INTUSSUSCEPTION RISK AFTER ROTAVIRUS VACCINATION IN U.S. INFANTS

Prepared by: W. Katherine Yih, PhD, MPH,[1] Tracy A. Lieu, MD, MPH,[1,2] Martin Kulldorff, PhD,[1] David Martin, MD, MPH,[3] Cheryl N. McMahill-Walraven, MSW, PhD,[4] Richard Platt, MD, MSc,[1] Nandini Selvam, PhD, MPH,[5] Mano Selvan, PhD,[6] Grace M. Lee, MD, MPH,[1] Michael Nguyen, MD[3]

Author Affiliations: 1. Department of Population Medicine, Harvard Medical School, and Harvard Pilgrim Health Care Institute, Boston, MA; 2. Division of Research, Kaiser Permanente Northern California, Oakland, CA; 3. Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD; 4. Aetna, Blue Bell, PA; 5. Government & Academic Research, HealthCore, Inc, Alexandria, VA; 6. Humana, Inc., Louisville, KY

June 12, 2013

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Intussusception Risk After Rotavirus Vaccination In U.S. Infants

Table of Contents

I. INTRODUCTION

In 1999, a tetravalent rhesus-human reassortant rotavirus vaccine (RotaShield; Wyeth Lederle) was voluntarily withdrawn from the U.S. market within a year of licensure due to an association with intussusception. The excess risk of intussusception was estimated at approximately 1-2 cases in 10,000 vaccine recipients.[1] In February 2006 and April 2008, respectively, a pentavalent bovine-human reassortant rotavirus vaccine (RotaTeq; Merck) and a monovalent human rotavirus vaccine (Rotarix; GlaxoSmithKline) were licensed following evaluation in clinical trials involving more than 60,000 infants, which provided enough statistical power to allow detection of an intussusception risk of similar magnitude as that observed after RotaShield. For RotaTeq, the pre-licensure data did not suggest an increased risk of intussusception in the 42-day period after any dose (relative risk (RR)=1.6 (95% CI: 0.4-6.4).[2] Similarly, in the case of Rotarix, no increased risk of intussusception was observed in the 31-day period after any dose (RR=0.85, 95% CI: 0.30-2.42).[3] In countries adopting these newer rotavirus vaccines, the impact on the burden of rotavirus gastroenteritis and severe childhood diarrhea has been substantial.[4-10]

Three post-licensure studies conducted outside of the U.S. point to an association between these vaccines and intussusception, although with much lower risks than were found for RotaShield in the U.S. In Australia, an active surveillance study found a statistically significant increased risk of this outcome during 1-7 days (RR=5.3, 95% CI: 1.1-15) and 1-21 days (RR=3.5, 95% CI: 1.3-7.6) after RotaTeq Dose 1.[11] The same study reported a non-statistically significant increased risk in the same time intervals after Rotarix Dose 1. The authors acknowledged that the small number of cases limited the precision of the estimates and made it impossible to compare the risks of the two vaccines. However, to aid in comparison with other studies, we can use these estimates, while acknowledging their imprecision, to calculate very approximate attributable risks (AR) by means of the following formula: (number of observed – number of expected cases in the risk window)/number of doses. This yields ARs of approximately 3-4 and 1 excess cases per 100,000 first-dose recipients of RotaTeq and Rotarix, respectively, in the Australian setting. A study of Rotarix in Mexico and Brazil reported an increased risk of intussusception in the 1-7 days after Dose 1 in Mexico, using both a self controlled case-series method (incidence ratio= 5.3, 95% CI: 3.0-9.3) and a case-control method (odds ratio=5.8, 95% CI: 2.6-13.0); an approximately two-fold increase in rate was seen in both the second and third weeks after Dose 2.[12] The ARs were determined to be approximately 1.5 and 2 excess cases per 100,000 vaccinated infants in Brazil and Mexico, respectively. A separate active surveillance study of Rotarix in Mexico, which used a self-controlled case-series design, found a relative incidence of intussusception in the 1-7 days after Dose 1 of 6.07 (95.5% CI: 4.20-8.63) and a lower but still statistically significant increased risk in the 1-31 days after Dose 1 (relative incidence=1.96, 95.5% CI: 1.46-2.63).[3] A tendency of intussusception to cluster in the 7 days after Dose 1 was also observed. The AR was estimated at 3-4 additional cases per 100,000 vaccinated infants in Mexico,[13] which has been translated to 1-3 additional intussusception hospitalizations per 100,000 vaccinated infants in the U.S. within 7 days after the first dose.[3]

In the U.S., post-licensure studies of RotaTeq safety have not reported a statistically significant increased risk of intussusception.[14-17] A cohort study in the Vaccine Safety Datalink (VSD) that included 309,844 first doses and 786,725 total doses of RotaTeq found standardized incidence ratios of 1.2 (95% CI: 0.03-6.8) and 1.2 (95% CI: 0.50-2.5) in the 1-7 and 1-30 days, respectively, after RotaTeq Dose 1 and an AR of 1 excess case of intussusception in about 1.8 million first-dose recipients. The authors noted, however, that a risk of less than 1 excess case per 65,287 (1.5 per 100,000) first dose recipients could not be ruled out, based on their 95% confidence interval.[16] A study of Vaccine Adverse Events Reporting System (VAERS) data similarly concluded that a small increase in risk could not be ruled out, and a concentration of cases was observed in the first 7 days after vaccination, especially after Dose 1.[14]

No U.S. post-licensure safety studies of Rotarix have been published.

Due to evidence of an association with intussusception emerging from the studies conducted in Australia and Mexico and concerns about lack of statistical power in the U.S.-based studies, the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research initiated the current study of RotaTeq and Rotarix in the Post-Licensure Rapid Immunization Safety Monitoring program (PRISM).[18] PRISM, a component of the Mini-Sentinel pilot program developed to conduct active surveillance for medical product safety,[19] provided the largest U.S. population heretofore available to address this question.

II. METHODS

A. STUDY POPULATION

The study population consisted of children 5-36.9 weeks of age who were members of Mini-Sentinel Data Partners Aetna, HealthCore, or Humana between January 2004 and September 2011. Each Data Partner provided at least 3 consecutive years of claims data during this period, using a distributed data model.[20,21] Continuous enrollment from birth through at least 42 days after the first dose of rotavirus vaccine or, if unvaccinated, from birth through at least 12.0 weeks of age was required, resulting in approximately 613,000 infant-years observed.

B. STUDY DESIGNS

A major challenge in studying rotavirus vaccines and intussusception is the strong confounding effect of age, as both vaccination and the risk of intussusception are age-dependent. In the U.S., the recommended ages for vaccination are 2, 4, and 6 months for RotaTeq and 2 and 4 months for Rotarix; and the incidence of intussusception hospitalizations in the U.S. in terms of cases per 100,000 person-years steadily increases from 2 at birth to 12 at 9 weeks of age to a peak of 62 at 26-29 weeks of age, subsequently falling to 26 by 52 weeks of age.[22] To confront this challenge, we used both a *self-controlled risk interval (SCRI)*[23,24] and a *cohort* design. A major advantage of the former, which was pre-specified as the primary method, is that it inherently controls for all fixed (non-time-varying) potential confounders such as gender, ethnicity, and chronic pre-disposing conditions. Another advantage is that it uses only exposed cases, thus minimizing potential misclassification bias due to incomplete data on vaccine exposure. The cohort design has higher statistical power than the self-controlled design, due to the relatively large amount of historical and concurrent unexposed data involved in the generation of expected counts. Also, it does not require extrinsic age-specific incidence (although such data can be incorporated, if desired). However, its ability to control for confounding is not as good as that of the self-controlled approach. It may also be subject to bias from misclassification of exposure if some vaccinations are missed.

Our original protocol described a third approach, the case-centered method.[25] This was included to provide another estimate using a method that controls well for age. However, it requires a wider distribution of exposures in time in order to have sufficient statistical power. This methodological requirement was not met, and therefore we do not present these results in the final report.

C. VACCINE EXPOSURES

RotaTeq and Rotarix vaccination were initially identified in claims data by means of CPT codes 90680 and 90681, respectively. Two risk intervals of interest were specified: 1-7 days and 1-21 days after vaccination. We conducted medical record review to validate vaccine exposure and type of rotavirus vaccination for all intussusception cases determined to be confirmed or possible (i.e. classified as Brighton Level 1 or 2), without regard to whether a prior rotavirus vaccination record existed in the electronic claims data.

D. OUTCOMES

Potential cases of intussusception during all person-time between ages 5 through 36.9 weeks (this includes the recommended ages of vaccination plus adequate follow-up time), irrespective of immunization status, were identified in claims data by any of the following codes in either the inpatient or emergency department (ED) setting: ICD9 codes 560.0 (intussusception) and 543.9 (other and unspecified diseases of the appendix, including intussusception) and CPT code 74283 (therapeutic enema, contrast or air, for reduction of intussusception or other intraluminal obstruction). Only first-ever diagnoses in either inpatient or ED setting were included, such that only incident cases were analyzed.

Case status was determined by adjudication based on review of de-identified full-text medical records of the event (admission note; daily notes during hospitalization; discharge summary; all surgical reports within 14 days of the date of the first code for intussusception; and all diagnostic procedures such as barium enemas and abdominal ultrasound, CT, and X-ray examinations). Cases were excluded if no intussusception was seen or an alternative diagnosis was made following surgery or air/liquid contrast enema. Each of the remaining potential intussusception cases was independently reviewed by one or more adjudicators with pediatric expertise.

Clinical adjudicators were blinded to vaccination history and instructed to classify cases using Brighton Collaboration criteria.[26] Brighton Level 1 cases were considered confirmed and used in primary analyses. Brighton Level 2 cases were included in separate sensitivity analyses. From the early adjudication experience, Brighton Level 2 cases were further differentiated into Levels 2A and 2B post hoc. Level 2A cases were considered possible intussusception on the basis of positive,, equivocal, or discordant radiological (ultrasound, abdominal X-ray, abdominal CT scan) test results, while Level 2B cases were considered less likely to be intussusception on the basis of negative radiological test results. For example, patients with an ultrasound suggestive of intussusception but with a normal air or contrast enema were classified as Level 2A. All discrepancies in classification were resolved by consensus between the two adjudicators.

E. STATISTICAL ANALYSIS

1. Self-controlled risk interval design

With the self-controlled design,[23,24] we compared counts of intussusception in risk and comparison intervals after Doses 1, 2, and (for RotaTeq) 3, and after all doses combined, using both the 1-7 and 1-21 day risk intervals (or “windows”). The control interval was always Days 22-42. Only vaccinated children with intussusception within 42 days of vaccination were included. For the analysis, we used logistic regression (PROC LOGISTIC in SAS), with an offset term to adjust for the differential risk of intussusception during the days of age in the risk and comparison intervals, respectively. Time-varying confounding such as by age must be controlled for explicitly. The protocol provided the flexibility of using either the age-specific risk of intussusception in the unexposed study population or, if those data were not sufficiently robust, a risk curve from the literature. In

light of the considerations presented in the section on "Further explanation of age adjustment in the self-controlled and cohort designs" below, we elected to use published age-specific background rates extracted by Tate el al. from the Healthcare Cost and Utilization Project's (HCUP) U.S. hospital-discharge data for 11 years during which no rotavirus vaccine was used.[22] As an alternative post hoc age adjustment, we used a quadratic risk function modeled from the unexposed study population, as was used with the cohort design (described immediately below).

2. Cohort design

In the cohort design, which was our secondary approach, exposed person-time was defined as that occurring in the 1-21 days after rotavirus vaccination. Unexposed person-time consisted of time during 5-36 weeks of age from unvaccinated infants and from vaccinated infants before and after the 0-21 days after any dose of any rotavirus vaccine. In contrast to the self-controlled design, data from the study population itself were used for age adjustment, the uncertainty in the age-dependent rates taken into account by the Poisson regression. A Poisson regression model, adjusted for age using a quadratic risk function, was used. Calendar time (to check for secular trends), different age-specific risk functions, and a number of interaction terms were examined during model-building. The independent covariates age, sex, Data Partner, and exposure status were retained in the final model. The number of intussusception cases was the dependent variable. We used PROC COUNTREG in SAS for the analyses. As an alternative post hoc age adjustment, we used the Tate et al. data in an offset term and removed age from the model.

Although we had pre-specified an analysis of the 1-7 day risk window using the cohort design, resource constraints for programming within the PRISM program as a whole led us to deliberately forgo this secondary analysis given that other risk estimates for this risk window would still be provided. (In view of the time that has elapsed, to attempt to obtain a risk estimate for the cohort design with the 1-7 day risk window at this point would entail running programs on data that have been refreshed several times since the original data were extracted, which would lead to changes in the underlying person-time and set of cases identified, causing a mismatch between the current and updated results.)

3. Further explanation of age adjustment in the self-controlled and cohort designs

As mentioned, since the incidence rate of intussusception varies by week of age, the self-controlled risk interval analysis must be adjusted for age, accounting for the relative difference in the background incidence rate in the risk versus control window. The most appropriate way to adjust for age in an observational study cannot be determined until the data have been collected, as the nature of the data cannot be controlled in the same way as it can in an experimental study. However, whether to use the external Tate data or the internal PRISM data for age adjustment in the primary analysis was decided prior to conducting the analyses producing risk estimates for the different age adjustment options, thereby maintaining the integrity of the study.

For the self-controlled age adjustment, the protocol stated that if the PRISM data did not appear robust enough to use, we would use unexposed age-specific incidence data from the literature. After examining the PRISM data in descriptive statistical analyses, it was decided that it was preferable to use data presented by Tate et al.,[22] for the following three reasons:

a. Stability of the incidence estimates: With 3,463 intussusception cases, the Tate et al. data provided a more reliable estimate of the incidence curve.
b. Greater accuracy at the edges of the age range for which chart review was conducted: The internal PRISM data on chart-confirmed cases were restricted to the 5-36 week age interval to keep time and

resource expenditures within limits. Some margin was allowed for early and late vaccination. To get good estimates at the edges of this interval, which were needed for the analysis, it was advantageous to have data from outside the interval as well, as provided by Tate et al.

c. Only relative incidence (the shape of the curve) mattered: While it is generally better to adjust based on internal rather than external data if precision is comparable, for a self-controlled analysis we only need the *relative* incidence rates at different ages, while the *absolute* incidence rate is irrelevant. Hence, it did not matter if the overall incidence rate for intussusception was higher or lower in the Tate data than in the PRISM population, as long as the percent excess or reduced risk was the same across all ages.

The background risk of intussusception by week of age was estimated by Tate et al. using splines; the data for mid-weekly points on the smoothed curve were provided to us by Jacqueline Tate. We used linear interpolation to estimate the background risk on days of age between the weekly mid-points.

For the cohort analysis, the protocol specified that internal PRISM data and a polynomial function should be used to model age in weeks as part of the Poisson regression. We tried linear, quadratic, cubic, fourth-order, and fifth-order functions, and decided to use the quadratic polynomial since the quadratic term was statistically significant compared to a linear function, while the cubic, fourth-order, and fifth-order terms were not statistically significant when added to a model with only the lower terms. While we know that the true age function is more complex than quadratic, the internal PRISM data are too sparse to model any higher-level terms, and their inclusion is just as likely to introduce noise as they are to model the true relationship.

In order to evaluate the robustness of the results, alternative methods for age adjustment were implemented as well, in a post-hoc fashion, after the original self-controlled and cohort analyses had been done. Specifically, the self-controlled analyses were also performed using internal PRISM data and a quadratic polynomial to model the age-related risk; and the cohort analysis was also performed using the age curve from the Tate et al paper. A limitation of the secondary self-controlled analysis with an age-adjustment using the PRISM data is that the age-related function for intussusception risk was treated as known without error in the logistic regression analysis. Since it is based on a small sample size, the estimate of that function will have some error associated with it, and that error was not taken into account when calculating the confidence limits.

4. Sensitivity analyses

To ensure our findings were robust, we conducted a series of sensitivity analyses based on our primary, self-controlled design. First, we added the Brighton Level 2 cases and, separately, the Level 2A cases in our analysis. Second, we considered the cases for which charts were not obtained. One analysis in this category used in the offset term an adjustment factor, 85/72, representing the ratio of the percentage of potential cases in the Days 1-21 risk interval for which charts were obtained to the percentage of potential cases in the Days 22-42 control interval for which charts were obtained. In other, separate analyses, we included all the potential cases lacking charts, just those in the risk window, and just those in the control window, as though they were true cases, creating intermediate, worst-case, and best-case scenarios with regard to risk estimates if some or all cases with unobtainable charts were true cases. Third, we did analyses implementing elements of each of these simultaneously rather than separately, specifically, the alternative age adjustment (not itself a sensitivity analysis) *and* inclusion of Brighton Level 2 cases *and* inclusion of all cases whose charts were unobtainable. Finally, we considered the possibility of a differential propensity to diagnose intussusception in the risk interval compared to the control interval if a patient's rotavirus vaccination history were known by the medical provider, selecting RotaTeq Dose 1 with the 1-7 day risk window as the test case and imputing cases one by one in the control window.

We also conducted the following sensitivity analyses for the secondary, cohort design: a) included the Brighton Level 2 cases, b) included the potential cases for whom charts were not obtained, and c) included both the Brighton Level 2 cases *and* all the potential cases for whom charts were not obtained.

5. Temporal scan statistics

The temporal scan statistic is a self-controlled design we used to identify clusters of intussusception onsets within the 1-21 days after rotavirus vaccination, using data from the 42 days after vaccination. We evaluated all potential risk windows starting 1-14 days after vaccination and ending 1-21 days after vaccination, with the method adjusting for the multiple testing inherent in the 203 intervals considered. In order to adjust for age, we used the HCUP rates from Tate et al.[22] to randomize cases according to the age-dependent incidence curve. For example, for a child receiving the vaccine at age 100 days, the random case was assigned a day of age in the Days 101-142 interval in proportion to the incidence curve in that interval. Analyses were conducted using the free SaTScan software.[27]

6. Attributable risk

Since the risk of intussusception varies greatly by age in weeks, the attributable risk is likely to vary by the age of vaccination. We present the average attributable risk based on the observed age distribution of the vaccinated children. Attributable risk was calculated as the number of excess intussusception cases per 100,000 vaccinated children, according to the formula 100000*#CasesInRiskWindow*(1-1/RR)/(#VaccineDoses*C), where C is the proportion of potential cases for which we were able to review charts. By including C in the equation, we adjusted the AR for the missing charts. This method of calculating attributable risk does not make use of absolute background rates. Thus, considering that hospital discharge data were used for the RR age adjustment, the AR estimates need not be augmented to account for cases that might have been seen only in the ED setting. Such adjustment would have been necessary had we used background rates in calculating AR.[28]

For RotaTeq, the 95% confidence intervals were calculated using Krishnamoorthy and Lee's moments method for calculating the difference in the mean of two Poisson distributions.[29] For Rotarix, because of the lower case counts, Krishnamoorthy and Lee's Jeffreys-based hybrid method was used instead.[29]

III. RESULTS

A. VACCINE DOSES ADMINISTERED

The analyses included 1,277,556 doses of RotaTeq, of which 507,874 were first doses, and 103,098 doses of Rotarix, of which 53,638 were first doses.

B. VALIDATION OF ROTAVIRUS VACCINE EXPOSURE AND OF INTUSSUCEPTION

The results of chart review for confirmation of rotavirus vaccine exposure are shown in Figure 1. In all 53 cases where affirmative information about rotavirus vaccination was available in both claims and charts, there was no contradiction between these two sources regarding rotavirus vaccine brand, although in 17 (32%), the charts lacked specificity about brand. For these 17, claims data, which were always specific, were used to assign the brand of rotavirus vaccine.

Within the targeted age range of 5-36 weeks of age, 343 potential cases of intussusception were identified in the electronic data. Of these, 267 (78%) had medical record review and were classified at the following Brighton or modified Brighton levels of diagnostic certainty: Level 1: 124; Level 2: 20 (Level

2A: 10; Level 2B: 10); Level 3: 11; reported intussusception according to chart but with insufficient evidence to classify case: 2; ruled out: 110. The positive predictive value of the intussusception case-finding algorithm was thus 124/267 or 46%. Charts for the remaining 76 potential cases (22%) were unobtainable due to inability to locate the provider (38), provider refusal to participate (26), or there being no record of the patient at the provider (12). The distribution of Brighton Level 1 cases by analysis type and other characteristics is shown in Table 1.

Although the intussusception case-finding algorithm included three codes in either of two medical settings, 100% of the confirmed (Brighton Level 1) cases had the main intussusception code of 560.0, and 98% of the confirmed cases were hospitalized, thus an algorithm using only 560.0 and inpatient setting would have captured most of the cases that were ultimately confirmed.

C. STATISTICAL ANALYSIS RESULTS

1. Risk estimates

Table 2 shows the results of the RotaTeq analyses. For Dose 1, in the self-controlled analysis with the Tate age adjustment, the relative risk was elevated and statistically significant for both risk windows (RR, 7-day risk window=9.1, 95% CI: 2.2-39; RR, 21-day risk window=4.2, 95% CI: 1.1-16). In the cohort analysis (with a 1-21 day risk interval) with age adjustment based on the study population, there was also a statistically significant elevated RR after Dose 1 (RR=2.6, 95% CI: 1.2-5.8). Looking at the post hoc analyses, in the self-controlled analysis with the age adjustment from the study population, the relative risk was elevated and statistically significant for the 7-day risk window (RR=7.0, 95% CI: 1.7-29) but not for the 21-day risk window (RR=3.4, 95% CI: 0.9-13). The cohort analysis using the Tate age adjustment had an elevated and statistically significant RR of 2.9 (95% CI: 1.4-6.0). The results of the alternative age adjustments are shown graphically for RotaTeq Dose 1 in Figure 2. The attributable risks associated with these relative risks were similar to each other, ranging from 1.1 to 1.5 excess cases per 100,000 Dose 1 vaccinees (maximum bounds from all 95% CIs: 0.0-3.3).

For RotaTeq Doses 2 and 3, no statistically significant increase in risk was seen. For the all-doses-combined analyses with 7-day risk window, both RRs were elevated (RR with Tate adjustment=3.3, 95% CI: 1.5-7.4; RR with study population age adjustment=3.0, 95% CI: 1.4-6.8), which was not the case for any of the analyses of all-doses using the 21-day risk window.

The results for Rotarix are shown in Table 3. The power of the self-controlled analysis was low, given few cases. For Dose 1, in the self-controlled analyses with both risk intervals, there was just 1 case in the risk interval and 0 cases in the comparison interval. Results of the cohort analyses were not statistically significant; RR point estimates were around 3. Attributable risks for Dose 1 ranged from 1.6 to 2.4 excess cases per 100,000 Dose 1 vaccinees but, like their associated relative risks, were not statistically significant.

For Rotarix Dose 2, RR point estimates from the self-controlled analyses were 3.5-3.6 for the 7-day risk window and 1.7 for the 21-day risk window, regardless of which age adjustment was used, but none was statistically significant. The Dose 2 cohort analysis showed statistically significant increased risks (RR with study-population age adjustment=5.1, 95% CI: 1.6-16; RR with Tate adjustment=4.6, 95% CI: 1.5-15). AR point estimates for Dose 2 from the self-controlled analyses were in the range of 3.7-4.4 and were not statistically significant. The attributable risks for Dose 2 from the cohort analyses were higher

and statistically significant (AR with study population age adjustment=7.30 (95% CI: 0.77-22), AR with Tate age adjustment=7.13 (95% CI: 0.59-22), both per 100,000 Dose 2 vaccinees.

The Rotarix all-doses self-controlled analyses did not show statistically significant relative risks, although RRs for the 7-day risk window were elevated and bordered on statistical significance (RR with Tate adjustment=5.7, 95% CI: 0.9-34; RR with study population age adjustment=5.5, 95% CI: 0.9-33). The all-doses cohort analyses produced statistically significant relative risks of 3.8 (95% CI: 1.4-10) with the study population age adjustment and 3.7 (95% CI: 1.4-10) with the Tate age adjustment.

The Tate age adjustment produced higher relative risk point estimates for Dose 1 of both vaccines than the age adjustment based on the function drawn from the study population. This was not the case for the other doses.

2. Sensitivity analyses

The first set of sensitivity analyses involved adding cases of lesser diagnostic certainty to the Brighton Level 1 cases, results of which are shown in Table 4 for the self-controlled analyses. Adding Brighton Level 2 cases decreased the RotaTeq Dose 1 estimate for the 1-7 risk window from 9.1 to 4.7, although the latter remained statistically significant. The RR for RotaTeq Dose 1 with the 1-21 day risk window decreased from 4.2 to 2.7 and was no longer statistically significant. The RotaTeq all-doses risk estimate for the 1-7 day risk window went from 3.3 to 2.8 and remained statistically significant. The addition of the Level 2 cases provided 1 case in the control window of Rotarix Dose 1, yielding non-statistically significant RR point estimates of 5.7 and 1.6 for the 1-7 day and 1-21 day risk windows, respectively. Changes for the other vaccine-dose number combinations were generally slight and not in any consistent direction. Adding only the Level 2A cases (considered more likely to be intussusception than the Level 2B cases, based on radiological test results) decreased the RotaTeq Dose 1 estimates less than adding all the Level 2 cases, from 9.1 to 6.9 (both statistically significant) and from 4.2 to 3.2 (the latter no longer statistically significant) for the 1-7 day and 1-21 day risk windows, respectively. There were no Level 2A cases in the 1-42 days after Rotarix. When Brighton Level 2 cases were added to the cohort analysis, the estimates for RotaTeq Dose 1 and Rotarix all-doses remained statistically significant (Table 5).

The second set of sensitivity analyses concerned the cases for which no charts were obtained, automated claims data being used to determine ages at vaccination and at intussusception diagnosis. In the self-controlled RotaTeq analysis using the adjustment factor for missing charts, the risk estimates decreased, although the Dose 1 and all-doses risk estimates for the 1-7 day risk window remained statistically significant (Table 7). When, instead of using the adjustment factor, all potential cases lacking charts were included as if they were true cases, the risk estimates again generally decreased, although the Dose 1 estimates for the 1-7 and 1-21 day risk windows and all-doses risk estimate for the 1-7 day risk window remained statistically significant. Not surprisingly, when only the potential cases without charts occurring in risk windows were added, the risk estimates increased (Table 8). Notably, when cases with unobtainable charts were added only to the *control* window, the RR for the RotaTeq Dose 1 analysis with the 7-day risk window remained statistically significant (RR=4.7, 95% CI: 1.4-16). For Rotarix, the RR for the all-doses analysis with the 7-day risk window became statistically significant (RR=5.2; 95% CI: 1.2-23) when all potential cases with unobtainable charts were included in the analysis (Table 7). In the cohort sensitivity analysis, in which all potential cases with unobtainable charts were added as if they were true cases, the risk estimates for RotaTeq decreased and were not statistically

significant, while the Dose 1 estimate for Rotarix became statistically significant (RR=4.4, 95% CI: 1.4-14) and the all-dose estimate remained so (RR=3.5, 95% CI: 1.5-7.9) (Table 5).

The third set of sensitivity analyses involved implementing several assumptions simultaneously, namely, that the age function based on the study population was more appropriate to use for age adjustment and that the Brighton Level 2 cases as well as the cases with unobtainable charts were all true cases. In the self-controlled analysis, under this scenario, there were no statistically significant elevated risks seen for either vaccine, although the point estimate for RotaTeq Dose 1 was 2.6 and the estimate for the all-doses analysis was 1.8 and the lower bound of both the associated 95% confidence intervals close to 1 (Table 9). In the corresponding cohort analysis, RotaTeq was not associated with a statistically significant elevated risk, but Rotarix was, with RRs of 3.9 (95% CI: 1.2-12) for Dose 1 and 3.1 (95% CI: 1.4-7.0) for all doses combined (Table 5).

A final sensitivity analysis examined the possibility that clinicians knowing the rotavirus vaccination status of a patient with symptoms consistent with intussusception might be more likely to suspect, code, and/or test for intussusception if the case presented soon after vaccination than later. By imputing hypothetically missed cases in the control window for RotaTeq Dose 1 with the 7-day risk window (where there were 5 confirmed cases in the risk interval and 3 in the control interval), it was determined that 8 of 11, or more than 70%, of cases in the Days 22-42 post-vaccination control window would have to have been missed in order for such a differential tendency to diagnose intussusception in the week after vaccination compared to the control interval to have produced a statistically significant appearance of increased risk.

3. Temporal Scan Statistics

For RotaTeq Dose 1 and all-doses, the temporal scan statistic found a statistically significant cluster of intussusception cases 3-7 days after vaccination (Dose 1: 5 out of 11 cases, RR=9.7, p=0.008; all-doses: 10 out of 30 cases, RR=4.5, p=0.004). For Rotarix all-doses, there was a significant cluster on Day 4 day after vaccination (3 out of 6 cases, RR=48, p=0.0008).

IV. DISCUSSION

This study included almost 1.3 million total doses and 508,000 first doses of RotaTeq and more than 100,000 total doses and 50,000 first doses of Rotarix, making it the largest population-based study of the association between these vaccines and intussusception to date in the U.S. For RotaTeq Dose 1, with the 1-21 day post-vaccination risk window, we found a statistically significant elevated risk of intussusception of 4.2 times the baseline risk. This Dose 1 risk was higher when the shorter, 1-7 day risk window was used, with a risk estimate of 9.1. The attributable risk estimates associated with these relative risks were 1.54 (95% CI: 0.19-3.22) and 1.12 (95% CI: 0.33-2.70) per 100,000 first-dose vaccinees, respectively. These estimates, roughly one-tenth the estimated attributable risk of RotaShield, were highly robust to different analysis methods and age adjustments. Later doses of RotaTeq did not carry a statistically significant increased risk of intussusception. For Rotarix, statistical power was lower, given the order-of-magnitude lower dose counts. Nonetheless, the results point to an increased risk of intussusception from this vaccine as well, with a statistically significant relative risk of 5.1 for Dose 2 and 3.8 for all doses combined, using the cohort design, and corresponding ARs of 7.30 (95% CI: 0.77-22) and 7.13 (95% CI: 0.59-22) excess cases per 100,000 second-dose vaccinees. Although

these point estimates are higher than the ARs for RotaTeq, the confidence intervals overlap, and it is not possible based on our current analyses to make a statement regarding any difference in risk between these two vaccines.

RR estimates vary widely depending on the length of risk window used. For instance, if the excess risk were completely confined to the 1-7 day risk window, which seems plausible based on the temporal scan statistic results, then a RR of 9.1 for that week would be mathematically equivalent to a RR of 1+(9.1-1)/3=3.7 during a 1-21 day risk window. Hence, even though the RR of 9.1 for the 1-7 day risk window is much higher than the RR of 4.2 for the 1-21 day risk window, the latter actually yields a higher attributable risk, as it is associated with a few more cases attributed to vaccine exposure. Although a 1-42 day risk window was not used in our study, it is instructive to mathematically convert our risk estimate into one for this longer window to facilitate comparison with the RotaTeq phase 3 clinical trial: The 9.1 RR in the 1-7 day risk window is equivalent to a RR of 1+(9.1-1)/6=2.3 during a 1-42 day risk window, which is only slightly higher than the 1.6 any-dose point estimate from the RotaTeq phase 3 clinical trial and well within its confidence interval of 0.4-6.4.[2] Critically, a relative risk should always be interpreted keeping in mind both the underlying incidence rate and the number of days of excess risk.

RR risk estimates for the primary SCRI analysis also varied somewhat depending on the age adjustment method used. We had chosen to use hospital discharge data from the literature instead of our own unexposed study population because of the much greater precision of the incidence estimates based on 11 years' worth of U.S. hospital discharge data and the availability of incidence estimates beyond the age period for which we did chart review. We acknowledge that the hospital discharge incidence data were based on ICD-9 code 560.0 in hospital settings, whereas our case-finding algorithm included two other codes and both hospital and ED settings. Also, the hospital discharge cases were not validated through chart review, whereas our cases were. However, all our confirmed cases had received code 560.0, and 98% of them were hospitalized, likely making them similar to the cases captured by HCUP that were used in Tate et al. Also, only the shape of the incidence curve matters in the age adjustment, not the absolute incidence values themselves. The PRISM age adjustment has greater internal validity but suffers from the following disadvantages: a large amount of random fluctuation in the observed age-specific incidences; lack of information beyond the interval for which chart review was done (ages 5-36 weeks), which would lead to greater inaccuracy in predicted rates at the edges of our age range; and the fact that the true age function is more complex than could be represented by the quadratic function used but data were too sparse to model any higher-level terms. Our relative risk estimates for RotaTeq Dose 1 decreased when the age-dependent risk function from the study population was used instead of the more precise Tate et al. hospital discharge data. However, the RRs of the RotaTeq Dose 1 and all-doses analyses with the 1-7 day risk window remained statistically significant (Table 2). No consistent decrease in RR with the alternative age adjustment was seen for the other doses of RotaTeq or for Rotarix.

Risk estimates also generally decreased with the addition of Brighton Level 2 cases and with the addition of cases for which charts were not obtained; but estimates that were statistically significant in the primary analysis generally retained their significance, and in fact some of the Rotarix estimates became statistically significant with the addition of these cases lacking charts (Table 5 and Table 7). The scenario using the risk curve from the study population and incorporating both the Brighton Level 2 cases and the cases for which charts were not obtained eliminated the statistically significant elevated risks (Table 9) except in the case of Rotarix in the cohort analysis (Table 5). The attenuation of observed risk is not

surprising, as we would expect greater misclassification of the outcome to be introduced by the addition of these unconfirmed potential cases, tending to cause bias toward the null. Furthermore, it is not clear that the validity of our risk estimate increases through the addition of Level 2 cases where there is less diagnostic certainty.

A sensitivity analysis addressing the possibility that knowledge of recent rotavirus vaccination in a child presenting with symptoms consistent with intussusception might have influenced a clinician to suspect, code for, and/or test for this condition (including transient, self-resolving cases) differentially more in the week after vaccination compared to later found that more than 70% of cases in the control interval would have to have been overlooked in order for such a tendency to have produced a statistically significant increased risk. In light of this, it seems unlikely for such a phenomenon to have been a major contributor to the observed increase in risk.

Our confidence intervals are highly overlapping with those reported in other published pre- and post-licensure studies. For RotaTeq Dose 1, 1-7 day risk interval, the Australian study reported a 95% CI of 1.1-15[11] compared with our 2.2-39. While both the VAERS study[14] and the VSD study[16] reported results that were not statistically significant, the VSD confidence intervals are highly overlapping with ours, so the results are not inconsistent. Our RR estimates for RotaTeq Dose 1 with the 1-21 day risk interval—4.2 (95% CI: 1.1-16) from the self-controlled design and 2.6 (95% CI: 1.2-5.8) from the cohort design—are closer to the corresponding relative risk in the Australian study of 3.5 (95% CI: 1.3-7.6).[11] Assuming that there is no elevated risk 8 to 42 days after vaccination, the RotaTeq phase 3 clinical trial with an any-dose relative risk of 1.6 (0.4-6.4) in the 1-42 day window corresponds to a RR of 2.2 in a 1-21 day window and 4.6 in a 1-7 day window, with the upper 95% confidence limits at 12 and 33, respectively. Hence, compared to the pre-licensure trial, the larger sample size in our cohort design allows us both to observe a statistically significant excess risk of intussusception after RotaTeq vaccine and to lower the worst case estimate of what this excess risk could be.

Our finding of a statistically significant increased relative risk of 5.1 (95% CI: 1.6-16) for Rotarix Dose 2 from the cohort analysis (with 1-21 day risk window) was higher than the post-Dose 2 increased risk found in Mexico in the Patel et al. study, which reported statistically significant incidence ratios and odds ratios of between 2.0 and 2.3 for Days 8-14 and 15-21 after Dose 2.[12]

A strength of our study was its employment of two complementary designs. The self-controlled design was designated primary because of its ability to control for fixed confounders, its avoidance of exposure misclassification bias by using only vaccinated cases, and the existence of precise background rates in the literature that could be used for age adjustment. The cohort design was designated as secondary because of the potential for confounding and exposure misclassification bias. However, the cohort design had greater statistical power and narrower confidence intervals. Because there are less potential sources of bias, we have greater trust in the self-controlled design when it comes to determining if there actually is an excess risk of intussusception after vaccination. On the other hand, because of its greater statistical power, we have greater trust in the cohort method when it comes to estimating the magnitude of the RR, given its much narrower confidence intervals. For estimates of the AR, the estimates from the cohort design are only slightly more precise than those from the self-controlled design.

There were a number of limitations to this study.

a. Age adjustment: Neither age adjustment was ideal, the Tate adjustment because it derived from external data, the PRISM-population adjustment because it was based on relatively few cases and the estimates were not robust. The Tate curve has a steeper slope than the study population curve in the weeks after Dose 1 is typically given. If the study-population curve was closer to the truth for this population, the Tate adjustment could have biased away from the null. If, on the other hand, the Tate curve was closer to the truth for this population, the study-population adjustment could have biased toward the null. In any case, for RotaTeq Dose 1, the vaccine and dose where the differences were greatest, the RRs using the alternative age adjustments are not dissimilar (9.1 and 7.0 for the self-controlled analyses with 7-day risk window, 4.2 and 3.4 for the self-controlled analyses with 21-day risk window, and 2.6 and 2.9 for the cohort analyses), and the AR point estimates are in the range of 1.1 to 1.5 per 100,000 first-dose vaccinees, with similar confidence intervals. Reiterating a caveat from above, a limitation of the self-controlled analysis using the PRISM data for age adjustment is that the age-related function for intussusception risk was treated as known without error in the logistic regression analysis. The estimate of that function had some error associated with it since it was based on a small sample size, and that error was not taken into account when calculating the confidence limits.

b. Missing charts: We did not obtain medical records to validate the diagnosis for 22% of the potential cases initially ascertained. However, our finding of a statistically significant increased risk in the 7 days after RotaTeq Dose 1 was reasonably robust to different scenarios of some or all of the cases with unobtainable charts being confirmed, including the most extreme scenario where we assumed that only the "unobtainable" cases in the control window were confirmed.

c. Statistical power: The missing charts, together with the positive predictive value of the case ascertainment algorithm of 46%, reduced the study's power and precision, affecting especially the self-controlled effect estimates and confidence intervals. Lower positive predictive value might be expected of claims data compared to electronic medical record data. However, with additional time and doses accrued and/or additional Data Partners participating, the Mini-Sentinel infrastructure could allow more powerful evaluations of the safety of rotavirus vaccines in the future.

V. CONCLUSION

In this large study using two complementary designs, we found evidence of an association between RotaTeq and intussusception. The risk was highest in the 3-7 days after the first dose. Although the power for the Rotarix analyses was lower, there was some evidence of an increased risk of intussusception associated with Rotarix as well, including after the second dose. The risk associated with RotaTeq Dose 1 was estimated at 1.12 (95% CI: 0.33-2.70) excess cases per 100,000 vaccinees, considering only the 7 days after vaccination, and at 1.54 (95% CI: 0.19-3.22) excess cases per 100,000 vaccinees, considering the 21 days after vaccination. The RotaTeq attributable risk estimates and their confidence intervals were similar for the various analysis and age adjustment methods used.

VI. ACKNOWLEDGEMENTS

Mini-Sentinel/PRISM is funded by the Food and Drug Administration through Department of Health and Human Services Contract Number HHSF223200910006I, Task Order Number HHSF22301003T.

We thank Jacqueline Tate for supplying her data for the main age adjustment, Ed Belongia for early guidance and adjudication, Michael Silverman for adjudication, and Ruihua Yin for statistical analysis. In addition, we gratefully acknowledge the contributions of the following people and organizations: Mini-Sentinel Operations Center: Carolyn Balsbaugh, David Cole, Claudia Coronel-Moreno, Lingling Li, Linda Pointon, Megan Reidy, Robert Rosofsky, and Diana Santiago; Aetna: Carolyn Jevit, Carolyn Neff, and Yihai Liu; HealthCore: Chunfu Liu, Tosmai Puenpatom, Marcus Wilson, and Amanda Rodriguez; Humana: Vinit Nair, Tom Stacey, and Qianli Ma.

VII. REFERENCES

1. Murphy TV, Gargiullo PM, Massoudi MS, et al. Intussusception among infants given an oral rotavirus vaccine. *The New England journal of medicine.* Feb 22 2001;344(8):564-572.
2. RotaTeq (Rotavirus Vaccine, Live Oral, Pentavalent) [package insert]. Merck & Co.; 2012. Available at http://www.merck.com/product/usa/pi_circulars/r/rotateq/rotateq_pi.pdf, Accessed March 21, 2013.
3. Rotarix (Rotavirus Vaccine, Live Oral) [package insert]. GlaxoSmithKline; 2012. Available at http://us.gsk.com/products/assets/us_rotarix.pdf, Accessed March 21, 2013.
4. Patel MM, Steele D, Gentsch JR, Wecker J, Glass RI, Parashar UD. Real-world impact of rotavirus vaccination. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S1-5.
5. Tate JE, Cortese MM, Payne DC, et al. Uptake, impact, and effectiveness of rotavirus vaccination in the United States: review of the first 3 years of postlicensure data. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S56-60.
6. Tate JE, Mutuc JD, Panozzo CA, et al. Sustained decline in rotavirus detections in the United States following the introduction of rotavirus vaccine in 2006. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S30-34.
7. Yen C, Armero Guardado JA, Alberto P, et al. Decline in rotavirus hospitalizations and health care visits for childhood diarrhea following rotavirus vaccination in El Salvador. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S6-S10.
8. Quintanar-Solares M, Yen C, Richardson V, Esparza-Aguilar M, Parashar UD, Patel MM. Impact of rotavirus vaccination on diarrhea-related hospitalizations among children < 5 years of age in Mexico. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S11-15.
9. Molto Y, Cortes JE, De Oliveira LH, et al. Reduction of diarrhea-associated hospitalizations among children aged < 5 Years in Panama following the introduction of rotavirus vaccine. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S16-20.
10. Buttery JP, Lambert SB, Grimwood K, et al. Reduction in rotavirus-associated acute gastroenteritis following introduction of rotavirus vaccine into Australia's National Childhood vaccine schedule. *The Pediatric infectious disease journal.* Jan 2011;30(1 Suppl):S25-29.

11. Buttery JP, Danchin MH, Lee KJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. *Vaccine.* Apr 5 2011;29(16):3061-3066.

12. Patel MM, Lopez-Collada VR, Bulhoes MM, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. *The New England journal of medicine.* Jun 16 2011;364(24):2283-2292.

13. Velazquez FR, Colindres RE, Grajales C, et al. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. *The Pediatric infectious disease journal.* Jul 2012;31(7):736-744.

14. Haber P, Patel M, Izurieta HS, et al. Postlicensure monitoring of intussusception after RotaTeq vaccination in the United States, February 1, 2006, to September 25, 2007. *Pediatrics.* Jun 2008;121(6):1206-1212.

15. Belongia EA, Irving SA, Shui IM, et al. Real-time surveillance to assess risk of intussusception and other adverse events after pentavalent, bovine-derived rotavirus vaccine. *The Pediatric infectious disease journal.* Jan 2010;29(1):1-5.

16. Shui IM, Baggs J, Patel M, et al. Risk of intussusception following administration of a pentavalent rotavirus vaccine in US infants. *JAMA : the journal of the American Medical Association.* Feb 8 2012;307(6):598-604.

17. Loughlin J, Mast TC, Doherty MC, Wang FT, Wong J, Seeger JD. Postmarketing evaluation of the short-term safety of the pentavalent rotavirus vaccine. *The Pediatric infectious disease journal.* Mar 2012;31(3):292-296.

18. Nguyen M, Ball R, Midthun K, Lieu TA. The Food and Drug Administration's Post-Licensure Rapid Immunization Safety Monitoring program: strengthening the federal vaccine safety enterprise. *Pharmacoepidemiology and drug safety.* Jan 2012;21 Suppl 1:291-297.

19. Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiology and drug safety.* Jan 2012;21 Suppl 1:1-8.

20. Maro JC, Platt R, Holmes JH, et al. Design of a national distributed health data network. *Annals of internal medicine.* Sep 1 2009;151(5):341-344.

21. Curtis LH, Weiner MG, Boudreau DM, et al. Design considerations, architecture, and use of the Mini-Sentinel distributed data system. *Pharmacoepidemiology and drug safety.* Jan 2012;21 Suppl 1:23-31.

22. Tate JE, Simonsen L, Viboud C, et al. Trends in intussusception hospitalizations among US infants, 1993-2004: implications for monitoring the safety of the new rotavirus vaccination program. *Pediatrics.* May 2008;121(5):e1125-1132.

23. Kramarz P, DeStefano F, Gargiullo PM, et al. Does influenza vaccination exacerbate asthma? Analysis of a large cohort of children with asthma. Vaccine Safety Datalink Team. *Archives of family medicine.* Jul 2000;9(7):617-623.

24. Klein NP, Hansen J, Lewis E, et al. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. *The Pediatric infectious disease journal.* Jul 2010;29(7):613-617.

25. Fireman B, Lee J, Lewis N, Bembom O, van der Laan M, Baxter R. Influenza vaccination and mortality: differentiating vaccine effects from bias. *American journal of epidemiology.* Sep 1 2009;170(5):650-656.

26. Bines JE, Kohl KS, Forster J, et al. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. *Vaccine.* Jan 26 2004;22(5-6):569-574.

27. SaTScan. SaTScan v7.0: software for the spatial and space-time scan statistics. Available at: www.satscan.org. . Accessed October 19, 2012.

28. Cortese MM, Staat MA, Weinberg GA, et al. Underestimates of intussusception rates among US infants based on inpatient discharge data: implications for monitoring the safety of rotavirus vaccines. *The Journal of infectious diseases.* Nov 1 2009;200 Suppl 1:S264-270.

29. Krishnamoorthy K, Lee M. New approximate confidence intervals for the difference between two Poisson means and comparison. *Journal of Statistical Computation and Simulation.* 2012:1-12.

VIII. TABLES AND FIGURES

Table 1. Distribution of Brighton Level 1 (BL1) cases by analysis type and other characteristics

All subsets (mutually exclusive)	**Total**
In RV5 SCRI & only RV5 cohort	17
In RV5 SCRI & neither cohort (ASO)	1
In RV5 SCRI & both cohorts	12
In RV1 SCRI & only RV1 cohort	4
In RV1 SCRI & both cohorts	2
In RV5 cohort, not RV1 cohort, not SCRI, vaccinated	1
In both cohorts, vaccinated at some point prior but not in SCRI	38
In both cohorts, not vaccinated per either source so not in SCRI	45
In neither SCRI nor cohort (ASO not in 1-42 d after any RV)	4
Total	124
Subsets in RotaTeq analyses	
In RV5 SCRI & only RV5 cohort	17
In RV5 SCRI & neither cohort (ASO)	1
In RV5 SCRI & both cohorts	12
In RV1 SCRI & both cohorts	2
In RV5 cohort, not RV1 cohort, not SCRI, vaccinated	1
In both cohorts, vaccinated at some point prior but not in SCRI	38
In both cohorts, not vaccinated per either source so not in SCRI	45
Total	116
Subsets in Rotarix analyses	
In RV5 SCRI & both cohorts	12
In RV1 SCRI & only RV1 cohort	4
In RV1 SCRI & both cohorts	2
In both cohorts, vaccinated at some point prior but not in SCRI	38
In both cohorts, not vaccinated per either source so not in SCRI	45
Total	101

Table 2. Case counts and risk estimates for Brighton Level 1 confirmed intussusception after RotaTeq, by dose, study design, and age adjustment. Attributable risk estimates incorporate a correction factor for cases lacking charts (which make up 22% of the total potential cases ascertained).

Dose #	Pre-specified vs. post hoc	Design	Age adjustment	Vaccine	Days in risk window	Cases in risk window	Cases in control window[a]	RR	95% CI	AR per 100k doses	95% CI lower bound	95% CI upper bound	Doses per case	95% CI lower bound	95% CI upper bound
1	Pre-specified	SCRI	Tate	RotaTeq	1-7	5	3	**9.1**	**2.2, 39**	**1.12**	**0.33**	**2.70**	**89,000**	**307,000**	**37,000**
		SCRI	Tate	RotaTeq	1-21	8	3	**4.2**	**1.1, 16**	**1.54**	**0.19**	**3.22**	**65,000**	**519,000**	**31,000**
		Cohort	PRISM	RotaTeq	1-21[b]	8	97	**2.6**	**1.2, 5.8**	**1.24**	**0.23**	**3.20**	**80,000**	**434,000**	**31,000**
	Post hoc	SCRI	PRISM	RotaTeq	1-7	5	3	**7.0**	**1.7, 29**	**1.08**	**0.27**	**2.63**	**92,000**	**376,000**	**38,000**
		SCRI	PRISM	RotaTeq	1-21	8	3	3.4	0.9, 13	1.43	-0.01	3.09	70,000	..	32,000
		Cohort	Tate	RotaTeq	1-21[b]	8	97	**2.9**	**1.4, 6.0**	**1.33**	**0.32**	**3.28**	**75,000**	**316,000**	**30,000**
2	Pre-specified	SCRI	Tate	RotaTeq	1-7	3	6	1.8	0.4, 7.2	0.39	-0.34	1.93	256,000	..	52,000
		SCRI	Tate	RotaTeq	1-21	5	6	1.0	0.3, 3.1	-0.07	-1.78	1.77	..	..	57,000
		Cohort	PRISM	RotaTeq	1-21[b]	5	97	0.9	0.4, 2.2	-0.19	-1.09	1.76	..	..	57,000
	Post hoc	SCRI	PRISM	RotaTeq	1-7	3	6	1.8	0.4, 7.2	0.39	-0.35	1.93	258,000	..	52,000
		SCRI	PRISM	RotaTeq	1-21	5	6	1.0	0.3, 3.1	-0.08	-1.78	1.77	..	..	57,000
		Cohort	Tate	RotaTeq	1-21[b]	5	97	0.8	0.3, 2.0	-0.35	-1.25	1.61	..	..	62,000
3	Pre-specified	SCRI	Tate	RotaTeq	1-7	3	4	2.2	0.5, 9.7	0.63	-0.39	2.62	159,000	..	38,000
		SCRI	Tate	RotaTeq	1-21	4	4	1.0	0.2, 3.9	-0.05	-2.26	2.12	..	..	47,000
		Cohort	PRISM	RotaTeq	1-21[b]	5[c]	97	0.9	0.4, 2.2	-0.29	-1.49	2.31	..	..	43,000
	Post hoc	SCRI	PRISM	RotaTeq	1-7	3	4	2.3	0.5, 10	0.66	-0.34	2.66	152,000	-.	38,000
		SCRI	PRISM	RotaTeq	1-21	4	4	1.0	0.2, 4.0	0.01	-2.14	2.17	10,402,000	..	46,000
		Cohort	Tate	RotaTeq	1-21[b]	5[c]	97	0.9	0.4, 2.2	-0.21	-1.40	2.39	..	..	42,000
All[d]	Pre-specified	SCRI	Tate	RotaTeq	1-7	11	13	**3.3**	**1.5, 7.4**	**0.77**	**0.20**	**1.59**	**131,000**	**497,000**	**63,000**
		SCRI	Tate	RotaTeq	1-21	17	13	1.6	0.8, 3.3	0.65	-0.35	1.66	154,000	..	60,000
		Cohort	PRISM	RotaTeq	1-21[b]	18[c]	97	1.3	0.8, 2.1	0.37	-0.37	1.43	272,000	..	70,000
	Post hoc	SCRI	PRISM	RotaTeq	1-7	11	13	**3.0**	**1.4, 6.8**	**0.74**	**0.19**	**1.58**	**135,000**	**540,000**	**63,000**
		SCRI	PRISM	RotaTeq	1-21	17	13	1.5	0.7, 3.1	0.58	-0.42	1.62	174,000	..	62,000
		Cohort	Tate	RotaTeq	1-21[b]	18[c]	97	1.3	0.8, 2.1	0.37	-0.37	1.43	273,000	..	70,000

[a] Control window for self-controlled design: Days 22-42 after RotaTeq vaccination; control period for cohort design: not 0-21 d after any rotavirus vaccination = 194,520,053 person-days.
[b] Numbers of exposed person-days: Dose 1—10,931,848; Dose 2—9,263,327; Dose 3—6,889,428; all doses—27,094,157.
[c] One of these cases was excluded from self-controlled analysis because vaccination age plus the required 42-day follow-up exceeded the cut-off age for chart review.
[d] Relative risk estimates for all-doses analyses represent a blend of the risks of the component doses. Attributable risk estimates for all-dose analyses are per 100,000 *doses*, so the total AR for 100,000 fully vaccinated *infants* is larger.

Table 3. Case counts and risk estimates for Brighton Level 1 confirmed intussusception after Rotarix, by dose, study design, and age adjustment. Attributable risk estimates incorporate a correction factor for cases lacking charts (which make up 22% of the total potential cases ascertained).

Dose #	Pre-specified vs. post hoc	Design	Age adjustment	Vaccine	Days in risk window	Cases in risk window	Cases in control window[a]	RR	95% CI	AR per 100k doses	95% CI lower bound	95% CI upper bound	Doses per case	95% CI lower bound	95% CI upper bound
1	Pre-specified	SCRI	Tate	Rotarix	1-7	1	0	infinity		2.39			42,000		
		SCRI	Tate	Rotarix	1-21	1	0	infinity		2.39			42,000		
		Cohort	PRISM	Rotarix	1-21[b]	1	97	2.9	0.4, 22	1.58	-0.56	10.36	63,000	..	10,000
	Post hoc	SCRI	PRISM	Rotarix	1-7	1	0	∞		2.39			42,000		
		SCRI	PRISM	Rotarix	1-21	1	0	∞		2.39			42,000		
		Cohort	Tate	Rotarix	1-21[b]	1	97	3.2	0.4, 23	1.64	-0.50	10.42	61,000	..	6,000
2	Pre-specified	SCRI	Tate	Rotarix	1-7	2	2	3.5	0.5, 25	4.34	-1.79	17.78	23,000	..	6,000
		SCRI	Tate	Rotarix	1-21	3	2	1.7	0.3, 10	3.68	-9.96	19.43	27,000	..	5,000
		Cohort	PRISM	Rotarix	1-21[b]	3	**97**	**5.1**	**1.6, 16**	**7.30**	**0.77**	**22.47**	**14,000**	**131,000**	**4,000**
	Post hoc	SCRI	PRISM	Rotarix	1-7	2	2	3.6	0.5, 25	4.36	-1.74	17.80	23,000	..	6,000
		SCRI	PRISM	Rotarix	1-21	3	2	1.7	0.3, 10	3.73	-9.77	19.48	27,000	..	5,000
		Cohort	Tate	Rotarix	1-21[b]	3	**97**	**4.6**	**1.5, 15**	**7.13**	**0.59**	**22.30**	**14,000**	**170.000**	**4,000**
All[c]	Pre-specified	SCRI	Tate	Rotarix	1-7	3	2	5.7	0.9, 34	3.07	0.01	9.31	33,000	13,810,000	11,000
		SCRI	Tate	Rotarix	1-21	4	2	2.3	0.4, 13	2.84	-2.94	9.89	35,000	..	10,000
		Cohort	PRISM	Rotarix	1-21[b]	4	**97**	**3.8**	**1.4, 10**	**3.65**	**0.35**	**10.51**	**27,000**	**288,000**	**10,000**
	Post hoc	SCRI	PRISM	Rotarix	1-7	3	2	5.5	0.9, 33	3.05	-0.02	9.30	33,000	..	11,000
		SCRI	PRISM	Rotarix	1-21	4	2	2.3	0.4, 13	2.82	-2.97	9.88	35,000	..	10,000
		Cohort	Tate	Rotarix	1-21[b]	4	**97**	**3.7**	**1.4, 10**	**3.63**	**0.32**	**10.49**	**28,000**	**313,000**	**10,000**

[a] Control window for self-controlled design: Days 22-42 after Rotarix vaccination; control period for cohort design: not 0-21 d after any rotavirus vaccination = 194,520,053 person-days.

[b] Numbers of exposed person-days: Dose 1—1,178,772; Dose 2—917,754; all doses—2,242,833.

[c] Relative risk estimates for all-doses analyses represent a blend of the risks of the component doses. Attributable risk estimates for all-dose analyses are per 100,000 *doses*, so the total AR for 100,000 fully vaccinated *infants* is larger.

Table 4. Self-controlled sensitivity analyses with Tate et al. age adjustment and sets of cases of differing levels of diagnostic certainty

	Brighton Level 1 (BL1) cases				BL1 + Level 2A cases			BL1 + BL2 cases		
Dose	**Risk win-dow (days)**	**IS in RW**	**IS in CW**	**RR (95% CI)**	**IS in RW**	**IS in CW**	**RR (95% CI)**	**IS in RW**	**IS in CW**	**RR (95% CI)**
RotaTeq										
1	1-7	5	3	**9.13 (2.16, 38.6)**	5	4	**6.92 (1.84, 26.0)**	5	6	**4.68 (1.42, 15.4)**
2	1-7	3	6	1.81 (0.45, 7.24)	4	7	2.06 (0.60, 7.05)	4	7	2.06 (0.60, 7.05)
3	1-7	3	4	2.17 (0.49, 9.70)	3	4	2.17 (0.49, 9.70)	3	4	2.17 (0.49, 9.70)
All	1-7	11	13	**3.27 (1.45, 7.36)**	12	15	**3.12 (1.45, 6.72)**	12	17	**2.83 (1.34, 5.98)**
1	1-21	8	3	**4.24 (1.12, 16.0)**	8	4	3.18 (0.96, 10.6)	10	6	2.69 (0.97, 7.41)
2	1-21	5	6	0.95 (0.29, 3.12)	7	7	1.13 (0.40-3.22)	7	7	1.13 (0.40, 3.22)
3	1-21	4	4	0.97 (0.24, 3.88)	4	4	0.97 (0.24, 3.88)	6	4	1.45 (0.41, 5.15)
All	1-21	17	13	1.61 (0.78-3.34)	19	15	1.56 (0.79-3.08)	23	17	1.70 (0.90, 3.20)
Rotarix (no Level 2A cases in 1-42 d after Rotarix)										
1	1-7	1	0	∞	1	0	∞	1	1	5.69 (0.35, 91.4)
2	1-7	2	2	3.52 (0.50, 25.1)	2	2	3.52 (0.50, 25.1)	2	2	3.52 (0.50, 25.1)
All	1-7	3	2	5.68 (0.94, 34.2)	3	2	5.68 (0.94, 34.2)	3	3	4.13 (0.82, 20.7)
1	1-21	1	0	∞	1	0	∞	1	1	1.56 (0.10, 25.0)
2	1-21	3	2	1.68 (0.28, 10.1)	3	2	1.68 (0.28, 10.1)	3	2	1.68 (0.28, 10.1)
All	1-21	4	2	2.34 (0.43, 12.8)	4	2	2.34 (0.43, 12.8)	4	3	1.64 (0.37, 7.38)

Table 5. Cohort sensitivity analyses with Brighton Level 2 cases added, potential cases lacking charts added, and both Brighton Level 2 cases and potential cases lacking charts added; age adjustment used polynomial risk function from study population.

Dose	Risk window (days)	RR (95% CI) for primary analysis: BL1 cases	RR (95% CI), BL1 + BL2 cases	RR (95% CI), BL1 cases + potential cases lacking charts	RR (95% CI), BL1 + BL2 cases + potential cases lacking charts
RotaTeq					
1	1-21	**2.61 (1.18, 5.76)**	**2.25 (1.03, 4.92)**	1.60 (0.82, 3.15)	1.69 (0.91-3.14)
All	1-21	1.26 (0.75, 2.10)	1.18 (0.72, 1.94)	1.03 (0.66, 1.60)	1.18 (0.79-1.76)
Rotarix					
1	1-21	2.95 (0.40, 21.8)	2.55 (0.35, 18.7)	**4.37 (1.37, 14.0)**	**3.87 (1.21-12.4)**
All	1-21	**3.77 (1.37, 10.4)**	**3.30 (1.20, 9.04)**	**3.45 (1.51, 7.87)**	**3.09 (1.36-7.03)**

Table 6. Case and person-day counts in cohort sensitivity analyses; exposed time corresponds to 1-21 days after rotavirus vaccination.

	Person-days for all sets of cases analyzed		BL1 cases		BL1 + BL2 cases		BL1 cases + potential cases lacking charts		BL1 + BL2 cases + potential cases lacking charts	
Dose	Exposed person-days	Unexposed person-days	IS in exposed	IS in unexposed	IS in exposed	IS in unexposed	IS in exposed	IS in unexposed	IS in exposed	IS in unexposed
RotaTeq										
1	10,931,848	194,520,053	8	97	10	111	10	156	12	170
All	27,094,157	194,520,053	18	97	24	111	23	156	29	170
Rotarix										
1	1,178,772	194,520,053	1	97	1	111	3	156	3	170
All	2,242,833	194,520,053	4	97	4	111	6	156	6	170

Table 7. Self-controlled sensitivity analyses with Tate et al. age adjustment and different treatments of potential cases with unobtainable charts

		BL1 cases only				BL1 cases + all potential cases lacking charts		
Dose	**Risk window (days)**	**IS in RW**	**IS in CW**	**Original RR (95% CI), no adjustment for potential cases without charts**	**RR (95% CI), adjustment for potential cases without charts in offset term**	**IS in RW**	**IS in CW**	**RR (95% CI)**
RotaTeq								
1	1-7	5	3	**9.13 (2.16, 38.6)**	**7.74 (1.83, 32.7**)	6	6	**5.72 (1.83, 17.9)**
2	1-7	3	6	1.81 (0.45, 7.24)	1.53 (0.38, 6.13)	3	11	0.99 (0.28, 3.56)
3	1-7	3	4	2.17 (0.49, 9.70)	1.84 (0.41, 8.21)	5	6	2.40 (0.73, 7.88)
All	1-7	11	13	**3.27 (1.45, 7.36)**	**2.77 (1.23, 6.23)**	14	23	**2.36 (1.21, 4.63)**
1	1-21	8	3	**4.24 (1.12, 16.0)**	3.59 (0.95, 13.6)	11	6	**2.90 (1.07, 7.86)**
2	1-21	5	6	0.95 (0.29, 3.12)	0.81 (0.25, 2.64)	6	11	0.63 (0.23, 1.70)
3	1-21	4	4	0.97 (0.24, 3.88)	0.82 (0.21, 3.29)	6	6	0.97 (0.31, 3.00)
All	1-21	17	13	1.61 (0.78, 3.34)	1.37 (0.66, 2.83)	23	23	1.24 (0.69, 2.21)
Rotarix								
1	1-7	1	0	∞	∞	2	0	∞
2	1-7	2	2	3.52 (0.50, 25.1)	2.99 (0.42, 21.2)	2	3	2.49 (0.41, 15.0)
All	1-7	3	2	5.68 (0.94, 34.2)	4.81 (0.80, 29.0)	4	3	**5.22 (1.16, 23.4)**
1	1-21	1	0	∞	∞	3	0	∞
2	1-21	3	2	1.68 (0.28, 10.1)	1.42 (0.24, 8.53)	3	3	1.16 (0.23, 5.76)
All	1-21	4	2	2.34 (0.43, 12.8)	1.98 (0.36, 10.8)	6	3	2.47 (0.62, 9.91)

Table 8. Self-controlled sensitivity analyses with Tate et al. age adjustment and including different sets of potential cases with unobtainable charts

		BL1 cases + only potential cases lacking charts in risk window			BL1 cases + only potential cases lacking charts in control window		
Dose	**Risk window (days)**	**IS in RW**	**IS in CW**	**RR (95% CI)**	**IS in RW**	**IS in CW**	**RR (95% CI)**
RotaTeq							
1	1-7	6	3	**11.1 (2.76, 44.8)**	5	6	**4.73 (1.43, 15.6)**
2	1-7	3	6	1.81 (0.45, 7.24)	3	11	0.99 (0.28, 3.56)
3	1-7	5	4	3.61 (0.97, 13.4)	3	6	1.44 (0.36, 5.77)
All	1-7	14	13	**4.16 (1.94, 8.92)**	11	23	1.86 (0.90, 3.84)
1	1-21	11	3	**5.73 (1.60, 20.6)**	8	6	2.14 (0.74, 6.19)
2	1-21	6	6	1.15 (0.37, 3.57)	5	11	0.52 (0.18, 1.50)
3	1-21	6	4	1.45 (0.41, 5.15)	4	6	0.65 (0.18, 2.29)
All	1-21	23	13	**2.19 (1.11, 4.35)**	17	23	0.91 (0.48, 1.71)
Rotarix							
1	1-7	2	0	∞	1	0	∞
2	1-7	2	2	3.52 (0.50, 25.1)	2	3	2.49 (0.41, 15.0)
All	1-7	4	2	**7.58 (1.38, 41.5)**	3	3	3.93 (0.79, 19.6)
1	1-21	3	0	∞	1	0	∞
2	1-21	3	2	1.68 (0.28, 10.1)	3	3	1.16 (0.23, 5.76)
All	1-21	6	2	3.66 (0.74, 18.2)	4	3	1.59 (0.36, 7.14)

Table 9. Self-controlled sensitivity analyses with multiple assumptions implemented simultaneously: age adjustment using polynomial risk function from study population,* BL1 + BL2 + potential cases lacking charts included

		BL1, adjustment with Tate et al. risk curve			**BL1 + BL2 + potential cases without charts, adjustment with study population risk function***		
		IS in RW	**IS in CW**	**Original RR (95% CI)**	**IS in RW**	**IS in CW**	**RR (95% CI)**
RotaTeq							
1	1-7	5	3	**9.13 (2.16, 38.6)**	6	9	2.59 (0.92-7.29)
2	1-7	3	6	1.81 (0.45, 7.24)	4	12	1.08 (0.35-3.36)
3	1-7	3	4	2.17 (0.49, 9.70)	5	6	2.28 (0.70-7.48)
All	1-7	11	13	**3.27 (1.45, 7.36)**	15	27	1.84 (0.97-3.46)
1	1-21	8	3	**4.24 (1.12, 16.0)**	13	9	1.74 (0.75-4.08)
2	1-21	5	6	0.95 (0.29, 3.12)	8	12	0.70 (0.29-1.72)
3	1-21	4	4	0.97 (0.24, 3.88)	8	6	1.24 (0.43-3.57)
All	1-21	17	13	1.61 (0.78-3.34)	29	27	1.16 (0.68-1.96)
Rotarix							
1	1-7	1	0	∞	2	1	7.40 (0.67-81.8)
2	1-7	2	2	3.52 (0.50, 25.1)	2	3	2.21 (0.37-13.2)
All	1-7	3	2	5.68 (0.94, 34.2)	4	4	3.45 (0.86-13.8)
1	1-21	1	0	∞	3	1	3.53 (0.37-33.9)
2	1-21	3	2	1.68 (0.28, 10.1)	3	3	1.07 (0.22-5.30)
All	1-21	4	2	2.34 (0.43, 12.8)	6	4	1.67 (0.47-5.91)

* Based on same categories of cases in Poisson regression model with polynomial (quadratic) risk-by-age function, namely, BL1 + BL2 + potential cases without charts

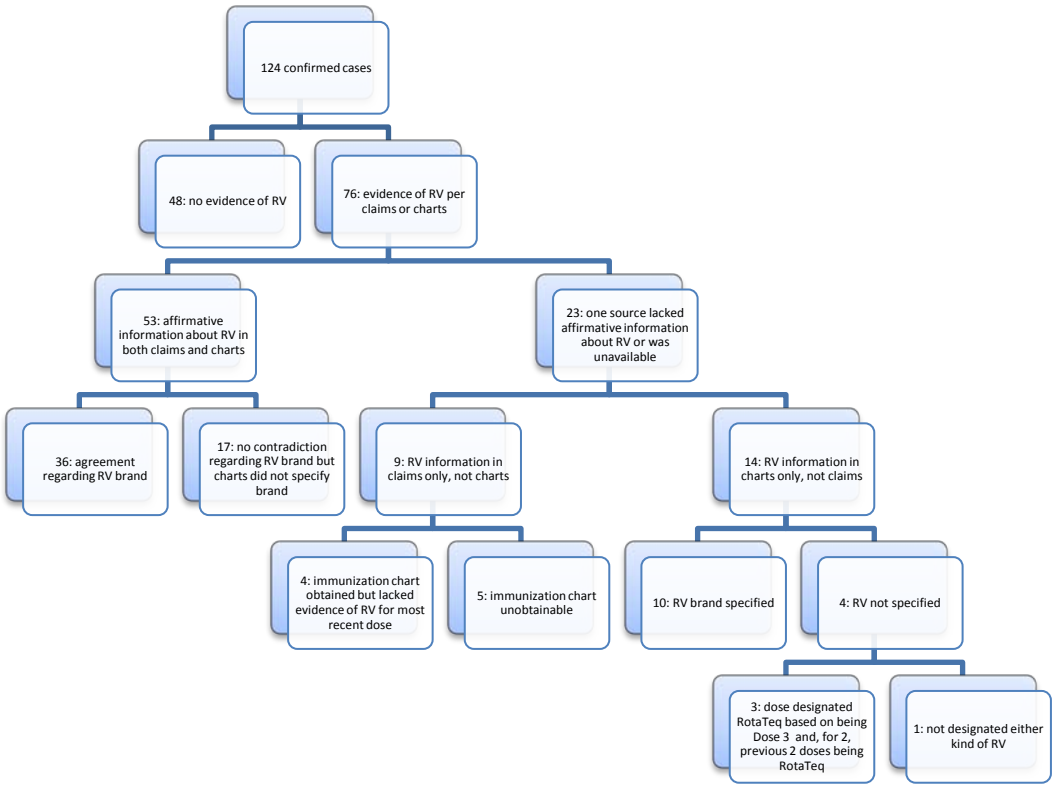

Figure 1. Overall availability and degree of concordance of rotavirus vaccination information in claims and medical records, for confirmed (Brighton Level 1) intussusception cases. No immunization registry data were used. Data pertain to the most recent dose prior to intussusception as determined from all the available data, whether claims and/or charts. In the figure, "RV" refers to rotavirus vaccination.

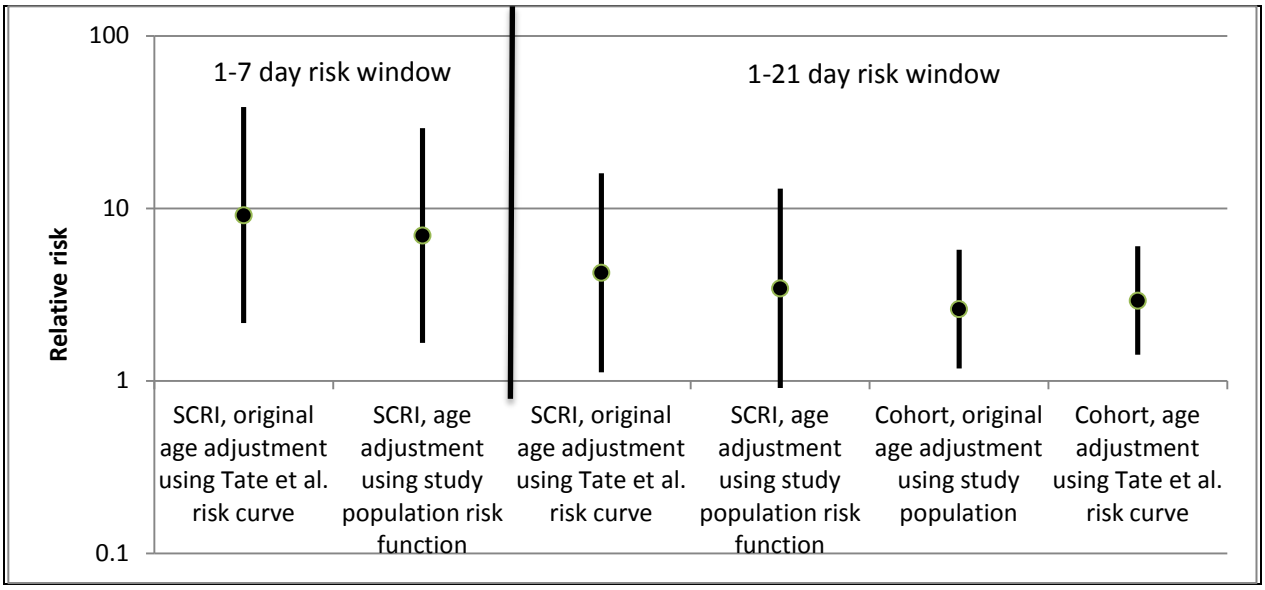

Figure 2. Results of analyses for RotaTeq Dose 1 with variations in age adjustment. For RotaTeq Dose 1, age adjustment using the polynomial risk function obtained from the study population produces somewhat lower relative risks than age adjustment using hospital discharge data from Tate et al.[22] The point estimates and confidence intervals are given in Table 2.