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# Intussusception Among Recipients of Rotavirus Vaccine: Reports to the Vaccine Adverse Event Reporting System

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**ABSTRACT.** *Background.* Rotavirus vaccine was licensed on August 31, 1998, and subsequently recommended for routine use among infants. To assess rare adverse events, postlicensure surveillance was conducted.

*Objective.* To describe the cases of intussusception among rotavirus vaccine recipients reported to the Vaccine Adverse Event Reporting System from October 1998 through December 1999.

*Setting and Participants.* Infants vaccinated with rotavirus vaccine in the United States.

*Outcome Measures.* Intussusception confirmed by radiology, surgery, or autopsy report with medical record documentation or confirmed by a primary health care provider.

*Results.* There were 98 confirmed cases of intussusception after vaccination with rotavirus vaccine reported to the Vaccine Adverse Event Reporting System; 60 of these developed intussusception within 1 week after vaccination. Based on calculations using vaccine distribution data and intussusception incidence rates from 2 separate databases, an estimated 7 to 16 cases would have been expected to occur in the week after vaccination by chance alone.

*Conclusion.* Using a passive surveillance system for vaccine adverse events, we observed at least a fourfold increase over the expected number of intussusception cases occurring within 1 week of receipt of rotavirus vaccine. Other studies were initiated to further define the relationship between rotavirus vaccine and intussusception. In light of these and other data, the rotavirus vaccine manufacturer voluntarily removed its product from the market, and the recommendation for routine use of rotavirus vaccine among US infants has been withdrawn. *Pediatrics* 2001;107(6). URL: <http://www.pediatrics.org/cgi/content/full/107/6/e97>; intussusception, rotavirus vaccine, Vaccine Adverse Event Reporting System, vaccine safety.

ABBREVIATIONS. RRV-TV, rhesus-human rotavirus reassortant-tetravalent vaccine; ACIP, Advisory Committee on Immunization Practices; VAERS, Vaccine Adverse Event Reporting System;

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CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; DTaP, diphtheria and tetanus toxoids and acellular pertussis vaccine; IPV, inactivated polio vaccine; Hib, *Haemophilus influenzae* type b vaccine.

The live, oral, rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV) was licensed for use in the United States on August 31, 1998. It was subsequently recommended for routine use in infants in a 3-dose series given at 2, 4, and 6 months of age.<sup>1,2</sup> This recommendation was based on the morbidity and economic burden of severe dehydrating rotavirus gastroenteritis among infants and young children.<sup>1</sup>

In prelicensure clinical trials, 5 cases of intussusception were noted among 10 054 vaccinees who had received 1 of 3 different formulations of rotavirus vaccine. Two of these 5 cases received RRV-TV. All 5 intussusception cases occurred after either dose 2 or 3. The cases occurred 6 to 51 days after rotavirus vaccination; 3 of these cases occurred on days 6 or 7. In contrast, 1 case of intussusception was noted among 4633 controls.<sup>3</sup> The difference in the proportion of children who developed intussusception in the vaccinated and unvaccinated groups was not statistically significant. Although there was insufficient evidence to conclude that the association between RRV-TV and intussusception was causal rather than temporal, intussusception was noted in the package insert, and postlicensure surveillance for intussusception was recommended by the Advisory Committee on Immunization Practices (ACIP).<sup>1</sup>

Distribution of RRV-TV commenced in October 1998. After vaccine introduction, reports to the Vaccine Adverse Event Reporting System (VAERS) were regularly monitored for cases of intussusception among recipients of rotavirus vaccine. By mid-July 1999, 15 such cases of intussusception had been reported to VAERS. Based on these data and preliminary active surveillance data from Northern California Kaiser Permanente and the state health department in Minnesota, the Centers for Disease Control and Prevention (CDC), and the American Academy of Pediatrics recommended on July 16, 1999 that the rotavirus vaccination program be suspended.<sup>4</sup> Subsequently, the vaccine manufacturer voluntarily withdrew its product from the market, and in October 1999, the ACIP withdrew its recommendation for use of RRV-TV in the United States.<sup>5</sup>

In this report, we describe the cases of intussus-

ception among recipients of RRV-TV reported to VAERS from October 1, 1998, through December 31, 1999. In particular, we will focus on cases of intussusception that occurred within 1 week of vaccination with RRV-TV, because the majority of cases were observed during this period and because they are most plausibly causally associated with receipt of RRV-TV.

## METHODS

VAERS is the national passive surveillance system for monitoring adverse events after receipt of US-licensed vaccines.<sup>6</sup> The primary objective of VAERS is to identify events potentially related to receipt of a vaccine. This is particularly important when a new vaccine is introduced because precensure clinical trials may lack the power to detect rare adverse events. Additional epidemiologic studies are usually required to confirm a suspected causal relationship between a vaccine and adverse event identified by VAERS. The system, operated jointly by the CDC and the Food and Drug Administration (FDA), receives reports from physicians, vaccine providers, vaccinees or their caregivers, and vaccine manufacturers.

Following the ACIP recommendation for postlicensure surveillance, VAERS data were searched by CDC and FDA staff on a regular basis for reports among RRV-TV recipients containing a diagnostic code for intussusception. Additionally, the data were searched for all serious gastrointestinal adverse events after rotavirus vaccination; these reports were reviewed to determine whether they were, in fact, cases of intussusception. Supplementary clinical information was requested for each reported case to confirm the report and verify the diagnosis. These additional data included 1 or more of the following: hospital discharge summary, emergency department or other clinical summary, operative report, radiology report, pathology report, or autopsy. Cases for whom medical record documentation of intussusception was unavailable had the diagnosis of intussusception confirmed by telephone interview with the patient's primary health care provider. VAERS reports of intussusception among RRV-TV recipients and medical record documentation were reviewed by 2 separate physician investigators (L.R.Z. and M.W.) and classified as confirmed or suspected (clinically consistent but not able to be confirmed) intussusception. Discrepancies in classification were resolved by joint review of case documentation.

For this study, reports to VAERS had to meet the following criteria to be classified as a case: 1) VAERS report received by December 31, 1999, with a diagnosis or clinical description consistent with intussusception; 2) onset of intussusception between October 1, 1998 and August 15, 1999; 3) intussusception confirmed by radiology, surgery, or autopsy with medical record documentation or confirmation by primary provider; and 4) receipt of at least 1 dose of RRV-TV before diagnosis of intussusception.

Fisher's exact test was performed using *SAS, Version 6.12 Software* (SAS Institute Inc, Cary, NC) to compare dose of RRV-TV received before intussusception between spontaneous reports with VAERS and reports stimulated by publicity. The Kruskal-Wallis test was performed using *Epi Info, Version 6.04b* (Centers for Disease Control and Prevention, Atlanta, GA) to compare reporting delay and interval from vaccination to onset of intussusception between spontaneous and stimulated reports.

We initially determined the background rate of intussusception from the New York State hospital discharge database<sup>4</sup>; the rate was calculated as the number of cases per infant-week. To estimate the expected number of cases among infants (<12 months of age) in the first week after receipt of RRV-TV, we determined the number of 1-week periods after vaccination equal to the estimated number of doses administered, which was provided by the manufacturer based on the number of doses distributed and returned. Thus, multiplying the background intussusception incidence rate (in infant-weeks) by the number of 1-week periods after vaccination yielded the approximate number of cases that would be expected to occur in the first week after vaccination among all RRV-TV recipients. This analysis was later conducted using background incidence data from a validated managed care database representing a geographically diverse population.<sup>7</sup> Additionally, for comparison purposes, we searched the historical VAERS da-

tabase (1990–1999) to identify reports of intussusception after receipt of any other vaccine.

## RESULTS

The following intussusception case descriptions illustrate the range of clinical reports received by VAERS. Most cases fully recovered; however, there were some complications and 1 death.

### Case 1

A 4-month-old boy developed fever, fussiness, and a large bloody stool 3 days after a first dose of RRV-TV and second doses of diphtheria and tetanus toxoids and acellular pertussis vaccine (DTaP), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b vaccine (Hib), and hepatitis B vaccine. Findings on abdominal radiographs suggested intussusception. An air enema confirmed the diagnosis and reduced the intussusception without complication.

### Case 2

A 4-month-old boy developed fussiness and non-bilious emesis 2 days after vaccination with a first dose of RRV-TV and second doses of DTaP, IPV, and Hib. The following day the infant presented to clinic with a distended abdomen, hypoactive bowel sounds, guarding, and passed bright red blood per rectum. The diagnosis of ileocolic intussusception was confirmed with barium enema, but the intussusception was not reduced. The infant underwent surgery for reduction of intussusception and partial small bowel resection (18 cm) including the ileocecal valve. Lymphoid hyperplasia was noted on examination of the surgical specimen.

### Case 3

A 5-month-old girl developed fussiness and vomiting 5 days after her first doses of rotavirus vaccine, DTaP, IPV, and combined Hib and hepatitis B vaccine. She was treated in the emergency department for pharyngitis and gastroenteritis and discharged. Grossly bloody stools, fever, and lethargy developed over the next 24 hours. The patient presented to the emergency department in hypovolemic shock and died while awaiting transport to a pediatric intensive care unit. Ileocolic intussusception with bowel necrosis was found at autopsy.

From October 1, 1998, to December 31, 1999, 112 reports of intussusception were received by VAERS with onset before August 15, 1999, 1 month after the suspension of the rotavirus vaccination program. None of the reported intussusception cases were associated with RRV-TV administered after the suspension of the rotavirus vaccination program. Ninety-five cases were confirmed by review of medical records, and 3 cases were confirmed by primary care provider interview. In the remainder of reports, intussusception was not confirmed ( $n = 13$ ) or the child had not been vaccinated with RRV-TV ( $n = 1$ ). In comparison, from 1990 to 1998, only 4 reports to VAERS of intussusception after a dose of any other vaccine were identified.

The first report of intussusception after RRV-TV

was received in December 1998, and 1 to 4 reports were received per month for the first 6 months of 1999. A substantial increase in reporting was seen after the *Morbidity and Mortality Weekly Report* article published on July 16, 1999, which recommended the suspension of rotavirus vaccination (Fig 1). Reports received before publication of the *Morbidity and Mortality Weekly Report* article had shorter intervals from vaccination to onset of intussusception than reports received after publication; however, reporting delays were not statistically different between the groups. The distribution of last rotavirus dose received before intussusception was not statistically different between the 2 groups (Table 1).

Of the 98 confirmed cases, 61 were boys (62%). The median age at time of intussusception was 4 months. Seventy-two cases (73%) followed the first dose of RRV-TV (Table 2). Reports were received from 27 states in a distribution that generally correlated with vaccine distribution reported by the manufacturer (data not shown). In 60 cases (61%), intussusception occurred within 7 days of vaccination with RRV-TV. Intussusception occurred within 14 days of vaccination in 68 cases (69%) and within 21 days in 71 cases (72%; Fig 2).

The remainder of this report will describe the 60 cases with onset of intussusception within 1 week of vaccination with RRV-TV. These cases were similar to all cases in regards to gender and age. Most reports of intussusception (82%) occurred after the first dose of rotavirus vaccine; 17% and 2% of cases occurred after doses 2 and 3, respectively (Table 2). Rotavirus was the only vaccine received at the medical visit immediately before intussusception in 18% of cases. Other vaccines were received simultaneously with RRV-TV in 82% of cases; the most common vaccines received were DTaP (75%), Hib (60%), IPV (58%), and hepatitis B (22%). Oral polio vaccine was received simultaneously in 2 cases (3%).

Reduction of intussusception by air or barium enema was successful in 27 cases (45%). One additional case was diagnosed by ultrasound, but the intussusception had reduced spontaneously before barium

**TABLE 1.** Cases of Intussusception Among RRV-TV Recipients Reported to VAERS Before and After July 16, 1999

Characteristics	Spontaneous Reports* (n = 15)	Stimulated Reports† (n = 83)	P Value
Median (mean) interval in d from vaccination to onset of intussusception	4.0 (9.7)	6.0 (20.7)	.01‡
Median (mean) time in d from intussusception to receipt of report	44.0 (54.0)	55.0 (77.8)	.35‡
Intussusception after dose			.63§
1	13 (87%)	59 (71%)	
2	2 (13%)	17 (20%)	
3	0 (0%)	7 (9%)	

\* Reports received before July 16, 1999.

† Reports received on or after July 16, 1999.

‡ Kruskal-Wallis test.

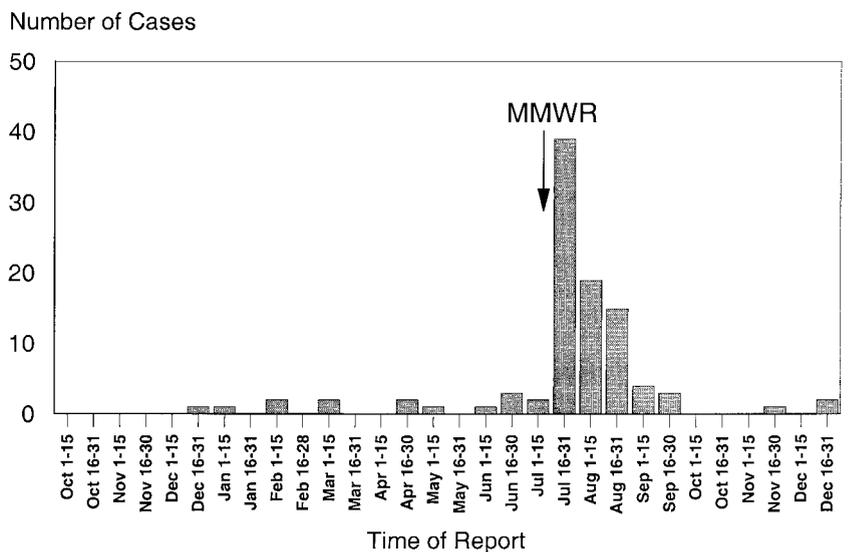
§ Fisher's exact test.

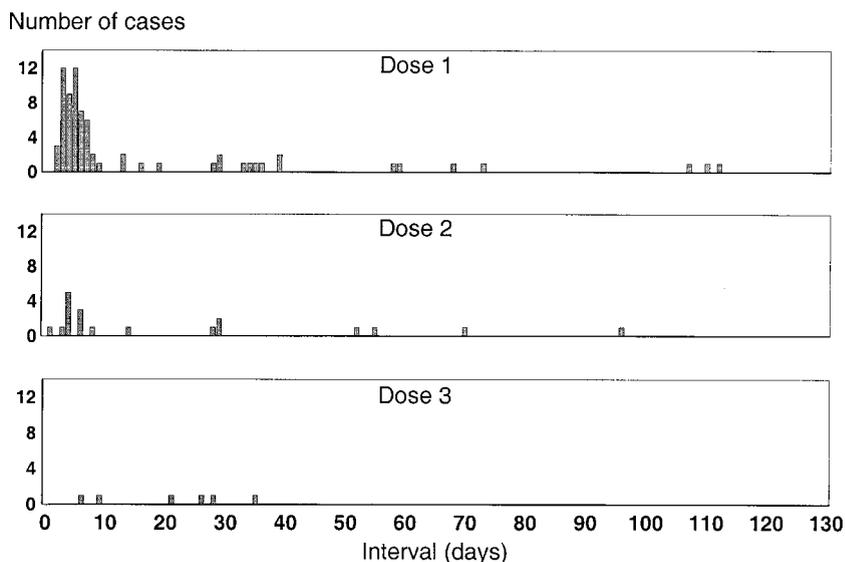
**TABLE 2.** Characteristics of All Confirmed Intussusception Cases and Confirmed Intussusception Cases With Onset Within One Week of Vaccination Reported to VAERS

Characteristics	All Cases (n = 98) n (%)	Cases With Onset Within 1 Week of Vaccination (n = 60) n (%)
Male	61 (62)	38 (63)
Median age in mo (range)	4 (2–11)	4 (2–11)
Intussusception after dose		
1	72 (73)	49 (82)
2	19 (19)	10 (17)
3	7 (7)	1 (2)
Percent requiring surgery	56	53

enema. Thirty-two (53%) of the 60 cases underwent surgery; spontaneous reduction was observed in 2. Seven cases underwent bowel resection, and an additional 2 had an anatomic lead point excised. Exploratory laparotomy was required for complica-

**Fig 1.** Cases of intussusception after rotavirus vaccine by date reported to VAERS, October 1, 1998 to December 31, 1999 (n = 98).





**Fig 2.** Interval from receipt of rotavirus vaccine to symptom onset by dose, VAERS, October 1, 1998, to August 15, 1999 ( $n = 98$ ).

tions after a reduction by enema in 1 case. One case was diagnosed at autopsy. This fatality occurred in a 5-month-old girl who developed intussusception 5 days after receipt of rotavirus vaccination (case 3, above; Table 3).

Most intussusception cases (33/60) with onset within 1 week of vaccination were ileocolic, but some were also reported as ileocecal (5), ileoileocolic (3), ileoileal (3), and colocolic (2). The location was unknown or not clearly indicated in 14 cases. Bowel perforation occurred in 1 case. A structural lead point was identified in 3 cases (5%), including a Meckel's diverticulum, a duplication cyst, and a terminal ileum pouch. In another case, an incidental Meckel's diverticulum was noted but was not the lead point for the intussusception. Of the 15 available pathology reports, 6 documented lymphoid hyperplasia (4 were appendix specimens and 2 were ileum). One specimen with lymphoid hyperplasia also had intestinal polyps; in this case, it was not clear which served as the lead point for the intussusception. In an additional 3 surgical cases, lymphoid hyperplasia (2) and mesenteric adenitis (1) were identified in surgery but no specimen was taken. Ultrasound findings suggested mesenteric adenitis in an additional patient who underwent reduction of intussusception by barium enema.

Reported intussusception case patients had been generally healthy before intussusception. Three cases

(5%) were premature (<37 weeks' gestation); gestational ages were 32 weeks (1) and 36 weeks (2). One of the 3 premature infants had a low birth weight (<5.5 lb). Other medical conditions were noted in 9 (15%) of 60 cases and included gastroesophageal reflux (4), sickle cell trait (2), history of pyloric stenosis (1), ventricular septal defect (1), torticollis (1), and hypospadias (1; Table 3). Atopic dermatitis was also reported in 4 of the 60 cases.

The vaccine manufacturer reported that as of June 1, 1999, 1.8 million doses of rotavirus vaccine had been distributed. Based on the number of doses returned after withdrawal of vaccine, the manufacturer estimated that 1.5 million doses were administered.<sup>4</sup> The rate of intussusception before introduction of rotavirus vaccine (1991–1997) from the New York State hospital discharge database was estimated to be 1 per 100 000 infant-weeks. Assuming that 1.5 million doses of vaccine were administered and no seasonality of intussusception, 14 to 16 cases of infant intussusception would be expected to occur within 1 week of receipt of any dose of rotavirus vaccine by chance alone.<sup>4</sup> In contrast, we observed 4 times as many cases of intussusception in the first week after vaccination with RRV-TV.

Despite limitations, the New York State hospital discharge database was initially used to estimate the rate of intussusception because it provided timely information for this investigation. More recently, a chart-validated database representing 10 geographically diverse managed care organizations was used to calculate an incidence of intussusception approximately half that of the New York State hospital discharge database or 0.5 per 100 000 infant-weeks.<sup>7</sup> When this lower baseline rate is applied to the analysis used above, only 7 or 8 cases of intussusception would have been expected to occur within 1 week of receipt of vaccine. Thus, VAERS would have demonstrated an eightfold increase in intussusception cases over the number of cases that would have been expected to occur by chance.

**TABLE 3.** Clinical Characteristics of Confirmed Intussusception Cases With Onset Within One Week of Vaccination Reported to VAERS ( $n = 60$ )

Characteristics	$n$ (%)
Reduced by air/barium enema	27 (45)
Surgery	32 (53)
Spontaneously reduced at surgery	2 (3)
Bowel resection	7 (12)
Fatal cases	1 (2)
Median length of hospital stay in d (range)	2 (1–32)
Underlying medical condition*	9 (15)

\* Includes gastrointestinal reflux, sickle cell trait, history of pyloric stenosis, ventricular septal defect, torticollis, and hypospadias.

## DISCUSSION

The 60 intussusception cases reported to VAERS that occurred within 1 week of receipt of RRV-TV demonstrated an increase in the risk of intussusception during the week after receipt of RRV-TV. Compared with the estimated number of cases expected, this risk was increased at least fourfold. These findings most likely differ from those observed in the prelicensure study<sup>3</sup> because the latter reviewed RRV-TV data in conjunction with data from 2 other rotavirus vaccine formulations. Furthermore, prelicensure trials frequently have too few children studied to detect a rare adverse event.

Intussusception cases reported to VAERS were clustered in the 3- to 7-day period after rotavirus vaccination. This distribution is distinctly different from that generally observed for reported adverse events after vaccination, with approximately two thirds of reports to VAERS concerning events on the day of vaccination (45.5%) or the following day (20.4%), and a rapid decline thereafter.<sup>8</sup> The clustering of intussusception cases during the period 3 to 7 days after receipt of RRV-TV is temporally similar to the occurrence of fever among recipients of RRV-TV in prelicensure studies,<sup>1</sup> suggesting that intussusception may be associated with replication of the rhesus-based, reassortant rotavirus vaccine. Notably, febrile responses are most marked after the first dose of RRV-TV,<sup>1</sup> and 82% of intussusception cases reported to VAERS occurring within 1 week of vaccination followed dose 1. The preponderance of intussusception cases after receipt of dose 1 may reflect a large number of first doses administered of this newly licensed vaccine, reporting bias, or a real increase in risk after dose 1 compared with subsequent doses. In contrast, in prelicensure studies of rhesus rotavirus vaccines, all cases of intussusception reported occurred after the second or third dose.<sup>3</sup>

Cases of intussusception reported to VAERS were younger and had higher rates of surgical intervention than cases reported in recent case series before availability of RRV-TV.<sup>9,10</sup> The young age at diagnosis may reflect the age at which administration of dose 1 of RRV-TV was recommended (2 months of age) and administered (6 weeks to 6 months of age). The high proportion of cases treated surgically may be attributable to: 1) reporting bias to VAERS, with better ascertainment of more severe cases; 2) the severity of disease in younger patients; or 3) the vaccine virus.

The cause of intussusception is poorly understood. Historically, in 2% to 12% of intussusception cases a focal lead point, such as a Meckel's diverticulum, can be identified.<sup>9</sup> Respiratory adenovirus infection has been associated with some cases of intussusception through the development of lymphoid hyperplasia in the gut.<sup>11-14</sup> The role of wild-type rotavirus as a causative agent for intussusception has not been well-defined. Epidemiologic data do not suggest that wild-type rotavirus infection is a significant cause of intussusception. The seasonality of each disease differs; rotavirus peaks in the winter months, whereas intussusception lacks a marked seasonality.<sup>3</sup> How-

ever, these data do not establish that rotavirus, along with other agents or factors, cannot account for a small proportion of cases.

The relationship between wild-type rotavirus infection and intussusception has been examined in 3 prospective uncontrolled studies. In a study in Japan, rotavirus was detected by electron microscopy in the stool of 37% of 30 intussusception cases.<sup>15</sup> This finding has not been replicated. Subsequent studies, in Australia and France, using less sensitive methods for identifying rotavirus, found evidence of rotavirus in 8% and 9% of intussusception cases, respectively.<sup>16,17</sup> Because these studies lacked control groups, it was impossible to determine the risk of intussusception attributable to wild-type rotavirus infection, if any. Available data are insufficient to determine the role of wild-type rotavirus as a cause of intussusception.

It is, however, biologically plausible that a rotavirus vaccine could be a cause of intussusception, even if wild-type rotavirus has no causal role. RRV-TV is a combination of rhesus and human strains of virus, which cause a local infection in the gut. Although designed to mimic wild-type rotavirus infection, the reassortant vaccine product may differ so that the risk for intussusception is increased. Lymphoid hyperplasia was present in the tissue specimens from some bowel resections and incidental appendectomies and may have acted as a focal lead point for intussusception. Vaccination also differs from wild-type rotavirus in that infection occurs at a younger age, usually 2 months of age when the first dose of vaccine is recommended. In contrast, wild-type rotavirus infection most commonly affects older infants and children (ages 4-23 months).<sup>18,19</sup> It is possible that early infection changes the risk for intussusception.

Several limitations of VAERS reports may be relevant to our study. First, because VAERS is a passive reporting system and reporting is incomplete,<sup>6,8,20,21</sup> the number of reports received underestimates the actual number of cases. In addition, at least some of the 14 reports in which intussusception could not be confirmed may have represented cases of intussusception that spontaneously resolved before their imaging study. Reports may overestimate the proportion of serious cases or cases occurring soon after vaccination; thus, VAERS data may not be representative because of reporting biases.<sup>6,8,20</sup> Finally, VAERS captures cases temporally but not necessarily causally related to the vaccine, and, in general, is unable to distinguish between cases expected by chance alone from those occurring as a result of vaccination.<sup>6,22</sup>

VAERS does not provide denominator data on the total number of persons vaccinated in the United States; therefore, rates of adverse events cannot be directly calculated.<sup>6</sup> Consequently, the number of observed reports must be compared with the number of cases expected to have occurred, which requires estimates of background incidence of the adverse event and the amount of vaccine administered. In this study, our background incidence may be overestimated for this study population (median age: 4

months), because intussusception incidence is highest in older infants. Also, the number of RRV-TV doses administered may have been overestimated because of vaccine wastage. However, these overestimates would produce a conservative result when determining the ratio of observed to expected reports.

Despite its limitations, VAERS effectively detected a possible problem soon after introduction of RRV-TV in the United States. VAERS, a passive surveillance system subject to underreporting, demonstrated at least a fourfold increase in intussusception within 1 week of receipt of RRV-TV. In response to the initial reports to VAERS, 2 studies of the association between RRV-TV and intussusception were initiated: a large, multistate, case-control study<sup>23</sup> and a cohort study investigating the relationship between rotavirus vaccine and intussusception using managed care automated databases for case finding and to ascertain vaccination status.<sup>7</sup> However, interim results for these studies were not available until October 1999. VAERS data, combined with preliminary case data from the case-control study in 1 state, and an early analysis of an ongoing postlicensure safety study prompted the CDC to recommend that use of RRV-TV be suspended on July 16, 1999.<sup>4</sup> This decision was made based on a high index of suspicion that intussusception was associated with RRV-TV. Moreover, because rotavirus season was still several months away, there was time to obtain additional data before infants were at risk for rotavirus disease. After the publicity regarding the suspension of the rotavirus vaccination program, reports to VAERS increased dramatically. More than 80% of intussusception reports to VAERS followed the announcement, and, therefore, were stimulated rather than passive reports. When preliminary results from additional studies became available, Wyeth Lederle Vaccines and Pediatrics voluntarily withdrew RRV-TV from the market on October 15, 1999, and on October 22, 1999, the ACIP withdrew its recommendation for use of RRV-TV in the United States.<sup>5</sup>

The childhood immunization schedule is increasingly complex, and each new vaccine presents challenges for monitoring safety postlicensure.<sup>24</sup> The occurrence of intussusception after receipt of rhesus-based rotavirus vaccines was noted in prelicensure studies, included in the package insert as a possible adverse reaction, and a large postlicensure safety study was initiated. Reports of intussusception among vaccinated infants to VAERS triggered an early analysis of that study, initiation of additional studies, and suspension of the US rotavirus vaccination program. VAERS—and the providers, parents, and others who report to it—are a critical component of this monitoring system that ensures safety of vaccines in the United States.

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