Worried about rare but severe side effects, 2 years ago Wyeth pulled from the market a new vaccine that prevents a major cause of diarrhea. Now the medical community is questioning that risk-benefit calculation

Rethinking a Vaccine's Risk

Two years ago, the manufacturer of a vaccine to prevent rotavirus infection—a diarrheal disease that kills up to 800,000 children worldwide each year—pulled the product off the market. Researchers had linked it to a rare but dangerous bowel obstruction called intussusception. Analysts calculated that the vaccine was too risky, and their argument carried the day. But the scientific and ethical controversy continued to smolder, and now it is springing back to life.

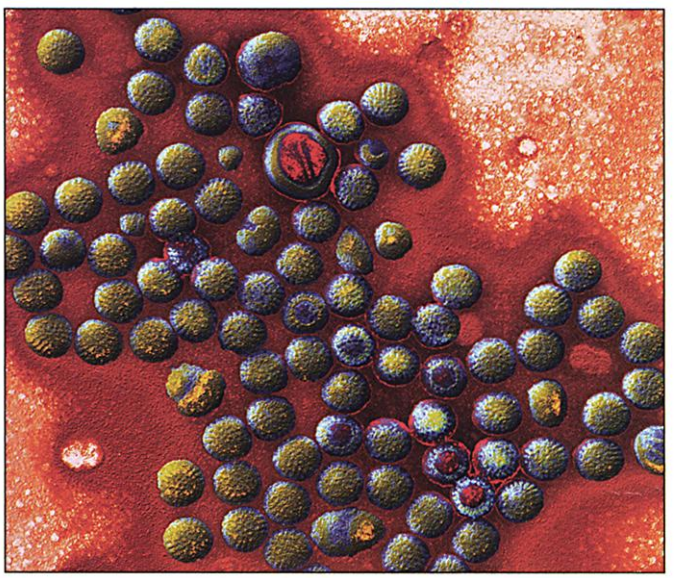
Two new studies suggest that the risk-benefit calculations in 1999 may have been in error, intensifying questions about the decision to withdraw "RotaShield," as the vaccine is called. The stakes are high—not just for North America, where the vaccine was briefly available, but for developing countries, where most rotavirus deaths occur.

The new findings will occupy center stage at a meeting set to begin on 5 September in Rosslyn, Virginia. Convened by the U.S. National Vaccine Program Office, which coordinates federal immunization efforts, and its National Vaccine Advisory Committee, the 3-day gathering will reassess RotaShield's risks and benefits. Several researchers at the U.S. National Institutes of Health (NIH), where the vaccine was first developed before being licensed to industry, are delighted. "A pause in the use was appropriate, but now that we know more about it and have a better sense of what the risks are, we need to reexamine the decision," says John La Montagne, deputy director of the National Institute of Allergy and Infectious Diseases (NIAID).

The reaction is decidedly more cautious at the Centers for Disease Control and Prevention (CDC), NIH's sister institution in Atlanta, Georgia, which first uncovered problems with the vaccine. "I think it would be very difficult to initiate a national program with this vaccine," says CDC epidemiologist John Livengood, who sees substantial problems with the new analyses.

Whatever the United States decides, its action will likely have a far-reaching impact. "There's a sense that the vaccine has to be approved for use here or it won't be touched by anyone overseas," says La Montagne. Yet the risk-benefit calculations are strikingly different for rich and poor countries.

Although rotavirus sends 55,000 U.S. children to the hospital each year (20 to 40 of whom die), for most it only causes a mild diarrhea. Livengood notes that North Americans have so many safety nets that some physicians view RotaShield as "a convenience vaccine." But in developing countries, as many as 1 in 200 infected children die, mainly from dehydration due to the diarrhea that the virus causes. Those countries can't afford the lifesaving rehydration therapy used to treat the disease, and for them, La Montagne and others conclude, RotaShield could provide a "tremendous benefit."



RotaShield's target. This electron micrograph shows particles of rotavirus, which causes a diarrhea that kills many children worldwide.

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Sounding the alarm

NIAID's Albert Kapikian began developing the vaccine 20 years ago by combining parts of rotavirus strains from humans and rhesus macaques. Efficacy trials in the United States, Finland, and Venezuela demonstrated that this live, "reassortant" virus vaccine could safely prevent severe diarrhea in up to 91% of immunized children. RotaShield came to market in the United States in October 1998, and many expected that it would soon make inroads against the disease worldwide. But 9 months later, after reports indicated an unusually high number of cases of intussusception among vaccinated children, the CDC recommended that clinicians stop administering RotaShield. A little-understood bowel obstruction that primarily afflicts infants, intussusception can usually be corrected with a barium enema, but it sometimes requires surgery and, if left untreated, can be fatal. No intussusception deaths, however, have been attributed to RotaShield.

As intussusception cases mounted among vaccinated children, RotaShield's manufacturer, Wyeth Lederle Vaccines of Radnor, Pennsylvania, voluntarily withdrew the vaccine from the market in October 1999. In the 22 February 2001 issue of *The New England Journal of Medicine* (*NEJM*), Livengood and his CDC colleagues published a detailed analysis of children who received the vaccine, concluding that RotaShield caused 1 case of intussusception for every 4670 to 9474 infants vaccinated. In the United States, this would amount to between 361 and 732 cases of vaccine-caused intussusception each year.

Those alarming estimates are now being called into question by analyses performed by two separate research groups, one led by NIAID's Lone Simonsen and the other by Hwa-Gan Chang of the New York State Department of Health in Albany. In the July issue of *Pediatrics*, Chang and his colleagues (two of whom work at CDC) reviewed 9 years of hospital discharge records in New York state to tally how many children were diagnosed with intussusception. In the 9 months that RotaShield was used, they found 81 cases, only three more than found during the same 9-month period in the preceding year. These three "excess cases," Simonsen says, "seemed to be less than you'd expect based on CDC's initial estimates of risk," which predicted 12 excess cases in New York state. "We thought that study was interesting but not powerful enough to answer the question," Simonsen says.

Simonsen, whose results are in press at *The Lancet*, says that she doesn't want to discuss her data in detail until they are published. However, she did present the data in May at a meeting of the Global Alliance for Vaccines and Immunization, and in her talk

there she reported that her team analyzed hospital discharge data from several states (*The Lancet* paper looks at 10), comparing the vaccine period to the five preceding years. Like the New York group, she failed to find a significant number of excess cases of intussusception in the vaccine year.

Charles Weijer, a physician and bioethicist at Dalhousie University in Halifax, Nova Scotia, says it is "absolutely fascinating" that data from new studies with large cohorts suggest no added risk or a risk that's smaller than expected. "It's really vindicating for the people who invested their lives in the development of this very important vaccine." Kapikian adds that the CDC's risk estimates have steadily dropped since the problem first surfaced. He suggests that the apparent risk could fade away. "I think it will be seen as a compelling story: Was there really any increase in intussusception in children in the United States?"

Still, the new reports agree that vaccination is linked to the bowel disorder. "All these cases occurred in the weeks following exposure," explains Simonsen. When a population is analyzed for a year's time, the temporal link between the vaccine and intussusception does increase the total number of intussusception cases.

How can this be? No one has a good explanation, but Simonsen and other researchers say it is possible that by some unknown mechanism, the vaccine merely "triggered" intussusception in children who would have developed it in any case during their first year of life. In essence, then, the vaccine advanced the age of onset. Another theory suggests that rotavirus itself causes intussusception, as researchers in Japan first reported in 1978. If this is right, as Toyoko Nakagomi of Japan's Akita University explained in an *NEJM* letter written in response to the CDC's report last February, the vaccine might, on balance, prevent more cases of intussusception than it causes.

Livengood and his coauthors challenge these assertions. They contend that there's no evidence—or even a plausible mechanism—to support the triggering thesis. And several studies have argued against a link between rotavirus itself and intussusception, noting, for example, that rotavirus infections peak at specific times of year in different regions of the United States, but intussusception cases do not.

The strength of both the Simonsen and Chang studies is that they look at large cohorts over long periods of time. Yet Livengood stresses that they share a weakness: Unlike the study published in *NEJM*, neither had information about individual children's vaccination status, so they could not link specific cases of intussusception to RotaShield. Livengood further notes that he has misgivings about these studies, because the CDC's Piotr Kramarz and coworkers did their own cohort study, published last April in *The Pediatric Infectious Disease Journal*, that also relied on hospital discharge data. A close examination of individual medical records and the hospital discharge data, cautions Livengood, revealed many discrepancies.

Outbreak. An upsurge in rotavirus infections early this year in El Salvador brought many children to a San Salvador hospital for treatment.

Vaccine developer. NIAID's Albert Kapikian produced the modified virus used to vaccinate against rotavirus.

One fundamental problem compromises all the studies so far: Researchers have only crude estimates of how much intussusception occurs naturally in the United States. This makes it difficult to determine the precise impact of the vaccine on intussusception, especially because the condition occurs so infrequently. (Estimates suggest about 1 case per 2000 children.) Researchers also disagree about how many doses of RotaShield went into children, which also alters the various models.

Even though different assumptions have led researchers to conflicting conclusions, Simonsen predicts that the studies ultimately will converge on an understanding of the links between intussusception and RotaShield. "These studies go together like a cocktail, and by learning what we can from all of these studies, we learn the bigger picture," she says.

Kapikian, the main driving force behind the vaccine, is frustrated that the debate continues to focus on U.S. concerns. He and others complain that high, early estimates of the intussusception risk have tainted a vaccine that could save a half-million children each year in the developing world. Harry Greenberg, who developed the vaccine with Kapikian and now is an executive at Aviron in Mountain View, California, agrees: "The [warning] bell needed to be rung immediately," he says, but people forgot that these were just "preliminary data."

Even the CDC's Livengood agrees that it may well make sense to use the vaccine in countries where many children are dying from rotavirus infections. "The cost-benefit equation in developing countries would be very, very positive for that vaccine," says Livengood. But at a World Health Organization meeting last year that gathered researchers from several developing countries to discuss rotavirus vaccines, Kapikian says he learned that politics stood in the way: "The concern was that the [negative] press would be devastating."

Even if the consensus were to shift in favor of using the vaccine, it's not clear that Wyeth would want to manufacture it now. "Our own surveys of Wyeth affiliates and local health experts in developing countries suggest that the product profile of RotaShield would not be acceptable," says Peter Paradiso, who heads Wyeth's RotaShield R&D team. Some researchers are hoping that Wyeth might be nudged into action by a favorable decision in the Advisory Committee on Immunization Practices, the federal group that recommends whether vaccines should or should not be used. It will conduct a review in October, and Wyeth has given conflicting signals about how it might respond.

Although two other companies—Merck and GlaxoSmithKline—have rotavirus vaccines in large human trials, Kapikian says that he's not sure either will make it to market, and he notes that both might cause intussusception, too. NIH, he says, may have to seek a new partner to license his vaccine. "The big tragedy is that as we talk, children die," says Kapikian. "And we'll continue talking for another 5 years before a new vaccine even has a chance of becoming available."

–JON COHEN

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