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Norovirus and Medically Attended Gastroenteritis in U.S. Children

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Abstract

BACKGROUND—Cases of rotavirus-associated acute gastroenteritis have declined since the introduction of rotavirus vaccines, but the burden of norovirus-associated acute gastroenteritis in children remains to be assessed.

METHODS—We conducted active surveillance for laboratory-confirmed cases of norovirus among children younger than 5 years of age with acute gastroenteritis in hospitals, emergency departments, and outpatient clinical settings. The children resided in one of three U.S. counties during the years 2009 and 2010. Fecal specimens were tested for norovirus and rotavirus. We calculated population-based rates of norovirus-associated acute gastroenteritis and reviewed billing records to determine medical costs; these data were extrapolated to the U.S. population of children younger than 5 years of age.

RESULTS—Norovirus was detected in 21% of young children (278 of 1295) seeking medical attention for acute gastroenteritis in 2009 and 2010, with norovirus detected in 22% (165 of 742) in 2009 and 20% (113 of 553) in 2010 (P = 0.43). The virus was also detected in 4% of healthy controls (19 of 493) in 2009. Rotavirus was identified in 12% of children with acute gastroenteritis

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(152 of 1295) in 2009 and 2010. The respective rates of hospitalization, emergency department visits, and outpatient visits for the norovirus were 8.6, 146.7, and 367.7 per 10,000 children younger than 5 years of age in 2009 and 5.8, 134.3, and 260.1 per 10,000 in 2010, with an estimated cost per episode of $3,918, $435, and $151, respectively, in 2009. Nationally, we estimate that the average numbers of annual hospitalizations, emergency department visits, and outpatient visits due to norovirus infection in 2009 and 2010 among U.S. children in this age group exceeded 14,000, 281,000, and 627,000, respectively, with more than $273 million in treatment costs each year.

CONCLUSIONS—Since the introduction of rotavirus vaccines, norovirus has become the leading cause of medically attended acute gastroenteritis in U.S. children and is associated with nearly 1 million health care visits annually. (Funded by the Centers for Disease Control and Prevention.)

Norovirus-associated acute gastroenteritis is characterized by the sudden onset of intense vomiting and dehydrating diarrhea, typically lasting 1 to 3 days, with high rates of transmission to persons of all ages.[1] Norovirus is a leading etiologic pathogen implicated in severe gastroenteritis outbreaks in the United States.[2,3] However, the endemic burden of norovirus-associated acute gastroenteritis identified through active, laboratory-confirmed surveillance of U.S. pediatric populations has not been fully characterized.

Given the substantial decline in pediatric rotavirus-associated acute gastroenteritis in the United States since the introduction of rotavirus vaccines,[4–8] and given recent advances in the development of candidate norovirus vaccines,[9–12] there is a need to directly measure the pediatric health care burden of norovirus-associated acute gastroenteritis.

In this prospective study, we identified cases of norovirus-associated acute gastroenteritis occurring in hospitals, emergency departments, and outpatient clinical settings in three defined county populations for two consecutive 12-month periods in order to calculate year-round rates of laboratory-confirmed, medically attended norovirus acute gastroenteritis in U.S. children younger than 5 years of age.

METHODS

ACTIVE, POPULATION-BASED SURVEILLANCE METHODS

The New Vaccine Surveillance Network (NVSN) (and the county populations represented at each site) includes the University of Rochester Medical Center (Monroe County, New York), Vanderbilt University Medical Center (Davidson County, Tennessee), and Cincinnati Children's Hospital Medical Center (Hamilton County, Ohio), hereafter referred to as Rochester, Nashville, and Cincinnati.[13] Each surveillance site cared for more than 95% of hospitalized children residing in their respective counties, providing a catchment population exceeding 141,000 children younger than 5 years of age. Approval for the study was obtained from the institutional review board at each site and from the Centers for Disease Control and Prevention.

The children included in the study were younger than 5 years of age, had symptoms of acute gastroenteritis (diarrhea [≥3 episodes within 24 hours], vomiting [≥1 episode within 24

hours], or both) with a duration of no more than 10 days, and were enrolled at hospitals, emergency departments, and outpatient clinics during two consecutive periods, October 2008 through September 2009 (referred to as the year 2009) and October 2009 through September 2010 (referred to as 2010). Children who had noninfectious diarrhea, were reported to have clinical immunodeficiency, had previously been enrolled for the same gastroenteritis episode, or had been transferred from another hospital after an admission of more than 48 hours were excluded. Whole stool specimens were obtained within 10 days after the date of visit or admission for symptoms of acute gastroenteritis (mean, 1.1 days; median, 0 days).

Healthy controls were children younger than 5 years of age who were systematically enrolled on arrival at scheduled well-child visits during 2009 and had no reported clinical immunodeficiency, no symptoms of acute gastroenteritis within 14 days before enrollment, and no symptoms of acute respiratory infection (cough, congestion, sore throat, runny nose, or wheezing) within 3 days before enrollment. The enrollment of healthy controls was frequency-matched to the enrollment of patients with acute gastroenteritis on the basis of age and calendar month; stool specimens from controls were collected within 5 days after enrollment.

Demographic, epidemiologic, and clinical data were systematically collected, as were data on verification of vaccination by a health care provider. Whole stool specimens from patients with acute gastroenteritis and from healthy controls were tested for norovirus genogroups GI and GII with the use of real-time reverse-transcriptase–poly-merase-chain-reaction (RT-PCR) assays (TaqMan, Life Technologies), and positive samples were genotyped by sequencing conventional RT-PCR products and comparing the results with norovirus prototype strains.[14] Stools were tested for rotavirus with the use of a commercial rotavirus enzyme immunoassay (Rotaclone, Meridian Bio-science).

DETERMINATION OF HOSPITALIZATION AND VISIT RATES

Rates of hospitalization per 10,000 children for norovirus infection and for rotavirus infection were calculated with the use of the weighted number of laboratory-confirmed hospitalizations divided by the number of children within the age cohort in the county population according to data from the U.S. Census. Weighting was performed to account for the number of surveillance days, the proportion of eligible children enrolled, and the percentages of stool specimens collected and tested.[13] We calculated 95% confidence intervals on the basis of 1000 bootstrap samples for each rate and used the resulting 2.5 and 97.5 percentiles as the lower and upper bounds of the confidence intervals, respectively.

The rates of visits to the emergency department for norovirus infection and for rotavirus infection were calculated by multiplying the proportions of children with positive test results who were actively enrolled in each emergency department by the number of visits to the emergency department for acute gastroenteritis from any cause during the full 24-hour surveillance period. We weighted our data to account for the proportion of county residents younger than 5 years of age who used emergency department medical services at the NVSN facilities where surveillance was conducted (rates of capture were 63% for the emergency

department in Nashville and 95% for the departments in Rochester and Cincinnati); precise calculation of 95% confidence intervals was precluded.[15]

Sentinel surveillance was used for rates of outpatient visits at NVSN sites. We estimated the burden of disease from norovirus infection and from rotavirus infection in outpatient clinical settings by multiplying the proportions of outpatients with positive test results for norovirus or rotavirus by the number of patients with acute gastroenteritis from any cause as identified in two national, complementary data sets using the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM). Data from the National Hospital Ambulatory Medical Care Survey (NHAMCS) and the National Ambulatory Medical Care Survey (NAMCS) represented visits to outpatient departments and medical offices, respectively, among children younger than 5 years of age in 2009 and 2010.

MEDICAL COST ESTIMATES

We obtained patient-level medical-billing data from the administrative and billing departments at NVSN sites for patients with positive test results for norovirus in 2009 and complete ICD-9-CM–coded discharge diagnoses for 2009 and 2010. These data were reviewed retrospectively to estimate norovirus-related health care costs and the frequency with which the norovirus ICD-9-CM code (008.63) was used.

By applying the average NVSN rates in 2009 and 2010 to the annual U.S. population younger than 5 years of age (approximately 20 million children),[15,16] we estimated the national incidence of medically attended visits for norovirus infection. Applying the median costs for hospitalizations, emergency department visits, and outpatient clinic visits for norovirus infection to these figures, we estimated national medical costs, expressed in 2009 U.S. dollars.

STATISTICAL ANALYSIS

For comparisons of demographic and epidemiologic characteristics, we used chi-square tests for categorical variables and Wilcoxon rank-sum or Kruskal–Wallis tests for continuous variables.

RESULTS

CASES OF NOROVIRUS INFECTION DETECTED

Of 2647 children with acute gastroenteritis, 1897 (72%) were enrolled as NVSN patients during 2 years of prospective surveillance (1077 in 2009 and 820 in 2010); 806 healthy controls were enrolled in 2009 only (Fig. 1). Among all enrolled children, norovirus testing was conducted on fecal specimens from 1295 children with acute gastroenteritis and 493 healthy controls. Overall, norovirus was detected in 278 of 1295 children with acute gastroenteritis (21%) (Fig. 1), including 165 of 742 children (22%) in 2009 and 113 of 553 (20%) in 2010 (P = 0.43). In 2009, norovirus was detected in 19 of the 493 healthy controls (4%). In comparison, rotavirus was detected (with the use of enzyme immunoassay) in 152 of the 1295 children with acute gastroenteritis (12%) in 2009 and 2010 combined (141 of 742 children with acute gastroenteritis [19%] in 2009 and 11 of 553 [2%] in 2010) and in 1

healthy control (<1%) in 2009. Five children with acute gastroenteritis (<1%) were coinfected with norovirus and rotavirus.

DETECTION ACCORDING TO SETTING, SITE, AGE, AND MONTH

For 2009 and 2010 combined, norovirus was detected in fecal specimens from 86 (17%) of the 514 children hospitalized with acute gastroenteritis, 139 (23%) of the 595 children seen in emergency departments, and 53 (28%) of the 186 outpatients seen in other clinical settings; there were no significant differences according to year between any of the clinical settings (Table 1). In comparison, rotavirus was detected in 69 (13%) of the hospitalized children, 72 (12%) of the children seen in emergency departments, and 11 (6%) of the outpatients seen in other clinical settings, and the differences according to year were significant.

Nearly half (47%) of all medically attended norovirus infections occurred in children who were 6 to 18 months of age. The mean age of children with acute gastroenteritis who had positive test results for norovirus was 17.0 months (median, 14) (Table 1). The average age of the healthy controls was 14.4 months (median, 10). The peak period for the onset of symptoms of norovirus infection was January in both 2009 and 2010; there were cases of symptom onset during the summer months, but at a much lower frequency (Fig. 2).

NOROVIRUS GENOTYPES

Of the 147 samples that were positive for norovirus in 2009 and could be genotyped, 142 (97%) showed infection with GII and 5 (3%) with GI. In 2009, GII.4 Minerva (2006b) was the most frequently detected type (in 71% of positive specimens), followed by GII.12 (in 11%); in the remaining 18% of positive samples, the genotypes identified included GII.3, GII.4 New Orleans, GII.4 Yerseke (2006a), GII.6, GII.7, GII.14, and GII.21. In 2010, among 100 samples genotyped, the predominant genotype was GII.4 New Orleans (in 35% of samples), followed by GII.12 (21%), GII.13 (16%), and GII.1 (12%); genotypes included in the remaining 16% of positive samples were GI.6, GI.7, GII.2, GII.3, GII.6, and GII.7 (see Fig. 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Among the 19 samples from healthy controls in 2009 that were positive for norovirus, 11 were successfully genotyped; GII.4 Minerva was identified in 5 samples (45%), and the other types identified were GI.4, GII.3, GII.6, and GII.12.

RATES OF HOSPITALIZATION AND EMERGENCY DEPARTMENT AND OUTPATIENT VISITS

Norovirus Infection—Among children younger than 5 years of age in the three NVSN surveillance counties, the rates of hospitalization for acute gastroenteritis due to laboratory-confirmed norovirus infection were 8.6 per 10,000 children (95% confidence interval [CI], 6.6 to 10.7) in 2009 and 5.8 per 10,000 (95% CI, 3.9 to 7.9) in 2010, for a mean rate of 7.2 per 10,000 (95% CI, 5.8 to 8.7) over the 2-year period (Fig. 3, and Fig. 1 in the Supplementary Appendix). During both years, rates of hospitalization for norovirus-associated acute gastroenteritis were highest among infants (16.7 per 10,000 [95% CI, 10.1 to 24.2] in 2009 and 11.0 per 10,000 [95% CI, 5.7 to 16.7] in 2010) and among 1-year-old

children (17.3 per 10,000 [95% CI, 10.7 to 24.7] in 2009 and 10.3 per 10,000 [95% CI, 4.5 to 16.4] in 2010) (Fig. 4).

Nearly one quarter of children with acute gastroenteritis who were seen in the emergency department had positive test results for norovirus (24% in 2009 and 23% in 2010). Norovirus-associated emergency department visits in 2009 and 2010 occurred at rates of 146.7 and 134.3 per 10,000 children younger than 5 years of age, respectively (mean rate, 140.7 per 10,000) (Fig. 3, and Fig. 1 in the Supplementary Appendix).

In 2009 and 2010, norovirus infections were confirmed by laboratory testing in 32% and 24%, respectively, of children with acute gastroenteritis who were seen in outpatient clinics. The combined NAMCS and NHAMCS rates of outpatient visits for acute gastroenteritis of any cause were 1145.4 per 10,000 children younger than 5 years of age and 1093.0 per 10,000 for the corresponding time frames. Applying the proportions of patients visiting outpatient clinics who had positive test results for norovirus to these national data sets, we estimate that the rates of outpatient visits for norovirus infection were 367.7 per 10,000 U.S. children younger than 5 years of age (95% CI, 204.1 to 531.3) in 2009 and 260.1 (95% CI, 183.5 to 336.7) per 10,000 in 2010. The mean adjusted outpatient rate for the 2 years was 319.0 per 10,000 children younger than 5 years of age.

Rotavirus Infection—Rates of hospitalization and emergency department and outpatient visits for rotavirus infection fluctuated dramatically between 2009 and 2010. In 2009, the hospitalization rate was 11.6 per 10,000 children younger than 5 years of age (95% CI, 9.0 to 14.6), as compared with 1.1 per 10,000 (95% CI, 0.4 to 1.9) in 2010, with most infections occurring in the youngest children (Fig. 3). Hospitalization rates for rotavirus infection among 1-year-old children in 2009 and 2010 (13.8 per 10,000 [95% CI, 7.6 to 22.2] and 3.1 per 10,000 [95% CI, 0.7 to 6.5], respectively) were both lower than the hospitalization rates for norovirus infection (Fig. 4). The rate of emergency department visits for rotavirus infection was 111.1 per 10,000 children younger than 5 years of age in 2009, as compared with 8.3 per 10,000 in 2010, a difference that was consistent among the individual surveillance sites (Fig. 3, and Fig. 1 in the Supplementary Appendix).

Applying the proportion of outpatient visits attributable to rotavirus infection in 2009 (10.4%) and 2010 (0%) to the combined NAMCS and NHAMCS rate for acute gastroenteritis from any cause in these years, we estimated that 119.1 outpatient visits per 10,000 U.S. children younger than 5 years of age (95% CI, 66.1 to 172.1) were associated with rotavirus infection in 2009; the incidence in 2010 was too low to extrapolate to the U.S. population of children (Fig. 3).

ESTIMATED COSTS

In 2009 U.S. dollars, the median costs for norovirus-associated hospitalizations, emergency department visits, and outpatient visits were $3,918 (mean, $4,948), $435 (mean, $876), and $151 (mean, $490), respectively. None of the 278 laboratory-confirmed cases of norovirus infection identified through active surveillance were assigned an ICD-9-CM code indicating that an independent, clinical diagnosis of norovirus infection had been made. On the basis of the average number of annual health care visits associated with norovirus in 2009 and 2010

among U.S. children younger than 5 years of age, which exceeded 14,000 hospitalizations, 281,000 emergency department visits, and 627,000 outpatient visits, we estimate that the treatment costs amounted to more than $273 million each year.

DISCUSSION

With the continuing decline in cases of rotavirus-associated gastroenteritis since the introduction of rotavirus vaccines,[5,6,17] norovirus infection has become the leading cause of medically attended acute gastroenteritis among U.S. children younger than 5 years of age. Extrapolating our surveillance results for this population, we found that norovirus infections are associated with nearly 1 million health care visits per year. According to our estimations, by their fifth birthday, 1 in 278 U.S. children are hospitalized for norovirus infection, 1 in 14 are seen in the emergency department, and 1 in 6 are seen by outpatient care providers (Fig. 3 in the Supplementary Appendix).

The disease burden of norovirus infection was consistently high in both 2009 and 2010, with a positive test result for norovirus in 20 to 22% of cases of acute gastroenteritis. The rates of norovirus-associated hospitalizations, emergency department visits, and outpatient visits in 2009 did not differ significantly from the rates in 2010. This consistency in the annual disease burden was observed despite a change in the predominant norovirus GII.4 variant from GII.4 Minerva in 2009 to GII.4 New Orleans in 2010. In contrast, the disease burden from rotavirus infection was substantially lower in 2010 than in 2009.

Rates of medically attended norovirus infection were highest among children 6 to 18 months of age, and the majority of these infections were caused by GII.4 variants. The GII.4 norovirus has emerged as the predominant strain in the United States and has been the leading cause of norovirus outbreaks worldwide.[18] In this study, norovirus was detected in 4% of healthy controls in 2009, confirming a relatively low rate of asymptomatic infection among U.S. children.

The overall health care utilization rates (rates of hospitalization, emergency department visits, and outpatient visits) associated with norovirus infection were more than twice as high as those associated with rotavirus infection since rotavirus vaccines were introduced (523.0 vs. 241.8 per 10,000 children younger than 5 years of age in 2009, and 401.6 vs. 9.4 per 10,000 in 2010). In fact, the rates of emergency department visits and outpatient visits for norovirus infection reported here are similar to those for influenza in children of the same age during a moderate influenza season (the 2002–2003 season in the same surveillance network).[16] Cases of norovirus infection were observed year-round during the study period, although most occurred in the winter months. Cases of rotavirus infection occurred almost exclusively during the winter months. The systematic fluctuations in the rates of rotavirus infection observed between 2009 and 2010 empirically suggest the emergence of a novel, biennial pattern of rotavirus activity that has previously been predicted in modeling simulations.[19,20]

During the study period, annual medical costs for hospitalizations, emergency department visits, and outpatient visits associated with norovirus infection approached $300 million for

U.S. children younger than 5 years of age. The median norovirus-associated hospitalization cost ($3,918) is similar to that reported for rotavirus infection in 2009 ($4,311)[21] and slightly lower than the costs estimated by Mast et al. on the basis of data from February 2005 through June 2006 ($4,565).[22]

In an indirect analysis of national health care data sets, Lopman et al. estimated that 71,000 norovirus-associated U.S. hospitalizations occurred each year from 1996 through 2007, including 18,000 hospitalizations per year among children younger than 5 years of age[23] – a figure similar to the direct, laboratory-confirmed estimate reported here. The proportion of children hospitalized for acute gastroenteritis who tested positive for norovirus in our study (17%) was higher than the pooled proportion in a literature review by Patel et al. (12%).[24] Despite the importance of norovirus-associated hospitalizations, the overwhelming majority of children with norovirus infection were seen in emergency departments and outpatient clinical settings. Data on visits to emergency departments and outpatient clinics are critical for the complete characterization of the burden of disease.

For the 2-year study period, our data indicate a shift in the predominant norovirus GII.4 variant. In 2009, the genotype detected in almost three quarters of the specimens that were positive for norovirus was GII.4 Minerva; however, none of the samples from 2010 were positive for GII.4 Minerva. The variant identified in all samples that were positive for GII.4 in 2010 was GII.4 New Orleans. As compared with other genotypes of norovirus, GII.4 norovirus is shed in larger numbers during infection,[25] causes more severe symptoms with greater likelihoods of transmission[26] and poor outcomes,[27] and may bind to multiple distinct histo–blood group antigens, which serve as norovirus-binding ligands on mucosal surfaces.[28] To be effective, a norovirus vaccine must induce immunity that is broad enough to provide protection against new variants, which can be expected to emerge on a regular basis, according to our data and to a recent report in which a novel GII.4 Sydney 2012 variant was identified.[29] Our results may be helpful in identifying the most appropriate vaccine candidates and in targeting populations for vaccination.

Our study has several limitations. Our surveillance may not be representative of the entire U.S. population of children, and it may not account for year-to-year variation in the natural disease burden. Census figures from 2000 were used as denominators to retain consistency with previously published rate estimates for these populations. Because of differences in the methods used for weighting data, we were unable to generate 95% bootstrap confidence intervals for emergency department rates.

In conclusion, our 2-year, prospective, population-based surveillance study indicates that norovirus has become the leading cause of medically attended acute gastroenteritis in U.S. children and is associated with substantial medical costs.

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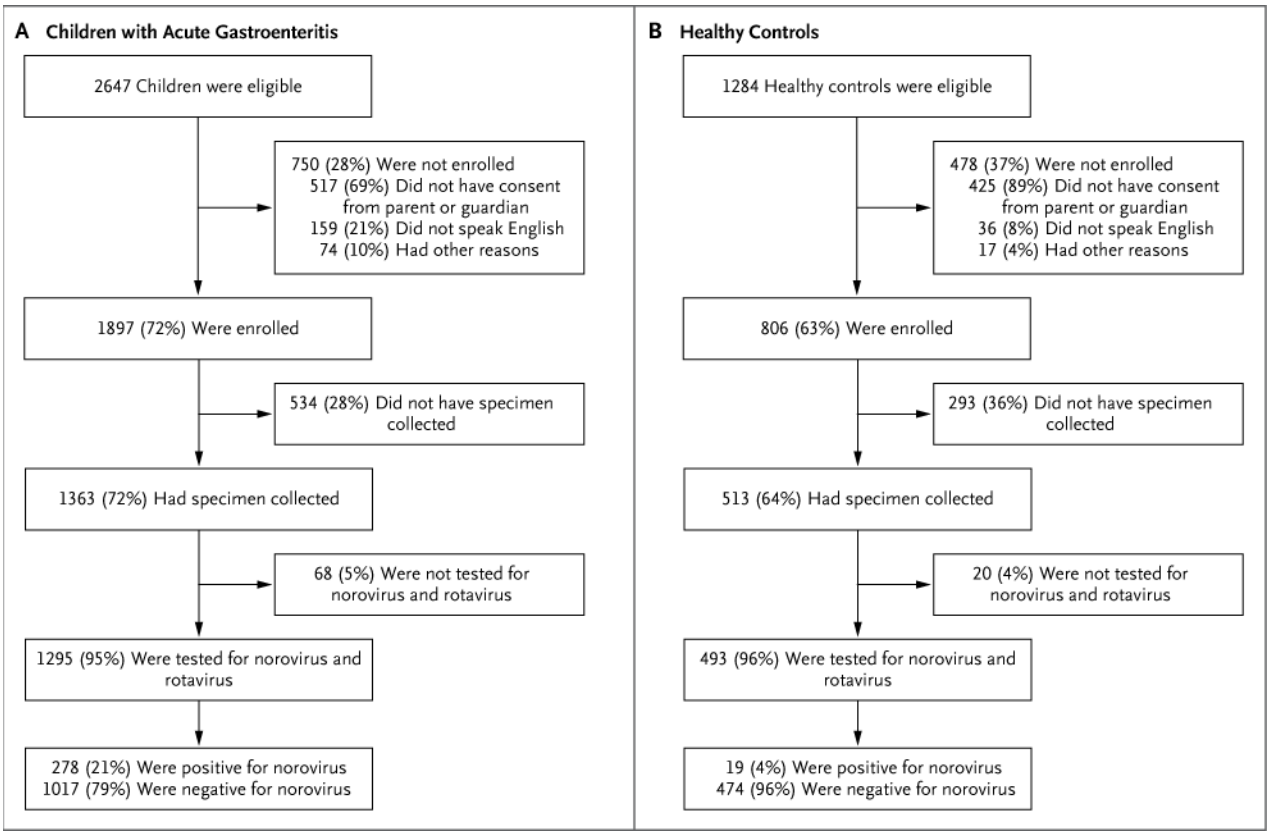

Figure 1.
Study Enrollment and Results of Norovirus Testing.

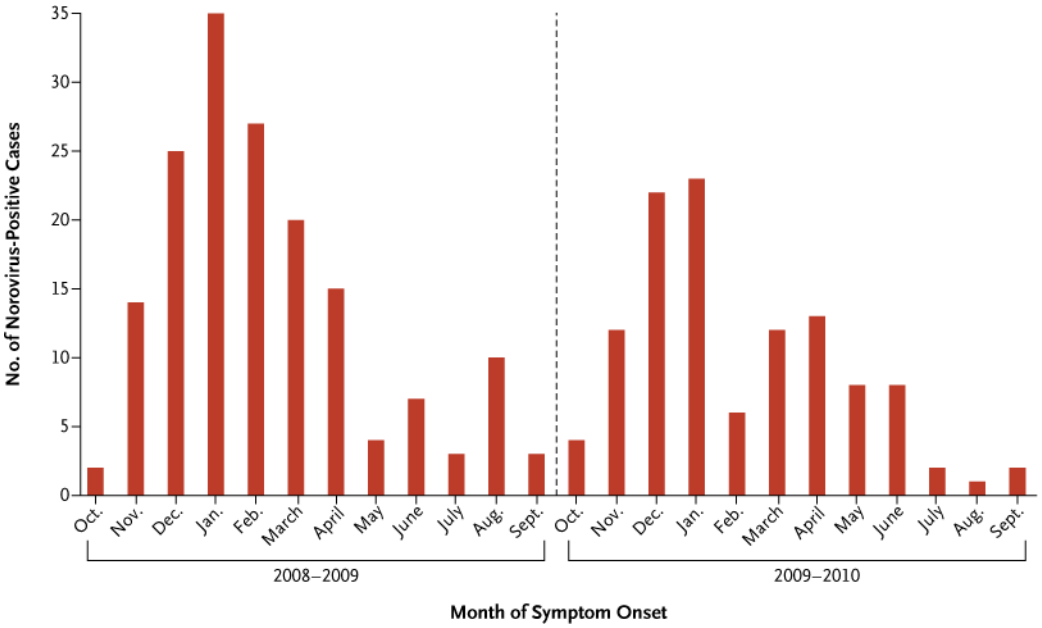

Figure 2. Norovirus Infection among Children with Acute Gastroenteritis, According to Month of Symptom Onset, 2009 and 2010

Data are for children younger than 5 years of age. The year 2009 refers to the period from October 2008 through September 2009, and 2010 refers to the period from October 2009 through September 2010. Data are from the New Vaccine Surveillance Network.

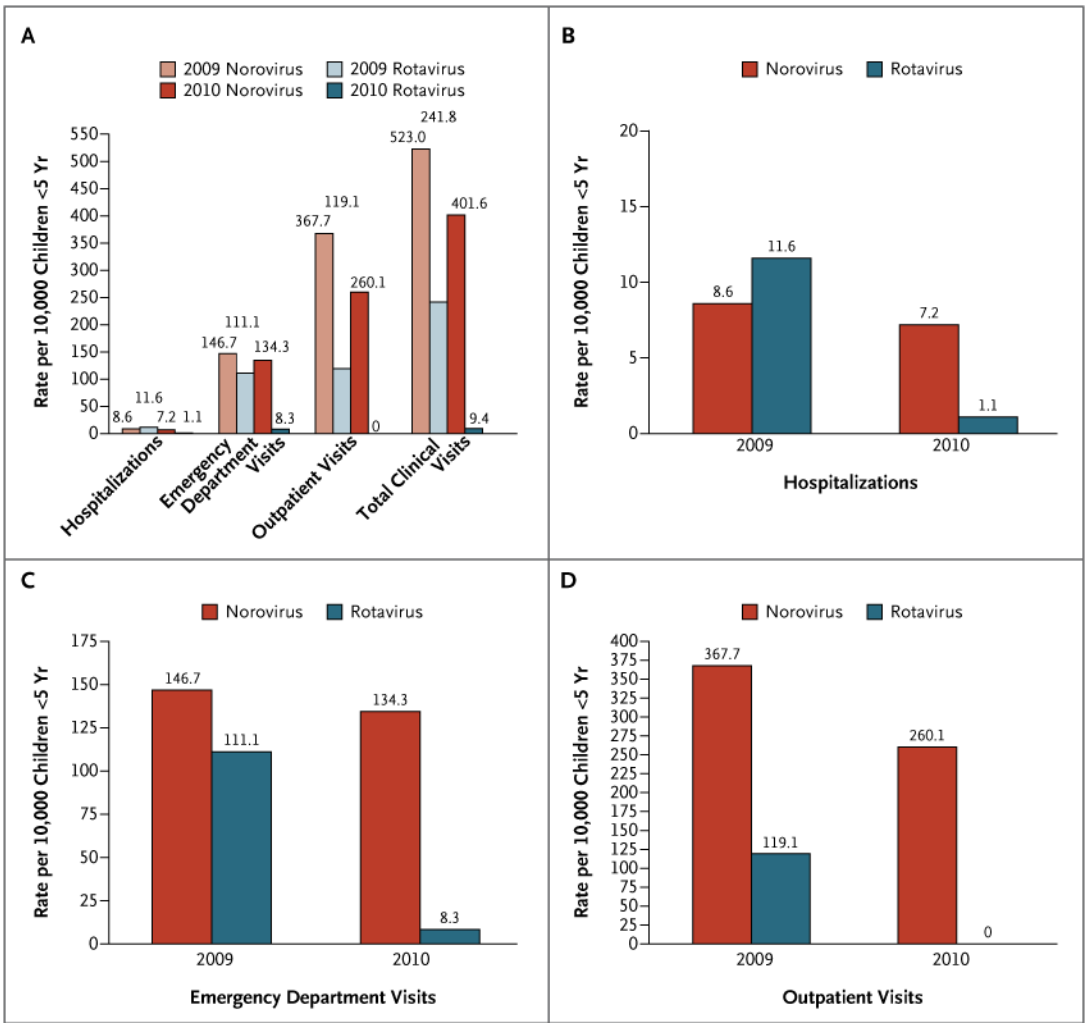

Figure 3. Norovirus and Rotavirus Infections among Children in Hospitals, Emergency Departments, and Outpatient Clinical Settings, 2009 and 2010

The rates for emergency departments visits in Nashville are based on data gathered through June 2010; all other rates are based on surveillance data gathered through September. Data are from the New Vaccine Surveillance Network.

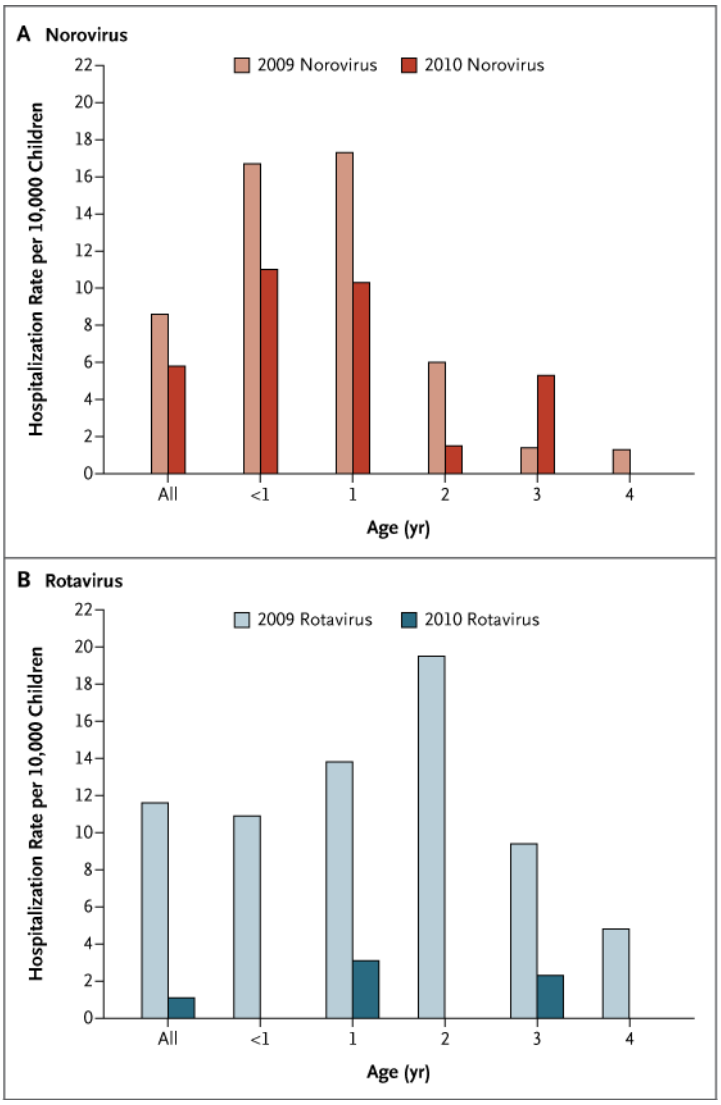

Figure 4. Rates of Hospitalization for Norovirus and Rotavirus Infection According to Age, 2009 and 2010

Data are from the New Vaccine Surveillance Network.

Table 1

Norovirus Test Results among Children with Acute Gastroenteritis, According to Clinical Setting, Surveillance Site, and Age, 2009–2010.*

Variable	Hospitalizations (N = 514)			Emergency Department Visits (N =595)			Outpatient Visits (N = 186)		
	Norovirus-Positive	Norovirus-Negative	P Value	Norovirus-Positive	Norovirus-Negative	P Value	Norovirus-Positive	Norovirus-Negative	P Value
All children with acute gastroenteritis, 2009–2010—no. (%)	86 (17)	428 (83)		139 (23)	456 (77)		53 (28)	133 (72)	
Surveillance year–no./ total no. (%)			0.61			0.87			0.21
2009	54/310 (17)	256/310 (83)		77/326 (24)	249/326 (76)		34/106 (32)	72/106 (68)	
2010	32/204 (16)	172/204 (84)		62/269 (23)	207/269 (77)		19/80 (24)	61/80 (76)	
Surveillance site – no./ total no. (%)			0.38			0.04			0.38
Rochester, NY	18/139(13)	121/139 (87)		30/103 (29)	73/103 (71)		18/60 (27)	48/60 (73)	
Nashville	24/131 (18)	107/131 (82)		33/112(29)	79/112(71)		20/57 (35)	37/57 (65)	
Cincinnati	44/244 (18)	200/244 (82)		76/380 (20)	304/380 (80)		15/63 (24)	48/63 (76)	
Age – no./total no. (%)			<0.001			0.18			0.59
<6 mo	14/187 (7)	173/187 (93)		16/108 (15)	92/108 (85)		10/42 (24)	32/42 (76)	
6–11 mo	21/76 (27)	56/76 (73)		37/121 (31)	84/121 (69)		10/30 (33)	20/30 (67)	
12–17 mo	24/70 (34)	46/70 (66)		27/112(24)	85/112(76)		11/33 (32)	23/33 (68)	
18–23 mo	9/49 (18)	40/49 (82)		21/78 (27)	57/78 (73)		12/31 (39)	19/31 (61)	
24–35 mo	11/69 (16)	58/69 (84)		25/114(22)	89/114(78)		5/40 (22)	18/40 (78)	
36–47 mo	5/36 (14)	31/36(86)		8/38 (21)	30/38 (79)		3/19(16)	16/19 (84)	
48–59 mo	2/26 (8)	24/26 (92)		5/24 (21)	19/24 (79)		2/7 (29)	5/7(71)	
All ages	86/514 (17)	428/514(83)		139/595 (23)	456/595 (77)		53/186 (28)	133/186 (72)	

*Data are from the New Vaccine Surveillance Network.