

RESEARCH ARTICLE

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Prospective surveillance for intussusception in Indian children aged under two years at nineteen tertiary care hospitals

The INCLEN Intussusception Surveillance Network Study Group

Abstract

Background: India introduced rotavirus vaccines (RVV, monovalent, Rotavac™ and pentavalent, Rotasiil™) in April 2016 with 6, 10 and 14 weeks schedule and expanded countrywide in phases. We describe the epidemiology of intussusception among children aged 2–23 months in India.

Methods: The prospective surveillance at 19 nationally representative sentinel hospitals from four regions recruited children with intussusception from April 2016 to September 2017. Data on sociodemography, immunization, clinical, treatment and outcome were collected. Along with descriptive analysis, key parameters between four regions were compared using Chi-Square/Fisher's exact/Mann–Whitney U/Kruskal–Wallis tests. The pre- and post-RVV periods were compared to estimate the risk ratios.

Results: Six hundred twenty-one children with intussusception from South ($n = 262$), East ($n = 190$), North ($n = 136$) and West ($n = 33$) regions were recruited. Majority ($n = 465$, 74.8%) were infants (40.0% aged 4–7 months) with median age 8 months (IQR 5, 13 months), predominantly males ($n = 408$, 65.7%) and half ($n = 311$, 50.0%) occurred during March–June months. A shorter interval between weaning and intussusception was observed for ragi based food (median 1 month, IQR 0–4.2 months) compared to rice (median 4 months, IQR 1–9 months) and wheat (median 3 months, IQR 1–7 months) based food ($p < 0.01$). Abdominal pain or excessive crying (82.8%), vomiting (72.6%), and bloody stool (58.1%) were the leading symptoms. Classical triad (abdominal pain, vomiting and bloody stool) was observed in 34.8% cases (24.4 to 45.8% across regions). 95.3% of the cases were diagnosed by ultrasound. 49.3% (10.5 to 82.4% across regions) cases were managed by reduction, 39.5% (11.5 to 71.1% across regions) cases underwent surgery and 11.1% spontaneously resolved. Eleven (1.8%) cases died. 89.1% cases met Brighton criteria level 1 and 7.6% met Level 2. RVV was received by 12 cases within 1–21 days prior to intussusception. No increase in case load (RR = 0.44; 95% CI 0.22–1.18) or case ratio (RR = 0.5; 95% CI 0.3–1.2) was observed after RVV introduction in select sites.

Conclusions: Intussusception cases were observed across all sites, although there were variations in cases, presentation and mode of management. The high case load age coincided with age of the RVV third dose. The association with ragi based weaning food in intussusception needs further evaluation.

Keywords: Intussusception, Prospective surveillance, Children, Epidemiology, Weaning food, Sociodemography, Rotavirus vaccine, India

Correspondence: drmanojkdas@gmail.com

The INCLEN Trust International, F1/5, Okhla Industrial Area, Phase 1, New Delhi 110020, India



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Background

To reduce the rotavirus diarrhoea related childhood deaths, the World Health Organization (WHO) has recommended introduction of rotavirus vaccine (RVV) in national immunization programmes (NIPs). Some increased risk of intussusception after the first (relative risk, RR: 4.7–13.8) and second (RR: 1.3–5.3) doses of RVVs was reported from several countries (Mexico, Brazil, Australia, United Kingdom, United States, Spain and Singapore) [1–8]. But no increased risk of intussusception after any dose of RVV was observed in some countries (Ethiopia, Ghana, Kenya, Malawi, Tanzania, Zambia, Zimbabwe and South Africa) [9, 10]. The impact of RVV on diarrhoea morbidity and mortality outweigh the risk of intussusception and associated mortality [11]. In view of the concern about intussusception, documentation of baseline and monitoring following RVV introduction have been recommended [12]. India introduced RVV into the NIP in April 2016 and by 2019 expanded countrywide in four phases [13]. Two types of RVV are used in NIP, Rotavac™ (RV1-116E; Bharat Biotech) in 26 states/union territories and Rotasill™ (RV5; Serum. Institute of India) in 11 states/union territories, both follow 6, 10, 14 weeks schedule. Intussusception is an acute severe clinical condition occurring mostly during infancy, which overlaps with the age of primary vaccinations. The nationally representative background epidemiology of intussusception in India is not clear. The reports from India primarily included retrospective data and considerably varied in the epidemiology, presentation and management [14, 15]. Information on population level rate in India is limited and the reported incidences of intussusception requiring hospitalization varied from 17.7 (95% CI 5.9–41.4) in Delhi (North India) to 254 (95% CI 102, 524) cases per 100,000 child-years in Vellore (South India) [16, 17]. The incidence of intussusception vary widely globally, across the different high and low-middle income countries [18]. The reasons for the variations are unknown. There is no information from India regarding the regional variation in intussusception epidemiology. Thus, documentation of the intussusception epidemiology prior to RVV introduction to establish a reliable baseline for monitoring the trend over time and identify potential risk factors was needed to support the vaccine safety surveillance efforts [19, 20]. Under the vaccine safety surveillance effort, we describe the epidemiology, clinical characteristics of intussusception among children aged under-2 years seeking hospital care in India and initial changes with RVV introduction documented through a nationally representative sentinel surveillance network.

Methods

Study area and participating hospitals

This prospective active hospital-based sentinel surveillance was conducted over 18 months, at 19 nationally representative

tertiary care hospitals (Supplementary Figure 1). From the four regions, 3–6 hospitals per region including medical colleges and private-sector hospitals (North region- 5 sites, 3 public and 2 private; South region- 5 sites, 2 public and 3 private; East region- 6 sites, 5 public and 1 private; West region- 3 sites, 2 public and 1 private) were selected through a systematic process. Out of these sites, four sites were located in the states where RVV was introduced in April 2017 under phase 1. At all sites the RVVs were available in private market during the study period, even prior to the introduction in NIP.

Case definition, case selection and data collection

The children aged 2–23 months admitted to these hospitals with diagnosis of intussusception were eligible. All the age-eligible patients admitted were screened to identify the suspected cases (any of the diagnoses: intussusception, acute or subacute intestinal obstruction, acute abdomen, abdominal pain, abdominal distension, and blood in stool with vomiting). These suspected cases were tracked till final diagnosis and all confirmed intussusception cases were recruited after written informed consent from parent or legally authorised representative. A log of screened, suspected and confirmed cases was maintained. The data on socio-demography, feeding and immunization (from immunization card), clinical features, investigation findings, hospital course, treatment and outcome were collected using common case record form (CRF). The symptoms were captured as recorded in the case sheets and reported by the parents. An independent Case Adjudication Committee (CAC) comprised of a paediatrician, paediatric surgeon, and radiologist reviewed the CRFs and investigations to assign the diagnostic certainty levels, according to Brighton Collaboration case definition (BCCD) [21].

Quality assurance

Multilevel quality assurance and data quality-checking processes were put in place to ascertain protocol adherence, rigor and completion of surveillance at all sites. A data team reviewed all the CRFs and data-related query was resolved at the earliest. Each site was visited by external experts (Technical Advisory Group, TAG) to assess the case surveillance and tracking, consent, and data extraction quality and completeness in the CRFs. The TAG members checked CRFs completeness and quality for few randomly identified cases with the case records. Subsequently members from the data team visited the study sites and checked the admissions for the study period from the medical records section using diagnoses and International Classification of Diseases (ICD) codes (ICD-9/10, codes listed in Supplementary Table 1), to identify any missed cases.

Data management and analysis

Double data entry was done for the CRFs using a customised data entry platform. The matched and verified data were stored in the server with authorised access

and daily backup. The standard of living index (SLI), representing the socioeconomic status was estimated using the scores for household assets ownership, with reference to the National Family and Health Survey for India [22]. The SLI was categorised into high, medium and low categories. The cases were categorised into levels 1 to 3 based on the BCCD criteria by the CAC [21]. In view of the number of sites, for representation we grouped the sites into four regions, North (5 sites), South (5 sites), East (6 sites) and West (3 sites) regions. The parameters (sociodemographic, feeding, clinical, intervention and outcomes) were compared between the regions to detect variations. The intussusception classical triad includes three features; abdominal pain, vomiting and blood in stools. We considered intussusception modified triad with abdominal pain, vomiting and rectal bleeding, detected either as blood in stool or blood on per-rectal examination. The descriptive analysis findings expressed the outputs as proportions, means and standard deviations, or median and interquartile range (IQR), as appropriate. The values between regions and groups were compared for statistical significance using Chi-Square or Fisher's exact tests for the proportions and Mann-Whitney U or Kruskal-Wallis tests for the medians depending on the skewness, sample and number of groups. The missing data were excluded from analysis. The statistical significance was considered if $p < 0.05$. The statistical analysis was performed using STATA version 15.0 (StataCorp LLC, Texas, USA). In the Indian context, there is no definite population catchment area for hospitals and no definite referral chain, which makes estimation of the intussusception incidence difficult. For comparison of the data across sites and intussusception time trend, in addition to case load (absolute number of cases), we attempted deriving the intussusception case rate per 1000 paediatric hospitalisations at the hospitals. On review, while the admission numbers in the paediatric medicine wards varied widely, the admission numbers in the paediatric surgery wards were relatively stable and the intussusception cases were primarily managed in the paediatric surgery wards. Thus we estimated the intussusception case rate per 1000 paediatric surgery admissions at these hospitals for comparison and trend analysis. For the four sites in three states (Odisha, Andhra Pradesh and Haryana), where RVV (monovalent Rotavac™, 3 doses at 6, 10, 14 weeks age) was introduced under NIP (in April 2017), the data for the post-introduction period (April to September 2017, 6 months) was compared with the pre-introduction periods (first: October 2016 to March 2017, immediate 6 months pre-introduction period and second: April 2016 to September 2016, calendar matched 6 months during the previous year) to document the risk ratio (95% confidence interval, CI). The detailed

methodology of the site selection and study implementation has been published as protocol [23].

Ethical issues

Informed written consent was obtained for all the eligible cases before recruitment and data collection. Confidentiality in data handling was maintained. The study protocol was reviewed and approved by the ethics committees of all participating institutes.

Results

Between April 2016 and September 2017, out of the 182,824 children (including 32,910 paediatric surgery admissions) admitted to the network hospitals, 1203 suspected intussusception cases were identified and 621 eligible children were recruited (Supplementary Figure 2). More cases were recruited from Southern region (42.2%; 262/621) followed by East (30.6%; 190/621), North (21.9%; 136/621) and West (5.3%; 33/621) regions. Past history of intussusception was present in 24 (3.8%) cases. Table 1 shows the sociodemographic characteristics of children with intussusception. A male predominance (male-female ratio: 1.9:1) was consistent across all regions. The median age at presentation was 8 months (IQR 5, 13 months) (Supplementary Figure 3). Three quarters of the cases were infants with equal share from the age bands of 2–6 months (37.2%) and 7–12 months (37.7%) ($p < 0.01$). Children aged 4–7 months contributed to 40.0% of the total cases. The pooled intussusception case rate per 1000 paediatric surgery admission was 18.4 (IQR 14.7, 23.4). The intussusception case rate per 1000 paediatric surgery admission was highest for South (25.3, IQR 23.4, 32.7) followed by North (14.5, IQR 11, 19.7), East (13.8, IQR 10.5, 22) and West (6.6, IQR 1.2, 19.2) regions respectively. The Fig. 1 shows monthly trends of pooled intussusception case load and case rates per 1000 paediatric surgery admission (Fig. 1a) and the regional case rates per 1000 paediatric surgery admission (Fig. 1b). More cases ($n = 311$, 50.0%) were seen during March to June months, in the summer season (Fig. 1). While 42.8% of the patients were resident of the same district where the hospital was based, 41.9% of the patients presented directly to the hospital. Among the children aged > 6 months, 23.2% were exclusively breastfed for 6 months and the median duration of breastfeeding was 4 months. Mixed feeding was initiated before 6 months of age in 53.9% children. The median weaning age was 6 months and 61.0% received rice based food. Ragi (finger millet) was given to 22.8% children, only in the South region. The interval between weaning and intussusception was significantly shorter for ragi (median 1 month, IQR 0–4.2 months) than rice (median 4 months, IQR 1–9 months) and wheat (median 3 months, IQR 1–7 months) based food (Table 1) ($p < 0.01$). On analysis for the South

Table 1 The sociodemographic parameters and dietary practices of children with intussusception in India

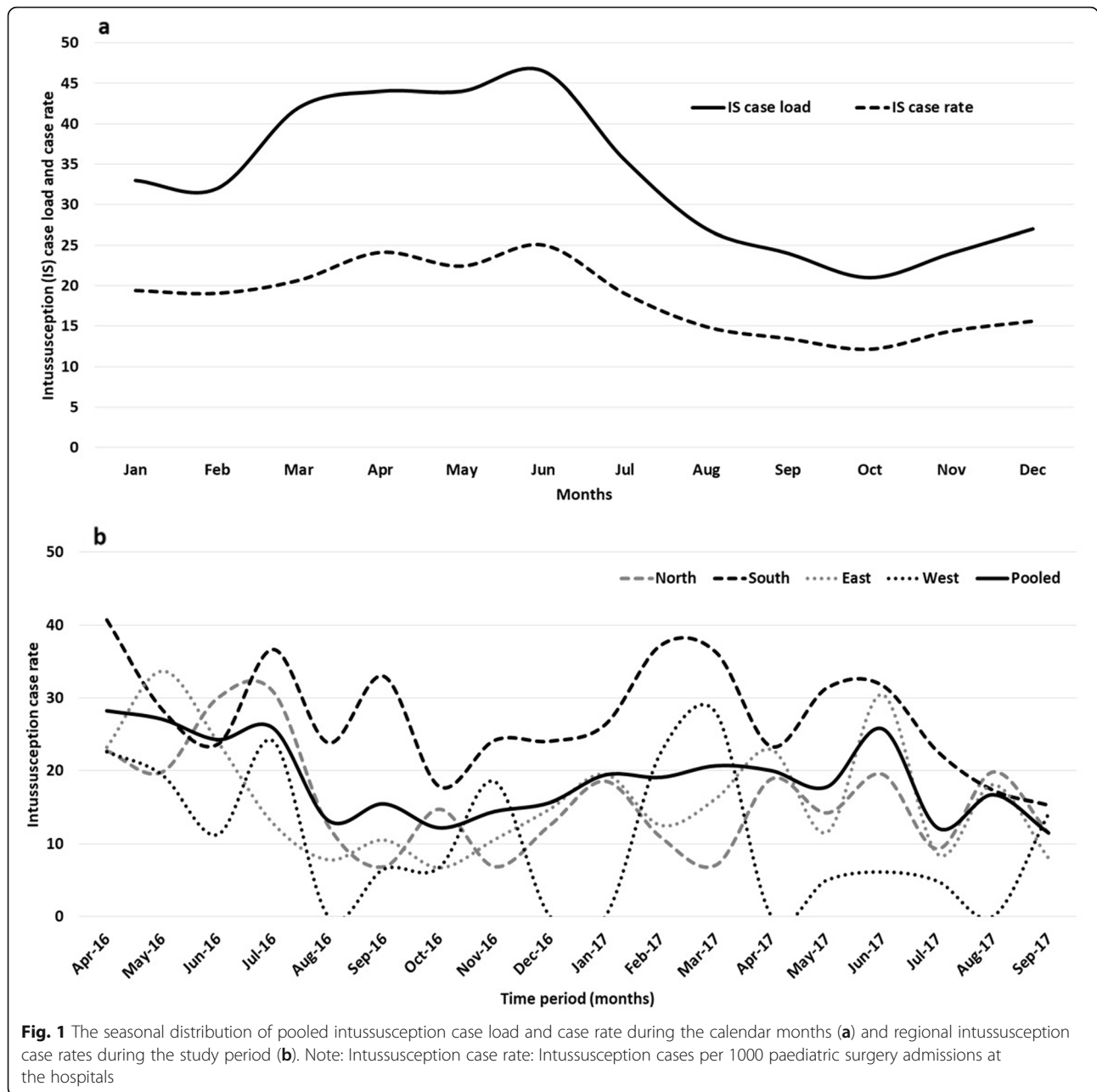
Variable Category		North (n = 136)	South (n = 262)	East (n = 190)	West (n = 33)	Total (n = 621)	P value
Age (in months)	2–6, n (%)	55 (40.4)	88 (33.6)	78 (41.1)	10 (30.3)	231 (37.2)	< 0.01
	7–12, n (%)	57 (41.9)	92 (35.1)	73 (38.4)	12 (36.4)	234 (37.7)	< 0.01
	13–18, n (%)	16 (11.8)	40 (15.3)	25 (13.2)	3 (9.1)	84 (13.5)	< 0.01
	19–23, n (%)	8 (5.9)	42 (16.0)	14 (7.4)	8 (24.2)	72 (11.6)	< 0.01
Gender	Male, n (%)	86 (63.2)	170 (64.9)	128 (67.4)	24 (72.7)	408 (65.7)	< 0.01
	Female, n (%)	50 (36.8)	92 (35.1)	62 (32.6)	8 (24.2)	212 (34.1)	< 0.01
	Other, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.0)	1 (0.2)	–
Family	Nuclear, n (%)	89 (65.4)	171 (65.2)	65 (34.2)	18 (54.5)	343 (55.2)	0.06
	Joint/extended, n (%)	47 (34.6)	91 (34.7)	125 (65.8)	15 (45.5)	278 (44.8)	0.06
Religion	Hindu, n (%)	48 (35.3)	179 (68.3)	136 (71.6)	22 (66.6)	385 (62.0)	< 0.01
	Muslim, n (%)	88 (64.7)	41 (15.6)	52 (27.3)	11 (33.3)	192 (30.9)	< 0.01
	Christian, n (%)	0 (0.0)	42 (16.0)	1 (0.5)	0 (0.0)	43 (7.0)	–
SLI status ^a	High, n (%)	56 (41.2)	93 (35.5)	19 (10.0)	6 (18.2)	174 (28.0)	< 0.01
	Medium, n (%)	33 (24.3)	124 (47.3)	65 (34.2)	6 (18.2)	228 (36.7)	< 0.01
	Low, n (%)	47 (34.5)	45 (17.2)	106 (55.8)	21 (63.6)	219 (35.3)	< 0.01
Place of residence	Same district, n (%)	49 (36.0)	162 (61.8)	35 (18.4)	20 (60.6)	266 (42.8)	< 0.01
	Other districts ^b , n (%)	74 (54.4)	86 (32.8)	151 (79.5)	13 (39.4)	324 (52.2)	< 0.01
	Outside state, n (%)	13 (9.6)	14 (5.3)	4 (2.1)	0 (0.0)	31 (5.0)	< 0.01
Referral status	Primary ^c , n (%)	91 (66.9)	64 (24.4)	87 (45.8)	18 (54.6)	260 (41.9)	< 0.01
	Referred ^d , n (%)	45 (33.1)	198 (75.6)	103 (54.2)	15 (45.5)	361 (58.1)	< 0.01
Feeding practices	Exclusively breastfed for 6 months ^e , n/N (%)	3/26 (11.5)	16/52 (30.7)	18/85 (21.2)	1/1 (100)	38/164 (23.2)	< 0.01
	Mixed food before 6 months age ^e , n/N (%)	25/78 (32.0)	130/197 (66.0)	46/100 (46.0)	12/20 (60.0)	213/395 (53.9)	0.08
	Exclusive breastfeeding period (in months), median (IQR)	5 (4–6)	4 (2–5)	4 (3–5)	5 (3.5–5)	4 (3–7)	–
	Mixed food initiation age in months, median (IQR)	6 (5–8)	4 (2–6)	5 (3–6)	5 (4–6)	5 (3–7)	–
	Weaning age in months, median (IQR)	7 (6–8.2)	6 (4–6)	6 (5–7)	6 (5–7)	6 (5–7)	–
Weaning food type	Rice, n (%)	48 (68.6)	116 (53.0)	80 (88.9)	5 (18.5)	249 (61.0)	< 0.01
	Wheat n (%)	12 (17.1)	5 (23.0)	3 (3.3)	11 (40.7)	31 (8.0)	< 0.01
	Ragi based ^f , n (%)	0 (0.0)	50 (22.8)	0 (0.0)	0 (0.0)	50 (12.0)	–
	Other, n (%)	4 (5.7)	7 (3.2)	3 (3.3)	4 (14.8)	18 (4.0)	0.08
	Mixed n (%)	6 (8.6)	41 (18.7)	4 (4.4)	7 (25.9)	58 (14.0)	0.05
Weaning initiation to illness onset interval (in months)	Rice based, median (IQR)	3 (0–6)	3 (1–9)	4 (1–9)	4 (2–11.5)	4 (1–9)	0.08
	Wheat based, median (IQR)	3 (2.5–7)	2.5 (1.2–5.2)	0 (0–1)	3 (2–7)	3 (1–7)	0.05
	Ragi ^f , median (IQR)	–	1 (0–4.2)	–	–	1 (0–4.2)	–
	Other food, median (IQR)	4 (1.5–6)	1 (0–3)	0 (0–1)	9.5 (5.2–13)	2.5 (0.7–5.5)	0.09
	Multiple food, median (IQR)	7 (2.5–9)	6 (2.7–12)	6 (3–12)	6 (3–12)	6 (3–12)	0.1
	Any food, median (IQR)	3 (1–7)	3 (1–8)	3.5 (1–8.2)	3 (1–9)	3.5 (1–8.2)	0.1

Notes:

Mixed food: Food used for weaning included at least two of the ingredients- rice, wheat, lentil and vegetables & fruits

^aSLI: Standard of living index, was estimated using the household assets ownership (22)^bThe residence of the patient was in other district in the state where the study hospital was based^cThe patient presented to the study hospital as the first institute^dThe patient was referred to the study hospital from another hospital^eThe denominators (N) indicate valid responses received for the parameters^fRagi: finger millet

The p values for some parameters could not be estimated due to small or no value in at least two groups



region only (where ragi based weaning practice was observed), the median interval between weaning and intussusception for ragi based food was significantly shorter (median 1 month, IQR 0–4 months) than rice (median 5 months, IQR 2–9 months) and wheat (median 3 months, IQR 2–8 months) based food ($p < 0.01$).

The pooled median interval between the onset to hospital admission was 2 days (IQR 1, 3), which varied across the regions; North- 2 days (IQR 1, 3), South- 1 day (IQR 1, 3), East- 2 days (IQR 1, 3) and West- 2 days (IQR 1, 2) ($p = 0.07$). Table 2 summarises the clinico-pathological parameters and management for the

recruited children. Abdominal pain or excessive crying (82.6%) was the most common symptom followed by vomiting (72.6%) and blood in stool (58.1%), as reported by the parents. More children had abdominal pain or excessive crying in North (84.6%) and East (72.6%) regions and blood in stool in the East region (73.2%). The classical triad (abdominal pain, vomiting and blood in stool) was observed in 34.8% cases, with 24.4 and 45.8% in the South and in East regions, respectively ($p < 0.01$). When blood on per-rectal examination was included, the modified intussusception triad (abdominal pain, vomiting and blood in stool or blood on per-rectal examination) was

Table 2 The clinicopathological characteristics and management of the children with intussusception in India

Variable Category		North (n = 136)	South (n = 262)	East (n = 190)	West (n = 33)	Total (n = 621)	P value
Symptoms, n (%)	Vomiting ^a	100 (73.5)	187 (71.4)	137 (72.1)	27 (81.8)	451 (72.6)	0.64
	Bilious vomiting ^b	21 (15.4)	26 (9.9)	34 (17.9)	9 (27.3)	90 (14.5)	0.02
	Abdominal pain	102 (75.0)	118 (45.0)	138 (72.6)	10 (30.3)	368 (59.3)	< 0.01
	Excessive crying	49 (36.0)	172 (65.7)	109 (57.4)	17 (51.5)	347 (55.9)	< 0.01
	Abdominal distension	34 (25.0)	29 (11.1)	69 (36.3)	3 (9.1)	135 (21.7)	< 0.01
	Rectal bleeding	81 (59.6)	123 (47.0)	139 (73.2)	18 (54.6)	361 (58.1)	< 0.01
	Diarrhoea	23 (16.9)	69 (26.3)	37 (19.5)	9 (27.3)	138 (22.2)	0.11
	Constipation	18 (13.2)	43 (16.4)	12 (6.3)	3 (9.1)	76 (12.2)	0.01
	Fever	34 (25.0)	64 (24.4)	31 (16.3)	13 (39.4)	142 (22.9)	0.02
	Lethargy	2 (1.5)	16 (6.1)	16 (8.4)	2 (6.1)	36 (5.8)	0.07
	Altered sensorium	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	–
	Classical triad ^c	52 (38.2)	64 (24.4)	87 (45.8)	13 (39.4)	216 (34.8)	< 0.01
	Signs, n (%)	Pallor	11 (8.1)	14 (5.3)	18 (9.5)	3 (9.1)	46 (7.4)
Dehydration		7 (5.2)	21 (8.0)	43 (22.6)	2 (6.1)	73 (11.8)	< 0.01
Fever		4 (2.9)	23 (8.8)	23 (12.1)	5 (15.2)	55 (8.9)	0.02
Lethargy		11 (8.1)	14 (5.3)	20 (10.5)	3 (9.1)	48 (7.7)	0.23
Abdominal distension		22 (16.2)	25 (9.5)	62 (32.6)	3 (9.1)	112 (18.0)	< 0.01
Abdominal tenderness		13 (9.6)	26 (9.9)	26 (13.7)	5 (15.2)	70 (11.3)	0.48
Abdominal mass		13 (9.6)	91 (34.7)	24 (12.6)	4 (12.1)	132 (21.3)	< 0.01
Bowel sound (absent/ abnormal)		11 (8.1)	10 (3.8)	43 (22.6)	2 (6.1)	66 (10.6)	< 0.01
Rectal prolapse		15 (11.0)	2 (0.8)	1 (0.5)	0 (0.0)	18 (2.9)	< 0.01
Rectal mass		3 (2.2)	4 (1.5)	11 (5.8)	0 (0.0)	18 (2.9)	0.04
Blood on PR examination		19 (14.0)	31 (11.8)	94 (49.5)	19 (57.6)	163 (26.3)	< 0.01
Modified triad ^d		83 (61.0)	125 (47.7)	143 (75.3)	21 (63.6)	372 (59.9)	< 0.01
Diagnosis method, n (%)		Ultrasound	121 (89.0)	262 (100)	179 (94.2)	30 (90.9)	592 (95.3)
	CT scan	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	–
	Barium enema	1 (0.7)	0 (0.0)	1 (0.5)	1 (3.0)	3 (0.5)	–
	Surgery	12 (8.8)	0 (0.0)	10 (5.3)	2 (6.1)	24 (3.9)	< 0.01
Intussusception location, n (%)	Colo-colic	3 (2.2)	10 (3.8)	5 (2.6)	3 (9.1)	21 (3.4)	< 0.01
	Ileo-colo-colic	8 (5.9)	7 (2.7)	4 (2.1)	2 (6.1)	21 (3.4)	< 0.01
	Ileo-ileal	11 (8.1)	3 (1.2)	10 (5.3)	6 (18.2)	30 (4.8)	< 0.01
	Ileo-ileo-colic	4 (2.9)	5 (1.9)	6 (3.2)	0 (0.0)	15 (2.4)	< 0.01
	Ileocolic	109 (80.2)	234 (89.3)	163 (85.8)	20 (60.1)	526 (84.7)	< 0.01
	Jejuno-jejunum	0 (0.0)	0 (0.0)	1 (0.9)	1 (3.0)	2 (0.3)	–
	> 1 location ^e	1 (0.7)	3 (1.2)	1(0.5)	1 (3.0)	6 (1.0)	–
Pathological lead point, n (%)	Lymph node	41 (30.1)	19 (7.2)	3 (1.6)	15 (45.4)	78 (12.6)	< 0.01
	Appendix	0 (0.0)	0 (0.0)	2 (1.0)	1 (3.0)	3 (0.4)	–
	Payer's patch	1 (0.7)	1 (0.3)	1 (0.5)	0 (0.0)	3 (0.4)	–
	Polyp	1 (0.7)	0 (0.0)	0 (0.0)	1 (3.0)	2 (0.3)	–
	Others ^f	2 (1.4)	0 (0.0)	3 (1.6)	0 (0.0)	5 (0.8)	–
	Any lead point	45 (33.0)	20 (7.6)	9 (4.7)	17 (51.5)	91 (14.6)	< 0.01
Treatment modality, n (%)	Reduction	56 (41.2)	216 (82.4)	20 (10.5)	14 (42.4)	306 (49.3)	< 0.01
	Surgery	68 (50.0)	30 (11.5)	135 (71.1)	12 (36.4)	245 (39.5)	< 0.01

Table 2 The clinicopathological characteristics and management of the children with intussusception in India (Continued)

Variable Category		North (n = 136)	South (n = 262)	East (n = 190)	West (n = 33)	Total (n = 621)	P value
Surgery type, n (%)	Spontaneously resolved ^g	12 (8.8)	16 (6.1)	34 (17.9)	7 (21.2)	69 (11.1)	< 0.01
	None ^h	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	1 (0.2)	–
Surgery type, n (%)	No resection ⁱ	41 (60.3)	25 (83.3)	106 (78.6)	9 (75)	181 (73.9)	< 0.01
	With resection ⁱ	27 (39.7)	5 (16.7)	29 (21.5)	3 (25.0)	64 (26.1)	< 0.01
Outcome, n (%)	Discharged	129 (94.9)	262 (100)	181 (95.3)	31 (93.9)	603 (97.1)	< 0.01
	Referred	0 (0.0)	0 (0.0)	1 (0.5)	2 (6.1)	3 (0.5)	–
	LAMA ^j	3 (2.2)	0 (0.0)	1 (0.5)	0 (0.0)	4 (0.6)	–
	Died	4 (2.9)	0 (0.0)	7 (3.7)	0 (0.0)	11 (1.8)	–
Brighton Collaboration Criteria level, n (%)	Level 1	125 (91.9)	246 (93.9)	156 (82.1)	26 (78.8)	553 (89.1)	< 0.01
	Level 2	5 (3.7)	15 (5.7)	24 (12.6)	3 (9.1)	47 (7.6)	< 0.01
	Level 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	–
	No level	6 (4.4)	1 (0.4)	10 (5.3)	4 (12.1)	21 (3.4)	< 0.01
Illness in last 4 weeks, n (%)	Diarrhoea	10 (7.4)	55 (21.0)	11 (5.8)	4 (12.1)	80 (12.9)	0.04
	ARI	17 (12.5)	104 (39.7)	21 (11.1)	5 (15.2)	147 (23.7)	0.04

Notes: PR Per-rectal, ARI Acute respiratory illnesses

^aIncludes all vomiting including bilious vomiting

^bIncludes only bilious vomiting

^cClassical triad includes abdominal pain, vomiting and blood in stool

^dModified triad includes abdominal pain, vomiting and rectal bleeding (detected either as blood in stool or blood on per-rectal examination)

^eThe location of intussusception at more than one site; such as Ileo-colic + Colo-colic, Ileo-colic + Ileo-colo-colic, Ileo-colic + Ileo-ileo-colic, Ileo-colic + Ileo-ileal

^fOthers include cyst, Meckel's diverticulum, incisional hernia, intraluminal growth and malrotation

^gSpontaneously resolved: The patient was managed with IV fluids and nil orally, not required any additional intervention

^hNone- No definite treatment could be provided, as the patient(s) was referred or died before any definite treatment

ⁱThe denominators used for percentage estimation include patients undergone surgery only

^jLAMA: Left against medical advice

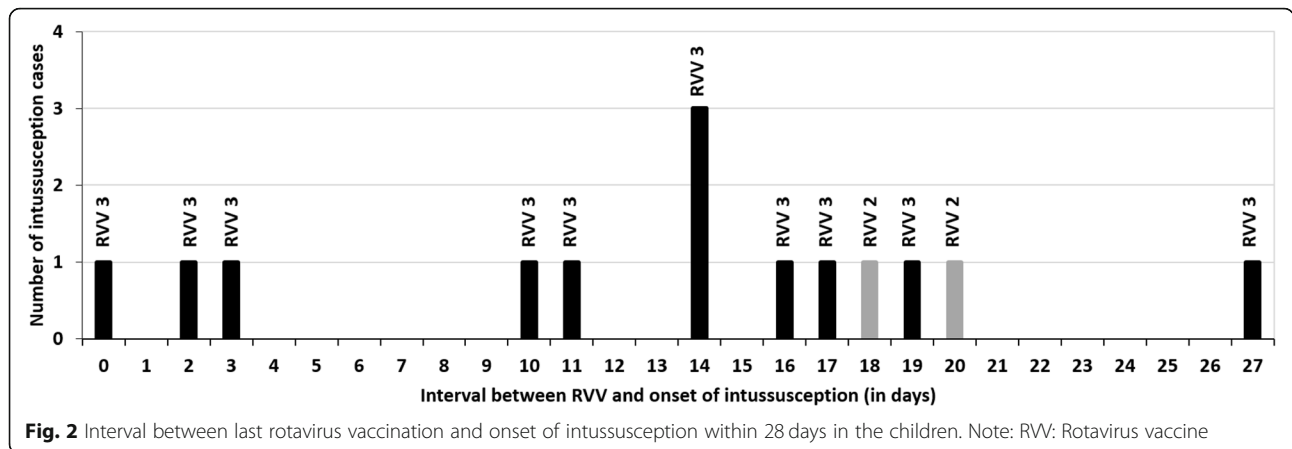
The p values for some parameters could not be estimated due to no value in at least two groups

present in 59.9% cases; 47.7% in South to 75.3% in East regions ($p < 0.01$).

Most of the cases (95.3%) were diagnosed by ultrasound. Ileocolic (84.7%) was the most common site of intussusception. A pathological lead point (PLP) was documented in 91 (14.6%) cases and lymph nodes or Payer's patch were the commonest (13.0%) and few had appendix or polyps (Table 2). While 49.3% cases were reduced, 39.5% underwent surgery and 11.1% resolved spontaneously. More children in East region (71.1%) underwent surgery followed by North region (50.0%) ($p < 0.01$). Among those who underwent surgery, 26.1% children required bowel resection, and 39.5% were from the North region. The onset-admission interval was longer for the cases who underwent surgery (median 2 days; IQR 1, 3) than reduction (median 1 day; IQR 1, 3) ($p < 0.01$) (Supplementary Table 2). Among the children who presented on the day of onset, 62.3% were managed by reduction (28.9% required surgery), which declined to 35.1% when they presented after 3 days (48.3% required surgery) ($p < 0.01$) (Supplementary Table 2). Seven hospitals (East-1, North-1, and South-1) were conducting only surgical management. At the hospitals with both facilities (reduction and surgery), 31.0% (127/404) children underwent surgery for indications: failed reduction

(32.2%), late presentation (> 3 days since onset, 28.3%) and associated complications (39.3%) ($p < 0.01$). Most of the cases (97.1%) recovered and were discharged. Eleven cases (North-4 and East-7) died of post-surgery sepsis, shock and multiorgan failure. The median hospitalisation period was 3 days (IQR 2, 6 days) ranging from 2 to 5 days (South: 2 days, IQR 2, 3 days; North: 3 days, IQR 1, 7 days; West: 4 days, IQR 2, 6 days; and East: 5 days, IQR 3, 8 days; $p < 0.01$). The median hospital stay periods for children who underwent surgery, reduction and spontaneously resolved were 7 days (IQR 5, 9 days), 2 days (IQR 1, 2 days) and 3 days (IQR 2, 5 days), respectively ($p < 0.01$) (Supplementary Table 2). CAC assigned 89.1% (553/621) and 7.6% cases as Level 1 and 2 respectively according to the BCCD. Diarrhoea and acute respiratory illnesses (ARIs) within 4 weeks prior to intussusception was reported in 12.9 and 23.7% children respectively. More children from South region had history of diarrhoea (21%) and ARIs (39.7%) than other regions ($p < 0.05$).

Vaccination information was available for 487 (78.4%) children and 391 (80.2%) of those with vaccination information had no RVV exposure. Out of 96 (15.4%) children who received any RVV (RVV-1, $n = 96$; RVV-2, $n = 88$; and RVV-3, $n = 65$), 12 children received RVV in



the 1–21 days preceding onset of intussusception and most ($n = 10$) after RVV-3 (median age 3.8 months, IQR 3.6, 4.2 months) (Supplementary Table 3). As shown in Fig. 2, only two cases occurred during 1–7 days after the third dose RVV and one case occurred on the vaccination day. At the four sites from three states where RVV (Rotavac™) was introduced, no increase in either intussusception case load (RR = 0.44; 95% CI 0.22, 1.18) or case rate per 1000 paediatric surgery admission (RR = 0.5; 95% CI 0.3, 1.2) during the post-RVV introduction period were observed (Table 3).

Discussion

We observed regional variances in the intussusception case load and case rate per 1000 paediatric surgery admission, high in the South region and low in the West region. Higher number of cases were observed during March to June months, which was comparable to other reports from India [14, 15, 17, 24, 25]. The male predominance (65.7%), median age at 8 months and high case load at 4–7 months of age (40.0%) were similar to

other reports from India and globally (proportion of male: 63.0–77.2%; median age: 5–8 months and high case load age: 4–9 months) [14, 15, 17, 18, 21, 24, 26, 27]. About 37.0% of cases occurred during 2nd to 6th month of age, the usual age for administration of RVV. The children came from all socioeconomic categories and in all the regions. The proportion of exclusively breastfed children (< 6 months) was lower than national average (52.1%, 2015–16) [22]. The children weaned with ragi food (only in South region) had intussusception earlier (median 1 month) than those weaned with wheat (median 3 months) and rice (median 4 months) based food. A shorter exclusive breastfeeding duration with mixed feeding and some weaning foods may have some role in intussusception occurrence. Exposure to foreign proteins and enteric infections are potential risk factors for intussusception, but we couldn't find any report on association with any specific diet. There were significant variations for several sociodemographic and dietary practice parameters across the regions (Table 1). The classical triad was documented in 34.8% cases, which was higher than reports

Table 3 The intussusception cases and case ratios during post-rotavirus vaccine introduction period compared to pre-introduction periods

Region (number of sites) ^a	Post-RVV period (Apr- Sep 2017)		Pre-RVV period (Oct 2016 - Mar 2017)				Pre-RVV period (Apr- Sep 2016)			
	No of cases	IS case rate	No of cases	IS case ratio	RR (95% CI) for cases	RR (95% CI) for IS case rate	No of cases	IS ratio	RR (95% CI) for cases	RR (95% CI) for IS case rate
East ($n = 2$) ^a	20	20.4	29	29.9	0.69 (0.33–1.2)	0.67 (0.3–1.28)	45	34.6	0.44 (0.2–1.15)	0.58 (0.32–1.2)
North ($n = 1$) ^a	0	0	2	27.4	–	–	3	37.5	–	–
South ($n = 1$) ^a	6	13.3	8	20.4	0.75 (0.45–1.24)	0.65 (0.48–1.23)	11	26.4	0.55 (0.28–1.2)	0.51 (0.3–1.22)
Pooled ($n = 4$) ^a	26	16.3	39	27.2	0.67 (0.34–1.19)	0.6 (0.3–1.18)	59	32.8	0.44 (0.22–1.18)	0.5 (0.3–1.2)

Note: IS Intussusception, *Intussusception (IS) case rate* Intussusception cases per 1000 paediatric surgery admission, *RVV* Rotavirus vaccine, *RR* risk ratio with 95% confidence interval (CI), *RVV*: Rotavirus vaccine

The comparison includes the data from four study sites in three states

^aNumbers in the bracket with the regions indicate the numbers of study sites per region where RVV was introduced

Post-RVV period: April 2017 to September 2017 (6 months)

Pre-RVV period: Comparison has been done for two pre-intervention periods of 6 months each; October 2016 to March 2017- the immediate pre-RVV introduction period and April 2016 to September 2016- the calendar months comparable period during the previous year

from India (19.0%) and South Korea (7.6%), but lower than Tanzania (42.5%) [15, 24, 28]. The regional variation in the classical triad appeared to parallel with the interval between illness onset and hospitalization. Ultrasound was the commonest (95.3%) mode of diagnosis, as reported (72.0–100%) from India and other countries [15, 18, 28–30]. Ileocolic was the most common location, similar to reports (68.0–79.0%) from India and globally [3, 7, 8, 14]. PLPs observed in this study was higher than reported in studies (8.0–9.0%) from India and Tanzania with appendix and lymph nodes as the common [31, 32]. The cases who presented early were more frequently managed non-surgically with shorter stay (2–3 days) compared to those with surgical intervention (7 days). There were significant variations in the clinical features among the children across the regions, which may be due to the interval for presentation or clinical practices followed at the hospitals (Table 2). Death was observed in 1.7% cases, which was comparable to reports from India (1.0%) and other countries from Asia (0.25–6.0%), Latin America (1.0–5.0%), but lower than the African countries (2.0–25.0%) [17, 18, 24, 28, 29, 31–33]. Level 1 BCCD was met by 89.1% of the cases, similar to other reports from India [5, 7, 14]. Failed documentation of reduction prevented some cases meeting the BCCD level 1 certainty.

From the limited period of post-RVV (Rotavac™) introduction at four sites (from three states), no increase in the intussusception case load and case rate per 1000 paediatric surgery admission were observed. Intussusception within 1–21 days was observed mostly after the third RVV dose, which also overlaps with the age of natural occurrence. Under the NIP, RVV is given at 6, 10, 14 weeks of age and allowed before 12 months of age [34]. A delay in RVV administration may coincide with the high case load age of natural intussusception (4–7 months age), which may make the interpretation of association with the vaccine difficult. In routine practice, documentation of vaccine exposure should improve and appropriate guidance to parents be given regarding the subsequent RVV vaccination. Monitoring of intussusception risk is recommended for countries as part of the RVV introduction program [35, 36]. In the absence of any specific population denominator for tertiary care hospitals, estimation of incidence in Indian context is difficult. The intussusception case rate per 1000 paediatric surgery admissions may be a proxy indicator for monitoring and comparison across the sites and regions with RVV introduction.

Early suspicion, case detection and referral to appropriate hospital are critical for minimizing the surgical interventions and favourable outcomes. Efforts are needed to equip and enable the public health facilities for non-surgical management in children, though this depends on the timing of the presentation to hospital.

The epidemiology, clinical presentation and management of intussusception in children across the regions may serve as baseline for future studies. The regional representation and mix of private- and public-sector hospitals were the advantages for this surveillance.

This study had some limitations. In absence of definite catchment population and referral pattern, population-based incidence or case rate estimation was not possible. The etiologies and risk factors for intussusception were not studied.

Conclusion

To conclude, the intussusception cases were seen all across the country and the majority of the cases occurred during the first year of life. The high case load age (4–7 months) for intussusception in children coincided with the age of RVV third dose. Some variations in case loads across the different regions and seasonality were observed. The potential role of diet exposure, weaning practices and food like ragi in intussusception needs further evaluation. No increased occurrence of intussusception cases was observed during the limited RVV post-introduction period. Early case detection, prompt referral and appropriate management are needed to avoid surgical intervention and complications. Immunization exposure must be documented to assess the vaccine associated risk. In absence of population-based incidence or case rate, the intussusception case rate per 1000 paediatric surgery admission may be used for inter-regional comparison and trend monitoring.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12887-020-02293-5>.

Additional file 1. Supplementary document 1- Supplementary Figure 1: The study sites and their locations according to the regions. Supplementary document 2- Supplementary Table 1: The International Classification of Diseases (ICD) codes for review of the cases from medical records. Supplementary document 3- Supplementary Figure 2: The flow chart for case screening and recruitment. Supplementary document 4- Supplementary Figure 3: Age distribution of children with intussusception in India (region wise and pooled). Supplementary document 5- Supplementary Table 2: The mode of treatment according to the interval between onset, admission and intervention for the children with intussusception. Supplementary document 6- Supplementary Table 3: The intussusception cases during risk periods after rotavirus vaccine exposure.

Abbreviations

CRF: Case record form; CAC: Case Adjudication Committee; ICD: International Classification of Diseases; IQR: Interquartile range; TAG: Technical Advisory Group; WHO: World Health Organization; RVV: Rotavirus vaccine; SLI: Standard of living index; NIP: National immunization programmes.

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'The INCLIN Intussusception Surveillance Network Study Group' list of authors

1. Manoja Kumar Das

Director Projects, The INCLIN Trust International, New Delhi, India
Email: manoj@inclintrust.org

2. Narendra Kumar Arora

Executive Director, The INCLIN Trust International, New Delhi, India
Email: nkarora@inclintrust.org

3. Bini Gupta

Assistant Research Officer, The INCLIN Trust International, New Delhi, India
Email: drbini.gupta02@gmail.com

4. Apoorva Sharan

Research Officer, The INCLIN Trust International, New Delhi, India
Email: apoorva@inclintrust.org

5. Mahesh K. Aggarwal

Deputy Commissioner-Immunization, Ministry of Health & Family Welfare, Government of India, New Delhi, India
Email: drmkagarwal2@gmail.com

6. Pradeep Haldar

Deputy Commissioner-Immunization, Ministry of Health & Family Welfare, Government of India, New Delhi, India
Email: pradeephaldar@yahoo.co.in

7. Patrick L F Zuber

Group Leader Global Vaccine Safety and Vigilance Team, World Health Organization, Geneva, Switzerland.
Email: zuberp@who.int

8. Jan Bonhoeffer

President; Brighton Collaboration Foundation and Assistant Professor; Infectious Diseases and Vaccines, University Children's Hospital, Basel, Switzerland
Email: jan.bonhoeffer@gmail.com

9. Arindam Ray

Senior Program Officer, Bill and Melinda Gates Foundation, India Country Office, New Delhi, India
Email: arindam.ray@gatesfoundation.org

10. Ashish Wakhlu

Professor, Department of Paediatric Surgery, King George's Medical University, Lucknow, Uttar Pradesh, India
Email: ashish_wakhlu@hotmail.com

11. Bhadrash R. Vyas

Professor, Department of Paediatrics, MP Shah Government Medical College, Jamnagar, Gujarat, India
Email: bhadreshryas@yahoo.co.uk

12. Javeed Iqbal Bhat

Assistant Professor, Department of Paediatrics, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India
Email: drjaveediqbal@gmail.com

13. Jayanta K. Goswami

Professor, Department of Paediatric Surgery, Gauhati Medical College, Guwahati, Assam, India
Email: jayantagoswami@hotmail.com

14. John Mathai

Professor, Department of Paediatrics, PSG Institute of Medical Sciences, Coimbatore, Tamil Nadu, India
Email: psg_peds@yahoo.com

15. Kameswari K.

Professor, Department of Paediatric Surgery, Andhra Medical College, Vishakhapatnam, Andhra Pradesh, India
Email: kameswari1956@gmail.com

16. Lalit Bharadia

Consultant Paediatric Gastroenterologist, Fortis Escorts Hospital, Jaipur, Rajasthan, India
Email: lalitbharadia@gmail.com

17. Lalit Sankhe

Assistant Professor, Department of Community Medicine, Grant Medical College & JJ Hospital, Mumbai, Maharashtra, India
Email: sankhelalit@yahoo.com

18. Ajayakumar M.K.

Professor, Department of Paediatric Surgery, Government Medical College & SAT Hospital, Thiruvananthapuram, Kerala, India
Email: drjaykumarmk@gmail.com

19. Neelam Mohan

Consultant Paediatrics Gastroenterology, Medanta—The Medicity, Gurgaon, Haryana, India
Email: drneelam@yahoo.com

20. Pradeep K. Jena

Professor, Department of Paediatric Surgery, SCB Medical College, Cuttack, Odisha, India
Email: drpkjena@gmail.com

21. Rachita Sarangi

Professor, Department of Paediatrics, IMS & SUM Medical College & Hospital, Bhubaneswar, Odisha, India
Email: rachitapaedia@gmail.com

22. Rashmi Shad

Consultant Paediatrics, Choithram Hospital and Research Centre, Indore, Madhya Pradesh, India
Email: drashmishad@yahoo.com

23. Sanjib K. Debbarma

Associate Professor, Department of Paediatrics, Agartala Government Medical College, Agartala, Tripura, India
Email: dr_sanjibdb@rediffmail.com

24. Shyamala J.

Consultant Paediatrics, Apollo Hospitals, Chennai, Tamil Nadu
Email: jaymoorthy@hotmail.com

25. Simmi K. Ratan

Professor, Department of Paediatric Surgery, Maulana Azad Medical College, Delhi, India
Email: drjohnsimmi@yahoo.com

26. Suman Sarkar

Assistant Professor, Department of Paediatrics, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India
Email: dr.sumansarkar@gmail.com

27. Vijayendra Kumar

Professor, Department of Paediatric Surgery, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India
Email: drvijayendrkr@rediffmail.com

28. Yoga Nagender

Consultant Paediatric Surgery, Apollo Hospital, Hyderabad, Telangana, India
Email: yogimamidi@yahoo.com

29. Anand P. Dubey

Professor, Department of Paediatrics, Maulana Azad Medical College, Delhi, India
Email: Anand_dubey52@hotmail.com

30. Atul Gupta

Consultant Paediatric Surgery, Fortis Escorts Hospital, Jaipur, Rajasthan, India
Email: atul.gupta1@fortishealthcare.com

31. Bashir Ahmad Charoo

Professor, Department of paediatrics, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India
Email: charoobash@gmail.com

32. Bikasha Bihary Tripathy

Associate Professor, Department of Paediatric Surgery, IMS & SUM Medical College & Hospital, Bhubaneswar, Odisha, India
Email: bbtripathy.dr@gmail.com

33. Cenita J. Sam

Professor, Department of Paediatric Surgery, PSG Institute of Medical Sciences, Coimbatore, Tamil Nadu, India
Email: cenitasivamani@yahoo.com

34. G. Rajendra Prasad

Professor, Department of Paediatric Surgery, Andhra Medical College, Vishakhapatnam, Andhra Pradesh, India
Email: dr.grajendrprasad@gmail.com

35. Gowhar Nazir Mufti

Assistant Professor, Department of Paediatric Surgery, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India
Email: gowharmufti@yahoo.co.in

36. Harish Kumar S.

Paediatrics Radiologist, Apollo Hospitals, Chennai, Tamil Nadu, India
Email: drharishkumar.s@gmail.com

37. Harsh Trivedi

Professor, Department of Paediatric Surgery, MP Shah Government Medical College, Jamnagar, Gujarat, India
Email: trivediharsh@indiatimes.com

38. Jimmy Shad

Consultant Paediatric Surgery, Apollo Hospitals, Chennai, Tamil Nadu, India
Email: shadjimmy@yahoo.co.in

39. K. Jothilakshmi

Professor, Department of Paediatrics, PSG Institute of Medical Sciences, Coimbatore, Tamil Nadu, India
Email: drjothi.cbe@gmail.com

40. K. Sharmila

Consultant Paediatrics, Apollo Hospital, Hyderabad, Telangana, India
Email: sharmilakaza@gmail.com

41. Kaushik Lahiri

Department of Paediatric Surgery, Gauhati Medical College, Guwahati, Assam, India
 Email: Kaushik_1671979@rediffmail.com

42. Meera Luthra

Consultant Paediatric Surgery, Medanta- The Medicity, Gurgaon, Haryana, India
 Email: meera.luthra@medanta.org

43. Nihar Ranjan Sarkar

Associate Professor, Department of Radiology, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India
 Email: dr.niharsarkar@gmail.com

44. P. Padmalatha

Professor, Department of Paediatrics, Andhra Medical College, Vishakhapatnam, Andhra Pradesh, India
 Email: padmap_2000@yahoo.com

45. Pavai Arunachalam

Professor, Department of Paediatric Surgery, PSG Institute of Medical Sciences, Coimbatore, Tamil Nadu, India
 Email: pavai4321@yahoo.com

46. Rakesh Kumar

Associate Professor, Department of Paediatrics, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India
 Email: drjaiswalrakesh@gmail.com

47. Ruchirendu Sarkar

Professor, Department of Paediatric Surgery, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India
 Email: ruchirendu@gmail.com

48. S.S.G. Mohapatra

Professor, Department of Radiology, IMS & SUM Medical College & Hospital, Bhubaneswar, Odisha, India
 Email: drartifact@gmail.com

49. Santosh Kumar A.

Professor, Department of Paediatrics, Government Medical College & SAT Hospital, Thiruvananthapuram, Kerala, India
 Email: hod.pediatrics.sath@gmail.com

50. Saurabh Garge

Consultant Paediatric Surgery, Choithram Hospital and Research Centre, Indore, Madhya Pradesh, India
 Email: saurabhgarge8@gmail.com

51. Subrat Kumar Sahoo

Associate Professor, Department of Paediatric Surgery, IMS & SUM Medical College & Hospital, Bhubaneswar, Odisha, India
 Email: dr_subratsahoo@yahoo.com

52. Sunil K. Ghosh

Associate Professor, Department of Pediatric Surgery, Agartala Government Medical College, Agartala, Tripura, India
 Email: sunilkrghosh752@gmail.com

53. Sushant Mane

Assistant Professor, Department of Paediatrics, Grant Medical College & JJ Hospital, Mumbai, Maharashtra, India
 Email: drsush2006@gmail.com

54. Christine G. Maure

Safety and Vigilance Team, Health Organization, Geneva, Switzerland
 Email: maurec@who.in

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Author's contributions

Study conceptualisation, study design, protocol development, training, data analysis, interpretation: MKD and NKA. Study coordination, monitoring, and data cleaning: MKD, BG, and AS. Data analysis, interpretation, and manuscript preparation: MKD and BG. Protocol development, quality assurance and monitoring: MKA, PH, PLFZ, JB, AR, and CGM. Participant recruitment and data collection: AW, BRV, JIB, JKG, JM, KK, LB, LS, AMK, NM, PKJ, RS-1, RS-2, SKD, SJ, SKR, SS, VK, YN, APD, AG, BBT, CJS, GRP, GNM, HKS, HT, JS, KJ, KS, KL, ML, NRS, PP, PA, RK, RS-3, SSGM, SKA, SG, SKS, SKG, and SM. All authors reviewed, provided critical input and approved the final version. The content represents the views of the authors alone and do not necessarily represent the official positions of their organizations, World Health Organization or Ministry of Health and Family Welfare, Government of India.

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All data is available with the investigators and can be provided by the corresponding author upon reasonable request.

Ethics approval and consent to participate

The study protocol was reviewed and approved by The INCLIN Independent Ethics Committee, The INCLIN Trust International, New Delhi, India (Ref: IIEC 23) and all participating Study Site Institute Ethics Committees. The list of ethics committees of the study site institutes included: Institutional Ethics Committee, King George's Medical University, Lucknow, Uttar Pradesh, India; Institutional Ethics Committee, MP Shah Government Medical College, Jamnagar, Gujarat, India; Institutional Ethics Committee, Sher-I-Kashmir Institute of Medical Sciences, Srinagar, Jammu & Kashmir, India; Institutional Ethics Committee, Gauhati Medical College, Guwahati, Assam, India; Institutional Human Ethics Committee, PSG Institute of Medical Sciences, Coimbatore, Tamil Nadu, India; Institutional Ethics Committee, King George Hospital, Andhra Medical College, Vishakhapatnam, Andhra Pradesh, India; Institutional Ethics Committee, Fortis Escorts Hospital, Jaipur, Rajasthan, India; Institutional Ethics Committee, Grant Medical College & JJ Hospital, Mumbai, Maharashtra, India; Institutional Ethics Committee, Government Medical College & SAT Hospital, Thiruvananthapuram, Kerala, India; Medanta Institutional Ethics Committee, Medanta—The Medicity, Gurgaon, Haryana, India; Institutional Ethics Committee, SCB Medical College, Cuttack, Odisha, India; Institutional Ethics Committee, IMS & SUM Medical College & Hospital, Bhubaneswar, Odisha, India; Institutional Ethics Committee; Choithram Hospital and Research Centre, Indore, Madhya Pradesh, India; Institutional Ethics Committee, Agartala Government Medical College, Agartala, Tripura, India; Institutional Ethics Committee- Clinical Studies, Apollo Hospitals, Chennai, Tamil Nadu; Institutional Ethics Committee, Maulana Azad Medical College, Delhi, India; Institutional Ethics Committee, Institute of Post Graduate Medical Education and Research, Kolkata, West Bengal, India; Institutional Ethics Committee, Indira Gandhi Institute of Medical Sciences, Patna, Bihar, India; and Ethics

Committee, Apollo Hospital, Hyderabad, Telengana, India. The interviews with stakeholders were done after obtaining written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that there is no competing interests and conflict of interest.

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