Reappraisal of the Association of Intussusception with the Licensed Live Rotavirus Vaccine Challenges Initial Conclusions

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RECENT STUDIES SUGGESTING AN ETIOLOGIC ASSOCIATION BETWEEN ROTAVIRUS VACCINE AND INTUSSUSCEPTION

Each year, rotaviruses are responsible for 500,000 physician visits, 50,000 hospitalizations, and 20–40 deaths in the United States [1]. In addition, they are estimated to cause up to 520,000 deaths annually among infants and young children worldwide (i.e., >1400 deaths/day), predominantly in developing nations [2]. The live rotavirus vaccine, named RotaShield (Wyeth-Lederle Vaccines and Pediatrics) and also referred to as rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV), consists of the rhesus rotavirus and 3 antigenic chimeric reassortant viruses constructed from it [3]. Its attenuation relies on a Jennerian and modified Jennerian approach, whereby an animal rotavirus and human-animal rotavirus reassortants are used as immunogens [3]. Extensive trials in infants demonstrated that RRV-TV was highly efficacious (up to 91%) for the prevention of severe diarrheal disease requiring hospitalization [4–7]. In February and June 1998, RRV-TV was recommended for routine use in healthy infants in a 3-dose sequence given orally at 2, 4, and 6 months of age by the US Advisory Committee on Immunization Practices (ACIP) [7]. In August 1998, RRV-TV was licensed by the US Food and Drug Administration (FDA) [7] and became available for use in October 1998. Nine months later, in July 1999, after up to 1 million of the 3.8–4.0 million US birth cohort had received at least 1 dose, the CDC recommended suspending further vaccination pending collection and analysis of additional data [8]. This suspension was prompted by reports to the CDC-FDA Vaccine Adverse Events Reporting System (VAERS) of 15 cases of intussusception, 11 of which had an onset within the first week after the first dose of RRV-TV. It is important to note that ~1300–2000 cases of intussusception occur annually in the United States [8–10] and occur mainly during the first year of life, peaking between 4 and 9 months of age [11]. The etiology of intussusception remains unclear, although adenovirus and, to a lesser extent, enterovirus infections have been associated with intussusception [12–14]. Data linking infection with wild-type human rotavirus to intussusception are equivocal [15, 16].

In October 1999, the CDC presented data from case-control, case series, and cohort studies to the ACIP, which led to the withdrawal of the recommendation for use of the vaccine [17–19]. The withdrawal was based on data from epidemiological investigations interpreted as indicating that the excess risk of intussusception attributable to RRV-TV was 1.8, 1.7, or 1.6, as estimated from case-control, single managed-care organization (MCO) cohort, and case-series studies, respectively. This led to projections that, if the entire US birth cohort of 4 million infants had been vaccinated, there would have been 1600, 1400, or 1200 excess cases, as estimated by the 3 respective studies (figure 1). The period of greatest increased risk was identified as occurring predominantly during the first week after the first dose of RRV-TV, such that the risk of developing intussusception 3–7 days after vaccination was estimated to be increased 25- and 19-fold for the case-control and case series studies, respectively, and increased 7.1-fold for the single MCO cohort study in the first week after vaccination with increases also described for an expanded 6 MCO cohort study [17–19].
Figure 1. The excess cases of intussusception shown for October 1999 were nos. from Centers for Disease Control and Prevention (CDC) studies presented at the October 1999 US Advisory Committee on Immunization Practices (ACIP) meeting, when the withdrawal recommendation for rhesus-human reassortant rotavirus tetravalent vaccine (RRV-TV) was made, assuming 100% vaccination in a birth cohort of 4 million infants. A background of \( \sim 2000 \) intussusception cases/year (or \( 51/100,000 \)) in the infants aged \(<1\) year was used in the calculation [8, 19]. The population attributable risk (PAR) for the case-control study, case-series study, and 1 managed-care organization (MCO) study was translated to be 1 in 2500 (relative risk [RR], 1.8), 1 in 3333 (RR, 1.7), and 1 in 2857 (RR, 1.7), respectively [18, 19]. In addition, estimates of 800, 838, or 888 excess cases and PARs ranging from 1:4323 to 1:5000 also were presented by the CDC. In the published CDC studies shown, a 90% vaccination rate of a 3.8 million birth cohort was assumed; a PAR of 1 in 9474 and 1 in 4670 for the case-control and case-series studies, respectively, was noted; the same estimate of the birth size of the birth cohort also was applied to the published PAR of 1:11,073 in calculating the excess cases in the expanded 10 MCO study [9, 10, 20]. For the 14 high-use states included in the National Institutes of Health in collaboration with the Department of Health and Human Services Agency for Healthcare Research and Quality (NIH-AHRQ) study, there was a decrease of 8 cases during the RRV-TV–use period relative to the previous year (a 3% decrease) in a population, in which \( \sim 250,000 \) infants had received \( \geq 1 \) RRV-TV dose. This translates to a negative PAR of minus 1 intussusception case/31,530 vaccine recipients. Applying this PAR estimate and assuming 90% vaccine coverage in a birth cohort of 3.8 million yields a prediction of a decrease of 108 intussusception cases in a national vaccination program in the United States.

THREE PUBLISHED CDC STUDIES THAT INVESTIGATED AN ASSOCIATION BETWEEN INTUSSUSCEPTION AND RRV-TV

The estimates of attributable risk in the published versions of the 3 CDC studies, which appeared 16–18 months after the withdrawal recommendation, were lowered, and, concomitantly, the estimates of the number of excess intussusception cases attributed to RRV-TV also were decreased (figure 1). Other factors contributing to the lower risk estimates in the 3 published studies were the use of a lowered estimate of the background intussusception cases used as a referent point and a lowered estimate of infants included in a national vaccination program (see figure 1). The first of the 3 CDC studies was a case-control investigation, in which 17% of intussusception cases and 13% of matched controls had received vaccine \( (P<.02) \) [9, 10]. A sharp peak in the odds ratio (OR; 37.2) for receipt of a first vaccine dose was observed 3–7 days before the intussusception event, and the projected number of excess cases of intussusception in the vaccinated population was lowered from the original case-control estimate of 1600 to 361 infants (figure 1). The second CDC study, which was a case-series analysis of cases collected for the case-control study, reported an incidence rate ratio of 58.9 on days 3–7 after the first dose and projected that there would be 732 excess intussusception cases under a national vaccination program (figure 1) [9, 10]. In the third CDC study, a further expanded cohort study that included 10 MCOs [20], the relative risk 3–7 days after the first dose of vaccine was 30.4, and the projected number of excess cases of intussusception was 309 (figure 1). The finalized projections of the excess number of cases of intussusception in vaccinated infants were important, because they served as a guide for our population-based study described later. A weakness in each of the 3 CDC studies was that the analysis of the effect of immunization on the occurrence of intussusception was essentially restricted to a short 3-week postimmunization period, and, consequently, the in-
After the vaccine was withdrawn, a study was carried out independently by the National Institutes of Health (NIH) in collaboration with the Department of Health and Human Services Agency for Healthcare Research and Quality (AHRQ) using a different approach that was prompted by a similar investigation in a single state (New York) [21]. In the NIH-AHRQ study, data were collected that would reflect the overall effect of RRV-TV use on the occurrence of hospitalization for intussusception in a large segment of the US infant population in 10 states during the period of time when RRV-TV was used [22]. The cases of intussusception identified by analysis of electronic hospital discharge records were comparable in severity with those studied by the CDC with regard to the need for surgery, and, in addition, the background rate of intussusception was also similar in both venues. Two factors during the postimmunization period were evaluated in this study: (1) an effect, if any, of exposure to RRV-TV on the number of intussusception hospitalizations over a period of up to 9 months after vaccination; and (2) the possibility of a compensatory decrease in intussusception after the first 3-week postimmunization interval.

To gain more statistical power, the 10-state study was expanded to include 10 additional states so that hospital discharge summaries from a total of 20 states could be analyzed for any mention of a diagnosis of intussusception (International Classification of Diseases, 9th Revision, 560.0) (L. Simonsen, A. Elixhauser, W. C. Blackwelder, and D. M. Morens, unpublished data) [23]. Fourteen of the 20 states were considered to be RRV-TV high-use states (>10% of infants being vaccinated) and were comprised of ~250,000 infants who received at least 1 dose of RRV-TV in a birth cohort of 1.3 million infants in these 14 high-use states. Overall, the 20-state sample was substantial, because it included 2.1 million infants representing 54% of the US birth cohort, who received 51% of the total RRV-TV doses that had been distributed [22] (L. Simonsen, A. Elixhauser, W. C. Blackwelder, and D. M. Morens, unpublished studies made available to ACIP in February 2002). The total number of hospitalizations for intussusception was determined for the interval when RRV-TV was used and was compared with the total number of intussusception hospitalizations in the same states during the same interval in the previous year and also with a preceding 5-year period, both periods when RRV-TV had not been used. A subanalysis compared the occurrence of hospitalizations for intussusception in 14 high-use states (17% coverage overall) with that in 6 low-use states (4% coverage), the latter serving as a non-narrative RRV-TV control group. The occurrence of intussusception was compared for all infants aged <1 year, as well as for infants aged 45–210 days.

Analysis of these data indicated that, in high-use states, there was a 3% decrease in hospitalization for intussusception in the infants aged <1 year relative to the previous year when RRV-TV had not been used, rather than the considerably larger increases projected from the case-control, case-series, and cohort studies (figure 1). In contrast, states with low vaccine usage experienced a modest overall increase in hospitalization for intussusception, which is consistent with the view that the decrease in the number of intussusception hospitalizations in the high-use states was not caused by a continuation of a decreasing trend in intussusception hospitalizations observed over the preceding 5-year period.

Infants aged 45–210 days were analyzed separately, because this age group had received virtually all the first doses of RRV-TV [22]. Infants in this age group in the high-use states experienced a small increase in intussusception hospitalizations (>5%), whereas those in the low-use states experienced an even larger relative increase (>14%), which suggests that an increase in intussusception specific to RRV-TV use had not taken place. Nevertheless, if we attribute the small increase for the infants aged 45–210 days in the high-use states to RRV-TV, it would correspond to an estimated risk of 1 excess case per ~32,000 infants (unadjusted for the 5-year trend), a value still far lower than the CDC risk estimates.
Thus, it was the first large-scale, multi-state investigation to address the possibilities that RRV-TV might have influenced events outside the immediate 3-week postimmunization period. Specifically, it examined the possibility that the rotavirus vaccine could induce a temporal shift in the occurrence of intussusception by provoking intussusception in a subset of infants who were destined to develop it later in infancy with or without vaccination and/or RRV-TV might prevent intussusception that occurs as a consequence of infection with wild type human rotavirus [16]. The possibility of a temporal shift of intussusception induced by RRV-TV has a precedent in the demonstration of an increased risk of serious acute neurological disorders in the week after diphtheria-pertussis-tetanus vaccination (OR >1.0), followed by a decreased risk during the ensuing 3-week period (OR <1.0), and no risk at 28 days (OR, 1.0) after vaccination [27]. For these reasons, L. Simonsen, D. M. Morens, and W. C. Blackwelder (unpublished data) also reanalyzed the findings from the CDC case-control study to determine whether the increased risk of intussusception was indeed followed by a compensatory decrease, as discussed below.

ADDITIONAL ANALYSIS OF THE CDC CASE-CONTROL STUDY DATABASE TO INCLUDE MORE Distant POST-RRV-TV WEEKS

In this recent reanalysis of the CDC case-control study database, Simonsen et al. addressed the possibility that a temporal shift in intussusception had occurred in RRV-TV recipients and was responsible for the compensatory decrease inferred from the analysis of the population-based study cited above (L. Simonsen, D. M. Morens, and W. C. Blackwelder, unpublished data; figure 2). After the initial increase in the risk of intussusception in the first 3 weeks after receiving the first dose of RRV-TV, CDC reported that there was a significant decrease in the relative odds of intussusception in the more distant weeks after RRV-TV administration (OR, 0.3; 95% confidence interval, 0.1–0.5) [28]. Thus, when the OR for the occurrence of intussusception (on log10 scale) was plotted by postvaccination weeks 1–12 (L. Simonsen, D. M. Morens, and W. C. Blackwelder, unpublished data; figure 2), the initial temporal increase in intussusception appeared to be compensated for by a decrease in the period beginning as early as 3 weeks after administration of RRV-TV (L. Simonsen, D. M. Morens, and W. C. Blackwelder, unpublished data). In this way, the compensatory decrease in intussusception that occurred in vaccine recipients later in infancy would counterbalance RRV-TV–induced intussusception that occurred in the immediate postvaccination weeks and would explain the failure to detect a corresponding increase in intussusception hospitalization of infants during the >9 months of RRV-TV use in the large population-based study (figure 1). It has been suggested by CDC that this compensatory decrease was an artifact and was explained by differences in the socioeconomic status between vaccinated and unvaccinated infants [28]. However, since Simonsen et al. failed to find a difference in the relative OR in the antecedent weeks, which also was studied in this reanalysis (data not shown), this alternative explanation seems unlikely. However, since the CDC population attributable risk estimates (1:2500 to 1:11,073) were based essentially on the period of temporal risk increase (i.e., 1–3 weeks postimmunization), the depressed risk we observed in later postvaccination weeks may have led to their overestimates of the total attributable risk for the first year of life derived from the case-control, case-series, and cohort studies. It is important to note that the risk estimate of 1 excess case of intussusception hospitalization per ∼32,000 RRV-TV vaccine recipients, as noted ear-
latter for the infants aged 45–210 days in the 20-state study, may not be comparable to the later CDC estimates (1 excess case per 4670–11,073 RRV-TV vaccine recipients; see figure 1) derived essentially from the early temporal risk period, because the time period examined by Simonsen et al. was not limited to the early temporal risk period but also may have included a portion of the compensatory decrease interval.

RECONCILIATION OF DISPARATE CONCLUSIONS DERIVED FROM THE NIH-AHRQ AND CDC STUDIES

In attempting to reconcile the apparent conflicting observations, we considered 4 hypotheses that serve to aid our examination of factors that could have contributed to the apparently disparate sets of data.

**Hypothesis 1: RRV-TV is not associated with intussusception and none of the estimates of risk are valid.** Findings consistent with an increase in the occurrence of intussusception in the immediate postimmunization period in 4 separate analyses would speak against this hypothesis. A placebo-controlled trial of the safety of the vaccine would be needed to define the actual attributable risk. Unfortunately, the number of vaccine recipients and controls in such a trial would have to be enormous if the actual attributable risk of intussusception in the immediate postimmunization period approaches 1 in ~32,000. However, our failure to detect a significant number of excess intussusception cases in the large population-based study indicates that such a placebo-controlled study would be very valuable and could serve to elucidate the scope of an association between RRV-TV immunization and the occurrence of intussusception.

**Hypothesis 2: RRV-TV has a unique and “uncompensated” adverse event associated with its use, namely the occurrence of intussusception.** This was the operative hypothesis in the early snapshot approach that the CDC used to predict an increase in the overall occurrence of intussusception, since the intussusception associated with RRV-TV would be additive to the background rate of intussusception. However, the observations from the large population-based study failed to confirm such an increase, but rather identified a slight decrease in the overall occurrence of hospitalization for intussusception in infants aged <1 year, which suggests that this hypothesis was not valid. Clearly, the occurrence of intussusception in the immediate postimmunization period was compensated for by a subsequent decrease in risk during the later months of infancy (figures 1 and 2). A further weakness of this hypothesis is that it seems unlikely that the tetravalent vaccine, each component of which grows less efficiently in humans than wild-type rotavirus, would cause a disease that has not been shown to be linked conclusively to naturally occurring human rotaviruses.

**Hypothesis 3: Infection by RRV-TV use triggers intussusception in intussusception-prone infants.** This hypothesis predicts that the overall excess number of cases of intussusception in infant vaccine recipients aged <1 year would be essentially zero, since every case of intussusception in a vaccine recipient would be balanced by the absence of a case in the same vaccine recipient at a later time. It is possible that the intussusception-prone infant could develop this illness after infection with any enteric agent. The finding of a close association in time between the early increased risk interval and the following period of compensatory decrease (figure 2) provides support for this hypothesis. The observation that the overall rate of intussusception in infant vaccine recipients aged <1 year actually decreased suggests that this hypothesis may not by itself explain the complete data set. The third hypothesis implies that the compensatory decrease illustrated in figure 2 can occur during intervals when wild-type human rotaviruses are not circulating in the population (see hypothesis 4).

**Hypothesis 4: RRV-TV is associated with intussusception in the immediate postimmunization period, but it protects against intussusception that occurs after subsequent infection with wild-type rotavirus.** This hypothesis implies that infection with wild-type rotavirus can result in intussusception in a small subset of infants [16]. It also implies that the occurrence of intussusception in RRV-TV recipients mimics this rare complication seen in infants infected with wild-type human rotavirus and, therefore, is not a new, unique, or unexpected adverse event. In order for rotavirus immunization to cause a decrease in the total number of cases of intussusception, the rate of intussusception in RRV-TV recipients must be less than that which occurs after infection with a wild-type human rotavirus. It is reasonable to assume that the incidence of a side effect, such as intussusception associated with infection by the rotavirus vaccine, should be lower than that caused by infection with a wild-type rotavirus. If this explanation is valid, it would predict that use of the vaccine could actually decrease the total number of cases of intussusception that occur in vaccinated infants, which would be consistent with the decrease observed for the infant population aged <1 year in the large population-based study. The weaknesses of this hypothesis are that wild-type rotavirus infection has not yet been established as an etiologic agent of intussusception and that the magnitude (3%) of the decrease in overall occurrence of intussusception in vaccine recipients during the first year of life was small, raising concerns of its validity. Importantly, this hypothesis predicts that the compensatory decrease in intussusception, as indicated in figure 2, would occur only during periods of time when wild-type rotaviruses circulate, a testable hypothesis that will require a large cohort of cases and controls, which may differentiate between hypotheses 3 and 4. The rarity of intussusception has hindered attempts to conclusively determine the role of rotaviruses in intussusception. However,
hypotheses 3 and 4 do not have to be mutually exclusive and both could independently contribute to the observed compensatory decrease.

**GAINS AND LOSSES RESULTING FROM THE WITHDRAWAL OF THE RECOMMENDATION FOR ROUTINE USE OF RRV-TV**

What was gained or lost by the decision to withdraw the recommendation for the use of RRV-TV initially made in 1999 and reaffirmed at the ACIP meeting in 2002? The clear gain is that cases of intussusception resulting from use of RRV-TV that would occur in the immediate postvaccination period would not occur after vaccine withdrawal, and the dictum of “first do no harm” would be maintained. At a minimum, RRV-TV was “intussusception neutral,” because the short-term increased risk was largely balanced by a later decreased risk. If wild-type human rotavirus is a cause of intussusception, not using RRV-TV could result in a failure to prevent intussusception associated with wild-type rotavirus infection, which, in turn, could possibly result in a net increase in the overall number of cases of intussusception. If this proves to be true, withdrawal of RRV-TV would result in a loss of this protective effect. If the original intent of withdrawal of vaccine was to prevent an increase in intussusception, it might be paradoxical that the actual effect could be quite the opposite.

In terms of prevention of rotavirus disease, what was gained or lost by the decision to withdraw the recommendation for the use of rotavirus vaccine? It would seem that there was no overall gain, only loss. Since RRV-TV was shown to be up to 91% efficacious in preventing severe rotavirus disease, failure to use RRV-TV or any other effective rotavirus vaccine, results in ∼45,000 otherwise preventable hospitalizations and 18–36 deaths/year in the United States alone. If the vaccine causes no net excess of intussusception in the infants aged <1 year as a result of the compensatory decrease cited earlier, then its use would be clearly beneficial. Moreover, the consequences of vaccination would be considerably less numerically than the morbidity and mortality associated with wild-type rotavirus infection, even if the vaccine’s population attributable risk of intussusception was ∼1:10,000 or 1:32,000 (i.e., 125–400 cases in a birth cohort of 4 million) and if it was associated with ∼4 deaths due to intussusception in a fully vaccinated infant population in the United States [9, 20, 29] (L. Simonsen, A. Elixhauser, W. C. Blackwelder, and D. M. Morens, unpublished data). Therefore, what is gained by not using the vaccine regarding the prevention of either intussusception or rotavirus disease is extremely small in comparison to the losses incurred both in the United States and, particularly, in developing countries where up to 520,000 infants die annually from severe rotavirus diarrheal disease.

The original decision of the ACIP for the vaccine’s withdrawal was made at a time when the number of excess cases of intussusception in vaccine recipients was estimated to reach up to 1600 in a fully vaccinated US infant population (figure 1), and it was assumed that the consequences of vaccination regarding intussusception were all short term. These 2 premises were not supported by the subsequent studies. This illustrates the problem of making decisions on vaccine utilization based on preliminary data and examining vaccine risk only over a short time interval without examining for compensatory benefits. In our view, it was regrettable that the ACIP did not, at a minimum, recommend at their February 2002 meeting a permissive use of RRV-TV when it was shown that the vaccine had a net effect of slightly decreasing the overall number of hospitalizations for intussusception during the first year of life.

There has been an additional and serious potential loss resulting from the decision not to approve a permissive recommendation for the use of RRV-TV. Despite the fact that RRV-TV remains licensed for use in the United States by the FDA, the withdrawal of the recommendation for its use in infants means that the further study of this vaccine either in the United States or in developing countries is extremely difficult. This is especially troubling when one considers the urgent need for its use in the developing world. At the present time, there is no available alternative licensed rotavirus vaccine in the United States, and there is no assurance that live attenuated rotavirus vaccine candidates under development will not pose the same dilemma. A permissive recommendation might have facilitated the manufacture and use of this highly effective vaccine in nations other than the United States. Although the US manufacturer indicated that approval for universal immunization was needed for the production of the vaccine to be economically feasible, it remains unclear why the ACIP did not support a permissive recommendation in light of the new data that clearly indicated that the predicted epidemic of intussusception did not occur after use of RRV-TV. What would have been lost if the ACIP had made such a recommendation that would have benefited infants in developing countries? In general terms, it may have been prudent if the recommendation made very recently by a group reviewing the thimerosal controversy had been anticipated. “In times of rapid decision-making regarding immunization policy, we recommend that all parties involved seek to analyze the short- and long-term intended and unintended consequences of their proposed actions” [30].

**IMPLICATIONS FOR THE RECOMMENDATION TO WITHDRAW USE OF RRV-TV ON DEVELOPMENT AND EVALUATION OF OTHER ROTAVIRUS VACCINES**

The considerations outlined above have implications for the ongoing evaluation of other candidate live attenuated rotavirus
might have permitted such a study to be undertaken as part of new studies for licensing of a rhesus rotavirus–based vaccine made by a new manufacturer. It has been noted by a physician-ethicist [37] who has been closely observing the RRV-TV dilemma, “Some have falsely assumed that inaction is a morally neutral state. But if one is culpable of vaccine related deaths, then one is also culpable for deaths caused by withholding the vaccine.”

References

27. Murphy TV, Gargiullo PM, Wharton M.