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Epidemiology study of pediatric primary intussusception aged ≤24 months in pre-rotavirus vaccine era of Jinan, China

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ABSTRACT

Introduction: Few studies have reported on the epidemiological characteristics of pediatric primary intussusception in the pre-rotavirus vaccine era of China. It is important to complementary baseline data before rotavirus vaccine introduction in China. This study conduct a retrospective investigation and evaluated the incidence rate, described the epidemiology of pediatric primary intussusception aged ≤24 months.

Methods: We conducted a retrospective investigation in all secondary- and tertiary-hospitals in Jinan. Pediatric primary intussusception inpatients aged ≤24 months were identified depending on ICD-10 discharge code from a total of 63 hospitals from 2011 to 2015. Demographic and clinical information were extracting from the electronic clinical record systems.

Results: A total of 575 pediatric primary intussusception inpatients were identified with average annual incidence of 86.5 per 100,000. A significantly higher incidence was observed in males ($\chi 2 = 13.8$, $P < 0.01$), in the ≤12 months old age group ($\chi 2 = 19.5$, $P < 0.01$) and from the urban areas ($\chi 2 = 63.31$, $P < 0.001$). No clear seasonality found. Abdominal pain (80.9%) and vomiting (63.3%) were the most frequently reported. Most intussusception cases occurred in ileo-cecum. Over 92% of intussusception cases were diagnosed by ultrasound alone and 77.4% was successfully treated by air enema. 99.7% were cured. The median time of hospitalization was 2 days (range: 0–35 days).

Conclusion: This retrospective study provides baseline information of incidence, epidemiologyand clinical characteristics of pediatric primary intussusception in Jinan City during 2011–2016 before the introduction of rotavirus vaccine. It will be important for evaluating safety of rotavirus vaccine if it will be introduced to the routine immunization program in China.

1. Introduction

Rotavirus is the leading cause of acute abdominal disease in infants and children worldwide [1,2]. In 1999, due to an increased risk of intussusception, a rotavirus vaccine (RotaShield) was withdrawn from the US market <1 year after its introduction [3]. In 2009, the World Health Organization (WHO) recommended the available second-generation rotavirus vaccines (Rotateq, also known as RV5 and Rotarix, also known as RV1) as a routine vaccine [2,4,5] and recommends post-marketing surveillance of any adverse events including intussusception to countries that implement rotavirus vaccination [6]. Post-marketing studies in some high and middle income countries (Australia, America, Mexico, Brazil and so on) have demonstrated an increased risks of intussusception in the first 7 days following the 1st dose of RV5 and RV1 [6–9].

Intussusception is the bowel obstruction caused by the invagination of one segment of the intestinal canal and its mesentery, including primary and secondary types [10–12] and it is the most common cause of bowel obstruction in infants [13]. Above 90% of intussusception cases were for primary intussusception; it usually occurs in children under 24 months old (more than 80%), especially in the age range of 4–10 months [11,12]. At present, pediatric primary intussusception occurs all over the world, especially in Asia, and it has become a worldwide public health issue for infants. Although there have been many reports on the disease burden,

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epidemiological characteristics, and determinants of pediatric primary intussusception, most studies were conducted in several major developed and developing countries, such as Nigeria, India, and Thailand [12].

China, with nearly 20% of the population of the world and about 2.2 billion children under 14 years old, is the biggest population country in Asia and rotavirus vaccination has not been introduced into the Chinese routine immunization program. The Lanzhou Lamb rotavirus vaccine (LLR) is the only vaccine licensed in China and belongs to the second-category list of the national immunization program. It is a domestic rotavirus vaccine developed by Rotorway Lanzhou Institute of Biological Products has been licensed since 1998 and is not compulsory with injection and needs to charge a user-fee [14].Only a few studies on the epidemiological characteristics of pediatric primary intussusception in mainland China have been reported in pre-rotavirus vaccine era [15–17]. Furthermore, previous studies that occurred in four cities (Suzhou, Linyi, Chenzhou and Kaifeng), the first two studies had an obvious limitation in that they all selected one hospital as the field site [15,16].

In addition, topics about seasonal feature in the occurrence of pediatric primary intussusception remain controversial [12,15–26]. Seasonal feature is the phenomenon of disease fluctuating with the season. There are two forms of seasonal feature: one is seasonal growth, in which a disease can occur throughout the year, but the incidence increases in a certain season, and the other is strict seasonality, in which a disease occurs only in certain seasons of the year. Some research about pediatric primary intussusception did not show a seasonal feature [12,15,18–21]. On the contrary, some surveys reported a seasonal feature [21–23,26]. In mainland China, only three studies analyzed the seasonal feature but remain controversial. Guo et al. explored a positive relationship between the occurrence of pediatric primary intussusception cases and climatic factors [16]. Cui et al. [15] and Na Liu et al. did not observed clear seasonality [17].

Considering that China may introduce rotavirus vaccines to the routine immunization program, it is important and necessary to understand the epidemiology and incidence of pediatric primary intussusception in pre-rotavirus vaccines era of China. Jinan, the capital of Shandong Province, holds a population of more than seven million and is located in the central area of China. Accordingly, a 5-year, city-level, retrospective investigation of inpatients aged under 24 months with pediatric primary intussusception was conducted in a total of 63 secondary and tertiary hospitals in Jinan City from January 2016 to January 2017.

2. Methods

This retrospective review was determined to be public health non-research by the Jinan Municipal Center for Disease Control and Prevention.

2.1. Case definition

Pediatric primary intussusception patients were defined as residential inpatients ≤24 months old, first time diagnosed with intussusception, coding as International Classification of Diseases-10 (ICD-10, K56.1) from January 1, 2011, to December 31, 2015, in Jinan City.

2.2. Data collection

Because pediatric intussusception is one of the children's acute abdomen, the parents generally send the children to the secondary or tertiary hospitals. Therefore, demographic information was collected from the Hospital Management Information Systems (HIS) of all secondary and tertiary hospitals (63 hospitals in total) in Jinan City, from January 1, 2011, to December 31, 2015. Demographic information included birth date, gender, address, admitting hospital, admission date, rotavirus vaccination and clinical characteristics were retrospectively reviewed. Some patients with multiple episodes only collected the first relevant data.

2.3. Statistical analysis

An incidence rate, epidemiology and clinical characteristics were described. Chi-square test was used to compare the differences between two age groups (≤12 months old and 13–24 months old), sex (male and female), and regions (urban areas and suburban areas).

All statistical analyses were performed using Microsoft® Excel® 2007 (Microsoft Corporation, WA, USA), IBM SPSS Statistics 24.0 (online version, Chicago, IL, USA) and Stata 15 (StataCorp LLC, TX, USA).

3. Results

In total, 575 pediatric primary intussusception cases were collected during the study period, including 376 males and 199 females; 341 cases were ≤12 months old, and 234 cases were 13–24 months old. The overall incidence rate was 86.5 per 100,000 with an obviously decreasing trend.

3.1. Population distribution

Table 1 shows the annual sex-specific, age-specific cases numbers and incidence rates of pediatric primary intussusception from January 1, 2011, to December 31, 2015, in Jinan City. The sex ratio of male and female was 1.9:1 (376 males: 199 females).

Age distribution of pediatric primary intussusception cases varied greatly by years, with a higher proportion of cases occurring at ≤12 months old, accounting for 59.30% (341/575). The median age of cases was 11 months, with peak incidence occurring in 9 months of age and the second peak occurring in 12 months of age (Fig. 1).

3.2. Spatial distribution

The total number of pediatric primary intussusception cases during study period in the top three districts were: Licheng district (158 cases), Tianqiao district (121 cases), and Shizhong district (73 cases), respectively (Fig. 2). The average incidence rates of the top three districts were all urban areas; from high to low, they were respectively Tianqiao district (209.2 per 100,100), Licheng district (152.4 per 100,100), and Shizhong district (131.6 per 100,100) (Fig. 3). The average incidence rate of the areas of the urban areas (including Tianqiao district, Huaiyin district, Lixia district, Shizhong district, and Licheng district) (144.2 per 100,100) was significantly higher than in the suburbs (including Shanghe county, Jiyang county, Zhangqiu district, Changqing district, and Pingyin county) (37.0 per 100,100) ($\chi^2 = 63.31$, $P < 0.001$).

3.3. Temporal distribution

We have not observed a clear seasonality of pediatric primary intussusception cases during study period, but for the highest number of cases was found in June or November (Figs. 4 and 5). Except in February, the monthly numbers of female cases were less than that of males distributed in other months.

Table 1
Numbers and incidence rates (per 100,000) of pediatric intussusception cases stratified by age and sex.

Year	Total		Male		Female		≤12 months		13–24 months	
	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence
2011	160	118.4	109	156.5	51	77.8	103	151.1	57	85.1
2012	124	95.8	75	109.1	49	80.7	69	106.4	55	85.1
2013	104	80.1	70	101.5	34	55.9	64	98.4	40	61.8
2014	89	66.0	57	79.0	32	51.0	51	75.3	38	56.6
2015	98	72.2	65	90.0	33	52.0	54	79.3	44	65.1
Total	575	86.5	376	106.9	199	63.5	341	102.1	234	70.7

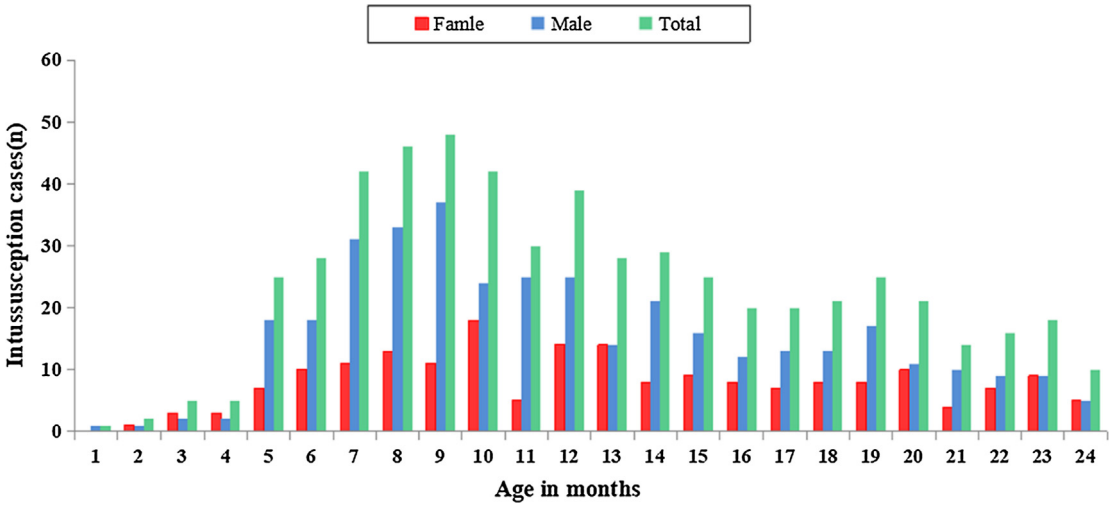

Fig. 1. Age distribution of pediatric intussusception cases classified by gender in Jinan City, China, 2011–2015. Figure showed the age distribution of intussusception cases classified by gender. Red histogram stands for female cases, blue for male cases, and green for total cases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.4. Clinical characteristics

Clinical symptoms observed between 2011 and 2015 included abdominal pain, diarrhea, vomiting, abdominal distension/mass, bloody stool, fever, and pallor (Table 2). Abdominal pain (80.9%) and vomiting (63.3%) were the most frequently reported. Most intussusception cases have the clinical syndrome occurred in ileo-cecum (44.3%), ileo-colon (25.1%), and ileo-ileo-colon (20.8%). 7 (1.2%) children were hospitalized for multiple episodes of intussusceptions. Total of 92.4% of intussusception cases were one-way diagnosed, including ultrasound method (92%) and radiography method (0.4%), meanwhile only 7.2% of cases were diagnosed combined above two ways together and others (Table 2). Of the 575 cases, the majority (77.4%) of them were successfully treated by air enema; 72 (12.5%) cases required surgery without intestinal resection, and 56 (9.7%) cases required surgery with resection. 73(15.4%) cases experienced complications, such as peritonitis, dehydrated electrolyte imbalance and others. 99.7% of the cases were recovered after the treatment (Table 2). The median time of cases' hospitalization was 2 days (range: 0–35 days).

4. Discussion

This is a 5-year hospital-based retrospective epidemiological study on pediatric primary intussusception in a mega city of China. We report the annual incidence rate of pediatric primary intussusception aged ≤24 months was 86.47 per 100,000 in Jinan between 2011 and 2015. Compared with the previous studies, our results was higher than 1.91 per 100,000 in Melbourne [27]. Further, the incidence rate of pediatric primary intussusception in children ≤12 months old in Jinan (102.1 per 100,000) was higher than the global level of 74 per 100,000 [12], 33.1–39.0 per 100,000 in the United States [18], 37.5 per 100,000 in France [19], 39 per 100,000 in Italy [28], and 65 per 100,000 in New Zealand [29]. Compared with the countries in Asia, the incidence rates in children ≤12months of age in our study (102.1 per 100,000) belong to the medium level, higher than that reported inTaiwan (77 per 100,000) [30], slightly lower than in Hong Kong of China (108 per 100,000) [31], significantly lower than in two Chinese city (Chenzhou and Kaifeng, 181.8 per 100,000) [17]and South Korea (328 per 100,000), Vietnam (302 per 100,000) [32], and Japan (185 per 100,000) [32]. Like other studies [25,29,33], we found the predominance of pediatric intussusception among the male population, to show a male-to-female ratio of 1.9–1.

We found the predominance of pediatric intussusception among the male, age group in ≤12 months old and central regions. Regional studies found that the occurrence of pediatric primary intussusception had significant regional differences, and the area of the center region was higher than in the suburbs. These differences were also found in New Zealand [23] and in Italy [28].

We observed no clear seasonal pattern in the distribution of intussusception cases peaked in June or November. Similar results stratified by sex and age are still noticeable. Views on seasonal patterns in pediatric primary intussusception remain controversial [12,18–21,23,29,30]. Guo et al. [16]analyzed hospitalization of pediatric primary intussusception under the age of 12 years and found a weak seasonal trend peaked in summer and spring in Suzhou City, China. Rosie et al. [23] found a weak seasonal trend with incidence peaked in March and September in children aged 0–36 months in New Zealand. Chen et al. [30] analyzed 7541

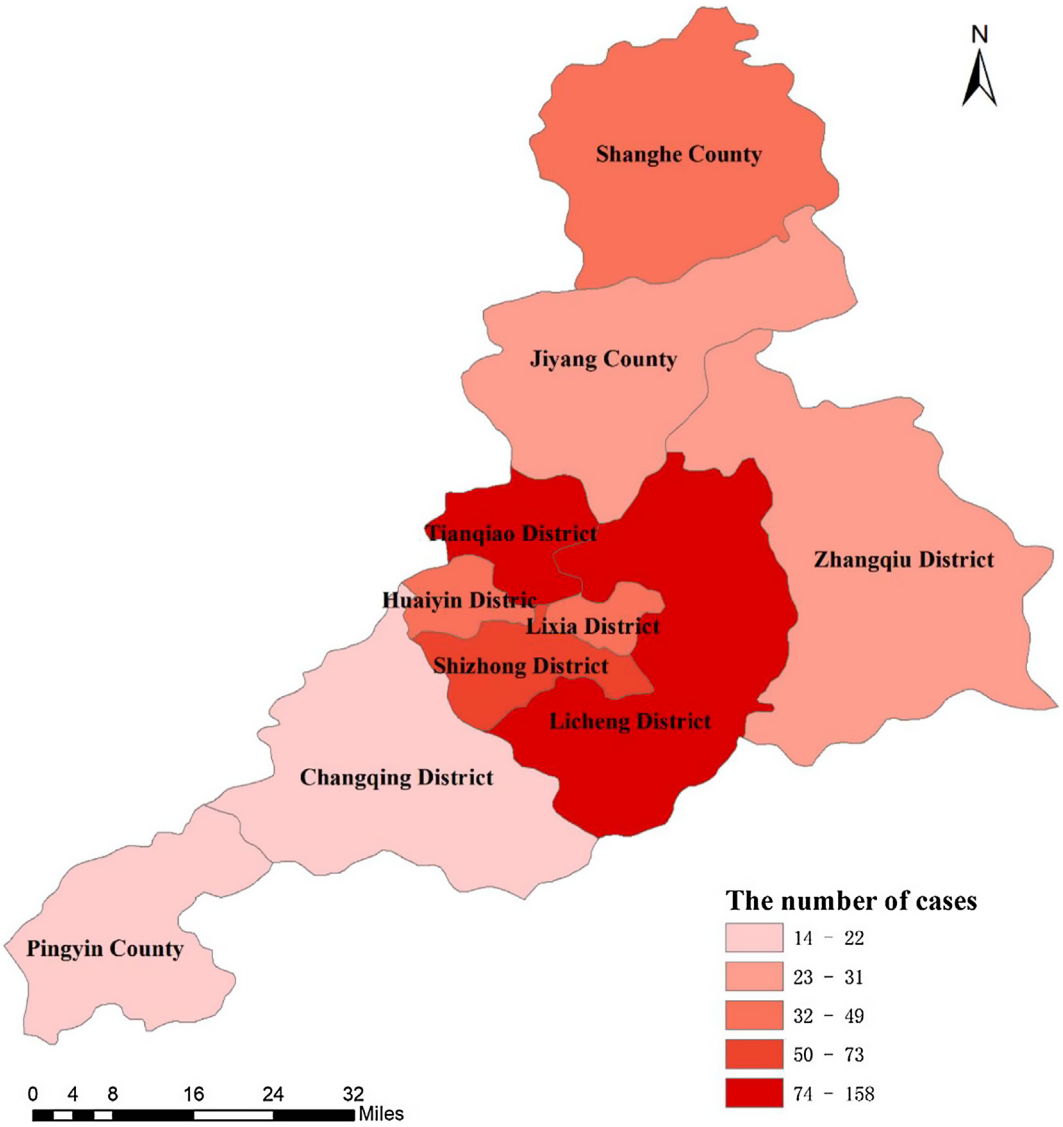

Fig. 2. The spatial distribution of the numbers of total pediatric intussusception cases. Figure showed the spatial distribution of total intussusception cases in ten districts of Jinan City between 2011 and 2015.

intussusception cases in children younger than 15 years old in Taiwan between 1998 and 2007 and concluded that intussusception occurring in the warmer months was significantly higher than that occurring in the cooler months. However, Ho et al. [21] did not found any seasonal trend, reporting 952 intussusception cases in Taiwan from 1999 to 2001, and some studies also got the same conclusion [12,18–20]. The present evidence showed unclear reasons of the seasonal controversy in pediatric primary intussusception. Jang et al [34] found that the seasonal epidemic trends in the intussusception consisted with some viruses peak time displayed, especially for nonenteric adenoviruses. These viruses related to intussusception may be one of the possible reasons for the controversy of seasonal feature.

Abdominal pain and vomiting were the most common clinical features which were consistent with classic features of intussusception reported in other studies [17,35]. Like other studies [35,36], ultrasound was used to diagnose most cases (92.3%), and reduction was usually performed by air enema in77.4% of the cases. Low rate of surgical intervention was consistent with other studied that are likely explained by the timely medical treatment. A high cure rate was 99.7%.

Approximately 47.8% of acute gastroenteritis hospitalization among under-five children attributed to rotavirus in China [37]. Rotavirus diarrhea is currently no specific treatment. Vaccination is considered to be the most effective way to reduce the burden of rotavirus infection. But the crude national LLR vaccination coverage is only 15.6% with 1 dose since 2000 [38]. This may help explain why some studies observed that rotavirus is one of the major causes of acute gastroenteritis hospitalization since 2000. The Lanzhou Lamb rotavirus vaccine (LLR) is the only vaccine licensed in China. A cost-benefit analysis of rotavirus vaccination in China shows that the effort LLR to prevent and reduce rotavirus infection in children under five years of age are limited, especially among children between 0.5 and 2 years of age, compared with these two international vaccines (RV1 and RV5) [14].Whether it is to expand the use of the current LLR or to introduce the two vaccines (RV1 and RV2) recommended by the WHO, the relationship between the vaccine and intussusception must be considered. Our study provides basic data before expanding or introduction the rotavirus vaccine.

This analysis is subject to several limitations. Firstly, we conducted a retrospective study, our data came from the Hospital

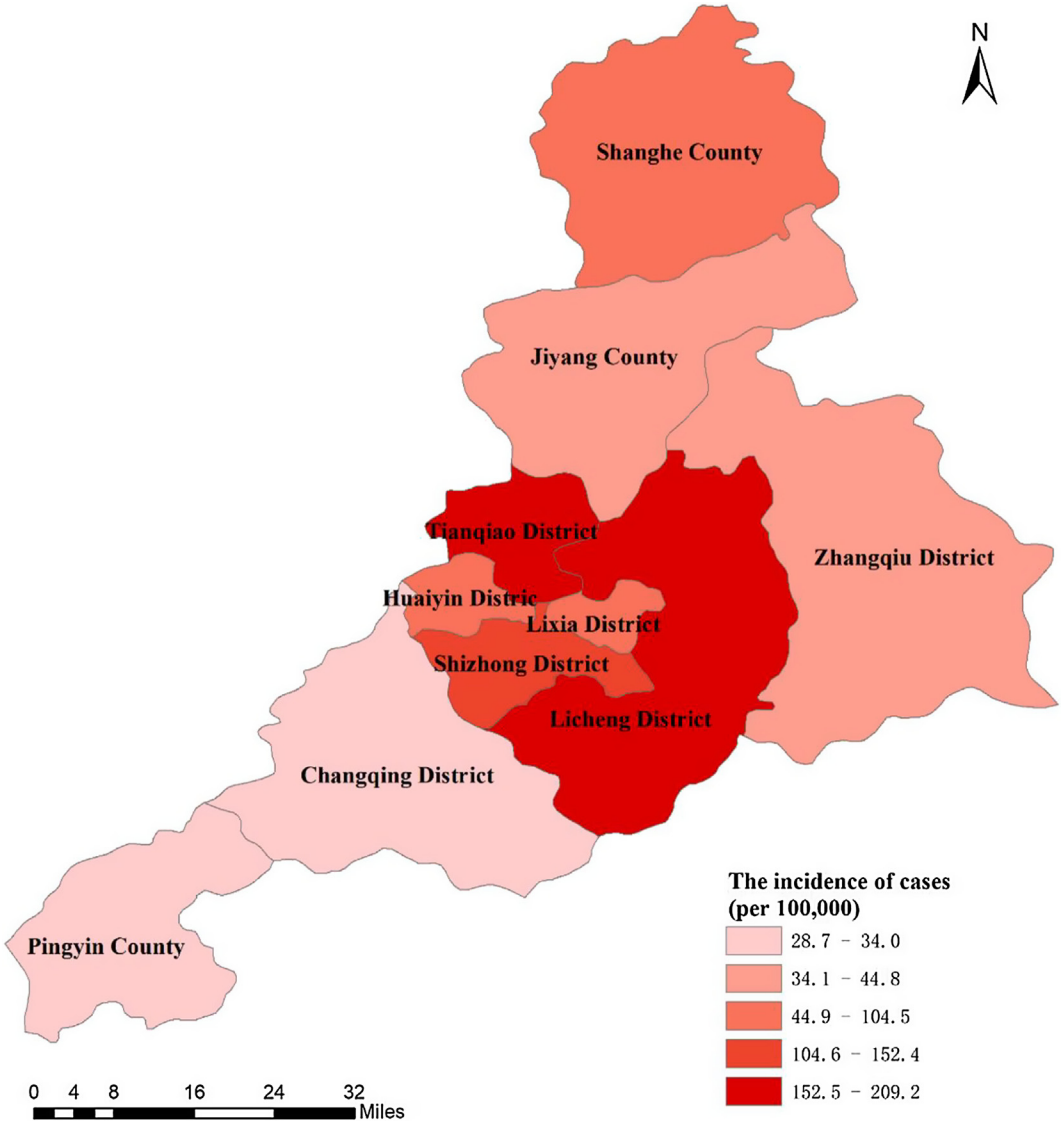

Fig. 3. The spatial distribution of the incidence rates of total pediatric intussusception cases. Figure showed the spatial distribution of incidence rates in ten districts of Jinan City between 2011 and 2015. The darker the color, the more of cases.

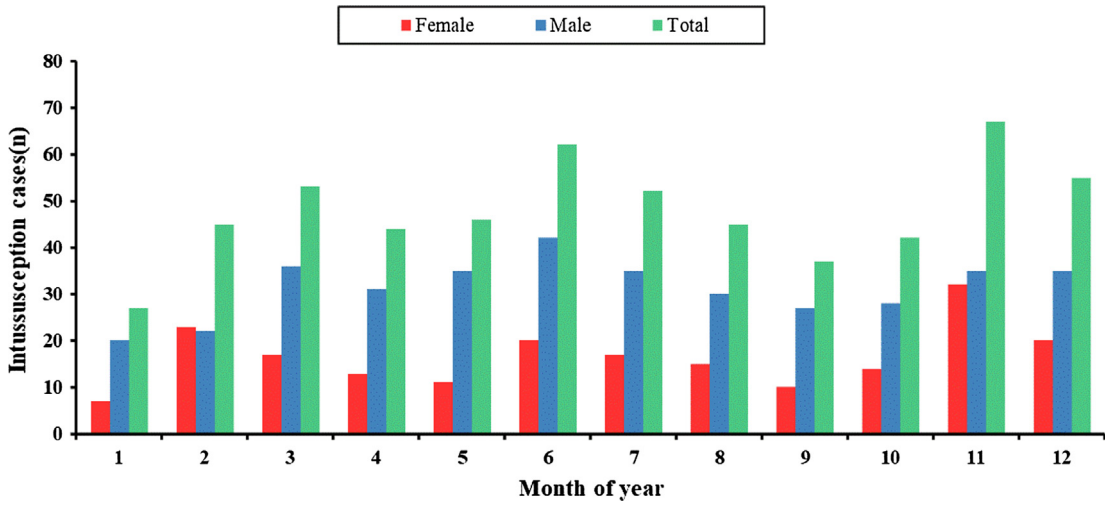

Fig. 4. Monthly distribution of pediatric primary intussusception cases classified by gender. Figure showed the monthly distribution of intussusception cases classified by gender. Red histogram stands for female cases, blue for male cases, and green for total cases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

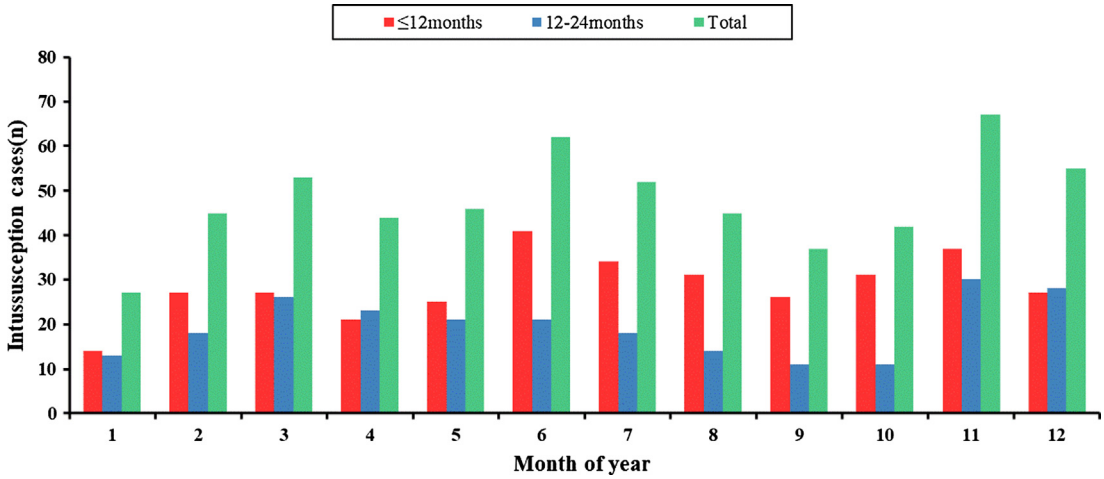

Fig. 5. Monthly distribution of pediatric primary intussusception cases classified by age. Figure showed the monthly distribution of intussusception cases classified by age group. Red histogram stands for ≤12 months of age, blue for >12 months of age, and green for total cases. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Clinical characteristics for pediatric intussusception cases in Jinan City, China, 2011–2015.

Clinical characteristics	No. (%) of patients
Clinical symptoms, no. (%)	575
Abdominal pain	465 (80.9)
Diarrhea	51 (8.9)
Vomiting	364 (63.3)
Abdominal distension/mass	167 (29.0)
Bloody stool	163 (28.3)
Fever	49 (8.5)
Pallor	180 (31.3)
Locations	183
Ileo-cecum	81 (44.3)
Ileo-colon	46 (25.1)
Ileo-ileo-colon	38 (20.8)
Ileo-cecal-colon	9 (4.9)
Ileum-ileum	6 (3.3)
Colon-colon	3 (1.6)
Frequency	573
1	566 (98.8)
2	5 (0.9)
3	2 (0.3)
Diagnosis, no. (%)	469
Ultrasound	433 (92.3)
Radiography	2 (0.4)
Ultrasound + Radiography	9 (1.9)
Ultrasound + Radiography + Contrast enema	1 (0.2)
Ultrasound + Digital examination	24 (5.1)
Treatment, no. (%)	575
Reduction by air enema	445 (77.4)
Surgery without resection	72 (12.5)
Surgery with resection	56 (9.7)
Transfer	2 (0.3)
Complications, no. (%)	474
None	401 (84.6)
Peritonitis	3 (0.6)
Dehydrated electrolyte imbalance	1 (0.2)
Other	69 (14.6)
Outcome, no. (%)	574
Cure	572 (99.7)
Transfer	2 (0.3)

Management Information Systems (HIS) and may were influenced by medical record keeping in HIS. Secondly, due to insufficient record keeping of locally licensed rotavirus vaccine in China, we could not collect the information about rotavirus vaccination of all intussusception cases. Despite these limitations, this study reports the epidemiology of pediatric primary intussusception for children ≤24 months of age selected from all secondary and tertiary hospitals in Jinan Citybetween2011 and 2015. It is important for monitoring intussusception in this population in the rotavirus vaccine era.

Declarations

All authors attest they meet the ICMJE criteria for authorship.

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Availability of data

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of the Jinan Municipal Center for Disease Control and Prevention. No patient consent was required because it is a retrospective review and we did not collect any private information.

Declarations of interests

The authors declare that they have no competing interests.

Authors' contributions

Tiantian Zhang designed the study and analyzed the baseline data, and drafted the manuscript. Liangliang Cui assisted with design and data collection. Xingyi Geng design the study and Xiaolin Yu contributed to data collection instruments. Ji Zhang monitored procedures, and provided leadership. All authors read and approved the final manuscript. All authors have approved the final submitted article and.

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