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RotaTeq vaccine adverse events and policy considerations

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Background:

Summary

Rotavirus is the leading cause of severe gastroenteritis in children <5 years-old worldwide. On February 3, 2006, the US Food and Drug Administration licensed RotaTeq™ (Merck and Co.), a bioengineered combination of five human-bovine hybridized reassortment rotaviruses. In August of 2006, the Advisory Committee on Immunization Practices recommended RotaTeq for routine vaccination of US infants administered orally at the ages 2, 4, and 6 months.

Material/Methods:

An evaluation of data reported to VAERS following the first five quarters of post-marketing surveillance of RotaTeq was undertaken. Trends in adverse events reported following RotaTeq and cost-effectiveness calculations of RotaTeq in the context of the disease burden of rotavirus in the US were examined.

Results:

From February 3, 2006 through July 31, 2007, a total of 160 (of the 165 reported) intussusception and 11 (of the 16 reported) Kawasaki disease adverse event reports were identified when RotaTeq was administered or co-administered with other vaccines. Time-trend analyses showed that there were significant increases in the total number of intussusception and Kawasaki disease adverse events entered into VAERS in comparison to previous years.

Conclusions:

These observations, coupled with limited rotavirus disease burden, cost-effectiveness, and potential contact viral transmission concerns, raise serious questions regarding the use of RotaTeq in the US. Healthcare providers should diligently report adverse events following RotaTeq vaccination to VAERS, and those who have experienced a vaccine-associated adverse event should be made aware that they may be eligible for compensation from the no-fault National Vaccine Injury Compensation Program (NVICP).

key words:

gastroenteritis • gastrointestinal hemorrhage • rotavirus infection • vaccine adverse event reporting system

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BACKGROUND

Worldwide, rotavirus is the leading cause of severe gastroenteritis in children under the age of 5 years [1,2]. On August 31, 1998, a tetravalent rhesus-based rotavirus vaccine, RotaShield™ (Wyeth Laboratories, Inc, Marietta, Pennsylvania), was licensed in the United States for the vaccination of healthy infants. In March of 1999, the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics, and the American Academy of Family Physicians then recommended routine use of RotaShield for vaccination of healthy infants [3].

During the period from September 1, 1998 to July 7, 1999, the Vaccine Adverse Event Reporting System (VAERS) received 15 adverse-event reports of intussusception (a bowel obstruction in which one segment of bowel becomes enfolded within another segment) among infants who had received RotaShield [3]. On July 16, 1999, the Centers for Disease Control and Prevention (CDC) recommended that healthcare providers suspend use of RotaShield. Subsequent analyses showed that RotaShield administration was associated with a significantly increased risk for intussusception and other gastrointestinal disorders [4,5].

In spite of the aforementioned problems, 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 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 [6]. Because Rotashield was withdrawn from the US market in 1999 after postmarketing surveillance identified an association with intussusception, the safety of RotaTeq was evaluated in a precensure clinical trial involving 71,725 infants who received either the vaccine or a placebo [7]. 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 VAERS following RotaTeq vaccination [8]. The second was an "Information Pertaining to Labeling Revision for RotaTeq" statement issued on June 15, 2007, disclosing that information from the vaccine manufacturer's phase-3 clinical trials showed an unadjusted relative risk of 4.9 for Kawasaki disease when comparing vaccine recipients to placebo recipients [9]. The second notice also acknowledged that 3 cases of Kawasaki disease had been received by VAERS following RotaTeq inoculation.

This study presents data from the first five quarters of post-marketing surveillance for adverse events reported to VAERS following RotaTeq vaccine administration. This study was undertaken to: assess reporting trends in adverse events following RotaTeq vaccine administration, and identify potential adverse events that may be associated with RotaTeq vaccine administration.

Additionally, the present study evaluated the cost-effectiveness of RotaTeq inoculation in the context of the disease burden of rotavirus in the US.

MATERIAL AND METHODS

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.

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 [10,11].

An assessment of the VAERS updated through July 31, 2007 was undertaken using Microsoft Access. The raw data examined in VAERS was compiled from the online public access VAERS website (<http://vaers.hhs.gov/scripts/data.cfm>).

The compiled VAERS database was searched to identify all adverse event reports with unique VAERS identification numbers where at least one of the "Vax1" through "Vax8" fields indicated that the RotaTeq vaccine ("ROTHB5") had been administered. All VAERS reports with a duplicate identification number were then eliminated. This assessment identified a net total of 1,526 adverse event reports in VAERS in which RotaTeq inoculation was reported.

The study then searched the symptom fields (Sym1 – Sym20) of the 1,526 RotaTeq-related adverse reports for reports where the gastrointestinal adverse events, including the Costart terms intussusception ("intussusception") or gastrointestinal disorders ("*gastro*"), had been reported. The symptoms fields were also searched for reports with the Costart term for Kawasaki Disease ("kawasaki's disease").

For each "Costart" category, all of the non-duplicate RotaTeq adverse event reports identified were analyzed for the total number of reports, male/female ratio, median age of vaccine recipients, median onset time in days, percent with life-threatening events, percent hospitalized, and median hospital stay.

The median onset time for each outcome under study was compared to the median onset time observed for the 1,526

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

Total reports	Male/female reports	Median age (years)	Median onset time (days)	Life-threatening event (n)	Hospitalized (n)	Median hospital stay (days)	Disabled (n)	Died (n)
1,526	620/561 (ratio=1.1)	0.30 (0.2–0.4)*	1 (0–5)*	5.5% (84)	21% (316)	2.0 (1–3)*	1% (14)	2.2% (34)

* Interquartile range of the distribution.

Table 2. A summary of intussusception, gastrointestinal disorders, and Kawasaki disease adverse events reported to VAERS following RotaTeq vaccine administration.

Type of adverse event report (n)	Male/female reports	Median age (years)	Median onset time (days)	Life-threatening event (n)	Hospitalized (n)	Median hospital stay (days)	Disabled (n)
Intussusception (160)	80/68 (ratio =1.2)	0.40 (0.2–1.0)**	34*** (12–49)**	34% (55)	86% (138)	2.0 (1–4)**	2.5% (4)
Gastrointestinal Disorders* (97)	44/43 (ratio =1.02)	0.20 (0.2–0.4)**	6 (1–20)**	6.2% (6)	53.6% (52)	2.0 (1–3)**	0% (0)
Kawasaki Disease (11)	7/4 (1.75)	0.30 (0.2–0.3)**	13 (2–40)**	18.2% (2)	81.8% (9)	4.0 (3–5)**	0% (0)

* Gastrointestinal disorders include adverse event reports with the following Costart Terms = Gastroenteritis, Gastroenteritis Viral, Gastrointestinal Disorder, Gastroesophageal Reflux Disease, Gastroenteritis Rotavirus, Gastrointestinal haemorrhage, Gastrointestinal Pain, Gastrointestinal Necrosis, Gastrointestinal Tract Mucosal Discolouration, Gastrointestinal Tube Insertion (excludes adverse event reports where intussusception was also included as an adverse event outcome).

** Interquartile range of the distribution.

*** The unpaired *t*-test statistic was utilized to evaluate the median onset time for general adverse event reports (as summarized in Table 1) in comparison to the median onset time for intussusception adverse event reports. The difference was statistically significant ($p < 0.001$).

total adverse event reports reported following RotaTeq vaccine administration. The null hypothesis employed was that there should be no difference in the onset times between the groups examined. An unpaired *t*-test statistical test was utilized to assess the validity of this null hypothesis and, given the sample size, a two-tailed *p*-value < 0.05 was considered statistically significant.

In addition, this study evaluated the time trends for the frequency of intussusception and Kawasaki disease adverse events reported to VAERS. This time-trend assessment evaluated the frequency of these adverse events reported to VAERS in relation to the introduction/withdrawal of both the rotavirus vaccines.

RESULTS

Table 1 summarizes the 1,526 adverse events reported to VAERS following RotaTeq vaccine administration. Generally, there were no sex-related recipient differences in the 1,526 adverse events reported to VAERS. Furthermore, for the 1,526 adverse events reported to VAERS the general median onset of symptoms occurred within a few days of RotaTeq vaccine administration.

Table 2 summarizes intussusception, gastrointestinal disorders, and Kawasaki disease adverse events reported to VAERS following RotaTeq vaccine administration. For the RotaTeq-as-

sociated Kawasaki disease adverse events reported to VAERS, there were more males (7) than females (4), whereas intussusception and gastrointestinal disorders were more equally reported to VAERS between the sexes. The median onset of symptoms for adverse events examined ranged from 6 days for gastrointestinal disorders to 34 days for intussusception. In the case of the intussusception reports, there was a statistically significantly delayed median onset time in comparison to median onset time observed for the total adverse events reported to VAERS following RotaTeq vaccine administration. In addition, both intussusception and Kawasaki disease adverse event reports indicated a significant percentage of individuals had experienced a potentially life-threatening condition and/or required hospitalization/surgery. Among those reporting adverse events classified as gastroenteritis rotavirus, 22 of 42 total reports (52.4%) had confirmatory laboratory tests that were positive for rotavirus.

From February 3, 2006 through July 31, 2007, a total of 165 adverse event reports in VAERS listed intussusception as a Costart term. Among these adverse event reports, RotaTeq was administered or co-administered with other vaccines in a total of 160 of these adverse events (97% of the total adverse event reports that listed intussusception as an adverse event). In the case of Kawasaki disease, from February 3, 2006 through July 31, 2007, 16 adverse event reports on VAERS listed Kawasaki disease as a Costart term. Among these adverse event reports, RotaTeq was administered or



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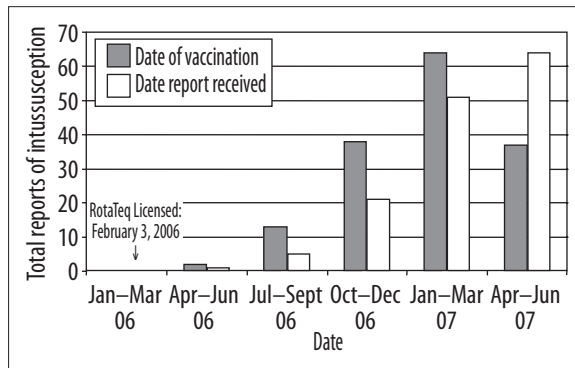


Figure 1. A summary of intussusception adverse events reported to VAERS from January 1, 2006 through July 31, 2007 following any type of vaccine.

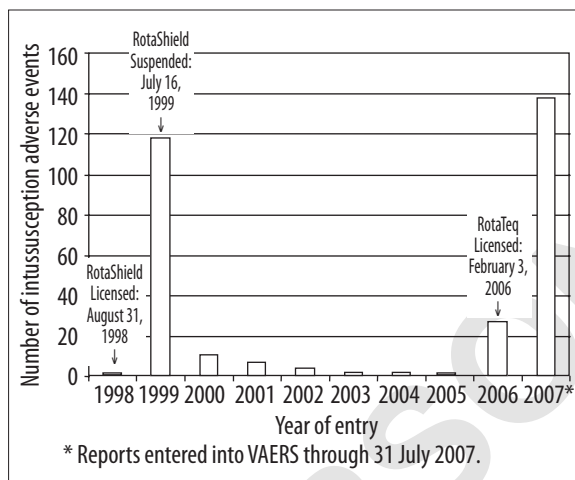


Figure 2. A yearly summary of intussusception adverse events entered into VAERS from 1998 through July 31, 2007.

co-administered with other vaccines in a total of 11 adverse events (69% of the total adverse event reports that listed Kawasaki disease as an adverse event).

Figures 1 and 2 summarize the time trends for adverse event reports in VAERS with an "intussusception" symptom. Figure 1 evaluates the date of entry and date of inoculation for intussusception adverse events in VAERS, and shows the significant increase by quarter in the number of intussusception adverse events reported to VAERS since the licensing of RotaTeq vaccine on February 3, 2006. Figure 2 highlights that intussusception adverse events were observed to significantly increase following the licensing of RotaShield vaccine on August 31, 1998, and, subsequently, to decline following the CDC's July 16, 1999 decision to halt RotaShield administration. In addition, Figure 2 shows the significant increase in intussusception adverse events following the licensing of RotaTeq vaccine on February 3, 2006.

Figure 3 depicts the time trend for Kawasaki disease adverse-event reports in VAERS by date of entry. Figure 3 also shows that the introduction of RotaTeq in 2006 was associated with a subsequent significant rise in the total number of Kawasaki disease adverse events entered into VAERS during the first seven months for 2007.

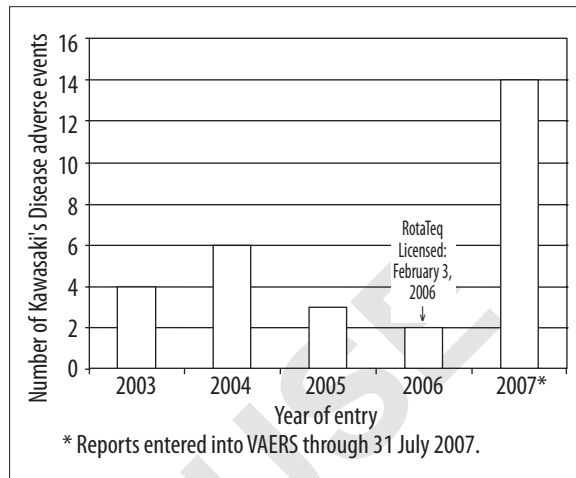


Figure 3. A yearly summary of Kawasaki disease adverse events entered into VAERS from 2003 through July 31, 2007.

DISCUSSION

VAERS findings

The present study is important because of the fact that post-marketing monitoring for adverse events after RotaTeq inoculation can identify possible differences in the characteristics of infants who received the vaccine in routine use, compared with the infants in the clinical trials. Also, the large numbers of infants being vaccinated provides an opportunity to detect adverse events occurring in the US at a low rate after inoculation.

In considering the results observed, a significant number of intussusception adverse events were reported to VAERS following RotaTeq vaccine administration. Considering the reports entered into VAERS through July 31, 2007, there have been approximately as many intussusception adverse events reported to VAERS as were reported to VAERS following use of RotaShield vaccine in the late 1990s. The results of the present study suggest that the intussusception adverse events reported to VAERS may be associated with RotaTeq immunization.

This study found that, after a significant decline in intussusception adverse events entered into VAERS after the withdrawal of RotaShield, the previous rotavirus vaccine, a significant, rapid increase in intussusception adverse-event reports was observed after the licensing of RotaTeq, the current rotavirus vaccine, on February 3, 2006. In addition, the median onset time reported for intussusception following RotaTeq vaccine administration was significantly delayed in comparison to other adverse events. Moreover, intussusception adverse events reported to VAERS following RotaTeq were accompanied by a significant number of reports of less serious, earlier occurring adverse gastrointestinal disorders. This finding is consistent with the fact that, if RotaTeq were inducing gastrointestinal disturbances following immunization, it would be expected that intussusception would be one of many different types of gastrointestinal disorders induced by the vaccine (i.e. from very mild to very severe). Furthermore, the gastrointestinal adverse events reported to VAERS are similar to those previ-

ously associated with RotaShield inoculation [4,5]. Finally, the data examined for Kawasaki disease also appears to indicate an association between this condition and RotaTeq vaccine administration.

In assessing the results from the present study, it is significant that about 160 intussusception adverse events have been reported to VAERS within about one month following RotaTeq inoculation. Given the FDA estimates that about 6 million doses of RotaTeq vaccine have been distributed during its approximately first year on the market [9], and presuming that the average infant has received the recommended 3 doses of RotaTeq vaccine, this means that less than one-half of US infants have received a full course of RotaTeq vaccine administration in the "year" following its recommendation for "universal" use, and yet 160 occurrences of intussusception have been reported to VAERS. Based upon the current data, it is possible to estimate the numbers of intussusception adverse events that may be received by VAERS when the vaccine uptake exceeds 90%. That estimate translates into more than 300 RotaTeq-associated intussusception adverse events annually reported to VAERS.

Limitations of the present study include the fact that not every individual experiencing an adverse event following RotaTeq vaccine administration will know to report such information to VAERS. This may be especially true since the original clinical trial of RotaTeq reported that this vaccine was not associated with outcomes such as Kawasaki disease or intussusception. However, this limitation should have little, if any, impact on the time-trend analysis method utilized in the present study, since both Kawasaki disease and intussusception were infrequently (<10 reports per year) reported to VAERS in the three-year period before licensed RotaTeq administration commenced.

In addition, the median onset times observed for intussusception, gastrointestinal disorders, and Kawasaki disease also argue against simple reporting biases affecting the trends observed. Namely, despite the natural inclination for adverse events to be reported within the first few days post-immunization, these three adverse event outcomes had median onset times that ranged from about one week to about one month following inoculation. Another limitation in the present study was the inability to calculate the precise incidence rate of adverse events following RotaTeq because the information regarding the exact numbers of vaccines administered was not available. Again, given the analysis methods employed, this limitation had a limited impact on this study's findings.

Finally, the current study was not able to adjust for potential factors that might have resulted in vaccine avoidance but which may have predisposed the avoiders toward the adverse events under study. Specifically, as Fine and Chen have reported, [12] there are several social and medical attributes associated with avoidance or delay of vaccination and an increased risk of adverse events, and confounding of this sort is a general problem for studies of adverse reactions to prophylactic interventions. This is the case as prophylactic interventions may be withheld from some individuals precisely because they are already at high risk of the adverse event. Fine and Chen also reported that studies, which fail to control adequately for such confounding fac-

tors, are likely to underestimate the risks of adverse events attributable to vaccine administration. As a result, the effects observed in the present study probably represent an underestimate of the true effects of RotaTeq inoculation on the risk of the adverse events examined.

On the whole, the results observed in the present study are supported by biological plausibility concerning the known adverse effects of natural rotavirus infection. For example, intussusception and other gastrointestinal disturbances are known complications of natural rotavirus infection [13]. Similarly, researchers have previously speculated that Kawasaki disease is a complication of natural rotavirus infection [14]. The biological plausibility of the present results are also supported by the fact that greater than 50% of the patients that reported gastroenteritis rotavirus as an adverse event following RotaTeq vaccination had positive lab tests for rotavirus.

In addition, the onset times reported for the adverse events examined in the present study were consistent with the biologically plausible time necessary for viral infection post-immunization. The spectrum of rotavirus illness ranges from mild, watery diarrhea of limited duration to severe diarrhea with vomiting and fever that can result in dehydration with shock, electrolyte imbalance, and death [15-19]. Following an incubation period of 1 to 3 days, the illness can begin abruptly, and vomiting often precedes the onset of diarrhea. Up to one third of patients have a temperature of >102°F (>39°C). Gastrointestinal symptoms generally resolve in 3 to 7 days.

Furthermore, in considering the results of the present study in context, it has been reported that rotavirus infects almost all children by age 5 years, but severe, dehydrating gastroenteritis occurs primarily among children aged 3 to 35 months. Moreover, rotavirus gastroenteritis results in relatively few childhood deaths in the United States (approximately 20 to 60 deaths per year among the 20-million-plus children under the age of 5 years) [20]. In addition, the CDC has estimated that nearly every child in the United States has been infected with rotavirus by age 5 years, and that the majority will have gastroenteritis, resulting in approximately 410,000 physician visits, 205,000 to 272,000 emergency department (ED) visits, and 55,000 to 70,000 hospitalizations each year and direct and indirect costs of approximately US\$1 billion [21-24].

Costs and risks of RotaTeq

In considering the cost of RotaTeq vaccine administration, RotaTeq is administered in a schedule of 3 doses (\$30 for each doctor's well-baby office visit to administer the vaccine × 3=\$90) during the first year of life and costs according to the CDC's discounted price about \$55 per dose [25]. Thus, the minimum annual total cost for the "universal" rotavirus inoculation program will be US\$255 per child times about 4 million births per year in the US, or a minimum of about US\$1.02 billion per year to vaccinate each yearly US birth cohort. As a result, presuming 100% effectiveness and hypothetically no adverse events associated with vaccine administration, RotaTeq inoculation costs as much, and perhaps more than, the annual costs associated with natural rotavirus infection. Furthermore, presuming an av-

erage of 40 deaths per year from rotavirus gastroenteritis, this means that the minimum cost, if RotaTeq inoculation is 100% effective and, contrary to reality, the vaccine has no associated side-effects, would be about \$25.5 million per death prevented.

Furthermore, when cost-benefit studies were conducted in the late-1990s before the introduction of the first rotavirus vaccine, it was concluded that the break-even point for medical expenses would be \$9 per dose [21]. It was also reported that the disease burden of rotavirus substantially decreased in the 1990s prior to the introduction of RotaShield. Subsequently, in 2007, researchers from the CDC reported that assuming costs of RotaTeq vaccine administration of \$10, the break-even price per dose of vaccine was \$42 from the societal perspective and \$12 from the health care perspective [26]. In addition, it was determined that RotaTeq vaccination would only very probably (i.e. >95% likely) be cost-saving from the health care perspective at less than \$1 per dose. These researchers concluded that, "routine rotavirus vaccination would unlikely be cost-saving in the United States at present." This reality seems especially true since the CDC discounted price for RotaTeq is \$55 per dose and the private sector price for RotaTeq is \$67 per dose [25].

Additionally, disease demographic data suggest that children from disadvantaged socioeconomic backgrounds and premature infants have an increased risk for potential adverse effects from rotavirus gastroenteritis [27]. Since RotaTeq is a relatively expensive vaccine, even at the discounted rate of \$165 per childhood series, many of those that are from disadvantaged socioeconomic backgrounds will be unable to afford the vaccine. As a result, the very populations that would gain the most benefit from RotaTeq vaccine will have the least access to the product. In addition, these disease demographics strongly suggest that a national vaccination program will unnecessarily expose children in other demographic groups to rotavirus even though these other demographic groups have little or no risk for contracting a serious clinical case of rotavirus absent rotavirus vaccination.

In considering this possibility, it was previously observed that the pattern of intussusception in New York State following the use of RotaShield vaccine was significantly altered [27]. Namely, it was observed that intussusception cases among unvaccinated children occurred throughout the first year of life and among a significant number of economically disadvantaged persons. By contrast, among those that received RotaShield vaccination, all cases of intussusception occurred within the first 6 months of life and all occurred among affluent members of the population. Based on the preceding demographic realities, it seems obvious that RotaTeq is not cost effective from a societal point of view. Considering the aforementioned concerns, many in the US may question the risk/benefit ratio of RotaTeq vaccination, especially given the shocking and potentially life-threatening nature of adverse events such as intussusception or Kawasaki disease occurring within temporal association to vaccine administration.

It is also important to consider the potential number of more than 300 annual intussusception adverse events that may be reported to VAERS temporally related to RotaTeq vaccine administration in the context of the fact that the

CDC estimates that in the United States, only about 1,200 to 1,400 cases of intussusception occur annually among children less than 1 year-old, in the absence of rotavirus vaccination [1]. This would mean, presuming that VAERS is capturing 100% intussusception adverse events occurring following RotaTeq vaccine administration and that every dose of RotaTeq vaccine distributed has been administered to infants, more than 25% of the annual number of cases of intussusception may be temporally related to RotaTeq vaccine administration in the US. By contrast, it was previously published that the reporting efficiency (reporting efficiency = number of a specific events/number of events expected) for selected vaccine-associated adverse events in VAERS ranged from a minimum of <1% to a maximum of 68% [10]. In addition, since the full-year "intussusception" reports for 2007 may actually exceed the sum of all of the intussusception reports to VAERS for the period from 2001 through 2005, when there was no rotavirus vaccine, by a factor of ten or more, it is clear that giving most children this infective human-bovine hybridized rotavirus may significantly increase the number of intussusception cases occurring in the US, and introduce infective levels of rotaviruses into demographic segments that, prior to vaccine deployment, had little or no risk of having a severe clinical case of rotavirus.

Furthermore, it is important to consider intussusception and Kawasaki disease adverse events reported following RotaTeq vaccine in the context that the vaccine is supposed to reduce the frequency of rotavirus infection. Since rotavirus infection has been associated with intussusception [28] and Kawasaki disease [14], one must presume that the vaccine should reduce the rate of intussusception relative to unvaccinated background populations. The results of the present study (showing apparently above-background reporting frequencies of intussusception and Kawasaki disease adverse events in VAERS following RotaTeq vaccine administration) coupled with the double-blind placebo controlled trial (where there was a significant, but, because of the small size of the clinical trial, non-statistically-significant increase in the frequency of both conditions observed following RotaTeq vaccine administration relative to the placebo group) raise questions about the safety profile of RotaTeq vaccination.

The present data suggests two possible alternatives regarding the effects of RotaTeq administration on the general population: presuming no increased rate of intussusception/Kawasaki disease following vaccine administration, then the vaccine is simply giving children intussusception/Kawasaki disease at the population rate and is, therefore, not effective in preventing rotavirus-associated intussusception/Kawasaki disease; or, alternatively, presuming that there is an increased rate of intussusception following vaccine administration, then rotavirus, particularly rotavirus-associated intussusception/Kawasaki disease, affects a limited number of children in the first six months of life, and, by vaccinating most children in the first six months of life, RotaTeq is altering the disease pattern of intussusception/Kawasaki disease among US vaccinated children.

Another very important aspect of RotaTeq vaccine administration that has received only limited consideration is that rotaviruses are shed in high concentrations in the stools of

infected children and are transmitted primarily by the fecal-oral route, both through close person-to-person contact and through fomites [29]. In addition, rotaviruses are also probably transmitted by other modes, such as fecally contaminated food and water and respiratory droplets [30].

In the clinical trials conducted with RotaTeq, shedding was evaluated among a subset of subjects 4 to 6 days after each dose and among all subjects who submitted a stool antigen rotavirus positive sample at any time [7]. RotaTeq was shed in the stool of 32 of 360 (8.9%, 95% confidence interval =6.2–12.3%) tested after the first dose. In phase 3 studies, shedding was observed as early as 1 day and as late as 15 days after a dose. Though, inexplicably, transmission was not evaluated, the manufacturer warns that caution is advised when considering whether to administer RotaTeq to individuals with close contacts who are immunodeficient. Finally, the manufacturer also states that there is a theoretical risk that the live virus vaccine can be transmitted to non-vaccinated contacts, and that the potential risk of transmission of vaccine virus should be weighed against the risk of acquiring and transmitting natural rotavirus.

Researchers have previously described that, in the US, natural rotavirus infection causes gastroenteritis in parents and persons caring for children with natural rotavirus gastroenteritis, immunocompromised persons, and older adults [31]. Furthermore, children and adults who are immunocompromised because of congenital immunodeficiency, hematopoietic transplantation, or solid organ transplantation sometimes experience severe, prolonged, and even fatal rotavirus gastroenteritis [32–35].

In light of the above concerns, a search of VAERS for transmission of rotavirus infection to secondary contacts (Costart Term = “secondary transmission”) revealed a total of seven adverse event reports. Each report described a secondary contact experiencing gastrointestinal disorder symptoms (including among adult relatives, and in one case in an immunocompromised father), and two adverse event reports identified the patients had laboratory test confirmed rotavirus.

Since RotaTeq vaccine contains live-unattenuated strains of a genetically engineered set of human-bovine hybrid rotaviruses and since it will be virtually impossible to shield others from fecal-oral transmission of the virus following inoculation, it would appear that RotaTeq vaccine administration may be a ubiquitous source of potential danger to others, particularly those that may be immunocompromised.

CONCLUSIONS

Based on the preceding realities, it would seem that the ACIP recommendations for the universal use of RotaTeq were, at best, premature and unwarranted. It is important that healthcare providers continue to report adverse events that occur following RotaTeq vaccine so that more information may be gleaned about its safety profile, and those patients that may have experienced an adverse effect of RotaTeq vaccination should be advised that they may be eligible for compensation from the no-fault National Vaccine Injury Compensation Program (NVICP). The acceptance of RotaTeq vaccination for the US market may be significantly

limited by its apparent lack of economic savings, and given the fact that it may alter disease patterns of intussusception/Kawasaki disease, so that they occur with greater frequency among segments of the population that previously had only limited experience with such conditions. Moreover, if the serious adverse events being reported following vaccination with RotaTeq are indeed vaccine related, then, like the previous rotavirus RotaShield, RotaTeq should be immediately withdrawn from the US market.

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