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Original Article

Estimation of Annual Incidence, Age-Specific Incidence Rate, and Cumulative Risk of Rotavirus Gastroenteritis among Children in Japan

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SUMMARY: Rotavirus gastroenteritis is a common childhood infection, but the exact morbidity of the disease is not well described in Japan. We aimed at estimating morbidity measures to determine the magnitude of rotavirus gastroenteritis. An estimate for acute infectious gastroenteritis of all causes, to which rotavirus gastroenteritis belongs, has been available since the enactment in 1999 of the Law concerning the Prevention of Infectious Diseases and Medical Care of Patients with Infectious Diseases. Using this estimate and another estimate for the detection proportion of rotavirus among outpatients with acute infectious gastroenteritis, we calculated the annual incidence, the age-specific annual incidence rate, and the cumulative risk by the age of 6 years for rotavirus gastroenteritis. The latter estimate was obtained by a meta-analysis of four independent studies previously performed in Japan. According to our estimates, approximately 800,000 children in Japan under the age of 6 years visit pediatric practices or the outpatient department of hospitals because of rotavirus gastroenteritis at a rate of 11 cases/100 persons/year, and one in two children will visit pediatricians before they go to primary school. Such pediatrician visits most frequently occur at the age of 1 year (27 cases/100 persons/year). Thus, the magnitude of the burden of rotavirus disease among Japanese children is substantial.

INTRODUCTION

Group A rotavirus, hereafter referred to as rotavirus, is the most common cause of severe gastroenteritis in infants and young children across the world (1). Almost all children are infected by the age of 3 - 5 years, but rotavirus infection continues to occur throughout life (2). However, the consequences of rotavirus infection in developing and industrialized countries are in sharp contrast. Whereas the estimated annual number death rates attributable to rotavirus infection is 670,000 to 800,000 in developing countries, the corresponding figures in developed countries are considered to be minimal (3). Nevertheless, the overall incidence of children seeking medical care at pediatric practices or the outpatient department of hospitals is thought to be extremely high. In the USA, it has been estimated by the Centers for Disease Control and Prevention (CDC) that one in 8 children will annually visit a doctor's office due to rotavirus gastroenteritis during the first few years of life and that the direct medical costs alone will total approximately 500 million US dollars (4).

However, in Japan such estimates of the rotavirus disease burden are lacking, and rotavirus infection has only captured marginal public attention. Major reforms in Japan's public health system against infectious diseases were implemented at the turn of the century; among these reforms was the enactment in 1999 of the Law concerning the Prevention of Infectious Diseases and Medical Care of Patients with Infectious Diseases (or the "Infectious Disease Control Law"). This new law, which was further reformed in November 2003, classifies infectious diseases into five categories according to the level of the potential seriousness of the infectious diseases in question. Acute infectious gastroenteritis, a larger disease category to which rotavirus gastroenteritis belongs, is one of 42 infectious diseases of Category V. As regards acute infectious gastroenteritis, doctors in approximately 3,000 sentinel clinics (pediatric practices) and outpatient departments of hospitals distributed throughout the nation are requested to provide weekly reports of the number and certain attributes of the patients with this disease to a local health center, and then this information is collectively transferred to the Infectious Disease Surveillance Center (IDSC) at the National Institute of Infectious Diseases (NIISD), through each local IDSC. On the basis that these sentinel points represent approximately 10% of the pediatric practices and hospitals in Japan, Nagai et al. recently reported for the first time that the annual incidence of acute infectious gastroenteritis in Japan was estimated to be 8.65 million cases for the year 2000 (5). The IDSC also publishes the Infectious Agents Surveillance Report in which, among other pathogens, the number of rotavirus cases detected by local public health institutes is listed; however, the size of and the age distribution of cases in the denominator from which rotavirus was detected are neither available nor directly linked to the gastroenteritis cases reported by the aforementioned sentinel surveillance points. It is therefore impossible to estimate the number of rotavirus gastroenteritis cases (i.e., the annual incidence) by simply multiplying the estimated number of cases of infectious gastroenteritis (8.65 million) by the proportion (%) of rotavirus cases detected among patients with infectious gastroenteritis, a number which is not available for the reasons stated above.

The aim of this study was therefore to obtain an estimate of the annual incidence, the age-specific annual incidence rate, and the cumulative risk by the age of 6 years of rotavirus gastroenteritis by multiplying the estimate for the annual

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incidence of acute infectious gastroenteritis (obtained from the IDSC's published record) by our estimate of the proportion of rotavirus detected among outpatients with acute infectious gastroenteritis. The latter estimate was obtained by a meta-analysis of four papers selected from the literature that contained a sufficient amount of information to perform such an analysis.

MATERIALS AND METHODS

Meta-analysis estimation of the rotavirus proportion detected among outpatients with acute infectious gastroenteritis in Japan: A meta-analysis was performed to estimate the percentage of rotavirus detected in the stool specimens of outpatients with acute infectious gastroenteritis (i.e., the rotavirus detection proportion) in Japan. The literature was extensively searched according to the following criteria. (i) The study was conducted in Japan, (ii) Study subjects were or included pediatric outpatients with acute diarrhea or gastroenteritis, (iii) The study was carried out throughout the year and at least for 1 year, and (iv) The study reported the number of subjects and the rotavirus detection proportion for each age-category. The fourth criterion was the most difficult to fulfill because different age categories were employed, depending on the paper. In this study, pediatric patients were grouped into four age-categories, i.e., <1 year old, 1 year old, 2-3 years old, and 4-5 years old. Four papers were finally selected that met these criteria (6-11). However, one (7) was used only for the age-category <1 year, since the method of categorization of the age category ≥1 year was different from that of the other studies. A pooled estimate of the rotavirus detection proportion for each age category was calculated as a weighted average; this was done by weighting each study estimate by the inverse of its variance. The 95% confidence interval of the rotavirus detection proportion was calculated as the pooled estimate ±1.96 x (square root of pooled variance), where the pooled variance was equal to $1/\Sigma$ (weight). The definition of rotavirus gastroenteritis did not exclude cases coinfected with other pathogens.

Estimation of the annual incidence of outpatients with rotavirus gastroenteritis for each age category in Japan: The annual incidence of outpatients with acute infectious gastroenteritis of all causes in Japan for the year 2000 has just been published in a report by Nagai et al. (5). Following the same procedure, the figure for the year 2001 was calculated using the information from the "Annual Data on Infectious Disease Surveillance in Japan". Thus, the annual incidence of outpatients with acute infectious gastroenteritis for each age category was estimated by the number of patients reported from all sentinels multiplied by the ratio defined as the total number of the pediatric practices and hospitals in Japan divided by the number of sentinels. As regards the number of patients from all sentinel points, we used the average of the most recently reported number of patients (those for the years 2000 and 2001) (12). The value of 31,000 was used as the total number of pediatric practices and hospitals for these 2 years, according to the report by the Nagai group (5). Accordingly, the total number of outpatients with rotavirus gastroenteritis for each age category was calculated by multiplying the annual incidence of outpatients with acute infectious gastroenteritis of all causes for each age category by the pooled estimate for the rotavirus detection proportion among outpatients with acute infectious gastroenteritis. When calculating the annual incidence, the age category of those under 1 year old was divided into 0-5 months and 6-11 months, because the number of cases varied between these two age categories. For both of these two categories, the detection proportion of rotavirus among those under 1 year old was used.

Estimation of the annual incidence rate of rotavirus gastroenteritis in each age category and the cumulative risk of rotavirus disease by the age of 6 years: The annual incidence rate of rotavirus gastroenteritis was estimated by dividing the number at all sentinels of rotavirus gastroenteritis cases in each age category by the virtual catchment population of the corresponding age category. The virtual catchment population for each age category was defined as the population for each age category derived from the census of 2000 multiplied by the ratio of the number of sentinels over the total number of pediatric practices and hospitals (i.e., 31,000). However, one-half of the infant population was assigned to the 0-5 month-old group, and one-half was assigned to the 6-11 month-old group. Calculation of 95% confidence intervals was performed using the STATA software package. The cumulative incidence or risk of rotavirus gastroenteritis from 0 to 5 years of age was calculated using the following equation: cumulative risk (%) $= 1 - \{\prod(1 - IR_i \times \Delta t_i)\}$, where IR denotes the incidence rate and Δt stands for the length of the subinterval (13).

RESULTS

Four studies selected for the meta-analysis to estimate the detection proportion of rotavirus infections were performed in four geographically diverse locations in Japan and during temporarily distinct periods spanning from 1980 to 1997; the first study was performed in the early 1980s, and the second and the third ones were in the early 1990s; the last one was in the mid 1990s (Table 1). Except for one study in the early 1980s, research spanned over multiple years, and all studies dealt with a relatively large number of gastroenteritis specimens (Table 1). The detection proportions of rotavirus in three studies, excluding the Tama Study, varied from 12 to 24% for the age category of 0-5 years (Table 1), and the pooled estimate for the overall detection proportion of rotavirus was 18% (Table 2). However, the pooled estimates of the age-specific detection proportion of rotavirus among outpatients with acute gastroenteritis were not uniform: the highest estimates were observed at 1 year of age (26%), followed by less than 1 year old (16%), 2-3 years old (14%), and 4-5 years old (7%). By coupling these age category-specific detection proportions of rotavirus with the reported number of patients with acute infectious gastroenteritis of all causes in each of the age categories, we obtained an estimate of the number of rotavirus gastroenteritis cases for each age category. Because the number of acute infectious gastroenteritis cases varied between the 0-5 and the 6-11 months groups, the annual incidence of rotavirus gastroenteritis was separately estimated for each of these two age categories. In fact, the number of rotavirus gastroenteritis cases in the age group of 6-11 months old was approximately five times that of the age group of 0-5 months old (Table 3). It was estimated that approximately 320,000 1-year-old children were seen by pediatricians due to rotavirus gastroenteritis. In this age group, the number of rotavirus gastroenteritis cases peaked, and then the number declined more sharply than did that of acute infectious gastroenteritis cases. Among children younger than 6 years old, it was estimated that 5,454,635

Table 1. Summary of studies used for meta-analysis

Geographic locations (Prefecture)	Period of study	Length of study	Method of detection[2)]	No. of cases	No. of rotavirus positives	Detection proportion (%)	References
Ichinoseki (Iwate)	January 1990-December 1992	3 y	ELISA	607[3)]	146[3)]	24.1	11
Matsuyama (Ehime)	September 1980-August 1981	1 y	EM	382[3)]	48[3)]	12.6	6
Three locations (Shimane)[1)]	July 1994-June 1997	3 y	ELISA	695[3)]	122[3)]	17.6	8, 9, 10
Tama area (Tokyo)	May 1991-December 1996	5.5 y	ELISA	260[4)]	30[4)]	11.5	7

[1)]: The results of three consecutive papers were combined.
[2)]: EM: electron microscopy, ELISA: enzyme-linked immunosorbent assay.
[3)]: Only cases under 6 years of age were extracted from the original papers.
[4)]: Only cases under 1 year of age were extracted from the original paper.

Table 2. Pooled detection proportion of rotavirus in stool specimens from patients with acute gastroenteritis for each age category

Age category	No. of cases	Pooled proportion	95% CI[1)]	References
<1 y	699	0.16	0.13 - 0.19	6, 7, 8, 9, 10, 11
1 y	466	0.26	0.22 - 0.30	6, 8, 9, 10, 11
2 - 3 y	404	0.14	0.10 - 0.17	6, 8, 9, 10, 11
4 - 5 y	375	0.07	0.04 - 0.09	6, 8, 9, 10, 11
0 - 5 y	1,684	0.18	0.16 - 0.20	6, 8, 9, 10, 11

[1)] CI: confidence interval.

Table 3. Reported or estimated number for each age category of patients with acute infectious gastroenteritis of all causes and with rotavirus gastroenteritis

Age category	Sentinels		Whole nation	
	Infectious gastroenteritis of all causes[1)]	Rotavirus gastroenteritis	Infectious gastroenteritis of all causes	Rotavirus gastroenteritis
<6 m	11,077	1,776	114,520	18,361
6 - <12 m	53,467	8,571	552,769	88,611
1 y	116,572	30,530	1,205,180	315,634
2 - 3 y	184,220	25,293	1,904,559	261,492
4 - 5 y	162,268	10,790	1,677,608	111,552
0 - 5 y	527,604	76,960	5,454,635	795,651

[1)]: Mean of numbers reported in 2000 and 2001, according to "Annual Data on Infectious Disease Surveillance in Japan".

Table 4. Annual incidence rate of gastroenteritis of all causes and of rotavirus gastroenteritis for each age category (case/100 persons)

Age category	Infectious gastroenteritis of all causes	95% CI[1)]	Rotavirus gastroenteritis	95% CI[1)]	Virtual catchment population[2)]
<6 m	19.55	19.19 - 19.92	3.13	2.99 - 3.28	56,664
6 - <12 m	94.36	93.56 - 95.16	15.13	14.81 - 15.45	56,664
1 y	103.35	102.75 - 103.94	27.07	26.76 - 27.37	112,798
2 - 3 y	79.97	79.61 - 80.34	10.98	10.85 - 11.12	230,349
4 - 5 y	70.22	69.88 - 70.57	4.67	4.58 - 4.76	231,074
0 - 5 y	76.74	76.53 - 76.94	11.19	11.11 - 11.27	687,549

[1)]: CI: confidence interval.
[2)]: Population from the census of 2000 multiplied by the ratio of the number of sentinels over the total number of pediatric practices and hospitals (31,000).

children visited pediatricians because of acute infectious gastroenteritis and it was estimated that 795,651 children did so because of rotavirus gastroenteritis. When the annual incidence of acute infectious gastroenteritis of all causes in the population under the age of 6 years (5,454,635) was multiplied by the pooled detection proportion of rotavirus (18%), the annual incidence of rotavirus-associated gastroenteritis was 981,834, i.e., approximately 186,000 cases above the estimated figure of 795,651.

Table 4 presents the estimated incidence rates of acute infectious gastroenteritis due to all causes and due to rotavirus gastroenteritis. The incidence rate was the highest in the age category of 1 year old for both acute infectious gastroenteritis of all causes (103 cases/100 persons/year) and rotavirus

gastroenteritis (27 cases/100 persons/year). The incidence rate in the age category of 0 - 5 years was 77 cases/100 persons/year for acute infectious gastroenteritis of all causes and 11 cases/100 persons/year for rotavirus gastroenteritis. The cumulative risk of rotavirus gastroenteritis in children from 0 to 5 years of age was thus estimated at 53%.

DISCUSSION

According to the vital statistics, death attributable to infectious gastroenteritis (listed as enteric infections) by the age of 5 years was less than 40 in 2001, and therefore rotavirus-associated death is considered as minimal, if not nonexistent, in Japan. Therefore, the evaluation of the overall public health impact of non-lethal infectious diseases, including rotavirus gastroenteritis, requires different measures other than mortality. Morbidity, as measured by the number of patients seeking medical treatment at a pediatric practice or at an outpatient department of a hospital, is one such measure, and the recent initiative taken by the Nagai study group to extrapolate the annual incidence of acute infectious gastroenteritis from the number of cases per sentinel point (5), among other category V infectious diseases, can best be utilized for the evaluation of the burden of rotavirus gastroenteritis among Japanese children.

Once a good estimate of the annual incidence of acute infectious gastroenteritis of all causes was obtained, obtaining the annual incidence of rotavirus gastroenteritis would be a straightforward process of carrying out a simple computational task. However, this was not the case for several reasons. First, the official data from the IDSC describing the number of rotavirus cases detected at local public health laboratories per month could not be utilized because the size of and the age distribution in the denominator are neither published nor available, even at the IDSC (Okabe, N., personal communication). Second, the nature of the denominator from which rotavirus was detected may not necessarily have reflected only gastroenteritis cases at the sentinel practices and hospitals, but may possibly have included other sources such as outbreak cases. Third, there is only scant literature from which necessary information can be extracted to calculate the detection proportion of rotavirus among acute infectious gastroenteritis cases, particularly from an outpatient population. Another issue related to the lack of studies appearing in the literature is that, whereas many studies have examined the presence of rotavirus in the stool specimens of gastroenteritis patients during the winter season, very few performed such examinations throughout the year. Fourth, simply multiplying the number of gastroenteritis cases by the detection proportion of rotavirus does not necessarily give an unbiased estimate of the annual incidence of rotavirus gastroenteritis cases, because the detection proportion of rotavirus varied according to age group. Thus, the age-specific detection proportion of rotavirus has to be used when multiplying the number of infectious gastroenteritis cases due to all causes by the detection proportion of rotavirus (see Results).

We therefore concluded that the best strategy to obtain the annual incidence of rotavirus gastroenteritis was to begin by searching for the best available proxy for the detection proportion of rotavirus in each age group of gastroenteritis patients. However, adopting this strategy substantially reduced the number of papers that could be utilized for the present study (Table 1). Despite the small number of papers that met our selection criteria (see Materials and Methods), and despite the fact that the average detection proportion obtained from each study varied from 12.6 to 24.1%, the resulting age-specific detection proportion of rotavirus appeared to be correctly estimated based on the fact that the calculated 95% confidence intervals were narrow (Table 2). In addition, the weighted average of the proportion of rotavirus detected in all age groups (0 - 14 years old), as computed from six studies (n = 6,187); (data not shown), was 0.19 (95% CI: 0.18 - 0.20), which was almost identical to the weighted average computed from the three main studies (0.18; 95% CI: 0.16 - 0.20) (Table 2). However, it remains difficult to validate how accurately we estimated the detection proportion of rotavirus among outpatients with acute infectious gastroenteritis. It was even more difficult to compare our results with the corresponding figures reported in the literature. Extensively reviewing the literature, Bresee et al. (3) reported that rotavirus infection accounted for a median of 28% of the outpatient or clinic visits. In an emergency department setting (excluding those cases requiring for hospitalization), rotavirus was detected in 14% of children with acute gastroenteritis in Greece (14). In another study in Australia, rotavirus was detected in 11.8% of outpatients with acute gastroenteritis (15). However, in Norway it was reported in the 1980s that as many as 41% of children with acute gastroenteritis were attributable to rotavirus infection (16). We therefore concluded that our estimate of 18% fell within a reasonable range of expected values for the detection proportion of rotavirus among children with acute infectious gastroenteritis seeking medical care at either a pediatric practice or the pediatric outpatient department in a hospital in the community.

This study revealed that the magnitude of the burden of rotavirus disease among Japanese children is substantial. Every year, approximately 800,000 children in Japan under the age of 6 years visit a doctor to seek medical care, and one in two children will visit a pediatric practice or the pediatric outpatient department in a hospital as a result of rotavirus gastroenteritis before attending primary school. Such pediatrician visits occur in more than one in four 1-year-old children, the age at which the annual incidence rate for rotavirus gastroenteritis is the highest (Table 4). According to the CDC studies (4), in the USA, one in eight children see a doctor annually due to rotavirus gastroenteritis during the first few years of life, and this rate corresponds to an annual incidence of 500,000 doctor visits. Thus, the burden of rotavirus gastroenteritis in terms of pediatrician visits in Japan is at least comparable to that in the USA and is likely to increase if the birth cohort of Japan (1.2 million) and that of the USA (3.9 million) are both taken into consideration. International variation in the burden of rotavirus gastroenteritis in the outpatient setting was recently reported in central European countries, where the estimated annual incidence rates for rotavirus gastroenteritis in patients under 5 years of age were 4.1 (Germany), 2.9 (Switzerland), and 0.84 (Austria) per 100 children-years (17). These estimates of the annual incidence rate are much smaller than our corresponding estimate of 11 per 100 children-years among those under 6 years of age (Table 4). However, it should be noted that in central Europe, the detection proportions of rotavirus among children with acute infectious gastroenteritis were higher than our corresponding figure (18%), i.e., 27% (Germany), 37.5% (Switzerland), and 29.5% (Austria) (17). Thus, one explanation for the observed differences in the annual incidence rate estimates may be that parents and caretakers of Japanese children bring even mild cases of gastroenteritis to the attention of pediatri-

cians. As regards the etiological agents and the severity of gastroenteritis, it is a received observation that the proportion of rotavirus positive cases is always higher among hospitalized children than among non-hospitalized children with acute gastroenteritis, as exemplified in a recent study in Australia (15). The annual incidence rate for acute infectious gastroenteritis of all causes in children under 5 years of age in Germany was calculated to be 26 per 100 person-years, according to the data presented in a study mentioned above (17); this figure amounts to one-third of the corresponding figure observed for children under 6 years of age in Japan (Table 4).

Despite the considerable differences in the annual incidence rates across different age groups, few studies have estimated age-specific annual incidence rates for rotavirus gastroenteritis. One interesting observation in this context is that the estimated annual incidence rate for infants younger than 6 months old was as low as 3.1 per 100 children-years (Table 4), and there were only 18,386 cases of rotavirus gastroenteritis (Table 3); these figures account for 2.3% of the total number of outpatient or clinic visits by persons under the age of 6 years. This finding deserves particular attention, because the primary objective of the study of the burden of rotavirus gastroenteritis is to assess the need for a rotavirus vaccine. As Nakagomi et al. (18) reported previously, the obtained results provide support for the introduction of a rotavirus vaccine. Such a vaccine is currently in the final stage of field trials, and will be given in a multiple-dose format to children under the age of 6 months; however, for this reason, the vaccine will be unable to protect those infants who experience rotavirus infection before the age of 6 months.

A potential bias of this study would be that the data used to estimate the detection proportion of rotavirus among patients with gastroenteritis did not match the period during which the national surveillance data for infectious gastroenteritis of all causes were obtained. The lag is primarily derived from the fact that the data used in the present study were unexpectedly the only data available in the published literature to date that met the minimum criteria required to do this type of study (see Materials and Methods). However, it is unlikely that the detection proportion of rotavirus among pediatric outpatients has greatly changed since 1980, because neither great changes in sanitary conditions, nor the introduction of a rotavirus vaccine have occurred in Japan during these 2 decades. Thus, despite the need for caution, our estimate remains among the best available to date.

A more accurate estimate of the national burden of rotavirus disease will be obtained, provided that a prospective study can be conducted in which pediatric patients with acute gastroenteritis are screened for the presence of rotavirus throughout the year, preferably at clinics and hospitals representing several sentinel points across the nation. Alternatively, although it would be less accurate than that of prospective studies, an estimate of the detection proportion of rotavirus could be obtained that would represent the surveillance data regarding acute infectious gastroenteritis from sentinel points; however, the IDSC would need to collect certain types of data from local public health institutes, such as the number of stool specimens from the patients with acute gastroenteritis, and their ages when seen at the sentinel clinics and hospitals where they were tested for rotavirus infection. This study provides a basis upon which such further studies will be planned.

In summary, this study provides for the first time an estimate for the national burden of rotavirus gastroenteritis in Japan in terms of the number of patients who visited a general pediatric practice or the pediatric outpatient department in a hospital. Although the number of pediatric visits serves as one important measure for evaluating the need for rotavirus vaccines in a country, there are a number of other factors that also need to be taken into consideration before coming to a decision regarding whether or not a rotavirus vaccine should be introduced. Such factors include, among other things, the direct and indirect medical costs associated with patient care, the overall severity of the disease, the possible adverse effects, cost and efficacy of the candidate vaccine.

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