

## Original Article

# Population-Based Estimates of the Cumulative Risk of Hospitalization Potentially Associated with Rotavirus Diarrhea among Children Living in Two Cities in Akita Prefecture, Japan

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(Received September 27, 2004. Accepted December 15, 2004)

**SUMMARY:** A 4-year retrospective population-based survey was conducted in two cities in Akita Prefecture, Japan, to estimate the incidence rate and the cumulative risk of hospitalization potentially associated with rotavirus diarrhea. At monthly occasions of the 3-year-old checkup, we asked each parent if his or her child had ever been hospitalized because of rotavirus diarrhea. Based on 3-year follow-up of the four consecutive birth cohorts (1996-1999), we calculated the incidence rate and the cumulative risk of rotavirus-associated hospitalizations by the age of 3 years. The incidence rates of rotavirus-associated hospitalization in 1-year-old children in Akita city and Honjo city were 9.7 and 16 hospitalizations per 1,000 children per year, respectively, whereas 1.9% of children in Akita city and 3.3% of children in Honjo city were hospitalized by their third birthday because of rotavirus-associated diarrhea. The burden of rotavirus diarrhea in this region of Japan, and probably across the nation, appears substantially large.

## INTRODUCTION

Rotavirus is the single most important etiological agent of severe gastroenteritis in infants and young children across the world (1). Almost all children experience rotavirus infection by the age of 3-5 years, irrespective of whether they live in developing or industrialized countries (2). Thus, a safe water supply and adequate sewage treatment alone are unlikely to prevent infection with rotavirus. However, the consequence of rotavirus infection is different between developing and industrialized countries. In developing countries, there is an updated estimate of 440,000 rotavirus-associated deaths annually of children under 5 years of age, whereas there is minimal mortality in industrialized countries (2). Thus, the need for an effective rotavirus vaccine to prevent deaths from rotavirus infection in developing countries is clear, whereas arguments for and against vaccine implementation need to be established based on knowledge of the health and economic burden imposed by rotavirus infection as calculated by measures other than mortality.

With regard to the magnitude of morbidity attributable to rotavirus infection in Japan, Yokoo et al. (3) have recently estimated that one in two children visits a pediatrician by the age of 6 years because of rotavirus gastroenteritis, and that these visits number approximately 800,000 per year for children under the age of 6 years. In the U. S., where relevant national databases are available, it has been estimated by the Centers for Disease Control and Prevention that one in 8 children visits a doctor's office due to rotavirus gastroenteritis by the age of 5 years, and that approximately one in 10 of such children is eventually hospitalized (4). Thus, the number

of admissions in the U. S. was one in 40 in the 1980s (5), and it was more recently estimated to be approximately one in 70 (6). Because the goal of rotavirus vaccines is to prevent severe, dehydrating diarrhea that causes deaths in developing countries and hospitalizations in industrialized countries in the first 2 to 3 years of life (1), the most basic measures in an argument for rotavirus vaccines should be the incidence rate and the cumulative risk of hospitalization due to rotavirus diarrhea by the age of 2 to 3 years, in which period most cases of rotavirus-associated hospitalizations occur. The aim of this study was, therefore, to estimate the hospitalization rates at the age of 1 year and the cumulative risk of hospitalization due to rotavirus diarrhea in Japan by having interviews with parents or caregivers of young children at the time of the 3-year-old checkup.

## MATERIALS AND METHODS

**Survey sites:** We chose Akita and Honjo, two cities in Akita Prefecture, as the sites for this retrospective cohort study. Akita city had a population of 310,000 and its birth cohort was 2,800, and Honjo city had a population of 45,000 and its birth cohort was 430, when this survey was conducted.

**Data collection by an interview with parents:** The past history of diarrheal and rotavirus-associated admissions was obtained retrospectively by an interview with each parent or caregiver of a child at the time of his or her 3-year-old checkup, which is provided by local governments according to the Maternal and Child Health Law. According to this law, children are provided with the opportunity to have a medical checkup when they are between 3 and 4 years old. During the 4-year period between May, 1999, and June, 2003, an interviewer (mostly IH) went to the medical checkup sites every month twice out of 4 occasions in Akita city and at the only one occasion in Honjo city. Following brief explanation of the purpose of the survey, those parents or caregivers who gave consent to be interviewed were asked if their children had ever been admitted to the hospital, and, if so, whether it was because of diarrhea. If the answer to this question was

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affirmative, the interviewer further asked about the discharge diagnosis provided. The interviewer specifically asked whether the pediatricians referred to rotavirus as the etiology of the disease for which their children had been hospitalized. The interviewer then asked about the age at which their children were hospitalized, the major symptoms, the duration of hospitalization, and whether intravenous fluid replacement therapy was performed. The birth month of a child was recorded, but any information that can identify and trace any individual child later on was not recorded for reasons of privacy. In this study, diarrheal hospitalization was defined as any hospitalization of a child who had diarrhea irrespective of his/her primary discharge diagnosis. Hospitalization that was potentially associated with rotavirus infection (or rotavirus-associated hospitalization, for short) was defined as hospitalization referred to by the pediatrician as either rotavirus gastroenteritis or acute infantile diarrhea.

**Estimations of hospitalization rates and the cumulative risk of hospitalization potentially associated with rotavirus infection:** The age-specific incidence rate of rotavirus-associated hospitalization was calculated using the total number of rotavirus-associated hospitalizations for each age group and the total number of children attending the 3-year-old checkup, and expressed as the number of hospitalizations per 1,000 children per year. The 95% confidence intervals were calculated according to the Poisson model. Here, the calculation presupposed that the size of the birth cohort did not change during the follow-up period. The cumulative risk of rotavirus-associated hospitalization was defined as the proportion (percentage) of children who were hospitalized because of diarrhea and whose parents were given by their children's doctors a discharge diagnosis of either rotavirus gastroenteritis or acute infantile diarrhea among all children born during the 4-year period between January 1996 and December 1999 and whose parents gave consent to be inter-

viewed. If the diarrhea was acquired nosocomially, i.e., diarrhea started after hospitalization, the case was excluded from calculation.

**Statistical analysis:** Difference in the cumulative risks of rotavirus-associated hospitalization by the age of 3 years between Akita and Honjo cities were examined by the chi-square test after adjustment in the birth year according to the Mantel-Haenszel method.

## RESULTS

Among 5,357 (Akita city) and 1,783 (Honjo city) children who underwent the examination, there were 4,952 (Akita city) and 1,618 (Honjo city) children who were born during the 4-year period between January 1996 and December 1999 and whose parents gave consent to participate in this survey. According to the vital statistics, there were a total of 11,295 live births (an average of 2,824 live births per year) in Akita city and 1,719 live births (an average of 430 live births per year) in Honjo city during this 4-year period. Thus, it was calculated that 44% (4,952/11,295) of the birth cohort in Akita city and 94% (1,618/1,719) of the birth cohort in Honjo city were followed up for 3-and-a-half years from birth.

Table 1 summarizes the number of admissions in Akita city that were accompanied by any diarrhea for each age-specific category and for each survey year. The first year of life is divided into two 6-month periods because these two periods of life have different medical implications, including maternal immunity and dietary customs, which may affect the susceptibility to rotavirus infection and the vaccination strategy. The hospitalizations accompanied by any diarrhea occurred most frequently in the second year of life (an average of 39%), and 62% of such hospitalizations occurred during the period from 6 months to 23 months of age. However, the hospitalization rate was highest in the 6- to 11-month-old

Table 1. The number of admissions in Akita city that accompanied any diarrhea for each age-specific category and for each survey year

	0-5	6-11	12-23	24-35	>36	unknown	Total
1996	13	19	29	23	3		87
1997	4	16	29	17	8	1	75
1998	3	15	21	15	5	1	60
1999	3	17	33	9	5		67
Total (%)	23 (8.0)	67 (23.2)	112 (38.8)	64 (22.1)	21 (7.3)	2	289
Incidence rate <sup>1)</sup>	9.3	27	23	13	—	—	18 <sup>2)</sup>

<sup>1)</sup>: Incidence rate was expressed as the number of hospitalizations per 1,000 children per year.

<sup>2)</sup>: Calculation of the incidence rate during the first 3 year period was conducted by excluding cases that had occurred in the >36-month age group and the unknowns.

Table 2. The number of rotavirus-associated hospitalizations in Akita city for each age-specific category and for each survey year

	0-5	6-11	12-23	24-35	>36	unknown	Total
1996	2	4	12	9	0		27
1997	1	5	9	1	0		16
1998	1	10	11	5	2	1	30
1999	0	6	16	2	0		24
Total (%)	4 (4.1)	25 (25.8)	48 (49.5)	17 (17.5)	2 (2.1)	1	97
Incidence rate <sup>1)</sup>	1.6	10	9.7	3.4	—	—	6.3 <sup>2)</sup>

<sup>1)</sup>: Incidence rate was expressed as the number of hospitalizations per 1,000 children per year.

<sup>2)</sup>: Calculation of the incidence rate during the first 3 year period was conducted by excluding cases that had occurred in the >36-month age group and the unknown.

Table 3. The number of admissions in Honjo city that accompanied any diarrhea for each age-specific category and for each survey year

	0-5	6-11	12-23	24-35	>36	Total
1996	14	11	23	12	3	63
1997	8	12	13	9	11	53
1998	8	7	23	12	7	57
1999	4	13	18	12	3	50
Total (%)	34 (15.2)	43 (19.3)	77 (34.5)	45 (20.2)	24 (10.8)	223
Incidence rate <sup>1)</sup>	42	53	47	27	–	41 <sup>2)</sup>

<sup>1)</sup>: Incidence rate was expressed as the number of hospitalizations per 1,000 children per year.

<sup>2)</sup>: Calculation of the incidence rate during the first 3 year period was conducted by excluding cases that had occurred in the >36-month age group.

Table 4. The number of rotavirus-associated hospitalizations in Honjo city for each age-specific category and for each survey year

	0-5	6-11	12-23	24-35	>36	Total
1996	1	3	4	3	0	11
1997	0	2	6	0	4	12
1998	0	5	10	5	3	23
1999	0	2	6	7	0	15
Total (%)	1 (1.6)	12 (19.7)	26 (42.6)	15 (25.0)	7 (11.5)	61
Incidence rate <sup>1)</sup>	1.2	15	16	9.3	–	11 <sup>2)</sup>

<sup>1)</sup>: Incidence rate was expressed as the number of hospitalizations per 1,000 children per year.

<sup>2)</sup>: Calculation of the incidence rate during the first 3 year period was conducted by excluding cases that had occurred in the >36-month age group.

group, followed by the 1-year-old group.

Table 2 summarizes the number of rotavirus-associated hospitalizations in Akita city for each age-specific category and for each survey year. The occurrence of rotavirus-associated hospitalizations in the second year of life (an average of 50%) is more prominent than hospitalizations accompanied by any diarrhea, and 75% of rotavirus-associated hospitalizations occurred during the period from 6- to 23-months of age. The incidence rates of rotavirus-associated hospitalization were equally high both in the 6- to 11-month-old group and in the 1-year-old group, for which the rates were calculated to be 10 hospitalizations per 1,000 children per year (95%CI: 6.5-15 per 1,000 children per year) and 9.7 hospitalizations per 1,000 children per year (95%CI: 7.1-13 per 1,000 children per year), respectively.

Table 3 summarizes the number of admissions in Honjo city that were accompanied by any diarrhea for each age-specific category and for each survey year. Like those observed in Akita city, the hospitalizations in Honjo accompanied by any diarrhea occurred most frequently in the second year of life (an average of 35%), and 54% of such hospitalizations occurred during the period from 6- to 23-months of age. However, the diarrheal hospitalization rates were almost equally high during the period from birth to 2 years of age (42-53 hospitalizations per 1,000 children per year).

Table 4 summarizes the number of rotavirus-associated hospitalizations in Honjo city for each age-specific category and for each survey year. Rotavirus-associated hospitalizations in the second year of life accounted for 43% on average, and those during the period from 6- to 23-months of age accounted for 62% of cases occurring throughout the survey period. Like those observed in Akita city, the incidence rates of rotavirus-associated hospitalization in Honjo were

equally high both in the 6- to 11-month-old group and in the 1-year-old group, for which the rates were calculated to be 15 hospitalizations per 1,000 children per year (95%CI: 9.7-26 per 1,000 children per year) and 16 hospitalizations per 1,000 children per year (95%CI: 10-24 per 1,000 children per year), respectively.

Based on the number of rotavirus-associated diarrhea cases shown in Tables 2 and 4, we calculated the cumulative risk of hospitalization by the age of 2 years and 3 years for each year's birth cohort in Akita city and Honjo city (Tables 5, 6).

Table 5. The cumulative risk (%) of hospitalization by the age of 2 years or 3 years for each year's birth cohort in Akita city

year	Size of cohort followed up	by 2 y	by 3 y
1996	1263	1.43	2.14
1997	1205	1.24	1.33
1998	1255	1.75	2.15
1999	1229	1.79	1.95
Average		1.55	1.89

Table 6. The cumulative risk (%) of hospitalization by the age of 2 years or 3 years for each year's birth cohort in Honjo city

	Size of cohort followed up	by 2 y	by 3 y
1996	402	1.99	2.74
1997	402	1.99	1.99
1998	407	3.69	4.91
1999	407	1.97	3.69
Average		2.41	3.33

The cumulative risk of rotavirus-associated hospitalization by the age of 2 years was calculated to be 1.6% in Akita city and 2.4% in Honjo city. Thus, it was estimated that approximately one in 65 children in Akita and one in 42 children in Honjo were admitted to the hospital due to rotavirus diarrhea in the first 2 years of life. The cumulative risk of rotavirus-associated hospitalization by the age of 3 years was similarly calculated to be 1.9% in Akita city and 3.3% in Honjo city. Thus, it was estimated that approximately one in 53 children in Akita and one in 30 children in Honjo were admitted to the hospital due to rotavirus diarrhea in the first 3 years of life. The difference in the cumulative risk between two populations was statistically significant ( $P = 0.002$ ) after the birth years were adjusted.

## DISCUSSION

This report provides estimates of the age-specific incidence rates and the cumulative risk of hospitalizations potentially associated with rotavirus infection in Akita and Honjo, two cities located in the northern part of Japan. These two cities likely represent medium-sized and small cities scattered across the nation in terms of the size of the population. To our knowledge, this is the first population-based study to address the rotavirus disease burden in Japan. Because even natural infection with rotavirus does not prevent subsequent infections, the goal of rotavirus vaccines is the prevention of severe, dehydrating diarrhea and not the prevention of mild diarrhea or infection itself (7). Thus, discussion about the need for a rotavirus vaccine should be based on, among other things, proper assessment of the cumulative risk of hospitalization due to rotavirus diarrhea during the first few years of life, which is when the majority of hospitalizations occur and the disease becomes most severe. In this regard, the cumulative risk that one in 53 children (1.9%) in Akita and one in 30 (3.3%) children in Honjo were hospitalized because of diarrheal illness that was potentially associated with rotavirus infection by the age of 3 years was considered to be substantially large. Regarding the observed difference in the cumulative risk between the two cities, we are unable to provide any plausible explanation. However, it may merit mention that hospitalization could be triggered by non-medical indications, and such practice could affect the observed difference in cumulative risk. It would be useful to address this issue further if the difference in hospitalization rates among overall diarrheal patients between the two cities had been known earlier.

Our cumulative risk estimates were for the first 3 years of life, which period is 2 years shorter than most of the estimates available in the literature; such risk estimates usually address the first 5 years of life. However, our estimates (one in 30-50) would fall within the range of corresponding figures reported in the literature, given that the relative proportion of rotavirus-associated hospitalizations occurring in the 3- and 4-year age groups is estimated to be approximately 10% of all rotavirus-associated hospitalizations occurring under 5 years of age (3). For example, the cumulative risk of hospitalization by the age of 5 years due to rotavirus gastroenteritis was estimated to be one in 80 in Spain (8), one in 70 in the U.S. (9), one in 65 in Poland (10), one in 39 in the United Kingdom (11), one in 33 in Finland (12), one in 31 in Argentina (13), one in 23-27 in Australia (14), and one in 19 in Ireland (15). Interestingly, the cumulative risk of rotavirus-associated hospitalization in Akita and Honjo, and possibly

in the entire nation, may well be within the scope of the cumulative risk in most countries, whereas the pediatrician visits due to rotavirus gastroenteritis in Japan (approximately one-half of all visits made by the age of 6 years) by far exceed the corresponding estimates in other developed countries (3). Thus, it may be that Japanese parents tend to bring children with mild rotavirus gastroenteritis to the attention of pediatrician, but pediatricians admit only children sufficiently severe enough to be hospitalized according to the standard that is more or less in effect across the world.

The overall response rates to the questionnaires were high and ranged from 83.7 to 96.7% in Akita city and 82.5 to 97.8% in Honjo city. Such high response rates, together with high attendance rates for the 3-year-old checkup, made this survey less prone to selection bias, although there is still a possibility that we missed a fraction of children who did not have the checkup because both parents had difficulty in bringing them to the examination sites on weekdays. High response rates were achieved probably because the survey was carried out in the form of an interview with the parents or caregivers of the children brought in for the 3-year-old checkup. Furthermore, because the attendance rates were high, we were able to collect the relevant information from an average of 44% of the birth cohorts in Akita city and from an average of 94% of the birth cohorts in Honjo city. The coverage in the Akita city cohort may seem low; this is due to the fact that interviews were conducted in only a half of the occasions (2 out of 4 days per month). It seems unlikely that children with a past history of rotavirus-associated hospitalization would cluster on any of these 4 days rather than randomly distribute. Thus, sampling sizes were considered large enough that our data may well represent the birth cohorts that we targeted. Strictly speaking, however, the cohort of children about whom we obtained information at 3-and-a-half years of age were not exactly the birth cohort for which we obtained the number of live births from the vital statistics. We had to assume that the individuals whom we lost because they left the cohort were offset by the individuals whom we obtained because they joined the cohort, and this may be a source of possible errors.

The major source of bias in this study was in the case definition for rotavirus-associated diarrhea, which we defined as a discharge diagnosis of either rotavirus diarrhea or acute infantile diarrhea, provided to the parents by their children's doctors. Inclusion of acute infantile diarrhea could potentially be a source of overestimation, but it was common practice in the 1990s that the diagnosis of acute infantile diarrhea in the first 3 years of life was used almost interchangeably with that of rotavirus diarrhea. This was true even under the infectious disease surveillance system before the enactment in 1999 of the Law concerning the Prevention of Infectious Diseases and Medical Care of Patients with Infectious Diseases. Furthermore, the observation that the overall proportion of rotavirus-associated diarrhea, as defined in this study, among patients hospitalized for any diarrhea was 34% in Akita city and 27% in Honjo city was in good agreement with the reported detection proportions of rotavirus among hospitalized patients with diarrhea (20-60%) (16). Thus, it is unlikely that we made a serious error of overestimation. Recall bias was thought to be minimal because admission to the hospital, if it occurred, was a major event memorable to the parents, and notes were often made in the mother-child notebook provided by the local government at the time of pregnancy.

Although it is tenuous to extrapolate from these local data to the entire nation, it would be interesting to compare the data obtained in this study with the national estimate of pediatrician visits due to rotavirus-associated gastroenteritis recently reported by Yokoo et al. (3). In the 1-year-old age group, the age at which the peak incidence of both clinic visits and hospitalizations due to rotavirus diarrhea occur, it was estimated that there were 270 clinic visits per 1,000 persons per year (3), and we found 9.7 to 16 hospitalizations per 1,000 persons per year (this study). This suggests that in Japan, 3.5 to 5.9% of children who visit pediatricians will eventually be hospitalized. The ratio of hospitalization to clinic visits was much smaller in Japan than the corresponding ratio in the U. S., which is one in 8 or 12.5% (4). As Yokoo et al. (3) discussed, parents and caregivers of Japanese children are more likely to bring milder cases of gastroenteritis to the attention of pediatricians because they do not incur any direct medical costs for their children's illness usually from birth to 2 years old.

In summary, we interviewed the parents or caregivers of children attending a 3-year-old checkup in Akita and Honjo during the 4-year period from May, 1999, through June, 2003, in order to obtain their children's past history of hospitalization, with a focus on rotavirus diarrhea. The 4 years of the survey were regarded as a proxy method of following up each of the birth cohorts of 1996-1999 for 3 years, thereby enabling us to calculate the cumulative risk of hospitalizations due to rotavirus-associated diarrhea by the age of 2 and 3 years. Although the estimates of cumulative risk in these two cities were significantly different, these estimates, 1.9% in Akita and 3.3% in Honjo by the third birthday, fell well within the range of cumulative risk available in the literature. Thus, the burden of rotavirus diarrhea in this region of Japan and probably across the nation appears substantially large.

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