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Preparing for rotavirus vaccine introduction – A retrospective assessment of the epidemiology of intussusception in children below 2 years of age in Nepal

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ABSTRACT

Background: Rotavirus is the most common cause of severe diarrhea in Nepali children, accounting for 25–33% of childhood diarrhea hospitalizations. Two rotavirus vaccines recommended for inclusion in national immunization programs have been associated with a low risk of intussusception in post-marketing studies conducted in several countries. Data on the epidemiology of intussusception hospitalizations are lacking in Nepal. Thus, we aimed to describe the epidemiology of intussusception-associated hospitalizations among Nepali children in preparation for rotavirus vaccine introduction.
Methods: A retrospective review of intussusception hospitalizations for a three year period was conducted at two major pediatric hospitals in Kathmandu, Nepal. Possible intussusception cases were identified through admission, discharge, and operation theater logs and ultrasound registers. Cases with a diagnosis of possible intussusception were selected for medical record review and classified as confirmed if they met the Brighton Collaboration level 1 criteria of diagnostic certainty and the child was aged < 24 months. Data on demographics, clinical course, and outcome were abstracted and analyzed.
Results: Eight-five confirmed intussusception cases were identified; most (96%) were confirmed at surgery. The number of intussusception cases peaked between ages 4–7 months; no cases occurred in children 0–2 months. Fifty-nine (64%) case-patients were male. The median duration of symptoms before admission was 2 days (range: 0–14). Abdominal pain, bloody stool, and vomiting were the most common clinical features. All cases underwent surgical treatment; there was only one death.
Conclusions: This is the first study to evaluate the epidemiology of intussusception hospitalizations among children aged < 24 months in Nepal. Because the public health impact of rotavirus vaccination could be substantial in Nepal, where childhood diarrhea-related morbidity and mortality are high, this baseline knowledge of intussusception prior to introduction of rotavirus vaccine in the national immunization schedule will provide useful information for post-vaccine introduction safety monitoring.

1. Introduction

Diarrhea is the second most common cause of death in Nepali children [1], and rotavirus is the most common cause of severe diarrhea in these children, accounting for 25–33% of childhood diarrhea hospitalizations [2,3]. Because of this substantial burden of disease, the Government of Nepal has included rotavirus vaccine on its priority list for new vaccines and plans to include rotavirus vaccine in the national immunization programme in the near future.

In 1999, a first generation oral rotavirus vaccine, Rotashield (Wyeth-Lederle), was withdrawn from the US market because of an increased risk of intussusception, estimated at one excess case occurring among every 10,000 vaccinated children, primarily in

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the first week after the first vaccine dose [4,5]. The two currently licensed oral rotavirus vaccines, Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq (RotaTeq, Merck and Co., Whitehouse Station, New Jersey), were assessed for intussusception in large pre-licensure clinical trials [6,7]. While no increased intussusception risk was observed in these trials, post-marketing studies in several upper middle to high income countries have detected a small increased risk of intussusception associated with both vaccines, with an estimated 1–5 excess cases per 100,000 vaccinated children [8–13]. Therefore, the World Health Organization recommends monitoring for intussusception in countries implementing rotavirus vaccines [14].

Intussusception is a rare condition in which the invagination of one segment of the bowel into another distal segment can result in obstruction, vascular compromise, necrosis of the intestine, perforation and even death if untreated. It is the most common cause of acute bowel obstruction in children below two years of age, with an estimated mean global incidence of 74 cases (range: 9–328) per 100,000 children aged < 1 year [15]. However, the incidence of intussusception varies substantially by geographic region and limited data on intussusception are available from low income countries of Asia and Africa. Genetic predisposition, circulating pathogens, differences in feeding practices and environments, and differences in access to health care and diagnostic practices could also contribute to the global differences in intussusception rates [15].

Data on the epidemiology of intussusception-associated hospitalizations are currently lacking in Nepal. Hence, we examined the immediate clinical outcomes and described the epidemiology of intussusception-associated hospitalizations among children in Nepal in preparation for rotavirus vaccine introduction.

2. Methods

We conducted a retrospective review of intussusception hospitalizations for a three year period from 1 July 2011 through 30 June 2014 at Kanti Children's Hospital (KCH), Maharajgunj and Ishan Children and Women's Hospital Pvt Ltd (ICWH), Basundhara, two major pediatric hospitals in Kathmandu, Nepal. These two sites were selected as they receive the majority of pediatric surgical case referrals and manage the majority of pediatric intussusception cases in Nepal. KCH is a public facility providing heavily subsidized to almost free care to residents of Nepal, while ICWH is a private facility where patients pay for services.

A member of the research team identified possible intussusception cases through review of hospital admission, discharge and operation theater logs and ultrasound registers. Any case with a diagnosis of intussusception was selected for medical record retrieval and case inclusion screening. Children with suspected intussusception were classified as having a confirmed case of intussusception if they met the following inclusion criteria: (1) age < 24 months and (2) criteria meeting the Brighton Collaboration level 1 of diagnostic certainty. Cases met Brighton level 1 diagnostic criteria if they had any of the following findings: (a) invagination of the intestine at surgery, (b) 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 pseudokidney or sandwich sign on longitudinal section), that was proven to be reduced by hydrostatic enema on post-reduction ultrasound, and/or (c) demonstration of invagination of the intestine at autopsy [16].

Medical records of all children with a confirmed diagnosis of intussusception were reviewed, and data on demographics, clinical illness course, and diagnostic, treatment and outcome information were abstracted using a standardized questionnaire. Descriptive epidemiological analyses were conducted using SPSS version 16 and SAS version 9.3.

This study was approved by the ethical committee of the Nepal Health Research Council and Ethical review board of Kanti Children's Hospital.

3. Results

Overall, we identified 106 possible cases of intussusception in children age < 24 months admitted to KCH and ICWH during the 3-year study period. Of the 106 cases, three (3%) had their specific age missing and 18 (17%) did not meet the Brighton Collaboration level 1 diagnostic criteria, so these cases were excluded. A total of 85 cases (74 [87%] from KCH and 11 [13%] from ICWH) were included in the analysis (Fig. 1); over half (68%) were children from the Central Development Region of Nepal (Table). Eighty-two cases (96%) were confirmed at surgery.

Of the 85 confirmed intussusception cases, the number of cases peaked between the ages of 4 and 7 months (Fig. 2), with a median age of 7 months (range: 3–23). No cases occurred in children aged 0–2 months, and there was no apparent seasonal pattern in case occurrence (Fig. 3). Fifty-nine (64%) case-patients were male; the male: female ratio of cases-patients was 2.3:1 (Table). The median duration of symptoms before admission was 2 days (range: 0–14). Abdominal pain (64%), bloody stool (60%), and vomiting (59%) were the most common clinical features reported. The most common type of intussusception was ileocolic (72%). All cases underwent surgical treatment – 73% underwent surgery with simple manual reduction of the intussusception and were discharged home without complications, while 27% required intestinal resection. There was only one death. For 72 cases with available admission and discharge date, the median length of hospital stay was 6 days.

4. Discussion

This study provides baseline epidemiological information on naturally occurring intussusception among children aged < 24 mo nths in Nepal. Important to note is the lack of cases that occurred during the first 3 months of life and the low mortality rate, despite the fact that all cases underwent surgical intervention. Our findings are consistent with other reports from the United Kingdom, Republic of Ireland, Australia, and Malaysia that have described the peak age of intussusception incidence occurring in the first year of life, with a very low incidence in the first 2–3 months of life [17–19]. Also consistent is the male predominance of cases [20–22]. This male predominance is not completely understood, but could suggest genetic predisposition to having intussusception and/or differences in access to health care. Although all intussusception cases underwent surgical intervention, the time between onset of symptoms and hospital admission was very short, likely resulting in the good outcomes seen in most cases. The probable reasons for the preference of surgical intervention are that, in Nepal, there is greater surgical experience in treating intussusception, and hydrostatic reduction is not common. Radiologists are not trained in hydrostatic intussusception reduction, and the pediatric surgeons who would be trained in hydrostatic reduction techniques are more experienced with surgical reduction.

This study had several limitations. First, this study may not be nationally representative of all intussusception cases in Nepali chil dren < 24 months of age as more than half of the intussusception cases were from the Central Development Region where the two hospitals are located. However, the distribution of cases from almost all the regions of Nepal and our informal survey of referral patterns for pediatric intussusception for which we found that

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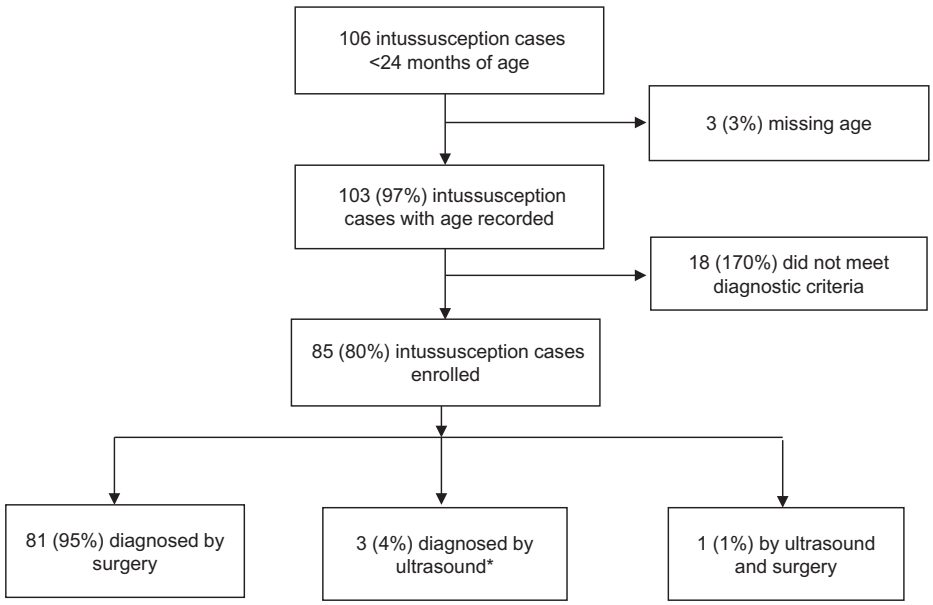

Fig. 1. Flow chart of children < 24 months of age admitted to KCH and ICWH with a diagnosis of intussusception – 1 July 2011 through 30 June 2014.

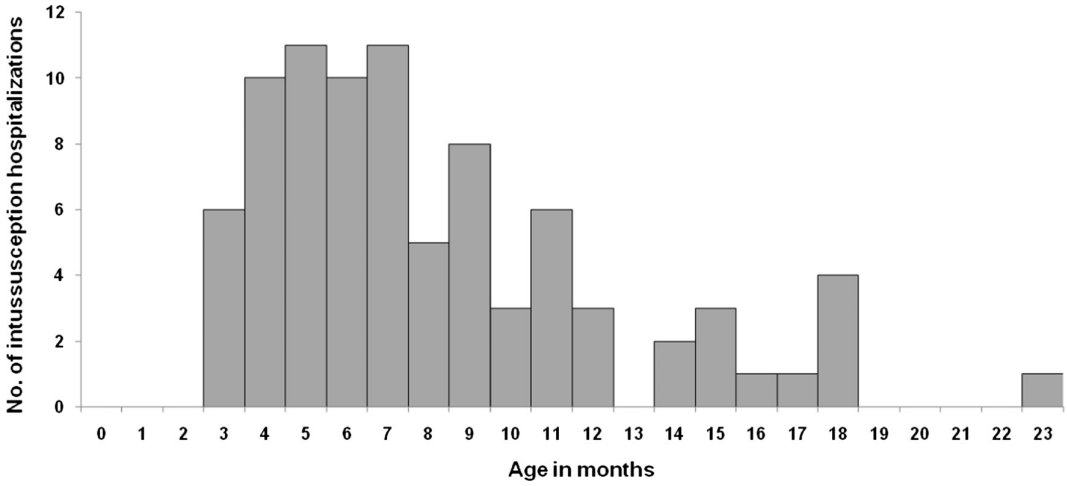

Fig. 2. Intussusception hospitalizations among children below 2 years of age at KCH and ICWH, by age in months – 1 July 2011 through 30 June 2014 (N = 85).

almost all cases are referred to Central Development Region hospitals provide support that our findings could be representative of the whole country. Second, recruitment of cases depended on retrospective review of the diagnosis of intussusception recorded on medical charts and other logs. Hence, those without clear documentation of diagnosis may have been missed. Additionally, some intussusception cases treated by general surgeons in other hospitals may have been missed. This selection bias could result in an underestimation of the total number of intussusception cases. Also, more recent cases may be more likely to be identified than cases which occurred earlier in the study period due to improved record keeping and record availability over time. Finally, rotavirus vaccines are available on the private market in Nepal however we were unable to reliably assess the vaccination status of enrolled cases due to the retrospective study design.

In conclusion, this is the first study to evaluate the epidemiology of intussusception hospitalizations among children aged < 24 months in Nepal. Because the public health impact of rotavirus vaccination could be substantial in settings like Nepal, where childhood diarrhea-related morbidity and mortality are high, this baseline knowledge of intussusception prior to introduction of rotavirus vaccine in the national immunization schedule will provide useful information for post-vaccine introduction safety monitoring.

Conflicts of interest

The authors declare that they have no conflicts of interest relevant to this article to disclose.

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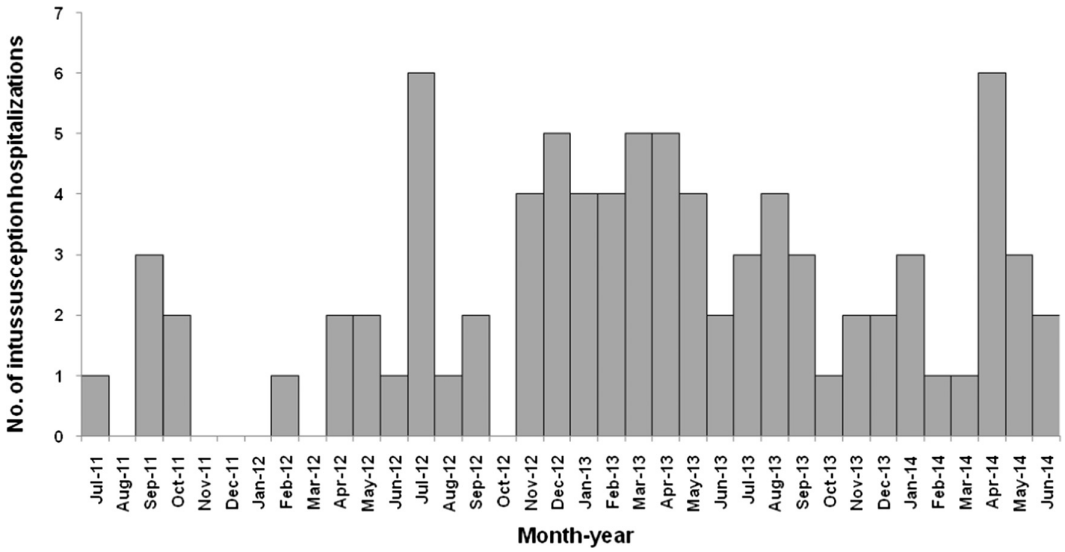

Fig. 3. Intussusception hospitalizations among children below 2 years of age at KCH and ICWH, by month and year – 1 July 2011 through 30 June 2014 (N = 85).

Table
Characteristics and clinical course of intussusception case-patients < 2 years of age admitted to KCH and ICWH, July 2011–June 2014.

Characteristics and clinical course	Intussusception case-patients (N = 85)
Median (range) age in months	7 (3–23)
Sex	
Male	59 (64%)
Female	26 (28%)
Region of residence	
Central	51 (68%)
Eastern	14 (19%)
Western	9 (12%)
Mid-western	1 (1%)
Unknown	10 (12%)
Median (range) days from symptom onset to hospital admission	2 (0–14)
Mode of diagnosis	
Surgery	81 (95%)
Ultrasound	3 (4%)
Ultrasound & surgery	1 (1%)
Presence of signs and symptoms	
Abdominal pain	54 (64%)
Bloody stools	51 (60%)
Vomiting	50 (59%)
Fever	17 (20%)
Diarrhea	10 (12%)
Constipation	3 (4%)
Location of intussusception	
Ileocolic	61 (72%)
Compound	11 (13%)
Unknown	9 (11%)
Ileoileal	4 (5%)
Colocolic	0 (0%)
Intussusception management	
Surgery without intestinal resection	62 (73%)
Surgery with intestinal resection	23 (27%)
Post-management complications	
No known complications	77 (91%)
Peritonitis	2 (2%)
Wound dehiscence and intestinal obstruction	2 (2%)
Secondary intestinal obstruction	2 (2%)
Wound dehiscence	1 (1%)
Wound infection	1 (1%)
Outcome	
Survived and discharged home	79 (93%)
Unknown	5 (6%)
Died	1 (1%)
Transferred to another health facility	0 (0%)

Disclaimer

The finding and conclusions of this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

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References

[1] Institute for Health Metrics and Evalaution. GBS Compare - Causes of death, Nepal, under 5 years. Available from: <http://vizhub.healthdata.org/gbd-compare/>; 2013 [accessed on 14 January 2016].
[2] Sherchand JB, Nakagomi O, Dove W, Nakagomi T, Yokoo M, Pandey BD, et al. Molecular epidemiology of rotavirus diarrhea among children aged <5 years in Nepal: predominance of emergent G12 strains during 2 years. J Infect Dis 2009;200(Suppl 1):S182–7.
[3] Sherchand JB, Tandukar S, Sherchan JB, Rayamajhi A, Gurung B, Shrestha L, et al. Hospital-based study in children with rotavirus gastroenteritis and other enteropathogens. J Nepal Health Res Counc 2012;10:130–5.
[4] Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344:564–72.
[5] Peter G, Myers MG. National Vaccine Advisory C, National Vaccine Program O. Intussusception, rotavirus, and oral vaccines: summary of a workshop. Pediatrics 2002;110:e67.
[6] Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11–22.
[7] Vesikari T, Matson DO, Dennehy P, Van Damme P, Santosham M, Rodriguez Z, et al. Safety and efficacy of a pentavalent human-bovine (WC3) reassortant rotavirus vaccine. N Engl J Med 2006;354:23–33.
[8] Buttery JP, Danchin MH, Lee KJ, Carlin JB, McIntyre PB, Elliott EJ, et al. Intussusception following rotavirus vaccine administration: post-marketing surveillance in the National Immunization Program in Australia. Vaccine 2011;29:3061–6.
[9] Carlin JB, Macartney KK, Lee KJ, Quinn HE, Buttery J, Lopert R, et al. Intussusception risk and disease prevention associated with rotavirus vaccines in Australia's National Immunization Program. Clin Infect Dis 2013;57:1427–34.

[10] Patel MM, Lopez-Collada VR, Bulhoes MM, De Oliveira LH, Bautista Marquez A, Flannery B, et al. Intussusception risk and health benefits of rotavirus vaccination in Mexico and Brazil. N Engl J Med 2011;364:2283–92.
[11] Velazquez FR, Colindres RE, Grajales C, Hernandez MT, Mercadillo MG, Torres FJ, et al. Postmarketing surveillance of intussusception following mass introduction of the attenuated human rotavirus vaccine in Mexico. Pediatr Infect Dis J 2012;31:736–44.
[12] Weintraub ES, Baggs J, Duffy J, Vellozzi C, Belongia EA, Irving S, et al. Risk of intussusception after monovalent rotavirus vaccination. N Engl J Med 2014.
[13] Yih WK, Lieu TA, Kulldorff M, Martin D, McMahill-Walraven CN, Platt R, et al. Intussusception Risk after Rotavirus Vaccination in U.S. Infants. N Engl J Med; 2014.
[14] WHO. Rotavirus vaccines. WHO position paper - January 2013. Wkly Epidemiol Rec 2013;88:49–64.
[15] Jiang J, Jiang B, Parashar U, Nguyen T, Bines J, Patel MM. Childhood intussusception: a literature review. PLoS One 2013;8:e68482.
[16] Bines JE, Liem NT, Justice F, Son TN, Carlin JB, de Campo M, et al. Validation of clinical case definition of acute intussusception in infants in Viet Nam and Australia. Bull World Health Organ 2006;84:569–75.
[17] Giak CL, Singh HS, Nallusamy R, Leong TY, Ng TL, Bock HL. Epidemiology of intussusception in Malaysia: a three-year review. Southeast Asian J Trop Med Public Health 2008;39:848–55.
[18] Palupi-Baroto R, Lee KJ, Carlin JB, Bines JE. Intussusception in Australia: epidemiology prior to the introduction of rotavirus vaccine. Aust N Z J Public Health 2015;39:11–4.
[19] Samad L, Cortina-Borja M, Bashir HE, Sutcliffe AG, Marven S, Cameron JC, et al. Intussusception incidence among infants in the UK and Republic of Ireland: a pre-rotavirus vaccine prospective surveillance study. Vaccine 2013;31:4098–102.
[20] Costantino C, Restivo V, Cuccia M, Furnari R, Amodio E, Vitale F. Analysis of hospitalizations due to intussusception in Sicily in the pre-rotavirus vaccination era (2003–2012). Ital J Pediatr 2015;41:52.
[21] Tran LA, Yoshida LM, Nakagomi T, Gauchan P, Ariyoshi K, Anh DD, et al. A high incidence of intussusception revealed by a retrospective hospital-based Study in Nha Trang, Vietnam between 2009 and 2011. Trop Med Health 2013;41:121–7.
[22] Takeuchi M, Osamura T, Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S. Intussusception among Japanese children: an epidemiologic study using an administrative database. BMC Pediatr 2012;12:36.

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