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Original Article

A Retrospective, Hospital-Based Study to Determine the Incidence of Rotavirus Hospitalizations among Children Less than 5 Years of Age over a 10-Year Period (2001–2011) in Akita Prefecture, Japan

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SUMMARY: Rotavirus is the most common cause of severe gastroenteritis in children worldwide. This retrospective, cross-sectional study was undertaken in a sentinel hospital that provides the only pediatric beds for the local population with an average of 4,400 children aged <5 years and determined the incidence of rotavirus hospitalizations. Medical charts that recorded acute gastroenteritis cases occurring in children aged <5 years living in the cites of Yuri-Honjo or Nikaho, Akita, Japan between 2001 and 2011 were retrieved and examined to enumerate rotavirus antigen-positive hospitalizations. Of the 1,596 acute gastroenteritis cases retrieved, antigen detection was performed in 834 cases, and 387 were positive; hence, the crude annual incidence rate of rotavirus hospitalizations was 8.8 per 1,000 person-years. The adjusted annual incidence rate of rotavirus hospitalizations was 13.7 per 1,000 person-years when untested samples collected during the peak season were extrapolated to the same rotavirus detection proportion as the tested samples (58.9%). We confirmed a high incidence of rotavirus hospitalizations in Akita Prefecture and revealed a considerable degree of annual fluctuation in the rotavirus hospitalization rates, which exceeded the degree of stochastic fluctuation. Thus, caution must be exercised when interpreting the impact of a rotavirus vaccine on the reduction of the number of rotavirus hospitalizations.

INTRODUCTION

Rotavirus is the major etiological agent of severe acute gastroenteritis in infants and young children worldwide, causing an estimated 527,000 deaths among children <5 years of age each year (1). Rotavirus-associated deaths occur mostly in developing countries (2), but rotavirus gastroenteritis imposes a large health and economic burden on the healthcare system and societies even in high-income countries (3–6). A recent retrospective, multicenter epidemiological study conducted in 8 hospitals across Japan revealed that 11.9%, 4.8%, and 0.6% of all hospitalizations occurring in children <6 years of age were due to acute gastroenteritis, rotavirus gastroenteritis, and hospital-acquired rotavirus gastroenteritis, respectively (7). However, Tajiri et al. (7) did not address the incidence rate of rotavirus hospitalizations in Japan, and only a limited number of retrospective and prospective studies have been conducted in central and northern Japan. These studies estimated the rotavirus hospitalization rate to be 2.8–14.7 per 1,000 person-years or a national estimate of 26,000–78,000 hospitalizations annually among children aged <5 years (8–12). Studies on Akita Prefecture conducted during the 1980s, 1990s, and early 2000s showed higher incidence rates of rotavirus hospitalizations (8,9) than those of more recent studies conducted in Mie and Kyoto Prefectures (10–12). Thus, it is unclear whether the difference in hospitalization rates is due to regional variations or a decreasing trend in rotavirus hospitalization rates over time. The incidence rate of rotavirus hospitalizations is a fundamental parameter that affects the assessment of rotavirus disease burden and decision-making regarding whether a rotavirus vaccination program should be incorporated into the national infant immunization schedule. Therefore, we conducted a retrospective, hospital-based study to determine the incidence rate of rotavirus hospitalizations among children <5 years of age in Akita Prefecture during a 10-year period between 2001 and 2011 to provide updated baseline data before the introduction of a rotavirus vaccine. We also determined the annual fluctuation level in rotavirus hospitalization rates.

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MATERIALS AND METHODS

This 10-year retrospective study was conducted at Yuri-Kumiai General Hospital, located in the center of a geographically well-defined administrative region of the southwestern part of Akita Prefecture comprising the cites of Honjo and Nikaho. The hospital has 724 beds, of which 35 are allocated for pediatric patients, and they

are the only pediatric inpatient beds available in the region. Thus, it was assumed that virtually all children living in Honjo and Nikaho with uncomplicated acute gastroenteritis would be admitted to this hospital.

The electronic hospital database for health insurance claims during the 10 year period between September 2001 and August 2011 was searched using the keywords ''acute gastroenteritis,'' ''rotavirus-enteritis,'' ''adenovirus-enteritis,'' ''viral gastroenteritis,'' and ''diarrheal disease'' as the primary or secondary discharge diagnosis for children of 0–59 months of age. We then retrieved corresponding hospital charts and examined whether the signs and symptoms of the patients were similar to those of acute gastroenteritis. In this study, patients were regarded as having acute gastroenteritis when their case record met one of the following criteria: (i) admitted for treatment of acute gastroenteritis, (ii) description matched with the presence of 3 or more times of defecating looser-than-usual stool or watery diarrhea within the preceding 24-h period, (iii) presence of intense vomiting and looser-than-usual stools, (iv) presence of intense vomiting without any identifiable cause other than gastroenteritis, and (v) laboratory testing was performed to detect of the rotavirus or adenovirus antigen (Immunochromatography; RapidTest®Rota Adeno; Sekisui Medical Co. Ltd., Tokyo, Japan). However, the following cases were excluded: children in whom the onset of acute gastroenteritis was after hospital admission, patients with acute gastroenteritis persisting >14 days before admission, children admitted with a primary diagnosis unrelated to acute gastroenteritis, and children living outside of the hospital catchment area (other administrative regions). If the patient's stool was examined and tested positive for the rotavirus antigen, the case was counted as rotavirus gastroenteritis. Variables, including age (date of birth), sex, dates of admission and discharge (length of hospital stay), and place of residence, were compiled.

To calculate the crude incidence rate of rotavirus hospitalizations, the total number of rotavirus-antigen positive cases was divided by the number of children 0–4 years of age in this administrative region, which was estimated from vital statistics data for Akita Prefecture, disregarding small infant mortality rates that fluctuated between 1.9 and 3.0 per 1,000 live births over the study period. The number of children <5 years of age living in this administrative region was on a continuous decline by 19% from 4,970 in 2001 to 4,020 in 2010 (average, 4,404). The Poisson model was used to calculate the 95% confidence interval (CI) of the incidence rates.

The adjusted incidence rate of rotavirus hospitalizations was calculated by estimating the number of rotavirus-positive patients that potentially existed among those whose specimens were not tested. First, 1 year was divided into two 6-month periods: peak-season months (January–June) and off-season months (July–December). Second, the number of rotavirus patients during the peak-season months was adjusted by the additional number of rotavirus-positive patients, which was estimated by multiplying the proportion of positive tests during the peak-season months by the number of untested patients. No adjustment was made for the number of rotavirus-positive patients during the off-season months; only positive-test patients were regarded as rotavirus-positive patients. Finally, the sum of the number of rotavirus patients during the peak-season months and that during the off-season months was divided by the number of children 0–4 years of age in this administrative region.

RESULTS

A total of 1,910 records were retrieved in which acute gastroenteritis was included in any discharge diagnoses. Of these, 109 were excluded because they were records for patients who lived outside the pre-defined catchment area for this study. After perusing the charts and applying the case definition for this study, we identified 1,596 cases of acute gastroenteritis that occurred in chil-

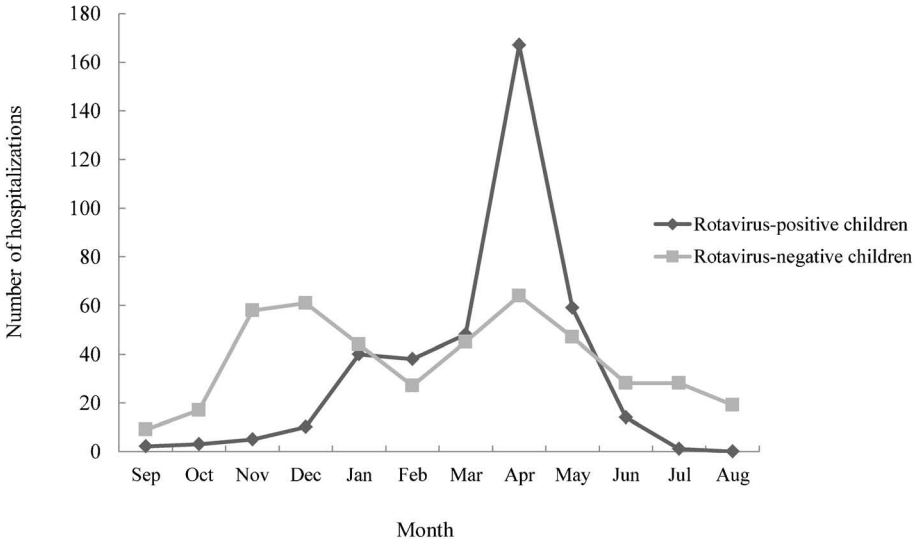

Fig. 1. Monthly occurrence of hospitalizations of rotavirus-positive or rotavirus-negative children <5 years of age at Yuri Kumiai General Hospital in Akita, Japan, from September 2001 through August 2011. The number of cases in each calendar month represents the sum of the number of the cases in each calendar month during the 10 year study period.

dren <5 years of age during the 10-year period between September 2001 and August 2011.

Of the 1,596 acute gastroenteritis cases, fecal specimens collected from 834 (52.3%) cases were subjected to an immunochromatographic assay for the detection of the rotavirus antigen: 621 (60.9%) during the peak-season months (from January to June), and 213 (37.0%) during the off-season months (from July to December). A strong trend for testing the rotavirus antigen during the peak-season months was observed ($P < 0.0001$). Of the 834 tested specimens, 387(46%) were positive for the rotavirus antigen, of which 366 were from the peak-season months, and 21 from the off-season months (Fig. 1). The rotavirus detection proportions corresponding to each of these 2 periods were 58.9% and 9.8%, respectively.

The annual incidence rates of rotavirus hospitalizations among children <5 years of age are shown in Table 1. The crude incidence of rotavirus hospitalizations, in which all untested specimens were regarded as rotavirus negative, was calculated at an average of 8.8 per 1,000 person-years (95%CI, 7.9–9.7). However, the incidence rate varied substantially each year, ranging from 5.2 (minimum) to 14.1 (maximum) per 1,000 person-years (Table 1).

The true incidence rate was never lower than the crude incidence rate because all untested specimens were unlikely to be rotavirus negative. Thus, the adjusted incidence rate of rotavirus hospitalizations was calculated to be 13.7 per 1,000 person-years (95%CI, 13.0–15.2). Similar to the crude incidence rates, the adjusted incidence rates varied substantially each year, ranging from 6.8 (minimum) to 20.7 (maximum) per 1,000 person-years (Table 1).

The crude and adjusted incidence rates of rotavirus hospitalizations were translated into cumulative risks of

Table 1. Annual number and incidence rates of rotavirus hospitalization among children <5 years of age at Yuri-Kumiai General Hospital

Period	Total number of patients	Number of patients during season (%)	Number of tested during season (%)	% rotavirus positive during season	Crude number of rotavirus-positive[1)]	Adjusted number of rotavirus-positive	Person-years	Crude incidence rate per 1,000 person-years (95% CI)[2)]	Adjusted incidence rate per 1,000 person-years (95% CI)[2)]
2001–2002	165	122 (73.9)	70 (42.4)	52.9	37	64.5	4,970	7.4 (5.24–10.26)	13 (10.09–16.44)
2002–2003	207	122 (58.9)	64 (30.9)	56.3	37	69.6	4,806	7.7 (5.42–10.61)	14.5 (11.35–18.17)
2003–2004	272	181 (66.5)	110 (40.4)	53.6	59	97.1	4,683	12.6 (9.59–16.25)	20.7 (16.99–25.27)
2004–2005	180	137 (76.1)	99 (54.4)	51	64	82.9	4,552	14.1 (10.83–17.95)	18.4 (14.52–22.36)
2005–2006	118	61 (51.7)	49 (41.5)	49	24	29.9	4,394	5.5 (3.50–8.13)	6.8 (4.61–9.48)
2006–2007	182	121 (66.5)	75 (41.2)	65.3	49	79.1	4,235	11.6 (8.56–15.30)	18.7 (14.98–23.25)
2007–2008	131	84 (64.1)	60 (45.8)	76.7	46	64.4	4,183	11 (8.05–14.67)	15.4 (11.99–19.54)
2008–2009	109	64 (58.7)	38 (34.9)	63.2	25	41.4	4,131	6.1 (3.92–8.93)	10.1 (7.33–13.46)
2009–2010	107	66 (61.7)	31 (29.0)	71	25	49.8	4,065	6.2 (3.98–9.08)	11.9 (9.13–15.94)
2010–2011	125	62 (49.6)	25 (20.0)	72	21	47.6	4,020	5.2 (3.23–7.99)	11.8 (8.8–15.55)
Total	1,596	1,020 (63.9)	621 (38.9)	58.9	387	622	44,039	8.8 (7.93–9.71)	13.7 (13.04–15.28)

[1)]: The number includes not only the number of rotavirus-positive cases during the season but also that of rotavirus-positive cases during the off season.
[2)]: CI, confidence interval.

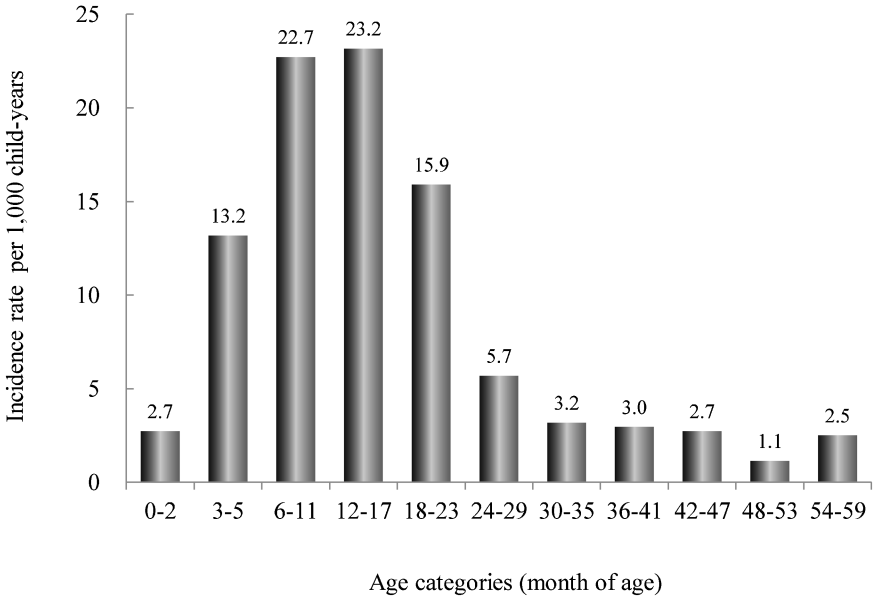

Fig. 2. Incidence rates of hospitalizations of rotavirus-positive children in different age groups at Yuri-Kumiai General Hospital in Akita, Japan, from September 2001 through August 2011.

rotavirus hospitalizations as 4.4 and 6.9%, respectively, by the age of 5 years. Thus, one child in 14 (adjusted estimate) or 23 (crude estimate) would have been hospitalized because of rotavirus gastroenteritis by the age of 5 years.

The age distribution of the crude incidence rate of rotavirus hospitalizations is shown in Fig. 2. The peak incidence rate of rotavirus hospitalizations occurred between 6 and 17 months of age, with an incidence rate of 23 hospitalizations per 1,000 person-years. Rotavirus hospitalizations among children between 6 and 23 months of age accounted for 70% (272/387) of all rotavirus hospitalizations among children <5 years of age, and those between 6 and 35 months of age accounted for 80% (311/387). The incidence rate of rotavirus hospitalizations between 0 and 2 months of age was the lowest and was equally as low as that between 30 and 59 months of age. Notably, the incidence rate abruptly increased between 3 and 6 months of age (Fig. 2).

DISCUSSION

Reports from early adopters of a rotavirus vaccine in the national immunization schedule showed that assessing the impact of a rotavirus vaccination program requires an indication of reduced rotavirus hospitalization incidence rates after introducing the vaccine beyond annual variations in the country or in predefined geographic regions (5,13–15).

Therefore, we performed a cross-sectional, retrospective hospital-based study encompassing 10 rotavirus seasons immediately prior to the use of any rotavirus vaccine in Japan to obtain an updated incidence rate of rotavirus hospitalizations among children <5 years of age living in Yuri-Honjo and Nikaho, a defined catchment area for the sentinel hospital in the southwest part of Akita Prefecture. The crude and adjusted average incidence rates of rotavirus hospitalizations obtained in this study 8.8 and 13.7 per 1,000 person-years respectively, and were in good agreement with those reported in earlier studies conducted using different study designs and during different time periods. A cross-sectional study that reviewed laboratory log books from 10 years (1987–1996) reported a rotavirus hospitalization incidence rate of 14.9 per 1,000 person-years among children <5 years of age (9). A 2-year prospective study based on the generic protocol provided by the World Health Organization reported an incidence rate of 12.7 per 1,000 person-years among children <5 years of age (16). Furthermore, a population-based survey estimated an incidence rate of 11 per 1,000 person-years among children 3 years of age (17).

We also confirmed that the updated incidence of rotavirus hospitalizations was higher in this region of Japan than in Mie Prefecture, where the incidence rate is 3.8–4.9 or 2.8–4.7 per 1,000 person-years among children <5 years of age (10,11) as well as in Kyoto Prefecture, where the incidence rate is 4.1–5.3 per 1,000 person-years among children <5 years of age (12). Notably, the crude incidence rate, which is highly likely to be an underestimation, exceeded the upper limit of 95% CI of any of the incidence estimates reported previously from central parts of Japan (10–12). Because a higher incidence of rotavirus hospitalizations in Akita Prefecture is consistent regardless of differences in the study design and the times when the studies were conducted, there appears to be a true regional difference in the incidence of rotavirus hospitalizations. Ito et al. (12) attributed a regional difference in the incidence of rotavirus hospitalizations to a few possible factors such as age structure, population density, and the contact pattern structure among small children (more children may visit day-care centers in areas where the percentage of both parents as working professionals is higher). Furthermore, the difference may also be caused by differences in healthcare utilization practices, in which children with moderately severe gastroenteritis are treated in hospital wards where the incidence of hospitalizations is high and in clinics and hospital outpatient departments where the incidence of hospitalizations is low. Thus, the incidence of outpatient visits as well as the ratio of hospitalizations over outpatient visits due to rotavirus gastroenteritis is useful to determine how different one region is from another. Information currently available in the literature is limited to the gross national level; however, Yokoo et al. (18) estimated that the incidence of outpatient visits due to rotavirus gastroenteritis among children <6 years of age is 110 per 1,000 person-years. In contrast, a recent Internet survey revealed that 7.3% or 1 in 14 children aged <3 years, who sought medical intervention due to rotavirus gastroenteritis, was admitted to the hospital (19). The ratios of hospitalizations over outpatient visits were 1:13 and 1:8, respectively, when the crude incidence rate and the adjusted incidence rate were applied, which is almost the range (1:5–10) in industrialized countries (20).

Considerable annual variation was observed in the incidence of rotavirus hospitalizations among children <5 years of age; the lowest incidence was 5.2 (crude estimate) and 6.8 (adjusted estimate) per 1,000 person-years, and the highest was 14.1 (crude) and 20.7 (adjusted) per 1,000 person-years (Table 1). Thus, an approximate 3-fold difference in the incidence rate was observed between the highest and lowest years. This observation is very similar to that reported by Nakagomi et al. (9) in which a 2.5-fold difference in the rotavirus hospitalization incidence rate was observed between the highest year (20.2 per 1,000 person-years) and the lowest (8.2 per 1,000 person-years) over a 10-year laboratory-based survey. The exact cause for this considerable variation is unknown, but the degree of observed annual variations exceeded the level of variation predicted by a computer simulation model developed to produce stochastic variations based on parameters obtained from an epidemiological study conducted in this same catchment area. That model predicted up to a 1.79-fold difference between the highest and lowest year (21). Thus, it is likely that other factors such as changes in dominant circulating strains and the immunity formed in the local population may play a role in the seasonal variation of the number of rotavirus hospitalizations. The number of rotavirus hospitalizations increased 3-fold when the dominant strain changed from common G1P [8] in 2006 to uncommon G12P [8] in 2007 in Rochester county, USA (22). Therefore, caution must be exercised when evaluating the impact of a rotavirus vaccine on the reduction of the number of rotavirus hospitalizations by considering annual varia-

tions.

The strength of this study is the availability of both prospective and retrospective studies conducted in the same catchment area but during different study periods (8,9,17). The level of annual variations was most appropriately assessed by a computer simulation model precisely developed on the basis of parameters obtained by epidemiological studies conducted in the same catchment area (21). However, this study had some limitations. First, the crude incidence rate of rotavirus hospitalizations was clearly underestimated because it is unlikely that all untested patients were negative for rotavirus. In contrast, the adjusted incidence rate of rotavirus hospitalizations calculated by extrapolating the proportion of positive test results during the peak-season months to untested samples during the peak-season months was likely overestimated because attending pediatricians did not suspect rotavirus as the etiological agent and did not test the samples. Thus, it is likely that the true incidence rate dropped in the range between the crude and adjusted incidence rates of rotavirus hospitalizations. However, a recent study conducted in the USA revealed that an indirect estimation of rotavirus hospitalization rate, including the method employed in this study, missed a substantial number of rotavirus hospitalizations that would be detected by active surveillance thus resulting in an underestimation (6). Second, we may have missed some patients who were admitted to other hospitals, despite that their residence being within the catchment area of this hospital, leading to a possible underestimation.

In conclusion, we replicated and confirmed the high incidence rate of rotavirus hospitalizations in Akita Prefecture, suggesting the existence of geographic differences within Japan, although the exact reason for such differences is unknown. A considerable degree of annual fluctuation was observed in the incidence rate of rotavirus hospitalizations which exceeded the level predicted by a simple stochastic variation model. Thus, caution must be exercised when interpreting the impact of a rotavirus vaccine on the reduction of the number of rotavirus hospitalizations.

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Conflict of interest None to declare.

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