

# An Analysis of Rotavirus Vaccine Reports to the Vaccine Adverse Event Reporting System: More Than Intussusception Alone?

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**ABSTRACT.** *Background.* The rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV) was licensed on August 31, 1998, and subsequently recommended for routine infant immunizations in the United States. After ~1 million doses had been administered, an increase in acute risk of intussusception in vaccinees led to the suspension of the use of RRV-TV and its withdrawal from the market. These postmarketing safety studies focused on a single adverse event (intussusception) and, to minimize the risk of a false-positive finding, accepted only cases that met a strict case definition. Safer rotavirus vaccines are needed to prevent the substantial global morbidity and mortality caused by rotavirus infections; their development and future use may benefit from a better understanding of the postmarketing safety profile of RRV-TV beyond intussusception.

*Objective.* To characterize more completely the postmarketing surveillance safety profile of RRV-TV more completely by review and analysis of Vaccine Adverse Event Reporting System (VAERS) case reports to better understand 1) whether severe adverse events other than intussusception may have occurred after RRV-TV and 2) the likely scope of gastrointestinal illnesses, of which the previously identified, highly specific intussusception cases may account for just a fraction.

*Setting and Participants.* Infants vaccinated with RRV-TV and other vaccines in the United States and for whom a report was submitted to VAERS during September 1, 1998, to December 31, 1999.

*Methodology.* To detect adverse events of interest other than intussusception, we used proportional morbidity analysis to compare the adverse event profile of VAERS reports among infants who received routine vaccines including RRV-TV (after excluding confirmed and suspected intussusception reports) with infants who received identical vaccine combinations but without RRV-

TV. Next, to better capture all described diagnoses, signs, and symptoms associated with the suspected adverse events, a set of new codes was developed and assigned to each VAERS report. All 448 nonfatal RRV-TV-associated reports (including intussusception) were recoded manually from the clinical description on the VAERS report and categorized into clinical groups to better describe a spectrum of reported illnesses after the vaccine. Each report was assigned to one of the following hierarchical and mutually exclusive clinical groups: 1) diagnosed intussusception; 2) suspected intussusception; 3) illness consistent with either gastroenteritis or intussusception; 4) gastroenteritis; 5) other gastrointestinal diagnoses (ie, not consistent with intussusception or rotavirus-like gastroenteritis); and 6) nongastrointestinal diagnoses.

*Results.* Even after excluding intussusception cases, a higher proportion of RRV-TV reports than non-RRV-TV reports included fever and various gastrointestinal symptoms, most notably bloody stool but also vomiting, diarrhea, abdominal pain, gastroenteritis, abnormal stool, and dehydration. Distribution of RRV-TV reports by clinical groups was as follows: diagnosed intussusception (109 [24%]), suspected intussusception (36 [8%]), and illness consistent with gastroenteritis or intussusception (33 [7%]), gastroenteritis (101 [22%]), other gastrointestinal diagnoses (10 [2%]), and nongastrointestinal outcomes (159 [35%]). The median time interval between vaccination and illness onset decreased incrementally among the first 4 clinical groups: from 7 days for diagnosed intussusceptions to 3 days for gastroenteritis.

*Conclusions.* Intussusception and gastroenteritis were the most commonly reported outcomes; however, a substantial number of reports indicate signs and symptoms consistent with either illness, possibly suggestive of a spectrum of gastrointestinal illness(es) related to RRV-TV. Although VAERS data have recognized limitations such as underreporting (that may differ by vaccine) and are nearly always insufficient to prove causality between a vaccine and an adverse event, this safety profile of RRV-TV may aid better understanding of the pathophysiology of intussusception as well as development of future safer rotavirus vaccines. *Pediatrics* 2004;113:e353–e359. URL: <http://www.pediatrics.org/cgi/content/full/113/4/e353>; rotavirus vaccine, Vaccine Adverse Event Reporting System, VAERS, vaccine safety, postmarketing surveillance, rotavirus vaccine.

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ABBREVIATIONS. RRV-TV, rhesus-human rotavirus reassortant-tetravalent vaccine; VAERS, Vaccine Adverse Event Reporting System; VAE, vaccine adverse event; COSTART, Coding Symbols for a Thesaurus of Adverse Reaction Terms; CI, confidence interval; SIDS, sudden infant death syndrome.

Rotavirus infection is the leading cause of severe diarrheal illness in infants and young children throughout the world. It is estimated that ~440 000 deaths occur per year from rotavirus worldwide among children <5 years old.<sup>1</sup> Rotavirus vaccine offers the opportunity to reduce this burden substantially.<sup>2</sup> A live, oral, recombinant, rhesus-human rotavirus reassortant-tetravalent vaccine (RRV-TV) was licensed for use in the United States on August 31, 1998, and was recommended for routine use in infants as a 3-dose series at ages 2, 4, and 6 months.<sup>3,4</sup>

In prelicensure trials in infants, the most common adverse event observed was low-grade fever (38°C/100.4°F). Decreased appetite, irritability, and decreased activity were also more common among recipients of RRV-TV than among placebo recipients but seemed to be associated with fever.<sup>5</sup> An increased rate of diarrhea after the first dose was observed in 1 trial.<sup>6</sup> Over the entire vaccine-development program, 5 cases of intussusceptions were observed among 10 054 vaccinees, compared with 1 case among 4633 controls.<sup>7</sup> Although this difference was not statistically significant, it did result in specific admonition to continue postlicensure surveillance for intussusception and inclusion in the product label as a possible adverse event.

Several months after the licensure of RRV-TV, the Vaccine Adverse Event Reporting System (VAERS)<sup>8</sup> detected a higher-than-expected number of intussusception reports in infants within 1 week of vaccination with RRV-TV. On July 16, 1999, the Centers for Disease Control and Prevention and the American Academy of Pediatrics (AAP) recommended that routine use of the vaccine be suspended.<sup>9</sup> Case-control and cohort studies confirmed an elevated acute risk between RRV-TV and intussusception.<sup>10,11</sup> In October 1999, the manufacturer withdrew RRV-TV, followed by withdrawal of recommendation for its use.<sup>12</sup>

A safe and effective rotavirus vaccine remains badly needed, especially for developing countries.<sup>2</sup> The development, future trials, and use of any new rotavirus vaccine may benefit from a more complete understanding of the safety profile of RRV-TV. As highlighted by the intussusception experience, post-marketing surveillance data play a key role because of the inherent limitations of prelicensure trials regarding sample size, short duration of follow-up, and population heterogeneity.<sup>8,13</sup>

Almost all attention on the safety of RRV-TV to date has focused on intussusception. To minimize the possibility of a false-positive finding, the major postmarketing safety studies of RRV-TV have generally included only the cases of intussusception that met a highly specific case definition (ie, confirmed by radiology, surgery, or autopsy).<sup>10,11,14</sup> This increased specificity in case identification inherently comes at the price of decreased sensitivity.<sup>15</sup> In this article, we use 2 approaches of examining RRV-TV VAERS reports to characterize the vaccine's safety profile more completely. This includes a review of the reports to VAERS to better understand 1) whether severe adverse events other than intussusception may have

occurred after RRV-TV and 2) the likely scope of gastrointestinal illnesses, of which the previously identified highly specific intussusception cases may account for just a fraction.

## METHODS

### The VAERS

The structure and methods of VAERS have been described.<sup>8</sup> In brief, VAERS is a national postmarketing passive surveillance system for vaccine adverse events (VAEs) after receipt of US-licensed vaccines. It is operated jointly by the Centers for Disease Control and Prevention and the Food and Drug Administration and receives reports from physicians, vaccine providers, vaccine manufacturers, vaccinees or their caregivers, and others.<sup>8,16-19</sup> All persons suspecting a possible relationship between a vaccination and subsequent adverse event are encouraged to report. The main objective of VAERS is to serve as a sentinel for detecting events potentially related to receipt of a vaccine, especially new vaccines. Reporters are asked to describe the adverse event in their own words; reports then are coded by trained nurses using *Coding Symbols for a Thesaurus of Adverse Reaction Terms* (COSTART).<sup>20</sup> By federal regulations, as implemented on the VAERS form, a report is considered "serious" if the event results in death, hospitalization, a life-threatening event, disability, or a prolonged hospital stay.<sup>21</sup>

For this study, we reviewed all VAERS reports from September 1, 1998, through December 31, 1999, in infants <1 year old. Each adverse event was categorized by severity as fatal, nonfatal serious, or nonserious. Serious reports indicating a possible gastrointestinal outcome were reviewed by L.R.Z. using medical records and surgical or radiologic reports. Autopsy reports were reviewed for all fatal reports.

### Proportional Morbidity Analysis

We used proportional morbidity analysis, a method widely used to analyze reports of suspected adverse drug reactions,<sup>22-24</sup> to describe more completely the safety profile of RRV-TV more completely. The method compares the proportion of reported events for a given vaccine with the proportion of the same events for another vaccine or group of vaccines administered simultaneously. An event with a higher proportion in the specific vaccine(s) of interest than the comparison vaccine(s) is a "signal" that requires additional attention or study. Because we were interested mostly in what adverse events occurred after RRV-TV other than intussusception, we first excluded from the total RRV-TV VAERS reports during the study period any confirmed or suspected intussusception cases described previously.<sup>14</sup> We next excluded the VAERS reports indicating receipt of RRV-TV alone. The remaining RRV-TV reports that indicated receipt of other vaccines simultaneously constitute group 1. We then identified as group 2 VAERS reports that did not indicate administration of RRV-TV but that otherwise had identical combinations of vaccines to group 1. We finally compared the proportion of a specific reported COSTART code in group 1 to the proportion of the same code in group 2.

VAERS data were analyzed by using SAS 8 software (SAS Institute Inc, Cary, NC). To evaluate the differences in reported outcomes, StatXact 5 (Cytel Software Corporation, Cambridge, MA) was applied to calculate 95% confidence intervals (CIs) of the ratios of proportions. The 95% CIs address only the random variations in different adverse events. There may be systematic biases in the VAERS data used in calculating these CIs; the 95% CIs do not account for such potential biases.

### Manual Clinical Grouping

To explore more completely the range of gastrointestinal events reported to VAERS after receipt of RRV-TV, all 448 nonfatal RRV-TV VAERS reports (including confirmed and suspected intussusception reports) for the same time period and age group were reviewed by L.R.Z., who was blinded to the original COSTART codes assigned by VAERS. To better capture all described diagnoses, signs, and symptoms associated with the suspected adverse events, a set of new codes was developed and assigned to each VAERS report. These new codes described gastrointestinal outcomes in greater detail than the COSTART code (eg, separate new codes were created for "currant jelly stool,"

“bloody diarrhea,” “heme-positive stool,” etc, which all would have been described by using the same COSTART code).

Each report was assigned to 1 of the following hierarchical and mutually exclusive clinical groups: 1) diagnosed intussusception; 2) suspected intussusception; 3) illness consistent with either gastroenteritis or intussusception; 4) gastroenteritis; 5) other gastrointestinal diagnoses (ie, not consistent with intussusception or rotavirus-like gastroenteritis); and 6) nongastrointestinal diagnoses. Reports were classified according to the following hierarchy: all reports with a diagnosis of intussusception were grouped as “intussusception”; all remaining reports with mention of suspected (but not confirmed) intussusception, currant jelly stools, bloody stools, rectal bleeding, or passing blood per rectum were grouped as “suspected intussusception”; all remaining reports with mention of dehydration, diarrhea with blood, dark stools, vomiting, or abdominal pain were grouped as “illness consistent with either gastroenteritis or intussusception”; all remaining reports with mention of gastroenteritis, diarrhea without blood, loose stools, frequent stools, or abnormal stools were grouped as “gastroenteritis”; all remaining reports with a definitive gastrointestinal diagnosis (excluding intussusception and gastroenteritis) were grouped as “other gastrointestinal illness”; and all remaining reports were grouped as “nongastrointestinal diagnosis” (most frequently reported outcomes were fever, persisting crying, rash, and decreased appetite). SAS 8 software (SAS Institute Inc) was used for data analysis. Reports in the other gastrointestinal and nongastrointestinal categories are described but were not included in the manual clinical grouping analysis.

## RESULTS

During the study period, 455 reports after RRV-TV were received. Of the 115 confirmed and suspected intussusception reports, 17 were received during the 10.5 months before the initial publication describing intussusception as a potential adverse event after RRV-TV in July 1999, and 98 were received during the 5.5 months after this publication.<sup>9</sup> This was an 11.1-fold increase from 1.6 intussusception reports per month in the prepublication period to 17.8 reports per month in the postpublication period. In contrast, 213 nonintussusception RRV-TV VAERS reports were received in the prepublication period (20.3 reports per month), and 127 nonintussusception reports were received in the postpublication period (23.1 reports per month). This is a 1.1-fold increase. Because the publication seems to have had only marginal influence on the rate of reporting for nonintussusception reports, this article combines both periods.

### Proportional Morbidity Analysis

From the total of 455 reports after RRV-TV, we excluded 1) 115 reports of confirmed or suspected intussusception and 2) 60 reports indicating receipt of RRV-TV alone. The remaining 280 (62%) nonintussusception reports indicated receipt of RRV-TV with other vaccines and constitute group 1. For the same age group and time period, there were 1420 VAERS reports with other recommended vaccines. Of these, 1248 (88%) reports noted the exact same vaccine combinations as group 1 but without RRV-TV and thus constitute group 2. Among nonfatal reports, 76 (28%) were nonfatal serious reports in group 1, compared with 234 (20%) nonfatal serious reports in group 2 (Table 1). This difference was mainly because of a higher proportion of hospitalizations in group 1 (27%) than in group 2 (18%). The proportion of fatal reports in group 1 (2%) was lower than in group 2 (7%), however.

**TABLE 1.** Reports of Nonintussusception Events by Severity and Vaccine Exposure Groups in Infants, VAERS, September 1, 1998 to December 31, 1999

	With RRV-TV (Group 1), N (%)	Without RRV-TV (Group 2), N (%)
Nonserious	199 (71)	923 (74)
Nonfatal serious*	76 (28)	234 (20)
Hospitalized	73 (27)	208 (18)
Disabled	5 (2)	43 (4)
Life-threatening illness	12 (4)	48 (4)
Prolonged hospital stay	3 (1)	24 (2)
Fatal	5 (2)	91 (7)
Total nonintussusception	280† (100)	1,248 (100)

\* Subcategories are not mutually exclusive.

† Sixty reports after sole RRV-TV were not included in this analysis.

The interval in days from vaccination to symptom onset was longer for RRV-TV recipients. Group 1 had a mean (median) interval of 5.3 (3.0) days (range: 0–73 days), and group 2 had a mean (median) interval of 4.0 (0) days (range: 0–638 days). An interval of 0 days indicates that the adverse event was observed on the same day as vaccination. The male to female ratio was similar in both groups. The mean (median) age for groups 1 and 2 was 3.1 (3) and 3.6 (3) months, respectively. For group 1, 212 (83%) reports followed the first dose of RRV-TV, 35 (14%) reports followed the second dose, and 10 (4%) reports followed the third dose.

Despite excluding confirmed and suspected intussusception cases, a higher proportion of group 1 reports compared with group 2 listed gastrointestinal signs and symptoms, most notably vomiting, diarrhea, and dehydration but also gastroenteritis, abdominal pain, blood in the stool, abdominal pain, and abnormal stool (Table 2). Nineteen nonfatal serious reports in group 1 noted hospitalizations because of gastrointestinal illnesses. Two reports indicated nonintussusception types of bowel obstruction: volvulus and a bowel obstruction resulting from a colonic stricture. Thirteen reports indicated gastroenteritis, the majority of which involved hospitalization for dehydration. One child with gastroenteritis had a positive stool culture for *Campylobacter*. Two reports indicated milk protein allergy. One report indicated allergic reaction, pneumonia, and bloody stools lasting 2 months. One report described inconsolable crying, diarrhea, bloody stool, vomiting, fever, and anorexia without providing a final diagnosis.

Reports in group 1 classified as serious included 5 deaths, of which 3 were attributed (per autopsy) to probable sudden infant death syndrome (SIDS); 1 of these also had a positive blood culture for nontypeable *Haemophilus influenzae*. One report indicated apnea and asphyxia as a cause of death, and 1 indicated urosepsis (*Escherichia coli*). For the same time period, in group 2 there were 91 (7%) reported deaths, of which 51 were attributed to SIDS or unusual sleep position.

**TABLE 2.** Most Frequent Nonfatal Serious and Nonserious COSTARTS\* by Vaccine Exposure Group Among Infants, VAERS, September 1, 1998 to December 31, 1999†

	With RRV-TV (Group 1) N (%)	Without RRV-TV (Group 2) N (%)	Ratio of Proportions	95% CI
<b>Nonfatal serious‡</b>				
	N = 76	N = 234		
Vomiting	33 (43)	25 (11)	3.9	2.6–6.3
Diarrhea	30 (39)	13 (6)	7.1	3.9–12.8
Fever	29 (38)	59 (25)	1.5	1.0–2.1
Agitation	18 (24)	43 (18)	1.3	0.8–2.1
Dehydration	16 (21)	12 (5)	4.1	2.1–8.2
Somnolence	12 (16)	22 (9)	1.7	0.9–3.3
Anorexia	10 (13)	25 (11)	1.2	0.6–2.4
Convulsions	10 (13)	70 (30)	0.4	0.2–0.8
Gastroenteritis	9 (12)	4 (2)	6.9	2.3–21.0
GI disorder (not specified)	9 (12)	12 (5)	2.3	1.0–5.1
Abdominal pain	9 (12)	2 (1)	13.9	3.4–65.1
<b>Nonserious</b>				
	N = 199	N = 923		
Fever	66 (33)	234 (25)	1.3	1.0–1.6
Diarrhea	64 (32)	25 (3)	11.9	7.7–18.3
Agitation	46 (23)	244 (26)	0.9	0.7–1.1
Vomiting	33 (17)	51 (6)	3.0	2.0–4.4
Bloody stool	25 (13)	1 (.1)	116.0	20.0–673.7
Anorexia	19 (10)	61 (7)	1.4	0.9–2.3
Inconsolable crying	17 (9)	144 (16)	0.5	0.3–0.9
Abdominal pain	17 (9)	8 (1)	9.9	4.4–22.0
Abnormal stool	15 (8)	2 (.2)	34.5	8.9–135.7
Hypertonia	10 (5)	31 (3)	1.5	0.8–2.9
Rash	10 (5)	87 (9)	0.5	0.3–1.0

\* Reports are not mutually exclusive, i.e., one or more adverse events may be reported for the same illness.

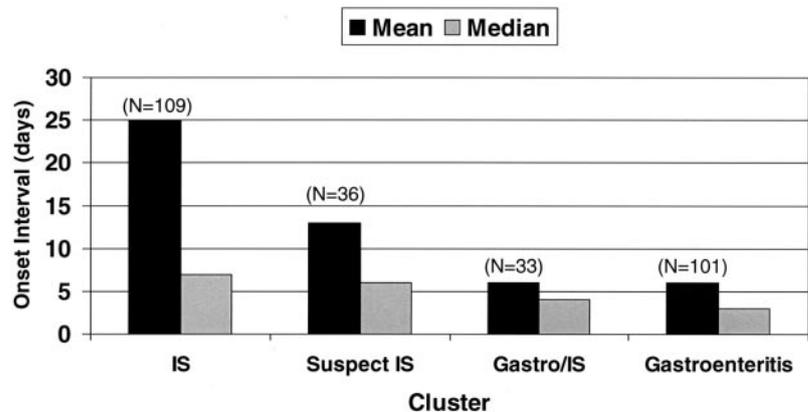
† Confirmed and suspected intussusception cases excluded.

‡ There were 5 reports of bloody stool in the nonfatal serious group 1 and 1 report in group 2 (ratio of proportions = 15.4; 95% CI: 2.41–98.64).

### Manual Clinical Grouping

Exploratory analysis of all 448 nonfatal reports using new codes, instead of the more general VAERS COSTART codes, yielded the following distribution: 109 (24%) diagnosed intussusception, 36 (8%) suspected intussusception, 33 (7%) illness consistent with either gastroenteritis or intussusception, 101 (22%) gastroenteritis, 10 (2%) other gastrointestinal diagnoses, and 159 (35%) nongastrointestinal outcomes. The median time interval from vaccination to onset of illness decreased progressively among the first 4 clinical groups from 7 days for diagnosed intussusception to 3 days for gastroenteritis (Fig 1). The most frequently reported signs and symptoms in the 4 intussusception/gastroenteritis groups are described in Table 3.

The 10 reports in the “other gastrointestinal” group included the following diagnoses: diarrheal illness caused by identified microorganisms (*Giardia*, *Campylobacter*, or *Aeromonas*), pneumatosis intestinalis, milk allergy, other gastrointestinal obstruction (strictures, volvulus, or pyloric stenosis), and gastroesophageal reflux disease. The most common diagnoses and symptoms in the nongastrointestinal group included constitutional symptoms (eg, fever, irritability, lethargy, and decreased appetite), rash, local reactions to injectable vaccine, and seizures or seizure-like activity. Of the 7 fatal reports, 5 were not gastrointestinal-related reports and are described in the previous section. One intussusception death is described elsewhere<sup>12</sup>; 1 child died from septic shock due to bowel ischemia with cecal dehiscence of unknown etiology.



**Fig 1.** Mean and median interval from receipt of rotavirus vaccine to symptom onset for clinical groups; the range of values from intussusception (IS) to gastroenteritis (GASTRO) are 0 to 152, 0 to 80, 0 to 34, and 0 to 148, respectively, for each of the 4 categories.

**TABLE 3.** Frequency of Diagnoses, Signs, and Symptoms by Clinical Group\*

Intussusception† (N = 109)	Suspect Intussusception (N = 36)	Illness Consistent With Either Intussusception or Gastroenteritis (N = 33)	Gastroenteritis (N = 101)
Vomiting (69%) Bloody stool‡ (36%) Irritability (26%)	Bloody stool‡ (86%) Irritability (50%) Vomiting (31%)	Vomiting (55%) Fever (39%) Diarrhea with blood ± mucous (33%) Irritability (30%) Abdominal pain (27%)	Diarrhea without blood (82%) Fever (39%) Vomiting (34%)
Lethargy (24%) Fever (21%) Dehydration (14%)	Diarrhea (22%) Abdominal pain (19%) Diagnosis of suspect intussusception (17%) Decreased appetite (14%) Fever (11%)		Decreased appetite (16%) Irritability (16%) Dehydration (14%)
Decreased appetite (12%) Abdominal pain (8%)			

\* Diagnoses, signs, and symptoms present in  $\geq 10\%$  of reports.

† Based on 72 reports indicating at least 1 sign and/or symptom in addition to the diagnosis of intussusception; this excludes 37 reports with only an intussusception diagnosis.

‡ Includes currant jelly stool, bloody stool, or bleeding per rectum.

## DISCUSSION

We used proportional morbidity analysis to describe the safety profile of RRV-TV more completely and did not find evidence of any rare, severe adverse events other than the previously described intussusception. However, compared with non-RRV-TV VAERS reports, we did find that a higher proportion of RRV-TV reports were classified as serious, mainly because of a higher proportion of hospitalizations among the RRV-TV recipients. Gastrointestinal symptoms were more common among the RRV-TV recipients; hence, diarrhea, vomiting, and resulting dehydration accounted for some of these hospitalizations. These findings were not surprising, given that RRV-TV contains live, orally administered virus, and an increased rate of gastroenteritis was observed in 1 clinical trial.<sup>6</sup>

However, an unexpectedly high proportion of RRV-TV reports also described bloody stool, a condition not reported previously in prelicensure trials. After additional review of these case reports, we noted that the COSTART for bloody stools had been used for findings ranging from heme-positive stool to currant jelly stool. To ensure a more complete and systematic description of gastrointestinal illness reports, we developed new codes more specific to gastrointestinal illnesses and manually recoded the clinical features of all the RRV-TV VAERS reports de novo, blinded to the original COSTART code. A spectrum of gastrointestinal illness emerged from the manual review of VAERS reports using the new codes, ranging from “confirmed intussusception” to “gastroenteritis.”

Clinical case reviews, including our review of the RRV-TV VAERS reports and the actual classification of each report into a category for the manual grouping analysis, are inherently qualitative and involve clinical judgment. We sought to reduce this subjectivity by having several physicians review and agree by consensus on the coding and grouping used. Most importantly, the stepwise decrease in mean and median onset interval among the 4 clinical categories, each with at least moderate sample sizes (106 to 33), provides independent quantitative evidence that these categories most likely represented a real clinical

spectrum of RRV-TV effects. These findings should be viewed considering the various strengths and weaknesses of VAERS data as applied to this specific situation.<sup>8,16,17</sup>

Pharmacovigilance systems such as VAERS, with its national scope, rely on clinicians to detect signals of rare reactions.<sup>13</sup> VAERS has demonstrated its value as a sentinel for previously unknown VAEs<sup>25</sup> as well as increases in known adverse events.<sup>26</sup> Most relevantly, VAERS identified intussusception as a potential risk shortly after introduction of RRV-TV in the United States.<sup>14,27</sup> Although VAERS has been successful in generating VAE signals, it is usually unable to distinguish between cases expected by chance alone from those that occur as a result of vaccination.<sup>8,13,16</sup> Therefore, follow-up studies are required to confirm a suspected association.

Similar to all passive surveillance systems, VAERS suffers from underreporting, and reporting rates vary by vaccine, suspected adverse event, and circumstance. For example, reporting is more likely when 1) VAEs are severe, 2) VAEs occur shortly after vaccination, 3) the vaccine is a new pharmaceutical product, and 4) there has been publicity about the adverse event.<sup>18,28</sup> Our proportional morbidity analysis may have been affected by the latter 2 limitations; however, all publicity was specific to intussusception, whereas the proportional morbidity analysis focused on events other than intussusception. Because of reporting biases in VAERS, more severe events are more likely to be reported and thus represented in the clinical groupings; however, clinical descriptors for all events should remain valid. Finally, because VAERS includes case reports for vaccinated but not unvaccinated persons and does not contain population data on doses administered, we were unable to estimate relative risk or calculate a rate.

Proportional morbidity analysis is generally less accurate than analyses based on incidence rates in detection of potential signals in pharmacovigilance.<sup>22–24</sup> We observed a higher proportion of convulsions in vaccine recipients who did not receive RRV-TV (group 2) than in the RRV-TV recipients (group 1). Because proportional morbidity analysis

compares proportions rather than rates of observed events, the proportion of convulsions in the group that did not receive RRV-TV (group 2) may be higher than in group 1 because of the excess of gastrointestinal reports in the group that received RRV-TV. In fact, when the reports indicating gastrointestinal symptoms are removed from analysis, the proportion of convulsions in group 2 is no longer elevated when compared with group 1. In contrast, when reports indicating convulsions are removed, the proportion of gastrointestinal symptoms remains higher in group 1 with the exception of GI disorder (not specified). We also observed a higher proportion of deaths in the non-RRV-TV group (group 2). Although there is no apparent reason for this difference, confounding by socioeconomic status and other factors may have contributed to this finding. Infants who received RRV-TV were more likely to be of higher socioeconomic status than children who did not receive RRV-TV,<sup>10,29</sup> and infant mortality decreases with higher socioeconomic status.<sup>30</sup> This may explain the lower non-SIDS deaths among RRV-TV recipients.

The presence of bloody stool in many nonintussusception VAERS reports after RRV-TV may represent occult cases of intussusception that resolved spontaneously before they were diagnosed.<sup>31,32</sup> Another possible explanation is that these represent coinfection with another organism that causes bloody diarrhea at the time of or shortly after vaccination with RRV-TV.<sup>33</sup> This is probably unlikely to be a major cause, because, in the United States, one would have expected culture results to be reported on some of the cases of bloody diarrhea, and only 3 VAERS reports indicated a coinfection. Finally, the vaccine may cause bloody stools and/or bloody diarrhea irrespective of coinfection or occult intussusception. Although wild rotavirus does not typically cause bloody stools or bloody diarrhea, RRV-TV is a reassortant virus of human and rhesus rotavirus strains. Therefore, it is possible that the vaccine virus is more invasive than wild rotavirus, causing bloody diarrhea and/or bloody stools. This may also explain why intussusception was seen shortly after vaccination with RRV-TV but is not believed to be associated with wild rotavirus.<sup>7,11,34</sup>

### CONCLUSIONS

Our study suggests that the 109 “diagnosed intussusception” reports may represent one end of a clinical spectrum of gastrointestinal-related illness (not previously well described) that is associated with RRV-TV. Part of this spectrum includes gastroenteritis and bloody stools. These findings emphasize the importance of postlicensure surveillance to detect and evaluate rare VAEs not seen in clinical studies.

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