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Original Article

The Burden of Rotavirus Gastroenteritis among Japanese Children during Its Peak Months: an Internet Survey

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SUMMARY: Rotavirus gastroenteritis (RVGE) is one of the most common early childhood diseases; however, little information exists on the frequency of RVGE attacks during peak epidemic months and the subsequent clinical consequences in Japanese children. Therefore, we conducted a nationwide internet survey that targeted mothers whose children recently experienced an episode of RVGE or influenza from January 2011 to April 2011. Data concerning the incidence and clinical consequences of RVGE and influenza among 15,137 children aged <3 years were collected. Of these, 1,286 children who experienced an RVGE episode and 1,487 children who experienced an influenza episode visited a physician or required hospital admission. Data analysis of 867 RVGE episodes and 897 influenza episodes found that 25% of children with RVGE required 8–14 days for recovery, 28% received intravenous rehydration, 7% were hospitalized, 15% visited an emergency department, 70% sought medical interventions ≥ 2 times, and 32% sought medical intervention ≥ 3 times. Compared with influenza, RVGE required a longer recovery period, and was associated with more frequent episodes of intravenous rehydration, hospitalization, and emergency department and physician visits. Our results indicate that, like influenza, RVGE occurring during peak epidemic months in children aged <3 years imposes a substantial burden on families and medical institutions in Japan.

INTRODUCTION

Acute gastroenteritis and acute respiratory infections are the two most common infectious diseases affecting children worldwide. Rotavirus is the leading cause of severe gastroenteritis, which annually claims the lives of an estimated 453,000 children aged <5 years, particularly those residing in developing countries (1–3). While mortality due to rotavirus gastroenteritis (RVGE) is low in industrialized countries, RVGE is a significant cause of morbidity in children and imposes a substantial burden on medical resources. In the United States, for example, before the introduction of the rotavirus vaccine, there were an estimated 410,000 physician visits, 70,000 hospitalizations, and 272,000 emergency department visits that were attributed to RVGE each year (4–6). Like influenza, RVGE is a seasonal disease that mainly occurs in the winter season, with a peak between February and March in Japan (7). Several hospital-based studies have reported on the incidence of RVGE among children aged <5 years; this incidence ranges from a minimum of 3.1 per 1,000 person-years to a maximum of 12.7 per 1,000 person-years (8–10). These local incidences were extrapolated to determine the annual number of rotavirus-associated hospitalizations, which was estimated to be 26,000–78,000 (8–10). However, few studies have estimated the annual number of physician visits attributed to RVGE in Japan. For example, a study estimated that approximately 790,000 children aged <6 years annually visited pediatric practices or hospital outpatient departments for the treatment of RVGE (11).

In view of the sparse data on the incidence and clinical consequences of RVGE in infants and young children in Japan, we conducted a nationwide internet-based survey that was targeted mothers with children aged <3 years, an age group that is most commonly affected with RVGE (5). The present study aimed to determine the incidence of RVGE during peak epidemic months among children aged <3 years, and describe the clinical consequences of this disease (major symptoms, medical resource use, and illness duration) and the frequency of associated complications such as dehydration and convulsions. For comparison, we collected a similar set of data on the incidence of influenza, which is another common viral infection with winter seasonality that affects children in the same age group.

MATERIALS AND METHODS

This retrospective cross-sectional study used an anonymous internet-based survey to evaluate disease episodes that occurred in children aged <3 years during a 4-month period from January 2011 to April 2011. The internet-based survey was chosen for the following reasons: it allowed a large number of samples to be collected over a short period of time, thereby facilitating a

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nationwide survey; it allowed data to be collected immediately after the epidemic period, thereby minimizing the possibility of recall bias; and it eliminated the possibility of inaccurate data because internet-literate respondents were expected to be sufficiently intelligent to provide accurate information.

Survey methods–participant selection and screening: The actual data were collected in May 2011 via an internet-based survey using the following two-step scheme. First, a Japanese population registered at Macromill, Inc. (www.macromill.com/global/), an internet-based survey company, was pre-screened to identify potential participants. The company sent an invitation e-mail to 42,292 women aged 20–44 years, who had registered with the company's website as a research monitor. Among them, women who intended to participate in the pre-screening survey accessed the questionnaire by clicking on the uniform resource locator pasted in the invitation e-mail. Initially, 24,492 women who expressed their willingness to participate in surveys concerning their children were invited to participate in the pre-screening survey. An additional 18,000 invitation e-mails were sent to potential participants who were randomly selected from 126,183 women registered with the company's website. The pre-screening survey began on May 9, 2011 and ended May 27, 2011, when the number of participants with a child aged <3 years reached 20,000. In the next step, candidate mothers of children who had experienced an episode of RVGE/influenza were invited to participate in the main survey. Participants were given incentive points according to the number of answered questions in both the pre-screening and main surveys.

Pre-screening to identify mothers of children who experienced episodes of RVGE and/or influenza: The participants (aged 20–44 years) were asked if they had a child aged <3 years, and if they did, whether the child had experienced a physician-diagnosed episode of RVGE and/or influenza during the period of January 2011 to April 2011. Mothers of children with an RVGE episode were asked to describe the symptoms of their infected child(ren) and the color of their stool. While an RVGE episode defined in this study was dependent on the memory of the mothers, a set of questionnaires was used to confirm the presence of diarrhea and/or vomiting in the absence of blood-stained stools in situations where the mothers did not remember the color of their child(ren)'s stool. All physician-diagnosed episodes of influenza reported by the mothers were included in the analysis. The incidence of RVGE and influenza was calculated from the number of episodes that occurred during the 4-month period mentioned above and the number of children screened:

Incidence (per 1,000 person-years) =
[Number of episodes during the 4-month period/
(Number of children screened $\times$ 4/12)] $\times$ 1,000

Survey of RVGE/influenza episodes: Candidate mothers of children who had experienced an episode of RVGE/influenza were invited to participate in the main survey. Those who agreed to participate were asked to provide the following information: the child(ren)'s age in months at the time of the disease onset, the observed symptoms, the number of days until recovery, the number of physician visits, and whether the child required intravenous rehydration, hospitalization, and/or an emergency department visit. Mothers with multiple children who had experienced RVGE/influenza episodes were instructed to answer the questions in terms of the most recent episode. The obtained RVGE and influenza data were then analyzed and compared. The chi-square (χ^2) test and the Wilcoxon's rank-sum test were used to calculate the statistical significance of differences between distributions of categorical variables and ordinal variables, respectively.

Ethical considerations: In accordance with the Declaration of Helsinki, the present protocol was approved by the administrator of the Ethics Committee of Nishi Hospital (Higashi-Osaka, Japan), who confirmed that it was designed in compliance with the Ethical Guidelines for Epidemiological Research in Japan (established in 2002 and revised in 2004, 2007, and 2008). The administrator decided that the reviewing process by the Ethics Committee could be omitted because all four conditions required by the Japanese guidelines were not applicable to the protocol.

Written informed consent for participation was not obtained from the mothers. However, the purpose of this study, how the data would be used, and the discontinuation policy were explained on the Macromill, Inc. website prior to initiation of the preliminary survey as well as the main survey, and responses were recieved only from those who consented to participate in each survey. The survey was designed to receive responses online in an anonymous manner, and we also assured the participants that their personal information would be strictly confidential.

RESULTS

A total of 20,000 mothers aged 20–44 years initially responded to the invitation e-mails during the period from May 9, 2011 to May 27, 2011 (Fig. 1). Of these, 13,674 mothers had a total of 15,137 children aged <3 years (Fig. 1). Table 1 shows the age distribution, residence, and employment status of these mothers. The residences of the participants were widely distributed throughout Japan, and approximately 75% mothers were aged 30–39 years. The number of children aged <1 year was approximately half the number of children aged <2 and <3 years (Table 1). A total of 1,588 mothers reported 1,647 children diagnosed with RVGE between January 2011 and April 2011, but the responses from 343 mothers with 361 children were excluded as described in Fig. 1. Therefore, a total of 1,245 mothers with 1,286 children were considered eligible to complete the main questionnaire (Fig. 1). Of these, 1,220 mothers agreed to participate in the main survey. A series of questionnaires were sent to the first 1,056 mothers, 867 (82%) of whom responded. Data for 867 children (only the most recent episode if multiple children had experienced RVGE) were thus obtained during the period from May 18, 2011 to May 27, 2011 (Fig. 1). Similarly, 1,440 mothers with a total of 1,487 children diagnosed with influenza between January 2011 and April 2011, responded, of whom 1,418 agreed to participate. Questionnaires were sent out to the first 1,140 mothers, 897 (79%) of whom responded and, provided data for 897 children (Fig. 1).

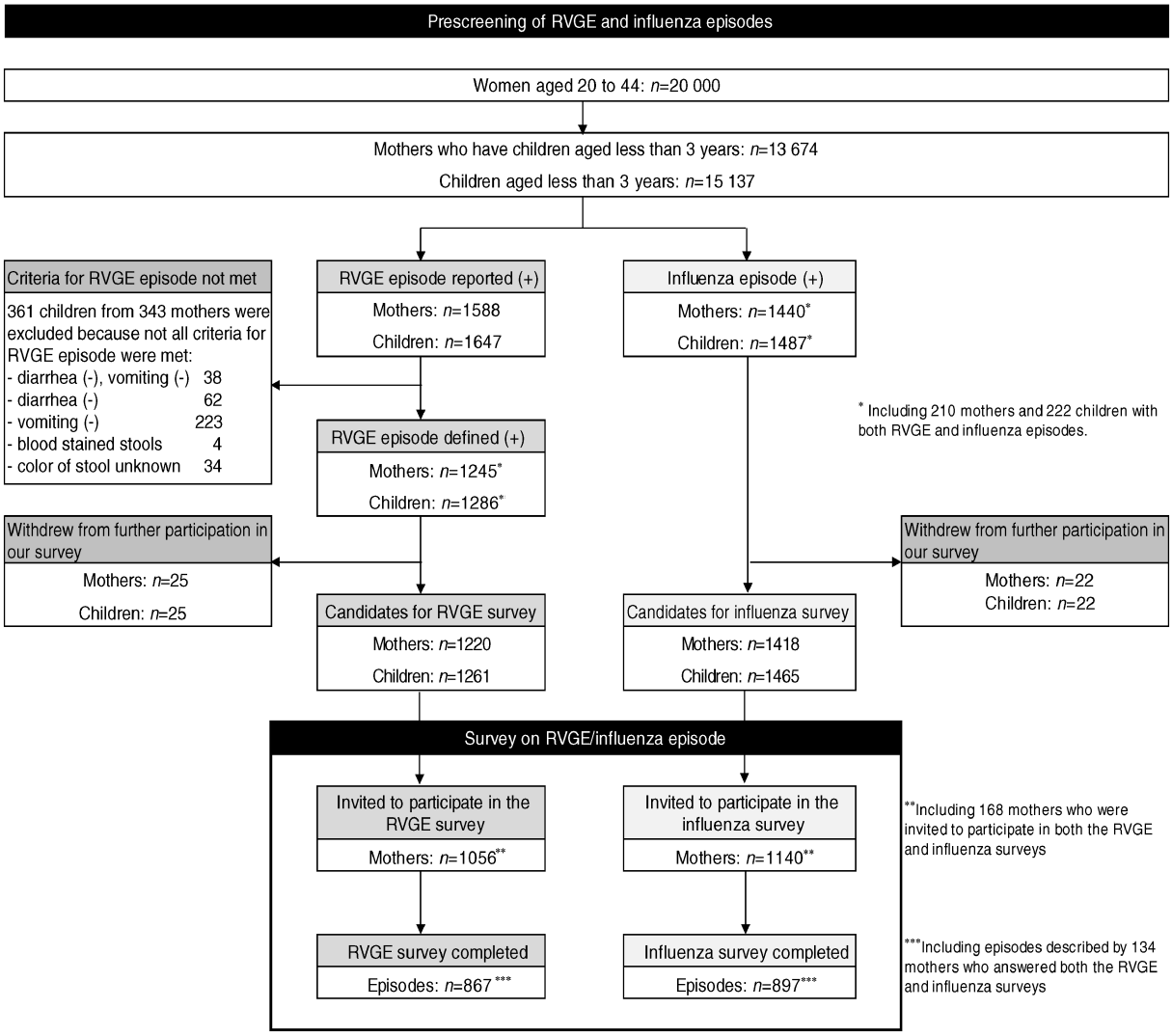

Fig. 1. An outline of the survey. A total of 20,000 initial responses were obtained from women aged 20–44 years during the period from May 9, 2011 to May 27, 2011. Finally, data from 867 children who experienced RVGE and 897 children who experienced influenza were analyzed.

Incidence of RVGE and influenza: The screening survey identified 1,286 children who had experienced an RVGE episode (0–11 months, $n = 120$; 12–23 months, $n = 664$; 24–35 months, $n = 502$), and 1,487 children who had experienced an influenza episode (0–11 months, $n = 128$; 12–23 months, $n = 626$; 24–35 months, $n = 733$). The incidence of RVGE and influenza episodes was 255 and 295 per 1,000 person-years, respectively, in children aged <3 years (Table 2). RVGE incidence was highest in the 12–23-month age group, while influenza incidence was highest in the 24–35-month age group. One in 3 children in the 12–23-month age group, and 1 in 4 children aged <3 years had experienced an RVGE episode during the peak rotavirus season in Japan (from January to April).

Symptoms: The symptoms of RVGE and influenza as reported by the mothers are presented in Fig. 2. Diarrhea and vomiting were present in 100% of children with RVGE because both symptoms were part of the case definition. Approximately 1 in 4 children with RVGE reportedly experienced dehydration and weight loss (reflecting the need for rehydration), whereas these symptoms were infrequently observed in children with influenza. Fever, however, was observed in nearly all children with influenza, while cough was observed in $>50\%$. Fever was also observed in 73% children with RVGE. Of note, convulsions occurred in 2.2% and 2.6% children with RVGE and influenza, respectively, with no significant difference between the two groups ($P = 0.608$, χ^2 test).

Illness duration: More than 60% children with RVGE and influenza reportedly recovered in 4–7 days (Fig. 3). However, the time to recovery for the two conditions differed for the remaining children. As shown in Fig. 3, 22% children with influenza quickly recovered within 3 days, whereas 25% of children with RVGE recovered within 8–14 days, indicating that recovery from an RVGE episode tended to take significantly longer than recovery from an influenza episode (Fig. 3, $P < 0.0001$, Wilcoxon's rank-sum test).

Proportion of children requiring intravenous rehydration, hospitalization, and/or an emergency department visit: Of the 867 children who had experienced an RVGE episode, 247 (28%) received in-

Table 1. Background information on respondents to the screening survey

	No. (%)
Demographic background of mothers with infants <3 yr	
Age distribution (yr)	
20–24	283 (2.1)
25–29	2,841 (20.8)
30–34	6,015 (44.0)
35–39	4,200 (30.7)
40–44	335 (2.4)
Region of residence	
Hokkaido	647 (4.7)
Tohoku	637 (4.7)
Kanto	4,875 (35.7)
Chubu	2,565 (18.8)
Kinki	2,537 (18.6)
Chugoku	808 (5.9)
Shikoku	326 (2.4)
Kyushu	1,279 (9.4)
Employment status	
Employed (including part-time and temporary workers)	3,164 (23.1)
Unemployed	10,510 (76.9)
Age distribution of children	
0 yr	3,107 (20.5)
1 yr	5,930 (39.1)
2 yr	6,100 (40.3)

Table 2. Incidence of RVGE and influenza episodes

Age of children (months)	Incidence (per 1,000 person-years)			
	RVGE	(95% CI)	Influenza	(95%CI)
0–11	116	(115–127)	124	(112–135)
12–23	336	(324–348)	317	(305–329)
24–35	247	(236–258)	360	(348–373)
0–35	255	(248–262)	295	(287–302)

RVGE, rotavirus gastroenteritis.

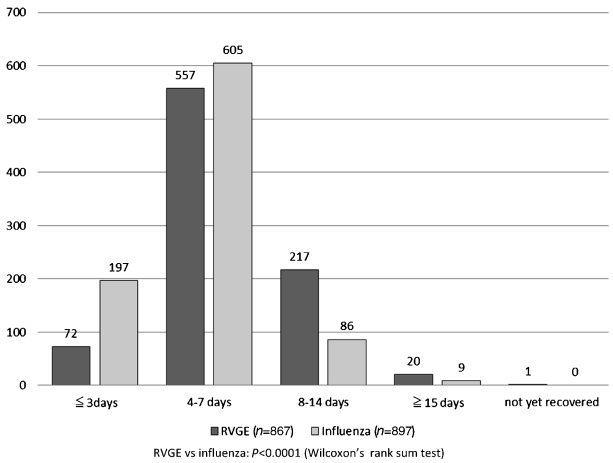

Fig. 3. Duration of illness. Dark gray bars represent RVGE patients and light gray bars represent influenza patients. The difference between children with RVGE and those with influenza was statistically significant ($P < 0.0001$) by the Wilcoxon's rank-sum test.

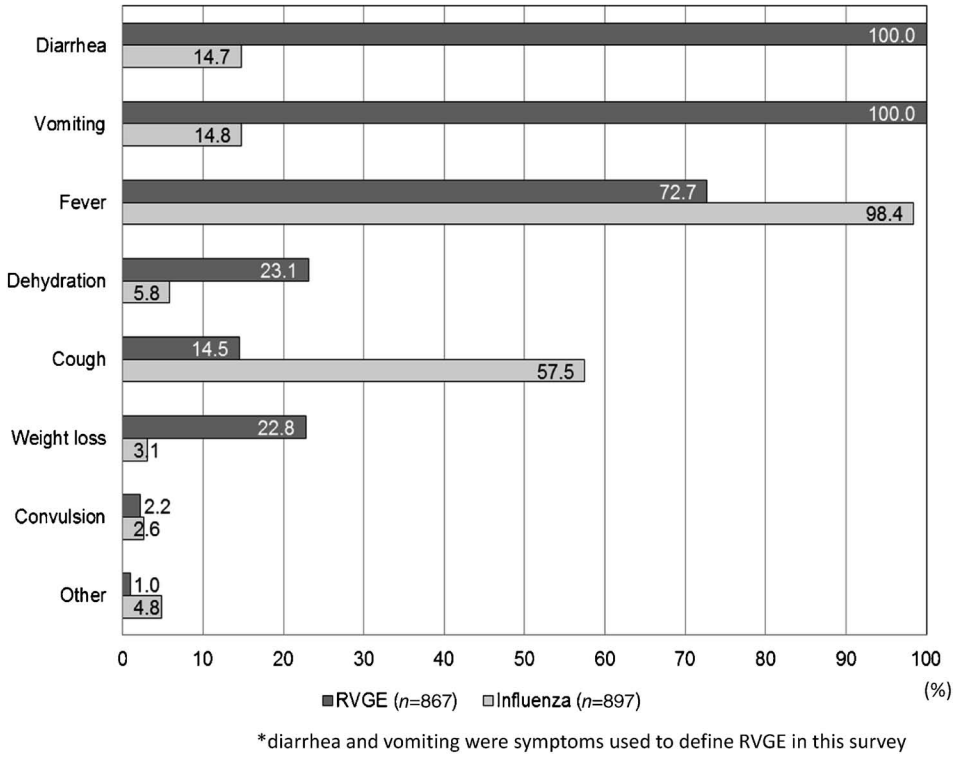

Fig. 2. Major symptoms during RVGE and influenza episodes as observed by the mothers of afflicted children. Dark gray bars represent RVGE patients and light gray bars represent influenza patients. *The presence of both diarrhea and vomiting were symptoms used to validate the memory of the mothers who reported that their child had experienced physician-diagnosed RVGE; therefore, the percentages of these symptoms were 100% in children with RVGE.

travenous rehydration, 63 (7.3%) were hospitalized, and 132 (15%) visited an emergency department (Fig. 4); these values were significantly higher than those for the children with influenza ($P < 0.0001$, χ^2 test). However, the median length of hospital stay was 5 days for both children with RVGE and those with influenza. Regarding intravenous fluid administration in children with RVGE, 75% (184/247) were treated in an outpatient department. The proportion of children who received intravenous rehydration was similar in all age groups ($P = 0.478$), as was the proportion of children who were hospitalized ($P = 0.653$).

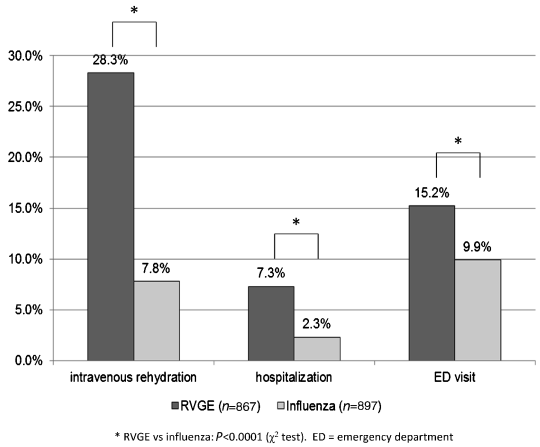

Fig. 4. Proportion of children who required intravenous rehydration, hospitalization, and/or an emergency department visit. Dark gray bars represent RVGE patients and light gray bars represent influenza patients. *The difference between children with RVGE and those with influenza was statistically significant ($P < 0.0001$) by the chi-square test. ED, emergency department.

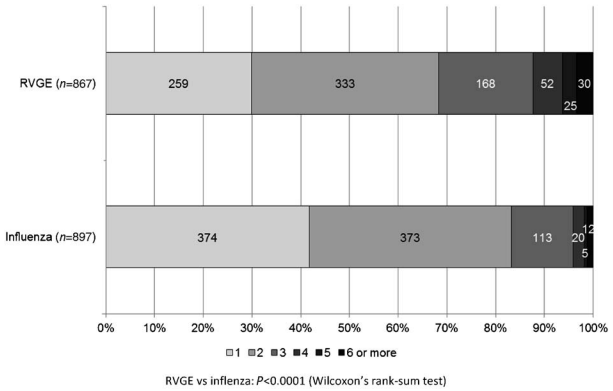

Fig. 5. The number of physician visits during each episode. The difference between children with RVGE and those with influenza was statistically significant ($P < 0.0001$) by Wilcoxon's rank-sum test.

Number of physician visits: Children with RVGE visited physicians more frequently (2 or more times, 70%; 3 or more times, 32%) compared with children with influenza (2 or more times, 58%; 3 or more times, 17%; $P < 0.0001$, Wilcoxon's rank-sum test; Fig. 5). The proportion of children with RVGE who received intravenous rehydration was higher among those who visited physicians at least twice (35%) than among those who visited physicians only once (14%; $P < 0.0001$, χ^2 test). While only 7.3% (63/867) children with RVGE were treated in a hospital, 83% (52/63) were hospitalized after 2 or more physician visits, and 81% (42/52) of the hospitalizations were because of exacerbation of illness (Table 3). These results suggest that only a small proportion of children with RVGE were ill enough to be hospitalized at the beginning of the illness; a vast majority required hospitalization in the advanced stage of the disease.

DISCUSSION

This is the first Japanese nationwide study, to the best of our knowledge, to assess the burden incurred by RVGE in comparison with the burden incurred by influenza, another common infection with winter seasonality. Notably, this study showed that the incidence of RVGE during peak epidemic months (January–April) was almost as high as that of influenza in children aged <3 years. The incidence rate of 255 RVGE episodes per 1,000 person-years (i.e., 21 RVGE episodes per 1,000 person-months) as determined in this study indicates that approximately 1 in 12 children aged <3 years will experience RVGE during the peak epidemic months in Japan and that approximately 1 in 9 children aged 12–23 months will suffer from RVGE.

With regard to the clinical consequences of RVGE, our results indicated that RVGE imposed as large a burden on affected children as influenza did. However, 25% of children with RVGE required 8–14 days for recovery, suggesting that RVGE can persist longer than influenza. This may be because of the lack of effective antiviral drugs for RVGE, as opposed to the easy availability of drugs for influenza, which are useful to decrease the duration of fever (12). The time to recovery in patients with RVGE, including primary care patients, has rarely been reported, although Sénécal et al. reported that diarrhea, vomiting, and fever lasted for a median of 8 days in RVGE patients aged <3 years

Table 3. Percentage of children with RVGE who received intravenous rehydration and/or needed hospitalization according to the number of physician visits

No. of medical facility visits	No. of RVGE children	Intravenous rehydration No. (%)	Hospitalization No. (%)
1 visit	259	35 (14)	11 (4.2)
2 or more visits	608	212 (35)	52 (8.6)
because of acute exacerbation	298	127 (43)	42 (14)
not because of acute exacerbation	310	85 (27)	10 (3.2)
Total	867	247 (28)	63 (7.3)

attending 59 clinics in Canada (13).

Moreover, the proportion of children who required intravenous rehydration, hospitalization, and/or an emergency department visit was significantly higher among those with RVGE than among those with influenza. Although the criteria to define RVGE was biased to exclude less severe cases by requiring the presence of both diarrhea and vomiting, the differences may also be explained by the lack of effective anti-viral drugs for RVGE, while anti-influenza drugs have already decreased the burden of influenza. Several primary-care-based epidemiological studies have investigated the proportions of children aged <5 years who were hospitalized with RVGE. In a study conducted in seven European countries (14), the proportion of hospitalization varied from 10.4% in Germany to 36% in Sweden. In another study conducted in 6 European countries, the proportion of hospitalization varied from 1.0% in Spain to 10.0% in Germany (15). Sénécal et al. reported that hospitalization was required in 12.9% of RVGE patients aged <3 years who visited 59 clinics in Canada (13), while Carlos et al. reported a hospitalization rate of 35% among RVGE patients aged <5 years who visited seven clinics/hospitals in Muntinlupa City, the Philippines (16).

Although it is not possible to make a direct comparison between countries because of differences in healthcare practices, the proportion of children hospitalized in the present study was 7.3% (1 of 14 children with RVGE), which is within the range reported in the aforementioned studies (13–16). The relatively small portion of children hospitalized may reflect a higher incidence of physician visits in Japan; this is consistent with the findings of a study by Yokoo et al. (11), who reported that nearly 50% children visited physicians for the treatment of RVGE by the age of 6 years. In this regard, it is also noteworthy that nearly 75% intravenous rehydration therapies were administered in outpatient clinics in our study (Table 3). Because the need for intravenous rehydration is the major reason for hospitalization, this practice may also have contributed to the lower percentage of hospitalization among all children with RVGE in Japan.

The current study was the first to reveal that only a small proportion (17%) of children who eventually required hospitalization for RVGE were ill enough to be hospitalized at the beginning of the illness; a vast majority were hospitalized during the advanced stage of the disease. Therefore, it is conceivable that hospital-based studies face difficulties in following the progression of the illness and the number of physician visits because not all patients receive treatment in the same hospital or clinic throughout the course of an RVGE episode.

This study had some limitations as outlined below: (i) Accuracy of disease episodes: The present analysis was based on data received via an internet-based survey that relied on mothers' recollection of thier child(ren)'s illnesses; therefore, it was possible that non-RVGE episodes could have been erroneously included. To minimize this error, RVGE was defined as a physician-diagnosed RVGE episode with both diarrhea and vomiting in the absence of blood-stained stools. Only those children with RVGE episodes who displayed these symptoms were included in the RVGE survey. In addition, this survey was conducted in May 2011, a period immediately after the epidemic season, to minimize recall bias. The incidence of fever (73%) in the present study was consistent with that reported in previous overseas studies (13–16). Therefore, the high incidnce of fever in the presence of both diarrhea and vomiting (the inclusion criteria) suggests that RVGE episodes were less likely to be misidentified in the present study. All physician-diagnosed influenza episodes reported by the mothers were included in the survey because diagnosis of influenza using point-of-care diagnostic kits is a very common practice for the immediate prescription of anti-influenza drugs in Japan (12). (ii) Bias resulting from the selection of only internet users: The present study used data from an internet-based survey in which responses to questions were received online, therefore, the respondents were limited to those who had access to the internet. In addition, we obtained no data concerning the internet penetration rate among the target population. However, internet access was unlikely to have affected the survey results, given that RVGE occurs irrespective of economic disparity (17). Moreover, direct medical costs for young children in Japan are virtually free of charge because they are covered by a universal health insurance program that is subsidized by local governmental healthcare plans. Therefore, we estimated that the potential bias due to economic status of mothers with internet access was relatively small compared with the benefit of obtaining reliable information from internet-literate mothers.

The present nationwide internet-based survey that targeted mothers with a child aged <3 years, revealed that the incidence of RVGE and influenza was 255 and 295 per 1,000 person-years, respectively. We found that 1 in 4 children with RVGE required more than 1 week for recovery, 1 in 4 received intravenous rehydration, 1 in 14 was hospitalized, 1 in 7 visited an emergency department, and 70% and 32% sought medical intervention at least 2 or 3 times, respectively. Compared with influenza, RVGE required a longer time for recovery; more frequent intravenous rehydration, hospitalization, emergency department visits, and more recurrent physician visits. In addition, the proportion of children who received intravenous rehydration and/or hospitalization because of worsening symptoms over time increased according to the progression of the illness. Our results indicate that, like influenza, RVGE occurring during peak epidemic months in children aged <3 years imposes a substantial burden on families and medical institutions in Japan.

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Conflict of interest KK was employed by GSK Japan and is employed by Japan Vaccine Co., Ltd., a GSK Japan-related company. TN, HT, and ON received honoraria for lectures on rotavirus and rotavirus vaccines in meetings supported by GSK Japan and/or MSD.

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