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The temporal relationship between RotaTeq immunization and intussusception adverse events in the Vaccine Adverse Event Reporting System (VAERS)

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: In August of 2006, the Advisory Committee on Immunization Practices (ACIP) recommended RotaTeq for routine vaccination of US infants. The hypothesis tested in the present study is that rotavirus vaccines are associated with an increased risk of intussusception adverse events (AEs) characterized by an onset in a biologically plausible a priori identified temporal period post-vaccination (days 3 to 7).

Material/Methods: The Vaccine Adverse Event Reporting System (VAERS) updated as of December 28, 2010 was analyzed.

Results: Following RotaTeq vaccination, a significantly ($p<0.001$) higher percentage of AEs were classified as serious, permanently disabling, resulted in hospitalizations, or were life-threatening among intussusception AEs in comparison to the total AE reports (removing intussusception AE reports) submitted to VAERS. A significantly greater portion of intussusception AEs in comparison to the portion of total AE reports (removing intussusception AE reports) were reported to VAERS in the onset interval from 3 to 7 days post-RotaTeq vaccination than within the onset interval from 1 to 2 days post-RotaTeq vaccination (78.7% *vs.* 29.1%, risk ratio=2.7, 95% CI=2.4–3.0, $p<0.0001$). It was assumed in our onset time-trend analyses of the distribution of AEs following Rota-Teq vaccination that the AE's should be equally likely to be reported with an onset time for each day, from 1 to 9 days post-vaccination or, alternatively, should follow similar daily proportions as observed for total AEs reports (removing intussusception AE reports). Results of this onset time-trend analyses of the distribution of intussusception AEs reported to VAERS following Rota-Teq vaccination revealed significant differences ($p<0.001$) from our expectations. Consistent and similarly remarkable trends were observed for intussusception AE reports associated with RotaShield vaccine.

Conclusions: The present study significantly associates RotaTeq vaccination with intussusception AEs.

key words: **intussusception • post-marketing surveillance • rotavirus • timing • vaccine**

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Background

On February 3, 2006, the US Food and Drug Administration (FDA) licensed another rotavirus vaccine, RotaTeq™ (Merck and Co., West Point, Pennsylvania), a bioengineered combination of five human-bovine hybridized reassortment rotaviruses. In August of 2006, the Advisory Committee on Immunization Practices (ACIP) recommended RotaTeq for routine vaccination of US infants with a nominal vaccination schedule of 3 doses, administered orally at the ages 2, 4, and 6 months. The ACIP also stated that RotaTeq could be given with other vaccines [1].

A previous tetravalent rhesus-based rotavirus vaccine, RotaShield™ (Wyeth Laboratories, Inc., Marietta, Pennsylvania), was withdrawn from the US market in 1999 after postmarketing surveillance identified a significant association with intussusception. In evaluating RotaShield adverse events, investigators reported that the period of greatest risk following RotaShield vaccination was among intussusception adverse event reports with an onset of symptoms from 3 to 7 days [2].

The safety of RotaTeq was evaluated in a prelicensure clinical trial involving 71,725 infants who received either the vaccine or a placebo [3]. In this controlled trial, a troubling but non-statistically significant elevated risk (relative risk =1.6) for intussusception was observed within a 42-day period after RotaTeq inoculation. Since then, the FDA has issued several statements on the safety of RotaTeq vaccine. The first was a Public Health Notification statement issued on February 13, 2007, identifying that 28 cases of intussusception had been received by the Vaccine Adverse Event Reporting System (VAERS) following RotaTeq vaccination [4]. We subsequently examined first five quarters of postmarketing surveillance for AEs reported to VAERS following RotaTeq vaccine administration, to assess reporting trends in adverse events following RotaTeq vaccine administration, and to identify potential AEs that may be associated with RotaTeq vaccine administration [5].

From February 3, 2006 through July 31, 2007, a total of 165 adverse event reports in VAERS listed intussusception as adverse event. Among these adverse event reports, RotaTeq was administered or co-administered with other vaccines in a total of 160 of these instances (97% of the total adverse event reports that listed intussusception as an adverse event). Time trends for intussusception adverse event reports in VAERS were observed to significantly increase following the licensing of RotaShield vaccine on August 31, 1998, and, subsequently, to significantly decline following the July 16, 1999 decision by the Centers for Disease Control and Prevention (CDC)'s to halt RotaShield administration. A significant increase in intussusception adverse events reported to VAERS also occurred following the licensing of RotaTeq vaccine on February 3, 2006. It was concluded that additional assessments of RotaTeq vaccination safety should be undertaken as additional data become available.

The purpose of the present study was to conduct a follow-up examination evaluating adverse events reported to VAERS in the further approximate 3.5 years since the previous study was published, as well as to further evaluate the distribution of the onset times for adverse events reported to VAERS following RotaTeq vaccination. Furthermore, the present study also examined the distribution of onset times for adverse events reported to VAERS following RotaTeq vaccination in comparison to those previously observed with RotaShield vaccination. The hypothesis tested in the present study is that RotaTeq vaccine administration is associated with an increased risk of intussusception adverse events with an onset in a biologically plausible a priori identified-temporal period post-vaccination (days 3 to 7).

Material and Methods

Overview

The VAERS is an epidemiological database that has been maintained jointly by the CDC and FDA since 1990 as a surveillance tool to evaluate vaccine safety. Specific adverse events following vaccination are required to be reported to this database as mandated by law, but other adverse events that occur following vaccine administration are passively reported to VAERS. The VAERS Working Group of the CDC has previously acknowledged that less than 5% of the total adverse events reported to VAERS are reported by parents. Additionally, specific serious adverse events and deaths reported to VAERS are followed-up by the CDC/FDA. The VAERS Working Group of the CDC and the FDA analyze and publish epidemiologic studies based upon VAERS [6,7].

The VAERS Working Group notes that VAERS is simple to use, flexible by design, and the data are available in a timely fashion, but it also warns that the potential limitations may include systematic error due to underreporting, erroneous reporting, frequent multiple exposures, multiple outcomes and lack of precise denominators. In addition, when evaluating data from VAERS, it is important to note that for any reported event, no cause and effect relationship has been established. VAERS is interested in all potential associations between vaccines and adverse events. Therefore, VAERS collects information on any adverse event following vaccination, be it coincidental or truly caused by a vaccine [6,7].

Data assembly

The VAERS database updated as of December 28, 2010 was analyzed in the present study using software available through the CDC Wonder online portal (*http://wonder.cdc.gov/vaers.html*). This portal provides a direct method for independent investigators to rapidly analyze up-to-date data in VAERS.

An initial search of VAERS was undertaken to examine reported adverse event reports to VAERS following RotaTeq vaccination. This involved refining the search characteristics through the CDC Wonder online portal so that the vaccine products field was defined as ROTHB5 (for RotaTeq vaccine, code: 1096). Summary data regarding the identified overall adverse events reported to VAERS following RotaTeq was gleaned for the total number of reports, onset interval (in days), gender ratio, severity of the outcomes (including permanently disabled, serious, hospitalization, and life-threatening). A similar search was conducted specifying that the adverse event report has to identify intussusception (code: 10022863) in the symptom field of the report. In addition, VAERS was also searched using the same parameters by defining the vaccine products as RV (for RotaShield vaccine, code: 300).

Table 1. A summary of adverse events reported to VAERS following RotaTeq vaccination.

Type of adverse event	Total number	Male/female (ratio)	Permanently disabled (% of total)	Serious (% of total)	Hospitalized (% of total)	Life-threatening (% of total)
Total adverse event reports*	5,187	2,380/2,140** (1.1)	52 (1.0)	961 (18.5)	773 (14.9)	145 (2.8)
Intussusception adverse event reports	555	303/230*** (1.3)	14 (2.5)	505 (91)	496 (89)	179 (32)

* Intussusception adverse events removed from the total reports; ** There were 667 reports with unknown gender status; *** There were 22 reports with unknown gender status.

Statistical analyses

In the present study the statistical package contained in StatsDirect (version 2.7.8) was utilized, and in all statistical tests a two-sided p-value <0.05 was considered statistically significant. The first null hypothesis tested in the present study was that the onset of symptoms in intussusception adverse events reported to VAERS would be similar for each day post-RotaTeq vaccination. The second null hypothesis tested in the present study was that intussusception adverse events reported to VAERS following RotaTeq vaccination would have no difference in severity of symptoms reported in comparison to the severity symptoms identified from examination of the total adverse event reports (removing intussusception adverse events reports) reported to VAERS following RotaTeq vaccination. The third null hypothesis tested in the present study was that intussusception adverse events reported to VAERS following RotaTeq vaccination would have a male/female ratio the same as the total adverse event reports (removing intussusception adverse events).

In order to examine the specific temporal period of interest from 3 to 7 days post-RotaTeq vaccination for intussusception adverse events, the ratio of intussusception adverse event reports with an onset of symptoms from 3 to 7 days post-vaccination to the number intussusception adverse event reports with an onset of symptoms from 1 to 2 days post-RotaTeq vaccination was compared to the ratio of total adverse event reports (removing intussusception adverse event reports) with an onset of symptoms from 3 to 7 days post-vaccination to the total adverse event reports (removing intussusception adverse event reports) with an onset of symptoms from 1 to 2 days post-RotaTeq vaccination utilizing the Fischer's Exact test statistic. A similar analysis was undertaken for adverse events reported to VAERS following RotaShield vaccination.

In addition, the time period distribution of intussusception adverse events reported to VAERS following RotaTeq vaccination with an onset of symptoms within 9 days post-vaccination was analyzed using the binomial single proportion Clopper-Pearson exact test statistic. Two different models were constructed to evaluate the onset of symptoms from 1 to 9 days post-vaccination among intussusception adverse events reported to VAERS following RotaTeq vaccination. The first assumed that the distribution of intussusception adverse events reported to VAERS following RotaTeq vaccination should be equally likely to be distributed across days 1 to 9 days post-vaccination (11.1% of reports per day). The assumed background equal daily proportion measurement of 11.1% was compared to the observed proportion of intussusception adverse event reported to VAERS with an onset from 3 to 7 days post-vaccination to the total number of intussusception adverse events reported to VAERS from 1 to 9 days post-vaccination. The second assumed that the distribution of onset times for intussusception adverse events reported to VAERS within 9 days following RotaTeq vaccination should follow a similar distribution from 3 to 7 days post-vaccination as total adverse event reports (removing intussusception adverse event reports) reported to VAERS following RotaTeq vaccination. Similar analyses were undertaken for adverse events reported to VAERS following RotaShield vaccination.

The proportion of various measurements of adverse event outcome severity, including the categories of life-threatening, permanent disability, hospitalization, and serious were examined among those reporting an intussusception adverse event report in comparison to total adverse event reports (removing intussusception adverse event reports) following RotaTeq vaccination utilizing the Fischer's Exact test statistic. The male/female ratio of intussusception adverse events were compared to total adverse events reports (removing intussusception adverse event reports) following RotaTeq vaccination also utilizing the Fischer's Exact test statistic.

Results

Table 1 summarizes the overall adverse events reported to VAERS following RotaTeq vaccination. It was observed that the male/female ratio was significantly ($p<0.05$) increased for intussusception adverse events (male/female ratio =1.3) in comparison to total adverse events (removing intussusception adverse event reports, male/female ratio =1.1) reported to VAERS following RotaTeq vaccination. It was also observed that a significant percentage of all adverse events reported (removing intussuception adverse event reports) to VAERS following RotaTeq vaccination were classified as serious (18.5%) or resulted in hospitalizations (14.9%). In contrast, a much smaller percentage of all adverse events reported to VAERS following RotaTeq vaccination were classified as life-threatening (2.8%) or as resulting in permanent disability (1.0%). Among intussusception adverse event reports made to VAERS following RotaTeq vaccination a significant percentage were classified as serious (91%), resulted in hospitalizations (89%), or life-threatening (32%).

Table 2. A summary of adverse events reported to VAERS following rotavirus vaccination by onset interval from 1 to 9 days.

Onset interval (days)	RotaTeq all adverse event reports* (% of total)	RotaTeq intussusception adverse event reports (% of total)	RotaShield all adverse event reports* (% of total)	RotaShield intussusception adverse event reports (% of total)
1	**816 (50.5)**	11 (6.8)	**60 (20.8)**	2 (2.9)
2	**292 (18.1)**	19 (11.8)	**66 (22.9)**	5 (7.3)
3	161 (10)	**26 (16.15)**	69 (24)	**11 (16)**
4	104 (6.4)	**17 (10.6)**	26 (9.0)	**13 (18.8)**
5	85 (5.2)	**28 (17.4)**	20 (6.9)	**18 (26.1)**
6	53 (3.3)	**26 (16.15)**	19 (6.6)	**7 (10.1)**
7	51 (3.2)	**14 (8.7)**	17 (6)	**8 (11.6)**
8	33 (2.0)	10 (6.2)	6 (2.1)	4 (5.8)
9	21 (1.3)	10 (6.2)	5 (1.7)	1 (1.4)

* Removed intussusception adverse event reports.

Overall, a significantly ($p<0.001$) higher percentage of adverse events were classified as serious, permanently disabled, resulted in hospitalizations, or life-threatening among intussusception adverse events in comparison to the total adverse event reports (removing intussusception adverse event reports) made to VAERS following RotaTeq vaccination.

Table 2 summarizes the onset interval for adverse events reported to VAERS following RotaTeq and RotaShield vaccination. Based on this data, it was observed that, within the onset interval of symptoms post-vaccination from days 1 to 7, there was a significantly greater portion of intussusception adverse events reported to VAERS within the interval from 3 to 7 days post-RotaTeq vaccination in comparison to portion of total adverse event reports (removing intussusception adverse event reports) made to VAERS within the interval from 1 to 2 days post-RotaTeq vaccination (78.7% *vs.* 29.1%, risk ratio =2.7, 95% Confidence Interval =2.4–3.04, $p<0.0001$). Similarly, the onset interval of symptoms post-vaccination from days 1 to 7 that a significantly greater portion of intussusception adverse events were reported to VAERS within the interval from 3 to 7 days post-RotaShield vaccination in comparison to portion of total adverse event reports (removing intussusception adverse event reports) made to VAERS within the interval from 1 to 2 days post-RotaShield vaccination (89.1% *vs.* 54.5%, risk ratio =1.63, 95% Confidence Interval =1.42–1.88, $p<0.0001$).

Furthermore, analysis of the temporal distribution of the onset of intussusception adverse event reported to VAERS assuming that they should be equally likely to report an onset time for each day from 1 to 9 days post-vaccination revealed a significant difference from the assumed background equal daily proportion measurement of 11.1% (55.5% for a 5 day period) in comparison the proportion of intussusception adverse events with an onset of symptoms from 3 to 7 days post-vaccination reported to VAERS following RotaTeq (69%, 95% confidence interval =61–76%, $p<0.001$) or RotaShield (82.6%, 95% confidence interval =72–91%, $p<0.0001$). Similarly, it was observed within the 9 days post-vaccination, the distribution of intussusception adverse events reported to VAERS with an onset time from 3 to 7 days post-vaccination occurred at a significantly higher proportion following RotaTeq (69% *vs.* 28.1%, 95% confidence interval =61–76%, $p<0.0001$) and RotaShield (82.6% *vs.* 52.5%, 95% confidence interval =72–91%, $p<0.0001$) in comparison to their respective proportions of total adverse event reports (removing intussusception adverse event reports) made to VAERS.

Discussion

The purpose of the present study was to conduct a follow-up examination to further evaluate adverse events reported to VAERS during the approximately 3.5 years since our previous study, as well as to further evaluate onset time distribution for intussusception adverse events reported to VAERS following RotaTeq vaccination. Furthermore, the present study also examined consistency of results observed for intussusception adverse events reported following RotaTeq vaccination with those observed using similar analyses techniques for RotaShield vaccination. Overall, the results observed are consistent with the hypothesis tested in the present study and suggest that RotaTeq vaccine administration is associated with an increased risk of intussusception adverse events within a defined onset period post-vaccination.

Other investigators have assessed intussusception reports after RotaTeq vaccination by using data from VAERS and by examining data from a cohort of children enrolled in managed care organizations and recorded in the Vaccine Safety Datalink (VSD) [8]. Observed versus expected rate ratios were determined by using vaccine dose distribution data and VSD background intussusception rates. These investigators reported that between February 1, 2006, and September 25, 2007, VAERS received 160 intussusception reports after RotaTeq vaccination. With the assumptions that reporting completeness was 75% and that 75% of the distributed doses of RotaTeq were administered, the observed

versus expected rate ratios were 0.53 and 0.91 for the 1–21 and 1–7 day interval after vaccination, respectively. In the VSD, 3 intussusception cases occurred within 30 days after 111,521 RotaTeq vaccinations, compared with 6 cases after 186,722 non-RotaTeq vaccinations during the same period. They then reported that if, like RotaShield, RotaTeq had a 37-fold increased risk of intussusception within 3 to 7 days after vaccination, then 8 intussusception cases would be expected within 3 to 7 days among the approximately 84,000 infants vaccinated with the first dose of RotaTeq recorded in the VSD (n=49,902) and the prelicensure trial (n=34,035) combined, whereas no cases have been observed. These investigators concluded that the available data do not indicate that RotaTeq is associated with intussusception. Although an intussusception risk similar in magnitude to that of RotaShield can be excluded, according to these researchers, continued monitoring is necessary for complete assessment of the safety profile of RotaTeq.

In a more updated assessment of the VSD, other investigators prospectively evaluated the risk of intussusception among RotaTeq recipients age 4 to 48 weeks who received RotaTeq between May 2006 and May 2008 [9]. Adverse events over the subsequent 30 days were ascertained from inpatient, outpatient, and emergency department files; cases of intussusception were validated by medical record review. An adaptation of sequential probability ratio testing was employed to compare the cumulative number of observed and expected adverse events on a weekly basis, and a "signal" was generated if the log-likelihood ratio reached a predetermined threshold. The expected number of cases of intussusception was determined from historical rates in the VSD population. Overall, these investigators determined 207,621 doses of RotaTeq were administered to the study population; 42% were first doses. Five children had computerized diagnosis codes for intussusception, and 6.75 cases were expected based on historical rates (relative risk =0.74). No elevation in risk was identified for intussusception. Two of five children with suspected intussusception based on diagnosis codes met the case criteria after medical record review. These investigators concluded that their study provides additional evidence that RotaTeq is not associated with an increased risk of intussusception.

In contrast to the aforementioned studies finding no significant relationship between RotaTeq vaccination and intussusception adverse events, the present study did find a significant relationship. The present study is differentiated from the previous studies in its employment of a methodology that examined the distribution of the onset times for intussusception adverse events reported to VAERS following RotaTeq vaccination, in contrast to previous studies comparing the frequency of intussusception to presumed background rat of intussusception in the absence of RotaTeq vaccination. Furthermore, the present study is differentiated from previous studies that primarily relied upon the VSD database because the present study examined the VAERS for adverse events reports generated from a much larger population (i.e. the VAERS captures reports from entire US population versus the VSD which only captures medical records from a population participating in Health Maintenance Organizations), and hence the present study was able to examine a much larger case-series of intussusception events reported following RotaTeq vaccination than previous studies.

Limitations

The main limitation of the present study is that it was not possible to compare the frequency of intussusception adverse events reported following RotaTeq vaccination in comparison to background rates in comparable, unvaccinated populations. The VAERS does not contain such a comparison group, and further VAERS may have underreporting of the true population frequency of adverse events following immunization. The present study overcame this hurdle by examining the onset time distribution of intussusception adverse events reported to VAERS following RotaTeq vaccination, and hence the present study only relied upon the adverse events reported to VAERS. Further, the present study relied upon information gleaned from reports made to VAERS. It is possible that factors such as erroneous reporting, frequent exposures, and multiple outcomes may impact the reports examined in the present study, but it difficult to understand why these factors would have contributed to the intussusception adverse events being reported to VAERS with onset times consistent with an a priori identified temporal period of maximum risk for intussusception from 3 to 7 days, previously identified from study of RotaShield vaccine-associated intussusception. Further, the consistency of the results observed for intussusception adverse events reported to VAERS following RotaTeq and RotaShield vaccines from the time trend analyses employed in the present argue against the present results being the result of a data artifact or mere statistical chance.

Conclusions

The present study is the first to reveal a significant association between RotaTeq vaccination and intussusception adverse events. The results suggest that RotaTeq vaccine administration is associated with an increased risk of intussusception adverse events within a defined onset period post-vaccination, and this relationship is consistent with that observed for RotaShield vaccination. Further, it was observed that intussusception adverse event reported to VAERS were made more often about males relative to females and were of significantly greater severity than those observed in the total adverse event reports (removing intussusception adverse event reports) following RotaTeq vaccinations. Future studies should further examine this relationship in other populations, and determine susceptibility factors that may predispose RotaTeq vaccine recipients to intussusception adverse events.

Potential conflicts of interest

David A. Geier and Mark R. Geier have been involved in vaccine/biologic litigation before the National Vaccine Injury Compensation Program (NVICP) and in civil litigation, but never in any cases involving rotavirus vaccines. Paul G King and Lisa K. Sykes have no conflict of interests with respect to rotavirus vaccines.

Refernces:

1. Centers for Disease Control and Prevention: Prevention of rotavirus gastroenteritis among infants and children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep, 2006; 55(RR12): 1–13
2. Verstraeten T Baughman AL, Cadwell B et al: Enhancing vaccine safety surveillance: a capture-recapture analysis of intussusception after rotavirus vaccination. Am J Epidemiol, 2001;154: 1006–12

3. Vesikari T, Matson DO, Dennehy P et al: Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med, 2006; 354: 23–33
4. *http://www.fda.gov/cber/safety/phnrota021307.htm* [last accessed October 14, 2007]
5. Geier DA, King PG, Sykes LK, Geier MR: RotaTeq vaccine adverse events and policy considerations. Med Sci Monit, 2008; 14(3): PH9–16
6. Singleton JA, Lloyd JC, Mootrey GT et al: An overview of the Vaccine Adverse Event Reporting System (VAERS) as a surveillance system. VAERS Working Group. Vaccine, 1999; 17: 2908–17
7. Geier DA, Geier MR: A review of the Vaccine Adverse Event Reporting System database. Expert Opin Pharmacother, 2004; 5: 691–98
8. Haber P, Patel M, Izurieta HS et al: Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006 to September 25, 2007. Pediatrics, 2008; 121: 1206–12
9. Belongia EA, Irving SA, Shui M et al: Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. Pediatr Infect Dis J, 2010; 29: 1–5