MINI-SENTINEL CBER SURVEILLANCE PROTOCOL

MONITORING FOR INTUSSUSCEPTION AFTER TWO ROTAVIRUS VACCINES BY THE PRISM PROGRAM

Version 2.0

Prepared by: *Collaborators*: Katherine Yih, PhD, MPH,[1] Tracy Lieu, MD, MPH,[1] Martin Kulldorff, PhD,[1] Sharon Greene, PhD, MPH,[1] Edward Belongia, MD,[2] Michael Nguyen, MD,[3] and Thomas Buttolph, MD[3]; *Data Partners*: Greg Daniel, PhD, MS, MPH,[4] and Vinit Nair, BS Pharm, MS, RPh.[5]

Author Affiliations: 1. Department of Population Medicine, Harvard Medical School / Harvard Pilgrim Health Care Institute, Boston, MA. 2. Marshfield Clinic, Marshfield, WI. 3. FDA / CBER, Rockville, MD. 4. HealthCore Inc, Alexandria, VA. 5. Humana, Louisville, KY.

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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.

Mini-Sentinel Rotavirus Vaccine Safety Surveillance Protocol Revisions

Notations

Symbol	Comment
~~Delete~~	A strike through indicates a deleted word or phrase
Bold	A bolded text indicates an inserted word or phrase
"*Quotes*"	Quote and italics indicates the subject of revision

Change log, 4/4/2012

Page and paragraph on the revised protocol	Change and comment
Throughout	All mention of sequential analysis has been removed. Sequential analysis was included in the original protocol as proof of concept. Now it will be done more systematically in a PRISM influenza vaccine safety activity instead.
4 and #18 and #27 in the reference list	The VSD follow-up study was published, so that reference was changed to "Shui 2012." Another recently published study, Loughlin 2012, also with null results, was added to the literature review.
5 (table comparing RV vaccines)	The Shui reference was updated. Mention of an upcoming VAERS study was added to the last row.
6	"incidence…stabilized in…" was changed to "incidence…stopped declining by…," which seemed more accurate upon examination of the graph in Shui 2012.
7 and table of years of available data	Aetna is contributing data, so the sentence saying they might not participate was removed. In the table, Aetna's range of available data was corrected from 1/2008-~~9/2010~~ to 1/2008-**9/2011**. Also, the footnote was removed, as the then-future data refresh to which it referred did occur.
8	Mention of registries as a source of rotavirus immunization data was removed, since 1) registry data were not available in time for the initial analyses and 2) registries are not expected to provide many additional instances of rotavirus vaccination over claims data.
8	The label "self-controlled analyses" was changed to "self-controlled risk interval analyses," which is more specific. The last sentence in the same paragraph was removed, as it was redundant with a previous sentence.
9 (analysis plan table)	"Self-controlled" was changed to "Self-controlled risk interval," mention of sequential analysis was removed, and mention of registries (IIS) as a source of vaccination data in the final analyses was removed.
9	Mention of CVX codes was removed, since CVX codes are used only by registries, whose data on rotavirus vaccination will not be used (see above).

11	Words were added to a sentence to make it clearer: "This **offset term** requires a good estimate of the natural incidence of intussusception by age." The possibility of using data from the literature was added at the end of the same paragraph: "**If the PRISM data do not appear robust enough to use, we will use unexposed age-specific incidence data from the literature.**"
13	A phrase was added to explain why power calculations were done both with and without Aetna: "…calculations were done…both with and without Aetna, **whose participation was in doubt when this project was launched**."
15 (Section G, 1st para.)	Mention of refresh frequency was removed, since no sequential analysis will be done and only one version of the data will be used. Mention of registries was removed.
15 (Section G, 2nd para.)	The description of the structure of the analysis datasets was made much more general, in order to be true of all the analysis datasets that are being created and used.
15 (Section H, 1st para. and throughout section)	The section title was changed to "Intussusception ~~case~~ **and rotavirus vaccination** validation," and several sentences were added to explain that we will review charts of intussusception cases to confirm rotavirus vaccine exposure (not just the intussusception diagnosis). A few other small changes related to this appear in other paragraphs of the section.
15 (Section H, 2nd para.)	The two sentences about the maximum number of cases to be reviewed were removed. (We will review all cases within certain age and calendar year ranges and are no longer specifying a maximum number beyond which sampling will be needed.)
16 (Section H, 4th para.)	Detail about which visits (all vs. top-ranked) will have identifiers attached to them was removed because one data partner is doing it one way and the others another. The detail isn't important for the protocol as it won't affect the results.
16 (Section H, 5th para.)	A couple of phrases were added for purposes of clarification ("**for intussusception chart extracts**" and "**standardized extraction form**"). An exception to the redaction plan was inserted: "**(The exception is that one data partner will not redact city, state, or zip code, because it discovered that one state is contributing a disproportionate number of cases. It will be important to see whether this disproportionality persists after chart review and consider possible causes.)**"
16 (Section H, 6th para.)	The number of charts for double expert review (as a test of whether single expert review would be sufficient for the rest) was increased from 10 to 20.

Mini-Sentinel CBER Surveillance Protocol

Monitoring for Intussusception after Two Rotavirus Vaccines by the PRISM Program

I. INTRODUCTION

The Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program was established in August 2009 as one of several 2009 H1N1 influenza vaccine safety surveillance efforts launched and supported by the federal government. With data from a large and diverse population, including records of immunizations delivered in non-traditional settings, PRISM conducted cohort-based active surveillance for post-vaccination adverse events during the pandemic. In September 2010, PRISM was incorporated into Mini-Sentinel to provide FDA with a routine near real-time active surveillance capability to inform regulatory decision-making. Thus, PRISM, focusing specifically on vaccines, is now a component of Mini-Sentinel, operating under its governance and sharing its scientific and informatics resources.

One of PRISM's major activities in its second year is to assess two vaccine-adverse event pairs in terms of the existence of an association between vaccine and adverse event and the validity of the algorithm used to detect the adverse event in electronic data. This protocol concerns one of these pairs, rotavirus vaccines and intussusception.

II. OBJECTIVES

1. To determine the existence and magnitude of any increased risk of intussusception in the 1 or 3 weeks following RotaTeq or Rotarix vaccination compared to unexposed person-time

2. To determine through medical chart review the positive predictive value of an ICD9-code-based algorithm for identifying intussusception

III. BACKGROUND

A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION

Diarrheal disease from rotavirus infection has been estimated to cause 600,000-870,000 deaths per year worldwide (Heymann 2004) and, prior to widespread rotavirus immunization, 20-60 deaths in the U.S. (FDA 2010), mostly in infants. In August 1998, FDA licensed the first rotavirus vaccine, Rotashield. Within less than a year, the immunization program was suspended and the vaccine voluntarily withdrawn from the market due to an increased risk of intussusception following Rotashield vaccination (Murphy 2001, Kramarz 2001). The excess risk after Rotashield was estimated to be between approximately 1 in 5,000 and 1 in 10,000 vaccine recipients (T. Murphy 2003). Subsequently, two new rotavirus vaccines, RotaTeq and Rotarix, were licensed following evaluation in clinical trials involving >60,000 infants. The impact of rotavirus vaccines on the burden of rotavirus gastroenteritis and severe childhood diarrhea has been substantial in countries that have adopted these vaccines (Patel 2011, Tate 2011a,b).

The risk of intussusception was assessed in the large prelicensure clinical trials of RotaTeq and Rotarix, and no increased risk of this outcome was observed; however, postlicensure studies to further evaluate the risk are necessary. First, intussusception is rare, and the studies were powered only to exclude a risk of similar magnitude to that observed for Rotashield; for example, the RotaTeq trial was powered to exclude a relative risk of 10 in a 42-day risk window (Heyse 2008, cited in Bines 2009). Second, the incidence of intussusception varies across populations and geographies, not all of which were included

in the clinical trials. Third, recent studies have suggested an increased risk after RotaTeq and/or Rotarix (Buttery 2011, Patel 2011b).

To date, postlicensure studies of RotaTeq safety in the U.S. have not found any increased risk of this outcome. A passive surveillance (VAERS) study reported no significantly elevated risk of intussusception above the age-adjusted background rate for the 1-7 day risk window after any dose or Dose 1 (Haber 2008). However, this analysis assumed 75% of cases were reported and 75% of doses distributed were administered; a sensitivity analysis determined that if these proportions were instead 50%, a statistically significant elevated risk would appear. A published study from the Vaccine Safety Datalink (VSD) analyzed 207,621 doses administered and did not find an increased risk. Although this VSD study had about 90% power to detect a relative risk of 3 or more in the 30-day risk window for all doses, it had only about 20% power to detect a relative risk of 1.5 (Belongia 2010). A VSD follow-up study, now with 786,725 doses administered, found no evidence of an increased risk of intussusception in the 1-7 days or 1-30 days after any dose (Shui 2012). A subsequent smaller study involving 85,397 doses of RotaTeq also did not find an elevated risk of intussusception, in either the 0-30 or 0-60 days after vaccination (Loughlin 2012).

No postlicensure studies of Rotarix in the U.S. have been published as yet.

However, data from three studies conducted in other countries suggest that each of these vaccines might be associated with intussusception. In Australia, active surveillance data suggested an increased risk for intussusception 1-7 days (RR 5.3, 95% CI: 1.1, 15.4) and the 1-21 days (RR 3.5, 95% CI: 1.3, 7.6) after RotaTeq Dose 1. Similarly, Australian officials reported a non-statistically significant increased risk in the same time intervals after Rotarix Dose 1 (1-7 days: RR 3.5, 95% CI: 0.7, 10.1; 1-21 days: RR 1.5, 95% CI: 0.4, 3.9) (Buttery 2011). Interim results of a postlicensure placebo-controlled trial of Rotarix in 1 million children in Mexico suggest an increased risk of intussusception in the prespecified risk window of 31 days after Dose 1 (RR 1.8, 99% CI: 1.0, 3.1), with most of the cases occurring within 7 days after vaccination (FDA 2010). 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 the case-series method (incidence ratio 5.3, 95% CI: 3.0, 9.3) and the case-control method (odds ratio 5.8, 95% CI: 2.6, 13.0) (Patel 2011b).

Some of the characteristics and postlicensure findings regarding the three rotavirus vaccines are summarized in the table below:

Vaccine name	**Rotashield (RV4)**	**RotaTeq (RV5)**	**Rotarix (RV1)**
Number of strains	4 (tetravalent)	5 (pentavalent)	1 (monovalent)
Type (all live attenuated)	Rhesus-human reassortant	Bovine-human reassortant	Human
Manufacturer	Wyeth Lederle	Merck	GlaxoSmithKline
FDA licensure date	Aug. 1998	Feb. 2006	April 2008
Dosing; min. spacing	2, 4, 6 mo.	2, 4, 6 mo.; 4 wks	2, 4 mo.; 4 wks.
Min., max. age for Dose 1		6 wks, 12 wks (RotaTeq	6 wks, 20 wks (Rotarix

Vaccine name	**Rotashield (RV4)**	**RotaTeq (RV5)**	**Rotarix (RV1)**
		label) 6 wks, 14 wks+6 days (CDC)	label) 6 wks, 14 wks+6 days (CDC)
Max. age at last dose		32 wks (RotaTeq label)	24 wks (Rotarix label)
Route	Oral	Oral	Oral
Reactogenicity (Patel 2009)	High	Low	Low
% infants shedding virus after Dose 1	~50% (Rotashield label)	9% (RotaTeq label)	26% (Rotarix label)
Doses distributed in U.S. as of Sept. 2010	[vaccine voluntarily withdrawn by the manufacturer in 1999]	27 million	2.7 million
		http://www.cdc.gov/vaccines/vpd-vac/rotavirus/intussusception-studies-acip.htm	
Evidence of risk of intussusception in postlicensure studies or surveillance	CDC case-control, case series (Murphy 2001), cohort (Kramarz 2001) studies found strong evidence of an increased risk in 1st 3 weeks; notion of compensatory decrease in risk after 3 weeks (B. Murphy 2003) was rebutted both theoretically (Hall 2001) and empirically (Murphy 2002)	None in VAERS (Haber 2008) or VSD (Belongia 2010, Shui 2012), but increased risk found in 1st week (RR 5.3, 95% CI: 1.1, 15.4) and 1st 3 weeks after Dose 1 during surveillance in Australia (Buttery 2011)	Increased risk found in 1st mo. after Dose 1 (RR 1.8, 99% CI 1.0, 3.1) in post-marketing study on 1M infants in Mexico (FDA 2010). Increased risk found in 1-7 days after Dose 1 in Mexico (case-series incidence ratio 5.3, 95% CI: 3.0, 9.3; case-control odds ratio 5.8, 95% CI: 2.6, 13.0) (Patel 2011b).
Timing of observed increased risk (references are in row above)	After Dose 1: Days 3-7 (highest) Days 8-14 After Dose 2: Days 3-7	After Dose 1: Days 1-7 (highest) Days 1-21	After Dose 1: Days 1-7 (most cases) Days 1-31
Caveats		VAERS result sensitive to reporting completeness; updated VAERS report to be published in ~2012	[Final data from trial in Mexico not yet available; Patel study did not find increased risk after Dose 1 in Brazil.]

Because 1) intussusception is relatively rare, 2) not all subpopulations were included in the prelicensure clinical trials, and 3) postmarketing studies conducted outside of the U.S. have suggested an increased

risk of intussusception after vaccination with one or the other of the two vaccines, it is important to continue monitoring the safety of both vaccines regarding this outcome.

B. INTUSSUSCEPTION

Intussusception, the most common cause of bowel obstruction in infants, is the telescoping of a segment of intestine into a more distal segment. This may compromise blood flow to the bowel, which in turn can lead to intestinal ischemia and possibly perforation. Treatment is by air-contrast or hydrostatic enema or by surgery. Untreated intussusception can be fatal (Bines 2009).

Intussusception is relatively rare, with an annual incidence of <100 per 100,000 among infants aged less than 1 year in most developed countries, and varies by country or region, (see Bines 2009 for table comparing incidences reported in the literature). In the U.S., the incidence of hospitalized intussusception has been estimated at ~34 per 100,000 infants per year (Tate 2008), while in Australia, one estimate of annual incidence is ~80 per 100,000 infants (Justice 2005). Vietnam's estimated annual incidence of hospitalized intussusception is considerably higher, >300 per 100,000 infants (Bines 2006). Risk factors underlying these differences have not been identified. During the 1990s, rates of intussusception declined in several countries, for reasons that are not fully understood (Tate 2008). In the U.S. at least, incidence appears to have stopped declining by the early 2000s (Shui 2012).

Tate et al. (2008) provide the following epidemiologic details for the U.S.: Approximately 1,200-1,400 cases of intussusception occur in infants each year. Incidence is strongly age-dependent in the first year of life, with rates rising slowly from birth to ~5 per 100,000 infants aged 8 weeks, then increasing steeply to a peak of ~62 per 100,000 infants at 26-29 weeks of age, and subsequently falling to 26 per 100,000 infants at 52 weeks of age (see figure from Tate 2008 below). The age range of highest incidence is 5-9 months. Rates are statistically significantly higher in boys than in girls—40 per 100,000 males vs. 27 per 100,000 females. There are statistically significant differences by race/ethnicity, also, with incidences in white, black, and Hispanic infants of 27, 37, and 45 per 100,000, respectively, although the differences are not apparent at ages of < 16 weeks. Rates vary by region as well, ranging from 27 to 37 per 100,000.

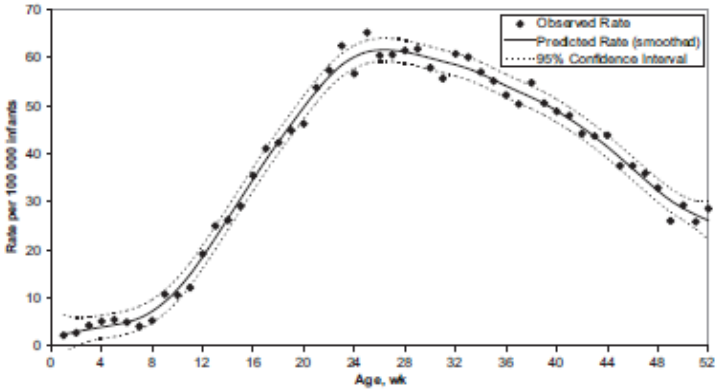

FIGURE 4
Intussusception hospitalization rates per 100 000 infants <12 months of age, by week of age. Analysis is based on all available records of intussusception hospitalizations from 39 Health Care Cost and Utilization Project states participating at least 1 year during 1993–2004. Note that the 39 states include AR, AZ, CA, CO, CT, FL, GA, HI, IL, IN, IA, KS, KY, ME, MD, MA, MI, MN, MO, NE, NV, NH, NJ, NY, NC, OH, OR, PA, RI, SC, SD, TN, TX, UT, VT, VA, WA, WV, and WI. Data from 1999 are excluded.

(Figure from Tate et al. 2008)

The cause of intussusception in most infants is unknown. Mesenteric lymphadenitis has been noted in association with intussusception, raising the question of whether an infectious agent might be involved.

The hypothesized mechanism is that an infection could cause a reaction in the mesenteric lymphoid tissue that might affect mucosal thickness or function of the small intestine, leading to intussusception (Bines 2009). In light of the association between Rotashield and intussusception, it would be reasonable to suspect rotavirus infection as a risk factor. However, no association has been found between wild-type rotavirus infection and intussusception (Bines 2006, Chang 2002).

IV. METHODS

A. STUDY POPULATION AND DATA SOURCES

The data partners participating in PRISM are HealthCore, Humana, and Aetna. The study population will consist of infants who were members of any of the participating data partners during the period of interest and who meet other enrollment criteria (below). The total study population is estimated at >1 million infant-years among the three data partners.

The maximum study period will be from January 2004 to a point in 2011 depending on the specific analysis. The period of data availability varies by data partner, with HealthCore's data starting in January 2004, Humana's in June 2007, and Aetna's in January 2008. The relationship between these periods of available data and February 2006, the licensing date of the first of the two rotavirus vaccines (RotaTeq), is shown below:

	Years of data relative to RotaTeq licensing date, February 2006		**Number of years of data relative to RotaTeq licensing date**	
	Before	After	Before	After
HealthCore	1/2004-1/2006	2/2006-8/2010	2	< 5
Humana	None	6/2007-6/2010	0	3
Aetna	None	1/2008-9/2011	0	< 3

Within these data, only the following categories of infants will be included in the study:

- Exposed to ≥1 dose of rotavirus vaccine and continuously enrolled in the data partner from birth through at least 42 days after their first dose of rotavirus vaccine
- Unexposed to rotavirus vaccine and continuously enrolled in the data partner from birth through at least the day they turned 12 weeks old

For both categories, continuously enrolled person-time through a maximum age of 365 days will be included, with the following proviso: If a vaccinated infant in the first category above has incomplete person-time during 0-42 days after Dose 2 or 3 of rotavirus vaccine, his/her person-time on and after the day of that vaccination will be excluded in order to avoid possible bias. For example, if a child gets Dose 1 at 2 months of age and Dose 2 at 4 months and then disenrolls at 5 months, only the person-time through the day before Dose 2 will be included.

Sources of immunization records and intussusception diagnosis records will be claims data.

B. STUDY DESIGN, NULL HYPOTHESIS, OVERVIEW OF ANALYSIS PLAN

A cohort study with multiple analysis methods (itemized in table below) is proposed for each vaccine. The null hypothesis is that there is no association between each rotavirus vaccine (RotaTeq and Rotarix) and intussusception in a defined risk window after vaccination. Exposed person-time will be person-time in the defined risk window after rotavirus vaccination, and unexposed will consist of either (a) person-time in a comparison window beyond 21 days after rotavirus vaccination (Days 22-42), for the logistic regression analyses, or (b) person-time from unvaccinated infants and from vaccinated infants before and after the 0-21 days after any dose of rotavirus vaccine, for analysis with Poisson regression and Poisson maxSPRT.

The initial case-centered and self-controlled risk interval analyses will use multi-variable regression models and automated claims data to examine the possibility of an association between each vaccine and intussusception. (These methods are discussed in greater depth in Subsection *e. Statistical analysis* below.) Chart-review of intussusception cases will proceed concurrently. We will repeat the case-centered and self-controlled analyses and conduct a Poisson regression analysis, using chart-confirmed data. Since the initial analyses will use automated data and are considered preliminary, there will be no adjustment for multiple testing or loss of statistical power in conducting these analyses again with chart-confirmed data.

The plan is shown schematically below:

Relative timing	Method	Analysis	Data to use	Strengths/weaknesses/notes
Initial	Case-centered (CC) (logistic regression)	Prelim.	Vaccines: claims Outcomes: claims	Provides more accurate age adjustment than SC, but the narrower the age range at vaccination, the less powerful and informative the test
	Self-controlled risk interval (SCRI) (logistic or conditional Poisson regression)	Prelim.		Controls for fixed potential confounders, but requires accurate age-specific background rates
Final	Case-centered (CC) (logistic regression)	2°	Vaccines: claims Outcomes: chart-confirmed subset of cases found in claims data in initial analyses, reclassified from diagnosis date to onset date	
	Poisson regression	2°		
	Self-controlled risk interval (SCRI) (logistic or conditional Poisson regression)	1°		

C. EXPOSURE CODES

RotaTeq and Rotarix vaccination will be identified by means of CPT codes 90680 and 90681, respectively, in the claims data. The 0-21-day periods following any rotavirus vaccination code will be excluded from person-time when calculating background rates.

D. OUTCOME DEFINITION

Potential cases of intussusception will be identified in the electronic 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 will be included, such that only incident cases are analyzed rather than any follow-up visits.

Two risk windows, Days 1-7 and Days 1-21, will be used for Dose 1 and for all doses in most analyses. However, Dose 1 and Days 1-7 will be the primary dose and risk window of interest, respectively. Further, Days 1-7 will be the *only* risk window used in the case-centered analyses due to the concentration of Dose 1 vaccination around age 2 months, which would reduce statistical power if a longer risk window were used.

Dose	Days 1-7	Days 1-21
1	Primary	Not for CC
All		Not for CC

E. STATISTICAL ANALYSIS

1. Descriptive analyses

A number of univariate and bivariate descriptive analyses in the form of tables, histograms, and other graphs will be carried out prior to any hypothesis-testing in order to characterize the rotavirus vaccine and intussusception data. These will include a frequency distribution of day of age at time of receipt of the various doses of each vaccine, to inform the case-centered method, and explorations of rates of intussusception by week of age in the unexposed, stratified by data partner, sex, and calendar year, to develop background rates for use in the statistical analyses.

2. Hypothesis-testing analyses

All analyses will need to adjust for age in fine increments, given the age-dependence of intussusception and rotavirus vaccination during infancy.

Fireman et al.'s case-centered method: One way to adjust for age is to use Fireman et al.'s case-centered method (Fireman 2009). For each child with intussusception who had a prior vaccination, we first note the age at diagnosis, making the analysis case-centered. We then note whether the vaccination was received during either the prior D (i.e., 1-7) days of age or during some time before those D days. Under the null hypothesis, the timing of the vaccination is the same for the child with intussusception as it is for the general population of the same demographic characteristics (age, sex, and data partner). This assumes that there is no relationship between the timing of vaccination and the risk for intussusception. Using our knowledge of the vaccination ages from the whole population, we calculate the probability that a person with intussusception on day t had their vaccination during the prior D days as P[t]=V[t-D,t]/V[0,t], where V[s,t] is the number of people in the same age-sex-data partner stratum getting the vaccination during days [s,t]. Analyses will be done using logistic regression, with P[t] as an offset. Children who were diagnosed with intussusception before receiving the vaccine will not be included in the analysis. Because age at vaccination is expected to be concentrated fairly tightly around 2 and 4 months, we will use only the Days 1-7 risk window so as to maximize power. In the Dose 1 analysis, we will exclude from each day-of-age-at-intussusception data stratum all vaccinees who received Dose 2 prior to the respective day of age. Similarly, in the all-doses analysis, each stratum will contain a specific dose number (x, which can equal 1, 2, or 3), and we will exclude from each stratum all vaccinees who received Dose x + 1 prior to the day-of-age-at-intussusception featured in the stratum.

Age-adjusted self-control risk interval analysis: A standard self-control risk interval analysis (Greene 2010) with an exposed Days 1-21 post-vaccination risk window and an unexposed Days 22-42 post-vaccination comparison window (or with a Days 1-7 risk window and a Days 22-42 comparison window) will be biased unless it is adjusted for age, since the incidence of intussusception varies by week of age. There are two possible ways of adjusting for age in the analysis. One is with conditional Poisson regression, in which the outcome is the occurrence of intussusception in the Days 1-7 or 1-21 risk

window vs. in the Days 22-42 comparison window, the exposure is RotaTeq or Rotarix (in separate analyses), and week of age is included in the model. The other is with logistic regression, using an offset term to adjust for the differential risk of intussusception at the ages in the risk and comparison windows, respectively. This offset term requires a good estimate of the natural incidence of intussusception by age. The incidence curve will be estimated using intussusception rates in all eligible unexposed infant-time. Using Poisson regression (described below), we will fit a polynomial risk function at different degrees to find the best fit. If the PRISM data do not appear robust enough to use, we will use unexposed age-specific incidence data from the literature.

A disadvantage of the conditional Poisson method is that it assumes that the risk of intussusception is equal throughout each week of age. A disadvantage of the logistic regression method is that the offset term requires an accurate estimate of the intussusception risk function by age, which might be difficult to achieve if there are few intussusception cases in the data. We propose to structure the analysis datasets so as to allow us to pursue either approach and decide which to use based on such criteria as the stability of the age-specific intussusception rates.

Poisson regression: The following covariates will be included in versions of the Poisson regression model before settling on the most parsimonious and explanatory model: vaccination (yes/no), age in weeks, sex, and data partner. If secular trend is apparent in the background rates, a term for calendar time will also be included. As shown in the table at the beginning of the Methods section, only one of the three data partners has data starting prior to licensure of RotaTeq (February 2006). Data for the other two data partner start in June 2007 and January 2008, respectively, after RotaTeq licensure. This means we will not be able to simply use all infant person-time and all infant intussusception cases prior to RotaTeq licensure as our unexposed time but rather will have to select only the person-time and cases occurring outside of Days 0-21 after rotavirus vaccination. Our ability to obtain a stable rate for each week of age will depend on the degree of variability in age at vaccination, but rates for inter-dose ages (e.g. 12-16 weeks) will be more stable, and a parametric regression model with a polynomial risk function will be used to extrapolate information across a range of age values and refine estimates of background rates by week of age during the first year of life. Other definitions and criteria are as follows:

Dose	Days 1-7	Days 1-21
1	Unexposed: Precisely assign all eligible infant-days except Days 0-21 after any rotavirus vaccine code to week-of-age strata. But censor from **day of Dose 2**, day after IS, or 1st birthday, whichever comes first. Exposed: Include **Days 1-7 after Dose 1**. Assign IS cases to week-of-age strata according to age at IS, not age at vaccination. Precisely divide person-time of vaccinated cases and non-cases between week of age at vaccination and subsequent week. Exclude Day 0 (day of vaccination) and censor from **day of Dose 2**, day after IS, or 1st birthday, whichever comes first.	Unexposed: As for Dose 1, Days 1-7. Exposed: Include **Days 1-21 after Dose 1**. Assign IS cases to week-of-age strata according to age at IS, not age at vaccination. Precisely divide person-time of vaccinated cases and non-cases among week of age at vaccination and subsequent **weeks**. Exclude Day 0 (day of vaccination) and censor from **day of Dose 2**, day after IS, or 1st birthday, whichever comes first.
All	Unexposed: As above, except **do not censor from day of Dose 2**, rather censor only from day after IS or 1st birthday, whichever comes first. Exposed: Include **Days 1-7 after Doses 1, 2, or 3**. Assign IS cases to week-of-age strata according to age at IS, not age at vaccination. Precisely divide person-time of vaccinated cases and non-cases between week of age at vaccination and subsequent week. Exclude Day 0 (day of vaccination) and censor only from day after IS or 1st birthday, whichever comes first. **(Do not censor from day of Dose 2.)**	Unexposed: As for All Doses, Days 1-7. Exposed: Include **Days 1-21 after Doses 1, 2, or 3**. Assign IS cases to week-of-age strata according to age at IS, not age at vaccination. Precisely divide person-time of vaccinated cases and non-cases between week of age at vaccination and subsequent **weeks**. Exclude Day 0 (day of vaccination) and censor only from day after IS or 1st birthday, whichever comes first. **(Do not censor from day of Dose 2.)**

Strengths and weaknesses of the methods: The **case-centered** method is expected to adjust for age very well, better than the self-controlled method, because the latter is highly dependent on accurate age-specific incidences and there may be periods of age (e.g. 2 mo.) for which unexposed person-time is scarce, making age-specific estimates of incidence for those age ranges unstable. However, the greater the tendency of children to be vaccinated at a specific, precise age (e.g. within a few days of 2 mo.), the less power the case-centered method will have and the less informative it will be. A major advantage of the **self-controlled** method is that it controls for fixed (non-time-varying) potential confounders such as race/ethnicity. Also, it will have greater statistical power than the case-centered method. However, as mentioned above, it will be sensitive to inaccuracies in incidence estimates that are expected due to scarcity of unexposed person-time at certain weeks of age. (To the extent that race/ethnicity is the potential confounder of greatest concern in any favoring of the self-controlled method, it should also be noted that differences in intussusception rates are not appreciable until after 16 weeks of age (Tate 2008), well beyond the typical age at which Dose 1 is received.) The **Poisson regression** method will have the highest statistical power, due to the relatively large amount of data involved in the generation of expected counts (historical and concurrent unexposed). However, its ability to control for confounding is not as good as the other two methods'.

3. Statistical power

One-sided power calculations were done for the self-controlled risk interval analysis and the Poisson analysis, alpha=0.05, Dose 1 and all doses, and the 1-21-day risk window, both with and without Aetna, whose participation was in doubt when this project was launched. Rotavirus vaccine dose counts were obtained from data of two PRISM data partners and estimated for the third and were distributed between RotaTeq and Rotarix based on distribution data from FDA and an assumption that Dose 2 and Dose 3 counts were 10% and 20% less than Dose 1 counts, respectively. Background rates of ICD9-code-identified intussusception were from VSD, which used a similar definition. These were simply assumed to be the same for PRISM as for VSD, and for simplicity were assumed to be known with certainty.

The results for the self-controlled analysis are shown in the table below. The highest power is for RotaTeq, all doses, with Aetna data; there will be 60% power to detect a relative risk of 1.5 and 96% to detect a relative risk of 2. For the corresponding Dose 1 analysis, the power to detect these relative risks will be 25% and 54%, respectively. Power for Rotarix is much lower, given that only one-tenth as much of that vaccine has been distributed; for all doses, with Aetna data, there will be only 14% power to detect a relative risk of 1.5 and 26% power to detect a relative risk of 2.

Power for self-controlled analysis

No. of data partners	Vaccine	Dose	1-21 day Incidence/ 100,000 doses	RR	Power
2	Rrix	1	1.29	1.5	8
2	Rrix	1	1.29	2	12
2	Rrix	1	1.29	4	29
2	Rrix	A	1.86	1.5	11
2	Rrix	A	1.86	2	19
2	Rrix	A	1.86	4	56
2	Rteq	1	1.29	1.5	18
2	Rteq	1	1.29	2	37
2	Rteq	1	1.29	4	92
2	Rteq	A	1.86	1.5	41
2	Rteq	A	1.86	2	83
2	Rteq	A	1.86	4	100
3	Rrix	1	1.29	1.5	10
3	Rrix	1	1.29	2	15
3	Rrix	1	1.29	4	41
3	Rrix	A	1.86	1.5	14
3	Rrix	A	1.86	2	26
3	Rrix	A	1.86	4	76
3	Rteq	1	1.29	1.5	25
3	Rteq	1	1.29	2	54
3	Rteq	1	1.29	4	99
3	Rteq	A	1.86	1.5	60
3	Rteq	A	1.86	2	96
3	Rteq	A	1.86	4	100

For the Poisson analysis, the power is higher, as shown below. For RotaTeq, all doses, with Aetna data, there will be 79% power to detect a relative risk of 1.5 and 100% to detect a relative risk of 2. For the

corresponding Dose 1 analysis, these powers will be 39% and 80%, respectively. For Rotarix, all doses, with Aetna data, there will be only 13% power to detect a relative risk of 1.5 and 33% power to detect a relative risk of 2.

Power for Poisson analysis

No. of data partners	Vaccine	Dose	1-21 day Incidence/100,000	RR	Power
2	Rrix	1	1.29	1.5	7
2	Rrix	1	1.29	2	14
2	Rrix	1	1.29	4	48
2	Rrix	A	1.68	1.5	10
2	Rrix	A	1.68	2	22
2	Rrix	A	1.68	4	76
2	Rteq	1	1.29	1.5	27
2	Rteq	1	1.29	2	60
2	Rteq	1	1.29	4	100
2	Rteq	A	1.68	1.5	58
2	Rteq	A	1.68	2	96
2	Rteq	A	1.68	4	100
3	Rrix	1	1.29	1.5	9
3	Rrix	1	1.29	2	19
3	Rrix	1	1.29	4	66
3	Rrix	A	1.68	1.5	13
3	Rrix	A	1.68	2	33
3	Rrix	A	1.68	4	93
3	Rteq	1	1.29	1.5	39
3	Rteq	1	1.29	2	80
3	Rteq	1	1.29	4	100
3	Rteq	A	1.68	1.5	79
3	Rteq	A	1.68	2	100
3	Rteq	A	1.68	4	100

F. SIGNAL INVESTIGATION

In the event of a statistically elevated risk found in any of the analyses, we will take the following actions:

1. Check data quality; descriptive statistics and background rates (if signal arises in Poisson) by age, sex, and data partner; and analysis inputs and programs.

2. Check the analysis code and reconsider models (if signal arises in regression analysis).

3. Look for patterns in time from exposure to outcome, using the temporal scan statistic to check for temporal clustering of intussusception cases in the weeks after the dose in question and adjusting for age

4. (If the signal arises in preliminary analyses:) Repeat the analyses, using chart-confirmed data and dates of symptom onset.

G. DATASET CREATION

PRISM uses Mini-Sentinel's distributed Common Data Model (MSCDM), by which the data partners maintain control over patient-level data. Data partners extract and organize data from their systems into eight files of standard format, of which the relevant ones for this study are: enrollment, demographics, encounter, diagnosis, and procedure.

PRISM programmers will provide the data partners with programs to run on the standard-format patient-level files, which will produce datasets for analysis. These will be provided to PRISM analysts, using Mini-Sentinel's secure file transport methods.

H. INTUSSUSCEPTION AND ROTAVIRUS VACCINATION VALIDATION

In principle, medical records of all cases of first-ever intussusception occurring during eligible infant-time in the study period will be reviewed in order to validate the diagnosis, regardless of vaccination status or timing relative to vaccination. In addition, records likely to contain vaccination information will be reviewed for intussusception cases in order to correctly identify rotavirus vaccine exposure. For all cases, the infant's most relevant or available primary care provider will be recorded during review of the record for intussusception. For cases with a prior rotavirus vaccination in the electronic claims data, the vaccination record prior to and closest to the intussusception event will be sought, to confirm or correct the vaccination timing, dose number, and type/manufacturer in the claims data. For cases without a prior rotavirus vaccination in the electronic claims data, if the case is ultimately classified as intussusception, then the immunization record will be sought from the infant's primary care provider, to confirm or correct the absence of rotavirus vaccination in the 42 days prior to intussusception onset.

The chart abstraction form developed by VSD will be used as a basis for intussusception validation. Information allowing classification of cases as Brighton Level 1, 2, or 3 will be collected. (Brighton Collaboration criteria are shown in the table from Bines et al. (2004) at the end of this subsection H.)

In order to identify the cases and obtain the medical charts, we will send programs for the data partners to run on their uniform-format patient-level files. These programs will produce a report of the number and characteristics (e.g. age and sex) of the cases and, for each case, a report listing the health care encounters occurring within a specified number of days of the first diagnosis of intussusception. The reports will include information on clinical setting, actual diagnosis, and date of the diagnosis).

Next, PRISM clinical investigators will rank the intussusception-related and the vaccination-related encounters of each case, based on which seem likely to produce the most definitive diagnostic and vaccination information, respectively, and return the ranked lists to the data partners. The plans will then attach patient name, insurance member number, and provider name and address to the visits. Another PRISM program to be run at the data partners will organize the list of charts to pull by facility.

Each data partner will identify a preferred vendor to create chart extracts. These chart extracts will consist of specific items that need to be photocopied or scanned by the vendor. Examples of such items for intussusception chart extracts include the admission note, the daily notes during hospitalization, the discharge summary, all surgical reports within 14 days of the index date (defined as the date of the first code for intussusception), and all diagnostic procedures such as barium enemas, abdominal ultrasound, abdominal CT, and abdominal X-ray examinations. Hospitalizations for intussusceptions typically last two to five days. Using the standardized extraction form provided by the data partner, the chart-review vendor will notify the facilities, contact them to obtain the charts, photocopy or scan the appropriate pages of the chart, and, with one exception, redact the record of all personal identifiers. (The exception is that one data partner will not redact city, state, or zip code, because it discovered that one state is contributing a disproportionate number of cases. It will be important to see whether this disproportionality persists after chart review and consider possible causes.) The data partners will have the option of reviewing the redacted records to ensure that the redaction is complete. The redacted records will be sent to the Mini-Sentinel operations center for further review and abstraction by the PRISM team.

Initially, PRISM clinical investigators will review the intussusception chart abstractions and classify the cases. Two clinical investigators will independently review 20 charts, blinded to vaccination history as well as to the other reviewer's decision. Investigators will complete an initial round of case classification to enable refinement of the classification rules. Using the refined set of rules, investigators will complete a second round of case classification. If there are zero discrepancies between reviewers after the second round, then the remainder of cases will distributed between the two reviewers, with none except the initial 20 being reviewed by both. If there are any discrepancies among the 20 test cases, double review of each subsequent case will be required. Adjudication by a radiologist will be arranged if deemed appropriate by FDA.

Analyses will be repeated after chart review is complete and will use the Brighton Level 1 chart-confirmed cases and their symptom onset dates. Level 1 of diagnostic certainty requires surgical, radiological, or autopsy criteria; radiologic evidence includes demonstration of intestinal invagination by either gas or liquid contrast enema, or demonstration of an intra-abdominal mass with specific features by ultrasound that is proven to be reduced by hydrostatic enema on postreduction ultrasound (Bines 2004). A sensitivity analysis will be conducted including the Brighton Level 2 cases, if these amount to more than 5% of the total number of confirmed cases that could be used in the analysis in question.

The positive predictive value of the intussusception definition to identify Brighton Level 1 confirmed cases will be determined for all the cases captured by the definition, stratified by data partner, setting, diagnosis or procedure code, rotavirus vaccine dose, and timing relative to rotavirus vaccination.

TABLE 1. *Clinical case definition for the diagnosis of Acute Intussusception*

Definite Intussusception (Level 1 of diagnostic certainty)
- Surgical criteria
  - The demonstration of invagination of the intestine at surgery, AND/OR
- Radiological criteria
  - The demonstration of invagination of the intestine by either gas or liquid contrast enema, OR
  - The demonstration of an intra-abdominal mass by abdominal ultrasound with specific features[1] that is proven to be reduced by hydrostatic enema on post-reduction ultrasound, AND/OR
- Autopsy criteria
  - The demonstration of invagination of the intestine

Probable Intussusception (Level 2 of diagnostic certainty)
- Clinical criteria
  - 2 major criteria, or
  - 1 major criterion[2] and 3 minor criteria

Possible Intussusception (Level 3 of diagnostic certainty)
- Clinical criteria
  - 4 or more minor criteria

For any level
- In the absence of surgical criteria with the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (such as volvulus)

Major Criteria
1. Evidence of intestinal obstruction
   - I. History of bile-stained vomiting and either
   - II. Examination findings of abdominal distension and abnormal or absent bowel sounds, or
   - III. Plain abdominal radiograph showing fluid levels and dilated bowel loops
2. Features of intestinal invagination
   One or more of the following:
   - I. abdominal mass
   - II. rectal mass
   - III. intestinal prolapse
   - IV. plain abdominal radiograph showing a visible intussusceptum or soft tissue mass
   - V. abdominal ultrasound showing a visible intussusceptum or soft tissue mass
   - VI. abdominal CT scan showing a visible intussusceptum or soft tissue mass
3. Evidence of intestinal vascular compromise or venous congestion
   - I. passage of blood per rectum, or
   - II. passage of stool containing "red currant jelly" material, or
   - III. blood detected on rectal examination

Minor criteria
- Age <1 year and male sex
- Abdominal pain
- Vomiting[3]
- Lethargy[4]
- Pallor[4]
- Hypovolemic shock
- Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern

Notes for Case Definition

[1]Target sign on doughnut sign on transverse section *and* a pseudo-kidney or sandwich sign on longitudinal section; [2]If 1 major criterion is rectal bleeding in the form of blood mixed with diarrhoea then consideration should be given to infectious causes, such as *E.coli, shigella* or *amoebiasis*. In such cases 2 major criteria should be met.

Notes for the criteria

[3]If the vomiting is bile-stained, it cannot be counted twice as a major and minor criterion; [4]lethargy and pallor typically occur intermittently in association with acute spasms of abdominal pain. In patients with severe or prolonged intussusception, lethargy and pallor may become a constant feature associated with a deterioration in cardiovascular status and impending hypovolemic shock.

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(Table from Bines et al. 2004)

I. INSTITUTIONAL REVIEW BOARD (IRB) APPROVAL AND OTHER AUTHORIZATIONS

Per the "Privacy" section of the Mini-Sentinel policies and procedures manual (http://mini-sentinel.org/about_us/principles_and_policies.aspx):

4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research

The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.

Additionally, FDA determined that Mini-Sentinel activities are public health activities in support of FDA's public health mission. It is therefore not necessary for the Collaborating Institutions to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to participate in Mini-Sentinel activities (45 CFR §164.512(b)).

The HIPAA Privacy Rule permits covered entities the use and disclosure of protected health information (PHI) to public health authorities without patient authorization. Public health authorities include the FDA. The Operations Center and Collaborating Institutions are also public health authorities for purposes of the Mini-Sentinel pilot, because they are acting under contract with and under the authority of the FDA.

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