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## Does Preventing Rotavirus Infections Through Vaccination Also Protect Against Naturally Occurring Intussusception Over Time?

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### To the Editor

Intestinal intussusception is an uncommon event (incidence approximately 30 per 100 000 per year in US infants) in which one part of the intestine folds into another. The condition is usually considered idiopathic, but numerous case reports link intussusception to enteric pathogens, notably adenovirus. Several case reports have linked wild-type rotavirus to intussusception, although evidence for this link is inconclusive [1].

In 1999, a previous rotavirus vaccine (Rotashield) was found to be associated with intussusception [2] and was withdrawn from the US market. Currently, 2 rotavirus vaccines are routinely administered to US infants: RotaTeq and Rotarix. Large clinical trials (>60 000 children each) found no statistical association between vaccination and intussusception within 42 days following any dose [3, 4]. Nonetheless, with the accumulation of study power over time, recent postlicensure rotavirus vaccine safety assessments in the United States [5,6] report a modest but significant risk of intussusception.

One could postulate that if vaccines based on 3 different live-attenuated rota-virus vaccine strains (rhesus in Rota-shield, bovine-human reassortants in RotaTeq, and human rotavirus in Rotarix) are statistically associated with intussusception, then the wild-type rotavirus (naturally nonattenuated and most virulent) could also plausibly be associated with intussusception. We studied a vaccine probe hypothesis: If wild-type rotavirus infection is causally associated with intussusception, then the prevention of such infections through vaccination could conceivably protect against intussusception during time periods after vaccination.

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To assess whether children protected by rotavirus vaccine were at lower risk for intussusception in the first year after completing their full vaccine series, we retrospectively analyzed a cohort of children born after rotavirus vaccine licensure (February 2006) and enrolled in the Vaccine Safety Datalink (VSD), a collaboration of managed care organizations capturing medical visits and vaccination data on more than 9 million individuals. Intussusception cases had ICD9-CM code 560.0 (intussusception) and 543.9 (other and unspecified diseases of appendix) in VSD hospitalization or emergency room automated data files. Based on previously published results, VSD's positive predictive value for these ICD-9-CM codes was 75% [7]. We calculated rates of intussusception from 4 to 55 weeks following last rotavirus vaccination among children receiving a full course of rotavirus vaccinations, limiting our analysis to those children having at least 1 other recommended vaccine. A time-to-event analysis using a Cox proportional hazards model accounted for gender, age at last vaccine dose, seasonality, VSD site, and index year of intussusception event.

Our cohort contained VSD data on 186 488 children receiving a full course of rotavirus vaccines and 64 089 children receiving none. We found 50 cases of intussusception among the vaccinated children (0.027%) and 22 cases among the children receiving no rotavirus vaccine (0.034%). Compared with children receiving no rotavirus vaccine, the incidence of intussusception among the vaccinated children was not statistically different (incidence rate ratio = 0.94 [95% confidence interval (CI), .50, 1.75]).

Previous analyses conducted before and after introduction of Rotashield [8] suggested that rotavirus vaccine receipt perhaps triggered "early-onset" intussusceptions among children biologically predisposed to experience this condition, which would then be followed by a period of compensatory, decreased risk later in infancy. A similar finding was suggested during a prelicensure randomized clinical trial of Rotarix, whereupon the relative risk of intussusception decreased from 0.56 (95% CI, .25, 1.24) for the 0–100 day postvaccination interval to 0.28 (95% CI, .10, .81) during the 0–1 year postvaccination interval [9].

Our findings, derived from a well-powered sample having good clinical and vaccine exposure accuracy, indicate that the risk of naturally occurring intussusception was not modified by rotavirus vaccination during the period of 1 month to 1 year following vaccination.

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