The development of vaccines has been a triumph of modern medicine. In addition to the eradication of smallpox and the near-eradication of polio, the past 30 years has seen an impressive decline in many vaccine-preventable diseases, including measles, hepatitis B virus, serious pneumococcal infection, hemophilus influenza, and, recently, rotavirus. Vaccination has been an enormously powerful force for health improvement because of the large societal benefits provided with remarkably small risks. However, some have expressed worry that current vaccines are dangerous and represent a considerable threat to the health of the recipients. These concerns often do not include an analysis of the benefits as well as the risks of a given vaccine.

Rotavirus infection is the most important cause of severe diarrheal disease in young children. In less-developed countries, rotavirus accounts for more than 500,000 childhood deaths annually; in developed countries, rotavirus is an infrequent cause of death but a common cause of hospitalizations and outpatient visits. RotaShield, a rotavirus vaccine composed of four human × simian reassortants (RV4), was recommended for universal pediatric use in the United States in 1998. Within a year, after the vaccine had been given to more than 500,000 children, it was found to cause a transient increased risk of intussusception (estimated to occur in 1 child in 10,000) in the first 10 days after the initial vaccination. It was rapidly withdrawn from the market before there was an opportunity for a detailed public discussion of the risks and benefits surrounding its use.

Two second-generation rotavirus vaccine candidates (one composed of five human × animal reassortants [RV5] and the other a monovalent attenuated human rotavirus vaccine [RV1]) were in development in 1999 and, after 7 additional years of study, were licensed in the United States and other countries. Both second-generation vaccines are efficacious, and both underwent extensive safety trials (together involving more than 130,000 subjects); no association with intussusception was detected in these trials. In the 4 years since RV1 and RV5 were licensed, we have witnessed a substantial reduction in the rates of hospitalization and death from rotavirus in both developed and less-developed countries. As part of the postlicensure safety follow-up, the possible effect of the widespread use of RV1 and RV5 on intussusception rates has been monitored in the United States and abroad. In this issue of the Journal, Patel et al. report the results of safety assessments of RV1 in Mexico and Brazil.

RV1 was found to be associated with a small excess risk of intussusception (approximately 1 in 51,000 vaccinated children) in Mexico in the first week after the initial vaccination. The timing of the excess risk is similar to that originally seen with RV4 and corresponds to the peak timing of vaccine replication. A smaller excess risk was observed after the second RV1 dose, but this occurred during the second and third week after vaccination and its significance is unclear. Interestingly, in Brazilian children receiving RV1, a smaller excess risk of intussusception was observed (approximately 1 in 68,000 vaccinated children) and then only in the first week after the second dose. The reasons for these differences in timing and rate are not clear but might include the fact that in Brazil, but not in Mexico, the first dose of RV1 was administered with the oral poliovirus vaccine, which suppresses rotavirus vaccine replication. Recent preliminary studies from Australia also suggest a link between RV5 and intussusception. Hence, we can infer from these studies that any orally administered live rotavirus vaccines will probably carry some detectable risk of intussusception, that the risks
associated with RV4 were not unique, and that the risk of intussusception seems to be small. Since RV1 was originally derived from a virulent human rotavirus, it is likely that natural, wild-type rotavirus infection is also associated with intussusception at a very low frequency.

A likely reason that the very large prelicensure safety trials of RV1 and RV5 did not detect an intussusception signal is that they were simply underpowered to pick up rare events occurring at rates below 1 in 50,000. The study by Patel et al. was insufficiently powered to determine whether the risk of intussusception associated with RV1 in infants receiving their first vaccination after 15 weeks of age was increased, as has been suggested previously in the case of recipients of RV4. Whether the various licensed or candidate live, attenuated rotavirus vaccines — or natural rotavirus infection, for that matter — actually carry different intrinsic risks of intussusception cannot be determined with the current data, but given the ability of viral strains to have distinct pathogenic phenotypes, this possibility is plausible. We do not know whether the temporally associated increase in the rate of intussusception in the first week after vaccination actually translates into an increase in the overall attributable risk of intussusception from rotavirus vaccine or whether there might be a compensatory decrease in the rates of intussusception at later times after vaccination, as was hinted in the original data from the RV1 safety trials, which showed a significant decrease in intussusceptions among children who received the vaccine as compared with those who received placebo during the year-long follow-up. Since RV1 and RV5 both efficiently prevent natural rotavirus infection, it is plausible that vaccination might reduce the overall intussusception burden if wild-type infection was also responsible for some sporadic cases.

The study by Patel et al. contextualizes the risks associated with RV1 vaccination and its increasingly well-documented and substantial benefits. It is crucial that the medical community in general, and the vaccine establishment in particular, work to better educate the public to the fact that virtually all beneficial interventions, including vaccination, come with some risk and that the key issue is to ensure that the ratio of benefit to risk is most favorable. As Patel and colleagues point out, in Mexico alone, RV1 vaccination would be expected to prevent 663 childhood deaths and 11,551 hospitalizations, while causing 41 excess hospitalizations and 2 additional deaths due to intussusception. Similar favorable ratios of benefit to risk would be expected to be found in virtually all less-developed countries, in which diarrheal disease remains a leading cause of death. A favorable ratio would probably also be present with RV4. Rotavirus infection is now a rare cause of death in the United States but remains a very common cause of hospitalization and physician visits. Intussusception is also a rare cause of death in the United States and other developed countries. Given the low rates of intussusception associated with rotavirus vaccine that were observed in Mexico and Brazil, as well as the possibility that rotavirus vaccination might actually reduce the absolute rate of intussusception, it seems both appropriate and advisable to continue to recommend the rotavirus vaccine for children in both the developed and the developing world, on the basis of the increasingly well documented and substantial benefits.

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

From the Stanford University School of Medicine, Stanford, CA.


Copyright © 2011 Massachusetts Medical Society.