Epidemiology of childhood intussusception in Bangladesh: Findings from an active national hospital based surveillance system, 2012–2016

Syed M. Satter[a,*], **Negar Aliabadi**[b], **Catherine Yen**[b], **Paul A. Gastañaduy**[b], **Makhdum Ahmed**[c], **Abdullah Mamun**[d], **Khaleda Islam**[e], **Meerjady S. Flora**[e], **Mahmudur Rahman**[e], **K. Zaman**[a], **Mustafizur Rahman**[a], **James D. Heffelfinger**[b], **Stephen P. Luby**[f], **Emily S. Gurley**[a], and **Umesh D. Parashar**[b]

[a]icddr,b, Bangladesh

[b]Centers for Disease Control and Prevention (CDC), Atlanta, USA

[c]The University of Texas MD Anderson Cancer Center, Houston, USA

[d]UBC and Vancouver General Hospital, Vancouver, Canada

[e]Institute of Epidemiology, Disease Control and Research (IEDCR), Dhaka, Bangladesh

[f]Center for Innovation in Global Health, Stanford University, USA

Abstract

Introduction—Rotavirus vaccines have significantly decreased the burden of diarrheal diseases in countries that have introduced them into their immunization programs. In some studies, there has been a small association between rotavirus vaccines and intussusception in post-marketing surveillance, high-lighting the importance of tracking incidence before and after vaccine introduction. The objective of this study was to describe the epidemiology of intussusception among Bangladeshi children pre-vaccine introduction.

Methods—We conducted active, hospital-based surveillance for intussusception at 7 tertiary care hospitals with pediatric surgical facilities during July 2012 to September 2016. Hospitalized children under 2 years of age were identified according to Brighton Collaboration level 1 criteria for intussusception. The frequency and proportion of intussusception among overall surgical admissions, as well as the demographic and clinical information of the cases is described.

Results—Overall 153 cases of intussusception among children <2 years-old were identified at participating sites over the enrolment period, confirmed by Level 1 Brighton criteria. These cases represented 2% of all surgical admissions under 2 years of age. One hundred twelve cases (73%)

*Corresponding author at: Programme for Emerging Infections, Infectious Diseases Division, icddr,b, Mohakhali, Dhaka 1212, Bangladesh. dr.satter@icddrb.org (S.M. Satter).

were male; the median age was 7 months; and the median duration of hospitalization was 7 days. One hundred forty-six (95%) children with intussusception required surgery, and 11 (7%) died.

Conclusions—Confirmed cases of intussusception represented nearly 2% of pediatric surgical admissions at tertiary referral centers in Bangladesh during the study period and 7% of children with intussusception died. Given the high burden of rotavirus disease in Bangladesh, vaccine introduction is warranted, however, further studies after introduction of rotavirus vaccine are necessary to determine any association between vaccine and intussusception in this setting.

Keywords

Bangladesh; Intussusception; Rotavirus; Hospital based surveillance; Rotavirus vaccination

1. Introduction

Since their introduction in 2006, rotavirus vaccines have decreased the morbidity and mortality of diarrheal disease in many countries that have included them in their national immunization programs [1–4]. Evidence from post-licensure studies continues to demonstrate decreases in rotavirus-related morbidity and mortality in these countries, however a low-level risk of intussusception has also been described following rotavirus vaccination [5–8].

Intussusception is a rare emergency medical condition that occurs in the absence of rotavirus infection, in which intestinal blockage results from part of the intestine folding into an adjacent portion. While spontaneous self-resolution of small-bowel intussusceptions has been reported [9,10], for the majority of intussusceptions, if treatment is not sought, this blockage can go on to create an obstruction, compromising blood circulation to involved portions of intestine. Intussusception cases occur most commonly in infants, with cases peaking between 4 and 6 months of age. The estimated global rate of intussusception is 74 cases per 100,000 children under 1 year of age, ranging between 9 and 328 case per 100,000 depending on geographic location [11]. The majority of cases, particularly among infants, are idiopathic [12].

A nearly 30-fold increased risk of intussusception was observed in the first 3–14 days after the first dose of the rhesus reassortant tetravalent vaccine Rotashield (RRV-TV; Wyeth Vaccines) following its introduction in the US in the late 1990s [13]. Subsequently, Rotashield was removed from the market and there was close vigilance for intussusception during clinical trials for two subsequently available rotavirus vaccines, the pentavalent Rotateq (RV5, Merck) and the monovalent Rotarix (RV1, GlaxoSmithKline) vaccines. Though intussusception was not associated with vaccine in the large-scale pre-licensure clinical trials [14,15] of RV5 and RV1, both vaccines were shown to be associated with a mild increased risk of intussusception (1–6 excess cases per 100,000 vaccinated children) in post-marketing surveillance in several high and middle income countries [5–8].

Post-licensure data on risk of intussusception with rotavirus vaccination from Asian countries data is lacking. The risk profile could differ in developing versus developed countries because of differences in vaccine performance as well as differences in the

epidemiology of intussusception. As Bangladesh prepares to introduce rotavirus vaccine into its national immunization program in the next 1–2 years, it is important to characterize the background epidemiology of intussusception and to plan for intussusception surveillance after vaccine introduction. This analysis aimed to describe the frequency, epidemiology and clinical characteristics of intussusception among children <2 years hospitalized at sentinel sites across Bangladesh.

2. Methods

2.1. Surveillance sites

In July 2012, an active, hospital-based rotavirus and intussusception surveillance system has begun in Bangladesh in collaboration with The Institute of Epidemiology, Disease Control and Research (IEDCR) under the Ministry of Health and Family Welfare and icddr,b. Geographically, Bangladesh is subdivided in seven different regions, and we aimed to have one hospital included per region. Sites began enrolment in three stages (Fig. 1), first in three sites (Dhaka, Rajshahi and Sylhet) in July 2012 followed by two sites (Rangpur and Chittagong) in February 2013 and in two additional sites (Khulna and Barisal) in August 2013 (Table 1). These hospitals were chosen based on the presence of surgical facilities and because they have high numbers of admissions for pediatric surgeries. The original site in Rangpur closed during July–December 2016 due to closer of pediatric surgery ward and so an alternative tertiary hospital in the area was added in its place in January 2016 (see Table 2).

2.2. Case definition and enrolment

Field surveillance staff reviewed hospitalization and radiology logbooks weekly and met with surgical and radiological staff daily to identify suspected intussusception cases among children <2 years of age. Once a potential intussusception case was identified, a surveillance physician reviewed the medical record to determine if the child met the case definition for confirmed intussusception as per Brighton Collaboration Level 1 criteria, (Box 1) [16]. Because autopsies are not commonly done in Bangladesh, autopsy criteria were not used for the detection cases. Brighton Collaboration Level 2 and 3 criteria were included to the case definition for the surveillance system beginning in December 2014 to enroll clinically suspected cases of intussusception.

Box 1

Level 1, 2, or 3 Brighton Collaboration criterion (i.e. "definite", "probable", and "possible" cases, respectively) for the diagnosis of intussusception among hospitalized children aged <2 years

Level 1 of diagnostic certainty (or "definite")

- Surgical criteria:
  - Demonstration of invagination of the intestine at surgery; and/or
- Radiological criteria:

– Demonstration of invagination of the intestine by either air or liquid contrast enema; or

– Demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features (target sign or doughnut sign on transverse section and a pseudo kidney or sandwich sign on longitudinal section), that is proven to be reduced by hydrostatic enema on post-reduction ultrasound; and/or

- Autopsy criteria:

  – Demonstration of invagination of the intestine at autopsy

Level 2 of diagnostic certainty (or "probable")

- Clinical criteria:

  Two major criteria or one major criterion and three minor criteria (see below)

Level 3 of diagnostic certainty (or "possible")

- Clinical criteria:

  Four or more minor criteria (see below)

  Major criteria:

  1. Evidence of intestinal obstruction, by either of the following: Bile-stained vomiting and either abdominal distention or abnormal or absent bowel sounds, or plain radiograph of abdomen showing dilated bowel loops and fluid levels.

  2. Features of intestinal invagination with any of the following: Abdominal mass, rectal mass, rectal prolapse, visible intussusceptum or soft-tissue mass observed on plain radiograph film, ultrasound, or CT scan.

  3. Evidence of intestinal vascular compromise or venous congestion with any of the following: Rectal bleeding or stool containing "red currant jelly" material or blood observed on rectal examination

  Minor criteria:

  1. Predisposing factors (age <1 year and male)

  2. Abdominal pain

  3. Vomiting

  4. Lethargy

  5. Pallor

  6. Hypovolemic shock

  7. Plain radiograph of abdomen showing nonspecific abnormalities

Upon enrolment, demographic information, rotavirus vaccination history, clinical information, including diagnostic procedures and outcome of hospitalization, were collected from the parents or caregivers and hospital records using a standard questionnaire. Each child's rotavirus vaccination status was ascertained by querying parents because although rotavirus vaccines are not routinely available in Bangladesh, they are available in the private market and have been used in clinical trials in some regions. In addition, detailed contact information of enrolled children's families was collected to ascertain outcomes at 30 days following discharge by telephone and in-person visit. In November 2015, a new question was added to the questionnaire inquiring about the date of onset of symptoms.

2.3. Analysis

We analyzed confirmed cases of intussusception. Aggregate numbers of admissions to the pediatric surgical ward and deaths among children under 2 years were extracted from hospital logbooks to obtain denominators for analyses.

We described the clinical characteristics of children admitted with intussusception and the frequency of intussusception-associated hospitalizations by site. To estimate the proportion of intussusception-associated hospitalizations among total pediatric surgical hospitalizations of children under two years, the overall number of children under two years admitted for intussusception was divided by the total number of pediatric surgery admissions of children under two years during the surveillance period.

2.4. Ethical considerations

We obtained written informed consent from the enrolled children's parents or guardians. The study protocol was reviewed and ethics approval obtained from the ethical review committee of icddr,b.

3. Results

From July 2012 to September 2016, we identified 153 children with confirmed Brighton level 1 intussusception, accounting for ~2% of 8346 children <2 years of age admitted for pediatric surgery (Table 1). The proportions of confirmed cases of intussusception among children admitted to pediatric surgical wards in the seven divisions ranged from 0 to 3.6%. Most patients with intussusception (91%) were <1 year of age (Fig. 2) with a median age of 7 months (IQR = 5–9); 65% were 6–11 months and 3% were   3 months old. Most children with intussusception were male (73%). Among the confirmed intussusception cases, 15 (10%) were diagnosed via ultrasound only and the rest were diagnosed during surgery with or without ultrasonagraphy. The majority of children were treated surgically (95%), and 58 (39%) required bowel resection. Children were hospitalized for a median of 7 days (IQR = 5–9) and no recurrences of intussusception were identified. None of the children with intussusception had a history of rotavirus vaccination. Intussusception cases were reported year-round with no evidence of seasonality (Fig. 3).

Eleven deaths (7%) were reported among the 153 children hospitalized with confirmed intussusception. During this surveillance period, 511 children <2 years age died due to any surgical procedure; of whom, 11 (2%) died due to intussusception. All 11 children who died

underwent surgical treatment; 8 died during hospitalization (3 due to circulatory shock and 5 due to septicemia) and 3 died following discharge from the hospital. The deaths of the three children who left the hospital before treatment was completed were confirmed by follow up with their parents but unfortunately, we failed to ascertained the cause of death. Of the 59 children with confirmed Level 1 intussusception enrolled after the addition of the question about date of onset of symptoms, the median duration of symptoms prior to admission was 3 (range: 0–17) days; the time from onset to admission was shorter for the 2 children who died (median: 1.5 day; range 1–2 days) than for the 57 children who survived (median 3 days; range 0–17 days, p = 0.17), though these findings were not statistically significant.

4. Discussion

We describe the results of over four years of active hospital-based surveillance for intussusception in all 7 seven divisions in Bangladesh. The proportion of males diagnosed with intussusception was higher than that of females, which is consistent with other reported data on intussusception cases occurring in the absence of rotavirus vaccine administration from both high and low income settings [17–22]. The reasons for this male predominance are unclear but may reflect greater healthcare seeking for male children with intussusception, genetic factors or both.

The age distribution of intussusception cases was similar to that seen in other studies in Asia which have reported that the majority of cases were unrelated to vaccination, occurred between 6 and 11 months of age and, importantly, that very few cases among those under 14 weeks of age [18,19,23]. In studies showing an association of intussusception with rotavirus vaccine, the risk has been noted primarily in the first week after vaccine administration [5,6,24]. In subjects in this study, none of whom had been previously vaccinated, no cases were identified among children less than 2 months of age, suggesting that targeting children <3 months for vaccination may avoid vaccine administration during the peak risk period for naturally occurring intussusception. Currently, the World Health Organization recommends that the first rotavirus vaccine dose should be administered as soon as possible after 6 weeks of age, with subsequent doses (1 for monovalent and 2 for pentavalent) administered at 4 weeks intervals [25].

The case-fatality rate among children with intussusception was 7% in this study. Few published data on intussusception fatality rates from countries in Asia region have been reported which can be used to comparison with findings from this studies. Two studies conducted in Vietnam found a lower rate, with one describing 869 identified intussusception cases (annual rate 296/100,000 infants) in a three year period, and no deaths [11,18]. One reason for this discrepancy may be that a greater proportion of children with intussusception in the current study were treated surgically than in the Vietnam study, and more than one-third of our surgically-treated cases had bowel resections. It is also possible, that there were longer delays between onsets of symptoms to admission among cases in this study compared than in the studies from Vietnam. In one of the studies from Vietnam, the median onset of symptoms to admission was 5 h [18], compared to 3 days in this study. It is possible that in our study, there was a greater severity of disease on admission due to the longer time between onset and admission, which could explain higher rates of surgical treatment and

death in our study. Indeed, case fatality rates as high as 28–34% have been reported in some studies conducted in Africa, where delays in presentation are common and the predominant mode of treatment is surgical [26]. An additional possible reason for the higher case-fatality rate observed in our study may be because it was a prospective study, which made it easier to follow-up with patients after discharge and determine their outcomes.

This analysis was subject to several limitations. We were unable to capture children who died on arrival or soon after arriving at the hospital and those who did not present to a hospital for care. Some sites did not identify any cases, which may indicate a lack of sensitivity of the surveillance system or interruptions in the availability of surgical resources. Another limitation was the lack of sentinel site catchment data, as such we were unable to report intussusception incidence rates to which post-vaccine introduction rates could be compared. A prior study from Bangladesh with both retrospective and prospective analyses, reported incidence rates of probable and possible intussusception in rural areas [27]. In this study, the retrospective surveillance estimated that the incidence of possible and probable intussusception ranged from 0 to 17.8 and 17.7–81.7 cases per 100,000 children under 2 years, respectively, whereas their prospective surveillance, estimated that the incidence of intussusception ranged from 0 to 18.7 and 0–9.7 cases per 100,000 population, respectively.

5. Conclusion

This study provides valuable information on the baseline epidemiology of childhood intussusception in Bangladeshi children prior to the introduction of rotavirus vaccination. Given the noted differences in case identification by site, the rarity of intussusception, and the small additional risk conferred by administration of rotavirus vaccine seen in other settings, further research is necessary to assess both health care utilization and post-vaccine introduction intussusception risk. Given the differences noted in identification of intussusception cases across sites, understanding health care utilization in these catchment areas is worth pursuing to refine the sensitivity of the surveillance system. To assess post-vaccine introduction risk, use of the case series approach, which will not require comparison of incidence rates, after vaccine introduction is warranted, as well as continued high-quality surveillance on diarrheal burden using a hospital-based rotavirus surveillance platform. Both of these will allow determination of benefits and risks of rotavirus vaccines in Bangladesh.

Acknowledgments

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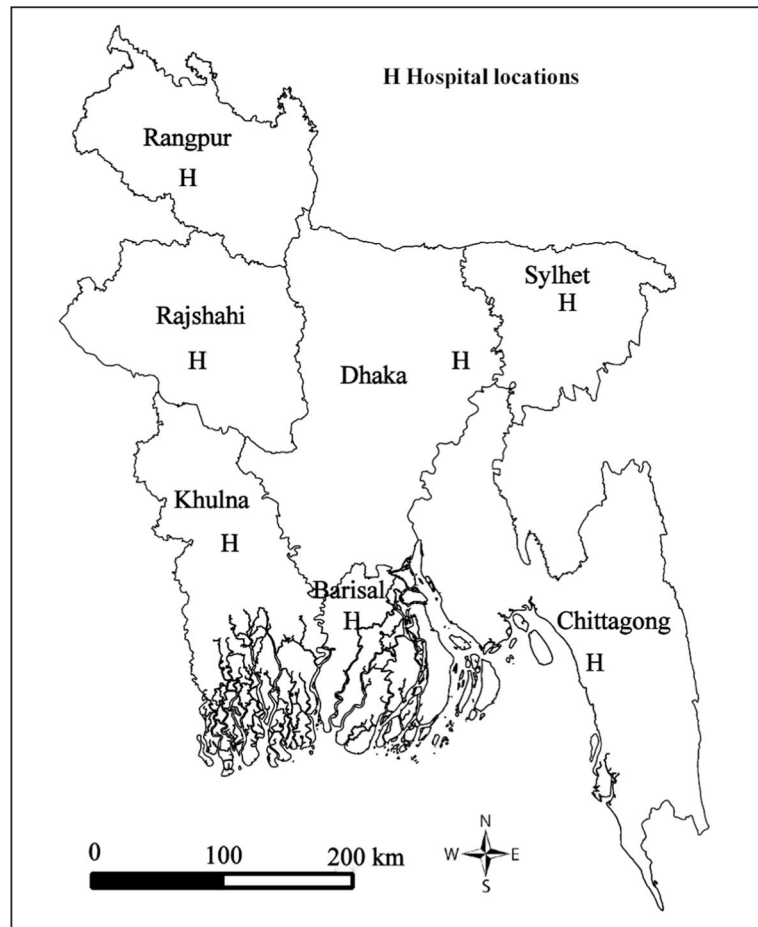
Fig. 1.
Locations of sentinel hospitals where intussusception surveillance was conducted in
Bangladesh, July 2012–September 2016. **H** represents the location of hospital within each
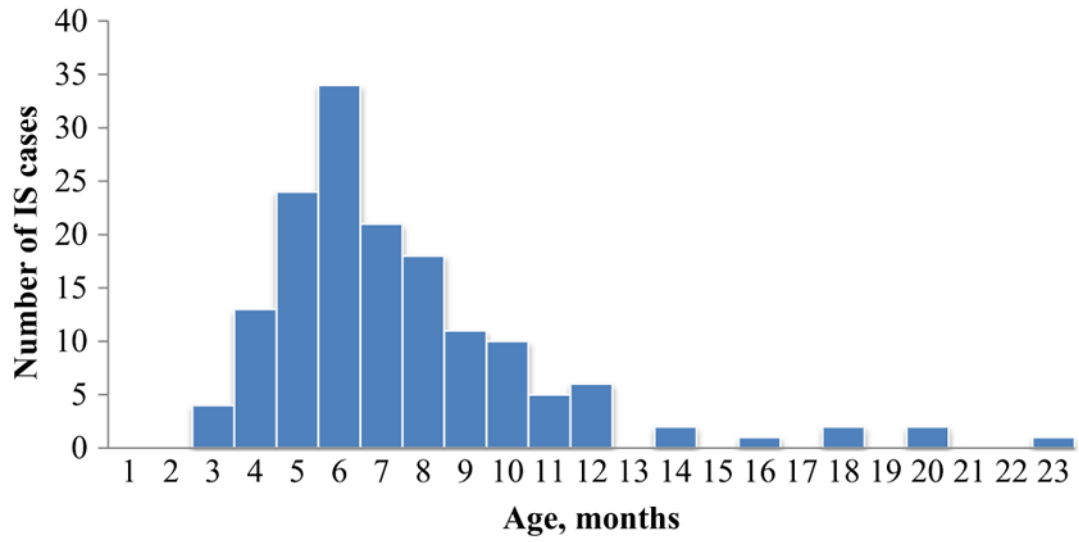division.

Fig. 2.
Age distribution of Intussusception associated hospitalizations among children <2 years of age (N = 153) at 8 sentinel hospitals in Bangladesh, July 2012–September 2016.
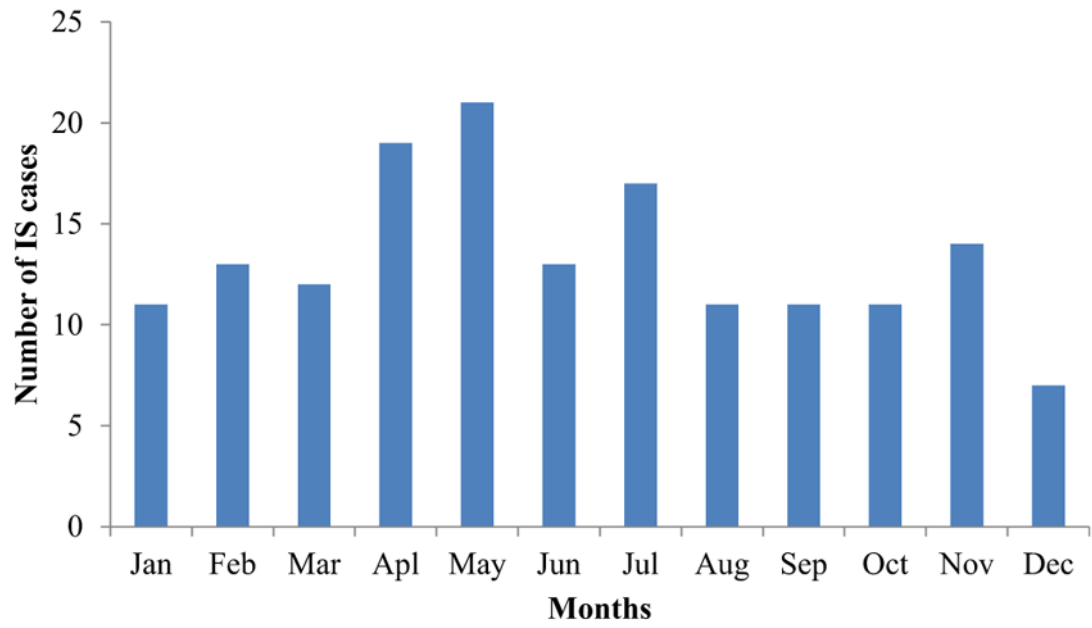
Fig. 3.
Hospitalization by month for Intussusception (N = 153) among children aged <2 years at sentinel hospitals in Bangladesh, July 2012–September 2016.

Table 1

Intussusception (IS) hospitalizations among children aged <2 years, by site in Bangladesh, July 2012 – September 2016.

Location of sentinel sites	Number of children admitted for pediatric surgery	Number of suspected IS cases	Number of confirmed IS cases	% of all pediatric surgical cases (95% CI)
Dhaka	1211	15	10	0.83 (0.40–1.51)
Rajshahi	3009	177	94	3.12 (2.53–3.81)
Sylhet	689	31	25	3.63 (2.36–5.31)
Chittagong	131	6	4	3.10 (0.84–7.63)
Rangpur[a]	20	0	0	0
Khulna	667	0	0	0
Barisal	1941	45	17	0.88 (0.51–1.40)
Rangpur[b]	678	8	3	0.44 (0.09–1.39)
All locations	8346	282	153	1.83 (1.66–2.14)

[a]First site.

[b]Second site.

Table 2

Characteristics of Children Aged <2 Years Hospitalized with Intussusception (IS) at 8 Sentinel Hospitals in Bangladesh, July 2012–September 2016.

Characteristic	Intussusception cases N=153 (%)
Age, median months (range)	7 (3–23)
Female	41 (27)
Brighton Collaboration criteria (N=160)	
Definite or Level 1	153 (95)
Probable or Level 2	6 (4)
Possible or Level 3	1 (1)
Method of diagnosis of Level 1IS cases	
Only ultrasound	15 (10)
Only during surgery	18 (12)
Both ultrasound and during surgery	120 (78)
History of rotavirus vaccination	0
Length of hospital stay, median days (range)	7 (0348)
Treatment[a]	
None, spontaneously resolved	5 (5)
Surgery	146 (95)
Bowel resected during surgery[b]	58 (39)
Recurrence after treatment	0 (0)
Deaths	
During hospitalization	8 (5)
After discharge	3 (2)

Note: Data are number (%) of children, unless otherwise indicated.

[a] Before treatment started, one children with intussusception were transferred to another hospital and one died.

[b] n = 146.