Original Article

The Epidemiology of Paediatric Intussusception in Singapore: 1997 to 2004

Irving Charles Boudville,[1] *MBBS, MSc, MPH*, Kong-Boo Phua,[2] *MBBS, MMed (Paediatrics), FAMS*, Seng-Hock Quak,[3] *MBBS, MMed (Paediatrics), MD (NUS)*, Bee-Wah Lee,[4] *MBBS, MMed (Paediatrics), MD (NUS)*, Htay-Htay Han,[1] *MBBS*, Thomas Verstraeten,[1] *MD, MSc*, Hans Ludwig Bock,[1] *MD*

Abstract

Introduction: The world's first rotavirus vaccine, Rotashield® or RRV-TV, was registered in the US in 1998, but withdrawn within a year because of an observed association with intussusception (IS). Surveillance for IS has consequently become important in safety monitoring of new-generation rotavirus vaccines during development. Post-marketing surveillance is also important, and requires the availability of local baseline epidemiology data on IS. Materials and Methods: An eight-year study of IS in children under 2 years of age in Singapore was performed by retrospective review of admissions to KK Women's and Children's Hospital, the main paediatric hospital, from 1997 to 2001, followed by prospective surveillance of all hospitals from 2001 to 2004, using the case definition of the Brighton Collaboration Intussusception Working Group. Results: The average IS incidence was 60 per 100,000 in under-ones, and 32 per 100,000 in under-twos, with a downward trend between 1999 and 2004. Ninety-two per cent of subjects were aged below one year, with 51% aged 6 months to 11 months. The mean age at which IS occurred increased from 6.4 months to 12.5 months over the study period. The male-to-female ratio was 1.3:1. No trend in IS numbers was observed over different months of the year. Conclusion: IS in Singapore shows no seasonality, but has demonstrated a trend of decreasing incidence in recent years. While highest in the first year of life, the risk of IS is increasing in the second year of life. Males have a slightly higher risk.

Ann Acad Med Singapore 2006;35:674-9

Key words: Adverse effects, Rotavirus vaccines

Introduction

Intussusception (IS) is the most common cause of intestinal obstruction in infants and young children.[1,2] The peak age of presentation is 4 to 8 months.[1] In the United States (US), approximately two-thirds of cases occur below the age of 1 year.[2] In developed countries, a favourable clinical outcome is more likely because of timely diagnosis and early treatment by the less invasive procedure of enema reduction.[2,3] By contrast, in developing countries, delayed diagnosis with ensuing bowel necrosis, followed by attempted operative reduction, is associated with high case fatality rates,[3] e.g., 18% in Nigeria,[3] 20% in Indonesia[4] and up to 54% in Ethiopia.[1]

In only about 6% of cases (ranging from 1.5% to 12% in various studies) is IS associated with a pathologic lead point, predominantly Meckel's diverticulum.[5] The vast majority of IS episodes, termed "idiopathic", arise in the ileum because of lymphoid hyperplasia of Peyer's patches,[6] suggestive of a response to infection. An infective aetiology is further suggested by the presence, in about 50% of children with IS, of viral shedding in the stools, together with the demonstration of virus particles in pathologic specimens.[7] Most evidence implicates adenovirus.[8-11] Other commonly suggested viral causes include enterovirus and cytomegalovirus.[8] Naturally occurring rotavirus infection – the commonest cause of childhood diarrhoea – has, despite intense scrutiny in recent years, remained unproven as a cause of IS.[7,12,13] The focus on natural rotavirus infection in turn followed the discovery of an association between the first-generation rotavirus vaccine Rotashield and IS in the US.[14,15]

Following the introduction in 1998 in the US of Rotashield, a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV) and the world's first licensed vaccine against

[1] GlaxoSmithKline Biologicals, Singapore
[2] Department of Gastroenterology, KK Women's and Childen's Hospital, Singapore
[3] Department of Paediatrics, Yong Loo Lin Faculty of Medicine, National University of Singapore, Singapore
[4] Mount Elizabeth Medical Centre, Singapore
Address for Reprints: Dr Irving C Boudville, GlaxoSmithKline Biologicals, 150 Beach Road, #22-00 Gateway West, Singapore 189720.
Email: irving.boudville@gsk.com

rotavirus,[16] the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control (CDC) and the American Academy of Pediatrics had recommended RRV-TV for routine immunisation of all US children.[17,18] At the time, many had hoped that the introduction of rotavirus vaccines to the rest of the world would lead to a reduction of the massive death toll from rotavirus diarrhoea, most recently estimated at about 611,000 per year.[19] However, less than a year after Rotashield had been licensed, a high frequency of IS reports following RRV-TV was picked up by the Vaccine Adverse Event Reporting System.[14,15] Epidemiological investigations detected a statistically significant increased risk of IS,[14,15] leading to the reversal of the recommendation by the ACIP[20] and the withdrawal of Rotashield by its manufacturer.

From retrospective reviews of these various epidemiological studies, experts have assessed the attributable risk of IS from RRV-TV to be about 1 in 10,000,[21] which for perspective should be balanced against the substantial global mortality from rotavirus diarrhoea that could have been prevented by this vaccine.

Diarrhoea is second only to acute respiratory infections as a cause of death in early childhood, being responsible for 15% or 1.6 million of the estimated total of 10.5 million deaths of children below the age of 5 years each year.[22] Natural rotavirus infection, in particular, is the cause of 25% of this global diarrhoea death toll[23] and 45% of hospitalisations in Asian countries.[24]

Acknowledging the urgent need for a rotavirus vaccine, pharmaceutical companies, with the endorsement of rotavirus experts and global health agencies, persevered with the development of second-generation rotavirus vaccines. To facilitate the assessment of rotavirus vaccine-associated risk both during and after clinical trials, epidemiological studies have been conducted in many countries to establish the baseline IS incidence.

We report here an 8-year study of the incidence of IS in Singapore. A small island, with a population of over 4.3 million[25] and GNI per capita in 2003 of US$21,230,[26] Singapore has an infant mortality rate of 2.0 per 1000.[25] As in other developed countries, deaths from diarrhoea are rare, but hospitalisations are not uncommon, and outpatient consultations frequent. KK Women's and Children's Hospital (KKH) is the national provider of tertiary health services for the paediatric population. Prospective IS surveillance was commenced in 2001 concurrent with the initiation of vaccine trials. At the same time, a retrospective study was conducted to establish IS incidence for as far back as computerised admission records were available, up to the year 1997. We describe here the epidemiology of IS in Singapore from 1997 to 2004, as covered by these 2 studies.

Materials and Methods

Clinical notes in KKH are summarised upon discharge, with the principal diagnoses encoded using the ICD-9-CM classification.[27] Cases of IS among Singapore children aged below 5 years who were admitted to KKH from May 1997 to April 2001 were identified retrospectively by screening clinical notes for which an ICD-9-CM code of 560.0 had been recorded in the hospital computerised database upon discharge. Associated radiology and surgery records were also checked to capture cases of IS that had undergone enema or surgical reduction but where this diagnosis had not been recorded at discharge. All record reviews were performed by the same investigator. Starting from May 2001, only children aged below 2 years were enrolled. Children with a diagnosis of IS were notified to the principal investigator at the time of diagnosis by any of the hospital paediatric surgeons or radiologists. For each enrolled child, the medical records were reviewed and information collected on date of birth, date of admission, date of diagnosis of IS, date of discharge, gender and ethnic group. We restricted the analyses to children with IS aged below 2 years who fulfilled level 1 diagnostic certainty by the criteria of the Brighton Collaboration Intussusception Working Group (Table 1).[28]

Although KKH provides the majority of inpatient clinical care for Singapore children, 7 other hospitals in Singapore also provide paediatric medical and surgical services. Therefore, we also collected information on the number of IS cases seen in all these hospitals from 2001 onwards. In the National University Hospital, the other major public hospital, this was done by manual screening of inpatient registers, while in the 6 private hospitals, this was done by conducting either manual or computerised searches for admissions. As in the case of KKH, it was verified that cases met the Brighton definition. From the relative distribution of cases between KKH and all other hospitals

Table 1. Brighton Collaboration Intussusception Working Group Case Definition of Acute Intussusception in Infants and Young Children: Level 1 Diagnostic Certainty[28]

Surgical criteria	The demonstration of invagination of the intestine at surgery
Radiologic criteria	The demonstration of invagination of the intestine by either air or liquid contrast enema; *or* the demonstration of an intra-abdominal mass by abdominal ultrasound with specific characteristic features* that is proven to be *reduced* by hydrostatic enema on *postreduction ultrasound*
Autopsy criteria	The demonstration of invagination of the intestine

* Target sign or doughnut sign on transverse section *and* a pseudo-kidney or sandwich sign on longitudinal section.

Table 2. Incidence of Intussusception among Singapore Children from 1997 to 2004*

Year	1997	1998	1999	2000	2001	2002	2003	2004
No. of births	45,356	41,636	41,327	44,765	39,281	38,555	35,474	35,135
No. of IS cases aged <1	31	38	42	31	16	16	12	8
No. of IS cases aged <2	31	38	42	31	16	21	22	16
Population aged 1 to <2	46,539	45,193	41,465	41,191	44,653	39,195	38,443	35,385
Population aged <2	93,872	88,857	84,801	88,188	86,104	79,955	75,928	72,559
Incidence <1	68.9	90.1	100.8	68.3	40.3	41.5	33.8	22.8
Incidence <2	33.3	42.2	49.1	34.6	18.4	26.3	29.0	22.1

*Adjusted for incomplete year of observation in 1997 and for incomplete population coverage of 72% from 1997 to April 2001

Table 3. Gender and Age of Singapore Children with Intussusception from 1997 to 2004

Year	Male:Female	Mean age (mo)
1997	2.00 : 1	6.4
1998	1.08 : 1	6.6
1999	1.00 : 1	6.5
2000	1.20 : 1	6.5
2001	3.67 : 1	6.8
2002	1.10 : 1	9.0
2003	1.30 : 1	12.1
2004	1.67 : 1	12.5
Overall	1.33 : 1	8.2

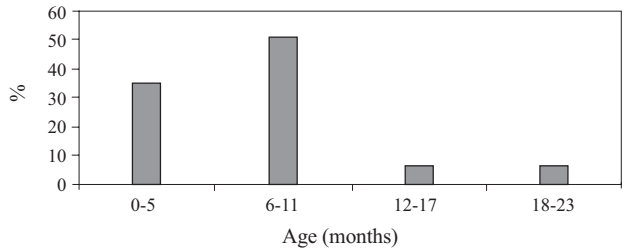

Fig. 1. Age distribution of Singapore children aged <2 with intussusception from 1997 to 2004.

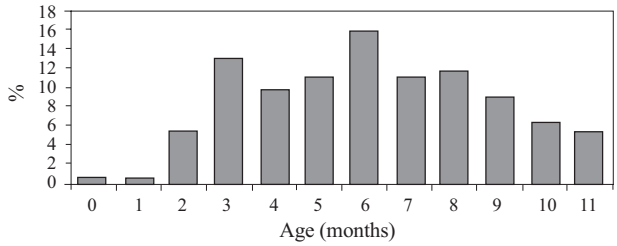

Fig. 2. Age distribution of Singapore children aged <1 with intussusception from 1997 to 2004.

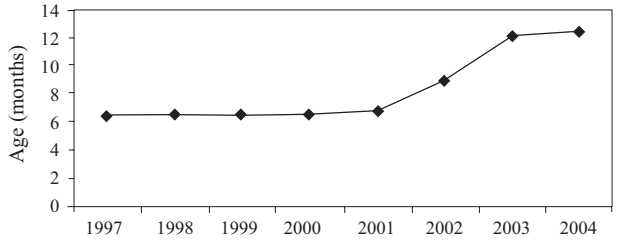

Fig. 3. Mean age of Singapore children aged <2 with intussusception from 1997 to 2004.

in the prospective study, we were able to estimate the total number of cases occurring in Singapore for the period of the retrospective study. To estimate the incidence rate of IS in infants in Singapore, livebirths for the years of the study, obtained from vital statistics published by the Government of Singapore (Table 2),[29] were used as denominators for the first year of life. To estimate the incidence in children under 2 years of age, we reduced the numbers of live births by the expected numbers of infant deaths occurring between 1 year and 2 years of age to obtain the denominators for the second year of life (Table 2).

Statistical analyses were performed using Stata 6.0 for Windows. Linear regression analysis was employed to test for trends in the age at which IS occurred and the incidence of IS over the study period. The ethnic distribution of the study population was compared to that of the birth cohort of the mid-period year of 2000 by computation of Pearson's chi-square.

Results

A total of 168 children aged below 2 years were admitted to KKH with IS during the 8-year study period. There were no deaths. Ninety-two per cent were aged below 1 year at the time of the IS episode, with 51% aged 6 months to 11 months, and the peak incidence at 6 months (Figs. 1 and 2). There was a significant increase in the age at IS among the under-two population between 1997 and 2004, with the mean age increasing from 6.4 months to 12.5 months (P = 0.005, Table 3, Fig. 3). While we did not observe any cases in the second year of life until 2002, cases aged between 1

Table 4. Ethnic Distribution of Singapore Children with Intussusception (IS) Compared with the Mid-Period Birth Cohort

Ethnic group	Children with IS	2000 births[29]
Chinese	69.1%	68.0%
Malay	16.4%	17.7%
Indian	5.5%	8.2%
Others	9.1%	6.1%
Total	100.0%	100.0%

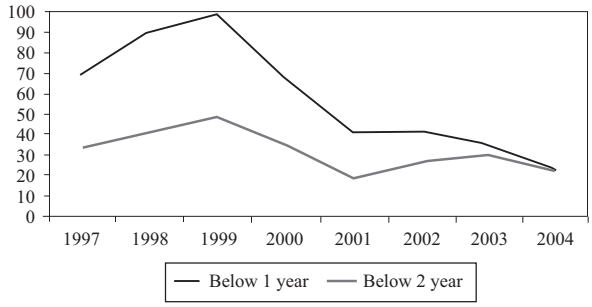

Fig. 5. Incidence of intussusception in Singapore from 1997 to 2004 (per 100,000).

year and 2 years made up nearly half of all cases observed in 2003.

The average male-to-female ratio for the study period was 1.3:1 (Table 3). Sixty-nine per cent of babies with IS were ethnic Chinese, 16% were Malays and 6% Indians, with the remaining 9% from other ethnic groups, a composition not significantly different from the ethnic distribution among babies born in the year 2000 ($P = 0.79$, Table 4).

IS occurred all year round with no clear seasonality and, in particular, no association with the cool and rainy monsoon season in December. The highest number of cases occurred in July (Fig. 4).

The proportion of all cases occurring in Singapore from May 2001 onwards that was seen at KKH was 72%.

The under-one incidence of IS in Singapore declined significantly from a peak of 101 per 100,000 in 1999 to 23 per 100,000 in 2004 ($P = 0.009$, Table 2, Fig. 5). Over the same period, the under-two incidence declined from 49 to 22 per 100,000, although this was not statistically significant ($P = 0.078$, Table 2, Fig. 5) The average incidence over the 8-year study period was 60 per 100,000 in under-ones, and 32 per 100,000 in under-twos.

Discussion

We estimate the incidence of IS in Singapore to be 60 per 100,000 in the first year of life. Data from a WHO-sponsored review of 269 published studies of IS from 70

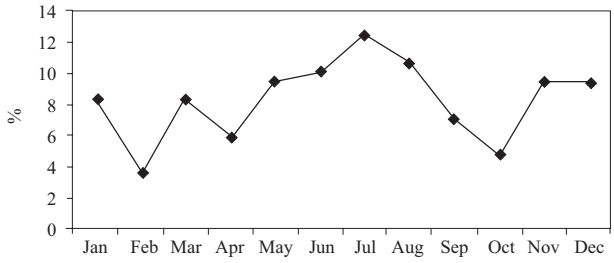

Fig. 4. Distribution by calendar month of IS cases in Singapore from 1997 to 2004.

countries by Bines and Ivanoff[1] show the risk of IS to vary substantially between countries, as well as over time within individual countries. In developed countries, first-year incidence ranges widely from as low as 66 per 100,000 in Sweden to as high as 1200 per 100,000 in the United Kingdom. Population-based incidence data from developing countries is generally lacking, particularly in Africa. Among the 12 Asian countries covered in the WHO review,[1] a population-based incidence of IS was reported only from Taipei, at 77 per 100,000 live-births in the 10-year period 1955 to 1964. In a more recent study, Nelson et al[30] reported the incidence of IS in children under 1 year of age from an analysis of public hospital discharge data in Hong Kong as 78 per 100,000 in 1997, and 100 per 100,000 in 1998. The authors commented that these figures probably represent an underestimate by about 13% of the true incidence in Hong Kong because cases at private hospitals were not captured. In Singapore, using a similar methodology, we found the average under-one incidence over the period 1997 to 2004 to be similar: 60 per 100,000. Taipei and Hong Kong are cities which share Singapore's developed status and predominantly Chinese population. In turn, IS rates from these 3 Asian cities do not seem to differ much from those in developed countries, as cited in the WHO review. In contrast, the incidence rates from Latin America from that review are remarkably lower. It is possible that some of these differences arise from varying completeness of IS case ascertainment. In any case, it is clear that there is a need for high-quality local surveillance of IS to establish baseline rates and trends for individual countries.

Geographical variations in rotavirus disease incidence also highlight that local data may usefully inform benefit-risk assessments of vaccines for adoption by individual countries. Rotavirus experts have already pointed out, in hindsight, the wisdom of balancing the substantial burden of childhood diarrhoeal deaths prevented against the relatively small risk of IS with RRV-TV.[31,32] It is reassuring though that large clinical trials of new generation rotavirus vaccines have shown no increased risk of IS,[33] offering

hope to developing countries that shoulder 82% of the global disease burden of rotavirus.[34]

We observed a significant decline in IS rates in Singapore. The incidence in children under 1 year decreased from 101 per 100,000 in 1999 to 23 per 100,000 in 2004, a fourfold difference. As cases occurring in the second year of life were only noted from 2002 onwards, the incidence in children under 2 years did not decrease as drastically over the study period. Countries such as Scotland,[35] Denmark,[36] the US[2] and Nigeria[1] seem to have experienced a secular trend of decline in IS cases over periods spanning decades. Although IS incidence in Taiwan likewise seemed to decline between the 1950s and 1990s,[37] in mainland China rising IS numbers were reported between the 1970s and 1980s.[38] In Singapore, a small island with one major paediatric centre, and employing robust sources of data set up for casemix-based government healthcare funding, we observed a clear downtrend in first-year IS incidence over a recent 8-year period. It is possible that reports of rising IS incidence – as in China,[38] Ghana,[1] the West Indies,[1] Venezuela[39] and other developing countries[1] – are an artefact of improving case ascertainment, perhaps accompanying the increasing salience of IS as a vaccine adverse effect. On the other hand, given the probable association with adenovirus[8-11] and possible associations with other viruses such as enterovirus and cytomegalovirus,[8] declining IS risk could be explained by improvements in hygiene with consequent lower exposure to these infections. An alternative explanation cited for Africa has been the Westernisation of a diet initially rich in root-fibre containing nitrosamine.[1]

We have also observed a significant shift of IS cases occurring in an older age group. Whereas we saw no cases beyond the first year of life until 2002, almost half of the cases occurred in the second year of life in 2003. Bines and Ivanoff,[1] in comparing the earlier and later studies in Taiwan, also highlight an apparent shift toward an older age of occurrence of IS. Such a shift has also been observed in the US[2] and Denmark.[36] As with the decline in incidence, such age-shifts in the occurrence of IS may be related to delayed or reduced exposure to childhood infections arising from improving standards of hygiene and sanitation in these countries. We saw no difference between the ethnic distribution of the IS children and the general population.

The absence of seasonality of IS has been used as an argument against its association with natural rotavirus infection, which is highly seasonal.[12] We did not observe a clear seasonality of IS in Singapore. Although rotavirus infection in tropical settings does not display the winter seasonality seen in temperate climates,[24] a slight peak during the year-end cool season has been observed in neighbouring countries such as Myanmar[40] and Malaysia.[41] Singapore has a similar cool season in December, however we observed – if anything – a mid-year peak, with the highest number of IS cases occurring in July. This preliminary indication of a lack of association between natural rotavirus infection and IS in Singapore is being further explored in an ongoing study of rotavirus epidemiology at KKH.

The main limitation of this study was that for the period 1997 to 2001 we only had data from 1 hospital. However, KKH is the main paediatric hospital in Singapore, treating by far the majority of IS cases. Moreover, prospectively collected data from May 2001 onwards reliably showed the proportion of IS cases treated at KKH to be 72%. This figure was then used to extrapolate the number of cases nationwide during the retrospective study period.

In conclusion, this report of our 8-year experience of IS in Singapore provides accurate baseline data, demonstrating an overall under-one incidence of 60 per 100,000, with a clear downward trend between 1999 and 2004, a shift in the vulnerable age group toward older children aged between 1 year and 2 years, and the absence of seasonality in the equatorial climate of Singapore.

Acknowledgements

Dr Anette Sundfor Jacobsen, Dr Ang Poon Liat, Dr Ang Ai Tin, Dr Chan Kit Yee, Dr Chang Sew Kee, Dr Cheah Siew Leng, Dr Chiang See Ping, Dr Chua Wan Hoi, Ms Feng Ying Ying, Dr Faith Fung, Dr Gong Wei Kin, Dr Ho Nai Kiong, Dr I Malathi, Dr John Hoe, Dr Kenny Ee Teong Tai, Dr Koh Poh Kian, Dr Krishnan Prabhakaran, Dr Lee Chien Yee, Dr Low Eu Hong, Dr Marion Margaret Aw, Dr Belinda Murugasu, Dr Ng Chi Fan, Dr Ng Moi Pen, Dr Ngaim Thye Eng, Dr Ong Woon Hong, Dr Sim Chiang Khi, Dr Tan Hui Kian, Dr Ravin Selvadurai, Dr S Sivasankaran, Dr Samuel Ng, Dr Teoh Yee-Leong, Harvey James, Dr Toh Kok Hong, Dr VK Pradeepkumar, Dr Vellayappan Karuppiah and Dr William Yip

REFERENCES

1. 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.
2. 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.
3. Meier DE, Coln CD, Rescorla FJ, OlaOlorun A, Tarpley JL. Intussusception in children: international perspective. World J Surg 1996;20:1035-40.
4. van Heek NT, Aronson DC, Halimun EM, Soewarno R, Molenaar JC, Vos A. Intussusception in a tropical country: comparison among patient populations in Jakarta, Jogyakarta, and Amsterdam. J Pediatr Gastroenterol Nutr 1999;29:402-5.
5. Blakelock RV, Beasley SW. The clinical implications of non-idiopathic intussusception. Pediatr Surg Int 1998;14:163-7.
6. Daneman A, Navarro O. Intussusception Part 1 : a review of diagnostic

approaches. Pediatr Radiol 2003;33:79-85.

7. Robinson CG, Hernanz-Schulman M, Zhu Y, Griffin MR, Gruber W, Edwards KM. Evaluation of anatomic changes in young children with natural rotavirus infection: is intussusception biologically plausible? J Infect Dis 2004;189:1382-7.
8. Hsu HY, Kao CL, Huang LM, Ni YH, Lai HS, Lin FY, et al. Viral etiology of intussusception in Taiwanese childhood. Pediatr Infect Dis J 1998;17:893-8.
9. Bode CO, Omilabu SA. Viral isolates of intussusception in Nigerian infants. S Afr J Surg 2002;40:57-8.
10. Porter HJ, Padfield CJ, Peres LC, Hirschowitz L, Berry PJ. Adenovirus and intranuclear inclusions in appendices in intussusception. J Clin Pathol 1993;46:154-8.
11. Bhisitkul DM, Todd KM, Listernick R. Adenovirus and childhood intussusception. Am J Dis Child 1992;146:1331-3.
12. 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.
13. Chang HG, 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.
14. Murphy TV, Gargiullo PM, Massoudi MS, Nelson DB, Jumaan AO, Okoro CA, et al; Rotavirus Intussusception Investigation Team. Intussusception among infants given an oral rotavirus vaccine. N Engl J Med 2001;344:564-72. Erratum in: N Engl J Med 2001;344:1564.
15. 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.
16. Offit PA, Clark FH. The rotavirus vaccine. Curr Opin Pediatr 1999;11:9-13.
17. Centers for Disease Control and Prevention. Rotavirus vaccine for the prevention of rotavirus gastroenteritis among children. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 1999;48:1-20.
18. American Academy of Pediatrics: Committee on Infectious Diseases. Prevention of rotavirus disease: guidelines for use of rotavirus vaccine. Pediatrics 1998;102:1483-91.
19. Parashar UD, Gibson, Bresee JS, Glass RI. Rotavirus and severe childhood diarrhea. Emerg Infect Dis 2006;12:304-6.
20. Centers for Disease Control and Prevention. Withdrawal of rotavirus vaccine recommendation. MMWR Morb Mortal Wkly Rep 1999;48:1007
21. Peter G, Myers MG. National Vaccine Advisory Committee; National Vaccine Program Office. Intussusception, rotavirus, and oral vaccines: summary of a workshop. Pediatrics 2002;110:e67.
22. World Health Organization. World Health Report 2004. Geneva Switzerland: World Health Organization, 2004.
23. Lanata CF, Mendoza W. Improving Diarrhoea Estimates. Geneva, Switzerland: World Health Organization, 2002.
24. Bresee J, Fang ZY, Wang B, Nelson EAS, Tam J, Soenarto Y, et al. First report from the Asian Rotavirus Surveillance Network. Emerg Infect Dis 2004;10:988-95.
25. Ministry of Health, Singapore [document on the Internet]. Key annual indicators. Singapore: Ministry of Health; 2006 [updated 2006 Jul 27; cited 2006 Aug 28]. Available at: http://www.singstat.gov.sg/keystats/annual/indicators.html. Accessed 28 August 2006.
26. World Bank. World development indicators 2005 [e-book]. Washington DC: World Bank; 2005 [cited 2006 Aug 28]. Available at: http://devdata.worldbank.org/wdi2005/Tables1.htm. Accessed 28 August 2006.
27. National Center for Health Statistics. [document on the Internet]. Hyattsville: National Center for Health Statistics; 2005. International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [updated 2005 Jan 27; cited 2006 Aug 28]. Available at: http://www.cdc.gov/nchs/about/otheract/icd9/abticd9.htm. Accessed 28 August 2006.
28. Bines JE, Kohl KS, Forster J, Zanardi LR, Davis RL, Hansen J, et al; Brighton Collaboration Intussusception Working Group. Acute intussusception in infants and children as an adverse event following immunization: case definition and guidelines of data collection, analysis, and presentation. Vaccine 2004;22:569-74.
29. Singapore Immigration and Registration Department. Report on Registration of Births and Deaths 2004. Singapore: Registry of Births and Deaths, 2004.
30. Nelson EA, Tam JS, Glass RI, Parashar UD, Fok TF. Incidence of rotavirus diarrhea and intussusception in Hong Kong using standardized hospital discharge data. Pediatr Infect Dis J 2002;21:701-3.
31. Murphy BR, Morens DM, Simonsen, L, Chanock RM, La Montagne JR, Kapikian AZ. Reappraisal of the association of intussusception with the licensed live rotavirus vaccine challenges initial conclusions. J Infect Dis 2003;187:1301-8.
32. Bines JE. Rotavirus vaccines and intussusception risk. Curr Opin Gastroenterol 2005;21:20-5.
33. Bresee JS, Parashar UD, Widdowson MA, Gentsch JR, Steele DA, Glass RI. Update on rotavirus vaccines. Pediatr Infect Dise 2005;24:947-52.
34. Parashar UD, Hummelman EG, Bresee JS, Miller MA, Glass RI. Global illness and deaths caused by rotavirus disease in children. Emerg Infect Dis 2003;9:565-72.
35. Pollet JE, Hems G. The decline in incidence of acute intussusception in childhood in north-east Scotland. J Epidemiol Community Health 1980;34:42-4.
36. Fischer TK, Bihrmann K, Perch M, Koch A, Wohlfahrt J, Kare M, et al. Intussusception in early childhood: a cohort study of 1.7 million children. Pediatrics 2004;114:782-5.
37. Clarke EJ, Jr, Phillips IA, Alexander ER. Adenovirus infection in intussusception in children in Taiwan. JAMA 1969;208:1671-4.
38. Guo JZ, Ma XY, Zhou QH. Results of air pressure enema reduction of intussusception: 6,396 cases in 13 years. J Pediatr Surg 1986;21:1201-3.
39. Perez-Schael I, Escalona M, Salinas B, Materan M, Perez ME, Gonzalez G. Intussusception-associated hospitalization among Venezuelan infants during 1998 through 2001: anticipating rotavirus vaccines. Pediatr Infect Dis J 2003;22:234-9.
40. Moe K, Hummelman EG, Oo WM, Lwin T, Htwe TT. Hospital-based surveillance for rotavirus diarrhea in children in Yangon, Myanmar. J Infect Dis 2005;192(Suppl 1):S111-S113.
41. Hsu VP, Abdul Rahman HB, Wong SL, Ibrahim LH, Yusoff AF, Chan LG et al. Estimates of the burden of rotavirus disease in Malaysia. J Infect Dis 2005;192(Suppl 1):S80-S86.