

Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes (MIRAGE): A prospective community-based study

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BACKGROUND: Current assessments of the burden of rotavirus (RV)-related gastroenteritis are needed to evaluate the potential benefits of RV immunization interventions. The objective of the present study was to characterize the burden of RV gastroenteritis among children presenting in outpatient settings with gastroenteritis.

METHODS: Between January and June 2005, 395 children younger than three years of age presenting with gastroenteritis symptoms (at least three watery or looser-than-normal stools, or forceful vomiting within the previous 24 h period) were recruited from 59 Canadian clinics and followed for two weeks. Stool specimens were tested for the RV antigen. Gastroenteritis-related symptoms, health care utilization, parental work loss and other cases of gastroenteritis in the household were assessed by questionnaires and daily symptom cards that were completed by caregivers.

RESULTS: Of 336 conclusive test results, 55.4% were RV positive (RV+). In addition to diarrhea, 67.2% and 89.3% of RV+ children experienced fever or vomiting, respectively. Compared with RV-negative (RV-) children, RV+ children were more likely to experience the three symptoms concurrently (57.0% versus 26.7%; $P < 0.001$), to be hospitalized (12.9% versus 3.9%; $P = 0.008$) and to induce parental work loss (53.8% versus 37.3%; $P = 0.003$). The median duration of gastroenteritis was eight days for RV+ children (nine days for RV- children). Additional cases of gastroenteritis were present in 46.8% of households in the RV+ group (51.3% of households in the RV- group).

CONCLUSIONS: RV gastroenteritis cases were more severe than other gastroenteritis cases, were hospitalized more often and were associated with considerably more work loss.

Key Words: Burden of illness; Gastroenteritis; Health care resource utilization; Rotavirus; Work loss

In both developed and developing countries, rotavirus (RV) remains a major cause of gastroenteritis among infants and young children (1). Severe dehydration that may lead to hospitalization is the most common consequence of RV gastroenteritis. In industrialized countries, RV gastroenteritis is the most frequent cause of hospitalization for dehydrating diarrhea and vomiting (2-9).

L'étude MIRAGE (pour *Measuring the Impact of Rotavirus Acute Gastroenteritis Episodes*) : Étude prospective basée dans la communauté

HISTORIQUE : Il est important de procéder à des évaluations actuelles du fardeau de la gastro-entérite liée au rotavirus (RV) si nous voulons évaluer les avantages potentiels des interventions d'immunisation anti-RV. L'objectif de la présente étude était de caractériser le fardeau de la gastro-entérite à RV chez des enfants non hospitalisés qui en sont atteints.

MÉTHODE : Entre janvier et juin 2005, 395 enfants de moins de trois ans pour des symptômes de gastro-entérite (au moins trois selles liquides ou plus molles que la normale ou vomissements violents au cours des 24 dernières heures) ont été recrutés dans 59 cliniques canadiennes et suivis pendant deux semaines. Les spécimens de selles ont été analysés pour recherche de l'antigène du RV. Les symptômes de gastro-entérite, l'utilisation des soins de santé, l'absentéisme des parents au travail et le déclenchement d'autres cas de gastro-entérite à la maison ont été évalués au moyen de questionnaires et de fiches quotidiennes de symptômes qui ont été complétées par les responsables des soins.

RÉSULTATS : Sur 336 tests concluants, 55,4 % étaient RV-positifs (RV+). En plus de la diarrhée, 67,2 % et 89,3 % des enfants RV+ présentaient respectivement de la fièvre ou des vomissements. Comparativement aux enfants RV-négatifs (RV-), les enfants RV+ étaient plus susceptibles de présenter concomitamment les trois symptômes, 57,0 % contre 26,7 %, $p < 0,001$, d'être hospitalisés 12,9 % contre 3,9 % ($p = 0,008$) et d'entraîner l'absentéisme des parents au travail (53,8 % contre 37,3 %, $p = 0,003$). La durée médiane de la gastro-entérite a été de huit jours chez les enfants RV+ (neuf jours chez les enfants RV-). D'autres cas de gastro-entérite se sont manifestés dans 46,8 % des foyers du groupe RV+ (51,3 % des foyers du groupe RV-).

CONCLUSION : Les cas de gastro-entérite à RV ont été plus graves que les autres cas de gastro-entérite, ont dû être hospitalisés plus souvent et ont été associés à beaucoup plus d'absentéisme au travail.

Recently, vaccines targeting the most common RV strains have been introduced, thus offering protection against RV gastroenteritis, with an anticipated impact on decreasing the associated burden of illness (3,10-17). Given that the burden of RV may not be consistent across different regions and over time, regional data that quantify the various aspects of the current burden of the disease are needed to facilitate the assessment of

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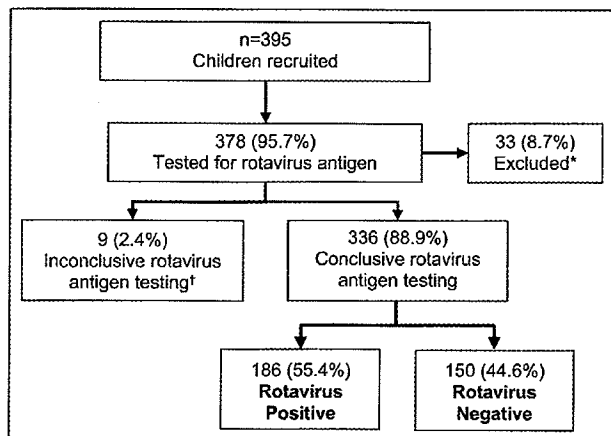


Figure 1) Study flow chart. *Patients for whom gastroenteritis symptoms began more than seven days before baseline physician visit; †Indeterminate result by ELISA testing

the potential benefit of immunization programs. In addition to providing valuable regional information, local studies will contribute to the data that will allow the assessment of the global RV gastroenteritis-related burden of illness, and will allow for the identification of between-region variations with respect to the epidemiology and burden of RV (3,15,18,19).

The current data in the literature have confirmed that RV gastroenteritis burden is significant in the United States (20-22), Europe (3,15,23-32) and Asia (33-42). With respect to Canada, there have been a number of published studies (43-45) that have described the epidemiology of RV gastroenteritis, but none have been conducted recently. Furthermore, Canadian studies (43,45) have mainly described RV gastroenteritis using data from hospitalized children, which limits both the understanding of the clinical presentation of RV gastroenteritis and its related burden of illness at the community level. At this point in time, considering the availability of RV vaccines, there is a need for recent data describing the societal impact of RV gastroenteritis.

The aim of the present prospective, community-based study was to characterize the burden of RV gastroenteritis episodes in infants and young children seeking health care for gastroenteritis in Canada. More specifically, the study describes symptoms, health care utilization, parental work loss and additional household gastroenteritis among children presenting with RV gastroenteritis in Canadian outpatient settings. A secondary objective of the study was to compare these aspects between RV-positive (RV+) and RV-negative (RV-) children experiencing gastroenteritis.

PATIENTS AND METHODS

Study design

The present study was a prospective, multicentre, observational study of children younger than three years of age presenting with gastroenteritis. Cohort inception took place between January 1 and June 31, 2005 – the expected epidemic RV season in Canada. Inclusion in the cohort took place at the time of presentation with gastroenteritis at the participating sites. Follow-up was for two weeks. Patients were enrolled from 59 practices across Canada, of which 28 (47%) were family physician and 31 (53%) were pediatrician practices. The majority of the sites (78.0%) were based in the provinces of Ontario (n=34) and Quebec (n=12). The other sites were based in the following provinces

– British Columbia (n=7), Manitoba (n=3), Saskatchewan (n=2) and Nova Scotia (n=1). Given that enrolment took place during the course of routine clinical practices, it was not feasible to ensure systematic recruitment of all eligible patients or to record all instances of eligible patients whose caregivers declined invitation to take part in the study. Therefore, the proportion of eligible patients who were included in the study sample was not documented.

The protocol and the informed consent sheet were approved by the Canadian SHIELD Ethics Review Board and the College of Physicians & Surgeons of Alberta.

Inclusion and exclusion criteria

To be eligible for inclusion in the study, patients had to be younger than three years of age at the time of presentation to the physicians' offices with gastroenteritis, and informed consent had to be provided by the parents or legal guardians. Inclusion criteria were defined as the presence of at least three watery or looser-than-normal stools, or forceful vomiting within the previous 24 h period. Patients were eligible irrespective of their gastroenteritis history, unless they had a gastroenteritis episode that required hospitalization. In addition, children for whom current gastroenteritis symptom onset was more than seven days before enrolment were excluded from the analysis. Patients were excluded if they had received treatment with antibiotics or immunoglobulins within 30 days before study entry. If the patient or the patient's mother was positive for HIV, hepatitis B or C, or had participated in an RV immunization program, he or she was also excluded from the study.

Data collection

At recruitment, the physician completed the case report form, which included questions about the patient (eg, age, sex, height and weight), and current and past symptoms attributable to the gastroenteritis episode. Caregivers completed a self-administered questionnaire regarding the socioeconomic setting, demographic profile, breastfeeding history and household characteristics, including the age of household members.

Within one week of recruitment, patient stool samples were obtained, refrigerated and shipped on dry ice to the Cincinnati Children's Hospital Medical Center (Ohio, USA). RV testing was conducted using ELISA developed at the James N Gamble Institute of Medical Research (Ohio, USA) (46,47). This test is a multistep procedure that uses a negative capture antibody control to eliminate false-positive reactions and biotin-avidin additions to increase the sensitivity of the assay. To be considered RV+, wells had to have an optic density of at least 0.31 and a positive to negative optic density ratio of at least 1.63. When the background was too high to be conclusive, specimens were diluted up to 1:50. If the values remained indeterminate, the results were reported as inconclusive. No information with respect to other etiological agents that may cause gastroenteritis was documented.

On days 1, 7 and 14 postrecruitment, caregivers completed a self-administered questionnaire that included questions regarding gastroenteritis-related emergency room (ER) visits and hospitalizations. The questionnaire also ascertained the work days lost by the father or the mother because of their child's (ie, the study patient) gastroenteritis episode. To document potential cases of RV transmissions between family members, caregivers were also asked whether there had been other cases of gastroenteritis in the household over a four-week period (from two weeks before to two weeks after enrolment of the study patient). Whether the

TABLE 1
Characteristics of children younger than three years of age presenting to physicians' offices with gastroenteritis*

Characteristic	Rotavirus positive (n=186)	Rotavirus negative (n=150)	P†
Age distribution in months			
<6	10 (5.4)	26 (17.3)	0.013
6-11	52 (28.0)	37 (24.7)	
12-17	53 (28.5)	29 (19.3)	
18-23	33 (17.7)	26 (17.3)	
24-29	17 (9.1)	16 (10.7)	
30-35	21 (11.3)	16 (10.7)	
Sex, male	109 (58.6)	79 (52.7)	0.276
Child care centre attendance	63 (33.9)	45 (30.0)	0.450
Ever been breastfed	122 (66.0)	111 (75.0)	0.073
At least one parent unemployed or on parental leave	98 (55.4)	83 (59.3)	0.484
Family income (\$)			
≤19,999	10 (5.4)	8 (5.3)	0.942
20,000-49,999	39 (21.0)	37 (24.7)	
50,000-69,999	22 (11.8)	18 (12.0)	
≥70,000	80 (43.0)	62 (41.3)	
Decline to reply	35 (18.8)	25 (16.7)	

Data are n (%) of patients. *Percentages reflect only patients for whom the information was available; †Statistical significance of the observed differences was determined using the χ^2 test for distributions of categorical variables and the Student's *t* test for means of continuous variables

other gastroenteritis episodes in the household began before or after the study patient's illness was not documented.

During the two-week follow-up, caregivers also completed daily symptom diary cards that recorded the presence and duration of diarrhea, vomiting and fever. Confirmed presence of diarrhea was defined as at least two watery or looser-than-normal stools per day; presence of fever was defined as a body temperature higher than 38°C at any time. During the two-week study follow-up period, caregivers were not aware of the RV results.

Statistical analysis

For each day of the study observation period (beginning from seven days before to 14 days after the baseline date), the proportion of patients with diarrhea, vomiting or fever, and with all three symptoms concurrently were described. The duration of each gastroenteritis episode was defined as the time elapsed from the onset of the first symptom (diarrhea, vomiting or fever) until all symptoms were resolved. An episode of diarrhea, vomiting or fever was assumed to be resolved when the specific symptom was absent for three consecutive days. In the data analysis, only the first incidence of each symptom was included; the occurrence of subsequent symptom incidences was not included in the analysis. For example, if diarrhea was reported on days 1 to 3 and then again on days 12 to 13, only the first incidence occurring from days 1 to 3 was included. The duration of a symptom episode was censored if it was still present at the end of follow-up or if an episode was reported at enrolment, but follow-up data for the episode were missing. When a symptom was not reported at enrolment and follow-up diary cards were not completed, the child was considered as not having experienced the symptom over the course of the disease.

TABLE 2
Symptoms experienced by children younger than three years of age who sought physician care because of gastroenteritis

	Rotavirus positive (n=186)	Rotavirus negative (n=150)	P*
Number of days between onset of the first symptom and baseline physician visit, mean \pm SD	2.9 \pm 1.7	3.0 \pm 1.8	0.397
Symptoms experienced over the course of the disease, n (%)			
Diarrhea	186 (100.0)	146 (97.3)	0.025
Vomiting	166 (89.3)	99 (66.0)	<0.001
Fever	125 (67.2)	80 (53.3)	0.010
Symptom episodes beginning after baseline physician visit†, n (%)			
Diarrhea	0 (0.0)	3 (2.1)	0.050
Vomiting (n=166)	6 (3.6)	21 (21.2)	<0.001
Fever (n=125)	32 (25.6)	39 (48.8)	<0.001
Combination of symptoms, n (%)			
Single symptom	10 (5.4)	33 (22.0)	<0.001
Diarrhea and fever, but no vomiting	10 (5.4)	22 (14.7)	
Diarrhea and vomiting, but no fever	51 (27.4)	37 (24.7)	
Diarrhea, vomiting and fever	115 (61.8)	58 (38.7)	
Intensity of symptoms reported at baseline physician visit‡, mean \pm SD			
Daily frequency of diarrhea§	5.4 \pm 3.5	5.1 \pm 2.5	0.254
Daily frequency of vomiting	4.3 \pm 3.0	2.8 \pm 2.1	<0.001
Highest recorded temperature (°C)	39.3 \pm 0.8	39.0 \pm 0.8	0.144
Duration of episodes, days, median (25th-75th percentile)¶			
Diarrhea	7 (5-10)	8 (6-12)	0.010
Vomiting	4 (3-6)	4 (2-6)	0.532
Fever	4 (2-5)	4 (2-6)	0.877
Gastroenteritis episode (any of the three symptoms)	8 (6-10)	9 (7-13)	<0.001
Duration with three concurrent symptoms, %¶¶			
≥1 day	57.0	26.7	<0.001
≥2 days	45.8	14.7	
≥4 days	23.7	3.2	

*Statistical significance of the observed differences was determined using the χ^2 test for distributions of categorical variables, the Student's *t* test for means of continuous variables and the log-rank test for durations; †The percentage is based on the number of children having experienced the symptom; ‡Represents episodes which began before baseline physician visit; §Number of watery or looser-than-normal stools; ¶Product-limit estimates

Work loss related to the gastroenteritis episode was described as the proportion of patients whose parents required time off from work. Similarly, the presence of other gastroenteritis episodes in family members was described as the proportion of patients whose household members experienced gastroenteritis during the two-week period before or the two-week period after the baseline visit, as well as the proportion of household members having experienced gastroenteritis during the four-week time window.

Gastroenteritis-related parameters were compared between RV+ and RV- groups. Student's *t* tests and χ^2 tests were used to assess the statistical significance of differences between means of

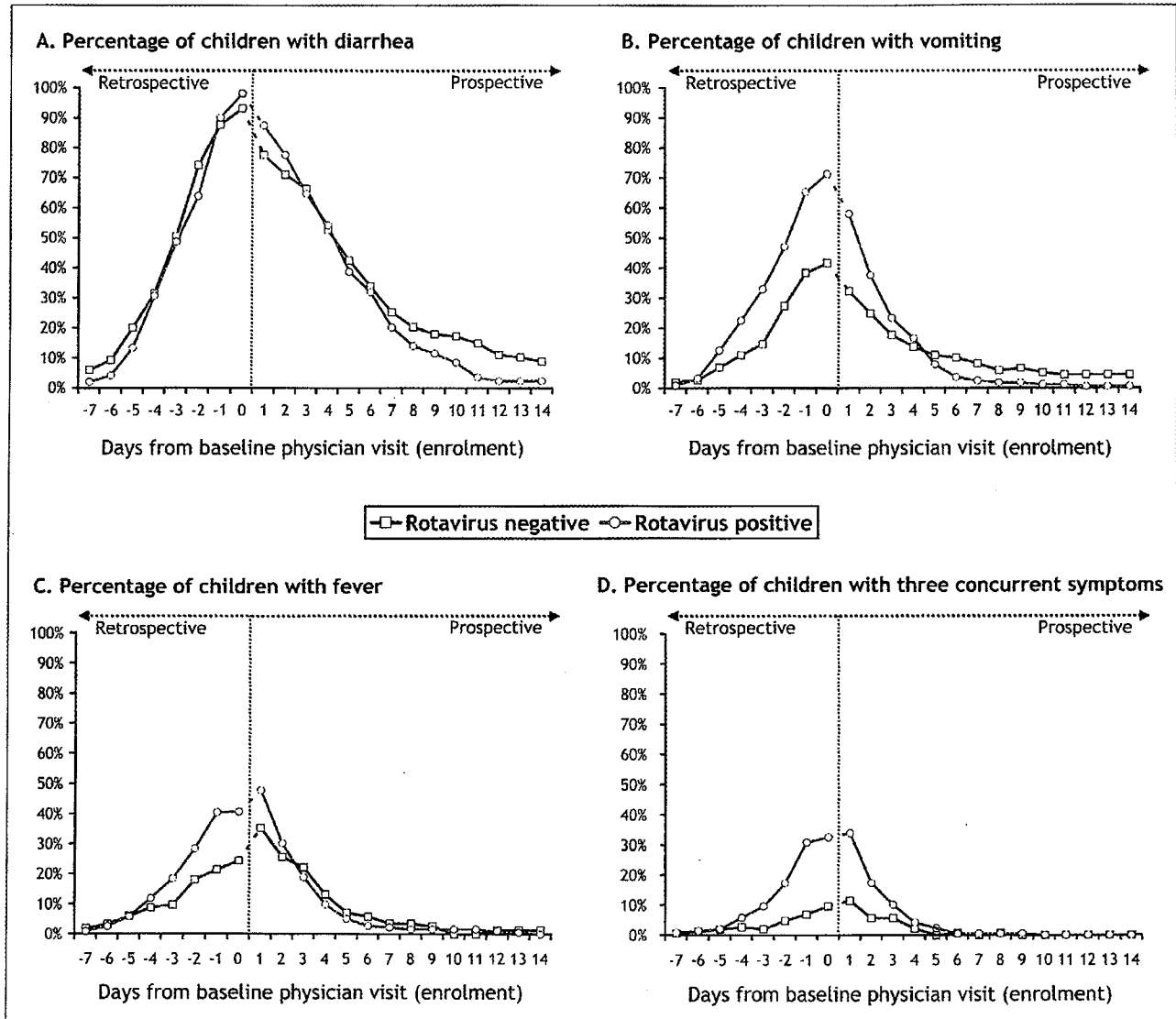


Figure 2) Presence of gastroenteritis symptoms over time – period going from seven days before baseline physician visit to 14 days after baseline physician visit (enrolment). At enrolment (day 0), the presence of symptoms for day -7 to day 0 was documented retrospectively by asking simple questions of caregivers about the presence and the onset of gastroenteritis symptoms. For day 1 to day 14, the daily presence of symptoms was documented prospectively through symptoms diary cards completed by caregivers

continuous variables and distributions of categorical variables, respectively. For each age group, the proportion of household members who experienced gastroenteritis was compared between the RV+ and RV- groups using logistic regression models with generalized estimating equations, which take into account the correlation between members of the same household. The duration of symptoms was analyzed using the Kaplan-Meier estimation method, and the statistical significance of differences between RV+ and RV- gastroenteritis cases with respect to the duration of symptoms was assessed using log-rank tests.

RESULTS

Study population

A total of 395 children were recruited, 378 (95.7%) of whom had their stools tested for RV antigen. There were 33 (8.7%) (14 RV+; 19 RV-) patients who were excluded from the analysis

due to symptom onset of more than seven days before enrolment. Nine (2.4%) additional children were excluded due to inconclusive RV test results. Of the remaining 336 children, 186 (55.4%) were RV+ and 150 (44.6%) were RV- (Figure 1). The two symptom diary cards were returned for 285 (84.8%) patients (86.0% RV+ and 83.3% RV-).

Description of study sample

The age distribution of children with RV+ and RV- gastroenteritis differed significantly ($P=0.013$), with the proportion of patients younger than six months of age in the RV- group being higher than the proportion of patients in the RV+ group (Table 1). Although not statistically significant, a higher proportion of RV- children had been breastfed compared with the RV+ group. Other baseline characteristics, including sex, child care, parents' employment status and family income were similar between RV+ and RV- patients (Table 1).