



HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2017 December 05.

Published in final edited form as:

N Engl J Med. 2014 February 06; 370(6): 568–570. doi:10.1056/NEJMe1315836.

Rotavirus Vaccines — Balancing Intussusception Risks and Health Benefits

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In January 2006, the *Journal* published two landmark articles reporting the safety and efficacy of two different vaccines — RotaTeq (Merck), a pentavalent vaccine (RV5),¹ and Rotarix (GlaxoSmithKline), a monovalent vaccine (RV1)² — to prevent rotavirus, the most common cause of severe childhood diarrhea worldwide and of deaths from diarrhea in low-income countries. Each trial enrolled more than 60,000 infants to determine whether these live oral vaccines caused intussusception, the rare complication that in 1999 forced the withdrawal of the first licensed rotavirus vaccine, RotaShield (Wyeth Lederle), less than a year after it was recommended for routine immunization of U.S. children.³ The trials showed no significant risk of intussusception with either RV5 or RV1; however, further postmarketing surveillance was recommended.

Today, these vaccines are recommended by the World Health Organization for immunization of children worldwide, and their introduction into the national immunization programs of more than 50 countries has shown tremendous health benefits. In the United States, where routine rotavirus vaccination began in 2006, hospitalizations and emergency department visits for rotavirus have decreased by more than 80% among immunized children,^{4,5} and herd protection has been documented among nonvaccinated children and even adults.⁶ Similar results have been reported in many countries in which vaccine coverage has been high. Furthermore, in Mexico, deaths from diarrhea decreased by 40% after implementation of the vaccination program, providing the first demonstration of the lifesaving potential of these vaccines.⁷

While assessing the huge and immediate impact of these vaccines on children's health, Australia, Mexico, and Brazil, each of which has high vaccine coverage and well-tuned medical record systems, also detected a small but significant increase in the risk of intussusception, primarily in the 1 to 7 days immediately after administration of the first dose of vaccine.^{8,9} In the United States, the first hint that intussusception might occur after immunization was detected by the national Vaccine Adverse Event Reporting System (VAERS), which passively receives reports of any adverse events from physicians or parents.¹⁰ Two independent postmarketing surveillance studies were then initiated, the

The findings and conclusions in this editorial are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Vaccine Safety Datalink (VSD) program of the Centers for Disease Control and Prevention (CDC),¹¹ which followed a cohort of children enrolled in six national health care organizations, and the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program of the Food and Drug Administration (FDA), which was based on surveillance of hospital discharge, emergency department, and outpatient clinic data from three large insurance groups.¹²

The results of these studies, now reported in the *Journal*,^{11,12} provide the most comprehensive description of the risk of intussusception after immunization with each of the rotavirus vaccines in the United States. The two groups used several complementary methods to assess the relative and attributable risks — the self-controlled case-series method and a cohort design that used electronic records and a known population base. Both groups of investigators recognized the need to assiduously adjudicate cases of intussusception and confirm the vaccination status of the infants, and the PRISM group used a detailed sensitivity analysis to show that even if some cases were missed or improperly assigned, the results would remain significant. The very fact that it took more than 7 years to document a significant risk speaks to the relatively low rate of intussusception after immunization with either vaccine and the large populations required to assess this with confidence, as well as the need to have an established system in place to monitor such rare events.

The two studies appear to report contrasting results, but cautious interpretation is required. The VSD study showed a significant association of RV1 with intussusception but no significant increase in the risk of intussusception after vaccination with RV5, whereas the PRISM study was not powered to detect risk after vaccination with RV1 but identified a significant association of RV5 with intussusception.

The PRISM study showed that there were approximately 1.5 excess cases of intussusception per 100,000 vaccinees after the first dose of RV5, on the basis of 8 cases of intussusception detected among approximately 500,000 vaccinees in the critical 21-day postvaccination window. In contrast, the VSD study showed no increased risk of intussusception with RV5, on the basis of 4 cases of intussusception reported among 493,000 vaccinees within 7 days after the first dose. Of note, the confidence intervals of these two estimates overlap.

Because RV1 was implemented 2 years after RV5 in the United States, the risk assessment of RV1 is based on fewer vaccine doses. The VSD study showed a significantly increased risk of intussusception within 7 days after the first or second dose of RV1, on the basis of 6 cases documented among approximately 200,000 doses administered, results that were similar to those of the underpowered PRISM study, in which 3 cases of intussusception occurred within 7 days after the first or second dose of RV1 among approximately 103,000 doses administered.

The differences between the studies are marginal, and it appears that both vaccines cause intussusception at low rates; therefore, small variations in case detection and in confirmation of vaccination status, as well as chance alone, can introduce considerable uncertainty into the analysis. Furthermore, Australia, which is the only other country to contemporaneously

use both rotavirus vaccines in its national immunization program, has found that the risk of intussusception is similar with the two vaccines.

What, then, is the message for the physician or nurse who administers rotavirus vaccines, and what is the implication for vaccine policy in developed countries? Certainly, the abundance of evidence in the United States and beyond indicates that intussusception can occur as a result of vaccination with either RV5 or RV1, but the risk is low, on the order of approximately 1 to 5 cases per 100,000 infants, with wide confidence limits. Given this low risk and the major impact that these vaccines have had on the reduction of hospitalizations, emergency department visits, and in some cases, deaths from diarrhea,¹³ policy makers have concluded that rotavirus vaccine remains a valuable addition to the national program for childhood immunizations. For example, in the U.S. cohort of 4.5 million babies born each year, vaccination is estimated to prevent approximately 53,000 hospitalizations and 170,000 emergency department visits for diarrhea, at the expense of causing 45 to 213 cases of intussusception nationwide.¹⁴

Many questions remain to be resolved: Is the risk of intussusception similar with the two vaccines? What is the mechanism for the event? Can we identify a subgroup of infants who may be at increased risk? And will the findings of the risk of intussusception from high-income and middle-income countries extend to low-income countries, where these vaccines are known to be less efficacious and, thus, may be associated with a lower risk? Answers to these questions will remain for further study. However, despite lower efficacy in low-income countries, the public health benefits of rotavirus vaccines in these settings, where the vast majority of deaths from rotavirus occur, are likely to be substantial and outweigh a small risk of intussusception.

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