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

Lynn R. Zanardi, MD, MPH*; Penina Haber, MPH‡; Gina T. Mootrey, DO, MPH‡; Manette T. Niu, MD§; Melinda Wharton, MD, MPH‡; and the VAERS Working Group

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its product from the market, and the recommendation for routine use of rotavirus vaccine among US infants has been withdrawn.

From the *Epidemic Intelligence Service Program, Epidemiology Program Office, Centers for Disease Control and Prevention, Atlanta, Georgia; ‡Epidemiology and Surveillance Division, National Immunization Program, Centers for Disease Control and Prevention, Atlanta, Georgia; and the §Vaccine Safety Branch, Division of Epidemiology, Office of Biostatistics and Epidemiology, Food and Drug Administration, Rockville, Maryland. Received for publication Nov 27, 2000; accepted Jan 29, 2001.

http://www.pediatrics.org/cgi/content/full/107/6/e97

ABBREVIATIONS. RRV-TV, rhesus-human rotavirus reassortant-tetravalent vaccine; ACIP, Advisory Committee on Immunization Practices; VAERS, Vaccine Adverse Event Reporting System; 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. This recommendation was based on the morbidity and economic burden of severe dehydrating rotavirus gastroenteritis among infants and young children.

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. 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).

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. 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.

In this report, we describe the cases of intussus-
intussusception 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.

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 nonbilious 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 Mor-tality 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 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-

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Spontaneous Reports*</th>
<th>Stimulated Reports†</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (mean) interval in d from vaccination to onset of intussusception</td>
<td>4.0 (9.7)</td>
<td>6.0 (20.7)</td>
<td>.01†</td>
</tr>
<tr>
<td>Median (mean) time in d from intussusception to receipt of report</td>
<td>44.0 (54.0)</td>
<td>55.0 (77.8)</td>
<td>.35‡</td>
</tr>
</tbody>
</table>

* 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

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

Fig 1. Cases of intussusception after rotavirus vaccine by date reported to VAERS, October 1, 1998 to December 31, 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. 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. 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. 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)

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

* Includes gastrointestinal reflux, sickle cell trait, history of pyloric stenosis, ventricular septal defect, torticollis, and hypospadias.
intussusception lacks a marked seasonality. How-efers; rotavirus peaks in the winter months, whereas intussusception. The seasonality of each disease dif-
wild-type rotavirus infection is a significant cause of well-defined. Epidemiologic data do not suggest that in the gut. The role of wild-type rotavirus as a cause of intussusception has been associated with some cases 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). 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, 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. 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.

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. 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 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. 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. 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.

The childhood immunization schedule is increasingly complex, and each new vaccine presents challenges for monitoring safety postlicensure. 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.

ACKNOWLEDGMENTS

Members of the VAERS Working Group include Dr Robert Ball, Dr Miles Braun, David Davis, Dr Susan Ellenberg, Phil Ferruci, Dr Marcel Salive, Dr Frederick Varrichio, and Dr Robert Wise (FDA); Dr Robert Chen, Dr Robert Pless, Dr Vitali Pool, Tara Strine, and Wendy Wattingly (CDC); and Dr Vito Caserta (Division of Vaccine Injury Compensation, Health Resources and Services Administration). We thank the VAERS staff, particularly Linda Umoleale and Nancy Aprill, for their assistance in case confirmation; Dr Larry Schonberger for helpful suggestions on analyses; Dr Larry Schonberger, Robert Holman, and Hwa-Gan Chang for sharing New York State hospital discharge data; Dr Piotr Kramarz for providing managed care organization data; Dr Wendy Stephenson, Wyeth Lederle Vaccines and Pediatrics, for helpful discussions; Dr Peter Paradiso, Wyeth Lederle Vaccines and Pediatrics, for providing vaccine distribution data; Drs Trudy Murphy, Rebecca Prevots, and Kris Bisgard for helpful comments; Dr Paul Garguillo for statistical assistance; and physicians and other health care providers and parents who reported to VAERS.

REFERENCES

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

Lynn R. Zanardi, Penina Haber, Gina T. Mootrey, Manette T. Niu, Melinda Wharton and the VAERS Working Group

_Pediatrics_ 2001;107;e97
DOI: 10.1542/peds.107.6.e97

Updated Information & Services
including high resolution figures, can be found at:
/content/107/6/e97.full.html

References
This article cites 21 articles, 2 of which can be accessed free at:
/content/107/6/e97.full.html#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
_Infectious Disease_
/cgi/collection/infectious_diseases_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
/site/misc/reprints.xhtml
Intussusception Among Recipients of Rotavirus Vaccine: Reports to the Vaccine
Adverse Event Reporting System
Lynn R. Zanardi, Penina Haber, Gina T. Mootrey, Manette T. Niu, Melinda Wharton
and the VAERS Working Group
Pediatrics 2001;107:e97
DOI: 10.1542/peds.107.6.e97

The online version of this article, along with updated information and services, is
located on the World Wide Web at:
/content/107/6/e97.full.html