

treatment or prevention of mucositis, earlier detection and identification of isolates, and revision of current antimicrobial drug protocols for empiric treatment of neutropenic fever.

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**Jennifer M. Schrimsher,  
Joseph P. McGuirk,  
and Daniel R. Hinthorn**

Author affiliations: University of Kansas Medical Center, Kansas City, Kansas, USA (J.M. Schrimsher, J.P. McGuirk, D.R. Hinthorn); and University of Kansas Cancer Center, Kansas City, (J.P. McGuirk)

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Address for correspondence: Jennifer M. Schrimsher, Department of Internal Medicine, University of Kansas Medical Center, 3901 Rainbow Blvd, Mailstop 1028, Kansas City, KS 66160, USA; email: [jschrimsher@kumc.edu](mailto:jschrimsher@kumc.edu)

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## Clinical Profile of Children with Norovirus Disease in Rotavirus Vaccine Era

**To the Editor:** After the substantial decrease in acute gastroenteritis (AGE) in children caused by rotavirus after introduction of 2 rotavirus vaccines (1), norovirus has become the leading cause of medically attended AGE in US children <5 years of age (2). We describe the clinical characteristics of norovirus disease and assessed whether rotavirus vaccine protected against norovirus AGE.

During October 2008–September 2010, the New Vaccine Surveillance Network enrolled 1,897 children <5 years of age with symptoms of AGE ( $\geq 3$  episodes of diarrhea or any episodes of vomiting within 24 hours lasting  $\leq 10$  days) who came to hospitals,

emergency departments, and outpatient clinics in Cincinnati, Ohio; Nashville, Tennessee; and Rochester, New York, USA, as described (2).

Epidemiologic, clinical, and vaccination data were systematically collected. Whole fecal specimens were obtained within 14 days of the date of visit and tested for rotavirus by using a commercial enzyme immunoassay (Rotaclone; Meridian Bioscience, Inc., Cincinnati, OH, USA) and for norovirus by using real-time reverse transcription quantitative PCR, followed by sequence analysis of positive samples (3,4). Clinical severity was assessed by using a 20-point scoring system (5), which was modified to use behavior as a proxy for dehydration. Odds ratios used to calculate vaccine effectiveness (VE) were adjusted for race and insurance status (online Technical Appendix, [wwwnc.cdc.gov/EID/article/19/10/13-0448-Techapp1.pdf](http://wwwnc.cdc.gov/EID/article/19/10/13-0448-Techapp1.pdf)).

Inclusion criteria for this study corresponded with criteria used in previous New Vaccine Surveillance Network studies (2,6). Children were age eligible for pentavalent rotavirus vaccination (RV5), had a fecal specimen tested for norovirus and rotavirus, and had complete vaccination and AGE symptom information (online Technical Appendix Figure 1). Children who received a dose of monovalent rotavirus vaccine or vaccine of unknown type or were positive for rotavirus and norovirus were excluded from analyses. Only unvaccinated rotavirus-positive children ( $n = 69$ , 72%) were used in severity score analyses because RV5 is known to attenuate rotavirus illness (6).

Of the enrolled children, 574 met the inclusion criteria; 144 (25%) norovirus-positive case-patients, 96 (17%) rotavirus-positive case-patients, and 334 (58%) patients negative for norovirus and rotavirus (control patients with AGE) (online Technical Appendix Figure 1). Of 144 norovirus-positive specimens, 10 (7%) could not be genotyped, 4 (3%) were positive

for genogroup (G) I, and 130 (90%) were positive for GII. The most common genotype was GII.4 Minerva (74 [51%]).

Norovirus case-patients were significantly more likely than control patients with AGE to have longer duration and more episodes of vomiting in a 24-hour period ( $p = 0.003$  and  $p < 0.0001$ , respectively) but were significantly less likely to report fever ( $p = 0.001$ ) (Table). However, the median severity score for norovirus case-patients did not differ from that for control patients with AGE (11 vs. 10, respectively). Individual severity score components and overall severity scores did not differ among case-

patients infected with norovirus who received 0, 1 or 2, or 3 doses of RV5, but the duration of vomiting was longer in case-patients infected with norovirus GII.4 than in those infected with a non-GII.4 genotype (online Technical Appendix Tables 1, 2; Figure 2).

Relative to the 69 unvaccinated rotavirus case-patients, norovirus case-patients had shorter duration and fewer episodes of diarrhea in a 24-hour period ( $p = 0.003$  and  $p = 0.0003$ , respectively). Norovirus case-patients were also significantly less likely to be hospitalized ( $p = 0.02$ ), have fever ( $p < 0.0001$ ), and have severe behavior changes ( $p < 0.0001$ ); they also had lower overall severity scores

( $p < 0.0001$ ) than unvaccinated rotavirus case-patients.

Compared control patients with AGE, VE of any dose of RV5 against norovirus disease was  $-0.9\%$  (95% CI  $-55\%$  to  $34\%$ ). A full course of RV5 likewise showed no evidence of protection against norovirus (VE 5%; 95% CI  $-50\%$  to  $40\%$ ), and results were consistent across age groups.

In conclusion, we found that norovirus AGE was associated with more frequent and prolonged vomiting but less fever than AGE not caused by norovirus or rotavirus. Case-patients infected with norovirus GII.4 also had a longer duration of vomiting than did case-patients

Table. Clinical profile and severity score of norovirus case-patients compared with AGE control patients and unvaccinated rotavirus case-patients, New Vaccine Surveillance Network, United States, 2008–2010\*

Severity score component	Severity score	Norovirus case-patients, n = 144	Unvaccinated rotavirus case-patients, n = 69	p value†	AGE control patients, n = 334	p value†
Duration of diarrhea, d, no. (%)				<b>0.003</b>		0.19
0	0	32 (22)	3 (4)		82 (25)	
1–4	1	87 (60)	55 (80)		171 (51)	
5	2	13 (9)	7 (10)		33 (10)	
≥6	3	12 (8)	4 (2)		48 (14)	
Diarrhea episodes/24 h, no. (%)				<b>0.0003</b>		0.24
0	0	32 (22)	3 (4)		82 (25)	
1–3	1	47 (33)	16 (23)		79 (24)	
4–5	2	22 (15)	14 (20)		64 (19)	
≥6	3	43 (30)	36 (52)		23 (33)	
Duration of vomiting, h, no. (%)				0.43		<b>0.003</b>
0	0	7 (5)	2 (3)		54 (16)	
1–23 (1 d)	1	28 (19)	10 (14)		64 (19)	
24–47 (2 d)	2	33 (23)	12 (17)		74 (22)	
>48 (≥3 d)	3	76 (53)	45 (65)		142 (43)	
Vomiting episodes/24 h, no. (%)				0.22		<b>&lt;0.0001</b>
0	0	7 (5)	2 (3)		54 (16)	
1	1	11 (8)	1 (1)		52 (16)	
2–4	2	45 (31)	20 (29)		117 (35)	
≥5	3	81 (56)	46 (67)		111 (33)	
Fever, °F, no. (%)				<b>&lt;0.0001</b>		<b>&lt;0.0001</b>
<98.6	0	80 (56)	15 (22)		102 (31)	
98.7–101.1	1	29 (20)	21 (30)		55 (16)	
101.2–102	2	9 (6)	18 (26)		45 (13)	
≥102.1	3	26 (18)	15 (22)		132 (40)	
Behavioral signs, no. (%)				<b>&lt;0.0001</b>		0.65
Normal	0	12 (8)	2 (3)		35 (10)	
Less playful/irritable	1	63 (44)	13 (19)		158 (47)	
Lethargic/listless	2	67 (47)	54 (78)		138 (41)	
Seizure	3	2 (1)	0 (0)		3 (1)	
Treatment, no. (%)				<b>0.02</b>		0.16
None	0	50 (35)	12 (17)		135 (40)	
Rehydration, no hospitalization	1	50 (35)	26 (38)		87 (26)	
Hospitalization	2	44 (31)	31 (45)		112 (34)	
Severity score, median	NA	11	13	<b>&lt;0.0001</b>	10	0.78

\*AGE control patients were those who had AGE (defined as ≥3 episodes of diarrhea or any episodes of vomiting within 24 h that lasted ≤10 d) but who were negative for norovirus and rotavirus. AGE, acute gastroenteritis; NA, not applicable.

†Severity scores were compared by Wilcoxon rank-sum test. All other components were compared by Fisher  $\chi^2$  test. Significant findings are indicated in **boldface**.

infected with non-GII.4 norovirus genotypes. However, AGE among unvaccinated rotavirus case-patients was more severe than among norovirus case-patients, and was characterized by higher fever and more frequent and severe diarrhea. This finding confirms findings in a study of children in Finland (7), although our study found no difference in frequency or severity of vomiting between patients with rotavirus disease and those with norovirus disease.

In addition, vaccination against rotavirus did not provide protection against norovirus and had no effect on the clinical course of norovirus disease, which is consistent with other findings (8). Although an earlier rotavirus vaccine, which has subsequently been withdrawn, may have provided some nonspecific protection by reducing intensity and duration of diarrhea associated with adenovirus and sapovirus (9,10), our study did not demonstrate a similar effect on norovirus-associated diarrhea after vaccination with RV5. This study reinforces the hypothesis that norovirus can cause severe AGE among young children and should be considered as a specific target for vaccine development.

**Mary E. Wikswo, Rishi Desai,  
Kathryn M. Edwards,  
Mary Allen Staat,  
Peter G. Szilagyi,  
Geoffrey A. Weinberg,  
Aaron T. Curns,  
Benjamin Lopman, Jan Vinjé,  
Umesh D. Parashar,  
Daniel C. Payne,  
and Aron J. Hall**

Author affiliations: Centers for Disease Control and Prevention, Atlanta, Georgia, USA (M.E. Wikswo, R. Desai, A.T. Curns, B. Lopman, J. Vinjé, U.D. Parashar, D.C. Payne, A.J. Hall); Vanderbilt University Medical Center, Nashville, Tennessee, USA (K.M. Edwards); Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA (M.A. Staat); and University of

Rochester School of Medicine and Dentistry, Rochester, New York, USA (P.G. Szilagyi, G.A. Weinberg)

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Address for correspondence: Mary E. Wikswo, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Mailstop A34, Atlanta, GA 30333, USA; email: [ezq1@cdc.gov](mailto:ezq1@cdc.gov)

## Leprosy in Pregnant Woman, United States

**To the Editor:** Hansen disease, or leprosy, in pregnancy is a rarely reported event in the United States. In 2009, a total of 213,036 new cases of leprosy were detected throughout the world (1). Nine countries in Africa, Asia, and Latin America consider it a public health problem, accounting for ≈75% of the global disease prevalence (1).

We describe a case of leprosy in a 27-year-old woman with 1 previous pregnancy and 1 live-born infant who had onset of subcutaneous nodules before she became pregnant. She appeared at her initial prenatal visit at 24.1 weeks of gestation after recently emigrating from Mexico. The patient reported that subcutaneous nodules had developed on her arms, legs, back, and abdomen ≈5 months before the visit, 2 weeks before her last menstrual period. A skin biopsy revealed acute and chronic panniculitis with acid-fast bacilli, and the condition was confirmed by PCR to be lepratamatous leprosy. Treatment included rifampin, Dapsone, clofazimine, and prednisone.

The patient's condition was monitored closely with ultrasounds at serial intervals; these showed consistent fetal growth at the 50th percentile. At 37 weeks and 1 day, her membranes

# Clinical Profile of Children with Norovirus Disease in Rotavirus Vaccine Era

## Technical Appendix

### Detailed Information on Clinical Profile of Children with Norovirus Disease in Rotavirus Vaccine Era

#### Methods

Persons included in the study were enrolled as New Vaccine Surveillance Network study participants ( $n = 1,897$ ) and had a fecal specimen collected ( $n = 1,363$ , 72%) that was tested for norovirus and rotavirus ( $n = 1,295$ , 95%) (Technical Appendix Figure 1). Pentavalent rotavirus vaccine (RV5) (RotaTeq; Merck and Co. Inc., Whitehouse Station, NJ, USA) was recommended for routine use in US infants in February 2006 in children 6–32 weeks of age. Therefore, to best gauge the possible effect of rotavirus vaccination on acute gastroenteritis (AGE) in this study population, we further restricted study participants to those born on or after April 1, 2006 ( $n = 1,178$ ), and who had reached the Advisory Committee on Immunization Practices–recommended age for completion of RV5 vaccine series (i.e.,  $\geq 8$  months of age), to avoid confounding by age at time of last dose ( $n = 759$ ) (1). Furthermore, only those children for whom a complete provider-verified vaccination record could be obtained were included ( $n = 748$ ). Only rotavirus vaccination doses administered  $>14$  days before AGE symptom onset were included. Study participants receiving any dose of monovalent rotavirus vaccine (Rotarix; GlaxoSmithKline Biologicals, Rixensart, Belgium) or a dose of unknown type were further excluded ( $n = 677$ ). To ensure a complete severity analysis, only persons with complete severity score data were included in final analysis ( $n = 577$ ). Of the remaining persons, 144 (25%) were positive for norovirus, 96 (17%) were positive for rotavirus, and 334 (58%) were negative for norovirus and rotavirus. Three persons positive for norovirus and rotavirus and were excluded from analysis.

Demographic characteristics of norovirus-positive case-patients and control patients with AGE were assessed for potential confounding of comparisons in clinical profile. Vaccine effectiveness (VE) of a full course and any dose of rotavirus vaccine were calculated at  $(1 - \text{adjusted odds ratio}) \times 100$ ; odds ratios were adjusted for race and insurance status on the basis of results of the analysis of demographic characteristics.

## Results

Current or past breastfeeding, premature birth, household size, highest household degree, and daycare attendance did not differ between norovirus case-patients and control patients with AGE (Technical Appendix Table 1). However, control patients with AGE were significantly more likely to be black, non-Hispanic ( $p = 0.02$ ), and use public insurance ( $p = 0.01$ ) than were norovirus case-patients. These groups may have been less likely to seek care for norovirus AGE given the lower occurrence of fever compared with other causes of AGE. Despite these differences, control patients with AGE have been found to be the most appropriate control group during other New Vaccine Surveillance Network studies (2,3).

Of 144 norovirus-positive specimens, 134 (93%) could be genotyped. Of these, 89 (66%) were positive for genogroup II type 4 (GII.4). Forty-one (31%) were positive for a GII genotype other than GII.4, and 4 (3%) were positive for GI. Of the 45 non-GII.4 genotypes found, GII.12 was the most common ( $n = 19$ , 46%). Case-patients with norovirus GII.4 reported a significantly longer duration of vomiting than patients with non-GII.4 norovirus ( $p = 0.05$ ), but the median overall severity score (11) for each group was the same (Technical Appendix Table 2).

To validate our results for vaccine effectiveness (VE) of RV5 against norovirus disease, we also calculated VE against rotavirus disease. VE of RV5 against rotavirus disease was 84% (95% CI 73%–90%) for any dose and 86% (95% CI 74% – 92%) for a full course, consistent with other recent studies (2–4). Furthermore, we compared individual severity score components and overall severity scores among norovirus case-patients receiving 0, 1 or 2, or 3 doses of RV5 (Technical Appendix Figure 2). There were no differences in any severity score components when case-patients with norovirus receiving 3 doses of RV5 were compared with to unvaccinated case-patients with norovirus, or when norovirus case-patients receiving 1 or 2

doses were compared with unvaccinated case-patients with norovirus. Median severity scores among each of these groups of case-patients with norovirus were likewise not different.

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Technical Appendix Table 1. Characteristics of norovirus case-patients and acute gastroenteritis control patients, New Vaccine Surveillance Network United States, 2008–2010\*

Characteristic	Norovirus case-patients, n = 144	Control patients with AGE, n = 334	p value†
Median age (range), mo	16.5 (8–46)	18 (8–49)	0.06
Sex, no. (%)			
M	74 (51)	188 (56)	0.37
F	70 (49)	146 (44)	
Race, no. (%)			
White, non-Hispanic	63 (44)	119 (36)	<b>0.02</b>
Black, non-Hispanic	44 (31)	146 (44)	
Hispanic	30 (21)	47 (14)	
Other/unknown	7 (5)	22 (7)	
Insurance, no. (%)			
Public or public/private	93 (65)	257 (77)	<b>0.01</b>
Private	45 (31)	63 (19)	
None/unknown	6 (4)	14 (4)	
Breastfeeding, no. (%)			
Never	53 (37)	124 (37)	0.32
Past	86 (60)	184 (55)	
Present	5 (3)	25 (7)	
Unknown	0 (0)	1 (<1)	
Premature birth, no. (%)			
No	127 (88)	297 (89)	0.88
Yes	17 (12)	35 (10)	
Unknown	0 (0)	2 (1)	
Daycare attendance, no. (%) children			
None	101 (70)	199 (60)	0.07
<6	16 (11)	37 (11)	
6–12	20 (14)	75 (22)	
>12	7 (5)	16 (5)	

Characteristic	Norovirus case-patients, n = 144	Control patients with AGE, n = 334	p value†
Unknown	0 (0)	7 (2)	
Highest degree achieved by any household member, no. (%)			0.55
None	16 (11)	35 (10)	
GED	9 (6)	26 (8)	
High school diploma	65 (45)	171 (51)	
2–4 y of college	37 (26)	71 (21)	
Graduate	12 (8)	26 (8)	
Unknown	5 (3)	5 (2)	
Household size, no. persons (%)			0.61
2–4	92 (64)	211 (63)	
5–7	44 (31)	108 (32)	
≥8	8 (6)	12 (4)	
Unknown	0 (0)	3 (1)	
RV5‡ vaccination, no. (%)			0.79
Not vaccinated	42 (29)	98 (29)	
Partial (1 or 2 doses)	72 (50)	175 (52)	
Full course (3 doses)	30 (21)	61 (18)	

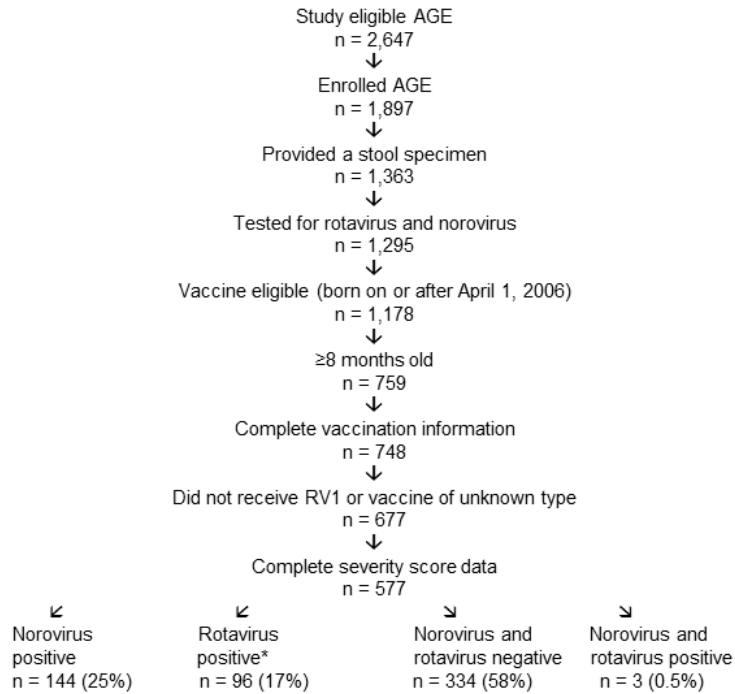
\*AGE, acute gastroenteritis; GED, general educational development; RV5, pentavalent rotavirus vaccine. Control patients with AGE had acute gastroenteritis defined as ≥3 episodes of diarrhea or any episodes of vomiting within 24 h lasting ≤10 d, but were negative for norovirus and rotavirus. †Ages were compared by Wilcoxon rank-sum test. All other characteristics were compared by Fisher  $\chi^2$  test. Significant findings are indicated in **boldface**. ‡RotaTeq (Merck and Co. Inc., Whitehouse Station, NJ, USA).

Technical Appendix Table 2. Clinical profile and severity score of case-patients infected with norovirus with GII.4 compared with case-patients infected with a norovirus non-GII.4 genotype, New Vaccine Surveillance Network, United States, 2008–2010\*

Severity score component	Severity score	Norovirus GII.4 case-patients, n = 89	Norovirus non-GII.4 case-patients, n = 45	p value†
Duration of diarrhea, d, no. (%)				0.06
0	0	16 (18)	15 (33)	
1–4	1	53 (60)	26 (58)	
5	2	12 (13)	1 (2)	
≥6	3	8 (9)	3 (7)	
Diarrhea episodes/24 h, no. (%)				0.07
0	0	16 (18)	15 (33)	
1–3	1	30 (34)	12 (27)	
4–5	2	11 (12)	9 (20)	
≥6	3	32 (36)	9 (20)	
Duration of vomiting, h, no. (%)				<b>0.05</b>
0	0	3 (3)	2 (4)	
1–23 (1 d)	1	16 (18)	10 (22)	
24–47 h (2 d)	2	14 (16)	15 (33)	
≥48 h (≥3 d)	3	56 (63)	18 (40)	
Vomiting episodes/24 h, no. (%)				1.0
0	0	3 (3)	2 (4)	
1	1	7 (8)	3 (7)	
2–4	2	28 (31)	14 (31)	
≥5	3	51 (57)	26 (58)	
Fever, °F, no. (%)				0.06
≤98.6	0	49 (55)	28 (62)	
98.7–101.1	1	22 (25)	4 (9)	
101.2–102	2	3 (3)	5 (11)	
≥102.1	3	8 (18)	15 (17)	
Signs, no. (%)				0.45
Normal	0	6 (7)	6 (13)	
Less playful/irritable	1	37 (42)	20 (44)	
Lethargic/listless	2	44 (49)	19 (42)	
Seizure	3	2 (2)	0 (0)	
Treatment, no. (%)				0.97
None	0	28 (31)	15 (33)	
Rehydration, no hospitalization	1	34 (38)	16 (36)	
Hospitalization	2	27 (30)	14 (31)	
Severity score, median	NA	11	11	0.12

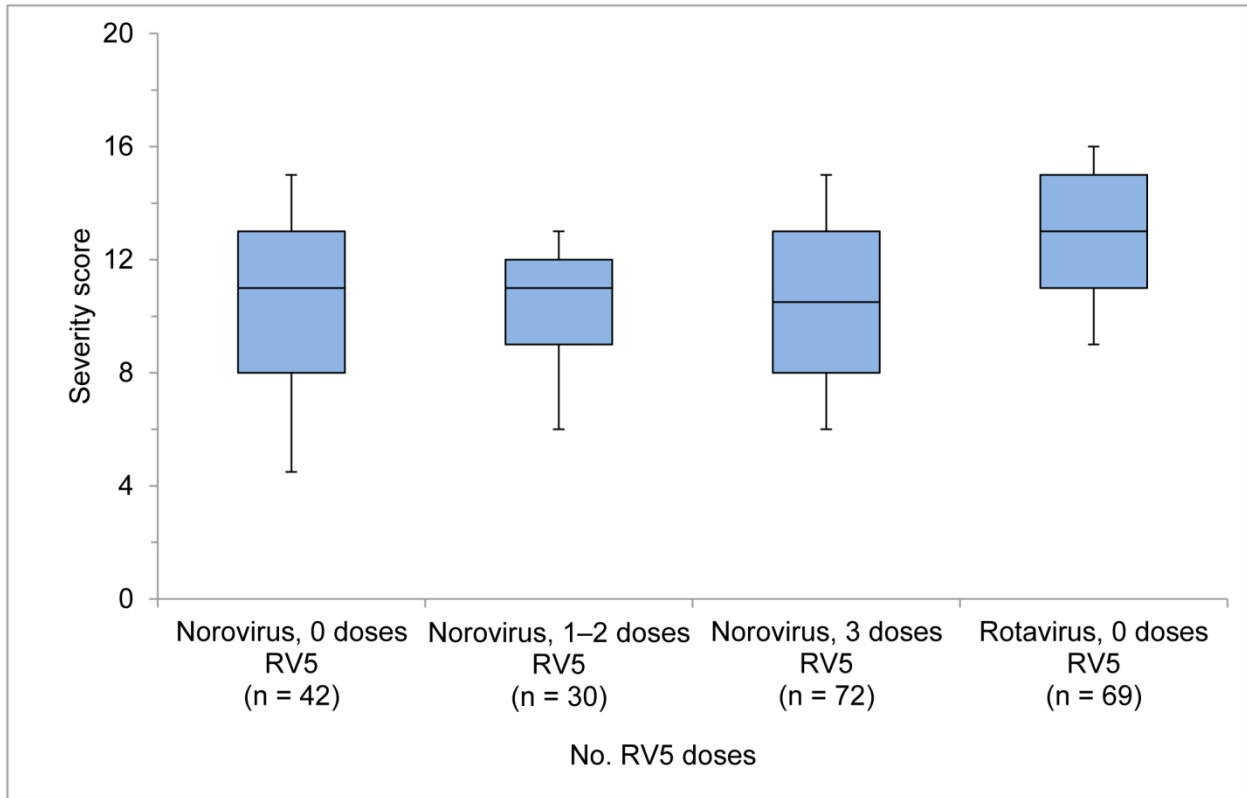
\*Significant findings are indicated in **boldface**. NA, not applicable.

†Severity scores compared by Wilcoxon rank-sum test. All other components compared by Fisher  $\chi^2$  test.



Technical Appendix Figure 1. Inclusion and exclusion criteria for patients with acute gastroenteritis (AGE), New Vaccine Surveillance Network, United States, 2008–2010. \*69 (72%) of rotavirus-positive persons with AGE were not vaccinated against rotavirus; 27 (28%) received  $\geq 1$  dose pentavalent rotavirus vaccine (RV5). RV1 monovalent rotavirus vaccine.





Technical Appendix Figure 2. Clinical severity scores among norovirus and rotavirus case-patients by no. pentavalent rotavirus vaccine (RV5) doses received, New Vaccine Surveillance Network, United States, 2008–2010. Horizontal lines indicate medians, error bars indicate interquartile ranges, and the minimum and maximum severity score values for each group. Rotavirus case-patient severity scores were significantly higher than those for each norovirus case-patient group by Wilcoxon rank-sum test ( $p < 0.05$ , for all comparisons).