In a large case-control study, Murphy et al. (1, 2) observed a sharp increase in risk of intussusception soon after receipt of tetravalent rhesus-human reassortant rotavirus (RRV-TV) vaccine. For example, the risk during days 3–7 following the first dose of vaccine was 37.2 times that among unvaccinated infants (95 percent confidence interval: 12.6, 110.1). In contrast, the corresponding relative risk for the period beginning 21 days following the most recent dose was 0.3 (95 percent confidence interval: 0.1, 0.5). As explanations for the late reduced risk of intussusception, Murphy et al. suggested two possibilities: 1) a “triggering” hypothesis, which posits a temporal shift in the case onset date as a result of vaccination but no overall change in intussusception incidence, and 2) the presence of confounding, that is, inherent differences between vaccinated and unvaccinated children that bear on the risk of intussusception. A third possibility is the existence of two separate vaccine effects: a genuine causal action of vaccination early on followed by a protective effect against intussusception related to natural rotavirus infection. To support the hypothesis of confounding, Murphy et al. presented data indicating that, compared with unvaccinated children, RRV-TV recipients also had a reduced rate of intussusception during the period prior to vaccination (relative risk = 0.52) (2).

However, the validity of a comparison of intussusception rates between prevaccinees and unvaccinated infants is dependent on the assumption that the occurrence of intussusception in a child has no later bearing on the decision to have the child immunized with RRV-TV. We believe that this assumption may not be correct, since physicians or parents might be reluctant to expose a child to rotavirus vaccination in the wake of a serious illness such as intussusception. If there is such a reluctance, the observed low relative risk of intussusception prior to RRV-TV immunization might have nothing at all to do with an inherently low underlying risk among children who receive the vaccine. Because of the above consideration, we think it would be premature to accept the hypothesis that confounding is the basis for the low rate of intussusception beginning several weeks after receipt of RRV-TV.

A decade earlier, Gable et al. (3) had also considered prevaccination experience to help gauge the impact of a vaccine—in that instance, the efficacy of pneumococcal vaccine. They observed that the incidence of pneumonia during the year following a person’s immunization was but 31 percent that of his/her incidence during the preceding year. However, vaccination against pneumococcal disease is not administered at random; vaccine is preferentially given to persons who have recently developed pneumococcal disease.

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pneumonia. This is because 1) there are several dozen common *Pneumococcus* serotypes, 2) infection with one of these serotypes does not offer immunity against the others, and 3) persons prone to one type of pneumococcal infection are at high risk of another. Thus, the incidence of pneumonia among vaccine recipients during the year prior to vaccination will not provide a good estimate of the incidence that would be expected in such persons had the vaccine not been given. Rather, it is likely to dramatically overstate that incidence and therefore lead to an estimate of vaccine efficacy that is falsely high.

The validity of nonrandomized studies of the safety or efficacy of immunization rests heavily on our being able to estimate what would have been the incidence of the outcome in question among vaccine recipients had they not been immunized. Misestimation of that incidence can result from confounding: Persons who choose (or are chosen) to be immunized may not be at typical risk of the potential adverse effect or condition that immunization seeks to prevent. For example, persons who are immunocompromised and/or debilitated in other ways tend to be selectively immunized against pneumococcus, and these same characteristics place them at increased risk of pneumococcal disease. Thus, a simple comparison of the incidence of pneumococcal disease between persons who receive pneumococcus vaccine and those who do not will be confounded, leading to a spuriously high rate among vaccinees and a spuriously low estimate of vaccine efficacy. In some respects, use of vaccinees’ experience *prior to* immunization as the basis for comparison is an attractive approach to controlling confounding, since stable factors that bear on the outcome(s) in question—for example, socioeconomic characteristics or a history of long-term illness—can be held constant. However, if the occurrence of the outcome event could have a bearing on the likelihood of being immunized, a contrast of this sort can produce an erroneous result. We suggest that it be used only with great caution.

REFERENCES