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 tetravalent 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 semiparametric 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 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 assertion 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.

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References


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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-