

## **Incidence of Intussusception: Five-Year Hospital-Based Retrospective Review**

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**Background and objective:** The aim of this study was to survey the baseline occurrence of intussusception (IS) among children less than five years of age who were hospitalized prior to the introduction of the new rotavirus vaccines.

**Design:** Retrospective cohort study.

**Setting:** Salmaniya Medical Complex, Ministry of Health.

**Method:** Intussusception cases in children less than five years, who were admitted to hospital from January 1999 to December 2003 were reviewed. The intussusception definition of Brighton Collaboration Working Group was adopted. The incidence of definite Intussusception per year was computed.

**Result:** Sixty-six cases were identified, 12 cases were excluded because the date of hospital admission was before the study period. Fifty-four cases fit the criteria and the period of the study.

The mean age of the subjects was 9.4 months. Thirty-four (63%) of the subjects were males. The incidence of definite intussusception was 17.8 per 100,000 per year in children less than five years of age, and was 72.4 per 100,000 per year in children less than one year of age.

Intussusception was high, forty-four (81.5%), in the 2-11 months age group. Intussusception occurred all year round, with no clear seasonal variations. There were no deaths and all subjects who participated in this study had recovered.

**Conclusion:** This study provides, for the first time, a baseline estimate for the incidence rate of intussusception in the Kingdom of Bahrain.

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Rotavirus (RV) is the most common cause of severe diarrhea in young children, causing more than 611,000 deaths each year in the developing countries<sup>1</sup>. They also result in a substantial disease burden for industrialized countries. Virtually all children are infected at least once before the age of 5 years, regardless of their nationality, level of hygiene, sanitation or access to clean water<sup>1,2</sup>. The high disease burden necessitated the development of vaccine against RV disease assuming that the implementation of the vaccine would result in measurable decrease in the number of hospitalizations and deaths associated with RV disease within 2-3 years<sup>3</sup>. Rapid progress was made in the developing and testing of vaccine in candidates to prevent RV disease.

Efforts at prevention received a setback when the first licensed RV vaccine, rhesus-human reassortant tetravalent vaccine (RRV-TV: *Rotashield*<sup>TM</sup>; Wyeth-Ayerst), was withdrawn in 1999 because of its association with intussusception (IS)<sup>4</sup>. Studies at the time concluded that RRV-TV was associated with increased risk of IS and this risk was highest 3 to 14 days after the first vaccination dose<sup>5</sup>. However, further analysis suggested that the withdrawal of the vaccine may have been premature because the short-term increased risk was largely balanced by a subsequent decreased risk; not using RRV-TV could result in a failure to prevent IS associated with wild-type RV infection<sup>6</sup>.

The setback of *Rotashield*<sup>TM</sup> and its probable association with IS created an opportunity, as well as presented a major challenge to the development of next generation RV vaccines<sup>7</sup>. The development of two alternate vaccines (*Rotateq*<sup>TM</sup> from Merck & Co, USA and *Rotarix*<sup>TM</sup> from GlaxoSmithKline Biologicals, Belgium) against RV disease has renewed the optimism for the reduction of global disease burden of RV disease<sup>8</sup>. The new orally administered live attenuated RV vaccines have been proven safe and efficacious<sup>9,10</sup>. There has been no evidence of an increased risk for intussusception in the pre-licensure studies of these new vaccines<sup>11,12</sup>.

It is useful to determine the country baseline incidence rate of IS for safety monitoring requirements after widespread use of the RV vaccines<sup>13</sup>. Data particularly of definite IS in the Kingdom of Bahrain is limited. Consequently, in this retrospective survey, investigators surveyed the occurrence of IS among children less than five years who were hospitalized prior to the introduction of new RV vaccines.

## METHOD

Intussusception cases in children less than five years, who were admitted to hospital from January 1999 to December 2003 were reviewed.

Cases included in the study met the definition criteria of the Brighton Collaboration Working Group on Intussusception<sup>14</sup>. Informed consent was not obtained from the subjects to review their medical records.

- **Surgical Criteria:** The demonstration of invagination of the intestine at surgery.
- **Radiological Criteria:** The demonstration of invagination of the intestine by either gas or liquid contrast enema; or the demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features (target sign or doughnut sign on

transverse section and a pseudo-kidney or sandwich sign on longitudinal section) that is proven to be reduced by hydrostatic enema on post-reduction ultrasound.

- **Autopsy Criteria:** The demonstration of invagination of the intestine.

Age, gender and details of the IS episode including clinical signs and symptoms, diagnosis, treatment and outcome were recorded. No samples were collected in this retrospective study. The study protocol was reviewed by the Public Health Directorate.

### **Estimating the Incidence of IS**

It was assumed that 90% of the children less than five years of age with symptoms of IS would visit the study hospital (Salmaniya Medical Complex). The live births during the study period, January 1999 to December 2003, were 67,493.

The incidence of definite IS per year was computed, using the following formula:

Incidence of cases = (Number of IS cases during the 5 years) / (90% of the birth cohort from 1999 to 2003 x 5).

The denominator was multiplied by 5 to compute the incidence rate in children less than five years of age.

The statistical analyses were performed using the Statistical Analysis Systems (SAS) version 8.2.

### **RESULT**

Sixty-six cases were identified, 12 cases were excluded because the date of hospital admission was before the study period. Fifty-four cases fit the criteria and the period of the study.

The mean age of the subjects was 9.4 months. Thirty-four (63%) of the subjects were males. Forty-seven (87.03%) were Bahraini, seven (13%) were from different nationalities, but were residents of Bahrain (Australia, India, Syria, Pakistan, USA and Yemen).

The incidence of definite IS was calculated to be 17.8 per 100 000 per year [95% CI: 13.0; 22.5] in subjects less than five years, assuming that the estimated percentage of subjects visiting the hospital was 90% of the total population, birth cohort of 67,493 infants, see Table 1. The incidence of IS was 72.4 per 100,000 per year (95% CI: 51.0; 93.8) in subjects <1 year of age, see Table 2.

Forty-four (81.5%) cases were seen in the 2-11 months age group, see Figure 1. IS had occurred all the year round, with no seasonal variation, see Figure 2.

Forty-eight (89%) had abdominal pain and vomiting; abdominal mass was reported in thirty-five (64.8%) other clinical symptoms included: diarrhea, red currant jelly stool and fever. The majority of IS, forty-seven (87%), was diagnosed by ultrasound. Radiological reduction had resolved thirty-eight (70.4%) of cases. Bowel resection was performed on 16 (29.6%) of the subjects, of which 12 were failed radiological reduction. There was no mortality and in this study all the subjects had recovered.

**Table 1: Incidence of Definite IS in Subjects Less Than Five Years of Age**

Year	Number of definite IS cases	Birth cohort	Incidence of IS (in 100 000)	Asymptotic 95%CI LL	UL
1999	9	13214	15.1	5.2	25
2000	8	13531	13.1	4	22.2
2001	12	13437	19.8	8.6	31.1
2002	9	13576	14.7	5.1	24.4
2003	16	13735*	25.9	13.2	38.6
<b>Total</b>	<b>54</b>	<b>67493</b>	<b>17.8</b>	<b>13</b>	<b>22.5</b>

IS = Intussusception, \*Estimated using the preceding 7 years of data

Incidence of IS = [Number of definite IS cases/(Birth cohort in a year x 0.90 x 5)] x 100 000

95%CI: Asymptotic 95% confidence interval (in 100 000); LL: Lower Limit; UL: Upper Limit

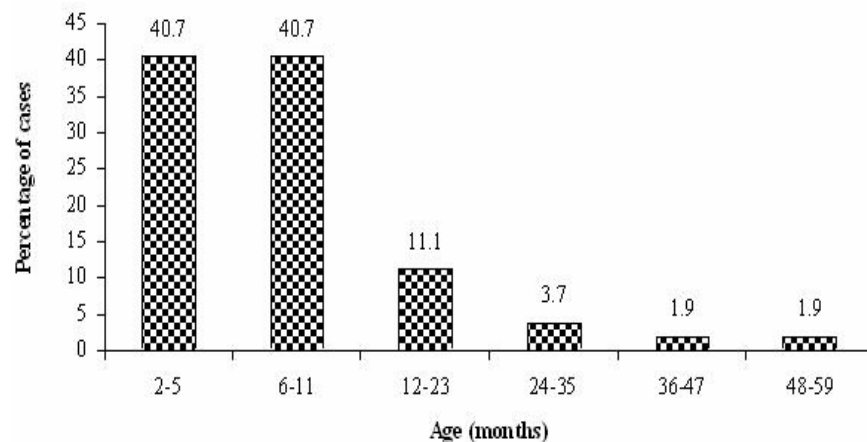
**Table 2: Incidence of Definite IS in Subjects Less Than One Year of Age**

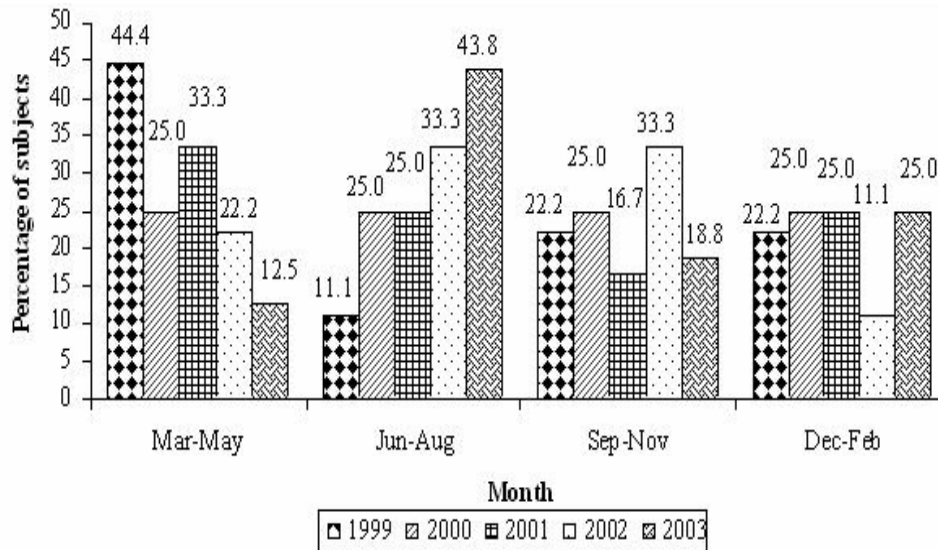
Year	Number of definite IS cases	Birth cohort	Incidence of IS (in 100 000)	Asymptotic 95%CI LL	UL
1999	6	13214	50.5	10.1	90.8
2000	6	13531	49.3	9.9	88.7
2001	12	13437	99.2	43.1	155.3
2002	7	13576	57.3	14.9	99.7
2003	13	13735*	105.2	48	162.3
<b>Total</b>	<b>44</b>	<b>67493</b>	<b>72.4</b>	<b>51</b>	<b>93.8</b>

IS = Intussusception, \*Estimated using the preceding 7 years of data

Incidence of IS = [Number of definite IS cases/(Birth cohort in a year x 0.90 x 1)] x 100 000

95%CI: Asymptotic 95% confidence interval (in 100 000); LL: Lower Limit; UL: Upper Limit

**Figure 1: Number of Cases of IS from 1999 To 2003**



**Figure 2: Distribution of IS According to Season from 1999 to 2003**

## DISCUSSION

Intussusception is a rare disease and its incidence varies depending on geographic location and study periods. A review by the World Health Organization showed the risk of IS is variable substantially between countries, as well as over time within individual countries<sup>14,15</sup>. In developed countries, the baseline incidence of IS is 0.5 to 4.3 cases per 1000 live births per year (i.e. 50 to 430 per 100 000) or 0.66 to 1.2 cases per 1000 children (i.e. 66 to 120 per 100 000) <1 year of age per year<sup>15-19</sup>. It is not clear whether these differences are associated with the accuracy and reliability of diagnosis or infants in specific regions are at increased risk of acute IS because of ethnic, genetic, cultural, dietary or environmental factors<sup>17</sup>.

Several countries are collecting data on incidence of IS in their own population to establish a baseline incidence rates prior to introduction of new RV vaccines.

In this study, the incidence of IS in children less than one year was comparable to New Zealand (65 per 100 000), Singapore (60 per 100 000), Australia (71-131 per 100 000) and United Kingdom (66-100 per 100 000)<sup>15-19</sup>. However, the incidence was lower than Japan (185 per 100 000), Israel (206 per 100 000) and Vietnam (302 per 100 000) and slightly higher than Chile (47-55 per 100 000) and Switzerland (56 per 100 000)<sup>12,18,20-22</sup>.

In this study, there was male predominance similar to almost all published studies<sup>22,23</sup>. Pain, vomiting and abdominal mass were the most commonly reported symptoms and signs in this study, typical consistent clinical features of IS<sup>24</sup>. Radiological reduction was the first line of management followed by surgery in 29.6% of subjects.

There was no seasonal variation of IS, consistent with published data<sup>18,19,25</sup>.

The limitation of this retrospective study is under-reporting either due to spontaneous resolution, lack of documentation or errors in coding.

## CONCLUSION

**This study provides for the first time in the region, an estimate for the baseline incidence rate of definite IS in the Kingdom of Bahrain. It may not, however, be possible to observe an association between IS and widespread use of new rotavirus vaccines given the small number of cases in a relatively small population. Standardization of reporting the assessment of cases does provide a valuable opportunity for future regional data comparisons and pooled data analyses.**

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