Update on the safety of rotavirus vaccines

A consensus statement from the World Health Organization, FDA, and CDC stated that the documented benefits of the two FDA-approved rotavirus vaccines, Rotarix (Merck) and Rotarix (GlaxoSmithKline), outweigh the suggested increased risk for intussusception—a condition that causes the proximal segment of the bowel to telescope into the adjacent portion of the distal bowel—or any other potential risks.

Rotavirus is the leading cause of severe gastroenteritis among infants and young children, particularly those aged 6 months to 2 years. Clinical features of rotavirus infection include severe, watery diarrhea, fever, abdominal pain, and vomiting, which may lead to severe dehydration and possibly death. Before the rotavirus vaccine was introduced in 2006, nearly all children in the United States were infected by rotavirus before 5 years of age. During that time, more than 400,000 physician visits and more than 200,000 emergency department visits each year in the United States were attributed to the infection. Internationally, rotavirus is responsible for half a million deaths each year in children younger than 5 years.

In 1998, FDA approved Wyeth-Ayerst's oral tetrivalent human-rhesus rotavirus reassortant vaccine (RotaShield). Although this vaccine was proven to effectively prevent rotavirus diarrhea, it was voluntarily withdrawn from the market in October 1999 because of concerns regarding intussusception. In February 2008, FDA approved RotaTeq, a live, oral, pentavalent human-bovine rotavirus reassortant vaccine that is given as a three-dose series (2, 4, and 6 months). Rotarix, a live, oral, monovalent human attenuated rotavirus vaccine that is completed in two doses (2 and 4 months), was approved in April 2008.

Two Phase III trials examined the safety and efficacy of RotaTeq. REST (Rotavirus Efficacy and Safety Trial) was a randomized placebo-controlled trial that evaluated healthy infants aged 6 to 12 weeks (n = 68,038). Investigators evaluated all infants for intussusception and found that it occurred in six RotaTeq recipients and five placebo recipients within 42 days after any dose. REST investigators therefore concluded that no evidence supported RotaTeq vaccine increasing the risk of intussusception compared with placebo.

The safety of the Rotarix vaccine was evaluated in eight randomized, double-blind, placebo-controlled Phase II and III trials. A Phase III trial studied 83,225 healthy infants and found that the vaccine did not increase the risk for intussusception within 31 days after any dose compared with placebo: 6 confirmed cases occurred among 31,673 infants who received Rotarix compared with 7 cases in 31,552 infants who received placebo. A summary of clinical trial evidence regarding the frequency of adverse effects with RotaTeq and Rotarix is shown in Table 1.

Results from a postmarketing study sponsored by GlaxoSmithKline suggested that a small increase in risk for intussusception might occur within the first 31 days after vaccination with Rotarix (relative risk 1.8 [99% CI 1.0-3.1]). A clustering of 18 cases was observed in this study during the first week after the first dose, which corresponds to an intussusception rate four to five times higher than in later periods after vaccination. Based on these data, the estimated incidence of intussusception in the United States is 0 to 4 cases per 100,000 vaccines.

In March 2010, FDA became aware of the presence of porcine circovirus (PCV) type 1 in Rotarix. PCV1 is a small, single-stranded circular DNA virus that is common in and can cause illness in pigs. After the virus was discovered, FDA recommended that health care providers temporarily suspend the use of Rotarix while the manufacturer investigated the virus further.

In April 2010, FDA released a statement from the U.S. Academic Researchers Group that viral sequences not related to the vaccine strain were found in Rotarix. However, the reported sequences were previously known, are associated with vaccine production, and have been determined to pose no safety risk. On May 6, 2010, Merck also identified fragments of PCV1 and PCV2 in RotaTeq. PCV2, like PCV1, is not known to cause infection or illness in humans. Subsequently, FDA, in consultation with the Vaccines and Related Biological Products Advisory Committee, concluded that because no evidence existed that PCV1 or PCV2 can cause infection or illness in humans, the benefits of vaccination outweigh the theoretical risk and clinicians should resume use of Rotarix and continue use of RotaTeq.

Overall, the safety of both RotaTeq and Rotarix vaccine are comparable. The main differences lie in their composition and administration schedules. At present, the Advisory Committee on Immunization Practices does not express a preference for one vaccine over the other.

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