The link between rotavirus vaccination and intussusception: implications for vaccine strategies

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Strong association between vaccination with RRV-TV and intussusception among otherwise healthy infants supports a causal relationship

Background: Intussusception is a form of intestinal obstruction in which a segment of the bowel prolapses into a more distal segment. Our investigation began on May 27, 1999, after nine cases of infants who had intussusception after receiving the tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) were reported to the Vaccine Adverse Event Reporting System.

Methods: In 19 states, we assessed the potential association between RRV-TV and intussusception among infants at least 1 but less than 12 months old. Infants hospitalized between November 1, 1998, and June 30, 1999, were identified by systematic reviews of medical and radiologic records. Each infant with intussusception was matched according to age with four healthy control infants who had been born at the same hospital as the infant with intussusception. Information on vaccinations was verified by the provider.

Results: Data were analyzed for 429 infants with intussusception and 1763 matched controls in a case-control analysis as well as for 432 infants with intussusception in a case-series analysis. Seventy-four of the 429 infants with intussusception (17.2 percent) and 226 of the 1763 controls (12.8 percent) had received RRV-TV (P=0.02). An increased risk of intussusception 3 to 14 days after the first dose of RRV-TV was found in the case-control analysis (adjusted odds ratio, 21.7; 95 percent confidence interval, 9.6 to 48.9). In the case-series analysis, the incidence-rate ratio was 29.4 (95 percent confidence interval, 16.1 to 53.6) for days 3 through 14 after a first dose. There was also an increase in the risk of intussusception after the second dose of the vaccine, but it was smaller than the increase in risk after the first dose. Assuming full implementation of a national program of vaccination with RRV-TV, we estimated that 1 case of intussusception attributable to the vaccine would occur for every 4670 to 9474 infants vaccinated.

Conclusions: The strong association between vaccination with RRV-TV and intussusception among otherwise healthy infants supports the existence of a causal relation. Rotavirus vaccines with an improved safety profile are urgently needed.
identified in infants with intussusception.\textsuperscript{7} The incidence of this complication may be serotype dependent,\textsuperscript{10} possibly because some serotype specific rotaviral enterotoxins can cause lymphoid hyperplasia and increased intestinal peristalsis.\textsuperscript{11} This clearly has implications for the selection of serotypes in novel rotavirus vaccines.

The third question raised by this vaccine experience is an ethical one. Withdrawal of RRV-TV by the manufacturer has huge implications for the developed world, where the benefits in terms of reduction in infant mortality are likely to be most significant. To date, the only trials of the vaccine outside Europe and the USA have been in South America where reduced vaccine efficacies were observed.\textsuperscript{12} This may be related to the prevalent rotavirus serotypes in South America, which differ from those in the USA and Europe.\textsuperscript{12} Information on the incidence of intussusception in this study population is not available. No studies have been undertaken in Africa, which has a similar serotype distribution to the USA and Europe,\textsuperscript{13} and thus where one might predict similarly good vaccine efficacy. While the risk-benefit analysis for RRV-TV and related vaccines may be favourable in some parts of the world, withdrawal of one rotavirus vaccine is likely to make pharmaceutical companies wary of pursuing current or future rotavirus vaccine developments.

There is little doubt of the worldwide need for an effective and safe rotavirus vaccine. However, without a full understanding of the pathophysiology of intestinal intussusception, it will be difficult to design vaccines that avoid this complication.

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REFERENCES