The First Rotavirus Vaccine and Intussusception: Epidemiological Studies and Policy Decisions

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Clinical cases of intussusception are a rare type of bowel obstruction characterized by telescoping of the intestinal tract, in which one segment of the intestine is folded into a cocoon-like configuration around a segment of the intestine above it. Among children, intussusception is the leading cause of intestinal obstruction and a leading cause of bowel perforation and death from dehydration among infants worldwide and is an important cause of death in developing countries [1]. RotaShield (also referred to as rhesus-human reassortant rotavirus tetravalent vaccine [RRV-TV]; Wyeth Lederle), the first licensed rotavirus vaccine, was withdrawn 1 year after it was released when it was found to increase the risk of intussusception [2, 3]. Rapid progress has since been made by manufacturers in the United States, Europe, and India on new rotavirus vaccines. These efforts are being fostered as one of the priorities of the Global Alliance for Vaccines and Immunization [4]. One of the experimental vaccines has been administered to >40,000 children in the United States, Europe, and Latin America in extended phase III trials (personal communication, Merck). International investigations of the epidemiology of rotavirus gastroenteritis are being conducted, and extensive information about intussusception has been acquired in preparation for use of these new rotavirus vaccines [4, 5].

In the “Perspective” in this issue of The Journal of Infectious Diseases [6], colleagues at the National Institute of Allergy and Infectious Diseases question the October 1999 precedent-setting decision by the Advisory Committee on Immunization Practices (ACIP) to withdraw the recommendation for use of RRV-TV [7] in the United States. B. Murphy et al. [6] express concern about the interpretation of the epidemiological data that supported the ACIP decision and the decision-making process that led to withdrawing the recommendation for RRV-TV, as well as highlight the importance of rotavirus infections globally.

The epidemiological data in question were from several studies that investigated a possible association between intussusception and RRV-TV conducted by the Centers for Disease Control and Prevention (CDC), including cohort [8] and matched case-control studies [9], as well as a case-series analysis of the cases of intussusception identified in the case-control study [9]. In addition, to measure the effect of RRV-TV in states where the vaccine was used, Simonsen et al. [10] subsequently performed an ecological analysis of intussusception using hospital discharge databases from 10 states and an expanded, unpublished 20-state analysis [6].

B. Murphy et al. [6] suggest that the “particular strengths” of the ecological analyses were not “widely appreciated” in considerations of policy decisions. Specifically, they assert that the ecological studies were conducted in a “large segment of the general US infant population” and assessed trends in intussusception over a “longer time window” than the case-control and cohort studies. These and other concerns, including an apparent lack of power of the ecological analyses to detect estimated increases in intussusception caused by RRV-TV and insufficient evidence to support hypotheses of a compensatory decrease in intussusceptions after RRV-TV were discussed extensively at a meeting sponsored by the National Vaccine Advisory Committee (NVAC) [5] and by a working group of the ACIP. After reviewing all relevant data and concerns, the ACIP voted in February 2002 to reaffirm its decision to withdraw the recommendation for use of RRV-TV in the United States [11]. Here, we reflect on these concerns and other considerations that led to the ACIP decision.

Epidemiological Analyses of RRV-TV and Intussusception

Epidemiological studies, including cohort, case-control, and ecological designs are nonexperimental and may be more subject to biases than studies with experimental designs (e.g., randomized clinical trials), unless there is careful control for bias [12]. Bias is easier to control for in studies with cohort and case-control designs than in...
studies with ecological design, because exposures (e.g., vaccination history) and potential confounders (e.g., socioeconomic differences that affect both the risk of intussusception and access to RRV-TV) can be measured for individual study subjects. In contrast, ecological studies evaluate questions in populations, and information is not available for individual subjects [12]. Because of the strengths and limitations of these designs, how should the various epidemiological studies of RRV-TV and intussusception be considered in decision-making?

The cohort study was conducted in 10 managed care organizations throughout the United States [8], and the case-control and case series studies were conducted in 19 states [9]. In these 2 CDC studies, potential cases were identified from systematic search of hospital and radiology records; all intussusception diagnoses were confirmed by a specific case definition, and all RRV-TV vaccinations were verified with the vaccine provider. Control subjects in the case-control study were matched to case patients by the hospital of birth and by age within 7 days, to control for socioeconomic factors, season, and changing risks of intussusception throughout the first year of life. Multivariate analysis controlled for confounders in the case-control study. The studies were designed to determine whether an increase in the risk of intussusception was associated temporally with receipt of RRV-TV, defined by “windows” or intervals up to 21 days after vaccination [8, 9].

The final results of the 3 CDC analyses were consistent with a substantial short-term increase in the risk of intussusception among RRV-TV recipients, primarily after the first dose. The increase attributable to vaccine was estimated as 1 case in 5000 to 1 case in 10,000 RRV-TV recipients. Criteria for causation were fulfilled by the strength and specificity of the association, the consistency among studies, and the biological plausibility of the association [12]. In the 1970s, the same approach led to identifying an increase in the risk of Guillain-Barré syndrome among recipients of swine influenza vaccine [13].

The ecological analyses reported by Simonsen et al. [10] and B. Murphy et al. [6] estimated the risk of intussusception from trends in *International Classification of Diseases*, ninth revision (ICD-9)–coded intussusception in hospital discharge databases before and during RRV-TV use. Limitations of these analyses include an inability to confirm case diagnosis, exclusion of short-stay (<24 h) hospitalizations, and the absence of vaccination histories. These differences and limitations inherent in ecological studies [12] may contribute to the apparent discrepancy in the findings of the ecological analyses and the case-control, case-series, and cohort studies. Lack of power to detect an increased risk of intussusception also might contribute. After evaluating the power of the ecological analyses to detect an increased risk of intussusception attributable to RRV-TV, we concluded that the most important reason for the differing results was insufficient statistical power in the ecological analyses to detect the attributable risk estimated in the previous studies [5, 14].

Using data obtained from the National Immunization Survey, which provides surveillance of vaccination coverage rates in the United States [15, 16], we estimated that ~504,585 (±61,854) children received RRV-TV nationally [14]. In the 10 states of the ecological study, 12.2% (±1.4%) of infants received RRV-TV. The chance of detecting an attributable risk of 1 case in 10,000 RRV-TV recipients in this ecological analysis, given a vaccination rate of 12.2%, would have been no more than 22%. Thus, the sample size of the study was not sufficiently large to ensure adequate statistical power to detect important values of the attributable risk. If the ecological analysis were expanded to include all 50 states and the District of Columbia, the chance that the analysis would detect an attributable risk of 1 case in 10,000 vaccine recipients, given the national vaccination rate of 13.4% (±1.6%), would have been no more than 46%. (Most studies strive for ≥80%.) The estimates of statistical power are low, because few children received RRV-TV and because few excess cases would have occurred, thereby limiting the ability of the ecological method to detect changes in historical trends [14].

Estimates of statistical power are based on the assumption that ascertainment of children with intussusception from the computerized database was accurate and complete. Kramarz et al. [8] found that, after review of case medical records, 40% cases of intussusception identified from a computerized hospital database were ineligible for the cohort study, because the diagnosis of intussusception in the database was inaccurate; in data from Cincinnati, a similar proportion of eligible short-stay (<24 h) admissions for confirmed intussusception were omitted from the database of hospitalized cases [5]. Imperfect ascertainment is known to lead to underestimation of measures of association in epidemiologic studies [12]. As a result, we believe that the actual statistical power of the analyses reported by Simonsen et al. [10] and B. Murphy et al. [6] could be even lower than the estimates described above.

Based on the number of children vaccinated and a risk of intussusception of 1 in 10,000 RRV-TV recipients, ~50 excess cases nationwide could have occurred during the period that RRV-TV was available; these estimates are consistent with the number of cases reported to the Vaccine Adverse Events Reporting System [17], assuming that ~50% of cases were reported, as estimated in capture-recapture analysis [18]. Because Simonsen et al. [10] and B. Murphy et al. [6] analyzed data from 20 states with 54% of the US population, as few as 27 excess cases might have been expected in those states. This number of expected excess cases is only 1–2 cases/state, a number that could have been missed in light of problems inherent in ecological studies and in using hospital discharge data.

The results of case-control, case-series, cohort, and ecological analyses were presented at the NVAC meeting in September.
2001 and were analyzed by experts in study design and methodology. The reviewers independently concluded that the cohort, case-control, and case series analyses should be given substantially more weight than the ecological analyses. A panel of policy makers agreed that the best estimate of the risk of RRV-TV–associated intussusception was 1 case in 10,000 vaccine recipients [5].

**IS RRV-TV-INDUCED INTUSSUSCEPTION OFFSET BY A SUBSEQUENT DECREASE?**

We previously reported an additional analysis from the case-control study for a risk period >3 weeks after RRV-TV, although the observation time in this open-ended interval was limited. The resulting adjusted odds ratio (OR) was 0.3 (95% confidence interval, 0.1–0.5) for intussusception among vaccinated (all doses) versus unvaccinated infants [19]. We suggested that confounding bias from socioeconomic status may be responsible for the low value of this OR. Infants with higher socioeconomic status were more likely to receive RRV-TV and had a lower risk of intussusception than were infants with lower socioeconomic status.

Two subsequent methodological improvements to the analysis were made. The ORs were estimated for clearly defined risk periods, rather than for an undefined risk period of >3 weeks after RRV-TV administration. The other improvement was to estimate the ORs separately by dose. Although one could define “exposure” as doses of RRV-TV administered during the retrospective time intervals before intussusception or the reference date, the ORs are interpreted prospectively as risk periods after vaccination. To have a unique and interpretable position on the timeline, the risk periods should follow individual vaccine doses, not all doses. The results of this analysis are shown in table 1.

ORs >3 weeks after the first and second doses were <1, but they were not statistically significant. Only 1 case patient received a third dose earlier than 3 weeks before intussusception; therefore, no ORs could be estimated. Although a compensatory decrease, a protective effect of vaccination, confounding due to socioeconomic status or random variation, might explain ORs <1, we concur with the conclusion from the NVAC meeting [5] that the hypotheses proposed by Simonsen et al. [10] and B. Murphy et al. [6], while intriguing, are not proven.

**RATIONALE FOR THE INITIAL AND RECONFIRMED ACIP POLICY DECISION**

The ACIP decision in October 1999 to withdraw its recommendation for RRV-TV vaccination was based on the significantly increased risk of a severe complication that was caused by RRV-TV [7]. As an introductory model, the ACIP was presented with relative risks of 1.6–1.8 for intussusception after vaccination with any dose of RRV-TV in the first year of life and the corresponding number of excess cases attributable to RRV-TV [7]. The ACIP was then presented with a more refined model. This model used relative risks from the case-control and case-series analyses for short periods within the first 3 weeks after each dose of RRV-TV; the resulting estimates were 838–888 excess cases [7]. It was emphasized that these data and calculations were preliminary, assumptions were specified, and caveats were highlighted [7]. After final data were available, the number of excess cases was recalculated using baseline rates of intussusception that were revised from 51/100,000 (ICD-9–coded hospital discharge data) to the more accurate 34/100,000 (chart review–confirmed diagnoses). These estimates of 361–732 excess cases were published elsewhere [9].

In February 2002, the ACIP reconfirmed its decision to withdraw the recommendation for RRV-TV, despite the revised, slightly lower estimates of excess intussus-

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**Table 1.** Odds ratios (ORs) for exposure to rhesus-human reassortant rotavirus tetravalent vaccine RRV-TV in retrospective intervals of time before intussusception (case patients) or the reference date (control subjects).

<table>
<thead>
<tr>
<th>RRV-TV dose, weeks before intussusception or reference date</th>
<th>Vaccinated in interval</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>43 (11.2)</td>
<td>39 (2.4)</td>
<td>8.3 (4.5–15.4)</td>
</tr>
<tr>
<td>4–9</td>
<td>8 (2.1)</td>
<td>54 (3.3)</td>
<td>0.9 (0.4–2.1)</td>
</tr>
<tr>
<td>10–15</td>
<td>7 (1.8)</td>
<td>47 (2.8)</td>
<td>0.8 (0.3–1.9)</td>
</tr>
<tr>
<td>16–21</td>
<td>2 (0.5)</td>
<td>21 (1.3)</td>
<td>0.5 (0.1–2.6)</td>
</tr>
<tr>
<td>17–22</td>
<td>2 (0.5)</td>
<td>10 (0.6)</td>
<td>0.9 (0.1–5.2)</td>
</tr>
<tr>
<td>Dose 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–3</td>
<td>9 (2.3)</td>
<td>32 (1.9)</td>
<td>1.1 (0.4–2.6)</td>
</tr>
<tr>
<td>4–9</td>
<td>2 (0.5)</td>
<td>22 (1.3)</td>
<td>0.3 (0.1–1.7)</td>
</tr>
<tr>
<td>10–15</td>
<td>2 (0.5)</td>
<td>21 (1.3)</td>
<td>0.5 (0.1–2.5)</td>
</tr>
<tr>
<td>16–21</td>
<td>0</td>
<td>8 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>17–22</td>
<td>0</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated. Reference date was the date of hospitalization for case patients or the date on which the matched control subject was the same age as the case patient at the time of hospitalization. CI, confidence interval.

* ORs have been adjusted for matching variables (age and the hospital where the infant was born, sex, race, mother’s level of education, type of health insurance, type of milk formula used for feeding, and time of first intake of solid food. ORs were calculated using 382 infants with intussusception and 1657 control subjects for whom complete data were available. Intervals of 6 weeks were analyzed, because they provide more stable estimates of the ORs than shorter intervals.
ception cases, the data and conclusions from the 20-state ecological analysis, and extensive discussion of the benefits, risks, and cost-effectiveness of vaccination [11].

What is the rationale for this decision, when the direct health benefits of RRV-TV were likely to exceed the direct health risks of intussusception? The ACIP Policy and Procedures Manual lists 6 factors to be considered in making vaccine recommendations [20]. One factor is feasibility, defined in part as acceptability to the community and patients, the effects on health care delivery, and on social, legal, and ethical considerations. The ACIP consists of 15 members (including a consumer member) who come from various geographic, racial, and ethnic backgrounds. Because of the diversity of expertise and experience, members evaluate possible recommendations from a wide variety of perspectives and make decisions that they believe are in the best interests of the overall vaccination program, described as one of the leading public health achievements of the 20th century [21].

Basing decisions solely on the balance of the mortality or morbidity prevented by vaccination versus the mortality or morbidity caused by vaccination is insufficient. At a time when many parents express concern about the safety of vaccines [22] and vaccine adverse events are the focus of increasing attention by the public, media, and US Congress, the wisdom of recommending a vaccine that causes a severe adverse reaction in an estimated 1 in 10,000 infants must be considered. It also is important that this adverse reaction, unlike, for example, febrile seizures, is not easily recognized and treated by pediatricians and family physicians. In a survey of Wisconsin pediatricians, 50% of respondents indicated that the lack of community resources for diagnosis and treatment of vaccine-related intussusception made reintroducing a rotavirus vaccine problematic; 65% of rural pediatricians were concerned about access to radiological and surgical services in the event of postvaccination intussusception [23]. Public confidence and the support of vaccine providers for vaccination recommendations, although difficult to quantify, are important factors in the decision-making process. Ethical distinctions between causing significant morbidity in some children while averting disease among others are a consideration, given that oral hydration therapy for rotavirus infection has no associated risks.

Although B. Murphy et al. [6] suggest that the ACIP could have made a permissive recommendation for RRV-TV, the manufacturer stated that it would not market RRV-TV without a universal recommendation for RRV-TV [11]. In Wisconsin, only 32% of pediatricians responding to a survey would provide RRV-TV under a permissive recommendation given a risk of intussusception of 1 in 10,000 vaccine recipients [23]. In Georgia, 51% of pediatricians responding to a similar survey would use RRV-TV only if the vaccine were safer than initially reported and if the American Academy of Pediatrics (AAP) and ACIP made a permissive recommendation [23]. Neither the AAP nor the American Academy of Family Physicians has expressed support for a permissive recommendation.

The justification for safe and effective rotavirus vaccines in the United States and globally is the heavy burden of morbidity and mortality from rotavirus infection. Rotavirus vaccine development and evaluation is proceeding. Important studies, catalyzed by the link between RRV-TV and intussusception, have strengthened this process. Much has been learned through program and policy discussions. Science and public health policy advance through an incremental process. Although controversies have surrounded RRV-TV, examination of the issues has contributed to more optimistic prospects for control of rotavirus gastroenteritis worldwide.

References


