CD Summary

July 20, 1999
Vol. 48, No. 15

Telephone 503/731-4024
Emergencies 503/731-4030
Fax 503/731-4798
cd.summary@state.or.us
www.ohd.hr.state.or.us/cdpe/

CENTER FOR DISEASE PREVENTION & EPIDEMIOLOGY • OREGON HEALTH DIVISION

CDC RECOMMENDS POSTPONEMENT OF ROTAVIRUS VACCINE

ROTAVIRUS VACCINE was recently licensed and recommended for universal use among infants in the United States. However, on July 16, 1999, the MMWR reported preliminary data suggesting the possibility of an association between receipt of this vaccine and subsequent development of intussusception. Until more definitive data become available, CDC recommends postponing administration of rotavirus vaccine to children. This issue of the *CD Summary* summarizes the MMWR report and its recommendations, and presents Oregon data regarding intussusception in infants.

Rotavirus is the most common cause of severe gastroenteritis in infants and children <5 years old in the United States, resulting in approximately 500,000 physician visits, 50,000 hospitalizations, and 20 deaths each year. It has a strong winter seasonality, with hospitalizations typically peaking in February and March.[1] Worldwide, rotavirus is a major cause of mortality in the <5-year age cohort, causing an estimated 600,000 deaths annually.

A vaccine against rotavirus is therefore a good thing. A live, oral vaccine was developed, incorporating a rhesus rotavirus strain with specificity for one serotype and three single-gene human-rhesus reassortants to cover three more serotypes pathogenic for humans. The resultant tetravalent rhesus-based rotavirus vaccine (RRV-TV; RotaShield™, Wyeth) was tested in the United States, Venezuela, and Finland. The vaccine proved 69%-91% effective in preventing severe rota-virus diarrhea.[2]

Side effects noted were predominantly fever and related symptoms, which occurred significantly more in vaccine recipients than in those receiving placebo (2% vs. 1%). A statistically insignificant increase in cases of intussusception was noted in vaccine recipients compared with placebo recipients (5 of 10,054 vs. 1 of 4,633; p=0.67). Three of the five cases in vaccine recipients occurred 6-7 days after receiving rotavirus vaccine. It should be noted that an association between intussusception and wild rotavirus infection has yet to be confirmed; and even in these vaccine recipients, the rate of intussusception was comparable to rates in non-vaccinated populations.[3] The vaccine was licensed on August 31, 1998.

RRV-TV was subsequently recommended for routine use in US infants, generally at 2, 4, and 6 months of age.[2, 4] On the basis of the data from pre-licensure studies, however, intussusception was included as a potential adverse reaction on the package insert, and the Advisory Committee on Immunization Practices (ACIP) recommended both post-licensure special studies and passive surveillance for intussusception following rotavirus vaccination through the Vaccine Adverse Events Reporting System (VAERS).

VAERS DATA

VAERS is a passive surveillance system for vaccine-related adverse events operated by the Food and Drug Administration and the Centers for Disease Control and Prevention (CDC). VAERS receives vaccine-related adverse event reports from vaccine manufacturers, health-care providers, vaccine recipients and families of vaccine recipients. Between September 1, 1998, and July 7, 1999, 15 cases of radiographically confirmed intussusception among infants who received RRV-TV were reported to VAERS. Onsets of reported illnesses occurred from November 21, 1998, to June 24, 1999. Thirteen developed intussusception following the first dose of the three-dose RRV-TV series, and 12 developed symptoms within 1 week of receiving any dose of RRV-TV. All infants recovered. Eight infants required surgical reduction, and one required resection of 7 inches (18 cm) of distal ileum and proximal colon. Histopathologic examination of the distal ileum indicated lymphoid hyperplasia and ischemic necrosis. The median age of patients was 3 months (range: 2-11 months). Ten were boys.

Given an estimated 1.5 million doses of RRV-TV administered during this period, 14-16 cases of intussusception would be expected by chance alone to have occurred during the week following vaccination. As with any passive surveillance system, however, the number of adverse events reported to VAERS is likely to be smaller than the number of adverse events that actually occurred.[5-7] Did the VAERS reports represent the tip of a larger iceberg? To explore further the putative association between administration of RRV-TV and intussusception in infants, a preliminary analysis of data from an ongoing post-licensure study at Northern California Kaiser Permanente (NCKP) was performed; and a multi-state investigation of intussusception in vaccine recipients was initiated.

NORTHERN CALIFORNIA KAISER PERMANENTE

From December 1, 1998 to June 10, 1999, NCKP had administered 16,627 doses of RRV-TV to 9,802 infants. Nine cases of radiographically or surgically confirmed intussusception during December 1, 1998, to June 10, 1999, were identified among infants 2-11 months old treated at NCKP. Three of the nine infants received rotavirus vaccine 3 days, 15 days, and 58 days prior to the onset of intussusception. The rates of intussusception were 45 per 100,000 infant-years among never-vaccinated infants and 125 per 100,000 infant-years among RRV-TV-vaccinated infants (3 infants). Vaccinated infants had a higher risk of intussusception, but this risk was not statistically significant (age-adjusted relative risk [RR]=1.9, 95% CI=0.5-7.7, p=0.39).

MINNESOTA

From October 1, 1998, to June 1, 1999, the manufacturer of rotavirus vaccine (Wyeth Laboratories, Inc., Marietta, Pennsylvania) had distributed 62,916 doses of rotavirus vaccine to health-care providers in Minnesota. Eighteen cases of radiographically or surgically confirmed intussusception between November 1, 1998, and June 30, 1999, were identified among infants 30 days to 11 months old. Five of the eighteen infants had received rotavirus vaccine; three of these five had received it within one week before developing intussusception. Based on these

CD Summary (ISSN 1058-7888) is published biweekly, free of charge, by the Oregon Health Division, a part of the Dept. of Human Resources. 800 NE Oregon St., Portland, Oregon 97232
Periodicals postage paid at Portland, Oregon.
Postmaster—send address changes to:
CD Summary, 800 NE Oregon St., Suite 730, Portland, OR 97232

PERIODICALS
POSTAGE
PAID
Portland, Oregon

three cases, the *annualized* rate of intussusception within 1 week of receipt of RRV-TV was 292 per 100,000 infants.

OREGON

To establish the baseline rate of intussusception in Oregon infants, epidemiologists from Oregon's Emerging Infections Program analyzed hospital discharge data for the period January 1, 1995, to December 31, 1997. Sixty-eight cases in the birth cohort of 130,125 during this period indicated a baseline incidence of 52 per 100,000 infant-years, within the range of the national incidence of 40-70 per 100,000 infant-years. What happened following release of RRV-TV? From November 1, 1998, to June 25, 1999, Wyeth had distributed just 9,852 doses of rotavirus vaccine to physicians in Oregon; according to the Oregon Immunization Registry (which receives information from 94% of Oregon physicians who give vaccines), 1,432 children, or 4.9% of those for whom it was recommended, had received one or more doses of rotavirus vaccine. We reviewed discharge summary data at the five Oregon facilities that had historically accounted for 90% of infant hospitalizations for intussusception. The results were, thankfully, underwhelming. In the eight-month period during which the rotavirus vaccine was available, November 1, 1998, to June 25, 1999, seven cases of intussusception had occurred (12 were expected); communication with cases' primary care physicians indicated that none had received rotavirus vaccine.

COMMENT

Preliminary data from VAERS, from NCKP, and from Minnesota suggest, but do not establish, an increased risk for intussusception following receipt of RRV-TV. Although these studies lack the power to establish a statistically significant difference in incidence of intussusception among vaccinated and unvaccinated children, the consistency of their findings raises concern. These concerns must be balanced against the benefits of the vaccine: routine, universal immunization with RRV-TV would prevent an estimated 1.08 million cases of diarrhea, 227,000 physician visits, and 34,000 hospitalizations associated with rotavirus each year in the United States.[8] Fortunately, rotavirus season is still 4-6 months away in most areas of the United States, so there is time to gather additional data. A large case-control study is underway in the 18 states that have had the highest rates of vaccination with RRV-TV since its release. Data from this study are expected this fall; they should determine whether a risk of intussusception attends rotavirus vaccination and, if so, whether that risk exceeds the benefit of vaccination. Meanwhile**, CDC recommends postponing administration of RRV-TV until November 1999**. The recommendation includes those who already have begun the RRV-TV series. Parents or caregivers of infants who have recently received rotavirus vaccine should promptly contact their health-care provider if the infant develops symptoms of intussusception, e.g., persistent vomiting, bloody stools, black stools, abdominal distention, or severe colic. Health-care providers should likewise consider intussusception in infants who have recently received RRV-TV and present with a compatible clinical syndrome; early diagnosis may increase the probability that the intussusception can be treated successfully without surgery. Vaccine providers, parents, and caregivers should report to VAERS intussusception and other adverse events following vaccination. Information about reporting to VAERS can be requested 24 hours a day by telephone (800/ 822-7967) or via the internet (http://www.nip.gov/nip/vaers.htm). The Oregon Health Division Immunization Program "phone-duty person" (503/731-4020) is standing by to answer questions about rotavirus vaccine.

REFERENCES

This article is adapted from CDC. Intussusception among recipients of rotavirus vaccine-United States, 1998-1999. MMWR 1999;48;577-81.

1. Parashar UD, Holman RC, Clarke MJ, Bresee JS, Glass RI. Hospitalizations associated with rotavirus diarrhea in the United States, 1993 through 1995: surveillance based on the new ICD-9-CM rotavirus-specific diagnostic code. J Infect Dis 1998;177:13-7.
2. Centers for Disease Control and Prevention. Recommendations for the prevention of rotavirus gastroenteritis among children. Recommendations of the advisory committee on immunizations practices (ACIP). MMWR 1999;48(RR-2):1-23.
3. Rennels MB, Parashar UD, Holman RC, Le CT, Chang HG, Glass RI. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. Pediatr Infect Dis J 1998;17:924-5.
4. American Academy of Pediatrics Committee on Infectious Diseases. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. American Academy of Pediatrics. Pediatrics 1998;102:1483-91.
5. Chen RT, Rastogi SC, Mullen JR, et al. The Vaccine Adverse Event Reporting System (VAERS). Vaccine 1994;12:542-50.
6. Food and Drug Administration. Surveillance for adverse events after vaccination: the national Vaccine Adverse Event Reporting System (VAERS). Food and Drug Administration Medwatch Continuing Education Article, November 1998. Available at http://www.fda.gov/medwatch/articles/vaers/vaersce.pdf. Accessed July 20, 1999.
7. Rosenthal S, Chen R. The reporting sensitivities of two passive surveillance systems for vaccine adverse events. Am J Public Health 1995;85:1706-9.
8. Tucker AW, Haddix AC, Bresee JS, Holman RC, Parashar UD, Glass RI. Cost-effectiveness analysis of a rotavirus immunization program for the United States. JAMA 1998;279:1371-6.