

An Update of Paediatric Intussusception Incidence in Singapore: 1997-2007, 11 Years of Intussusception Surveillance

Nancy Tan,¹MBBS, MMed (Paed), MRCPC (Paed), Yee-Leong Teoh,²MBBS, MMed (Public Health) FAMS, Kong-Boo Phua,¹MBBS, MMed (Paed), FAMS, Seng-Hock Quak,³MBBS, MMed (Paed), MD (NUS), Bee-Wah Lee,⁴MBBS, MMed (Paed), MD (NUS), Harvey James EL Teo,¹MBBS, MMed, Anette Jacobsen,¹FRCS (Edin), MMed (Surg), FAMS (Paed Surg), Irving Charles Boudville,²MBBS, MSc, MPH, Timothy Ng,²MD, Thomas Verstraeten,²MD, MSc, Hans Ludwig Bock,²MD

Abstract

Introduction: Understanding baseline epidemiology of intussusception (IS) in different geographical settings is important for the safety assessment of rotavirus vaccines. This paper presents IS surveillance data from Singapore between 1997 and 2007, including the period between November 2005 and December 2007 when rotavirus vaccines (primarily Rotarix™) were available to newborns in Singapore. **Materials and Methods:** Case ascertainment, collection, analyses and presentation of IS data was done as per recommendations of the Brighton Collaboration Working Group. For estimating the IS incidence rate in infants, live births for the years of the study were used as denominators, while for incidence in children age <2 years, the expected numbers of infant deaths occurring between 1 and 2 years of age was deducted from the combined live births for the 2 years, to obtain the denominator. **Results:** The incidence of IS among children aged <1 year throughout this 10-year period was higher than the incidence of IS in children between 1 and 2 years of age. In 2005, 2006 and 2007, the incidence of IS per 100,000 was 39.9, 26.4 and 35.6 in children aged <1 year and 26.2, 23.8 and 28.7 in children <2 years. **Conclusion:** This IS surveillance study provides reassuring preliminary evidence that there is no increase in the incidence of IS in Singapore after the introduction of rotavirus vaccines (including Rotarix™) in Singapore.

Ann Acad Med Singapore 2009;38:690-2

Key words: Epidemiology, Incidence, Rotarix, Rotavirus

Introduction

This is an update to the previously published paper by Boudville et al¹ on 8 years of intussusception (IS) surveillance in Singapore. IS is a rare but serious gastrointestinal disease in infants and young children.^{2,3} The focus on natural rotavirus infection as a potential cause of IS followed the discovery of an association between the first generation rotavirus vaccine Rotashield™ (Wyeth-Lederle) and IS in the US.^{4,5} The link between Rotashield™ and IS was noted through the Vaccine Adverse Event Reporting System (VAERS) within a year of the vaccine being licensed.^{4,5} Epidemiological investigations detected a statistically significant increased risk of IS, leading to the reversal of the recommendation by the ACIP (Advisory Committee on Immunization Practices) and the withdrawal of Rotashield™

by its manufacturer.^{4,5} Nevertheless, despite intense scrutiny in recent years, naturally occurring rotavirus infection – the most common cause of childhood diarrhoea – has remained unproven as a cause of IS.⁶⁻⁸

Two new rotavirus vaccines have been licensed in recent years. The first one, Rotarix™, from GlaxoSmithKline (GSK) was first licensed in Mexico in 2004 and is now registered in over 100 countries worldwide. The second vaccine, RotaTeq™, by Merck, Sharp and Dohme (MSD), was first licensed in the US in 2006. In Singapore, Rotarix was launched in November 2005, and was the only rotavirus vaccine available until RotaTeq™ was licensed in Singapore in July 2007. In the third quarter of 2007, sales of Rotarix™ comprised more than 90% of the sale of rotavirus vaccines in Singapore.⁹ Both vaccines were found to be safe in

¹ Department of Paediatrics, KK Women's and Children's Hospital, Singapore

² GlaxoSmithKline Biologicals, Rixensart, Belgium

³ Department of Paediatrics, National University of Singapore, Singapore

⁴ Mount Elizabeth Medical Centre, Singapore

Address for Correspondence: Dr Teoh Yee Leong, GlaxoSmithKline Biologicals, 150 Beach Road, #22-00 Gateway West, Singapore 189720.

Email: yee-leong.y.teoh@gsk.com

large clinical trials which showed no increased risk of IS associated with vaccination.^{10,11}

On February 13 2007, the US Food and Drug Administration (FDA) issued a public health notification that 28 cases of IS had been reported after administration of RotaTeq™ since its licensure in February 2006. No deaths were reported. The number of intussusception cases did not exceed the number expected based on background rates. Clinicians were encouraged to report any cases of IS following vaccination with RotaTeq™ to the VAERS. Additional post-marketing studies by MSD and the Centers for Disease Control and Prevention (CDC) will evaluate IS rates. CDC and FDA continue to monitor adverse events that are reported after this (and other) vaccine administration.

This paper will describe the update on the surveillance of IS in Singapore for the period of 1997 to 2007, including November 2005 to December 2007 where rotavirus vaccines (primarily Rotarix™) were available to newborns in Singapore.

Materials and Methods

Cases of IS among Singapore children aged below 5 years who were admitted to KK Women's and Children's Hospital (KKH) between 1997 and 2007 were identified by screening clinical notes for which an ICD-9-CM code of 560.0 had been recorded in the hospital computerised database. Associated radiology and surgery records were also checked to capture cases of IS that had undergone enema or surgical reduction, but had not been recorded in the database. All record reviews were performed by the same investigator. Case definition (eg surgical, radiological or autopsy criteria), collection, analyses and presentation of IS data was done as per recommendations of the Brighton Collaboration Working Group.^{1,2} To estimate the incidence rate of IS in infants in Singapore, live births for the years of the study, obtained from vital statistics published by the Government of Singapore, were used as denominators for the first year of life.¹² To estimate the incidence in children age <2 years, we combined the live births for the 2 years and deducted the expected numbers of infant deaths occurring between 1 and 2 years of age to obtain the denominators for the second year of life [Study EPI-IS-193] (Table 1).

Results

A total of 217 children aged <2 years were admitted to KKWCH with definite or probable IS during the 11-year study period, including 60 new cases for the period of January 2005 to December 2007. No deaths were reported. The incidence rates of IS per 100,000 of the population during the 11 years of this study are presented in Table 1.

The incidence of IS among children aged <1 year throughout this 10-year period was higher than the incidence

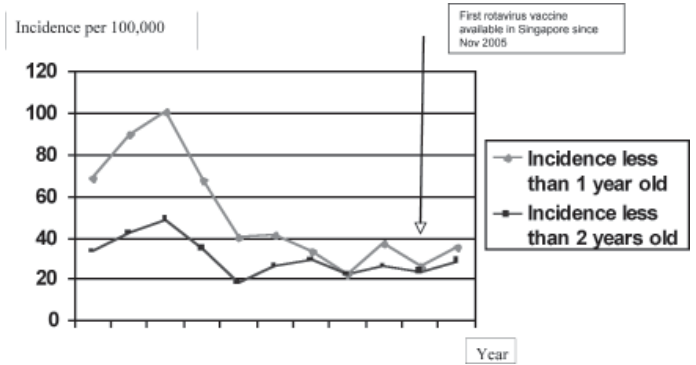


Fig. 1. Intussusception incidence in Singapore from 1997 to 2007.

of IS in children between 1 to 2 years of age. The incidence of IS in children aged <1 year in 2005, 2006 and 2007 was 39.9, 26.4 and 35.6 per 100,000, respectively (19 cases in 2005, 18 cases in 2006 and 22 cases in 2007). There was no increase in IS incidence in 2006 and 2007 when rotavirus vaccines were available in Singapore (Fig. 1).

Discussion

Baseline incidence rates of IS in Singapore from this ongoing surveillance study were described in an earlier publication by Boudville et al.¹ An additional 3 years of surveillance, including the years 2006 and 2007 when rotavirus vaccines were available in Singapore, does not show an increase in the incidence of IS among children aged <1 year. A total of 821 doses of Rotarix™ vaccine were administered between November and December 2005, 13 and 610 doses between January and December 2006, and about 10,000 doses for the period of January to June 2007, before RotaTeq™ was licensed in the third quarter of 2007.⁹ Since Rotarix™ is a 2-dose vaccine and is only indicated in infants, it can be estimated that around 15% to 18% of the 38,000 infants born in 2006 and up to 25% of those born in 2007 may have received Rotarix™. There is no indication of changes in the epidemiology of IS after Rotarix™ introduction. This result is in line with the previous observation of no association between rotavirus vaccines and IS in the phase III clinical trials.^{10,11}

Despite its limitation that there is no direct analysis between the IS cases and history of rotavirus vaccination, this IS surveillance study provides reassuring preliminary evidence that there is no increase in the incidence of IS in Singapore after the introduction of rotavirus vaccines in Singapore. The results complement the good safety profile of Rotarix as observed in clinical trials and helps support the case for implementation of rotavirus vaccination as rotavirus diarrhoea is a serious and common illness, not only in many other parts of the world¹³, but also in Singapore.¹⁴

Table 1. Intussusception (IS) Incidence from 1997 to 2007

Year	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
No. of births	45,356	41,636	41,327	44,765	39,281	38,555	35,474	35,135	37,492	38,317	39,375
Infant mortality rate (per 1000)	3.6	4.1	3.3	2.5	2.2	2.9	2.5	2.0	2.1	2.6	2.4
No. of IS cases aged <1	31	38	42	31	16	16	12	8	14	10	14
No. of IS cases aged 1 to <2	0	0	0	0	0	5	10	8	5	8	8
No. of IS cases aged <2	31	38	42	31	16	21	22	16	19	18	22
Population aged 1 to <2	46,539	45,193	41,465	41,191	44,653	39,195	38,443	35,385	35,065	37,413	38,825
Population aged <2	93,872	88,857	84,801	88,188	86,104	79,955	75,928	72,559	72,557	75,712	76,770
Incidence per 100,000 for age <1	68.9	90.1	100.8	68.3	40.3	41.5	33.8	22.8	37.3	26.1	35.6
Incidence per 100,000 for age <2	33.3	42.2	49.1	34.6	18.4	26.3	29.0	22.1	26.2	23.8	28.7

Rotarix is a trademark of the GlaxoSmithKline group of companies

Rotateq is a trademark of Merck, Sharp and Dohme

Rotashield is a trademark of Wyeth

REFERENCES

- Boudville IC, Phua KB, Quak SH, Lee BW, Han HH, Verstraeten T, et al. The epidemiology of Paediatric Intussusception in Singapore: 1997 to 2004. *Ann Acad Med Singapore* 2006;35:674-9.
- Bines J, Ivanoff B. Acute Intussusception in Infants and Children: Incidence, Clinical Presentation and Management: A Global Perspective. Geneva, Switzerland: World Health Organization, 2002. Report 02.19.
- Parashar UD, Holman RC, Cummings KC, Staggs NW, Curns AT, Zimmerman CM, et al. Trends in intussusception-associated hospitalizations and deaths among US infants. *Pediatrics* 2000;106:1413-21.
- Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al. Rotavirus Intussusception Investigation Team. *N Engl J Med* 2001;344:564-72.
- Kramarz P, France EK, Destefano F, Black SB, Shinefield H, Ward JI, et al. Population-based study of rotavirus vaccination and intussusception. *Pediatr Infect Dis J* 2001;20:410-6.
- Robinson CG, Hernanz-Schulman M, Zhu Y, Griffin MR, Gruber W, Edwards KM, et al. Evaluation of anatomic changes in young children with natural rotavirus infection: is intussusception biologically plausible? *J Infect Dis* 2004;189:1382-7.
- Rennels MB, Parashar UD, Homlam RC, Le CT, Chang HG, Glass RI. Lack of an apparent association between intussusception and wild or vaccine rotavirus infection. *Pediatr Infect Dis J* 1998;17:924-5.
- Chang HGH, Smith PF, Ackelsberg J, Morse DL, Glass RI. Intussusception, rotavirus diarrhea, and rotavirus vaccine use among children in New York State. *Pediatrics* 2001;108:54-60.
- IMS Health Malaysia/Singapore Pharmaceutical Audit Report data Singapore, 3rd Quarter 2007. Singapore: IMS, 2008.
- Palacios GMR, Schael IP, Velasquez FR, Abate H, Breuer T, Clemens SAC, et al. Safety and efficacy of an attenuated vaccine against severe Rotavirus gastroenteritis. *N Engl J Med* 2006;351:11-22.
- Vesikari T, Matson DO, Dennehy P. Safety and Efficacy of a Pentavalent Human-Bovine (WC3) reassortant Rotavirus Vaccine. *N Engl J Med* 2006;354:22-3.
- Singapore Immigration and Registration Department. Report on Registration of Births and Deaths 2004. Singapore: Registry of Births and Deaths, 2004.
- Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. *Emerg Infect Dis* 2003;9:565-2.
- Quak SH. Gastrointestinal infections in Singapore children. *Ann Acad Med Singapore* 1991;20:265-8.