Intussusception Risk and Health Benefits of Rotavirus Vaccination in Mexico and Brazil

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ABSTRACT

BACKGROUND
Because postlicensure surveillance determined that a previous rotavirus vaccine, RotaShield, caused intussusception in 1 of every 10,000 recipients, we assessed the association of the new monovalent rotavirus vaccine (RV1) with intussusception after routine immunization of infants in Mexico and Brazil.

METHODS
We used case-series and case–control methods to assess the association between RV1 and intussusception. Infants with intussusception were identified through active surveillance at 69 hospitals (16 in Mexico and 53 in Brazil), and age-matched infants from the same neighborhood were enrolled as controls. Vaccination dates were verified by a review of vaccination cards or clinic records.

RESULTS
We enrolled 615 case patients (285 in Mexico and 330 in Brazil) and 2050 controls. An increased risk of intussusception 1 to 7 days after the first dose of RV1 was identified among infants in Mexico with the use of both the case-series method (incidence ratio, 5.3; 95% confidence interval [CI], 3.0 to 9.3) and the case–control method (odds ratio, 5.8; 95% CI, 2.6 to 13.0). No significant risk was found after the first dose among infants in Brazil, but an increased risk, albeit smaller than that seen after the first dose in Mexico — an increase by a factor of 1.9 to 2.6 — was seen 1 to 7 days after the second dose. A combined annual excess of 96 cases of intussusception in Mexico (approximately 1 per 51,000 infants) and in Brazil (approximately 1 per 68,000 infants) and of 5 deaths due to intussusception was attributable to RV1. However, RV1 prevented approximately 80,000 hospitalizations and 1300 deaths from diarrhea each year in these two countries.

CONCLUSIONS
RV1 was associated with a short-term risk of intussusception in approximately 1 of every 51,000 to 68,000 vaccinated infants. The absolute number of deaths and hospitalizations averted because of vaccination far exceeded the number of intussusception cases that may have been associated with vaccination. (Funded in part by the GAVI Alliance and the U.S. Department of Health and Human Services.)
IN 1999, A ROTAVIRUS VACCINE (ROTASHIELD, Wyeth Laboratories) was withdrawn from the market in the United States because it was associated with intussusception, a form of bowel obstruction.\(^1\) The risk was greatest (an increase by a factor of approximately 37) during the period 3 to 7 days after the first dose was administered, correlating with the peak period of replication of the vaccine virus in the intestines, and translated to an excess of approximately 1 case of intussusception in 10,000 recipients of RotaShield.\(^1,2\) Because of this association, two clinical trials, each of which involved more than 60,000 infants, evaluated the risk of intussusception with both of the next-generation oral rotavirus vaccines — pentavalent bovine–human reassortant vaccine (RV5, RotaTeq, Merck) and monovalent human vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals).\(^3,4\) No elevated risk was found during the 42-day and 30-day periods after vaccination with RV5 and RV1, respectively, and both vaccines are now recommended for global use by the World Health Organization (WHO).\(^5,6\)

In March 2006 and May 2007, Brazil and Mexico, respectively, added RV1 to their national childhood immunization programs. The combined annual birth cohort of approximately 6 million in these two countries provided an opportunity to assess whether routine vaccination with RV1 was associated with intussusception.

METHODS

STUDY DESIGN

We used the self-controlled case-series method to assess the within-person ratio of the incidence of intussusception in predefined risk periods after RV1 vaccination to the incidence in later periods.\(^7,8\) We compared estimates of the rate ratio in the case series with estimates of the odds ratio of the association between intussusception and RV1 vaccination obtained with the use of the case–control design.

On the basis of findings regarding the risk of intussusception after vaccination with RotaShield and the timing of peak intestinal replication of the RV1 vaccine virus, we hypothesized that the risk would be greatest 1 to 7 days after vaccination. The study was approved by the office of human subjects research at each participating institution, and the parents of all the participants provided written informed consent before enrollment.

The study was conducted from August 2008 through August 2010 at 53 hospitals in 7 states in Brazil and at 16 hospitals in 10 states in Mexico. In both countries, vaccination with RV1 is recommended when the infant is 2 months of age (dose 1) and when the infant is 4 months of age (dose 2), but at the very least, the series should be initiated before the infant is 15 weeks of age.

PATIENTS AND CONTROLS

Case patients were identified independently of their vaccination status through prospective enrollment and retrospective review of records. Trained coordinators conducted periodic reviews of the records of admissions, discharges, surgeries, and radiologic procedures in infants with intussusception.

Case patients were enrolled in the study if intussusception was confirmed by findings obtained during surgery or autopsy or by means of contrast enema or ultrasonography, thus meeting level I criteria for definite intussusception according to the Brighton Collaboration criteria for adverse events after immunization;\(^9\) if the infant was between 6 and 35 weeks of age at the time of the diagnosis of intussusception; and if the infant was born after June 1, 2006, in Brazil or after August 1, 2007, in Mexico, and thus met the age eligibility criteria for RV1 vaccination. For each case patient, we enrolled as controls up to four infants in the same neighborhood whose dates of birth were individually matched (within 30 days before or after) to the date of birth of the case patient.

DATA COLLECTION

Clinical records were reviewed to confirm the diagnosis of intussusception and to obtain information on the sex of the patient, the dates of symptom onset and hospitalization, the treatment, the need for intestinal resection, the duration of hospitalization, and the outcome. Equal efforts were made to confirm the vaccination status (through a review of the vaccination cards or provider records) of case patients and controls. Parents were interviewed in person to verify these data.

The infants were observed from the time they were 45 days of age until they were 245 days of age. The primary risk window within this observation period was 1 to 7 days after RV1 vaccination, but we also assessed the risk during the periods 8 to 14 days and 15 to 21 days after vaccination.

STATISTICAL ANALYSIS

We estimated that with approximately 250 cases of intussusception, the study would have 80% power...
to exclude a relative risk of intussusception of 3 or more within 7 days after the first dose of RV1, assuming vaccine coverage of 50%, at a type I alpha level of 0.05. For the case-series analysis, we calculated dose-specific incidence ratios and 95% confidence intervals using a conditional Poisson regression model by comparing for each infant the incidence of intussusception within each risk period with the incidence within all other observation periods. We adjusted for age in 14-day intervals to account for the varying background incidence of intussusception during the observation period and included an interaction term for country. The occurrence of intussusception before RV1 vaccination could decrease the probability that the infant would receive subsequent doses in the short term or could perhaps contraindicate subsequent vaccination. To account for this effect, only the time after exposure to the vaccine was included in the observation period.7,11

For the case–control analysis, a conditional logistic-regression model was used to assess the ratio of the odds that case patients were vaccinated within the risk windows to the odds that age-matched controls were vaccinated within those windows, including an interaction term for country. The season of birth and regional variations in the incidence of intussusception and vaccination were implicitly adjusted for by matching case patients with controls according to neighborhood and date of birth. In addition, the infants in each matched set of case patient and controls in the final model were the same age in days. This was accomplished by creating a “reference date” for controls, which was the date on which the matched control was the same age as the case patient was at the time of hospitalization. Exposure to vaccination was determined within risk windows before this reference date. Therefore, exposure status was age-matched between case patients and controls. Strata of cases with the same reference date were collapsed. No variables other than sex and vaccination were collected, and thus the final model considered only these variables. P values of less than 0.05 were considered to indicate statistical significance. All reported P values are two-sided.

We also performed a benefit–risk analysis. We used existing epidemiologic and vaccination data to model the benefits and risks associated with having no rotavirus vaccination program as compared with the benefits and risks associated with having a vaccination program in Mexico and Brazil. In summary, a birth cohort from each country was assumed to have been vaccinated with RV1 and was followed for 5 years. The benefits of a vaccination program were assessed as the estimated number of rotavirus-associated deaths and hospitalizations that were prevented by age 5, on the basis of published estimates of vaccine efficacy (approximately 85% for the series5,12-14) and the baseline rotavirus disease burden in the region. The risk of a rotavirus vaccination program was estimated as the excess number of vaccine-associated deaths and hospitalizations due to intussusception, which was calculated as the product of the baseline incidence of intussusception, the vaccination coverage, and the country-specific risk of intussusception associated with RV1 vaccination from the current study.

Data were analyzed with the use of SAS software, version 9.1 (SAS Institute). Additional details of study methods are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.

## RESULTS

A total of 615 infants with intussusception (285 in Mexico and 330 in Brazil) and 2050 controls (739 in Mexico and 1311 in Brazil) were enrolled. Of these, 594 case patients (97%) and 2033 controls (99%) had a history of vaccination as confirmed by a vaccination card. All the infants with intussusception were hospitalized; in Mexico, 3 infants (1%) died, of whom 1 had been vaccinated with the first dose 1 to 7 days previously. In Brazil, 16 (5%) died, of whom 2 had been vaccinated with the second dose 1 to 7 days previously. Intussusception was diagnosed and treated surgically in 87% of the case patients in Mexico, with 24% of all case patients requiring resection, and in 95% of the case patients in Brazil, with 46% requiring resection (Table 1).

In Mexico, intussusception developed after the first or second dose in 260 of the 285 case patients with a history of vaccination (91%) — in 114 (44%) after the first dose and in 146 (56%) after the second dose. Of the cases occurring after the first dose, a higher proportion occurred within 1 to 7 days after vaccination than during days 8 to 14 or days 15 to 21 after vaccination (21% vs. 5% and 4%, respectively), with a peak of 18 infants hospitalized on days 4 and 5 after vaccination (Fig. 1). In the case-series analysis, the rate of intussusception in Mexico was significantly higher 1 to 7 days after vaccination with the first dose than during the time outside the risk periods (incidence ratio, 5.3;
After the second dose, no elevated rate was observed 1 to 7 days after vaccination, but an increase in the rate by a factor of 2 was observed during the second and third week after vaccination. All corresponding point estimates using the case–control method were similar to those from the case-series analysis.

In Brazil, 95% of the patients and 96% of the controls received RV1 before the reference date. Neither a clustering of cases after the first dose nor a risk of the magnitude noted in Mexico was observed in Brazil (Fig. 2 and Table 2). However, a small but significantly elevated rate was noted 1 to 7 days after the second dose, both in the case-series analysis (incidence ratio, 2.6; 95% CI, 1.3 to 5.2) and the case–control analysis (odds ratio, 1.9; 95% CI, 1.1 to 3.4).

Most infants received the first dose of RV1 when they were 14 weeks of age or younger (see the figure in the Supplementary Appendix), thus limiting analysis of the potential effect of the age at vaccination on risk. However, the available data did not indicate an effect of age on risk in Mexico (P = 0.52) or Brazil (P = 0.93).

Our benefit–risk analysis indicated that an RV1 vaccination program would avert 663 deaths and 11,551 hospitalizations due to rotavirus disease in Mexico and 640 deaths and 69,572 hospitalizations in Brazil among children younger than 5 years of age (Table 3). In contrast, we predict that a vaccination program would cause 41 excess hospitalizations (approximately 1 per 51,000 vaccinated infants) and 2 deaths due to intussusception in Mexico and 55 excess hospitalizations (approximately 1 per 68,000 vaccinated infants) and 3 deaths in Brazil.

### DISCUSSION

We found an association between intussusception and the first dose of RV1 vaccination among infants in Mexico but did not find a similar risk among infants in Brazil. Several lines of evidence support a causal link in Mexico. First, similar to the experience with RotaShield, the increased risk of intussusception after RV1 occurred primarily in the first week after the first dose. This corresponds to the dose and period in which there is peak intestinal replication of vaccine virus and in which a local inflammatory response in the lymphatic tissue or intestines may occur — a response that has been implicated in the pathogenesis of intussusception. Second, cases of intussusception peaked on days 4 and 5 after the first dose of RV1. There may have been a bias related to the detection of intussusception in vaccinated infants who had relatively mild disease that would otherwise have resolved spontaneously, owing to heightened awareness of the association between intussusception and rotavirus vaccination. However, such a bias would not be expected to cause clustering on specific days after only one of the two vaccine doses. Finally, an increased risk of intussusception after the first dose of RV1 has also been noted in a study conducted by the manufacturer in a separate population in Mexico, and in Australia, postlicensure surveillance data have identified an increase in risk by a factor of approximately 3 to 5 relative to the background risk 1 to 7 days after vaccination with either RV1 or RV5.
The absence of risk associated with the first RV1 dose in Brazil was perplexing, given that the sample sizes, the study methods, and the analysis were similar to those in Mexico. One notable difference is that in Brazil, RV1 is administered together with the oral poliovirus vaccine, whereas in Mexico it is given together with the inactivated poliovirus vaccine. The first dose of oral poliovirus vaccine, which is the dose associated with the greatest replication of vaccine poliovirus strains, is known to decrease the immunogenicity of the first dose of RV1 when these two oral vaccines are administered together. In a trial conducted in South Africa, seroconversion was lower among infants who were given the first dose of RV1 with the oral poliovirus vaccine than among those who were given the first dose of RV1 with the inactivated poliovirus vaccine (13% vs. 33%).

Other factors, such as differences in the diets of the infants, breast-feeding practices, the natural risk of intussusception, and maternal antibody levels, might also have contributed to the variation in risk between Mexico and Brazil. Additional studies are needed to elucidate the reasons for the differences in risk patterns; one such study should compare the immune response and patterns of viral shedding after rotavirus vaccination between countries that use the inactivated poliovirus vaccine and those that use the oral poliovirus vaccine.

The relevance for developing countries of these findings from Mexico and Brazil remains uncertain. Most developing countries use the oral poliovirus vaccine, and the immune response to rotavirus vaccination and fecal shedding of vaccine-virus strains in developing countries are also generally lower than they are in industrialized countries.

Thus, it is important to recognize that the risk of intussusception that was observed in Mexico may...
not be seen in developing countries, particularly if differences in the use of oral poliovirus vaccine and inactivated poliovirus vaccine contributed to the differences in risk between Mexico and Brazil and if the risk of intussusception correlates with the vaccine immune response.

In Mexico, an increase by a factor of 2 in the risk of intussusception after vaccination was noted during the second and third weeks after dose 2 but not during the first week after dose 2. This pattern of risk is not consistent with the pattern of vaccine-virus replication, which peaks during the first week after vaccination, raising questions about the biologic plausibility of the association.

In Brazil, however, a small but significant increase in risk was noted in the first week after dose 2, which would be consistent with the timing of replication of the vaccine virus. It is possible that because of the reduced immunogenicity of the first dose of RV1 when it is given with the oral poliovirus vaccine, as it is in Brazil, the second dose of RV1 would effectively be the first immunizing dose.
in some infants and could be associated with greater replication of the vaccine virus. However, given the fairly small increased risk observed with dose 2, the association may be spurious and warrants further study.

Because intussusception is relatively uncommon, particularly at the young age at which the first dose of RV1 is administered, the short-term increased risk of intussusception translates into relatively few excess cases of intussusception attributable to vaccination, and the real-world benefits of rotavirus vaccination, which have been sustained for 3 years, numerically far outweigh the risks. After the withdrawal of RotaShield, another issue with respect to an assessment of benefit versus risk was also raised, when a post hoc analysis suggested that there was a lower risk of intussusception with the RotaShield vaccine after the 3-week risk window than during that window. In a subgroup of infants from the large RV1 prelicensure trial, a similar significantly lower risk of intussusception was observed in recipients of the vaccine as compared with recipients of placebo after 1 year of follow-up (relative risk, 0.28; 95% CI, 0.1 to 0.81). These findings suggest that the short-term increase in the risk of intussusception after rotavirus vaccination in early infancy may be offset by a decrease in the longer-term risk of intussusception during the first year of life.

Our study faced some key analytic challenges and had several limitations. First, because the background rate of intussusception in infants increases with age, some residual confounding in the case series might bias results toward the null even after adjustment for 14-day intervals of age. Second, the possibility of a lower risk of intussusception after the 3-week risk window could affect the case-series results. However, we were reassured...
by the concordant results obtained from the case–control analysis, which would not be affected by this phenomenon. Third, because the case and control status was not concealed from the interviewers, there may have been some differences in the effort made by the interviewers with respect to ascertaining vaccination history. However, the study personnel collecting data on vaccination were unaware of the risk windows. Finally, our evaluation was not powered to assess whether the risk of intussusception with RV1 relative to the background risk was greater among infants receiving their first dose after 15 weeks of age than among those receiving the vaccine at the recommended age of 6 to 15 weeks. Because of the higher background rates of intussusception among older infants, the excess number of intussusception cases attributable to the vaccine would be higher among infants vaccinated after 15 weeks of age even with the same increase in relative risk across age groups. To minimize this risk, the WHO guidelines recommend that dose 1 be administered when infants are 14 weeks of age or younger; however, the WHO Global Advisory Committee on Vaccine Safety has recognized that in regions with high mortality from rotavirus and delays in initiating vaccination, the lifesaving benefits of vaccinating children older than 15 weeks of age would far outweigh the potential risk of intussusception.

In conclusion, in Mexico, RV1 was associated with an increased risk of intussusception in the first week after vaccination. In Brazil, a risk was not seen after dose 1, but a possible risk was noted in the first week after dose 2. These increased risks translated to an annual excess of 96 hospitalizations for intussusception and 5 deaths in the two countries combined, figures that are outweighed by the real-world benefits of RV1 vaccination, which has annually prevented more than 80,000 hospitalizations and 1300 deaths in Mexico and Brazil. These emerging data on safety and benefits have been reviewed by the WHO as well as by regulatory agencies and immunization advisory committees in Brazil, Mexico, and the United States.

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Table 3. Effect of a Rotavirus Vaccination Program, as Compared with No Rotavirus Vaccination Program, on Deaths and Hospitalizations Associated with Diarrhea and Intussusception in Mexico and Brazil.

<table>
<thead>
<tr>
<th>Event</th>
<th>Without Vaccination Program</th>
<th>With Vaccination Program</th>
<th>No. of Events Averted or Caused</th>
<th>No. of Vaccinated Infants per Event Averted or Caused</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mexico</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus diarrhea</td>
<td>923</td>
<td>260</td>
<td>663 averted</td>
<td>3,164</td>
</tr>
<tr>
<td>Intussusception</td>
<td>61</td>
<td>63</td>
<td>2 caused</td>
<td>1,026,737</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus diarrhea</td>
<td>16,086</td>
<td>4,535</td>
<td>11,551 averted</td>
<td>182</td>
</tr>
<tr>
<td>Intussusception</td>
<td>1,215</td>
<td>1,256</td>
<td>41 caused</td>
<td>51,337</td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus diarrhea</td>
<td>850</td>
<td>210</td>
<td>640 averted</td>
<td>5,789</td>
</tr>
<tr>
<td>Intussusception</td>
<td>107</td>
<td>110</td>
<td>3 caused</td>
<td>1,354,737</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rotavirus diarrhea</td>
<td>92,453</td>
<td>22,881</td>
<td>69,572 averted</td>
<td>53</td>
</tr>
<tr>
<td>Intussusception</td>
<td>2,146</td>
<td>2,200</td>
<td>55 caused</td>
<td>67,737</td>
</tr>
</tbody>
</table>

* Details of the model used in this analysis are provided in the Supplementary Appendix.
† These values were obtained by taking the number of events averted or caused, dividing it by the respective country’s birth cohort, and then calculating the inverse.
Benign and potentially fatal rotavirus disease. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. Funded in part by the GAVI Alliance under a collaborative agreement with the Program for Appropriate Technology in Health (PATH) and in part by the U.S. Department of Health and Human Services. No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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