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EDITORIAL

Rotavirus Vaccine and Intussusception

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On February 13, 2007, the Food and Drug Administration (FDA) released a public health notification on RotaTeq (Live, Oral, Pentavalent Vaccine—Merck and Co.) and intussusception.[1] The report stated that there were 28 cases of intussusception in the ongoing post-marketing surveillance. Also, this notification stated that the purpose of this notification was to encourage the reporting of additional cases and to remind providers that "intussusception is a potential complication of RotaTeq." The level of alarm may have been misrepresented, however, since the number of cases does not exceed the background expected rate. This information was buried in the body of the report, and even more was left unstated.

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Intussusception is defined as a prolapsing of a part of the intestine into another section of the intestine, similar to a collapsible telescope.[2,3] This is considered a medical emergency that causes intestinal obstruction and ultimately ischemia, gangrene, and perforation. Early recognition and treatment are paramount. The initial symptoms include recurrent, colicky abdominal pain that occurs every 15 to 20 minutes, often with vomiting and followed by a period of well-being. In addition, there is often the passing of mucus and blood, which results in a "red currant jelly stool." Diagnosis is usually made by ultrasound, x-ray, or computed tomography scan. Sometimes a mass may be palpated. In some cases, the intussusception may be reduced by barium or air enema; however, surgical reduction is needed if the enema is not effective or if the intestine is damaged.

ABBREVIATIONS ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control; FDA, Food and Drug Administration; NIH, National Institutes of Health; REST, Rotavirus Efficacy and Safety Trial; US, United States; VAERS, Vaccine Adverse Event Reporting Systems

Most cases of intussusception are idiopathic with no identifying lesions noted. While it can occur at any age, it is most common in patients under the age of 12 months. The Centers for Disease Control (CDC) reports that each year in the United States (US) approximately 1,400 infants in this age group are hospitalized for intussusception.[4] The expected number of cases, or background rate, of intussusception is 18 to 43 per 100,000 per year for unvaccinated children aged 6-35 weeks.

The first rotavirus vaccine (RotaShield (Rotavirus, Live, Oral, Tetravalent – Wyeth)was licensed and recommended for routine use in the US by the Advisory Committee on Immunization Practices (ACIP) in 1998.[5] This vaccine, was evaluated in 18,000 infants. A summary of the pre-licensing trials reported five cases of intussusception among 10,054 infants receiving vaccine and one case in 4,633 placebo patients (0.05% vs. 0.02%, $P > .45$). The FDA approved the vaccine on August 31, 1998, and the ACIP recommended routine use the following Oc-

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tober for infants at age 2, 4, and six months. On July 16, 1999, the Vaccine Adverse Event Reporting Systems (VAERS) reported 15 cases of intussusception among recipients.[6] The CDC placed a temporary suspension on routine administration until a case control investigation could evaluate these cases.[7] This investigation demonstrated a strong relationship between RotaShield and intussusception, prompting the ACIP to withdraw its recommendation for routine use in October, 1999.[8] The manufacturer voluntarily withdrew this product from the market shortly thereafter.

The CDC began an investigation of cases of intussusception in 19 states to assess the potential relationship between RotaShield and intussusception.[9] Seventy-four cases of intussusception in infants receiving the vaccine were discovered. The initial review of the data did not find any risk factor associated with the vaccine with the exception of a decrease in incidence of intussusception in breast-fed infants. However, the majority of the cases clustered in the time period immediately following the first two doses. Most of the cases were reported 3 to 14 days after the first dose (43 cases) and 3 to 14 days after the second dose (nine cases). One case occurred within 3 to 14 days of the third dose. Fourteen cases occurred more than 14 days after one of the three doses, and seven cases occurred in vaccine recipients before the first dose of vaccine was administered.

A reanalysis of the data, by researchers at the National Institutes of Health (NIH), showed that the age at vaccination strongly affected the risk of intussusception.[10] Sixty-two percent of all infants received the first dose of vaccine < 90 days of age. Thirty-eight percent received the vaccine ≥ 90 days of age, which was considered a "catch-up" period for older infants. Nine of the 45 infants (20%) who developed intussusception within 21 days of vaccination had received the vaccine at less than 90 days of age even though this group had received the majority of the vaccine doses (62%). None of the infants who received the vaccine before the 60th day of life (16% of all doses) developed intussusception. The authors concluded that the number of cases of intussusception with the first dose of RotaShield (defined as within 21 days) increases with age. They recommended catch-up immunization with future rotavirus vaccine be avoided and the entire series be completed at the earliest age possible.

Two very large studies were recently published on two new rotavirus vaccines. The first, sponsored by GlaxoSmithKline, evaluated 63,225 infants in a randomized, double-blind, phase three clinical trial of an attenuated rotavirus vaccine.[11] This vaccine contained serotypes G1 and P1a[8]. There were 31,673 patients in the vaccine group and 31,552 patients in the placebo group. This vaccine was given orally in two doses at approximately two months and four months of age. A total of 25 cases of intussusception were reported, of which 13 were diagnosed within 31 days of administration of either dose (six in the vaccine group and seven in the placebo group). In the time period following the 31 days post vaccination, there were nine cases of intussusception in the placebo group and three in the vaccine group. In these 25 cases of intussusception, 10 occurred following dose one (three in the vaccine group and seven in the placebo group), and 15 occurred after dose two (six in the vaccine group and nine in the placebo group). This vaccine is awaiting approval by the FDA at this time.

The second study, sponsored by Merck, evaluated 68,038 infants (34,035 in the vaccine group and 34,003 in the placebo group) in the Rotavirus Efficacy and Safety Trial (REST).[12] The vaccine used in this trial was a pentavalent human-bovine reassortant rotavirus vaccine against serogroups G1, G2, G3, G4, and P[8] given in three doses. The first dose was given between 6 to 12 months of age, followed by two more doses spaced four to 10 weeks apart. Confirmed cases of intussusception occurred in 12 vaccine recipients and in 15 members of the placebo group over a surveillance period of one year following dose one. There were 6 cases of intussusception within 42 days after any dose in the vaccine group and 5 cases in the placebo group. There were no cases in the vaccine group within 42 days of the first dose and 1 case in the placebo group. This data was submitted to the FDA, and it led to the approval of RotaTeq (Rotavirus, Live, Oral, Pentavalent—Merck). The ACIP recommendations were published on August 11, 2006.[13]

Researchers from the CDC created a model to explore whether a strict vaccination schedule (i.e., all doses given within one month of

the scheduled dose at 2, 4, and 6 months) as compared to a "free schedule" (recommended at 2, 4, and 6 months but given at any time within one year).[14] The authors used data on estimated incidence and timing of intussusception from three published surveillance studies and from the estimated vaccination coverage from the 2003 National Immunization Survey. They concluded there would be 182 cases of intussusception, by chance alone, within two weeks of administration of any dose in the free schedule and 138 cases within two weeks of any dose in a strict schedule. Notably, there would be 2,123,800 fewer doses of vaccine given in a strict schedule because the infants would be too old to receive the vaccine.

The withdrawal of RotaShield from the market created many issues. First, a high mortality rate from rotavirus diarrheal disease in developing countries continued for several years (1 in 300 who were infected died with the disease; 500,000 deaths each year) despite a very low rate of intussusception.[15] Also, the new large studies that looked at efficacy and safety demonstrated that these new vaccines have an enormous impact on office visits, hospitalizations, and deaths due to rotavirus disease.[16] Unfortunately, even with the large safety trials, healthcare providers and the parents will continue to be concerned about vaccine-induced intussusception.

The data from recent VAERS reports were discussed at the ACIP meeting in Atlanta, Georgia, on February 21-22, 2007. As of January 31, 2007, 3.6 million doses of RotaTeq have been distributed. Thirty-five confirmed intussusception cases have been reported in patients receiving the vaccine. Seventeen of these cases were within 21 days of vaccination; 11 within 7 days. The expected number of cases of intussusception within 21 days of vaccination is 52, with 17 expected within the 7-day interval. While VAERS data is not as accurate as published studies, the CDC is still comfortable with an ongoing monitoring program and is continuing with its recommendation for routine vaccination of all infants at 2, 4, and 6 months of age.[4]

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