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RECURRENT INTUSSUSCEPTION AMONG INFANTS LESS THAN 2 YEARS OF AGE IN VIETNAM

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Abstract

In some settings, rotavirus vaccines have been associated with a low-level risk of intussusception, the most common cause of bowel obstruction in infants. As Vietnam prepares to introduce rotavirus vaccine into the national immunization program, we sought to better characterize the epidemiology of recurrent intussusception. We enrolled children <2 years of age who were hospitalized for intussusception retrospectively from January 2013 through December 2014 and prospectively from January 2015 through December 2016 at 2 hospitals in Vietnam. We enrolled 2,477 children. Nearly all children were successfully treated by enema with low surgery rate (1%). We found 10% of children (n=254) experienced at least once recurrence (range: 1–6) and 57% of first recurrences happened within the first 12 weeks after treatment of the first episode. The median age at first intussusception was 13 months for children without a recurrent episode and 10 months for children with a recurrence. The symptoms of the recurrent cases were milder with less vomiting (67%), bloody stool (7%) and fever (10%) compared to the initial cases ($p<0.01$). We found the rate of recurrences following enema reduction of intussusception to be similar to that reported from other countries. Due to the high rate of intussusception and recurrent episodes in Vietnam, a better understanding of the cause of recurrent intussusception will be critical in assessing intussusception cases after rotavirus introduction.

INTRODUCTION

Intussusception is the most common cause of acute intestinal obstruction in infants, typically involving the ileum invaginating through the ileocecal valve into the cecum and occurring between 4 and 10 months of age (1). As the small bowel intussuscepts, it pulls along its blood supply, resulting in intestinal ischemia and possibly perforation if not treated in a timely manner. While some intussusceptions resolve spontaneously, most require

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hospitalization with either enema or surgical treatment. Mortality rates are largely dependent on timely access to adequate treatment, ranging from <1% in developed countries to up to 10% in low income settings (2).

Some children experience a recurrence of intussusception after being treated for an initial episode. The rates of recurrence vary by treatment method and are higher among children treated by enema compared to surgery. A recent meta-analysis showed 12% recurrence rate for contrast enema, 8% for fluoroscopy-guided air enema, and 7% recurrence rate for ultrasound guided non-contrast enema (3). Overall in Vietnam, the reported rate of intussusception is about four-fold higher than the global average (287–302 per 100,000 vs. 74 per 100,000) (2, 4, 5) and, among children treated for intussusception, an earlier study found 9% experienced ≥1 recurrence (6). In Vietnam, the most common treatment method is ultrasound guided non-contrast air enema.

Current globally licensed rotavirus vaccines have been associated with a low-level risk of intussusception in some settings (7–11). As Vietnam prepares to introduce rotavirus vaccine into the national immunization program, we wanted to better characterize the epidemiology of intussusception. Several previously published articles have described the epidemiology of intussusception; however, recurrent episodes of intussusception have not been well described. The objective of this analysis is to describe recurrent episodes of intussusception among children <2 years of age in the absence of routine rotavirus vaccination at two hospitals in Vietnam. We also compared demographic and clinical characteristics of children who experienced recurrences with those who did not.

MATERIALS AND METHODS

We conducted prospective and retrospective intussusception surveillance among children <2 years of age at two hospitals: Hai Phong Children's Hospital, a 500-bed hospital, and Pediatric Center - Hue Central Hospital, a 260-bed hospital. The city of Hai Phong is situated in the North Coast line of Vietnam, with a humid subtropical climate (Figure 1). Thua Thien Hue province is situated in the Central region of Vietnam, with a sub-tropical monsoon climate.

From January 2015 through December 2016, pediatric patients aged <2 years who were admitted to the hospital and diagnosed with intussusception by ultrasound were prospectively enrolled into the surveillance system. Parents/legal guardians provided informed consent for the surveillance enrollment interview. Clinical symptoms, previous medical history, intussusception treatment method and outcomes, ultrasound description, demographic information, vaccination history, and household information were collected. Caregivers were also asked if the child had previously been treated for intussusception. Additionally, we retrospectively reviewed electronic healthcare records from January 2013 through December 2014 at both hospitals by searching for the ICD-10-CM code (K56.1) among children aged <2 years. The paper medical record for each child was obtained to confirm the case met Brighton Level I criteria; relevant clinical and demographic data were also abstracted. Household information and stool specimens were unavailable for children identified during the retrospective review.

We identified prospectively and retrospectively enrolled children who experienced repeat occurrences of intussusception during the first 2 years of life using a combination of hospital record number, children's names, date of birth, addresses and parents' names to identify recurrent episodes, in addition to caregiver report. We considered any recurrent episode to be one identified after an earlier intussusception was successfully resolved.

All descriptive analyses were performed using SAS 9.4. The cumulative incidence curve was generated using R3.2.4.

Both the prospective surveillance and retrospective review were approved by Institutional Review Boards at the National Institute of Hygiene and Epidemiology and at the US Centers for Disease Control and Prevention.

RESULTS

Recurrent rate of Intussusception among children admitted to Hai Phong and Hue hospitals

Of 2,857 intussusception episodes, we identified 634 records from 254 children with recurrent intussusception episodes during the period from 2013–2016 (Table 1). Among children with only one documented intussusception, the median age was 13 months (range: 2–23). Among children who experienced more than one intussusception, the median age at first intussusception was 10 months (range: 3–23). The median number of intussusception episodes for children with >1 episodes was 2 (range: 2–7 episodes). There was a higher proportion of male children among both non-recurrent and recurrent cases. Approximately 90% of enrolled children were from Hai Phong city and Thua Thien Hue province; 10% were from the neighboring provinces. Maternal information was collected from prospectively enrolled cases. The median maternal age at the time of first intussusception admission was 29 years for the non-recurrent and 30 years for the recurrent population; 77% (n=687) and 72% (n=63) of mothers reported attending secondary school or higher among non-recurrent and recurrent children, respectively.

The overall rate of recurrent episodes was 10%; it was 11% in Hai Phong Children's Hospital and 9% in Hue Central Hospital. At the first intussusception admission, caregivers primarily reported symptoms of vomiting (81% non-recurrent and 81% recurrent), bloody stools (23% non-recurrent and 27% recurrent), and fever (15% non-recurrent and 17% recurrent) (Table 2). Among any subsequent intussusception admission, 67% reported vomiting, 7% reported bloody stool, and 10% reported fever. The differences in symptoms reported between first episodes and recurrent episodes were statistically significant (vomiting: $p<0.001$; bloody stools: $p<0.001$; fever $p=0.003$).

Among first intussusception incidents, 98% of non-recurrent cases and 99% of recurrent cases were treated by enema; 1% were treated with surgery in both groups and 1% of non-recurrent cases were treated by resection. Among subsequent intussusception admissions, 99% (n=377) were treated with enema, 1% (n=2) were treated with surgery, and 1 child was treated with resection. For all children, the median hospital stay was 2 days. Outcome was reported for 94% of children. Rounding up, among children with a reported outcome, 100%

of non-recurrent cases were discharged home, 100% of children with recurrent cases were discharged home after their first admission, and 100% after subsequent admissions. Seven children who did not have a recurrence and 2 children during a subsequent admission were transferred to another facility. None of the children died.

Frequency of occurrence

Of children who were admitted for more than one incidence of intussusception, 33% (n=83) had three intussusceptions, 12% (n=30) had four intussusceptions, and 4% (n=10) had five intussusceptions (Table 3). There were two children with six episodes of intussusception and one child with seven episodes of intussusception. In all, except for one of these children, air enema still successfully resolved the intussusception even after 3rd, 4th 5th or 6th recurred episodes (Suppl Table 1). The time from discharge for the first intussusception hospitalization to admission for the first recurrence ranged from <24 hours to >1 year. Within one week of the first episode, 13% of second cases occurred. The majority (44%) occurred from 1–12 weeks after the initial episode. Cumulative incidence by week after discharge is visualized by order of recurrence in Figure 2.

DISCUSSION

Using prospective and active intussusception surveillance among children aged <2 years, we found 10% of children in Vietnam with an episode of intussusception experienced at least one recurrence, the majority within 3 months of the first episode. Our findings are comparable to other published recurrence rates among children treated by enema reduction (3, 6). Children enrolled in this surveillance system were overwhelmingly successfully treated by air enema. Though the number of children treated with surgery was quite small (usually performed due to failure of enema to resolve to the intussusception), in our population about 12% of children treated by enema experienced ≥1 recurrence and 7% of children treated with any type of surgery experienced ≥1 recurrence. In a meta-analysis comparing air and liquid enema for intussusception treatment, Sadigh et al concluded that air enema has higher success rate over liquid enema for intussusception reduction, with no difference in in intestinal perforation rate and lower rate of recurrence (12). In the hospitals' practice, surgery was not considered after some recurrent episodes as suggested by Hsu et al as long as air enema could still resolve the IS condition (13).

Incident episodes of intussusception were similar in terms of symptoms and outcome between children with only one occurrence and children who went on to have multiple episodes. During subsequent intussusception episodes, a lower proportion of cases reported these symptoms. This may be because parents and caregivers of children with recurrences may be more familiar with or attuned to subtler signs and symptoms of intussusception and may present to hospital before vomiting, bloody stool, or fever develop, although we did not find a difference the median days from symptom onset to admission. There may be other factors that predispose children to intussusception that were not captured in this evaluation.

Children with recurrences were first admitted for an episode of intussusception at younger ages than children who did not have a recurrence. One possible explanation for this difference is that children who intussuscept for the first time at an older age had less time to

have a second episode before their second birthday, however the age range for first episodes is similar for both groups and includes children up to 23 months of age. The scope of this analysis did not allow us to explore this difference further. Earlier studies reported a median age of 9 months for intussusception generally and 8 months for children who experienced ≥1 recurrence in Vietnam (4–6).

While rotavirus vaccine has not been introduced into the national routine vaccination program in Vietnam, rotavirus vaccines are available on the private market and a small number of children with recurrences reported receiving rotavirus vaccine. Of the children with dates of rotavirus receipt available, the earliest intussusception episode was more than 4 months after the last dose of vaccine received. Given this temporal relationship, these cases do not appear to be vaccine-related.

There are several limitations to our surveillance system and analysis. As this was a secondary analysis, our intussusception surveillance system was not originally designed to link repeated episodes, nor does the case report form collect information specific to recurrent cases. This restricts our ability to describe these children, compare episodes, and draw conclusions about the causes of intussusception recurrence in this population. Additionally, this secondary analysis was unable to distinguish recurrent episodes from treatment failures for episodes that occurred within 48 hours. Our methods may have underestimated the number of recurrences in this population because we partially relied on parental recall and some recurrent cases may have been missed if subsequent episodes were admitted and treated at hospitals outside of the surveillance system. Other missed recurrences may have occurred during the same admission but were not necessarily captured in a separate case report form. Finally, the mix of prospective and retrospective data collection limits our knowledge of these children outside of what was recorded in their medical records.

We found the rate of recurrences following enema reduction of intussusception to be similar to that reported from other countries (5.5% in Tunisia, 8.5% in Korea, 16% in Iran, 12% worldwide) (3, 14–16). Though children who experienced ≥1 recurrence were hospitalized for a first intussusception at a younger age, incident cases of intussusception presented with similar signs and symptoms for children who had recurrences and those that did not. Our findings highlight several questions for future research, including biological, physical and microbiological causes of recurrent intussusception.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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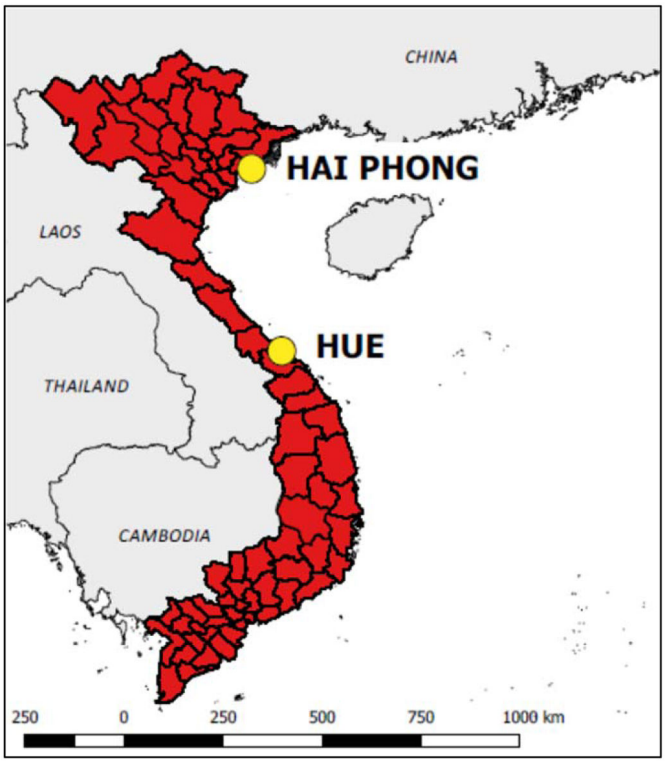

Figure 1.
Map of Vietnam showing the 2 sentinel surveillance sites in circles.

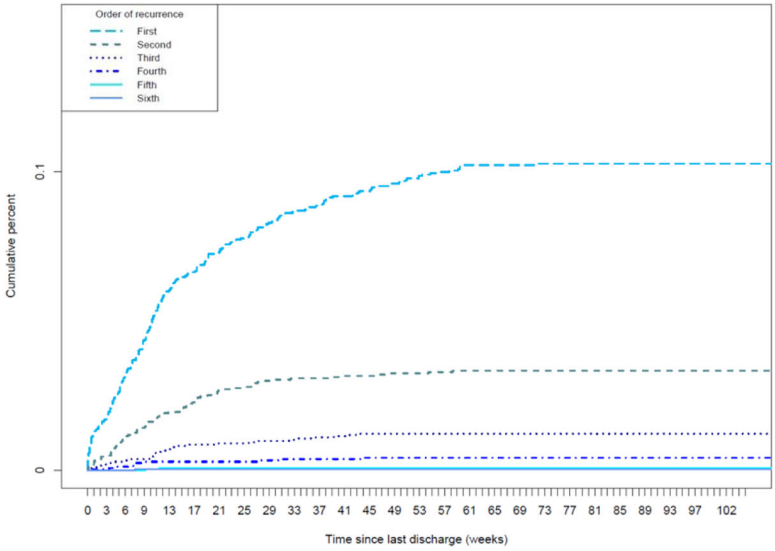

Figure 2.

Time from hospital discharge for preceding episode to symptom onset for repeated intussusception admissions among children <2 years old in Vietnam

Table 1

Characteristics of recurrent and non-recurrent intussusception cases in Vietnam, 2013–2016

	Hai Phong Children's Hospital		Hue Central Hospital		Both hospitals	
	No recurrence	Recurrent	No recurrence	Recurrent	No recurrence	Recurrent
Number of children	1666	201	557	53	2223	254
Age of first occurrence median (min, max)	12 (2, 23)	9 (3, 23)	13 (2, 23)	11 (4, 21)	13 (2, 23)	10 (3, 23)
Number of episodes/child median (min, max)	1	2 (2–7)	1	2 (2–5)	1	2 (2–7)
Male: Female	1023:641 (1.6:1)	120:82 (1.5:1)	320:236 (1.4:1)	31:22 (1.4:1)	1343:877 (1.5:1)	151:103 (1.5:1)
Urban: Suburban	718:948 (0.8:1)	79:122 (0.6:1)	322:235 (1.4:1)	30:23 (1.3:1)	1040:1183 (0.9:1)	109:145 (0.8:1)

Table 2

Characteristics of intussusception hospitalizations in Vietnam, 2013–2016

	Hai Phong Children's Hospital			Hue Central Hospital			Both hospitals		
	No recurrence	Recurrent		No recurrence	Recurrent		No recurrence	Recurrent	
		1st intussusception	Recurrences		1st intussusception	Recurrences		1st intussusception	Recurrences
	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)	n(%)
Number of hospital admissions	1666 (100)	201 (100)	306 (100)	557 (100)	53 (100)	74 (100)	2223 (100)	254 (100)	380 (100)
Symptoms									
Vomiting	1350 (81)	167 (83)	203 (66)	445 (80)	40 (75)	52 (70)	1795 (81)	207 (81)	255 (67)
Bloody stools	408 (24)	57 (28)	20 (7)	108 (20)	12 (23)	6 (8)	516 (23)	69 (27)	26 (7)
Fever	220 (13)	30 (15)	18 (6)	123 (22)	13 (25)	19 (26)	343 (15)	43 (17)	37 (10)
Symptom onset to admission, median (range)	0 (0, 11)	0 (0, 3)	0 (0, 5)	0 (0, 7)	0 (0, 8)	0 (0, 2)	0 (0, 11)	0 (0, 8)	0 (0, 5)
Treatment									
Enema	1638 (98)	198 (99)	305 (100)	538 (97)	53 (100)	72 (97)	2176 (98)	251 (99)	377 (99)
Surgery	22(1)	3 (1)	1 (0)	11 (2)	0 (0)	1 (1)	33 (1)	3 (1)	2 (1)
Resection	6 (0)	0 (0)	0 (0)	7 (1)	0 (0)	1(1)	13 (1)	0 (0)	1(0)
Days hospitalized, median (range)	2 (0, 42)	2 (0, 8)	1 (0, 12)	2 (0, 33)	2 (0, 6)	2 (1, 11)	2 (0, 42)	2 (0, 8)	2 (0, 12)
Discharged to home	1528 (92)	195 (97)	274 (90)	556 (100)	53 (100)	74 (100)	2084 (94)	248 (98)	348 (92)

Table 3

Number and frequency of recurrent cases among patients

	Hai Phong Children's Hospital n (%)	Hue Central Hospital n (%)	Both hospitals n (%)
Number of children	1867	610	2477
Children with ≥1 documented recurrence	201 (11)	53 (9)	254 (10)
Number of recurrences			
1	201 (100)	53 (100)	254 (100)
2	70 (35)	13 (25)	83 (33)
3	24 (12)	6 (11)	30 (12)
4	8 (4)	2(4)	10 (4)
5	2 (1)	0	2 (1)
6	1 (0)	0	1 (0)
Time between intussusception and first recurrence			
0–1 days	13 (6)	2 (4)	15 (6)
2 days	5 (2)	2 (4)	6 (2)
3–7 days	9 (4)	3 (6)	12 (5)
1–12 weeks	84 (42)	28 (53)	112 (44)
>12 weeks–52 weeks	80 (40)	17 (32)	97 (38)
≥ 1 year	10 (5)	1 (2)	11 (5)