Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants

Irene M. Shui, ScD

James Baggs, PhD

Manish Patel, MD, MPH

Umesh D. Parashar, MBBS, MPH

Melisa Rett, MPH

Edward A. Belongia, MD

Simon J. Hambidge, MD, PhD

Jason M. Glanz, PhD

Nicola P. Klein, MD, PhD

Eric Weintraub, MPH

I N 1999, THE RHESUS TETRAVALENT rotavirus vaccine (RRV, Rotashield, Wyeth) was withdrawn from the US market due to a significantly increased risk of intussusception following vaccination. The largest increased risk (>30-fold) of intussusception was observed during the 3 to 7 days following the first dose of the vaccine.[1-3]

Since then, 2 vaccines to prevent rotavirus infection have been licensed for use in the United States: a pentavalent rotavirus vaccine (RV5, RotaTeq, Merck) in 2006 and a monovalent rotavirus vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals) in 2008.[4,5] The pentavalent rotavirus vaccine is a 3-dose series that, according to the Advisory Committee on Immunization Practices, should be given at ages 2, 4, and 6 months; RV1 is a 2-dose series to be

See also Patient Page.

Author Video Interview available at www.jama.com.

Context Current rotavirus vaccines were not associated with intussusception in large prelicensure trials. However, recent postlicensure data from international settings suggest the possibility of a low-level elevated risk, primarily in the first week after the first vaccine dose.

Objective To examine the risk of intussusception following pentavalent rotavirus vaccine (RV5) in US infants.

Design, Setting, and Patients This cohort study included infants 4 to 34 weeks of age, enrolled in the Vaccine Safety Datalink (VSD) who received RV5 from May 2006-February 2010. We calculated standardized incidence ratios (SIRs), relative risks (RRs), and 95% confidence intervals for the association between intussusception and RV5 by comparing the rates of intussusception in infants who had received RV5 with the rates of intussusception in infants who received other recommended vaccines without concomitant RV5 during the concurrent period and with the expected number of intussusception visits based on background rates assessed prior to US licensure of the RV5 (2001-2005).

Main Outcome Measure Intussusception occurring in the 1- to 7-day and 1- to 30-day risk windows following RV5 vaccination.

Results During the study period, 786 725 total RV5 doses, which included 309 844 first doses, were administered. We did not observe a statistically significant increased risk of intussusception with RV5 for either comparison group following any dose in either the 1- to 7-day or 1- to 30-day risk window. For the 1- to 30-day window following all RV5 doses, we observed 21 cases of intussusception compared with 20.9 expected cases (SIR, 1.01; 95% CI, 0.62-1.54); following dose 1, we observed 7 cases compared with 5.7 expected cases (SIR, 1.23; 95% CI, 0.5-2.54). For the 1- to 7-day window following all RV5 doses, we observed 4 cases compared with 4.3 expected cases (SIR, 0.92; 95% CI, 0.25-2.36); for dose 1, we observed 1 case compared with 0.8 expected case (SIR, 1.21; 95% CI, 0.03-6.75). The upper 95% CI limit of the SIR (6.75) from the historical comparison translates to an upper limit for the attributable risk of 1 intussusception case per 65 287 RV5 dose-1 recipients.

Conclusion Among US infants aged 4 to 34 weeks who received RV5, the risk of intussusception was not increased compared with infants who did not receive the rotavirus vaccine.

Author Affiliations: Department of Epidemiology, Harvard School of Public Health (Dr Shui), and Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, Massachusetts (Dr Shui and Ms Rett); Centers for Disease Control and Prevention, Atlanta, Georgia (Drs Baggs, Patel, and Parashar and Mr Weintraub); Marshfield Clinic Research Foundation, Marshfield, Wisconsin (Dr Belongia); Institute for Health Research, Kaiser Permanente Colorado (Drs Hambidge and Glanz), Community Health Services, Denver Health (Dr Hambidge), and Department of Epidemiology, University of Colorado School of Public Health, Denver (Drs Hambidge and Glanz); Vaccine Study Center, Northern California Kaiser Permanente, Oakland (Dr Klein).
Corresponding Author: Irene M. Shui, ScD, Department of Epidemiology, Harvard School of Public Health, 677 Huntington Ave, Boston, MA 02115 (ishui@hsph.harvard.edu).

given at ages 2 and 4 months. The maximum recommended age for the first dose is 15 weeks and all doses must be administered by 8 months. Because of the prior association between RRV and intussusception, large prelicensure trials that involved approximately 70 000 infants for the RV5 vaccine and 60 000 infants for the RV1 vaccine were conducted. No increased risk for intussusception was observed during either the 42-day period after the RV5 vaccination or the 30-day period after the RV1 vaccination.[6,7]

A postlicensure safety study in the United States performed in the Vaccine Safety Datalink (VSD) population after 2 years of surveillance (~200 000 doses) did not find evidence for an increased risk of intussusception in the 30-day period following RV5, nor did the study detect any confirmed cases of intussusception following the first dose.[8] However, 2 recent international postlicensure evaluations have observed an increased risk of intussusception in the first week after administration of the first dose of rotavirus vaccines. The first, an Australian study, found a statistically significant increased risk of nearly 5-fold for intussusception in the week following the first dose of RV5.[9] The second study, conducted in Mexico and Brazil, found an approximate 5-fold increased risk of intussusception in the first week following the first dose of RV1 in Mexico but not in Brazil.[10]

As of February 2010, 786 725 doses of RV5 had been administered in the VSD population, of which 309 844 were first doses. Because of the new data on intussusception risk from international settings and the almost 4-fold increase in rotavirus vaccine doses administered in the VSD population since the previous analysis, we reexamined intussusception risk associated with rotavirus vaccination in the VSD population, with a specific focus on the 1- to 7-day risk window after dose 1 administration. In addition, we characterized population-level trends in the incidence of intussusception since 1991 in the VSD population.

METHODS
Study Population and Case Ascertainment

The VSD is a large collaborative project between the US Centers for Disease Control and Prevention and managed care organizations, 8 of which participated in this study. The participating sites provide access to electronic data assembled using a standardized data dictionary containing information on demographic and medical services for their members, such as age and sex, health plan enrollment, vaccinations, hospitalizations, outpatient clinic visits, emergency department (ED) visits, urgent care visits, mortality data, and additional birth information (eg, birth weight) when available. Additionally, members' medical records are available for review.[11]

Our study population included the cohort of infants aged 4 to 34 weeks from May 2006 to February 2010 who received at least 1 licensed recommended childhood vaccine. We excluded infants who received RV5 doses at ages older than recommended (6.5% of first doses were administered at age >15 weeks and <1% of third doses were administered at >34 weeks). Hospital, ED, and outpatient visits for intussusception occurring 1 to 30 days following vaccination were identified using the *International Classification of Diseases, Ninth Revision (ICD-9)* codes (*ICD-9* code 543.9 for other and unspecified disease of the appendix including intussusception; and *ICD-9* code 560.0 for intussusception).

The following algorithm was applied if the infant was seen in 2 or more different settings within a 2-day period. If an intussusception code occurred during an ED or outpatient visit and a subsequent code was given for an inpatient admission, the episode was classified as a hospital event. If the first code was given during an ED or hospital visit and a subsequent code was given in the outpatient setting, the visit was classified as an ED visit or hospitalization, respectively. Visits were only classified as outpatient if the infant had a diagnosis code in an outpatient setting without indication of referral to the ED or hospital.

We excluded outpatient-only visits from our calculation of background rates because they were unlikely to be true cases of intussusception. We only considered the first intussusception episode for our study population because it would be rare for an infant to have 2 independent intussusception episodes during the first 47 weeks of life and subsequent codes that would likely be due to follow-up visits were excluded. We validated intussusception visits identified by the *ICD-9* codes from 2006-2010 through medical record review using criteria based on the Brighton Collaboration definition (see eTable 1 for criteria, available at http://www.jama.com).[12] This study was approved by the institutional review boards at the respective institutions. The human subjects committees determined that the study met the regulatory requirements necessary to waive informed consent.

Analytic Approach

We assessed the association between RV5 vaccine and intussusception by comparing the rates of intussusception in infants who had received RV5 with the rates of intussusception in infants who received other recommended vaccines without concomitant RV5 during the concurrent period (May 2006-February 2010) and with the expected number of intussusception visits based on background rates (2001-2005). Because vaccine uptake for RV1 in the VSD population was minimal, infants who received RV1 were excluded from the analysis.

For the concurrent comparison, we used exact logistic regression to assess whether the risk of intussusception was higher in infants receiving RV5 than the risk in a group of infants of the same age range receiving other vaccines but not concomitant RV5. Only medical-record confirmed cases were included in this analysis. Furthermore, we describe the positive predictive value (PPV) for the *ICD-9* codes. Models were adjusted for age using the following age groups: 4 to 15 weeks (dose 1), 16 to 24 weeks (dose 2), and 25 to 34 weeks (dose 3).

For the historical comparison, we first calculated background rates for intussusception visits from 1991 to 2009. Using the electronically available data, the incidence of ED and hospital visits with the specified *ICD-9* codes 543.9 and 560.0 was determined for infants aged 4 to 47 weeks enrolled in VSD from 1991 through 2009. Rates were stratified by week of age and year of diagnosis; these rates were not based on diagnoses confirmed by medical record review. To avoid biasing our analyses due to the downward secular trend in the rates prior to 2001 (**FIGURE 1**), we restricted to more recent years, 2001-2005 for the historical comparison. To account for variation of intussusception by age in the infant population, we stratified by week of age (**FIGURE 2**) and by managed care organization site.

We calculated the expected number of visits for intussusception using the age and site distribution in the RV5 exposed population and the unexposed comparison rates. The standardized incidence ratio (SIR) was computed by dividing the number of observed visits for intussusception following RV5 by the number of expected visits; corresponding 95% confidence intervals were determined using the Poisson distribution. Because we did not have access to chart review data for the background rates, these rates were based on both confirmed and nonconfirmed cases. Thus, both confirmed and nonconfirmed visits for intussusception following RV5 in the ED or hospital settings were included in this analysis to complement the background rates. Intussusception codes from the outpatient setting without a record of an ED admission or hospitalization were excluded from the analysis using the historical rates due to the low PPV (22%) for these codes.

For both comparison groups, we conducted separate analyses for each dose and for both the 1- to 7-day or the 1- to 30-day risk window following vaccination. Analyses were conducted using SAS version 9.2 (SAS Institute) and R (http://cran.r-project.org) statistical packages. All statistical tests were 2 sided and $P < .05$ were considered statistically significant.

RESULTS

FIGURE 3 describes the intussusception cases identified during the study period (2006-2010). A total of 56 cases were identified from the electronic medical records in either the hospital, ED, or outpatient settings in the 30 days following either an RV5 (n=30) or comparison vaccine (n=26). Twenty-one of the 30 post-RV5 cases were diagnosed in the ED or hospital and were included in the analysis using the historical rates comparison.
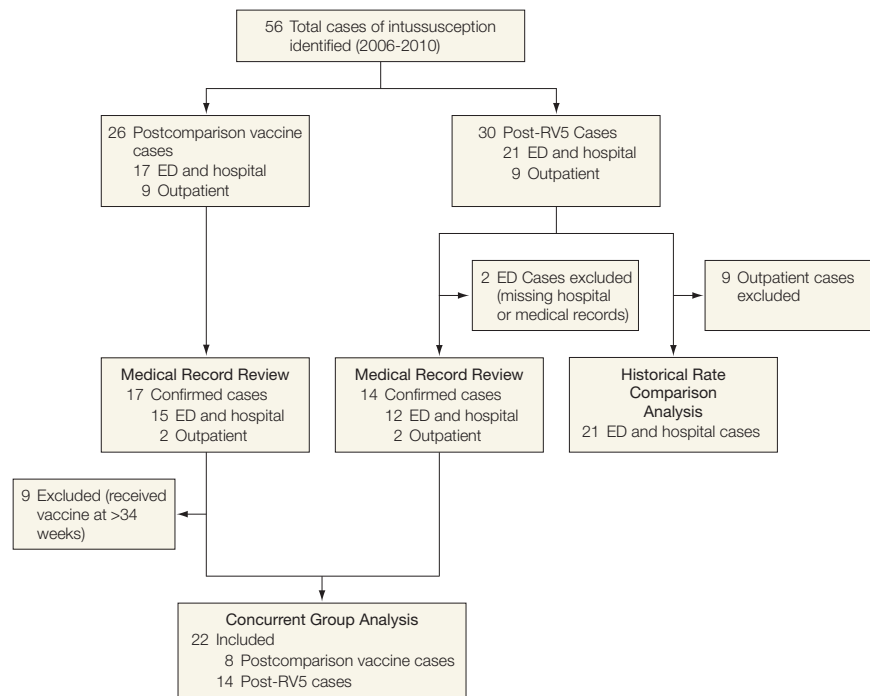
For the concurrent comparison, we completed medical record review. Medical records for 2 cases after RV5 vaccination from the ED setting were not available, so these cases were excluded

Figure 1. Rates of Emergency Department and Hospital Visits for Intussusception in the Vaccine Safety Datalink From 1991 to 2009[a]
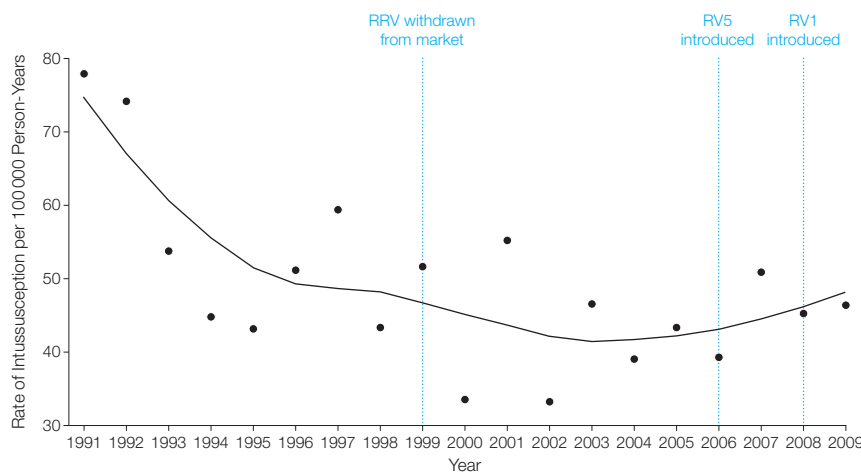
[a] Smoothed line fit using local polynomial regression.
RV5 indicates pentavalent rotavirus vaccine; RRV, rhesus tetravalent rotavirus vaccine; RV1, monavalent rotavirus vaccine. The actual number of intussusception and 95% confidence intervals are reported in eTable 2B, available at http://www.jama.com.

Figure 2. Rates of Emergency Department and Hospital Visits for Intussusception in the Vaccine Safety Datalink from 1991 to 2009[a]
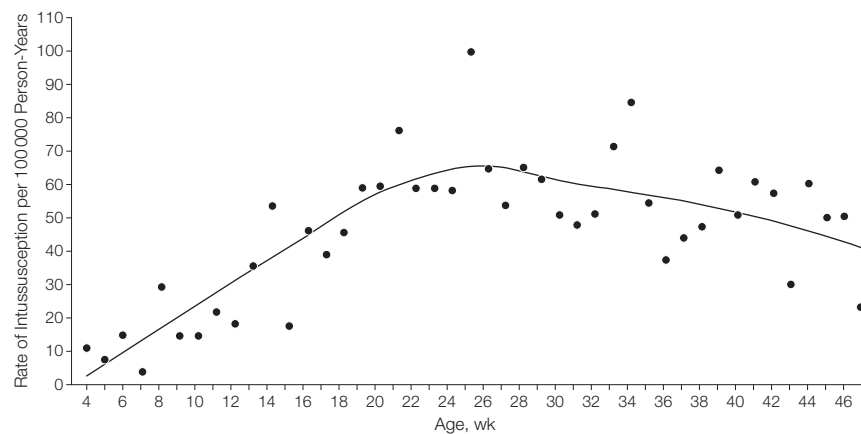
[a] Smoothed line fit using local polynomial regression (LOESS). The actual number of intussusception and 95% confidence intervals are reported in eTable 2A, available at http://www.jama.com.

from further analysis. Of the 54 visits with medical records, 31 cases were confirmed yielding a PPV of 57%. Ninety-four percent (29 of 31) of confirmed cases met the criteria for Brighton level 1 classification. When we restricted our analysis to visits from the ED and hospital settings, 27 of the 36 cases were confirmed, resulting in a substantially higher PPV of 75%; only 4 outpatient visits of 18 were confirmed resulting in a PPV of 22%. Nonconfirmed cases' codes were mostly for visits to rule out intussusception for symptoms of abdominal pain, and there was often clear evidence for an alternative diagnosis (eg, gastroenteritis, Wilms tumor, colic) or a statement in the medical record indicating no evidence of intussusception or that diagnostic test findings were not consistent for intussusception. For the concurrent analysis, we included the 14 confirmed post-RV5 cases and 8 confirmed postcomparison vaccine cases (9 of the confirmed postcomparison vaccine cases were vaccinated at >34 weeks of age so were excluded).

Concurrent Analysis

From May 2006 through February 2010, 786 725 doses of RV5 were administered. Of these, 39% were first doses, 33% second doses, and 28% third doses (TABLE 1). Our comparison cohort included 389 026 visits. There were no statistically significant increased risks in either the 1- to 30-day window or the 1- to 7-day risk window for all doses combined or in dose-specific analyses, after adjusting for age. However, the numbers were relatively sparse for the dose-specific analyses. For example, in the 1- to 7-day risk window, there was only 1 intussusception case following 309 844 RV5 first doses and 0 intussusception cases following the 102 523 comparison vaccines. Therefore, we were unable to calculate specific point estimates due to the 0-confirmed unexposed cases. Sensitivity analyses excluding the 2 Brighton level 2 cases, and including the 2 exposed cases without medical records to review did not change our overall interpretation of the results. None of the sen-

sitivity analyses changed the results for the 1- to 7-day window because each of the cases occurred outside this window. Because 1 of the Brighton level 2 cases occurred after age 35 weeks, it was not included in the analysis. Excluding the other level 2 case that occurred in a 17-week-old on day 17 resulted in an RR of 1.09 (95% CI, 0.41-0.85) following all doses and an RR of 0.44 (95% CI, 0.08-2.38) following dose 2 in the 1- to 30-day risk window. Including the 2 exposed cases without medical records (1 case occurred on day 13 following dose 1 and the other case occurred on day 12 following dose 2) resulted in an RR of 1.05 (95% CI, 0.42-2.88) following all doses, an RR of 0.43 (95% CI, 0.10-1.92) following dose 2, and an RR of undefined (95% CI, 0.30, undefined) following dose 1 in the 1- to 30-day risk window.

Historical Analysis

We calculated rates of intussusception visits in the ED and hospital settings from

1991 to 2009. During this time, a total of 589 visits with an *ICD-9* code for intussusception were identified in 1 249 861 person-years of observation, for an overall incidence of 47.1 per 100 000 person-years (95% CI, 43.4-51.1) for infants 4 to 47 weeks of age. Intussusception rates declined during 1991-2000 and then remained stable from 2001 to 2009; no clear trend in intussusception rates was noted after the implementation of rotavirus vaccination in 2006 (Figure 1). By age, intussusception rates were lowest at the youngest ages and then increased rapidly to peak at 26 weeks of age before decreasing with older ages (Figure 2). eTable 2A and B (available at http://www.jama.com) provide the point estimates and confidence intervals for the rates in Figure 1 and Figure 2.

In the 1- to 30-day risk window following RV5, 21 ED and hospital intussusception events (confirmed and nonconfirmed) were identified based on *ICD-9* codes (7 following dose 1, 7 following dose 2, and 7 following dose 3; TABLE 2).

Figure 3. Flow Chart Depicting Intussusception Cases Identified in the Vaccine Safety Datalink Following Pentavalent Rotavirus Vaccine or Another Vaccination Without Concomitant Pentavalent Rotavirus Vaccine From 2006-2010

ED indicates emergency department; RV5, pentavalent rotavirus vaccine.

Table 1. Medical-Record Confirmed Intussusception Following RV5 Vaccine vs a Concurrent Comparison Group Following Other Vaccines

RV5 Dose	Risk Window, Days	Exposed Cases	Total RV5 (Exposed) Doses	Unexposed Cases	Total Comparison Vaccine (Unexposed) Doses	Relative Risk (95% CI)
All doses[a]	1 to 30	14	786 725	8	389 026	0.95 (0.37-2.63)
	1 to 7	3		2		0.90 (0.10-11.08)
Dose 1	1 to 30	4	309 844	0	102 523	Undefined (0.22, undefined)
	1 to 7	1		0		Undefined (0.01, undefined)
Dose 2	1 to 30	4	257 915	5	114 385	0.36 (0.07-1.65)
	1 to 7	0		1		0 (0.0-17.3)
Dose 3	1 to 30	6	218 966	3	172 118	1.57 (0.34-9.72)
	1 to 7	2		1		1.57 (0.08-92.75)

Abbreviation: RV5, pentavalent rotavirus vaccine.
[a] All doses analysis was adjusted for age groups: 4 to 15 weeks, dose 1; 16 to 24 weeks, dose 2; and 25-34 weeks, dose 3.

Table 2. Emergency Department and Hospital Visits With *International Classification of Diseases, Ninth Revision* Codes for Intussusception Following RV5 Vaccine (2006-2010) vs Historical Unexposed Rates (2001-2005)

RV5 Dose	No. of Doses	Risk Window, Days	Observed	Expected	SIR (95% CI)
All doses[a]	786 725	1 to 30	21	20.9	1.01 (0.62-1.54)
		1 to 7	4	4.3	0.92 (0.25-2.36)
Dose 1	309 844	1 to 30	7	5.7	1.23 (0.50-2.54)
		1 to 7	1	0.8	1.21 (0.03-6.75)
Dose 2	257 915	1 to 30	7	7.2	0.97 (0.39-2.00)
		1 to 7	1	1.6	0.62 (0.13-3.80)
Dose 3	218 966	1 to 30	7	8	0.88 (0.35-1.81)
		1 to 7	2	1.9	1.05 (0.25-2.36)

Abbreviations: RV5 pentavalent rotavirus vaccine; SIR, standardized incidence ratio.
[a] Adjusted for age in weeks and site.

Of these 21 events, 4 occurred within 1 to 7 days of RV5 vaccination (1 following dose 1, 1 following dose 2, and 2 following dose 3). Based on the expected numbers of events calculated from the historical background rates (2001-2005), the SIRs were not significantly elevated for any dose in either of the risk windows. In particular, the SIR for the 1- to 7-day risk window for dose 1 was 1.21 (95% CI, 0.03-6.75; *P* = .85). Our point estimate for the 1- to 7-day window following dose 1 translates to an attributable risk of intussusception of 1 in about 1.8 million RV5 first-dose recipients. The upper 95% confidence limit of the SIR (6.75) from the historical comparison would translate to an upper limit for the attributable risk of 1 in 65 287 RV5 dose-1 recipients in the VSD population.

COMMENT

Our study is the largest prospective study to date to assess the association of RV5 and intussusception. With almost 800 000 doses of RV5 vaccine administered, including more than 300 000 first doses, we did not find an increased risk of intussusception following RV5 vaccination in either the 1- to 30-day or 1- to 7-day risk windows. Based on our analysis, an excess risk of 1 intussusception event per 65 287 RV5 vaccines following dose 1 can be reliably excluded, although we cannot rule out the possibility of a lower-level risk. Furthermore, we noted no significant secular trend in intussusception rates in the VSD population following RV5 introduction compared with prevaccine years. In contrast, large declines in severe rotavirus disease have occurred in US infants since the rotavirus vaccine was introduced in 2006,[13-16] with an estimated reduction of 55 000 rotavirus hospitalizations in 2008. Thus, the known benefits of rotavirus vaccination in the US outweigh any potential low-level risk for intussusception that might exist. These findings are especially important given that rotavirus vaccine coverage in the United States has steadily increased since its introduction and averaged 72% in June 2009 among 5-month olds selected from 8 different sentinel sites across the country.[17]

Our findings are consistent with the prior VSD analysis that found no association of intussusception and RV5 in the 30 days following vaccination.[8] However, unlike 2 other recent international studies, we did not find an increased risk of intussusception in the 1 to 7 days following the administration of the first dose of RV5 or RV1.[9,10] Our study only evaluated RV5, while the study in Mexico and Brazil assessed RV1 and found differing conclusions in each country with a statistically significant increased risk in the 1 to 7 days following dose 1 in Mexico, but not Brazil.[10] The Australian study examined both RV5 and RV1 but only found a statistically significant increased risk following dose 1 for RV5 and an elevated but nonsignificant risk for RV1.

Reasons for the inconsistent results between different studies are unclear. Because intussusception is a rare event, we cannot rule out a chance finding of risk in Australia and Mexico as well as the possibility of not detecting a low-level risk in the United States and Brazil. Another possible explanation might be effect modification of the rotavirus vaccine–intussusception association by an environmental or genetic factor that differs between the populations. For example, rates of natural intussusception among infants in Australia are approximately 1.7-fold higher (~81/100 000 infant-years) than rates in the United States (~47/100 000 infant-years).[18,19] Other

factors that are hypothesized to affect risk of intussusception or the immune response to rotavirus vaccines—including differences in infant diet,[20] breastfeeding,[21] concomitant administration of oral poliovirus vaccine vs inactivated poliovirus vaccine,[22] and maternal antibody levels[23]—may also have contributed to the variation in risk by country. However, our study was not able to assess effect modification by these factors because we did not have access to information about environmental or genetic exposures or the power to examine concomitant administration of other vaccines. Given biological differences between the various rotavirus vaccine strains, including rates of intestinal vaccine virus replication and shedding in fecal specimens, any potential risk of intussusception might vary between different products.

The VSD is an excellent tool for conducting postmarketing safety studies of vaccines using a large population with well-documented demographic and medical information.[11,24] Our study had several strengths. We included different comparison groups and obtained similar results. Using a prospective cohort design with near complete ascertainment of diagnoses codes for the population minimized the potential for bias in case ascertainment that can be an issue in case series analyses. The prospective design also eliminated the potential for selecting controls that are not representative of the source population (selection bias) and recall bias both of which can be issues in case-control studies.

We did not use self-controlled analysis because rates of intussusception are extremely variable by age in infant population making it problematic to completely control for confounding by age in a self-controlled analysis. Moreover, there is some evidence that after day 21 a compensatory decreased risk of intussusception may occur following RRV[25] and RV1[26,27]; if this hypothesized compensatory decrease were true, a self-controlled case series comparing risk windows fewer than 21 days to the reference period of more than 21

days could be biased. The background rates for the historical analysis were calculated using the same data source as our study population, and thus we were able to assess and limit the potential for bias due to temporal trends in the background rates. For the comparison of the exposed group with the concurrent unexposed group, all diagnoses were chart confirmed, adding to the validity of this comparison. Furthermore, the VSD vaccination data has previously been shown to be highly accurate.[28]

It is necessary to discuss several limitations to our study design. First, in our analysis using the historical background rates, we were not able to review medical records for the intussusception visits used to calculate these rates. However, we restricted records to the inpatient and ED settings, which were shown to have a higher PPV (75%) than that of visits in the outpatient setting (22%). An earlier study conducted in 1992-1999 at one VSD managed care organization reported a similar PPV (81%) for visits of intussusception identified by the same *ICD-9* codes used in the ED and inpatient settings, although this study included children up to 35 months of age and also had access to computerized radiology records for contrast enemas, which may account for the slightly higher PPV.[29] Assuming that the misclassification did not change based on the implementation of RV5 it is likely that this misclassification is nondifferential. Studies have shown that for outcomes with a PPV more than 65%, the biases in RR due to nondifferential outcome misclassification were relatively modest (eg, –9.1% to –12.5% for an RR of 2).[30,31] Second, it is possible that the children who did not receive RV5 in the concurrent comparison group are systematically different from those who received RV5, and that these systematic differences could also be related to the risk of intussusception. Although we are unable to rule out this type of unmeasured confounding, the likelihood of bias most likely was reduced because infants in the comparison group were required to have received at least 1 recommended vaccine in the same age range as the RV5 vac-

cines, the study occurred during the rollout period of RV5 when uptake was still relatively low, so it was not abnormal for children to receive other routine vaccines without RV5, and all of our cohort members are insured with access to health care.

Third, although our study is the largest prospective postmarketing cohort study of RV5 and intussusception, data became relatively sparse when stratified by dose and we were unable to calculate point estimates or an upper limit to the confidence interval for the dose-1 specific analysis using the concurrent comparison group. However, our analyses using the historical rates as a comparison group provided improved power to detect dose-specific associations. Given an $\alpha = .05$ we had 80% power to detect an RR of approximately 1.7 for the 1- to 30-day and 3.1 for the 1- to 7-day risk window, following all doses and 2.5 for the 1- to 30-day risk and 6.4 for the 1- to 7-day risk window, following dose 1. Thus, although our study was potentially underpowered to detect low-level risks, the point estimates and confidence intervals from the analysis using historical rates do not provide evidence for an increased risk. Also, because VSD includes only an insured population, these data may not be generalizable to all US infants.

Finally, although an increased risk of intussusception associated with rotavirus vaccination has not been documented in US infants, the US Advisory Committee on Immunization Practices reviewed modeling data and noted that the benefits of rotavirus vaccination in US infants would outweigh the potential risks, even if a risk similar to that seen in Mexico or Australia exists in the United States.[32]

CONCLUSIONS

In this large, prospective postlicensure safety monitoring study of almost 800 000 doses of RV5 vaccine, with more than 300 000 first doses, we did not observe any increased risk of intussusception following RV5 vaccination. The introduction of rotavirus vaccines has had a substantial public health effect on se-

vere rotavirus disease in US infants. Although we cannot entirely exclude the possibility of a very low-level risk, the findings of our study strengthen the evidence base in favor of vaccination for effective control of severe childhood rotavirus disease.

REFERENCES

1. Murphy TV, Smith PJ, Gargiullo PM, Schwartz B. The first rotavirus vaccine and intussusception: epidemiological studies and policy decisions. *J Infect Dis*. 2003;187(8):1309-1313.
2. Murphy TV, Gargiullo PM, Massoudi MS, et al; Rotavirus Intussusception Investigation Team. Intussusception among infants given an oral rotavirus vaccine. *N Engl J Med*. 2001;344(8):564-572.
3. Kramarz P, France EK, Destefano F, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J*. 2001;20(4):410-416.
4. Parashar UD, Alexander JP, Glass RI; Advisory Committee on Immunization Practices (ACIP), Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006;55(RR-12):1-13.
5. Cortese MM, Parashar UD; Centers for Disease Control and Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2009;58(RR-2):1-25.
6. Vesikari T, Matson DO, Dennehy P, et al; Rotavirus Efficacy and Safety Trial (REST) Study Team. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. *N Engl J Med*. 2006;354(1):23-33.
7. Ruiz-Palacios GM, Pérez-Schael I, Velázquez FR, et al; Human Rotavirus Vaccine Study Group. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. *N Engl J Med*. 2006;354(1):11-22.
8. Belongia EA, Irving SA, Shui IM, et al; Vaccine Safety Datalink Investigation Group. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *Pediatr Infect Dis J*. 2010;29(1):1-5.
9. Buttery JP, Danchin MH, Lee KJ, et al; PAEDS/APSU Study Group. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine*. 2011;29(16):3061-3066.
10. Patel MM, López-Collada VR, Bulhões MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *N Engl J Med*. 2011;364(24):2283-2292.
11. Baggs J, Gee J, Lewis E, et al. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics*. 2011;127(127)(suppl 1):S45-S53.
12. Bines JE, Kohl KS, Forster J, et al; Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. *Vaccine*. 2004;22(5-6):569-574.
13. Tate JE, Panozzo CA, Payne DC, et al. Decline and change in seasonality of US rotavirus activity after the introduction of rotavirus vaccine. *Pediatrics*. 2009;124(2):465-471.
14. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *Pediatr Infect Dis J*. 2011;30(1)(suppl):S30-S34.
15. Tate JE, Cortese MM, Payne DC, et al. Uptake,

impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. *Pediatr Infect Dis J*. 2011;30(1)(suppl):S56-S60.
16. Curns AT, Steiner CA, Barrett M, Hunter K, Wilson E, Parashar UD. Reduction in acute gastroenteritis hospitalizations among US children after introduction of rotavirus vaccine: analysis of hospital discharge data from 18 US states. *J Infect Dis*. 2010;201(11):1617-1624.
17. Centers for Disease Control and Prevention (CDC). Rotavirus vaccination coverage among infants aged 5 months—immunization information system sentinel sites, United States, June 2006-June 2009. *MMWR Morb Mortal Wkly Rep*. 2010;59(17):521-524.
18. Justice F, Carlin J, Bines J. Changing epidemiology of intussusception in Australia. *J Paediatr Child Health*. 2005;41(9-10):475-478.
19. Bines JE, Patel M, Parashar U. Assessment of postlicensure safety of rotavirus vaccines, with emphasis on intussusception. *J Infect Dis*. 2009;200(suppl 1):S282-S290.
20. Johnson B, Gargiullo P, Murphy TV, Parashar UD, Patel MM. Sociodemographic and dietary risk factors for natural infant intussusception in the United States. *J Pediatr Gastroenterol Nutr*. 2010;51(4):458-463.
21. Patel M, Shane AL, Parashar UD, Jiang B, Gentsch JR, Glass RI. Oral rotavirus vaccines: how well will they work where they are needed most? *J Infect Dis*. 2009;200(suppl 1):S39-S48.
22. Steele AD, De Vos B, Tumbo J, et al. Co-administration study in South African infants of a live-attenuated oral human rotavirus vaccine (RIX4414) and poliovirus vaccines. *Vaccine*. 2010;28(39):6542-6548.
23. Moon SS, Wang Y, Shane AL, et al. Inhibitory effect of breast milk on infectivity of live oral rotavirus vaccines. *Pediatr Infect Dis J*. 2010;29(10):919-923.
24. Lieu TA, Kulldorff M, Davis RL, et al; for the Vaccine Safety Datalink Rapid Cycle Analysis Team. Real-time vaccine safety surveillance for the early detection of adverse events. *Med Care*. 2007;45(10)(suppl 2):S89-S95.
25. Simonsen L, Morens D, Elixhauser A, Gerber M, Van Raden M, Blackwelder W. Effect of rotavirus vaccination programme on trends in admission of infants to hospital for intussusception. *Lancet*. 2001;358(9289):1224-1229.
26. Macias M, Lopez P, Velazquez FR, Vergara RF, Salmeron J. The Rotavirus vaccine RIX 4414 (Rotarix) is not associated with intussusception in one year old infants [abstract]. Presented at: the 45th ICAAC Annual Meeting; December 16-19; Washington, DC. Poster G-841.
27. Greenberg HB. Rotavirus vaccination and intussusception—act two. *N Engl J Med*. 2011;364(24):2354-2355.
28. Mullooly J, Drew L, DeStefano F, et al. Quality of HMO vaccination databases used to monitor childhood vaccine safety. Vaccine Safety DataLink Team. *Am J Epidemiol*. 1999;149(2):186-194.
29. Chang EJ, Zangwill KM, Lee H, Ward JI. Lack of association between rotavirus infection and intussusception: implications for use of attenuated rotavirus vaccines. *Pediatr Infect Dis J*. 2002;21(2):97-102.
30. Shui IM, Shi P, Dutta-Linn MM, et al; Vaccine Safety Datalink Research Team. Predictive value of seizure *ICD-9* codes for vaccine safety research. *Vaccine*. 2009;27(39):5307-5312.
31. Mullooly JP, Donahue JG, DeStefano F, Baggs J, Eriksen E; VSD Data Quality Working Group. Predictive value of *ICD-9-CM* codes used in vaccine safety research. *Methods Inf Med*. 2008;47(4):328-335.
32. Cortese M. Estimates of benefits and potential risks of rotavirus vaccination in the United States. Presented at the Advisory Committee on Immunization Practices Meeting; Atlanta, GA, USA; October 28, 2010.