

**Incidence of Intussusception in Children Less than 2 Years**

Muna Al Musawi, MBBch, FMSC, DPM\* Saeed Jaffer Alhindi, MD, CABS, FRCSI\*\*

Sameh Anis, MD, DCH \*\*\* Robert Pawinski, MBChB, Dip (OBST), DTMH, MSc\*\*\*\*

**Background:** Surveillance of baseline incidence of intussusception (IS) in children less than 2 years of age is important for the safety monitoring of second-generation rotavirus vaccines.

**Objective:** To estimate the incidence of IS in children aged less than two years, before the implementation of rotavirus vaccination as part of the routine immunization program in Bahrain.

**Setting:** Salmaniya Medical Complex (SMC), Kingdom of Bahrain.

**Design:** Retrospective Study.

**Method:** Children aged <2 years with definite IS were identified by daily reviews of the medical records at Salmaniya Medical Complex. The annual incidence of IS was calculated for children aged <1 year and 1–2 years, using the number of subjects with definite IS residing in the study area as numerator and the study area population aged <1 year and 1–2 years, respectively, as the denominator.

**Result:** Twenty-one children, 10 males and 11 females, were diagnosed with definite IS (2004–2006). The incidence of IS ranged from 35.4–56.3 per 100,000 children aged <1 year and from 6.7–21.7 per 100,000 in children aged 1–2 years (overall 23.4–39.2 per 100,000 children aged <2 years). Sixteen (76.2%) IS cases occurred in children aged <1 year; incidence peaked between 5–8 months of age. IS cases demonstrated no seasonality. Twenty (95.2%) children had abdominal pain and 17 (81%) had vomiting. No deaths were reported.

**Conclusion:** Incidence of IS in Bahrain reveals a decreasing trend from 2004 to 2006. The incidence was high in the first year of life. These baseline data on IS incidence will facilitate the risk/benefit assessment of rotavirus vaccination once it is routinely used for immunizing infants in Bahrain.

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\* Public Health Consultant for International Health Regulations, National IHR Focal Officer

\*\* Consultant Pediatric Surgeon and Clinical Lecturer  
Division of Pediatric Surgery, Salmaniya Medical Complex

\*\*\* Director, Clinical R&D and Medical Affairs, Vaccines, Middle East & North Africa  
GlaxoSmithKline Pharmaceuticals, Dubai, United Arab Emirates

\*\*\*\* Director, Epidemiology, Africa and Middle East, GlaxoSmithKline Biologicals, Belgium (at the time of the study)

Email: dr.almusawi@gmail.com; mmousawi@health.gov.bh

Intussusception (IS) occurs when a proximal segment of the intestine prolapses into a distal segment of the intestine and may be fatal if left untreated<sup>1,2</sup>. Globally, IS peaks between the fourth and seventh month of life and males are twice prone to IS compared to females<sup>3</sup>. Intussusception is a rare disease. In the absence of timely diagnosis and early treatment opportunities, IS related mortality in the developing countries is higher compared to developed countries<sup>2</sup>. The cause of IS remains undetermined in the majority of cases<sup>1</sup>.

The first oral, live-attenuated rotavirus vaccine (RRV-TV: Rotashield™; Wyeth Lederle) licensed for mass vaccination in the United States (USA) in 1999 was withdrawn, following concerns regarding temporal association between administration of the vaccine and increased risk of IS in the recipients<sup>1,4</sup>. Pre-licensure trials for the rotavirus vaccine, which was developed after Rotashield™ have not found any evidence of increased risk of IS in recipients and have been subsequently licensed in the USA and Europe<sup>5-8</sup>. However, the World Health Organization (WHO) continues to recommend the review of local baseline epidemiological data on IS from different geographical settings for effective safety monitoring of licensed second-generation rotavirus vaccines<sup>3,5</sup>.

Recently published data on IS incidence from Bahrain is limited to two retrospective studies; one was conducted between 1980 and 1986 and the other between 1999 and 2003<sup>9,10</sup>.

The aim of the study is to investigate the current baseline incidence and epidemiology of naturally occurring IS in children aged <2 years prior to the introduction of rotavirus vaccination in the country.

## **METHOD**

This was hospital-based (Salmaniya Medical Complex) single center study performed from January 2004 to May 2006. Ninety percent of the total birth cohort between 2004 and 2006 was estimated to visit SMC for the treatment of IS<sup>11</sup>.

Children <2 years of age residing in the study area covered by SMC were included in the study. Admission logs, computerized hospital admission records, emergency department records, surgical records and radiology logs were reviewed. Children without a previous history of confirmed diagnosis of IS and who were hospitalized or were receiving treatment at the hospital diagnosed with IS, based on the guidelines from the Brighton Collaboration Working Group and whose parents gave written informed consent were enrolled in the study<sup>12</sup>.

Gestational age, breast-feeding practices, vaccination history, administration of medications before admission were obtained through interviewing the parent/guardian of the children. Clinical signs and symptoms on admission, diagnostic procedures, microbiological results, surgical procedures performed and the outcome of admissions were documented.

The study was conducted according to the principles of Good Clinical Practice and applicable local regulations.

## **Statistical Analyses**

The incidence of IS was calculated with 95% confidence interval (CI); only those children diagnosed with definite IS and who were residing in the study area were considered for analysis.

The annual incidence of IS for the years 2004, 2005 and 2006 per 100,000 children for aged <1 year, 1–2 years and overall <2 years were calculated using the following formula:

$$\text{Annual incidence of IS} = \frac{\text{Number of definite IS cases observed at the study hospital}}{\text{Children aged <1 year or 1–2 years or overall <2 years residing in the study area x duration of study in days}} \times 100,000 \times 365$$

The populations <1 year, 1–2 years and overall <2 years of age residing in the study area were obtained from the database of the Ministry of Health<sup>13</sup>. All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.2.

Population data for January-May 2006 available from the Ministry of Health, Bahrain, were extrapolated to compute the annual incidence of IS (January to December 2006, in table 1).

**Table 1: Population of Interest during the Study Period by Age and Calendar Year**

Year	Study Start	Study End	Number of Children Aged <1 Year	Number of Children Aged 1–2 Year	Total Number of Children Aged <2 Year
2004	17 Jan 2004	31 Dec 2004	14827	14460	29287
2005	01 Jan 2005	31 Dec 2005	15064	14841	29905
2006*	01 Jan 2006	18 May 2006	14937	15074	30011

\* for the year 2006, available population data for the study duration between January and May obtained from the ministry of health, Bahrain database were extrapolated to obtain the annual incidence of IS (January to December 2006)

## RESULT

Twenty-three children hospitalized with IS were identified and enrolled in the study. One child was excluded for being over two years of age. Another child was initially diagnosed with IS, but the symptoms did not progress into definite IS according to the Brighton Collaboration case definition; therefore, the child was excluded. The remaining 21 children, 10 males and 11 females, with definite IS were included in the study. All cases were independently reviewed by the investigators according to the Brighton Collaboration Working Group case definition, in order to confirm diagnosis of definite IS.

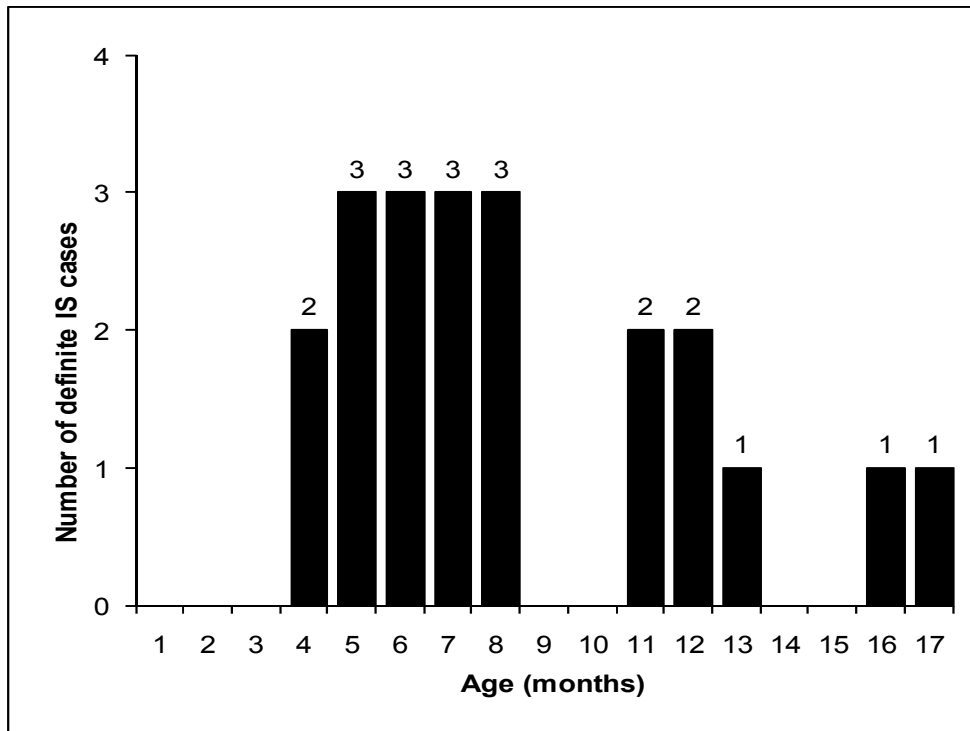
Mean age of children was 8.9 months (SD 3.8 months, range 4.2-17.3 months; median 7.3 months). Nineteen children (90.5%) were Bahraini, two (9.5%) were expatriate residing in Bahrain, one Egyptian and one Indian. All children were born after a normal gestation period. Weight at the time of admission varied between 5.8 and 11.5 kilograms (mean 8.2 kilograms, SD 1.7 kilograms). Ten (47.6%) children were exclusively breast-fed at the time of admission and 17 (81%) did not receive any antibiotic within two weeks before being diagnosed with definite IS.

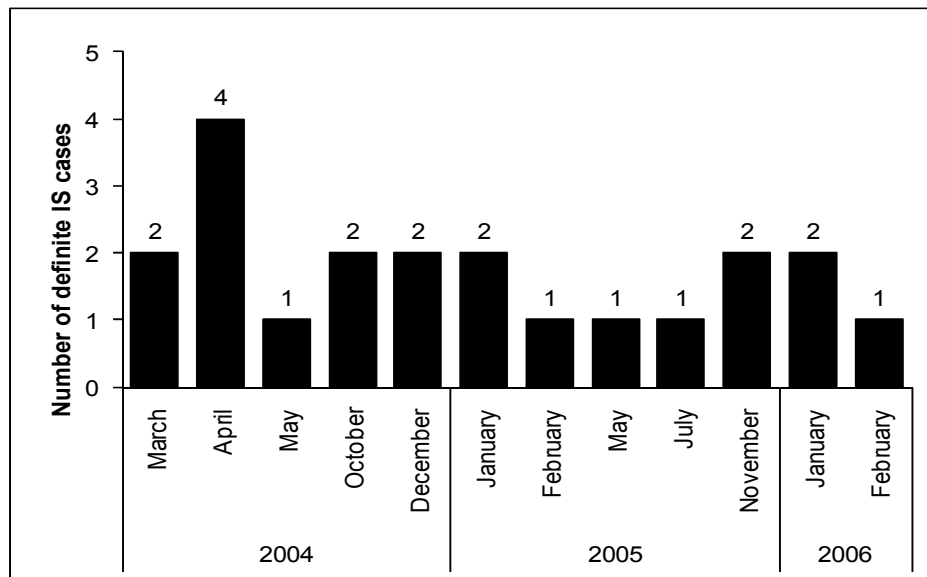
Definite IS cases occurred in 16 (76.2%) children <1 year of age and IS incidence peaked between five and eight months of age, see figure 1A. The incidence of IS ranged from 35.4-56.3 per 100,000 children aged <1 year and from 6.7 - 21.7 per 100,000 in children aged 1–2 years (overall 23.4 to 39.2 per 100,000 children aged <2 years), see table 2. All children with definite IS met the criterion for calculating the incidence of IS (resided in the study area). IS cases occurred throughout the year with no distinct seasonality, see figure 1B.

**Table 2: Annual Incidence of IS in Children Aged <1 Year and <2 Years from 2004 – 2006**

Year	Age of Children	Number of IS Cases	Number of Children Residing in Study Area	Incidence of IS per 100,000 % (95% CI)
2004	<1 year	8	14827	56.3 (17.3–95.3)
	1–2 years	3	14460	21.7 (0.0–46.1)
	Total	11	29287	39.2 (16.0–62.4)
2005	<1 year	6	15064	39.9 (8.0–71.7)
	1–2 years	1	14841	6.7 (0.0–20.0)
	Total	7	29905	23.4 (6.1–40.8)
2006*	<1 year	2	14937	35.4 (0.0–84.6)
	1–2 years	1	15074	17.6 (0.0–52.0)
	Total	3	30011	26.5 (0.0–56.4)

\* For the year 2006, available population data for the study duration between January and May obtained from the Ministry of Health, Bahrain database were extrapolated to obtain the annual incidence of IS (January to December 2006) CI: Confidence Interval

**Figure 1A: Number of IS Cases per Age Category in All Children (N=21)**



**Figure 1B: Frequency Distribution of IS Cases throughout the Study Period**

Twenty (95.2%) children had abdominal pain and 17 (81%) had vomiting. Other clinical features included fever, diarrhea, bloody stool, red currant jelly stool, lethargy and pallor, see table 3. Thirteen children (62%) had five or more symptoms at the time of admission.

**Table 3: Clinical Symptoms of Children with Definite IS at Admission (N=21)**

Symptoms	Number (%)
Fever	3 (14.3)
Vomiting	17 (81)
Bile-stained vomiting	1 (4.8)
Diarrhea	7 (33.3)
Bloody stool	10 (47.6)
Rectal bleeding	2 (9.5)
Blood on rectal exam	7 (33.3)
Red jelly stool	10 (47.6)
Abdominal mass	13 (62)
Rectal mass	1 (4.8)
Rectal prolapse	0 (0)
Abdominal pain	20 (95.2)
Lethargy	15 (71.4)
Pallor	8 (38.1)
Hypovolemic shock	0 (0)
Abdominal distension	2 (9.5)
Abnormal or absent bowel sounds	3 (14.3)
Others	2 (9.5)

All values were rounded off, N = number of subjects in a given category

Gas/liquid enema (n=20), abdominal ultrasound (n=19), abdominal radiograph (n=17) and abdominal CT scan (n=3) were the procedures used to ascertain the diagnosis of IS. IS-related invagination was observed in 20 children, abdominal and intra-abdominal mass was observed in 19 children and an abdominal mass characteristic of IS was observed in 14 children.

Six (28.6%) children with definite IS had surgery. Delay in surgery from the onset of clinical symptoms of IS could be one day. The six children who had surgery, four had the IS located in the ileocecal, one ileoileal and one ileocolic. Ileal thickening was revealed in five children and mesenteric adenopathy in four children.

Fifteen (71.4%) children who did not undergo surgery, the location of IS was in the ileocolic region. The duration of the hospital stay ranged between 1-10 days (mean 3 days, SD 2 days). All children recovered completely without any sequelae. No deaths were reported.

## DISCUSSION

In 2002, the birth cohort in the Kingdom of Bahrain was 13,576, of which 5,403 children were born at the SMC alone<sup>13</sup>. Although it was a single-center study, this study covered ninety percent of the population of interest (children aged <2 years) between 2004 and 2006<sup>11</sup>. In addition, SMC was found to be the hospital of choice in previous studies investigating IS in Bahrain<sup>9</sup>.

Incidence of IS in children varies across different regions of the world. According to a comprehensive review conducted by the World Health Organization (WHO), between 1983 and 2001 the IS incidence rates in infants and children in Europe, the USA and New Zealand varied between 50 and 430 per 100,000 live births (<1 year 66–120 per 100,000 children)<sup>3</sup>. Another study on Europe (1940–1988) reported that the incidence of pediatric IS varied between 66 and 224 per 100,000 children<sup>14</sup>. Recent publications from Australia and Switzerland (1994–2000 and 2003–2006) reported that the incidence of intussusception is 38–101 per 100,000 and 31 per 100,000 for children aged <1 year and <2 years, respectively<sup>1,7</sup>. Conclusive data on the incidence of IS in the developing countries are limited<sup>3,8</sup>. According to the last comprehensive WHO review (1983–2001), in Africa, the incidence of IS was reported to be high in <1 year-old children, under-reporting undermined the accuracy of the estimated rates (1–60 cases per year)<sup>12</sup>. In Japan and Singapore, the incidence of IS in the first year of life was reported to be 185 per 100,000 children and 26.4–39.9 per 100,000 children, respectively<sup>8,15</sup>. In the majority of the developing countries, IS-associated mortality is high<sup>3</sup>.

The overall mean annual incidence of IS in Saudi Arabia, Kuwait, Qatar, Iran and Lebanon ranges from <1 to 23.3 cases<sup>3</sup>. Only two papers documented the incidence of IS in Bahrain. The first study reported an overall annual IS incidence of 109 per 100,000 live births in children aged <5 years; a recent study reported that the incidence of intussusception is 72.4 per 100,000 children in the first year of life and 17.8 per 100,000 aged <5 years<sup>9,10</sup>.

In the present study, the annual incidence of IS in Bahrain between 2004-2006 appeared to be on the decline (from 56.3 and 21.7 per 100,000 in children aged <1 year and 1–2 years, respectively in 2004 to 35.4 and 17.6 per 100,000 in 2006). However, it is to be noted that the number of cases under evaluation in the previous two studies (79 and 66 cases, respectively) was higher than that in the present study (21 cases)<sup>9,10</sup>. The decline in the incidence of IS has also been recorded in other regions of the world. The declining incidence of IS over time observed in the USA (1994–1996,

from 5.6 to 1.8 per 10,000 live births), Australia (1994–2000, 13 to 8.1 per 10,000 infants <1 year) and in Europe (1988–2006, 110–430 to 50–230 per 100,000 live births)<sup>3,7,14,16</sup>.

The majority of IS in the present study occurred in the first year of life, which is similar to the two previous studies performed in Bahrain. Studies from Asian countries, Europe and the USA have also reported a similar age distribution<sup>9,10,14-18</sup>. The peak IS incidence (between five and eight months of age) observed in this study was similar to the peak incidences recorded in two previous studies in Bahrain (3-6 months) and other countries<sup>3,9,16,17</sup>. The occurrence of IS in the present study was comparable in both males and females (10 males and 11 females), which is in contrast to predominance of IS in males observed in other studies<sup>1,3,8</sup>. The IS occurred throughout the year and there appeared to be no seasonal variation associated with the occurrence of IS, which is similar to previously published data<sup>1,3,9</sup>.

In Africa and Asia (1962–2000), IS-associated mortality was up to 58%; in Middle-east countries (1962–1989), it was up to 10.7%<sup>3</sup>. In the present study, all children recovered and no deaths were reported. Therefore, IS-associated deaths in Bahrain and the surrounding region appear to be on the decline, a trend, which has been observed with increasing frequency worldwide<sup>7,14</sup>.

The relatively short duration of the study, the small number of participants and lack of data on the non-enrolled children (whose parents refused to give consent for participation) may have underestimated the true incidence of IS in Bahrain<sup>9</sup>. The data presented in this study should be interpreted with caution as the incidence of IS for the year 2006 was calculated based on extrapolation of available data for five months (January–May 2006) and the relatively higher IS incidence observed in 2004 might be due to chance. However, considering that Bahrain is a small country with a population of 740,000 at the time of the study and that the SMC provides healthcare for all IS cases in the country, this study is likely to comprehensively present the incidence of IS in children aged <2 years in Bahrain<sup>19</sup>.

## CONCLUSION

**This study revealed that the incidence of IS in Bahrain is declining. The time from the onset of symptoms and presentation of the IS to the hospital has decreased considerably; therefore, reducing IS-associated mortality. The findings presented here provide baseline data on IS incidence in children in Bahrain and will be an additional source of data for future pooled analyses to monitor trends in IS incidence post-rotavirus vaccine introduction in the region.**

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**Competing interest:** None

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