Intussusception and Monovalent Rotavirus Vaccination in Singapore: Self-Controlled Case Series and Risk-Benefit Study

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Objective To investigate the association between monovalent human rotavirus vaccine (RV1) and intussusception among Asian infants and the impact of older age of vaccination. To perform risk-benefit analysis of RV1 vaccination programs in Singapore.

Study design We performed a self-controlled case series by extracting intussusception cases in infants aged <12 months from hospital databases (2005-2012) and with vaccination histories from a national immunization registry. Relative incidences were calculated by comparing incidence during defined risk periods after vaccination with times outside these periods. In the risk benefit analysis, we estimated excess intussusception hospitalization in relation to the number of infants vaccinated for hypothetical vaccination coverage scenarios.

Results There were 86 infants hospitalized with intussusception; 20 cases had received at least 1 dose of RV1. Nearly all (19) had received their first dose at age >12 weeks old. The age-adjusted relative incidence of intussusception in the 1- to 7-day period post dose one was 8.36 (95% CI 2.42-28.96). Of all childhood hospitalizations because of rotavirus, 71% (570 cases) could be prevented with 90% vaccination coverage. There would be approximately 1 excess intussusception case per 65 000 infants vaccinated.

Conclusions Risk of intussusception increases about 8-fold during 1-7 days after receipt of first dose RV1 in infants of Chinese, Malay, and Indian ethnicity in Singapore, Asia. High vaccine coverage program in Singapore would be beneficial with only a low risk of excess intussusception. The relative risk of intussusception post-RV1 vaccination is not higher in Asia despite differences in background intussusception incidence compared with US and Australia, or older age of vaccination. *(J Pediatr 2015;167:163-68)*.

Globally, rotavirus infections are the primary cause of severe childhood gastroenteritis. Every year, it is estimated that rotavirus infection contributes to about 25 million clinic visits, 2 million hospital admissions, and up to 173 000 deaths in children <5 years old.[1] Progress to reduce the burden of rotavirus-associated disease including deaths was dealt a major set-back in 1999 when the first licensed vaccine, RotaShield (Wyeth Laboratories, Inc, Marietta, Pennsylvania) (rhesus rotavirus tetravalent vaccine [RRV-TV]) was withdrawn from use because of an association with intussusception. The risk of intussusception was found to be 37 times above the background rate of 3-7 days after the first dose of RRV-TV, which equates to 1 in about 10 000 vaccine recipients.[2] Consequently, 2 new oral rotavirus vaccines, a pentavalent human-bovine reassortant vaccine (RV5; RotaTeq, Merck, West Point, Pennsylvania) and a monovalent human rotavirus vaccine (RV1; Rotarix, GlaxoSmithKline Biologics, Research Triangle Park, North Carolina), underwent large-scale prelicensure clinical trials to ensure that there was no association with intussusception before licensure.[3,4]

RV1 and RV5 have demonstrated significant impact on both mortality and morbidity following their introduction in a number of countries. Studies in Mexico and Brazil have shown a reduction in childhood diarrhea mortality.[5,6] In Australia, the US, Mexico, Belgium, Brazil, and El Salvador, hospitalization rates because of diarrhea have declined.[7-11] However, in recent years, limited postlicensure studies have again reported a causal link between both RV1 and RV5 with intussusception, although the risk appears substantially lower compared with RRV-TV. To date, positive associations have been identified in 3 regional settings: US, Latin America, and Australia.[12-20] These studies have reported a 5- to 10-fold increase in intussusception in the first week after the first dose of vaccine, as well as a lower but elevated risk after the second dose in a smaller number of studies. Because the

RI	Relative incidence
RRV-TV	Rhesus rotavirus tetravalent vaccine
RV1	Monovalent human rotavirus vaccine
RV5	Pentavalent human-bovine reassortant vaccine
SCCS	Self-controlled case series
WHO	World Health Organization

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risk of intussusception could vary depending on geography, ethnicity, prevalence of enteropathogens, diets of infants, breastfeeding practices, and maternal rotavirus antibody levels, there is an urgent need for more postlicensure data to clarify whether increase in risk could vary, thereby affecting the risk/benefit ratio in particular settings.[21] Furthermore, questions remain whether the relative incidence (RI) of intussusception postrotavirus vaccination varies with age of vaccination.

In Singapore, nearly one-third of gastroenteritis hospitalizations among children <5 years old were found to be caused by rotavirus.[22] However, mortality was negligible with only 1 rotavirus positive child being reported to have died from encephalitis during a study from 2005 to 2008.[22] Live attenuated oral rotavirus vaccines were licensed in Singapore in November 2005, for RV1, followed by RV5 in July 2007. The recommended schedule for rotavirus vaccine was dose 1 at 2 months and dose 2 at 4 months of age, with RV5 requiring a third dose at 6 months of age. However, both vaccines were only available on a private basis as it was not part of the national immunization program. Rotavirus vaccine uptake based on vaccine sales data have been reported to range between 15% and 25% in 2006-2007.[23] Mortality because of intussusception is very low with a 2-year hospital-based prospective study of intussusception in children <2 years reporting only 1 death (0.6%) from septic shock.[24]

In this study, we aimed to investigate the association between RV1 and intussusception over the 7 years since the availability of the vaccine in Singapore and perform a risk:benefit analysis to explore the potential impact of a wider RV1 vaccination program.

Methods

All hospitalized cases of intussusception from October 1, 2005, to September 30, 2012, at KK Women's and Children's Hospital, the largest women's and children's hospital in Singapore, were extracted. Cases were identified from hospital discharge databases using *International Classification of Diseases, Ninth Revision and Tenth Revision* intussusception codes 5600 and K561, respectively, in any diagnostic field. Only cases with age of onset <1 years of age were included in the study. Case notes were reviewed by a consultant pediatrician and a research staff to ensure the highest level of diagnostic certainty (ie, level 1 of the Brighton Collaboration classification).[25] Case ascertainment was independent of vaccination history. The vaccination history of each case was obtained using the unique identity number system in Singapore from the National Immunization Registry. The National Immunization Registry records include nearly 100% of all childhood vaccinations in Singapore because it is a legal requirement for all practitioners to notify the registry after childhood vaccination. Ethics approval was obtained from the institutional review board of KK Women's and Children's hospital, Singapore.

Risk:Benefit Analysis

We carried out a risk:benefit analysis using published rotavirus and intussusception epidemiologic data to model the impact of a vaccination program with either 20% or 90% coverage scenarios compared with no vaccination program. Based on the methodology by Patel et al, we used a birth cohort in 2005 to estimate the number of hospitalizations attributable to rotavirus that potentially could be prevented and the number of excess intussusception hospitalizations that could be caused by the vaccination programs.[15] We also calculated the number of infants who would need to be vaccinated to prevent 1 rotavirus hospitalization or cause one excess intussusception hospitalization.

Because rotavirus and intussusception mortality is negligible in Singapore, we analyzed hospitalization as our outcome of interest. The number of rotavirus-attributable hospitalizations prevented by age 5 years was computed as a product of vaccination coverage, baseline rotavirus hospitalization estimates, and vaccine efficacy. We assumed that vaccination coverage was 0% at <3 months and either 20% or 90% subsequently. Vaccine effectiveness against rotavirus hospitalization was set at 0% in the 0- to 3-month age group, 50% in the 3- to <6-month age group, and 80% in those ≥6 months of age.[3,15,18,26-28] Baseline age-specific rotavirus hospitalization information was obtained from published active surveillance of children <5 years of age hospitalized for acute gastroenteritis conducted between September 2005, and April 2008[22] (**Table I**; available at www.jpeds.com). Although rotavirus vaccines were available from 2005, uptake was low, and, hence, it is unlikely that there would have been any major impact on baseline rates. However, if the baseline rate we used was an underestimate, it would bias our results against potential benefits of the vaccine. The population estimates entered for the calculations used a 2005 age-specific population derived from the average of available 2000 and 2010 national census data.[29]

The risk of the rotavirus vaccination programs was computed as a product of baseline intussusception incidence, vaccination coverage, and any statistically significant RI of intussusception after vaccination as per findings from the self-controlled case series (SCCS) analysis. Age-specific baseline intussusception cases were derived mainly from Boudville et al who reported at epidemiology of intussusception in Singapore from 1997 to 2004 before the availability of rotavirus vaccination[30] (**Table I**). Where local data were not available, incidence data from a systematic review of published studies were used.[31]

Statistical Analyses

We used the SCCS method, which uses case patients only to compare the chance of an outcome occurring in fixed periods of time after vaccination relative to unexposed times.[32] Two risk periods after each rotavirus vaccine dose were identified based on previously published papers: 1-7 days and 8-21 days after vaccination with day 0 being the day of vaccination. We estimated that a sample size of 19 would provide 80% power