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Intussusception-related Hospitalizations among Infants before and after Private Market Licensure of Rotavirus Vaccines in Taiwan, 2001-2013

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Abstract

Introduction: Rotavirus is a leading cause of acute gastroenteritis among Taiwanese children. Two globally licensed rotavirus vaccines recommended for inclusion in routine immunization programs that have been available for private market use in Taiwan since 2006 have been associated with a low risk of intussusception in post-marketing studies conducted in several countries. Our objective was to examine trends and characteristics of intussusception hospitalizations in Taiwan among children aged <12 months before and after rotavirus vaccine licensure to provide updated baseline and early post-licensure data.

Methods: We extracted data on intussusception-related hospitalizations among children aged <12 months during 2001–2013 from the National Health Insurance Research Database. We examined patient demographics, clinical outcome, and hospitalization trends, focusing on recommended ages for rotavirus vaccination (6–14 weeks, 15–24 weeks, and 25–34 weeks). We compared mean hospitalization rates for pre-vaccine licensure years 2001–2005 with those for post-vaccine licensure years 2007–2013 using Poisson regression analysis.

Results: During 2001–2013, 1998 intussusceptions hospitalizations were recorded. The mean age of hospitalization was 33 weeks. Almost all children recovered; 3 deaths occurred. The overall

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intussusception hospitalization rate was 75.1 per 100,000; seasonality was not evident. Hospitalization rates were greatest in children aged ≥25 weeks and occurred more frequently in boys. Pre-vaccine and post-vaccine licensure trends in annual hospitalization rates did not significantly differ. However, mean hospitalization rates were lower during the post-vaccine licensure period for children aged <12 months (RR: 0.84, 95% CI: 0.76–0.92) with the greatest decline among children aged 25–34 weeks (RR: 0.66, 95% CI: 0.55–0.78).

Conclusions: Infant intussusception in Taiwan occurs at a rate within the range of other Asian countries, is rare among children aged <3 months, has a male predominance, and does not have a clear seasonality pattern. We did not observe a post-licensure increase in intussusception hospitalization rates in children aged 6–14 weeks.

Keywords

intussusception; rotavirus vaccine

INTRODUCTION

Intussusception is a rare clinical condition in which the intestine folds into itself, leading to bowel obstruction that, in turn, can lead to tissue edema, necrosis, and possibly intestinal perforation [1, 2]. Death may occur if the intussusception does not self-resolve or is not managed promptly. Management of intussusception includes reduction by air or hydrostatic enema or surgery [1, 2]. The cause of intussusception in most infant cases is not known. However, some infectious pathogens, such as respiratory adenovirus and various enteric bacteria, have been temporally associated in several studies [3–7]. Additionally, lymphoid hyperplasia, intestinal inflammation, and alterations in gastrointestinal motility have been proposed as mechanisms for intussusception in children [2, 8, 9].

Worldwide, the estimated mean incidence of naturally occurring intussusception among children aged <12 months is 74 cases (range: 9–328) per 100,000 children, with higher rates occurring in certain Asian countries such as Japan, the Republic of Korea, and Vietnam (range: 158–328 cases per 100,000 children) [10, 11]. A previous study conducted in Taiwan for 1998 through 2007 estimated an incidence rate of 77 cases per 100,000 person-years among children ≤12 months of age [12]. Reasons for the higher rates observed in certain Asian countries are not clear, but potential reasons include genetic predisposition, environmental differences including circulating pathogens, different feeding practices, and different diagnostic practices and access to health care [10].

In 1999, the first licensed rotavirus vaccine, Rotashield (Wyeth), was removed from the market due to an association with intussusception on the order of 1 excess case per 10,000 vaccinated infants in the US [13]. Following this, large clinical trials were conducted for the two current globally licensed rotavirus vaccines, Rotarix (GlaxoSmithKline, Rixensart, Belgium) and RotaTeq (Merck & Co., Kenilworth, NJ) [14, 15]. These trials did not detect an increased risk of intussusception. However, post-marketing evaluations in several upper middle to high income countries have detected a risk of vaccine-associated intussusception with both vaccines on the order of ~1–5 excess cases of intussusception per 100,000 vaccinated infants [16–22]. Various national- and global-level expert bodies have reviewed

these risks alongside rotavirus vaccination impact data and have concluded that, based on the available evidence, the benefits of rotavirus vaccination outweigh the risks of intussusception [23]. The World Health Organization (WHO) continues to recommend that rotavirus vaccines be included in all national immunization programs [24].

In Taiwan, previous studies have estimated that rotavirus accounts for 25–43% of all acute gastroenteritis hospitalizations in children aged <5 years [25, 26]. Both Rotarix and RotaTeq have been available for private market use in Taiwan since 2006. However, costs for these vaccines are not covered by the National Health Insurance Program, so parents must pay out-of-pocket if they would like their children to receive either of these vaccines. Administrative data-based reports from healthcare providers to the Taiwan Centers for Disease Control (TCDC) indicate that rotavirus vaccination coverage of at least one dose of vaccine only reached ~53% by 2014 [27]. As rotavirus remains a leading cause of acute gastroenteritis among children in Taiwan and policy makers consider including rotavirus vaccines in the routine immunization program, updated baseline data and early post-vaccine licensure monitoring of intussusception epidemiology and trends in infants will be useful for post-vaccine introduction safety monitoring. Our objective was to examine trends and describe the epidemiological characteristics of hospitalizations related to intussusception among children aged <12 months before and after licensure of rotavirus vaccines in Taiwan using a robust insurance claims database that represents over 99% of the population of Taiwan.

METHODS

Hospitalization data

We conducted a retrospective analysis of intussusception-related health care visits among children aged <12 months in Taiwan from 2001 through 2013 using data obtained from the National Health Insurance Research Database (NHIRD) [28]. In Taiwan, 99.6% of the population participates in the National Health Insurance (NHI) program, and the NHIRD contains health care claims data for all NHI participants [29].

For this analysis, we defined an intussusception-related hospitalization as one with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for intussusception (560.0) listed as any diagnosis. Additionally, we identified intussusception hospitalizations requiring surgical intervention as those that had an ICD-9-CM procedure code of 45.0–48.9 or 54.0–54.2 listed as a procedure performed during the hospitalization.

Population data

We calculated intussusception hospitalization rates using mid-year population data for children <12 months of age provided by the Department of Household Registration Affairs, Ministry of the Interior [30]. We assumed births to be evenly distributed throughout the year when calculating intussusception hospitalization rates by age in weeks as data on births by shorter time periods such as weeks or months were not available.

Analysis

We examined patient demographic characteristics, the number of intussusception hospitalizations per child, clinical outcomes, length of hospitalization, and pre-rotavirus vaccine licensure intussusception hospitalization incidence by week of age where incidence was modeled using a spline curve fit to weekly estimates of intussusception incidence. For children who had >1 intussusception hospitalization recorded, hospitalizations that were part of a hospital transfer for the initial course of illness were not counted as a separate intussusception episode. If a child was discharged home and hospitalized again for intussusception at a later date, this was counted as a separate episode. We assessed intussusception seasonality by reviewing monthly hospitalization rates for the entire study period and examined overall trends in the total number and rate of intussusception hospitalizations and rate trends by age groups with a focus on the recommended age windows for rotavirus vaccine administration in Taiwan (i.e., 6–14 weeks, 15–24 weeks, and 25–34 weeks).

To examine intussusception hospitalization rates during pre- and post-rotavirus vaccine licensure time periods by age group, we compared annual rate trends and mean hospitalization rates for pre-vaccine licensure years 2001 through 2005 with those for post-vaccine licensure years 2007 through 2013. We excluded data from 2006 as this was the year of rotavirus vaccine licensure in Taiwan. We calculated rate ratios (RR) and 95% confidence intervals (CI) using Poisson regression analysis.

This study was approved by the Institutional Review Board of the National Health Research Institutes of Taiwan.

RESULTS

Epidemiology of intussusception hospitalizations

During 2001–2013, 1998 intussusceptions hospitalizations were recorded in the NHIRD. The mean age of children at the time of admission was 33 weeks (range: 0 to 51 weeks) (Table 1). During 2001–2005, prior to rotavirus vaccine licensure, intussusception hospitalization rates by week of age showed a steady increase starting at about 8 weeks of age, with a peak in rates between 30 and 44 weeks of age (Figure 1). Of the 1998 recorded hospitalizations, 1887 occurred in children who had one documented intussusception hospitalization over the study period, while the remaining 111 hospitalizations occurred in 52 children who had more than one documented intussusception hospitalization (range: 2 to 5 hospitalizations per child) (Table 1); the median time between hospitalizations for children who had recurrent episodes was 48 days (range: 2 to 280 days). Hospitalization rates were greatest in the older age groups of 25–34 weeks and ≥35 weeks, and there was a male predominance in hospitalizations – 58.1% of hospitalizations occurred in boys, and 41.9% occurred in girls for a ratio of 1.4:1 (Table 1). Overall, 36.7% (annual range: 30.6%−41.5%) of intussusception hospitalizations required surgical treatment, and surgical rates showed no clear trends over time. Most children were discharged home alive (Table 1); only 3 deaths were recorded over the entire study period – one each in 2004, 2009, and 2012 and all in

cases that had required surgery. The mean length of hospital stay was 2.7 days (range: 0–40 days) for non-surgical cases and 6.6 days (range: 0–108 days) for surgical cases (Table 1).

Trends in intussusception hospitalizations

During 2001–2013, the overall rate of intussusception hospitalizations was 75.1 per 100,000 children aged <12 months. Annual intussusception hospitalizations rates were relatively stable during 2001–2005 (range: 74.2 to 87.5 hospitalizations per 100,000), declined during 2006–2008 (minimum rate of 64.8 per 100,000 in 2008), and subsequently remained relatively stable during 2009–2013 (range: 64.0 to 72.5 per 100,000) (Figure 2). The overall declines seen during 2006–2008 largely reflect declines in hospitalization rates among children in the 25–34 week age group, whereas hospitalizations rates for children in the 6–14 week and 15–24 week age groups did not show similar trends (Figure 3). There was no clear pattern of seasonality in hospitalizations (Figure 4).

Although annual hospitalization rates varied over time, the overall trend in annual rates during the pre-vaccine licensure period 2001 through 2005 was not significantly different from the overall trend in annual rates for the post-vaccine licensure period 2007 through 2013. However, mean rates of intussusception hospitalization were significantly lower during the post-vaccine licensure period for the overall group of children aged <12 months (RR: 0.84, 95% CI: 0.76–0.92), more specifically for children aged 25–34 weeks (RR: 0.66, 95% CI: 0.55–0.78) and not for children in the other age groups (Table 2).

DISCUSSION

This study provides over a decade of robust, nationally representative data on the epidemiology and trends of intussusception-related hospitalizations among infants in Taiwan. Our findings demonstrate that infant intussusception in Taiwan occurs at a rate that is similar to the global average of 74 per 100,000 children aged <12 months [10, 12] and falls within the range of those reported for other Asian locations with low to very low under-5 mortality rates. The overall rate of 75.1 intussusception hospitalizations per 100,000 children aged <12 months for Taiwan is lower than rates reported for Hong Kong, Japan, the Republic of Korea, and Vietnam (range: 108–328 per 100,000), but higher than those for Malaysia, Singapore, and Thailand (range: 18–51 per 100,000) [10, 31]. One difference in our findings from these other Asian locations is the higher proportion of cases undergoing surgical treatment in Taiwan. In other similar Asian locations, barium or air enema reduction is the predominant treatment for intussusception and is performed in the majority of hospitalized intussusception cases [31–38]. A potential reason for the higher surgical rate observed in Taiwan may be clinician bias to hospitalize only those that will need surgery and discharge those who undergo air or barium enema reduction from the emergency department. Despite this, clinical outcomes of surgical cases were good, and the mortality rate was close to zero.

Similar to other places worldwide, we found that intussusception is very rare among children aged <3 months in Taiwan, is more frequently seen in boys, and occurs without a clear pattern of seasonality [10, 31, 32, 34, 35, 39–46]. The finding of a male predominance in

infant intussusception cases is not well understood, but could suggest a genetic predisposition by sex.

For comparisons between pre- and post-vaccine licensure years, we did not observe a post-licensure increase in intussusception hospitalization rates in the 6–14 week age group, the time during which the first dose of rotavirus vaccine that has been associated with an increased risk for intussusception would be given [16–22]. However, given a small birth cohort that ranged from ~170,000 to 200,000 during 2007–2013 and rotavirus vaccination coverage that ranged from 13% in 2007 to 49% in 2013 [27], it would be difficult to see in our data analysis an ecological trend that would point to the vaccine-associated intussusception risk of 1–5 excess cases per 100,000 vaccinated children seen in other countries [16–22]. Even in 2013 when the vaccination coverage was almost 50%, only 1–5 excess intussusception cases would have been expected in a birth cohort of 201,344, should a similar vaccine-associated intussusception risk exist. While the overall decline in hospitalization rates for children aged <12 months is similar to pre-vaccine introduction trends seen in other countries [47–49], it seems to be driven by the significant decline in hospitalizations observed in children aged 25–34 weeks. Reasons for this finding are unknown given that much of the decline occurred in such a specific age group. It is unlikely that earlier hospitalizations rates were affected by something that would have resulted in higher than normal rates of intussusception, such as outbreaks of respiratory adenovirus, as we would have seen the same trend in other age groups, and it is unlikely that later rates were affected by things such as changes in clinical or coding practices as these also would have affected a wider age range.

This study has some limitations. First, intussusception cases were identified by ICD-9-CM code and were not validated by retrospective medical chart review and use of the Brighton Collaboration case definition for a definitive diagnosis of intussusception [50]. This may have resulted in an overestimation of intussusception incidence, which would further support the finding that intussusception is a rare event among infants in Taiwan. Additionally, our findings provide generally representative information on intussusception among infants in Taiwan at the population level, something that would be difficult to obtain without an established active intussusception surveillance network in all hospitals that manage these cases; no such network exists in Taiwan currently. Second, as technology improves and treatment of intussusception shifts toward non-surgical procedures in Taiwan, some cases of intussusception may only be treated in emergency departments and not captured in hospitalization data; this would result in an underestimation of intussusception incidence in later years. Given this possibility, we examined emergency department (ED) visit data included in the NHIRD. However, while an analysis of intussusception-related ED visits for children aged <12 months showed no uniform trends over time, only one of 1828 records with an ICD-9-CM code for intussusception also included a procedure code for intussusception reduction (code 96.29). Therefore, without medical chart confirmation, we could not confidently conclude which cases were confirmed intussusception cases treated in the ED as opposed to cases for which intussusception was ruled out. Third, since rotavirus vaccine is only available on the private market and therefore not included in the NHIRD, we were not able to assess the rotavirus vaccination status of the children hospitalized with

intussusception. Should rotavirus vaccine be included in the routine immunization program, future NHIRD analyses will be able to link vaccination data with intussusception records.

In conclusion, this study provides important baseline and early post-rotavirus vaccine licensure data on infant intussusception hospitalizations in Taiwan. In the future, these data will be important for monitoring the safety of rotavirus vaccines as their use becomes more widespread or should they be included in Taiwan's Expanded Program on Immunization. This study also highlights the utility of databases like NHIRD for monitoring trends in medical conditions and health care use and providing key stakeholders with robust information that can help inform policy decisions.

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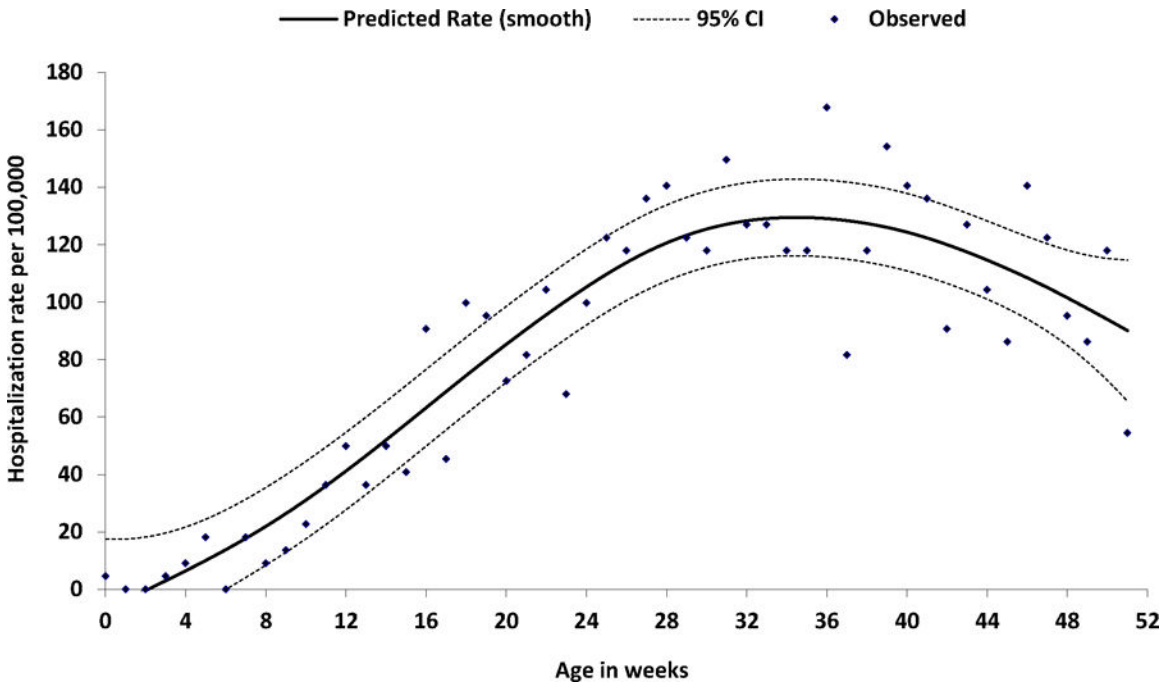

Figure 1.

Observed and predicated rates of intussusception hospitalization by week of age — Taiwan, 2001–2005

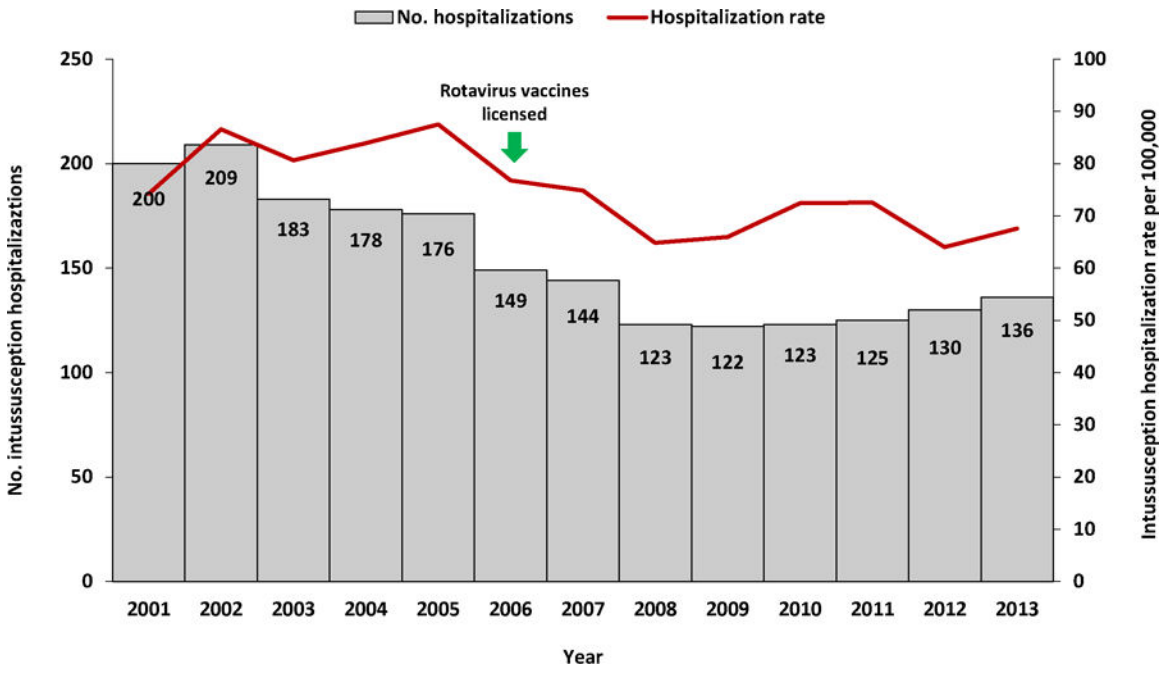

Figure 2.

Annual numbers and rates of intussusception hospitalizations among children aged <12 months — Taiwan, 2001–2013

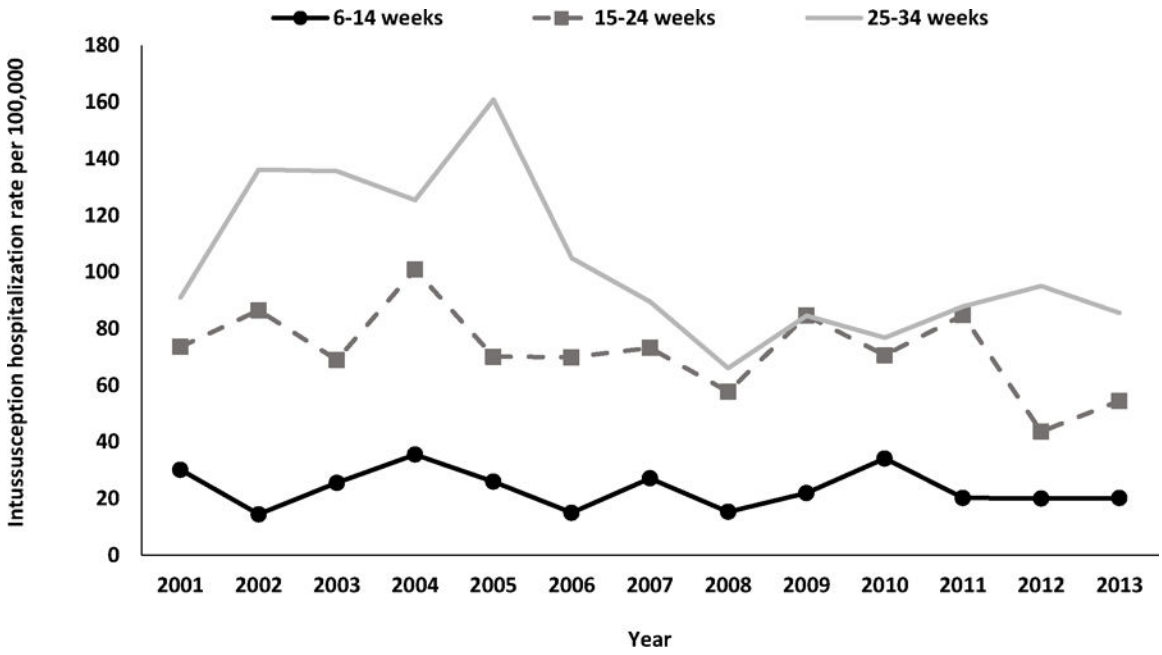

Figure 3.

Annual rates of intussusception hospitalizations among children aged <12 months, by age group — Taiwan, 2001–2013

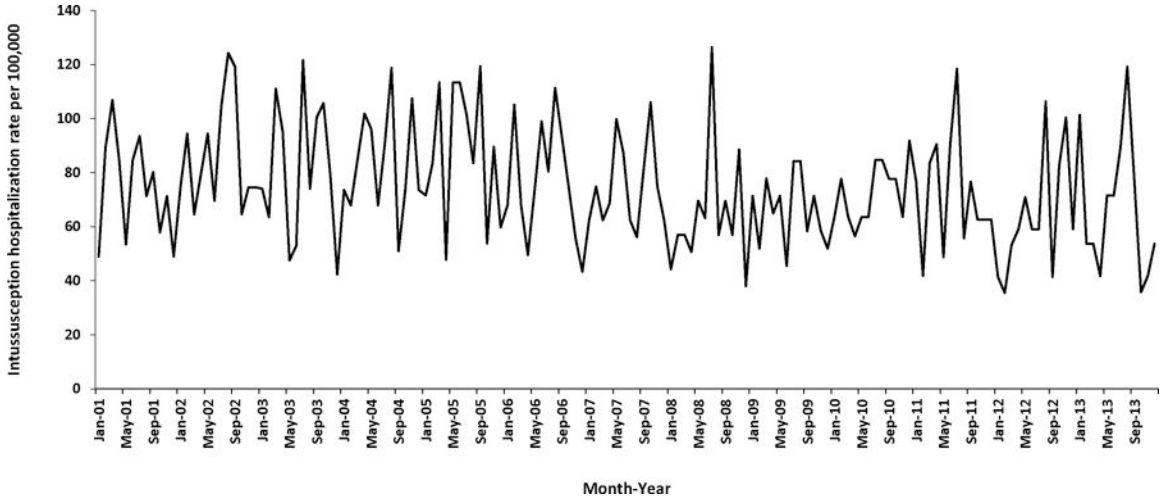

Figure 4.

Monthly rates of intussusception hospitalizations among children aged <12 months — Taiwan, 2001–2013

Table 1.

Demographic characteristics and clinical course of children <12 months of age hospitalized for intussusception − Taiwan, 2001–2013

Characteristic or clinical course	N (%), Mean (Range)	Rate per 100,000 children
Total number of intussusception hospitalizations	1998	75.1
Mean age of children with intussusception (range)	33 weeks (0–51)	
Episodes of intussusception per child		
No. of children with 1 episode	1887 (97%)	
No. of children with >1 episode (range: 2–5)	52 (3%)	
Intussusception hospitalizations, by age group		
0–5 weeks	14 (0.7%)	4.6
6–14 weeks	108 (5.4%)	23.5
15–24 weeks	369 (18.5%)	72.4
25–34 weeks	532 (26.6%)	104.4
35+ weeks	975 (48.8%)	112.5
Intussusception hospitalizations, by sex		
Male	1161 (58.1%)	83.6
Female	837 (41.9%)	65.8
Intussusception hospitalizations, by surgical status		
Non-surgical case	1264 (63.3%)	47.5
Surgical case	734 (36.7%)	27.6
Outcomes of intussusception hospitalizations		
Discharged home	1927 (96.4%)	
Left hospital against medical advice	34 (1.7%)	
Transferred	31 (1.5%)	
Remained in hospital for other reasons	3 (0.2%)	
Died[1]	3 (0.2%)	
Mean length of stay (range), by surgical status		
Non-surgical case	2.7 days (0–40)	
Surgical case	6.6 days (0–108)	

[1] All deaths occurred in cases that had undergone surgery – 1 death occurred each in 2004, 2009, and 2012

Table 2.

Intussusception hospitalizations rates per 100,000 and rate ratios and 95% confidence intervals (CI) by age group in the pre- (2001–2005) and post- (2007–2013) rotavirus vaccine introduction years, by age group

Age group	2001–2005		2007–2013		Rate ratio (95% CI)	p-value
	Average annual no.	Mean rate (min, max)	Average annual no.	Mean rate (min, max)		
<12 months	189	82.2 (77.1, 87.6)	129	68.7 (64.4, 73.3)	0.84 (0.76, 0.92)	0.0001
0–5 weeks	2	6.0 (3.0, 12.1)	1	4.6 (2.2, 9.7)	0.77 (0.28, 2.11)	0.6077
6–14 weeks	10	26.2 (20.0, 34.4)	7	22.5 (17.1, 29.6)	0.86 (0.58, 1.26)	0.4418
15–24 weeks	35	79.8 (68.8, 92.5)	24	66.3 (57.0, 77.2)	0.83 (0.67, 1.03)	0.0874
25–34 weeks	56	127.8 (113.7, 143.6)	30	83.8 (73.2, 95.9)	0.66 (0.55, 0.78)	<.0001
35+ weeks	86	114.1 (103.8, 125.4)	67	109.3 (99.8, 119.7)	0.96 (0.84, 1.09)	0.5222

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