

# THE WITHDRAWAL OF THE ROTASHIELD ROTAVIRUS VACCINATION DUE TO AN ASSOCIATION WITH INTUSSUSCEPTION: FACT OR FICTION?

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**Abstract** - Rotavirus exists throughout the world and is estimated to have infected every individual by their fifth birthday. For this reason, there has been a significant drive for the development of a vaccination for the virus. After much failure, Rotashield, a tetravalent rhesus-based live attenuated vaccine was developed and approved in 1998. Following over 1.5 million administrations, it was suspended from the market in July 1999 and finally removed entirely in November of the same year due to fears of increased rates of intussusception following vaccination. Previous studies have shown a relationship between adenovirus infection and increased rates of intussusception. However similar relationships with wild-type rotavirus infection have not been demonstrated. Though studies have shown as much as a 25 times greater risk of developing intussusception within one week of vaccination, they fail to provide convincing conclusions. Past studies have either failed to include proper control groups which account for recency of wild-type rotavirus infection, consider cumulative rates of intussusception, or include sample sizes large enough to detect differences in intussusception rates.

## INTRODUCTION

It is estimated that by the age of five, every child in the United States will have been infected by rotavirus at least once. The virus is the reason for nearly 50,000 hospitalizations and 500,000 primary care visits every year in the United States (Cockey, et al., 2000). Additionally, in the developing world, the effects are much more grave: 800,000 deaths annually from gastroenteritis (Ramsay, 1999). Dehydration due to rotavirus infections account for only 4% of the 1 billion diarrheal episodes but 40% of the diarrheal deaths (Barnes, 2000). For several years, there has been pressure on the scientific community to develop a vaccine for the virus. On August 31<sup>st</sup>, 1998, American Home Products (formerly Wyeth-Ayerst Laboratories) released Rotashield, a tetravalent, live attenuated rhesus vaccine (RRV-TV). This vaccine, which proved able to prevent nearly 100% of serious rotaviral diarrheal episodes, was only on the market for a year: pulled off the market in November 1999 due to a presumed association with intussusception. Was this action warranted? Do averted side effects warrant the deaths of more than half a million children each year?

## VACCINE DEVELOPMENT AND ADMINISTRATION

Rotashield, which was developed in the United States, was not the first attempt at developing a rotavirus vaccine. Originally, the

vaccine was bovine-based. Unfortunately, this vaccine only provided protection for serotype 1 of the virus. Research then turned to the utilization of a rhesus monkey-derived vaccine. Several different rhesus-based vaccines were attempted, including MMU 18006, though they failed to prove safe for administration in infants (Clemens, et al., 1999). In order to ensure protection against the four predominant serotypes afflicting humans, the double helixed genome was recombined to include the surface glycoproteins for three of the human serotypes (Bass, 2000). The vaccine was administered orally and utilized the Jennerian approach of stimulating immunity of the intestinal mucosa through direct exposure. Because the virus replicated very poorly in humans, very high titers of virus were needed in order to stimulate immunity (Bass, 2000). The vaccine was administered in three sessions: at 2, 4, and 6 months of age.

The efficacy of the vaccine was measured in pre-licensure trials in the United States, Finland, and Venezuela. In the United States, 1278 healthy infants (age 5-25 weeks) were given either RRV serotype 1, RRV-TV, or a placebo at ages 2, 4, and 6 months. It was found that the RRV-TV reduced the number of rotavirus episodes by 49%, eliminating the occurrence of dehydrating rotavirus illness (Barnes, 2000). Additionally, the trials in Finland (n=2,398) and Venezuela paralleled the U.S. trials in structure and showed a similar protection against the virus, reducing the occurrence of severe diarrhea

by as much as 88% (Barnes, 2000). The documented side effects in these studies were primarily fever or a slight chance of abdominal cramping or decreased appetite. The findings appeared conclusive and following FDA approval and endorsement by the Advisory Committee on Immunization Practices (ACIP) and the American Academy of Pediatrics (AAP), the Rotashield vaccine was widely used in the United States; an estimated 1.5 million doses were administered by June 1999 (Sherman, et al., 1999).

#### SIDE EFFECT

In June 1999, the Vaccine Adverse Events Reporting System (VAERS) recorded 13 cases of intussusception in infants who had been administered the vaccine. Though this was not significantly different than the 10 to 16 cases that would be expected in the general population during this time period, the recency of the intussusception from the vaccination warranted closer examination. As a result, the AAP temporarily suspended administration of the vaccine so that further research could be done.

During pre-licensure trials, six cases of intussusception were documented (5 in the vaccine group and 1 in the control population). This study by Rennels, et al. (1998) examined all children who had participated in the vaccine trials (n= 10,054) and were hospitalized for intussusception. Additionally, the number of children who were hospitalized for rotavirus diarrhea was examined. The control population consisted of children from the general population who had not participated in the trials (n=4,633). The results showed that there were five cases of intussusception in the vaccine group and only one case in the control population. A Poisson regression analysis showed that these measurements were not significantly different. The results did show an increased occurrence of intussusception within 7 weeks from the vaccination. However, because the findings were not significant, the vaccine was approved for public administration.

#### WILD-TYPE ROTAVIRUS AND INTUSSUSCEPTION

The use of the general population as a control group, in nearly all studies done, makes the assumption that there is no association between rotavirus infection and intussusception. Many studies, including that by Rennels, et al.

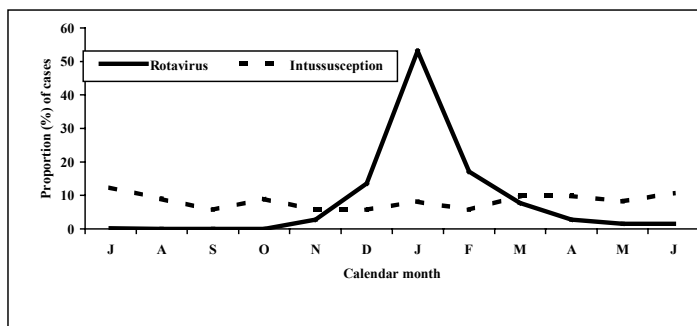
(1998), assert that there was a temporal proximity between the case of intussusception and the Rotashield vaccination; most cases occurred within a two weeks of vaccination. However, there is no control for the time of an infant's exposure to the wild-type virus in the general population. Previous studies have shown there to be a close association with other viruses and intussusception, with over 50% of cases of intussusception (n=64) found to be correlated with a virological infection (Nicolas, 1982). Though adenovirus was present in 41% of intussusception cases, only 10% of patients had a rotavirus infection at the time of the study. The assumption of no association between wild-type infection and intussusception has been further supported by two studies.

Chang, et al. (unpublished) examined the existence of a relationship between rotavirus infection and intussusception in a two part, prospective and retrospective study. The retrospective portion examined 122 cases of intussusception in children under the age of 3 between 1992-1999. Among this population, it was found that there were zero cases of prior rotavirus disease. The prospective portion examined the other perspective, looking at patients who has been treated for rotavirus diarrhea (n=480) to see what the later incidence of intussusception would be. Of this population, there were zero cases of subsequent intussusception. Though the construction of this study and proper control group was proper, the sample size was far too small to find any significant effects. Consider that since the natural rate of intussusception is approximately 50/100,000 infants (or 45/100,000 infant-years), a sample size of such a small magnitude would not be expected to find any cases of or be able to make any conclusions about the rate of intussusception.

Rennels, et al. (1998) also compared the temporal distribution of cases of intussusception and cases of rotavirus infection over the course of the year in New York State. Though there was a highly seasonal variation in the prevalence of rotavirus infection, primarily present in the late winter and early spring months, there was no evident seasonal variation in the number of cases of intussusception. The absence of a seasonal pattern association indicated an absence of relationship between the two events.

Chang, et al.(unpublished) conducted a two-part examination of wild-type rotavirus infection and cases of intussusception. The prospective portion of the examination consisted of active surveillance of California hospitals and clinics,

**Table 1: Seasonal Distribution of Rotavirus Disease and Intussusception in children < 3 yrs old (WHO Conference, 2000)**



from November 1997 through July 1999, for children under the age of three with rotavirus diarrhea. Alternatively, the incidence of intussusception was examined through a retrospective review of clinical charts, from October 1992 thru July 1999, for diagnosis of intussusception. The results demonstrated no association: the 480 cases of rotavirus diarrhea had no cases of subsequent intussusception and the 122 cases of diagnosed intussusception had no cases of prior rotavirus infection. It was found that the peak age of intussusception was between 4 to 9 months of age and there was no seasonality in its frequency (Chart 1). This study mirrored the structure of a previous study by Mulcahy, et al. (1982) which also utilized electron microscopy, ELISA tests, and immunofluorescence to confirm the rotavirus infection in the prospective section. This study found 2 patients who had intussusception after a rotavirus infection, however they reached the same conclusions as the other studies mentioned. Hence, these studies claim that there exists no association between wild-type rotavirus infection and intussusception.

**ROTASHIELD ASSOCIATED WITH INTUSSUSCEPTION**

The question still remains if these findings support the assertion that the Rotashield vaccine results in a higher rate of intussusception. The decision to suspend administration and the association publicized by MMWR was initiated by the discovery by VAERS of a high rate of intussusception closely following the administration of the Rotashield vaccine. Of the fifteen cases of intussusception reported between the vaccine release and July 7, 1999, thirteen (87%) of the cases had appeared soon after the first RRV-TV dose and twelve (80%) of the cases appeared within one week of an administration of a Rotashield dose (MMWR, 7/16/99). These findings only examined the first 21 days following vaccination and failed to

consider the cumulative risk of intussusception over the first two years of life.

The effects of the vaccine on the patient samples were first examined through active surveillance in the Northern California Kaiser Permanente (NCKP) population and a population of infants in Minnesota. Throughout the NCKP system, over 16,000 doses of the vaccine had been administered since licensure. There were nine cases of radiographically confirmed intussusception in infants who had received the vaccine. As a result, it was found that the rate of intussusception among vaccinated children was 125/100,000 infant-years versus a rate of 45/100,000 infant-years in the non-vaccinated population (age-adjusted relative risk = 1.9). Additionally, infants who had been administered the vaccine within a week had a rate of intussusception of 314/100,000 infant-years (age-adjusted relative risk = 5.7). These findings were shown to approach significance (p<0.4 and p<0.2 respectively). In Minnesota, nearly 63,000 doses of the vaccine had been distributed and eighteen cases of intussusception were identified (including five infants who had received the RRV-TV). Through a similar examination, it was found that within one week of vaccine administration, the observed rate of intussusception in Minnesota was 292/100,000 infant-years (MMWR, 7/16/99).

These initial findings prompted much closer controlled examinations of the relationship of Rotashield with intussusception. A large-scale multi-state study was conducted by The National Immunization Program and the Centers for Disease Control and Prevention. This study examined patients in geographic areas that had received the vaccination. The patient population age ranged from one to eleven months. And, contrary to the NCKP and Minnesota studies, the control was a matched case-control (with 4 controls/case) according to demographic and geographic factors. The examination found a very significant (p<.001) difference in the chance of intussusception following both dose 1 and dose 2 (see tables 1 and 2).

**Table 1: Odds Ratios by Window Interim Case Control Analysis: Dose 1**

Window (days)	Odds Ratio	95% CI	p-value
0 - 2	---	---	---
3 - 7	24.8	9.5 – 65.1	.0001
8 - 14	7.1	2.3 – 21.9	.0007
15 - 21	0.7	0.2 – 3.4	.6957

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**Table 2: Odds Ratios by Window Interim Case Control Analysis: Dose 2**

Window (days)	Odds Ratio	95% CI	p-value
0 - 2	---	---	---
3 - 7	13.4	2.6 – 69.0	.0019
8 - 14	1.8	0.3 – 11.2	.5453
15 - 21	1.8	0.2 – 20.0	.6335

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One week following the administration of the first dose, the infants had nearly a 25 times greater chance of intussusception than their matched case controls. Within one week of the second dose, the infants were more than 14 times more likely to develop intussusception. It was also noted that the greatest frequency of cases of intussusception in the control population were between ages 3 to 8 months. However, in the vaccinated population, the majority of cases appeared before the age of 5 months. This was shown in a 394% increase in the number of cases of intussusception in patients of 1 to 2 months of age (CDC, unpublished). Once again, these studies fail to examine the cumulative occurrence of intussusception beyond the 21 day time window.

#### COST-BENEFIT ANALYSIS

Despite the conclusions, however unwarranted, of the association between Rotashield and intussusception, the potential benefits of the vaccine need to be considered, because of the prevalence of rotaviral infections in the world. Tucker, et al. (1998) examined the costs and benefits of the implementation of a universal Rotavirus Immunization program in the United States. It was estimated that such a program would prevent 1.08 million cases of diarrhea each year, 34,000 hospitalizations, 95,000 emergency room visits, and 227,000 physician visits for children under the age of 5. This would translate, assuming a vaccination price of \$20 per dose, into a cost to the health care system of \$107 million, but a societal savings of \$296 million. Using a sensitivity analysis, it was shown that the net benefit to society would persist even in the worst-case scenario.

The analysis for the United States cannot be translated into the international arena, because the access to care and the mortality from infection significantly differs. As presented by Glass (unpublished) at the WHO conference on rotavirus vaccine, rotaviral disease in developing

countries occurs at a younger age, has more co-infections, and possesses more serotypes than in developed nations. Findings have actually shown a lower annual rate of intussusception in developing areas, such as 24 per 100,000 in Venezuela, 4 per 100,000 in Brazil, and 20 per 100,000 in South Africa. This may be due to different feeding practices, more GI infections, or an altered thickness of the bowel wall. However, the mortality from rotaviral diarrhea (400/100,000) and intussusception (20/100) is much higher in these countries than in the developed world. Considering these factors, Miller, et al. (unpublished) calculated that considering the said mortality rate from rotaviral gastroenteritis, a conservative efficacy of the tetravalent vaccine of 30%, an incidence of intussusception of 1 per 4,700 vaccinees, and a 20% mortality rate from cases of intussusception, then the risk of dying from RV gastroenteritis would be 25 times greater than dying from vaccine-induced intussusception (assuming a relationship does occur). This raises the consideration of the international implications and potential costs of the removal of the Rotashield vaccination from the U.S. market.

What are the implications of these studies and the future of rotavirus vaccine research? The current body of research has shown no definitive difference in the rate of intussusception between vaccinees and the control population: failing to take into consideration the cumulative risk of intussusception or not considering the recency of wild-type rotaviral infection in the control populations. The enormous need for a rotaviral vaccination has been repeatedly shown and development must continue in other avenues of research: such as through other routes of administration, basing the vaccine on a different animal virus, administration in scaled increasing dose concentrations, or the use of the empty capsid. Over the next year, more reliable research should be conducted on the cumulative intussusception rates and actual vaccine efficacy of the population who were vaccinated between November 1998 and July 1999. These findings should provide a more reliable and definitive assessment of the advantages and potential risks of the rotavirus vaccination.

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