONTROLS VACCINATED DURING RISK PERIOD	UNADJUSTED ODDS RATIO (95% CI)‡	P VALUE	ADJUSTED ODDS RATIO (95% CI)§	P VALUE
	days						
All	Any day before reference date¶	67	190	1.8 (1.3-2.5)	0.001	2.2 (1.5-3.3)	<0.001
	0-2	0	19	—	0.99	—	0.99
	3-14	53	47	9.2 (5.3-16.2)	<0.001	10.6 (5.7-19.6)	<0.001
	3-7	41	22	13.7 (7.0-26.8)	<0.001	14.4 (7.0-29.6)	<0.001
	8-14	12	25	3.9 (1.6-9.2)	0.002	5.3 (2.1-13.9)	0.001
	15-21	4	24	0.9 (0.3-2.6)	0.79	1.1 (0.3-3.3)	0.91
First	0-2	0	8	—	1.00	—	1.00
	3-14	43	22	16.8 (8.3-34.3)	<0.001	21.7 (9.6-48.9)	<0.001
	3-7	35	12	27.9 (10.8-72.1)	<0.001	37.2 (12.6-110.1)	<0.001
	8-14	8	10	6.4 (2.1-19.1)	0.001	8.2 (2.4-27.6)	0.001
	15-21	2	15	0.7 (0.1-3.2)	0.63	1.1 (0.2-5.4)	0.87
Second	0-2	0	8	—	1.00	—	1.00
	3-14	9	21	3.4 (1.3-9.2)	0.02	3.3 (1.1-9.8)	0.03
	3-7	6	8	5.0 (1.4-17.3)	0.01	3.8 (1.0-14.0)	0.05
	8-14	3	13	1.5 (0.3-6.6)	0.61	1.8 (0.4-9.5)	0.47
	15-21	1	6	0.9 (0.1-8.0)	0.93	0.9 (0.1-8.6)	0.94

*CI denotes confidence interval.

†The risk period is an interval of time before the reference date. The reference date is the date of hospitalization (for infants with intussusception) or the date on which the matched control was the same age as the infant with intussusception at the time of hospitalization (for controls). The risk period that serves as a referent for the odds ratios pertains to infants who were never vaccinated or who were vaccinated with RRV-TV but not during the overall 21-day risk period for any dose.

‡Odds ratios have been adjusted for the matching variables (age and the hospital where the infant was born). Odds ratios for the third dose were not significant.

§Adjusted odds ratios have been adjusted for sex, race, mother's level of education, type of health insurance, type of milk or formula used for feeding, and time of first intake of solid food (in addition to the matching variables) and were calculated for the 382 infants with intussusception and the 1657 controls for whom complete data were available.

¶Because the amount of observation time before the reference date varied, these odds ratios were calculated for an average risk period of 3.7 months.

TABLE 3. INCIDENCE-RATE RATIOS IN THE CASE-SERIES ANALYSIS OF INTUSSUSCEPTION AFTER VACCINATION WITH RRV-TV.*

DOSE	RISK PERIOD	CASES OF INTUSSUSCEPTION DURING RISK PERIOD	FOLLOW-UP	INCIDENCE-RATE RATIO (95% CI)†	P VALUE
	days after vaccination		child-months		
First	3–14	43	29.1	29.4 (16.1–53.6)	<0.001
	3–7	35	12.2	58.9 (31.7–109.6)	<0.001
	8–14	8	17.0	9.4 (3.9–22.3)	<0.001
	15–21	2	16.5	2.3 (0.5–10.2)	0.26
Second	3–14	9	17.3	6.8 (2.8–16.3)	<0.001
	3–7	6	7.2	11.0 (4.1–29.5)	<0.001
	8–14	3	10.1	3.8 (1.1–13.6)	0.04
	15–21	1	9.5	1.4 (0.2–10.6)	0.76

*Data are from a series of 432 cases with sufficient information for analysis.

†Incidence-rate ratios have been adjusted for age (in months) with use of conditional Poisson regression. Incidence-rate ratios are defined as the incidence rate of intussusception within each risk period divided by a referent incidence rate of intussusception that is outside all the risk periods. The reference incidence rates or denominators of these ratios were based on 375 cases of intussusception during 2846 child-months of follow-up, which excluded the 3-to-21-day risk periods for the first, second, and third doses. Person-time during the first two days after vaccination was excluded from the analysis. Incidence-rate ratios for the third dose were not significant. CI denotes confidence interval.

50 [4.0 percent] vs. 15 of 361 [4.2 percent], $P=1.00$). No deaths occurred among the infants with intussusception who had received RRV-TV during the preceding 14 days; one death occurred among the other infants with intussusception. The frequency of recurrent intussusception and of serious or chronic health problems did not vary between these recently vaccinated infants and the other infants with intussusception.

We estimated that 1291 background cases of intussusception would occur annually in the absence of RRV-TV vaccination. According to the results of our adjusted case-control analysis, if a national program of vaccination with RRV-TV were fully implemented, 361 cases of intussusception attributable to RRV-TV would occur in addition to the 1291 background cases, for an increase of 28.0 percent. According to the results of our case-series analysis, 732 additional cases attributable to intussusception would occur, for an increase of 56.7 percent. The number of infants who would be vaccinated for each case of intussusception that was attributable to RRV-TV would be 9474 according to the case-control results and 4670 according to the case-series results.

DISCUSSION

This study provides evidence of a causal association between RRV-TV and intussusception.¹⁴ The association was strong, temporal, and specific. The findings were consistent with the results of a retrospective cohort study of 10 managed-care organizations¹⁵ and

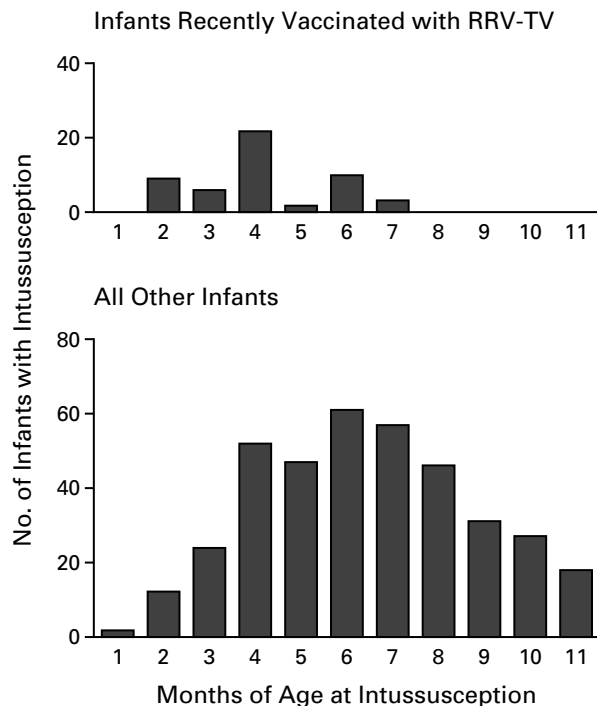


Figure 2. Age at the Time of Intussusception.

The top graph shows the ages of 52 infants who were vaccinated with the first, second, or third dose of RRV-TV 14 or fewer days before intussusception. The bottom graph shows the ages of 355 infants with intussusception who were never vaccinated with RRV-TV, 7 who were vaccinated with RRV-TV after intussusception, and 15 who were vaccinated with RRV-TV more than 14 days before intussusception.

voluntary reports of cases to the Vaccine Adverse Event Reporting System.¹⁶ The size of the odds ratio varied according to dose (first, second, or third) and according to the length of time after vaccination. In the case-control analysis, most of the adjusted odds ratios were higher than the unadjusted odds ratios, indicating the presence of confounding. In the case-series analyses, adjustment for confounding factors was more complete than in the case-control analysis, and the incidence-rate ratios obtained were higher than the adjusted odds ratios.

We found no factor that modified the relation between RRV-TV and intussusception, except perhaps feeding with breast milk. The odds ratio for intussusception was substantially less among RRV-TV-vaccinated infants who were fed breast milk than among RRV-TV-vaccinated infants who were fed other types of milk or formula. Data from prelicensing trials with candidate rotavirus vaccines suggested that replication of RRV-TV is lower among breast-fed infants.^{3,17,18} Age was not found to modify the effect of RRV-TV on the risk of intussusception, although the statistical power of our study may not have been sufficient to detect differences according to age.

Diagnostic biases or biases due to the availability of information could have affected the results if concern about intussusception had prompted earlier diagnosis in vaccinated infants than in unvaccinated infants or prompted diagnosis of less severe intussusception in vaccinated infants. This is unlikely, however, since the infants with intussusception in our study had a higher rate of surgery and bowel resection than the rates generally reported.¹⁹⁻²¹ Moreover, medical providers did not appear to associate RRV-TV with intussusception. Almost half of the RRV-TV-vaccinated infants received another dose of RRV-TV after intussusception, and few of the cases of intussusception that occurred within 14 days after vaccination were reported to the Vaccine Adverse Event Reporting System until after the use of RRV-TV was suspended.¹⁶ Our study period ended before the use of RRV-TV was suspended.

The pathogenesis of intussusception is not well understood, although an anatomical mass (in lymphatic or other tissue) and abnormal peristalsis have been proposed as contributing factors.²² In our study, lymphoid hyperplasia was inconsistently noted among the infants with intussusception who underwent surgery. Results in a murine model of intussusception²³ and anecdotal reports have led to the suggestion that endotoxin and enterotoxins induce transient slowing of peristalsis.²⁴ Wild human rotaviruses, which are detected uncommonly in cases of intussusception,²⁵⁻²⁷ elaborate an enterotoxin that has age-dependent and dose-dependent functions in humans.²⁸ In mice, the human rotavirus enterotoxin affects the secretion of fluid and electrolytes by activating the enteric nervous system,²⁹ which is also integral to peristalsis.³⁰ The

actions of putative enterotoxins derived from strains in the RRV-TV or human strains of rotavirus^{6,31-34} on the intestinal tract of infants may result in aberrations of peristalsis that affect the probability of intussusception.

Despite the significantly increased risk of intussusception associated with recent RRV-TV vaccination, the annual rate of hospitalization for intussusception attributable to RRV-TV vaccination in a U.S. program would be far lower than the rate of hospitalization attributable to the rotavirus gastroenteritis that is potentially preventable by such vaccination.^{1,35} Illness and death may result both from wild rotavirus disease and from intussusception related to RRV-TV¹ (and Zanardi LR: personal communication), although the net effect of a national program of vaccination with RRV-TV is not known.

In October 1999, the Advisory Committee on Immunization Practices withdrew its recommendation of RRV-TV.³⁶ Important considerations were the desire to limit harm and the perceived low level of severity of most rotavirus infections, since in the United States most complications can be prevented by oral rehydration.³⁷

The morbidity and mortality associated with rotavirus gastroenteritis are much greater in developing countries than in the United States.² Accordingly, the benefits and the risks of vaccination against rotavirus in developing countries will differ from those in the United States.³⁸ A better understanding of the pathogenesis of intussusception associated with RRV-TV may facilitate decisions regarding the use of RRV-TV in countries where the risk of death due to rotavirus-related illness is high. Rotavirus vaccines with an improved safety profile are urgently needed.

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APPENDIX

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REFERENCES

- Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. *J Infect Dis* 1996;174:Suppl 1:S5-S11.
- Bresee JS, Glass RI, Ivanoff B, Gentsch JR. Current status and future

- priorities for rotavirus vaccine development, evaluation and implementation in developing countries. *Vaccine* 1999;17:2207-22.
- Kapikian AZ, Flores J, Hoshino Y, et al. Rotavirus: the major etiologic agent of severe infantile diarrhea may be controllable by a "Jennerian" approach to vaccination. *J Infect Dis* 1986;153:815-22.
- Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep* 1999;48(RR-2):1-20.
- Clemens J, Keckich N, Naficy A, Glass R, Rao M. Public health considerations for the introduction of new rotavirus vaccines for infants: a case study of tetravalent rhesus rotavirus-based reassortant vaccine. *Epidemiol Rev* 1999;21:24-42.
- Joensuu J, Koskenniemi E, Vesikari T. Symptoms associated with rhesus-human reassortant rotavirus vaccine in infants. *Pediatr Infect Dis J* 1998;17:334-40.
- Rennels MB, Parashar UD, Holman RC, Le CT, Chang H-G, Glass RI. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. *Pediatr Infect Dis J* 1998;17:924-5.
- American Academy of Pediatrics. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. *Pediatrics* 1998;102:1483-91.
- Intussusception among recipients of rotavirus vaccine — United States, 1998–1999. *MMWR Morb Mortal Wkly Rep* 1999;48:577-81.
- Alpert JJ. *PedComm: AAP member alert*. Elk Grove Village, Ill.: American Academy of Pediatrics, July 15, 1999.
- SAS/STAT software: changes and enhancements through release 6.12. Cary, N.C.: SAS Institute, 1997.
- Farrington CP, Nash J, Miller E. Case series analysis of adverse reactions to vaccines: a comparative evaluation. *Am J Epidemiol* 1996;143:1165-73. [Erratum, *Am J Epidemiol* 1998;147:93.]
- Chen RT, DeStefano F, Davis RL, et al. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. *Bull World Health Organ* 2000;78:186-94.
- Rothman KJ, Greenland S. Causation and causal inference. In: Rothman KJ, Greenland S, eds. *Modern epidemiology*. 2nd ed. Philadelphia: Lippincott-Raven, 1998:7-28.
- Kramarz P, France EK, DeStefano F, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J* (in press).
- Zanard LR, Haber P, Mootrey GT, et al. Intussusception among recipients of rotavirus vaccine: reports to the Vaccine Adverse Event Reporting System. *Pediatrics* (in press).
- Rennels MB. Influence of breast-feeding and oral poliovirus vaccine on the immunogenicity and efficacy of rotavirus vaccines. *J Infect Dis* 1996;174:Suppl 1:S107-S111.
- Friedman MG, Segal B, Zedaka R, et al. Serum and salivary responses to oral tetravalent reassortant rotavirus vaccine in newborns. *Clin Exp Immunol* 1993;92:194-9.
- Stringer MD, Pablot SM, Brereton RJ. Paediatric intussusception. *Br J Surg* 1992;79:867-76.
- Orenstein J. Update on intussusception. *Contemp Pediatr* 2000;17:180, 185-91.
- Ein SH, Alton D, Palder SB, Shandling B, Stringer D. Intussusception in the 1990s: has 25 years made a difference? *Pediatr Surg Int* 1997;12:374-6.
- Perrin WS, Lindsay EC. Intussusception: a monograph based on 400 cases. *Br J Surg* 1921;9:46-71.
- Lin Z, Cohen P, Nissan A, Allweis TM, Freund HR, Hanani M. Bacterial wall lipopolysaccharide as a cause of intussusception in mice. *J Pediatr Gastroenterol Nutr* 1998;27:301-5.
- Hemano I, Hitchens JT, Beiler JM. Paradoxical intestinal inhibitory effects of staphylococcal enterotoxin. *Gastroenterology* 1967;53:71-7.
- Konno T, Suzuki H, Kutsuzawa T, et al. Human rotavirus infection in infants and young children with intussusception. *J Med Virol* 1978;2:265-9.
- Mulcahy DL, Kamath KR, de Silva LM, Hodges S, Carter IW, Cloonan MJ. A two-part study of the aetiological role of rotavirus in intussusception. *J Med Virol* 1982;9:51-5.
- Nicolas JC, Ingrand D, Fortier B, Bricout F. A one-year virological survey of acute intussusception in childhood. *J Med Virol* 1982;9:267-71.
- Ball JM, Tian P, Zeng CQY, Morris AP, Estes MK. Age-dependent diarrhea induced by a rotaviral nonstructural glycoprotein. *Science* 1996;272:101-4.
- Lundgren O, Peregrin AT, Persson K, Kordasti S, Uhnou I, Svensson L. Role of the enteric nervous system in the fluid and electrolyte secretion of rotavirus diarrhea. *Science* 2000;287:491-5.
- Stevens RJ, Publicover NG, Smith TK. Induction and organization of Ca²⁺ waves by enteric neural reflexes. *Nature* 1999;399:62-6.
- Dunn SJ, Cross TL, Greenberg HB. Comparison of the rotavirus nonstructural protein NSP1 (NS53) from different species by sequence analysis and northern blot hybridization. *Virology* 1994;203:178-83.

- 32.** Ciarlet M, Liprandi F, Conner ME, Estes MK. Species specificity and interspecies relatedness of NSP4 genetic groups by comparative NSP4 sequence analyses of animal rotaviruses. *Arch Virol* 2000;145:371-83.
- 33.** Ofit PA. Host factors associated with protection against rotavirus disease: the skies are clearing. *J Infect Dis* 1996;174:Suppl 1:S59-S64.
- 34.** Ward RL, Dinsmore AM, Goldberg G, Sander DS, Rappaport RS, Zito ET. Shedding of rotavirus after administration of the tetravalent rhesus rotavirus vaccine. *Pediatr Infect Dis J* 1998;17:386-90.
- 35.** Parashar UD, Holman RC, Cummings KC, et al. Trends in intussusception-associated hospitalizations and deaths among US infants. *Pediatrics* 2000;106:1413-21.
- 36.** Withdrawal of rotavirus vaccine recommendation. *MMWR Morb Mortal Wkly Rep* 1999;48:1007.
- 37.** Provisional Committee on Quality Improvement, Subcommittee on Acute Gastroenteritis. Practice parameter: the management of acute gastroenteritis in young children. *Pediatrics* 1996;97:424-35.
- 38.** Melton L. Lifesaving vaccine caught in an ethical minefield. *Lancet* 2000;356:318.

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CORRECTION

Intussusception among Infants Given an Oral Rotavirus Vaccine

Intussusception among Infants Given an Oral Rotavirus Vaccine . On page 564, in the list of authors "John R. Livingood, M.D." should have read, "John R. Livengood, M.D." On page 569, the sentence that begins on line 17 of the left-hand column should have read, "According to the results of our case-series analysis, 732 additional cases attributable to RRV-TV," not "attributable to *intussusception*," as printed. On page 570, beginning seven lines from the bottom of the left-hand column, the sentences should have read, "Wild human rotaviruses are detected uncommonly in cases of intussusception.^{25,26,27} Rotaviruses elaborate an enterotoxin that has age-dependent and dose-dependent functions.²⁸ In mice infected with RRV (rhesus rotavirus), secretion of fluid and electrolytes involves activation of the enteric nervous system,²⁹ which is also integral to peristalsis.³⁰" Also on page 570, on line 7 of the Appendix, "C. Robmann" should have read, "C. Rebmann." The following names should be added to the Appendix: "*Epidemic Intelligence Service Officers and Preventive Medicine Residents of the CDC*: M. Cooper (Texas)"; and "*Commissioned Corps, Public Health Advisors, Fellows, Epidemiologists, and Other Staff at the CDC*: L. Anderson, B. Barylska, G. Buckett, C. Danovaro, K. Galil, J. Gilbert, P. Haber, R. Jones, H. McKnight, D. Miller, M. Mitchell, and S. Weems." On page 571, the first author's last name in reference 16 should have read, "Zanardi," not "Zanard," as printed.