International Journal of Risk & Safety in Medicine 1 (2024) 1–9
DOI 10.3233/JRS-230049
IOS Press
CORRECTED PROOF

Self-controlled risk interval study of rotavirus vaccine safety: Findings and implications

Jacob Puliyel[a,*] and Brian S. Hooker[b,c]
[a]*International Institute of Health Management Research New Delhi India*
ORCID: https://orcid.org/0000-0002-6303-000X
[b]*Simpson University Redding CA USA*
[c]*Children's Health Defence Franklin Lakes NJ USA*

Received 22 September 2023
Accepted 2 May 2024

Abstract
BACKGROUND: The self-controlled case series (SCCS) is often used to monitor vaccine safety. The evaluation of intussusception after the rotavirus vaccine is complicated because the baseline rate varies with age. Time-varying baseline risk adjustments with data from unexposed cohorts are utilised. Self-controlled risk interval (SCRI), with a shorter observation period, can also mitigate the problem by studying a control period close to the risk period.
OBJECTIVE: An Indian rotavirus vaccine has previously been studied using SCCS. The risk of intussusception in the high-risk windows (21 days after vaccination) was comparable to the background risk. The aim was to re-analyse data of an existing SCCS study using alternate statistical methods to examine vaccine safety.
METHODS: We examined the mean age of intussusception in the vaccinated and the unvaccinated. We performed an SCRI analysis of the surveillance data from the SCCS study, limiting the observation period to 180 days. We analysed the time-to-intussusception from the last vaccination. Finally, we performed an SCCS analysis, excluding unvaccinated cases from the analysis.
RESULTS: We found that the mean age of intussusception was significantly lower in the vaccinated (205 days) compared to the unvaccinated (223 days) (p-value 0.0026). The Incident Risk Ratio (IRR) on SCRI analysis was 1.62 (95% CI 1.07-2.44). There were significantly more intussusceptions in the first 30 days after vaccination compared to the next 30-day window. (92 vs 63 p-value = 0.009). We found that excluding unvaccinated infants from the SCCS analysis demonstrated significantly increased risk for the risk period 1–21 days after the 3rd dose (IRR 2.47, 95% CI 1.70-3.59). The risks of intussusception were missed in traditional SCCS analysis using unvaccinated infants as controls.
CONCLUSION: Traditional risk adjustments using data from unexposed cohorts in SCCS may not be appropriate for investigating the risk of intussusception where vaccination lowers the mean age of intussusception.

Keywords: Rotavac, vaccine adverse effects, self-controlled case series, intussusception, time-to-intussusception, vaccines, microbiology, pharmacoepidemiology, pharmacovigilance

1 Background

Randomised control trials (RCTs) done before the licensure of vaccines are often not powered to detect rare adverse events. Post-licensure monitoring of safety is crucial for this. Databases of people

* Address for correspondence: Jacob Puliyel, 37 Panchavatti, Cochin 682019, Kerala, India. E-mail: puliyel@gmail.com.

with their immunization histories and medical outcomes may be used to look for adverse events among the vaccinated compared to the unvaccinated. However, vaccine coverage is often high and matched unvaccinated controls may be difficult to find.

The self-controlled case series (SCCS) can detect the temporal association between vaccination and adverse events [1]. The incidence of the adverse event within a period where the risk is assumed to be high is compared with the incidence during other periods. Individuals act as their own controls for all fixed covariates (which do not vary with time) in this epidemiological analysis. The method performs less well where covariates change with time like the age of young children. Time-varying baseline risk adjustments have to be made in such instances, often using data from unexposed cohorts. Carlin describes how adjustments can be made for age [2]. SCCS has been used in several studies looking at intussusceptions after the deployment of rotavirus vaccines [3–9].

Intussusceptions are known to be age-dependent [10] with low incidence in the first 6 months of life when the vaccine is administered. The incidence of naturally occurring intussusception (intussusception in the unvaccinated) is higher in the second 6 months of life. Age-adjusted SCCS, using unvaccinated infants in the control group, have been used under such circumstances. However, if the act of vaccination lowers the mean age of intussusception, it may be inappropriate to use unexposed babies as controls.

We reanalyse data from a published SCCS study [3] of rotavirus vaccination which had reported that the risk of intussusception 1–21 days after any dose was not higher than the background risk. We use four alternative analyses to examine if the mean age of intussusception in the vaccinated is different from the unvaccinated and if the conclusions drawn on SCCS analysis are valid.

2 Materials and methods

A SCCS study of an Indian live attenuated rotavirus vaccine (116E) (G9P [11]) Rotavac (Bharat Biotech) has been reported [3]. Rotavirus vaccination status was ascertained from the vaccination record. Among the 589 infants with intussusception selected for the SCCS, 212 had not received the vaccine and 377 received at least one dose of the vaccine. 33 had received only one dose of the vaccine, 55 received 2 doses and 289 received all three doses. Although contraindicated, 22 children received another dose of rotavirus vaccine after intussusception. There were 4 cases of intussusception in the risk window of 21 days after the first dose of the vaccine, 19 cases after the second dose and 37 cases in the 21-day risk period after the third dose. We were provided with the anonymised raw data on all 589 cases of Brighton criteria Level 1 intussusception (radiological or surgical diagnosis of intussusception). 377 of them had received the study rotavirus vaccine in the sentinel surveillance. This data was provided as part of the public record available with a public authority. The data was transferred to an Excel sheet by the authors and is available as a supplement.

Analysis 1. In our preliminary analysis, we examined the age at which intussusception developed in the 377 vaccinated babies compared to the 212 who had not received the rotavirus vaccine. The mean difference and 95% confidence interval of the difference were calculated.

Analysis 2. In the second analysis, we used the self-controlled risk interval (SCRI) design [11]. In this analysis, to minimise confounding by age, a shortened control period close to the risk period is studied. We selected to limit our analysis to 6 months because intussusceptions peak around 7 months in the unvaccinated [10].

The first 21 days after any dose of the vaccine was the high-risk period studied. The control period was the period of observation from 29 days to 180 days, excluding the high-risk period. SCRI analysis has

Table 1
Age of intussusception vaccinated vs. unvaccinated

	Vaccinated	Unvaccinated
Mean age at intussusception	205.36 days	223.25 days
Standard deviation	65.8	74.12
Mean difference	−17.89	
Standard error	5.915	
95% CI	−29.51 to −6.27	
p value	0.0026	

been used in the study of rotavirus in the USA previously [12]. The data was analysed using the statistical software package STATA developed by StataCorp LLC (College Station, TX, USA).

Analysis 3. Vaccination is contraindicated after intussusception, so intussusceptions can be attributed to the last vaccination or otherwise to the background risk of intussusception. In the third analysis, we examined the time-to-intussusception from the last dose of vaccine received. We compared the frequency of intussusception in 2 time windows, 0 to 30 days and 31 to 60 days after the last rotavirus vaccination. We did this analysis to detect a temporal association with vaccination. We assumed that if intussusceptions were unrelated to vaccination there would be no temporal association to vaccination.

Analysis 4. If vaccination reduces the mean age of intussusception significantly it would be inappropriate to use unvaccinated infants as controls in SCCS analysis. We performed an SCCS analysis including only the 377 vaccinated infants. The observation period was from day 30 to day 365. The high-risk period was 21 days after any vaccination dose. The risk period i.e. 1–7 days, 8–21 days, and 1–21 days after each dose of vaccine was studied. The period of observation outside the high-risk period was considered the control period. We considered age groups as less than and greater than 6 months separately in the Poisson regression model, because intussusceptions are generally expected beyond 6 months [10]. The relative incidences (RIs) were calculated on the statistical software STATA.

We looked at 95% confidence intervals and *p*-values to study statistical significance. A *p*-value less than 0.05 was considered statistically significant.

3 Results

3.1. Age of intussusception

The mean age of intussusception was 205 days in the 377 vaccinated babies compared to 223 days in the 212 unvaccinated. This was statistically significant (*p*-value 0.002). The results are tabulated in Table 1. Intussusception was seen at a younger age in the vaccinated cohort than the unvaccinated.

3.2. SCRI analysis

In the SCRI analysis, we limited the period of observation to age 6 months (180 days) starting at 29 days. 149 individuals developed intussusception during the observation period. There were 59 cases in the high-risk window and 90 cases in the low-risk window. The Incidence Risk Ratio was 1.62 (95% CI 1.07-2.44). The data is tabulated in Table 2.

Table 2
Risk of intussusception after vaccination (SCRI analysis)

Number of cases in the risk period 1–21 days after any vaccine	Number of control cases in the low-risk period during the observation from 28 days to 180 days	IRR (95% CI) (adjustment for age; grouped in intervals of 30 days)
59	90	1.62 (95% CI 1.07-2.44)

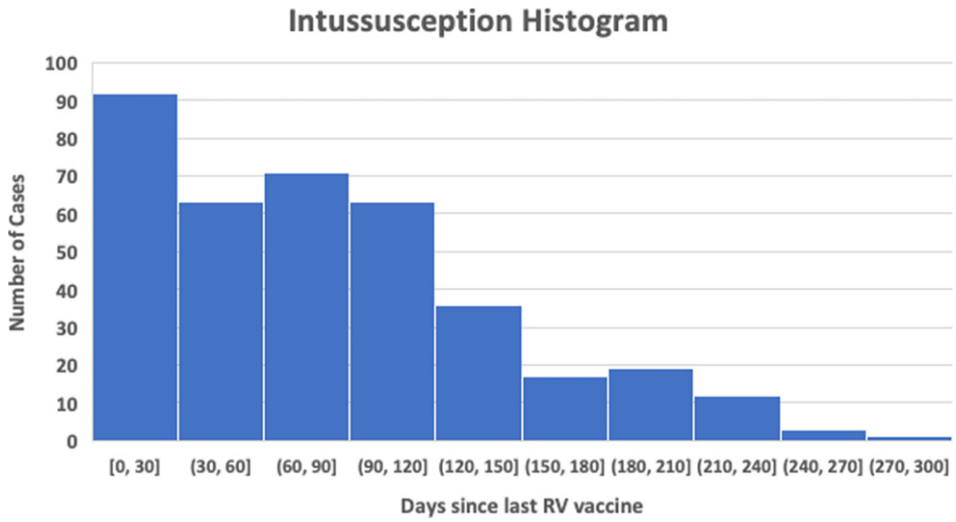

Fig. 1. Cases of intussusception against time since last rotavirus vaccination.

Table 3
Cases of intussusception within the first 30 days of vaccination compared to cases in the next 30 days

	Within 30 days of vaccination	Between 31 and 60 days from vaccination
Cases	92	63
Non-cases	285	314

Odds Ratio 1.61 (95% CI: 1.12-2.30) p-value = 0.009. (Pearson Chi-Square without the Yate's correction).

3.3. *Time to intussusception from vaccination*

Figure 1 is a histogram showing the number of intussusception cases against time elapsed from the last rotavirus vaccination, shown at 30-day intervals. The histogram shows that the incidence of cases tapers off with time. Table 3 compares the number of cases of intussusception in the first two time frames of 30 days. 92 cases of intussusception occurred within 30 days of the last dose of the rotavirus vaccine whereas there were only 63 cases in the second interval between 31 and 60 days ($p = 0.009$).

Table 4
The relative incidence of intussusception in vaccinated babies in the risk periods 0–7 days and 8–21 days after each dose of the rotavirus vaccination by self-controlled case series method

Doses of rotavirus vaccine	Risk period (days)	No. of cases in risk period	IRR (95% CI)
Dose 1	1–7 days	2	0.26 (0.06-1.06)
	8–21 days	2	0.15 (0.03-0.61)
	1–21 days	4	0.19 (0.07-0.51)
Dose 2	1–7 days	4	0.72 (0.29-1.79)
	8–21 days	15	1.25 (0.72-2.17)
	1–21 days	19	1.06 (0.65-1.72
Dose 3	1–7 days	15	3.15 (1.90-5.22)
	8–21 days	22	2.12(1.32-3.40)
	1–21 days	37	2.47 (1.70-3.59)

3.4. SCCS excluding the unexposed

Of the 377 infants who developed intussusception 60 developed it during the high-risk period of 21 days after rotavirus vaccination (any dose). Four developed it after the first dose, 19 after the second dose and 37 after the 3rd dose. The analysis showed a significantly increased risk after the 3rd dose both in the risk window 1–7 days (IRR 3.15 95% CI 1.90-5.22) and the risk window 8–21 days (IRR 2.12: 1.32-3.40). The data are depicted in Table 4. Traditional SCCS (3) using unvaccinated controls failed to detect this risk.

4 Discussion

Our analysis found that intussusception occurred early in the vaccinated and there were significantly more intussusceptions (1.62-fold increase) within 3 weeks of rotavirus vaccination which was not detected using SCCS analysis [3].

4.1. Age of intussusception

There was a significant lowering of the mean age intussusception among the vaccinated. If vaccination is merely a coincidental event and it does not disturb the normal incidence of intussusceptions in the population, the mean age of intussusception would be the same in the vaccinated and the unvaccinated. Tate et al have noted that there was an increase in intussusception in the USA among younger (8 to 11-week-old) infants after the introduction of rotavirus vaccines compared to the era before vaccines [13]. We discuss later, how this lowering of the mean age of intussusception may have blunted the safety signal in the SCCS analysis.

4.2. SCRI analysis

Limiting our observation to the first 6 months of life showed that the risk of intussusception with the rotavirus vaccine was significantly higher in the high-risk period. The selection of risk periods is

based on intelligent guesswork and it is not uncommon to examine multiple risk periods to cover different possible risk windows [14]. The susceptibility to adverse events need not be highest immediately after vaccination, especially if reactions manifest after a lag period. For vaccines administered repeatedly at monthly intervals, the high-risk period of two doses may overlap. For comparison with the previous study (3) we considered 21 days after a dose of the vaccine as the high-risk window. For the SCRI we selected 21 days after any dose as the high-risk period.

The statistical power of an SCRI analysis is less than that of an SCCS study because of the reduced number of events in the shorter control duration [11]. Despite this lowered power, a statistically significant increased risk of intussusception from the vaccine was seen. This increased risk of intussusception went unnoticed in the published SCCS study where the observation period was between 28 and 365 days [3].

The incidence of naturally occurring (non-vaccine induced) intussusceptions increases from 5 to 6 months and peaks at around 7 months [10]. Even using the SCRI design, the risk of vaccine-induced intussusception would be underestimated because the baseline risk of natural intussusception is comparatively low in the 21-day risk periods, which ends by 4.5 months in most children (those taking the doses on the schedule advised, complete their vaccinations by 14 weeks), compared to the control period between 5 and 6 months.

4.3. Time to intussusception from vaccination

We looked at the time that had elapsed between the last dose of vaccine administered and intussusception. We found significantly more intussusceptions in the period proximal to vaccination when we chose 30-day intervals. This analysis, where a high-risk period is compared to a period with a lower risk (further away, temporarily, from the exposure), is easier to perform and more straightforward to understand than the SCCS and SCRI analyses while utilising the same underlying principle. It also points to vaccine-induced intussusception. The analysis includes only vaccinated infants. In this aspect, it is similar to SCRI and different from the traditional SCCS analysis which employs unexposed controls. This type of analysis has been used previously to detect safety signals. Adverse events after herpes zoster vaccination in the first 28 days compared with days 29–56 have been studied. The authors of the herpes study used data mining techniques that are more complex than the analysis we adopted [15].

4.4. SCCS analysis

The previous SCCS [3] had studied the risk windows 1–7 days, 7–21 days and 1–21 days, so we used the same risk periods for our SCCS analysis. In the new analysis, we excluded unvaccinated children from the analysis. Unexposed babies who have intussusception at a later stage in life, are not appropriate cases to consider as controls. We hypothesised that including unvaccinated infants in the original SCCS analysis [3] may have blunted its ability to detect safety signals. Excluding unvaccinated babies from the SCCS analysis, we were able to detect an increased risk of adverse events after the 3rd dose of the vaccine.

4.5. Relevance of the findings

The rotavirus vaccine (116E) (G9P [11]) Rotavac (Bharat Biotech) was licenced after a small randomised control trial (RCT) involving 6719 infants (4532 received the vaccine and 2187 were controls) [16]. RCT investigators calculated that there was an excess of 11 cases of intussusception per 10,000 among the vaccinated, compared to controls although they did not show statistical significance in the small