Postmarketing Surveillance of Intussusception Following Mass Introduction of the Attenuated Human Rotavirus Vaccine in Mexico

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Background: Mexico initiated mass vaccination with the attenuated human rotavirus vaccine (Rotarix) in 2006. This postlicensure study aimed to assess any potential temporal association between vaccination and intussusception in Mexican infants.

Methods: Prospective, active surveillance for intussusception among infants aged less than 1 year was conducted in 221 hospitals across Mexico from the Mexican Institute of Social Security between January 2008 and October 2010. The temporal association between vaccination and intussusception was assessed by self-controlled case-series analysis.

Results: Of the 753 episodes of intussusception reported in 750 infants, 701 were in vaccinated infants (34.5% post–dose 1, 65.5% post–dose 2). The relative incidence of intussusception within 31 days of vaccination was 1.75 (95.5% confidence interval [CI]: 1.24–2.48; $P = 0.001$) post–dose 1 and 1.06 (95.5% CI: 0.75–1.48; $P = 0.75$) post–dose 2. The relative incidence of intussusception within 7 days of vaccination was 6.49 post–dose 1 (95.5% CI: 4.17–10.09; $P < 0.001$) and 1.29 post–dose 2 (95.5% CI: 0.80–2.11; $P = 0.29$). Clustering of intussusception within 7 days of vaccination was observed post–dose 1. An attributable risk of 3 to 4 additional cases of intussusception per 100,000 vaccinated infants was estimated.

Conclusion: This is the largest surveillance study for intussusception after rotavirus vaccination to date. A temporal increase in the risk for intussusception was seen within 7 days of administration of the first vaccine dose. It is still uncertain whether rotavirus vaccination has any impact on the overall incidence of intussusception. This finding has to be put in perspective with the well-documented substantial benefits of rotavirus vaccination.

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Mexico was one of the first countries to introduce the attenuated human rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) into its national immunization program, as a consequence of the long-term–detected rotavirus disease burden.[1] Mass vaccination was initiated in 2006 and since then, significant reductions in diarrhea-related hospitalizations and deaths among Mexican children younger than 5 years of age have been reported.[2–4]

A previous tetravalent rhesus–human reassortant rotavirus vaccine (RotaShield; Wyeth-Lederle Vaccine, Philadelphia, PA) licensed in the United States was withdrawn from the market due to an association with intussusception.[5,6] Intussusception is a rare form of intestinal obstruction in which a segment of the bowel prolapses into a more distal portion. Intussusception constitutes the most common cause of intestinal obstruction among children younger than 3 years of age, with most cases occurring in male infants aged less than 1 year.[7] Case-control analysis showed an increased risk of intussusception 3–14 days after the first dose of tetravalent rhesus–human reassortant rotavirus vaccine (adjusted odds ratio: 21.7; 95% confidence interval [CI]: 9.6–48.9).[8] In a case-series analysis, the incidence-rate ratio was 29.4 (95% CI: 16.1–53.6) for days 3–14 after the first vaccine dose.[8] A small increase in the risk of intussusception was also noted after the second dose of the vaccine.[8] These findings led experts to a consensus intussusception risk estimate of 10–20 cases per 100,000 vaccinated infants.[7]

Before initiation of a prelicensure phase III clinical trial of the attenuated human rotavirus vaccine in Latin America, a large surveillance study was conducted to estimate the baseline incidence of intussusception in 11 countries from the region (unpublished data, Sáez-Llorens X, et al). From January 2003 to May 2005, the reported mean incidence of definite intussusception in infants aged less than 1 year was 51 per 100,000 child-years. In Mexico, the reported incidence of definite intussusception in this age group was 87.8 (95% CI: 70.4–105.1) per 100,000 child-years. Median age at presentation was 6.5 months, with 91% of all cases of definite intussusception found to occur in infants younger than 1 year of age.

The attenuated human rotavirus vaccine was not found to be associated with an increased risk of intussusception in a large prelicensure placebo-controlled, clinical trial involving 63,225 infants in 11 Latin American countries and Finland.[9] During the prespecified 31-day period after each vaccine dose, 6 cases of intussusception were observed in infants who received the vaccine

versus 7 cases among infants who received placebo (relative risk: 0.85; 95% CI: 0.30–2.42). No evidence of clustering of intussusception was seen after either vaccine dose, and no episodes of intussusception with onset within 14 days after the first vaccine dose were reported.

Postlicensure surveillance, including targeted studies of adverse events of interest, is an important method of evaluating the safety of vaccines when used in routine clinical practice. This article presents results of a postmarketing study initiated to prospectively assess any potential temporal association between the attenuated human rotavirus vaccine and intussusception occurring within 31 days after vaccination in infants aged less than 1 year in Mexico using the self-controlled case-series (SCCS) method.

METHODS

Study Design

This phase IV, postmarketing, observational, epidemiologic safety study was undertaken collaboratively by GlaxoSmithKline Biologicals and the Mexican Institute of Social Security (Instituto Mexicano del Seguro Social [IMSS]). The IMSS is one of the largest social security institutions in Latin America, providing health services to approximately 40% of the Mexican population including 500,000 newborn infants each year (which corresponds to approximately 25% of the total annual birth cohort).[10–12] The IMSS started mass vaccination with the attenuated human rotavirus vaccine in 2007, with infants receiving 2 doses of vaccine at 2 and 4 months of age. Prospective, active surveillance for intussusception among infants younger than 1 year of age was conducted from January 2008 to October 2010 at 221 IMSS hospitals with pediatric wards across Mexico. Because 96% of all cases enrolled during the first 18 months of the study were reported from 67 referral hospitals with pediatric surgical facilities, from July 2009 onward surveillance was maintained by focusing on these referral hospitals.

Case Definition and Enrollment

Infants younger than 1 year of age with definite intussusception were included in this analysis after parents/guardians provided informed consent. Cases were identified by electronic and manual review of hospital admission and discharge logs, and emergency department, pediatric ward, surgery and radiology files. Episodes of intussusception were classified as definite according to the case definition developed by the Brighton Collaboration Working Group for Intussusception,[13] and were confirmed by radiography, surgery or postmortem examination. Participation in the study consisted of interviews with the infants' parents/guardians and review of the infants' medical charts and vaccination records. Vaccination history was confirmed by review of Expanded Program on Immunization cards. If direct review of Expanded Program on Immunization cards was not possible, vaccination history was confirmed from available clinical files (medical charts or the IMSS database). If this was not possible, vaccination history was confirmed through parent/guardian recall.

Statistical Analysis

The temporal association between vaccination with the attenuated human rotavirus vaccine and definite intussusception was assessed for 3 postvaccination time periods: days 0–30 (primary study objective), days 0–15 and days 0–6 (identified as the highest risk periods for intussusception after vaccination with the tetravalent rhesus–human reassortant rotavirus vaccine).[7] The relative incidence of intussusception during each predefined risk period compared with that during the control period from 31 days postvaccination up to 1 year of age (excluding the day of the first birthday) was calculated by SCCS analysis. As the occurrence of intussusception before exposure to the vaccine would be expected to contraindicate subsequent vaccination, preexposure time was not included in the SCCS analysis. The SCCS method provides an estimate of the incidence of an acute outcome relative to a transient exposure, such as the association between intussusception and rotavirus vaccination. SCCS analysis only requires data for subjects experiencing the event of interest during the risk or the control period and their history of vaccination with the attenuated human rotavirus vaccine; no separate controls are needed. An important restriction of the SCCS method is the ideal requirement that the occurrence of an event should not change an individual's subsequent exposure history. It is also assumed that occurrence of an event does not alter the subsequent observation period. Furthermore, complete information on exposure status throughout the observation period of each individual is required. However, in the present study, it was expected that infants who experienced definite intussusception after the first dose of the attenuated human rotavirus vaccine would not receive the second vaccine dose. In addition, because vaccination data collection occurred at the time of the actual event, postevent vaccinations were not documented. This restriction implies that it is not possible to analyze both doses in the same model without introducing bias. Consequently, the association between vaccination and intussusception was analyzed for each dose separately and sequentially, starting with the second vaccine dose. If no effect was found after the second vaccine dose, then data after the first vaccine dose were to be analyzed. Relative incidence estimates were adjusted for age (in 1-month intervals) by means of a conditional Poisson regression model.[14] The overall impact of vaccination on intussusception over the 12-month period was not studied.

For the SCCS analyses, α was adjusted similar to the O'Brien-Fleming adjustment.[15] For an overall α of 0.05, this final analysis was performed with an α of 0.045 to adjust for an earlier planned interim analysis. Two-sided 95.5% CI were computed by Wald method. The primary objective was to exclude an additional risk estimate of 10 episodes of intussusception per 100,000 population based on the experience with the tetravalent rhesus–human reassortant rotavirus vaccine.[7] The primary objective of this study was considered met if the upper limit of the 95.5% CI of the relative incidence of intussusception was less than 2.67 post–dose 1 and less than 1.59 post–dose 2, based on the number of cases of intussusception seen in the placebo group during the 31 days after each vaccine dose in a previous large clinical trial.[9] It was estimated that 660 episodes of definite intussusception in vaccinated infants would provide at least 80% power to conclude on the primary objective.[16]

The number of potential excess cases of intussusception that could be attributable to vaccination with the attenuated human rotavirus vaccine was estimated per 100,000 vaccinated subjects. This calculation was based on the incidence of intussusception during the first year of life and the proportion of these cases expected to occur within 31 days of administration of the first and/or second dose of the attenuated human rotavirus vaccine based on surveillance undertaken before vaccine introduction (P31) (unpublished data, Sáez-Llorens X, et al) and the relative incidence of intussusception within 31 days of vaccination observed in this study. The number of excess cases was calculated as P31 × incidence of intussusception × (relative incidence – 1).

Clinical characteristics, management and outcome of episodes of intussusception occurring in vaccinated and unvaccinated infants and those occurring during the risk and control periods were compared using Fisher exact test for categorical variables or the Wilcoxon rank-sum test for continuous variables. All *P* values were 2-sided. All statistical analyses were performed using SAS statistical software, version 9.2 (SAS Institute Inc, Cary, NC).

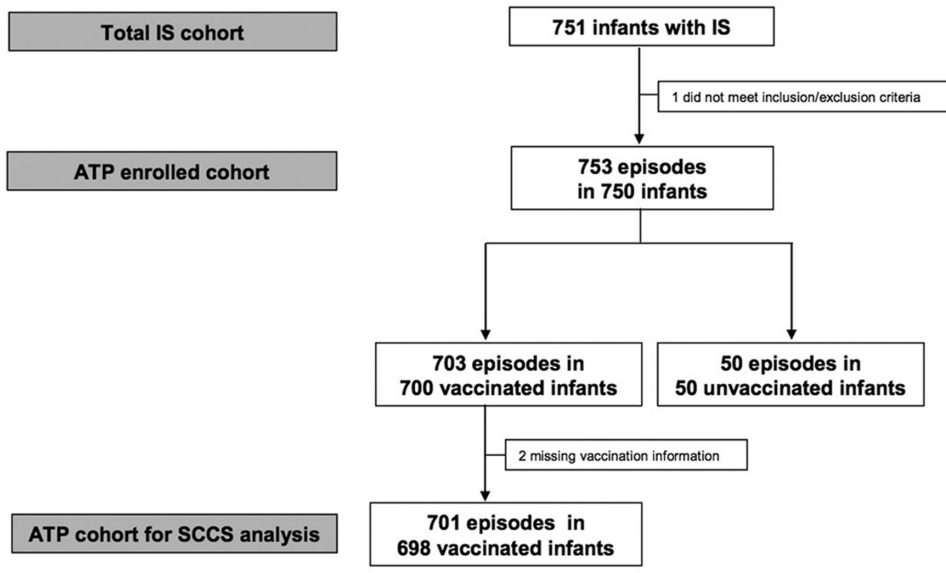

FIGURE 1. Subject flow chart.

RESULTS

Study Population

A total of 751 infants with definite intussusception were enrolled (Fig. 1). One subject did not meet the study inclusion criteria and was excluded (exact date of onset of intussusception missing). There were 753 episodes of intussusception in the remaining 750 infants (3 infants each experienced 2 intussusception episodes). Mean (standard deviation) age of infants with definite intussusception at the time of enrollment into the study was 6.21 (3.39) months, and 61.9% were male.

Of the 700 subjects vaccinated with the attenuated human rotavirus vaccine (93.3%), most had received both vaccine doses (65.6%). Vaccination history was confirmed by Expanded Program on Immunization card review for 442 infants (63.1%), by medical file review for 124 infants (17.7%), by IMSS database review for 1 infant (0.1%) and by parental/guardian interview for the remaining 133 infants (19.0%). Exact dates of vaccination were missing or incomplete for 2 subjects. A total of 701 episodes of intussusception in 698 vaccinated infants were therefore included in the SCCS analysis. Most infants in this cohort had received the first dose of attenuated human rotavirus vaccine at 2 months of age (530/698; 75.9%) and the second dose at 4 months of age (327/457; 71.6%). In all, 34.5% (242/701) of intussusception episodes in the according-to-protocol cohort for the SCCS analysis occurred post–dose 1 and 65.5% (459/701) occurred post–dose 2. Of the 242 infants who developed intussusception post–dose 1, only 44 (18.2%) had received the first vaccine dose after the recommended upper age limit of 16 weeks.

Disease Characteristics

Age distribution of intussusception episodes according to vaccination status is shown in Figure 2. The most commonly observed symptoms of intussusception were vomiting (685 episodes; 91.0%), bloody or bright red stool (620 episodes; 82.3%), abdominal pain (596 episodes; 79.2%) and abnormal or absent bowel sounds (575 episodes; 76.4%). All intussusception episodes resulted in hospitalization. Median duration of hospitalization was 5 days. Surgery was performed in most cases (90.2%), with bowel resection required in 15.6% of episodes. Most episodes of intussusception resolved without sequelae (97.2%). Six infants (0.8%) died as a result of complications after intussusception surgery, all of whom had received at least 1 dose of the attenuated human rotavirus vaccine. Onset of intussusception occurred during the risk period after vaccination in 2 of the deceased infants (1 day post–dose 1 and 12 days post–dose 2, respectively) and during the control period in the other 4 infants. Very few differences in clinical characteristics, management or outcome were found to be statistically significant at the 5% level between episodes of intussusception in vaccinated and unvaccinated infants (Table 1) or between episodes of intussusception in vaccinated infants that occurred during the risk and control periods (Table 2).

Risk of Intussusception

In all, 42.1% of the definite intussusception episodes post–dose 1 and 28.5% of those post–dose 2 occurred within 31 days of vaccination. Clustering of definite intussusception episodes within 7 days of vaccination was observed post–dose 1 (23.1%), but not post–dose 2 (7.8%; Fig. 3).

Post–dose 1, the relative incidence of intussusception within 31 days of vaccination versus the control period was 1.75 (95.5% CI: 1.24–2.48; $P = 0.001$; Table 3). Post–dose 2, the relative incidence of intussusception within 31 days of vaccination versus the control period was 1.06 (95.5% CI: 0.75–1.48; $P = 0.75$).

The relative incidence of intussusception within 16 days of vaccination versus the control period was 3.24 post–dose 1 (95.5% CI: 2.15–4.87; $P < 0.001$) and 1.06 post–dose 2 (95.5% CI: 0.69–1.61; $P = 0.79$). The relative incidence of intussusception within 7 days of vaccination versus the control period was 6.49 post–dose 1 (95.5% CI: 4.17–10.09; $P < 0.001$) and 1.29 post–dose 2 (95.5% CI: 0.80–2.11; $P = 0.29$).

To account for the fact that vaccination history could not be verified from written sources in 19% of infants, an exploratory analysis was performed excluding cases in whom vaccination status was based solely on parent report. This was not found to impact significantly on relative incidence estimates (data not shown).

This study was not powered to assess the risk of intussusception among infants receiving their first vaccine dose after 16 weeks of age. However, an exploratory analysis showed no increase in risk of

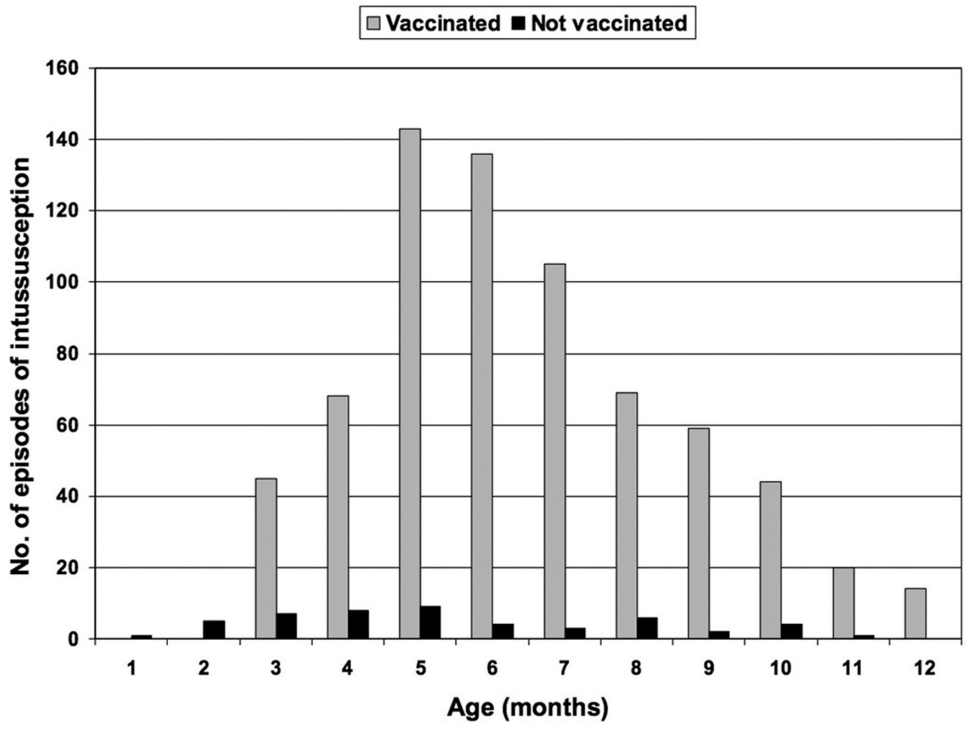

FIGURE 2. Age distribution of episodes of definite intussusception according to vaccination status.

intussusception among infants who received the first vaccine dose after 14 weeks of age compared with those who had received the first vaccine dose before or at 14 weeks of age (data not shown).

Attributable Risk

The number of additional cases of intussusception attributable to vaccination with the attenuated human rotavirus vaccine in Mexico was estimated to be 3.7 (95.5% CI: 1.2–7.3) cases per 100,000 person-years (assuming a baseline incidence of intussusception of 87 cases per 100,000 person-years).

DISCUSSION

This is the largest study for active surveillance of intussusception after rotavirus vaccination undertaken to date, with approximately 1.5 million infants under surveillance during the study period of almost 3 years. The attenuated human rotavirus vaccine was not found to be associated with a risk of intussusception of the magnitude previously observed with the tetravalent rhesus–human reassortant rotavirus vaccine.[7] However, a temporal association between vaccination and intussusception was observed within 31 days of administration of the first dose of the attenuated human rotavirus vaccine. This effect mostly occurred during the first week after vaccination. No temporal association between vaccination and intussusception was seen post–dose 2. These data correspond to a risk of 3 to 4 additional cases of intussusception per 100,000 infants vaccinated. Few significant differences were observed between age of onset, clinical presentation and outcome of episodes of intussusception in vaccinated and unvaccinated infants in this study. Similarly, few significant differences in outcome were observed between episodes of intussusception occurring during the risk period after vaccination and episodes occurring during the control period.

Postlicensure evaluation of the potential risk of intussusception after vaccination with the attenuated human rotavirus vaccine has also been undertaken in Mexico and Brazil by local investigators in collaboration with the Pan American Health Organization and the Centers for Disease Control and Prevention.[17] A temporal increase in the relative risk of intussusception within 7 days post–dose 1 was observed in Mexican infants, corresponding to a risk of approximately 2 additional hospitalizations for intussusception per 100,000 infants vaccinated. In Brazilian infants, no increase in the relative risk of intussusception was seen after the first vaccine dose; however, an increased risk was seen 1–7 days after the second dose, although this was smaller than that seen after the first dose in Mexico.[17] Recent data from the Australian National Immunization Program suggest a possible temporal clustering of intussusception episodes during the 7 days post–dose 1 with both the attenuated human rotavirus vaccine and the pentavalent bovine–human rotavirus vaccine.[18] However, this finding was based on relatively few cases, and no increase in overall risk of intussusception at 12 months of age was seen with either vaccine.

Active surveillance for intussusception episodes with diagnostic evaluation of all potential cases and verification of diagnosis through review of clinical features is considered the reference standard for postlicensure studies of rotavirus vaccines.[19] Because intussusception is an uncommon event, traditional cohort-based evaluations would require follow-up data on extremely large numbers of children to assess a low level of risk. The SCCS method is designed to study the association between an acute event and a transient exposure using data only on cases; no separate controls are needed.[16] As such, this method controls for possible confounders that do not vary with time, such as socioeconomic status, sex, race/ethnicity and geographic location.[14] The SCCS method is well-suited for study of adverse reactions to childhood vaccinations, where high levels of coverage in the population make the selection of a control group difficult.[16,20] In this study, more than 90% of children with intussusception had received at least 1 dose of the attenuated human rotavirus vaccine.

Three key issues in the assessment of the risk of intussusception by the SCCS method deserve special attention.[19] First,

TABLE 1. Clinical Characteristics, Management and Outcome of Episodes of Definite Intussusception According to Vaccination Status

Characteristic	Episodes in Vaccinated Infants (N = 703)	Episodes in Unvaccinated Infants (N = 50)	*P*
Age at onset, mo			
Median	5	4	—
Mean (SD)	5.52 (2.15)	4.42 (2.58)	
Range	2–11	0–10	
Symptoms, n (%)			
Vomiting	643 (91.5)	42 (84.0)	0.06*
Bloody or bright red stool	580 (82.5)	40 (80.0)	0.29*
Abdominal pain	555 (78.9)	41 (82.0)	1*
Abnormal/absent bowel sounds	539 (76.7)	36 (72.0)	0.23*
Redcurrant jelly stool	429 (61.0)	28 (56.0)	0.30*
Abdominal distension	423 (60.2)	29 (58.0)	0.87*
Time from onset to confirmation (days)			
Median	2	3	0.83†
Mean (SD)	2.8 (1.6)	2.8 (1.6)	
Range	1–16	1–8	
Duration of hospitalization (days)			
Median	5	7	0.02†
Mean (SD)	7.0 (6.1)	9.1 (8.7)	
Range	1–66	3–47	
Surgery performed during hospitalization, n (%)			
Yes	637 (90.6)	42 (84.0)	0.14*
Bowel resection	94 (14.8)	12 (28.6)	0.03*
Outcome, n (%)			
Resolved	685 (97.4)	47 (94.0)	—
Resolved with sequelae	11 (1.6)	2 (4.0)	0.21*
Improved	1 (0.1)	1 (2.0)	—
Fatal	6 (0.9)	0 (0.0)	1*

*Fisher exact test.
†Wilcoxon rank-sum test.
N indicates total number of episodes of intussusception; n (%), number (percentage) of episodes in a given category; SD, standard deviation.

TABLE 2. Clinical Characteristics, Management and Outcome of Episodes of Definite Intussusception According to Time of Onset (risk period versus control period)

Characteristic	Episodes During Risk Period (N = 233)	Episodes During Control Period (N = 468)	*P*
Symptoms, n (%)			
Vomiting	210 (90.1)	431 (92.1)	0.30*
Bloody or bright red stool	192 (82.4)	387 (82.7)	0.56
Abdominal pain	186 (79.8)	367 (78.4)	1*
Abnormal/absent bowel sounds	182 (78.1)	355 (75.9)	1*
Redcurrant jelly stool	140 (60.1)	288 (61.5)	0.50*
Abdominal distension	155 (66.5)	267 (57.1)	0.05*
Time from onset to confirmation (days)			
Median	2	2	0.83†
Mean (SD)	2.8 (1.5)	2.8 (1.7)	
Range	1–12	1–16	
Duration of hospitalization (days)			
Median	5	5	0.65†
Mean (SD)	7.1 (6.2)	6.9 (6.0)	
Range	1–58	1–66	
Surgery performed during hospitalization, n (%)			
Yes	219 (94.0)	416 (88.9)	0.03*
Bowel resection	34 (15.5)	60 (14.4)	0.73*
Outcome, n (%)			
Resolved	229 (98.3)	454 (97.0)	—
Resolved with sequelae	1 (0.4)	10 (2.1)	0.11*
Fatal	2 (0.9)	4 (0.9)	1*

*Fisher exact test.
†Wilcoxon rank-sum test.
N indicates total number of episodes of intussusception; n (%), number (percentage) of episodes in a given category; SD, standard deviation.

because the rate of intussusception varies substantially during the first year of life and because the vaccine is administered around the same age that intussusception usually occurs, it is important to adjust for age at onset. In this study, we adjusted for this age effect by a conditional Poisson regression model. As in previous similar studies,[8,21] relative incidence estimates were adjusted for age in 1-month intervals. An exploratory analysis has subsequently been performed in which relative incidence estimates were adjusted for

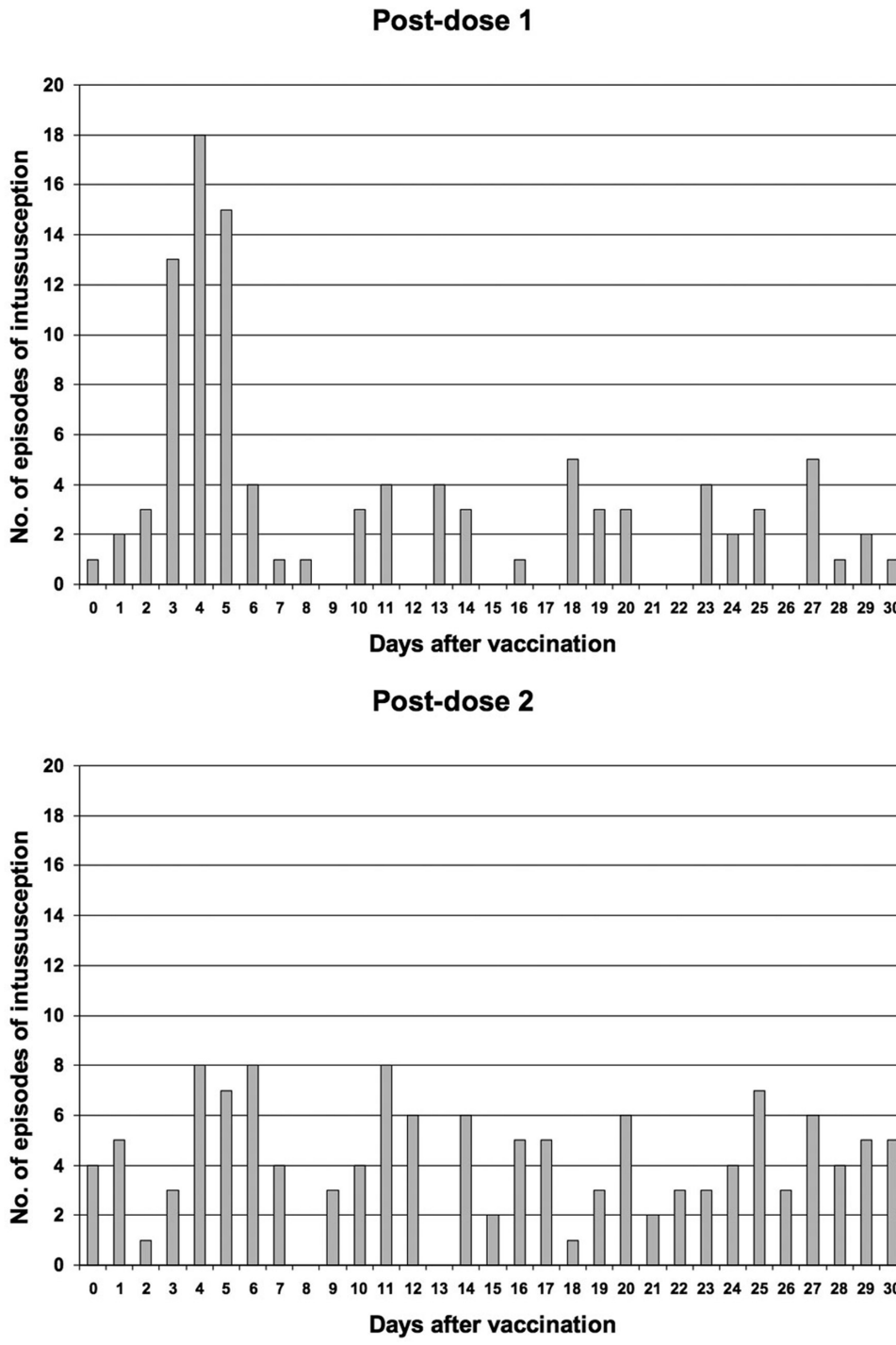

FIGURE 3. Distribution of episodes of definite intussusception with onset within 31 days of vaccination by vaccine dose.

age in 2-week intervals. This had no significant impact on relative incidence estimates, suggesting that age adjustment in 1-month intervals was satisfactory. Second, data from clinical trials of the attenuated human rotavirus vaccine suggest that the rate of intussusception may be reduced among vaccinated infants compared with placebo recipients over the first year after vaccination.[22] If the vaccine does impact on the overall risk of developing intussusception during the first year of life, then the fundamental assumption of the SCCS method that the incidence in the control period is unchanged from baseline in the absence of vaccination would be violated and a falsely elevated risk estimate could be derived. Finally, there may be reporting bias due to increased vigilance and diagnosis of intussusception soon after vaccination compared with at a later time point, highlighting the need for cautious interpretation of elevated temporal risks of smaller magnitude following vaccination. However, the relative incidence of intussusception was not increased post–dose 2 in this study, which would be expected if such a reporting bias existed.

TABLE 3. Relative Incidence of Intussusception During the Three Predefined Risk Periods After Vaccination With the Attenuated Human Rotavirus Vaccine*

Dose	Risk Period (days after vaccination)	Episodes of Definite Intussusception During Risk Period	Episodes of Definite Intussusception During Control Period	Follow-up Time in Risk Period (child-months)	Follow-up Time in Control Period (child-months)	Relative Incidence†	95.5% CI	*P*
1	0–30	102	599	698	6045	1.75	1.24–2.48	0.001
2	0–30	131	328	456	3009	1.06	0.75–1.48	0.75
1	0–15	72	599	360.3	6045	3.24	2.15–4.87	<0.001
2	0–15	69	328	235.4	3009	1.06	0.69–1.61	0.79
1	0–6	56	599	157.6	6045	6.49	4.17–10.09	<0.001
2	0–6	36	328	103.0	3009	1.29	0.80–2.11	0.29

*Analysis is based on 701 definite intussusception episodes in infants who received the attenuated human rotavirus vaccine.
†Relative incidence estimates have been adjusted for age (in 1-month intervals) with use of conditional Poisson regression.
95.5% CI indicates 95.5% confidence interval.
P value of Wald test.

Rotavirus is the most common cause of severe acute diarrhea requiring medical attention or hospitalization in young children worldwide, accounting for approximately 2.4 million hospitalizations and more than half a million deaths annually among children less than 5 years of age.[23–26] The attenuated human rotavirus vaccine has been shown to be safe and highly effective for the prevention of severe rotavirus diarrhea and associated hospitalizations in large-scale clinical trials[9,27–30] and postlicensure studies.[31–36] In particular, considerable reductions in hospital admissions and mortality due to diarrhea of any cause have been observed in Mexican and Brazilian children after inclusion of the attenuated human rotavirus vaccine into the national childhood immunization schedules.[2–4,37,38] In Mexico, sustained reductions in diarrhea-related mortality and hospitalizations among children aged less than 5 years have been observed over the 3 years since vaccine introduction (2008–2010).[2–4] Diarrhea-related hospitalizations in this age group declined by 11% during the first rotavirus season after vaccine introduction and by 40% during the second season, with greatest reductions seen in infants less than 1 year of age.[2] Diarrhea-related mortality among children aged less than 5 years declined from an average of 18 deaths per 100,000 children per year before vaccine introduction to 9 deaths per 100,000 children per year after vaccine introduction, a rate reduction of 46% ($P < 0.001$).[4] This translates into a cumulative reduction of approximately 2640 diarrhea-related deaths among children aged less than 5 years during the 3 years since introduction of the attenuated human rotavirus vaccine.[4]

Available data suggest that the known benefits of the attenuated human rotavirus vaccine outweigh the potential temporal increase in risk for intussusception within 7 days post–dose 1. A quantitative benefit-risk analysis of the attenuated human rotavirus vaccine in Mexico estimated that there would be 282 rotavirus-related hospital admissions and 332 rotavirus-related deaths averted by vaccination for each additional intussusception-related event that may be observed with the vaccine.[17] Although an increased risk of intussusception after vaccination with the attenuated human rotavirus vaccine has not been documented in the United States, if a risk does exist of a similar magnitude to that observed in Mexico, it is estimated that approximately 1 additional case of intussusception would occur per 100,000 US infants vaccinated following age recommendations.[39] However, an estimated 1100 rotavirus-related hospital admissions and 80 rotavirus-related deaths would be expected to be averted for each additional intussusception-related event that may be observed with vaccination.[40]

In summary, this is the largest postlicensure study of the safety of any rotavirus vaccine, with a degree of precision that allows detection of an extremely low level temporal risk of intussusception. Results show that the attenuated human rotavirus vaccine is not associated with a risk of the magnitude associated with the previous rotavirus vaccine that was withdrawn. The temporal increase in the risk for intussusception observed within 7 days post–dose 1 in this and other studies needs to be put in perspective with the well-documented substantial benefits of vaccination. In addition, it is still uncertain whether rotavirus vaccination has any impact on the overall incidence of intussusception. After reviewing recent data concerning the risks and benefits of rotavirus vaccination, the World Health Organization has reaffirmed its recommendation that rotavirus vaccines should be included into all national immunization programs.[41,42] The risk of intussusception should be monitored as these vaccines are introduced into new geographic areas, which may require strengthening surveillance in countries that do not have adequate capacity to detect adverse events.

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