Table of contents

Figure S1: Flow diagram for cases included in the self-controlled case series analysis (SCCS) to evaluate the association of the rotavirus vaccine under study with intussusception

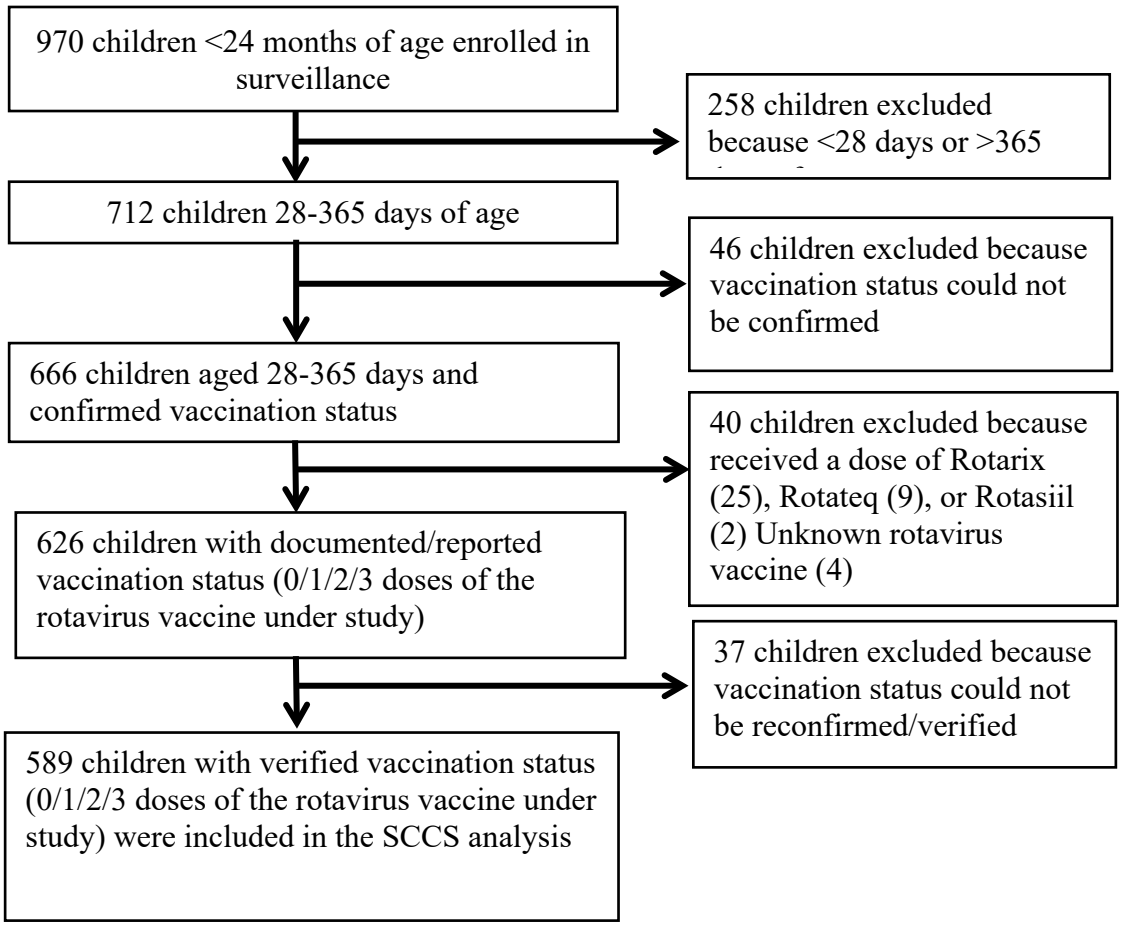

Table S1: Site locations and enrolment of intussusception cases in children less than two years of age from April 2016 to June 2019 in Indian states that introduced rotavirus vaccination

State	Vaccine introduction date	Hospital name	City	Surveillance period	No. of cases enrolled in surveillance	No. of cases included in the SCCS* analysis
Andhra Pradesh	20 Apr 2016	Kurnool Medical College	Kurnool	01 Jun 2016- 30 Jun 2019	22	13
		Government General Hospital and Rangaraya Medical College	Kakinada	01 Aug 2017- 30 Jun 2019	8	8
		King George Hospital and Andhra Medical College	Vishakhapatnam	01 Jul 2016- 30 Jun 2019	12	11
		Sri Venkateshwara Medical College	Tirupati	01 Jul 2016- 30 Jun 2019	20	13
Odisha	26 Mar 2016	Sardar Valla Bhai Patel Post Graduate Institute of Paediatrics	Cuttack	15 Apr 2016- 30 Jun 2019	80	58
		Kalinga Institute of Medical Sciences	Bhubaneswar	01 Oct 2016- 30 Jun 2019	27	14
		Institute of Medical Sciences and SUM Hospital	Bhubaneswar	1 Dec 2016- 30 Jun 2019	11	6
		Hi-Tech Hospital	Bhubaneswar	02 Feb 2017- 30 Jun 2019	5	2
Haryana	11 Apr 2016	Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences	Rohtak	02 Jul 2016- 30 Jun 2019	21	16
		Shaheed Hasan Khan Mewati Government Medical College	Mewat	20 Feb 2016- 30 Jun 2019	5	2
Chandigarh	11 Apr 2016	Post Graduate Institute of Medical Education and Research	Chandigarh	19 Sept 2016- 30 Jun 2019	198	101
Kerala	No vaccine	Malankara Orthodox Syrian Church Medical College Hospital	Kolencherry	1 Aug 2016- 30 Jul 2018	29	18
Tamil Nadu	20 Sept 2017	Christian Medical College	Vellore	20 Sept 2017- 30 Jun 2019	36	20

		Government Vellore Medical College	Vellore	20 Sept 2017- 30 Jun 2019	2	1
		Kanchi Kama Koti Child Trust Hospital	Chennai	20 May 2017- 30 Jun 2019	77	26
		Institute of Child Health	Chennai	20 Jul 2017- 30 Jun 2019	93	61
		Coimbatore Medical College	Coimbatore	21 Aug 2017- 30 Jun 2019	18	12
		Government Rajaji Hospital and Madurai Medical College	Madurai	26 Dec 2017- 30 Jun 2019	23	18
Puducherry	No Vaccine	Jawaharlal Nehru Institute of Post-graduate Medical Education & Research	Puducherry	27 Sept 2017- 30 Jun 2019	38	26
Rajasthan	23 Mar 2017	Sawai Man Singh Medical College	Jaipur	17 Aug 2017- 30 Jun 2019	98	73
		Rabindranath Tagore Medical College	Udaipur	25 Aug 2017- 30 Jun 2019	20	12
		Dr. Sampurnanand Medical College	Jodhpur	01 Aug 2017- 30 Jun 2019	46	23
Madhya Pradesh	03 Apr 2017	Mahatma Gandhi Memorial Medical College	Indore	24 Aug 2017- 30 Jun 2019	24	17
Uttar Pradesh	16 Jul 2018	Mangala Hospital & Research Centre	Bijnor	01 Nov 2018- 30 Jun 2019	0	0
	16 Jul 2018	King George Medical College	Lucknow	20 Jul 2017- 30 Jun 2019	28	16
	16 Jul 2018	Institute of Medical Sciences, Banaras Hindu University	Varanasi	21 Apr 2018- 30 Jun 2019	10	6
Assam	14 Jun 2017	Government Medical College	Guwahati	15 Mar 2018- 30 Jun 2019	19	16
Total					970	589

*Self-controlled case series

Table S2: Brighton Collaboration Criteria for intussusception

Definition	Intussusception is the invagination of one segment of intestine into a segment of distal intestine
Level 1 of Diagnostic Certainty	*Surgical criteria*: The demonstration of invagination of the intestine at surgery; *and/or Radiologic criteria*: The demonstration of invagination of the intestine by either air or liquid contrast enema; *or* The demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features[2] that is proven to be *reduced* by hydrostatic enema on *postreduction ultrasound*; *and/or Autopsy criteria*: The demonstration of invagination of the intestine.
Level 2 of Diagnostic Certainty	*Clinical criteria*: Two major criteria (see major and minor criteria for diagnosis below); *or* One major criterion[3] and three minor criteria (see major and minor criteria for diagnosis below).
Level 3 of Diagnostic Certainty	*Clinical criteria*: Four or more minor criteria (see minor criteria for diagnosis below).
Any Level of Diagnostic Certainty	*In the absence of surgical criteria with* the definitive demonstration of an alternative cause of bowel obstruction or intestinal infarction at surgery (e.g., volvulus or congenital pyloric stenosis).
Major criteria	1. *Evidence of intestinal obstruction*: I. History of bile-stained vomiting; *and either* II. Examination findings of acute 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 a stool containing "red currant jelly" material; *or* III. Blood detected on rectal examination.
Minor criteria	Predisposing factors: age <1 year and male sex; • Abdominal pain; • Vomiting; • Lethargy; • Pallor; • Hypovolemic shock; • Plain abdominal radiograph showing an abnormal but non-specific bowel gas pattern.

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 2004;22:569–74.

Table S3: Socio-demographic and clinical characteristics of children included in the self-controlled case series analysis

Variable	**Category**	**Frequency (%)**
Age	1-5 months	219 (37%)
	6-11 months	370 (63%)
Gender	Female	196 (33%)
	Male	393 (67%)
Clinical features	Fever	202 (34%)
	Vomiting	438 (74%)
	Diarrhoea	240 (41%)
	Blood in stools	481 (82%)
	Constipation	55 (9%)
	Abdominal pain	481 (82%)
Location of Intussusception	Ileo-colic	498 (84%)
	Ileo-ileal	33 (6%)
	Colo-colic	22 (4%)
	Compound	17 (3%)
	Unknown	19 (3%)
Treatment modality	Hydrostatic/pneumatic reduction	200 (34%)
	Surgical reduction	321 (54%)
	Intestinal resection	68 (12%)
Treatment outcome	Survived (Discharged home)	583 (99%)
	Died	6 (1%)

Table S4: Comparison of clinical characteristics, treatment modalities and treatment outcomes between vaccinated and unvaccinated children

Variable	Categories	Unvaccinated (N=212) n(%)	Vaccinated (N=377) n(%)	P-value*
Fever	Yes	78 (36.8%)	124 (32.9%)	0.33
	No	134 (63.2%)	253 (67.1%)	
Vomiting	Yes	162 (76.4%)	276 (73.2%)	0.39
	No	50 (23.6%)	101 (26.8%)	
Diarrhoea	Yes	80 (37.7%)	160 (42.4%)	0.26
	No	132 (62.3%)	217 (57.6%)	
Constipation	Yes	27 (12.7%)	28 (7.4%)	0.03
	No	185 (87.3%)	349 (92.6%)	
Abdominal Pain	Yes	178 (84%)	303 (80.4%)	0.28
	No	34 (16%)	74 (19.6%)	
Blood in stools	Yes	160 (75.5%)	321 (85%)	0.004
	No	52 (24.5%)	56 (15%)	
Treatment outcome	Death	1 (0.5%)	5 (1.3%)	0.32
	Survived (Discharged home)	211 (99.5%)	372 (98.7%)	
Intestinal resection	Required	27 (13%)	41 (11%)	
	Not required	185 (87%)	336 (89%)	
Repeated episode of Intussusception during follow up#	Yes	3 (1.8%)	5 (1.7%)	
	No	166 (98.2%)	281 (98.5%)	

**Chi-square test, p-value less than 0.05 was considered statistically significant*
 # 455 children were followed up at 18 months of age

Table S5: Follow up of children included in the self-controlled case series (SCCS) analysis

Variable	Frequency
No. of children in SCCS analysis	589
No. of children traced and followed up	455
Median age at follow up (Inter-quartile range)	16 (13-22)
No. of children who were discharged home and died before reaching the age of follow up	7 (1.5%)
Repeated intussusception episode after current admission	8 (1.8%)
No. of children given rotavirus vaccine after an episode of intussusception	22 (5%)

Table S6: Relative incidence (RI, with 95% confidence intervals, CI) of intussusception in the risk periods after first, second and third doses of the rotavirus vaccine under study in infants from 27 hospitals in 10 Indian states by the self-controlled case series analysis[#]

Doses of Rotavac vaccine	Risk Period (days)	No. of cases in risk period	RI (95% CI)
Dose 1	1-7 days	2	1.02 (0, 4.27)
	8-21 days	2	0.64 (0, 2.05)
	1-21 days	4	0.78 (0.31, 1.96)
Dose 2	1-7 days	3	0.72 (0.26, 1.94)
	8-21 days	13	1.03 (0.60, 1.76)
	1-21 days	16	0.97 (0.60, 1.57)
Dose 3	1-7 days	14	1.40 (0.81, 2.42)
	8-21 days	20	0.95 (0.60, 1.49)
	1-21 days	34	1.09 (0.76, 1.57)

The date of intussusception onset was defined as the date of admission at the surveillance hospital

Table S7: Matched odds of intussusception in the risk window after first, second and third dose of rotavirus vaccination in 150 matched case-control pairs[#]

Doses of rotavirus vaccine under study	Risk window relative to reference date	No. of cases in risk window	No. of controls in risk window	Matched odds ratio
Dose 1	1-7 days	1	0	0
	8-21 days	1	5	0 (0, 1.51)
	1-21 days	2	5	0 (0, 2.42)
Dose 2	1-7 days	1	0	0
	8-21 days	2	4	0.33 (0.01, 4.15)
	1-21 days	3	4	0.66 (0.05, 5.81)
Dose 3	1-7 days	6	2	5 (0.56, 236.48)
	8-21 days	5	6	0.8 (0.16, 3.72)
	1-21 days	11	8	1.6 (0.46, 6.22)

Sensitivity analysis using the date of onset of intussusception as the date of admission at the surveillance hospital.

Table S8: Comparison of risk estimates from self-controlled case series analysis (SCCS) and matched case control analysis[@] for 162 intussusception cases included in both analyses[#]

Doses of rotavirus vaccine under study	Risk Period# (days)	No. of cases in risk period	SCCS analysis RI (95% CI)	Case-control analysis Matched Odds Ratio (95% CI)
Dose 1	1-7 days	1	0.89 (0-5.37)	1 (0.12-78.49)
	8-21 days	1	0.45 (0-2.09)	0 (0-1.51)
	1-21 days	2	0.63 (0-2.39)	0 (0-1.51)
Dose 2	1-7 days	1	0.54 (0-2.45)	1 (0.01-78.49)
	8-21 days	3	0.66 (0-2.08)	1 (0.07-13.79)
	1-21 days	4	0.61 (0.12-1.76)	1 (0.13-7.46)
Dose 3*	1-7 days	6	2.30 (0.68-5.53)	2.5 (0.41-26.25)
	8-21 days	7	1.28 (0.42-2.76)	1 (0.26-3.74)
	1-21 days	13	1.57 (0.73-3.04)	1.4 (0.49-4.42)

The date of onset of intussusception was defined as the date of symptom onset

[@]In the case-control analysis to detect an odds ratio of 2, with data from our study showing 66% of controls vaccinated with at least one dose, with one control enrolled per each case, at 5% level of significance, with 162 case control pairs, the power of the study is 78%.

*For dose 3, the 1-7 day window, although not significant, the RI for the SCCS is 2.3 and the matched odds ratio for the case-control analysis is 2.5. It is feasible that that there may be a difference in risk from dose 3 (or any dose) depending on whether the dose was given on time or later when intussusception peaks, but the study is not powered to examine age related differences.

Figure S2: Flow diagram for cases included in the matched case control analysis