



Research article

Epidemiology of intussusception among children less than 2 years of age; findings from baseline surveillance before rotavirus vaccine introduction in Myanmar

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ABSTRACT

Background: Rotavirus vaccine was planned to be introduced in the National Immunization Program of Myanmar in 2020. Reported potential association of a small increased risk of intussusception after rotavirus vaccination in some countries is a major safety concern and it is mandatory to collect baseline information before vaccine introduction.**Methods:** Retrospective study reviewed medical records of intussusception cases for past 3 years (2015–2018) and prospective, active study was conducted from August 2018 to January 2020 at three tertiary children hospitals where pediatric surgical facility is present. Brighton Level 1 Criteria was used for confirmation of intussusception among children <2 years of age admitted to surgical wards. Demographic, clinical, diagnostic and treatment practices data were collected and descriptive data analysis was performed.**Results:** A total of 697 (421 in retrospective and 276 in prospective) confirmed intussusception cases were identified. Majority of intussusception cases (550/697, 78.9%) were observed in the first year of life and most frequent between 5–7 months of age (292/697, 41.9%) with a peak at 6 months (114/697, 16.4%). The most common clinical presentations were vomiting and bloody diarrhea accounting 82.1% and 77.5% respectively. Regarding diagnosis and treatment, 458/697 (65.7%) required surgical intervention either manual reduction or intestinal resection and 34.4% by either air or barium enema. Overall mortality was 0.7% (5/697) and four out of five children died needed intestinal resection. Late arrival to hospital (>3days after onset) is significantly associated with requirement of surgery (61/85, 71.8%), which in turn is significantly associated with longer hospital stay (296/452, 65.5%) ($p < 0.05$).**Conclusions:** Intussusception occurrence is most frequent between 5–7 months age group which is old enough to be vaccinated under the schedule that has now been introduced in Myanmar. More than half of the cases were treated by surgery and late arrival to hospital enhances requirement of surgery and poor outcome. Findings of this baseline surveillance provide important facts for public health officials in balancing risks and benefits of rotavirus vaccine introduction, defining targeted age and dosage scheduling and facilitate monitoring system in post-vaccination.

1. Introduction

Intussusception is invagination of one segment of a bowel into a distal segment and is the commonest cause of abdominal surgical emergencies in infants and children. Some intussusception cases can resolve

spontaneously, however, it can sometimes result in obstruction and necrosis of the intestine and delaying proper treatment can lead to death [1]. The exact mechanism that triggers intussusception is still unclear, however, a lesion in the bowel wall or irritant within the bowel lumen may lead to a hyperactive peristaltic pattern resulting in invagination of

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one segment into adjacent one [2, 3]. Intussusception occurs commonly in infants, peaking in 5–7 months of age [4]. The estimated global rate of intussusception is 74 cases per 100,000 children under one year of age, ranging between 9 and 328 cases per 100,000 depending on geographic location [4].

Rotavirus is the most common cause of severe diarrheal disease in children under five years of age worldwide and vaccination is the best way to prevent it. There are four WHO prequalified rotavirus vaccines currently available: Rotarix (RV1, GlaxoSmithKline), Rotateq (RV5, Merck), Rotasil (BRV-PV, Serum Institute of India) and Rotavac (116E, Bharat Biotech). Rotarix and Rotateq were not associated with intussusception in the large-scale pre-licensure clinical trials and Rotavac and Rotasil did not show an association with intussusception during clinical trials, however the trials were not large enough to detect a small increased risk for intussusception [5, 6, 7, 8]. However, in post-marketing surveillance in some high and middle income countries, RV1 and RV5 were shown to be associated with a mild increased risk of intussusception (1–6 excess cases per 100,000 vaccinated infants) [9, 10, 11, 12].

Rotavirus surveillance in Myanmar reported that a high proportion (42–56%) of diarrhea hospitalizations is due to rotavirus among children <5 years old [13] and that enhanced the decision makers to consider rotavirus vaccine introduction. In February 2020, rotavirus vaccine (Rotarix) was introduced to the routine infant vaccination schedule nation-wide in Myanmar. The dose schedule is 2 month and 4 month of age for the first and second dose respectively. This called for a mandatory action on assessment of baseline epidemiology of intussusception. Therefore this study was conducted with the aim to provide information on frequency, epidemiology and clinical characteristics of intussusceptions before rotavirus vaccine introduction which is important for public health professionals and the Government in decision-making on vaccine introduction and plan for intussusception monitoring system in post-vaccination period.

2. Materials and methods

2.1. Study design and setting

This study is a hospital-based, retrospective review of hospital records and prospective surveillance conducted at three tertiary Children Hospitals where pediatric surgical facilities were available. The selected sites were (1) Yangon Children's Hospital (YCH) (1300 beds) (2) Yankin Children Hospital (YKCH) (550 beds) and (3) 550 bedded Children's Hospital, Mandalay (550 MCH).

A retrospective, chart review of intussusception cases was performed to ensure that the selected hospitals routinely treat children with intussusception and also to provide information about clinical presentation, treatment practices and outcomes for these children. Prospective, active study enrolment was conducted to provide more complete data including rotavirus vaccine history. Retrospective study was conducted for the past three year (January 2015–July 2018) and prospective study was conducted from August 2018 to January 2020.

2.2. Study population and enrolment

For both retrospective and prospective studies, all children aged <2 years who met the Casedefinition of Level 1 Brighton criteria [14] to make diagnosis of confirmed intussusception at the time of admission or any time during hospital stay were regarded as eligible for enrolment. For retrospective study, intussusception cases were identified through review of hospital records, patient's charts and operation notes. For prospective study, intussusception cases admitted to the hospitals were identified by the pediatric surgeons at their respective sentinel hospitals. All cases that fulfill the Level 1 Brighton criteria were enrolled and completed a case report form.

Case definition. Level 1 Brighton criteria of diagnostic certainty (or “definite”) [14].

- Surgical criteria:
 - o Demonstration of invagination of the intestine at surgery; **and/or**
- Radiological criteria:
 - o Demonstration of invagination of the intestine by either air or liquid contrast enema; **or**
 - o Demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features (target sign or doughnut sign on transverse section and a pseudokidney or sandwich sign on longitudinal section), that is proven to be reduced by hydrostatic enema on post-reduction ultrasound; **and/or**
- Autopsy criteria:
 - o Demonstration of invagination of the intestine at autopsy

2.3. Data collection and analysis

Upon enrolment, demographic data, clinical information including diagnostic and treatment procedures, duration of hospital stay and outcome data were collected in structured Case report forms. Additionally in prospective study, rotavirus vaccination history was collected from parents/care givers. Descriptive data analysis was performed. Estimated population incidence of intussusception per 100,000 population was calculated by dividing the number of intussusception among <1 year in 2019 by the <1 year population in 2019.

2.4. Ethical consideration

This study was conducted after getting approval from the Ethics Review Committee, Department of Medical Research and conducted according to its guidelines (Approval No. Ethics/DMR/2018/079). This study posed no physical risk to involved participants and written informed consent was taken from parents/guardians upon enrolment.

3. Results

A total of 697 confirmed intussusception cases (421 in retrospective and 276 in prospective) were identified of which 260/697 (37.3%) were from YCH, 158/697 (22.7%) were from YKCH and 279/697 (40.0%) were from 550 MCH (Table 1).

Figure 1 shows the age distribution of confirmed intussusception cases. In general, majority of intussusceptions cases (550/697, 78.9%) were found in the first year of life and most frequent between 5-7 months of age 292/697 (41.9%) with a peak at 6 months (114/696, 16.4%). More specifically, the percentage of cases at 3 month of age that would be shortly after the first dose of vaccine was 2.6% (18/697) and the percentage at 5 month of age that would be shortly after the second dose was 11.2% (78/697). Among 697 cases, 418 (60.0%) were male children and male to female ratio is 1.5:1.

Intussusception hospitalizations occurred year-round throughout the study years (2015–2020) in combination of both retrospective and prospective studies in all three hospitals without any particular pattern or seasonality (data not shown).

Overall, the most common complaints at the time of presentation to hospitals were vomiting (572/697, 82.1%) and bloody stool (540/697, 77.5%). At YKCH, most of the patients (82.3%) were diagnosed surgically when compared to YCH (66.5%) and 550 MCH (55.6%). Regarding treatment, proportion of patients treated by hydrostatic/pneumatic enema is higher in MCH (44.4%) than YCH (33.5%) and YKCH (17.7%). Overall, the most common diagnostic tools used were surgery (65.7%) followed by abdominal ultrasound (21.8%) and 65.7% of patients required surgical intervention either manual reduction or intestinal resection and the rest 34.3% by either hydrostatic or pneumatic enema. Four out of 279 cases at 550 MCH (1.4%) and 1 out of 158 cases at YKCH

Table 1. Clinical, diagnostic and treatment characteristics of children <2 years of age presented with confirmed intussusception at the sentinel hospitals (2015–2020).

Characteristics	Yangon Children's Hospital n = 260 (%)	Yankin Children Hospital n = 158 (%)	550 bedded Children's Hospital, Mandalay n = 279 (%)	Total n = 697 (%)
Enrolment				
Retrospective	187 (44.4)	81 (19.2)	153 (36.4)	421 (100)
Prospective	73 (26.4)	77 (27.9)	126 (45.7)	276 (100)
Clinical Symptoms				
Vomiting	216 (83.1)	129 (81.6)	227 (81.4)	572 (82.1)
Bloody stool	204 (78.5)	113 (74.5)	223 (79.9)	540 (77.5)
Fever	136 (52.3)	87 (55.1)	111 (39.8)	334 (47.9)
Diarrhea	46 (17.7)	45 (28.5)	56 (20.1)	147 (21.1)
Constipation	43 (16.5)	27 (17.1)	33 (11.8)	103 (14.8)
Diagnostic criteria (Brighton Level 1)				
Surgery	173 (66.5)	130 (82.3)	155 (55.6)	458 (65.7)
Radiology (USG)	65 (25.0)	9 (5.7)	78 (28.0)	152 (21.8)
Enema (air/liquid)	22 (8.5)	19 (12.0)	46 (16.4)	87 (12.5)
Treatment criteria				
Surgery (Manual reduction)	131 (50.3)	118 (74.7)	102 (36.6)	351 (50.3)
Intestinal resection	42 (16.2)	12 (7.6)	53 (19.0)	107 (15.4)
Hydrostatic/Pneumatic enema	87 (33.5)	28 (17.7)	124 (44.4)	239 (34.3)
Outcome				
Survived	259 (99.6)	157 (99.4)	275 (98.6)	691 (99.1)
Died	0	1 (0.6)	4 (1.4)	5 (0.7)
Left against medical advice	1 (0.4)	0	0	1 (0.2)
Transferred from another hospital				
Yes	129 (49.6)	63 (39.9)	118 (42.3)	310 (44.5)
No	131 (50.4)	95 (60.1)	161 (57.7)	387 (55.5)
Rotavirus vaccine				
Yes	0	0	0	0
No	260	158	279	697

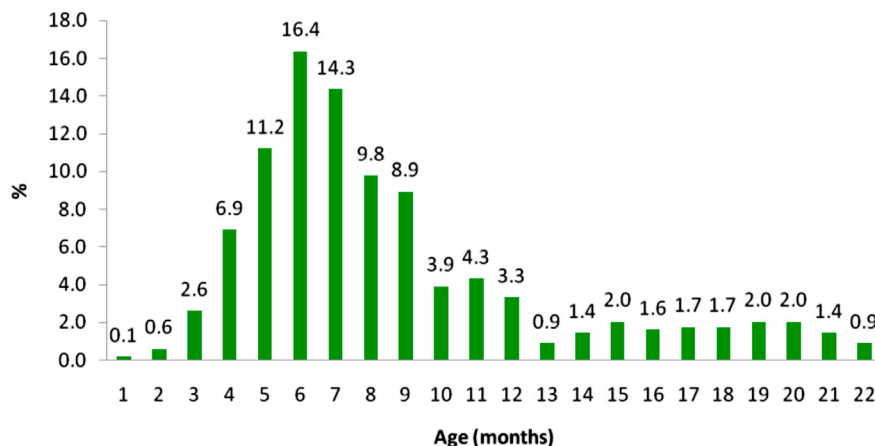


Figure 1. Age distribution of intussusception-hospitalizations among children <2 years of age at three sentinel hospitals (n = 697).

(0.6%) died post-operatively while no deaths occurred at YCH. Overall mortality was 0.7% (5/697). Nearly half of the patients (44.5%) were transferred from other hospitals and none of the participants received any dose of rotavirus vaccine (Table 1).

Table 2 shows association between duration from onset to admission and treatment criteria as well as treatment criteria and hospital stay after excluding data from Yankin Children Hospital where pneumatic reduction facility is absent and some incomplete data from retrospective study. It was found that most of the cases (421/506, 83.2%) arrived to hospital within 3 days of onset of symptom and of which 42.8% (180/421) were

successfully managed by enema reduction and 57.2% (241/421) required surgical treatment. Among 85 cases hospitalized >3 days of onset, 71.8% (61/85) underwent surgical intervention and only 28.2% (24/85) were released by enema and this difference is statistically significant (p < 0.05). Moreover, among the patients who needed hospital stay of ≤3 days, majority (48/54, 88.9%) were treated by enema and only (6/54, 11.1%) were treated by surgery. In patients with longer hospital stay of >3 days, majority (296/452, 65.5%) were treated by surgery and (156/452, 34.5%) was treated by enema and this difference is also statistically significant (p < 0.05). It can be implied that late

Table 2. Association between treatment criteria and duration from onset to admission and duration of hospital stay of intussusceptions cases.

	Treatment criteria			p value
	Enema n = 204 (%)	Surgery/resection n = 302 (%)	Total n = 506 (%)	
Duration from onset to admission				
≤3 days	180 (42.8)	241 (57.2)	421 (100)	<0.05
>3 days	24 (28.2%)	61 (71.8%)	85 (100)	
Hospital stay				
≤3 days	48 (88.9)	6 (11.1)	54 (100)	<0.05
>3 days	156 (34.5)	296 (65.5)	452 (100)	

arrival to hospital had greater chance of requirement of surgical intervention and those underwent surgical intervention had longer hospital stay.

4. Discussion

According to recommendations of WHO, monitoring the risk of intussusception in countries introducing rotavirus vaccine is mandatory [15]. This is the first study reporting epidemiology of confirmed intussusception among children <2 years of age at three major referral and tertiary children hospitals in Myanmar before vaccine introduction.

This study observed that intussusception was uncommon before 2 months of age and started rising from 4 months of age up to 9 months with peak occurrence at 6 months of age. This finding is similar to that of neighbor Asian countries [16, 17]. The WHO recommends to administer rotavirus vaccine at 6 weeks and 10 weeks of age for the first and second dose respectively because the incidence of naturally occurring intussusception is very low in that age [18]. This study evidenced that the background number of intussusception is very low at 2 months of age that would receive the first dose of rotavirus vaccine and supporting the WHO's recommendation. Moreover, the peak occurrence of intussusception cases at age 6 months underscores the importance of timely vaccination to complete all doses of rotavirus vaccine earlier in life before 6 months to avoid the occurrence of intussusception by chance alone post vaccination. Rotavirus vaccination could prevent a large proportion of intussusception cases associated with rotavirus infection since most cases occur currently in children old enough to be vaccinated.

The estimated population incidence of intussusception in Myanmar according to this study is 70 per 100,000 < 1 year which is higher than other Asian countries like Bangladesh (9/100,000), Thailand (36/100,000) and Singapore (51/100,000) but lower than Vietnam (302/100,000) [4].

Male predominance (60.0%) was found in this study which is consistent with other reported data and some suggestions for this male preponderance are genetic or greater healthcare seeking for male or both although the exact mechanism is poorly understood [16, 19]. Similarly like other studies, intussusception hospitalizations occurred year-round in this study without any particular pattern or seasonality [16, 17, 19]. There is very clear seasonal trend of rotavirus diarrhea peaking in cold and dry months (November to February) of every year in Myanmar [13], and lack of seasonal pattern in occurrence of intussusception suggests that wild-type rotavirus may not be a major cause of intussusception [20]. Case-control studies have also failed to show an association between wild-type rotavirus and intussusception.

The most common clinical presentations in this study were vomiting (82.1%) and bloody stools (77.5%) which is similar to those from Pakistan, India and China studies [17, 19, 20, 21]. According to Brighton Level 1 criteria, diagnosis of definite intussusception made through surgery was highest in YKCH (82.3%) and management by surgery/intestinal resection was also highest in YKCH (74.7%). Diagnosis made through abdominal radiology (USG) was highest in 550 MCH (33.0%) as well as management by barium/air enema was higher in 550 MCH

(44.8%) and YCH (33.5%) when compared to YKCH (17.7%). This may be because pneumatic reduction facility is available and routinely done only in YCH and 550 MCH. The overall mortality was 0.7% which is lower than African region (9%) and same with Asian region (<1%) according to WHO regional analysis [4].

This study also highlighted that the longer the duration from onset to admission, the increased risk for needing surgical intervention and the length of hospital stay was longer in those who underwent surgical intervention. Similar findings were reported from studies conducted in Thailand, Australia and Saudi Arabia [22, 23, 24]. Delay in arrival to tertiary hospitals may be due to lack of awareness of symptoms or time-consuming referral process through primary or secondary health care centers and GP clinics to tertiary hospitals. Delay in seeking proper diagnosis and management interventions may worsen the condition and necessitating surgical interventions and intestinal resection. Four out of 5 deaths in this study underwent intestinal resection. Based on these findings, this study recommended that health education and training on clinical symptoms, early diagnosis and referral of suspected intussusception children directly to tertiary pediatric hospitals with facility of intussusception management is an integral part of rotavirus vaccine introduction plan. It is also important to carry on monitoring of intussusception continuously in post vaccination period to assess whether there is true association between the vaccine and intussusception or not.

5. Conclusion

This study provided important large-scale baseline epidemiological data on intussusception among children <2 years of age in Myanmar for the first time which is vital to public health officials in assessing the risk of intussusception, balancing risks and benefits of rotavirus vaccine and facilitate the monitoring system in post vaccination.

6. Limitations and strength

Retrospective chart review has certain limitations. Firstly, we may miss some cases that might have been admitted with diagnosis for some other condition at the time of admission and in some cases although the admission diagnosis is intussusceptions, we were unable to find the medical charts. Secondly, the medical records of some cases were incomplete and unable to screen for inclusion criteria. The strength is that we used standard Case definition for identification of only confirmed intussusception cases avoiding any potential misclassification and overestimating.

Declarations

Author contribution statement

Theingi Win Myat: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Hlaing Myat Thu, Aye Aye, Nyo Nyo Win, Maung Maung Lwin and Moh Moh Htun: Conceived and designed the experiments; Wrote the paper.

Nway Nway Thin Aung, Htin Lin, Nang Sarm Hom and Kyaw Swar Lin: Performed the experiments; Analyzed and interpreted the data.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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