

## Short Communication

# The Occurrence of Severe Rotavirus Gastroenteritis in Children under 3 Years of Age before and after the Introduction of Rotavirus Vaccine: a Prospective Observational Study in Three Pediatric Clinics in Shibata City, Niigata Prefecture, Japan

Tomohiro Oishi<sup>1\*</sup>, Tetsuo Taguchi<sup>2</sup>, Tokushi Nakano<sup>3</sup>, Shoji Sudo<sup>4</sup>,  
and Hiroaki Kuwajima<sup>5</sup>, for the Shibata RVGE Study Group

<sup>1</sup>*Department of Pediatrics, Niigata University Medical and Dental Hospital, Niigata 951-8510;*

<sup>2</sup>*Pediatric Department, Niigata Prefectural Shibata Hospital, Niigata 957-005;*

<sup>3</sup>*Nakano Children's Clinic, Niigata 957-0065;*

<sup>4</sup>*Sudo Pediatric Clinic, Niigata 957-0016; and*

<sup>5</sup>*Pediatric Department, Kuwajima Clinic, Niigata 957-0052, Japan*

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**SUMMARY:** The occurrence of severe rotavirus gastroenteritis (RVGE) in children under 3 years of age before and after the introduction of rotavirus vaccine was prospectively surveyed in three pediatric clinics in Shibata City, Niigata Prefecture, Japan, during the 2011 and 2012 RVGE epidemic seasons. In this observational study, a significantly lower occurrence of severe RVGE among severe gastroenteritis cases was observed in 2012. The incidence rate of severe RVGE among outpatients in 2012 was significantly lower than that in 2011. Despite the significant reduction in severe RVGE, the results must be interpreted with caution because the surveillance period is short and requires extension to conclude whether the reduction in the incidence of severe RVGE is a direct effect of rotavirus vaccination. Therefore, we will continue the survey to evaluate the impact of vaccination.

Rotavirus gastroenteritis (RVGE) is an acute viral gastroenteritis (GE) that affects infants and children in winter (1). RVGE is universally present both in developed and developing countries. Patients may develop severe dehydration, which can be life-threatening if body fluid imbalances are not appropriately corrected. Approximately 453,000 infants or children are estimated to die of RVGE each year worldwide (2).

Although fatal cases are rare in developed countries because of the advanced medical care, it has been reported that approximately 40% of hospitalizations of infants and children due to GE are associated with RVGE (3). In Japan, approximately 790,000 children under 6 years of age visit hospitals/clinics as outpatients because of RVGE (4) and approximately 78,000 children under 5 years of age are hospitalized annually (5).

At present, two oral vaccines for the prevention of RVGE are approved in more than 100 countries. In some of these countries in which these vaccines have been introduced, the number of hospitalizations due to RVGE has dramatically decreased by the direct and herd immunity effects of the vaccination (6,7). Since the review of recent evidence on the efficacy and safety of rotavirus (RV) vaccines, the World Health Organization (WHO) has recommended the use of RV vaccines in all national immunization programs (8). In Japan, two

oral vaccines for the prevention of RVGE, Rotarix (GlaxoSmithKline Biologicals, Rixensart, Belgium) and RotaTeq (Merck & Co., Inc., Whitehouse Station, NJ, USA), have been on the market since November 2011 and July 2012, respectively.

In an assessment of the impact of RV vaccination, continuous monitoring of the occurrence of RVGE in certain restricted regions and over specific time periods, including seasons before and after the introduction of RV vaccination, may reveal useful information. We therefore conducted this prospective observational study in three pediatric clinics in Shibata City, Niigata Prefecture, Japan, during the 2011 and 2012 RVGE epidemic seasons for assessing the occurrence of severe RVGE in children under 3 years of age.

Shibata City is a small city with a stable population of approximately 100,000 inhabitants, and approximately 770 babies are born each year. There are three primary care pediatric clinics and one hospital with a pediatric department (Niigata Prefectural Shibata Hospital) in the city. We assumed that almost all children living in Shibata City will visit one of the three pediatric clinics when they have an illness such as acute GE.

This study was conducted in compliance with the Ethical Guidelines for Epidemiological Research (June 17, 2002; partial revision, December 1, 2008; The Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan) in accordance with the Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects. Before conducting this study, the Ethical Review Committees of Niigata Prefectural Shibata Hospital reviewed both ethical and scientific

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\*Corresponding author: Mailing address: Department of Pediatrics, Niigata University Medical and Dental Hospital, 754 Ichibancho, Asahimachidori, Chuo-ku, Niigata 951-8510, Japan. Tel: +81-25-227-2222, Fax: +81-25-227-0778, E-mail: oo0612@med.niigata-u.ac.jp

aspects of the study protocol (e.g., study design, population, and time period) and approved the study conduct.

Children under 3 years of age who visited a study site between February and May in 2011 and 2012 because of acute GE and required intravenous rehydration were defined as patients with severe GE and included in the study. Acute GE was defined as the occurrence of GE symptoms for less than 14 days. After informed consent was obtained from the parents/guardians of the patients, a fecal RV antigen test using Immunocard ST Rotavirus (TFB, Tokyo, Japan) was performed to determine whether a patient with severe GE was RV positive. The total number of acute GE patients under 3 years of age was also collected.

The chi-square test was used to determine the statistical significance of differences between distributions of categorical variables, and the *t*-test was used to compare means of numerical variables. The incidence rates and 95% confidence intervals of severe RVGE, severe GE, and all acute GE were calculated from the numbers of patients who visited the three clinics during each observation period and the number of children under 3 years of age who lived in Shibata City.

The number of patients with acute GE, severe GE, and severe RVGE was 397, 62, and 52 in 2011, and 353, 29, and 12 in 2012, respectively. The occurrence of severe RVGE among severe GE cases in 2012 was 41.4% (12/29), which was significantly lower than that (83.9% [52/62]) in 2011 ( $P < 0.001$ , chi-square test). The occurrence of severe RVGE and severe GE among all acute GE cases was 3.4% (12/353) and 8.2% (29/353) in 2012, respectively, which was significantly lower than the occurrence (13.1% [52/397] and 15.6% [62/397], respectively) in 2011 ( $P < 0.001$  and  $P = 0.019$ , respectively, chi-square test). All 12 patients with severe RVGE in 2012 had not been vaccinated.

As shown in Table 1, the incidence rates of severe RVGE, severe GE, and acute GE in 2012 were significantly lower than those in 2011. The incidence rates

may be underestimated in both 2011 and 2012 because it was considered that a small percentage of patients visited sites other than the three study sites for medical care of acute GE in both the years.

The peak month of severe RVGE was April in both 2011 and 2012 (Fig. 1). The background and severity profiles of severe RVGE patients are shown in Table 2. The severity score of severe RVGE based on an 11-point scoring scale using 4 out of 7 items of the 20-point Vesikari scale (9) was  $6.04 \pm 0.26$  and  $6.44 \pm 0.53$  for 2011 and 2012, respectively ( $P = 0.544$ , *t*-test).

Thus, the occurrence of severe RVGE in the season after the introduction of RV vaccination was found to be reduced compared with that in the season before the introduction of RV vaccination. In Shibata City, RV vaccination was initiated from the end of 2011 with the first RV vaccine Rotarix, and at the end of the 2012 observation period, Rotarix was the only RV vaccine in use

Table 1. Incidence rates of severe RVGE, severe GE, and acute GE during 2011 and 2012 rotavirus seasons (February–May) among children under 3 years of age in Shibata City, Niigata Prefecture, Japan

	Incidence per 1,000 children-years (95% CI)	
	2011 <sup>1)</sup>	2012 <sup>2)</sup>
Severe RVGE	77.1 (70.9–83.6)	15.7 (14.3–17.1)
Severe GE	92.0 (84.5–99.7)	37.9 (34.6–41.2)
Acute GE	588.8 (541.1–638.2)	460.8 (421.2–501.8)

<sup>1)</sup>: No. of children under 3 years of age in population as of March 31, 2,300. Observation period, 107 days (February 14 to May 31).

<sup>2)</sup>: No. of children under 3 years of age in population as of March 31, 2,311. Observation period, 121 days (February 1 to May 31).

Incidence per 1,000 children-years was calculated according to the formula below: Incidence (per 1,000 children-years) = {No. of patients during each observation period / (No. of children under 3 years of age who lived in Shibata City as of March 31 × observation days/365)} × 1,000

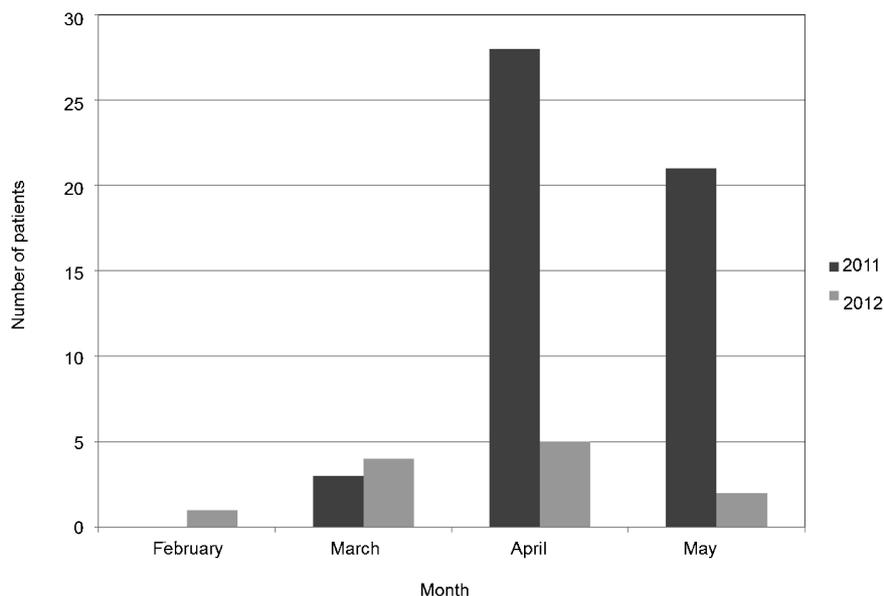


Fig. 1. Monthly number of patients with severe RVGE. The peak month was April in both 2011 and 2012. Total number of severe RVGE patients was 52 in 2011 and 12 in 2012.

Table 2. Profile of severe RVGE patients

	2011	2012
Sex		
Male	27	5
Female	25	7
Age in months		
0–5	2	1
6–11	7	1
12–23	24	5
24–35	19	5
Severity score <sup>1)</sup>		
≤5	20	3
6–8	30	5
9≤	2	1
NC <sup>2)</sup>	0	3

<sup>1)</sup>: An 11-point severity scale was used to evaluate the severity of gastroenteritis (modified from the 20-point Vesikari scale). Points were given for each clinical sign or symptom: no. of diarrhea stools in 24 h: 1–3, 1; 4–5, 2; ≥6, 3; no. of vomiting episodes in 24 h: 1, 1; 2–4, 2; ≥5, 3; body temperature (°C): 37.1–38.4, 1; 38.5–38.9, 2; ≥39.0, 3; and for treatment: rehydration, 1; hospitalization, 2. Duration (days) of diarrhea, duration (days) of vomiting, and severity of dehydration were not used for severity evaluation because of difficulties in gathering information.

<sup>2)</sup>: Not calculated because of absence of one or more data for severity scale.

in Japan. The vaccination coverage was estimated to be approximately 32% during the 2012 epidemic season (from November 2011 to May 2012) in the city on the basis of data from three pediatric clinics and Niigata Prefectural Shibata Hospital; in total, 125 infants were vaccinated with at least 1 dose of Rotarix among an estimated 385 infants, half of the total annual newborn babies, during the half-year period. Rapid decreases in the numbers and proportions of severe RVGE patients have been reported in hospital-based observational studies in Belgium (7) and the United States (6), with an estimated vaccination coverage of 80% and 50–60%, respectively.

This is the first attempt to estimate the RV vaccine impact in a prospective observational study in Japan. Despite a significant reduction in the incidence of RVGE, the results need to be interpreted with caution because they may be affected by the short surveillance period and seasonal variation. Therefore, we will continue the survey to evaluate the impact of RV vaccination on severe RVGE to determine whether the effects of this vaccination are similar to those observed in other countries.

**Conflict of interest** None to declare.

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