

Correspondence

Age Dependence of the Relation between Reassortant Rotavirus Vaccine (RotaShield) and Intussusception

To the Editor—Murphy et al. [1] have reported a strong relation between tetra-valent rhesus-human reassortant rotavirus vaccine (RRV-TV) (RotaShield) and intussusception, using data from a multicenter case-control study (relative risk [RR], 22 [95% confidence interval, 9.6–49], for intussusception at 3–14 days after vaccination). They also have reported that there was “no evidence that age or other variables, except for feeding with breast milk, modified the risk of intussusception among infants given RRV-TV” [2, p. 568]. After considering the same data, however, Simonsen et al. [2] reported that RR increased with the age at the first dose of vaccine. This trend, however, was statistically unstable and sensitive to the category boundaries chosen for age [2].

Murphy et al. have kindly shared their data with us and have allowed us to explore further the dependence of the RR on the age at first dose. We have examined the relation between age and the risk of intussusception with a smoothed semi-parametric curve, using a quadratic spline with knots at ages 85 days, 120 days, and 155 days (figure 1).

The curve confirms the findings reported by Simonsen et al.: the relation between RotaShield and intussusception is weak for those vaccinated at the earliest ages and increases gradually during age 3–6 months. The temporary reversal in direction, in the middle of the curve, is presumably a statistical artifact reflecting the sparsity of data. In other analyses, we have found that, among those who had received the first dose of RotaShield before age 85

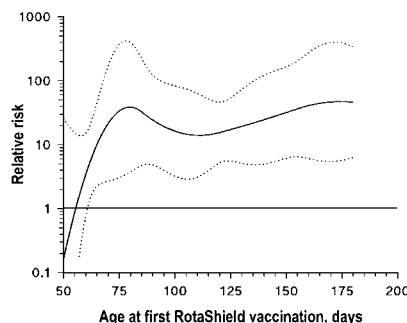


Figure 1. Spline-smoothed estimates of the relative risk and 95% confidence bands relating RotaShield and intussusception within 3–14 days, by age at first dose, based on data reported by Murphy et al. [1].

days, the effect of age at receipt of the second dose of vaccine was unremarkable.

Simonsen et al. [2] have pointed out that the increasing incidence of intussusception during the first year of life implies that, even if the vaccine-associated RR is constant with age, the added risk attributable to vaccination would be proportional to the background risk—and, therefore, would be highly age dependent. Because the RR appears to be increasing with age, as the spline curve indicates, the risk difference, which is the key measure in the assessment of health risks versus benefits, would be an even stronger function of age.

It appears that age at vaccination may be an important susceptibility factor for intussusception. Age-related modification of the effect of RotaShield vaccination has important implications for vaccination practice, should the vaccine be reintroduced. RotaShield has been licensed for oral administration to infants at age 2, 4, and 6 months, but many initial vaccinations were of older infants who had not been vaccinated when the vaccine was first introduced. As shown in figure 1, the data support Simonsen et al.’s as-

sertion that much of the adverse effect that vaccination has on the occurrence of intussusception can be averted by confining the vaccinations to very young infants.

Acknowledgments

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Reply to Rothman et al.

To the Editor—We are delighted with the independent demonstration by Rothman et al. [1] that the relative risk (RR) of intussusception after vaccination with reassortant rotavirus vaccine (RotaShield) is age dependent—not least because earlier studies had suggested that this was not the case [2]. These authors’ elegant spline regression approach, which is considerably more robust than our rather coarse anal-

ysis stratified by age group [3], puts the existence of the age dependence of the RR beyond doubt.

This age dependence is important because it strongly suggests that the number of intussusception events associated with RotaShield could have been sharply reduced had the vaccine been given only to younger infants. And, coincident with the increase in RR with age, the background risk of intussusception increases to a peak at ~4–9 months of age. Indeed, the combined trends in background risk and RR explain why, in the case-control study conducted by the Centers for Disease Control and Prevention (CDC) [2], 81% of the vaccine-associated intussusception events that occurred during the 9 months that RotaShield was on the market were in infants who had received their first dose after the target age maximum of 90 days [3]. We therefore believe that “catch-up” vaccination of older infants was the greatest contributor to the demise in the use of the vaccine.

Using our estimates of the age-specific RRs, we had projected in our articles that vaccination on a 2-dose neonatal schedule (first vaccine dose at <30 days of age, second vaccine dose at <60 days of age) would produce 59 cases of intussusception annually in a fully immunized US infant population [3, 4]. But the lower RR that Rothman et al. projected for very young infants suggests that even this modest estimate was probably too high, as does the observation that no cases of intussusception occurred among the ~70,000 infants who received the first vaccine dose at <60 days of age during the RotaShield-use period [3]. In any event, it is now clear that a 2-dose neonatal schedule would produce far fewer intussusception events than the up to 1600 projected from preliminary data at the time that the Advisory Committee on Immunization Practices (ACIP) withdrew its recommendation for RotaShield use [5].

The short, unhappy career of RotaShield was a bitter experience for all involved. Disappointment was bad enough

in the United States, where rotavirus causes ~50,000 hospitalizations and ~20 deaths every year; but the impact of the withdrawal of the vaccine was far more keenly felt in the developing world, where the virus continues to cause ~600,000 infant deaths from diarrhea annually. Today, 6 years after ACIP withdrew its recommendation, rotavirus vaccines are available only in a few developing countries.

What can we learn from the RotaShield experience? One lesson is that interagency cooperation and data sharing are powerful tools. Only extended analyses of the CDC case-control–study database, combined with complementary analyses of state-based hospital-admission data from the Agency for Health Care Research and Quality’s Healthcare Cost and Utilization Project and age-detailed RotaShield coverage data from the National Center for Health Statistics’ National Immunization Survey, allowed the new understanding of RotaShield’s risks to emerge, albeit slowly.

Perhaps the most important lesson is that, in the future, advisory groups need to allow sufficient time for study before making any binding recommendations. With RotaShield, this did not occur—on 22 October 1999 [6], just 14 weeks after CDC had recommended that physicians suspend use of the vaccine, ACIP withdrew its recommendation that all infants receive RotaShield [7]. Now that we understand the effect that increased age at first dose has on the risk of intussusception, we have a much clearer picture of RotaShield’s dangers—and of how to avoid them. In light of this insight, it now is clear that RotaShield would have posed only a minor risk had the first dose been given solely to infants <90 days of age—and would have posed a very minimal risk, if any, had it been given on a 2-dose neonatal schedule.

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Human Illness and Isolation of Low-Pathogenicity Avian Influenza Virus of the H7N3 Subtype in British Columbia, Canada

To the Editor—In the 15 October 2005 issue of the *Journal*, Puzelli et al. reported the first serological evidence for transmission of low-pathogenicity avian influenza (LPAI) viruses to humans and suggested that all previous human infections have involved only high-pathogenicity avian influenza (HPAI) strains [1]. We would like to respond to this assertion, on the basis of our experience with the H7N3 subtype